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Financial Management Analysis in Supply Chain of Amazon, Swiggy, and BlueDART !

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Chief Editor's Message

Editorial

Prof R K Kotnala
FNASC, FIGU, FMSI
Chief Editor, Current Natural Sciences & Engineering, (CNS&E) Journal

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Email: chiefeditor@cnsejournals.org

The Importance of AI in Healthcare and in the Supply Chain Financial Management Analysis

The Current Natural Sciences & Engineering (CNS&E) Journal is committed to fostering the next generation of scientific leaders through the rapid advancement of S&T. The CNS&E Journal has taken a unique challenge to fulfil aspirations of young researchers by providing a supportive environment to publish their innovations & creativity for the society. Further, it elevates new scientific findings impactfully to disseminate high-quality, disruptive ideas and technologies by shaping the future of technology to serve mankind.

A special focus on Artificial Intelligence "AI" based studies have been presented in this issue by emphasising on interdisciplinary research at the intersection of health care and in the Supply Chain Financial Management Analysis of Amazon, Swiggy, and BlueDART. It essentially correlates analysis using AI and highlights the distinct strategies of these companies implemented within the larger supply chain management framework, with their financial tactics and operational models adapting to both internal dynamics and external influences. The instances of weak or negative correlations further emphasizes the unique business models and market environments in which each company operates, illustrating that each organization's expense management is distinctly customized to meet its individual business requirements and competitive challenges.

Besides, a critical role of anaplastic lymphoma kinase (ALK) in non-small cell lung cancer has been eluciated.This study focuses on ALK protein mutagenesis analysis as a cornerstone of precision oncology by systematically characterizing resistance mutations such as L1196M, G1269A, F1174L, and G1202R, with a prediction of treatment failure, guide therapeutic selection, and design next-generation inhibitors with improved efficacy. Through techniques including site-directed mutagenesis, CRISPR-Cas9 gene editing, and structure-based drug design

supported by crystallographic studies, researchers are developing more potent compounds tailored to mutant ALK protein conformations. Moreover, this research aims to advance personalized medicine by integrating molecular diagnostics, real-time mutation monitoring, and adaptive treatment strategies. Understanding the complex interplay between ALK mutagenesis and therapeutic response will enable clinicians to overcome resistance mechanisms, optimize combination therapies, and ultimately improve survival outcomes for ALK-positive lung cancer patients. Such, approach represents a critical step toward transforming lung cancer from a uniformly fatal disease to a manageable chronic condition through precision-targeted interventions.

A concise review explores bio-memristor evolution, key switching mechanisms, and bio-inspired designs, categorizing bio-memristors based on their resistive switching behavior and highlighting applications in neuromorphic AI, neuroprosthetics, and energy-efficient IoT. Finally, it addresses challenges in scalability, integration, and ethical considerations, paving the way for computing systems that learn and evolve like the human brain. The ever-growing demands of AI and data-driven computing expose the inefficiencies of conventional CMOS, HPC, and AI workloads (GPUs & TPUs), which suffers from the von Neumann bottleneck. Another very important aspect of Bio-memristors offer a transformative alternative, merging memory and computation for real-time, energy-efficient processing.

Nevertheless, a short review work on the Variations in mitochondria in nervous system disorders has been also elaborated very well embedded with science, nanoscience, and engineering. Variations in mitochondria in nervous system disorders have been detailed by reviewing the basic needs of the advent of next-generation sequencing (NGS), which has further accelerated the field by enabling comprehensive analysis of both mitochondrial and nuclear genomes in a single workflow.

Ultimately, A Quote on AI is to be remembered from Dr R K Kotnala:

"Human Brain Intelligence cannot be Dwarfed by AI (Artificial Intelligence), a Brain Child of Human, But a Remarkable Tool to Handle Colossal Data more Efficiently with a Greater Speed, Accuracy using Smart Algorithms Devoid of Emotions & New Science!"

Current Natural Sciences & Engineering
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A Comparative Analysis of Financial Expenses in Supply Chain Management: Case Studies of Amazon, Swiggy, and BlueDART

A. Dhadve[1], V. Tawal[2], S. Majumder[3], S. Basu Choudhury*[4]

[1]*Department of Management, ISMS Sankalp Business School, Pune, Maharashtra, India*
[2]*Department of Finance, ISMS Sankalp Business School, Pune, Maharashtra, India*
[3]*Department of Human Resource Management, ISMS Sankalp Business School, Pune, Maharashtra, India*
[4]*Department of Business Analytics, ISMS Sankalp Business School, Pune, Maharashtra, India*

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Corresponding author: *subhrodiptobasuchoudhury@gmail.com*

Abstract

This research provides a comparative overview of the financial costs associated with supply chain management (SCM) among three industry frontrunners—Amazon, Swiggy, and Blue Dart. These organizations operate across different sectors, with Amazon and Blue Dart positioned within the FMCG and logistics sectors, and Swiggy in the food delivery market. The study analyzes their financial documents from 2020 to 2022, concentrating on major expense categories such as transportation, warehousing, technology infrastructure, and human resources. Employing a mix of qualitative and quantitative methods, including financial data analysis and correlation assessments, the research illuminates the variances in the financial strategies these companies utilize to control SCM expenditures. The results emphasize the distinct operational frameworks and cost management tactics tailored to each company's market conditions and business goals. This study provides useful insights for other entities looking to enhance their financial management in the supply chain and boost operational efficiency, while acknowledging contextual and structural limitations arising from sectoral differences and pandemic-related disruptions.

Keywords: Supply Chain Management, Financial Costs, Logistics, Transportation, Warehousing, Technology Infrastructure, Human Resources, Comparative Study, Financial Documents, Operating Expenses.

Introduction:

In the ever-changing landscape of supply chain management, effective financial management is essential for ensuring operational efficiency and fostering business growth. Firms such as Amazon, Swiggy, and Blue Dart operate in different market sectors but face similar logistical hurdles that necessitate smart financial resource allocation. The supply chain costs incurred by these companies have a direct impact on their capacity to satisfy customer demands, uphold profit margins, and promote innovation.

This research intends to perform a comparative analysis of the financial expenditures of Amazon, Swiggy, and Blue Dart, concentrating on the critical areas where these companies direct their resources, including transportation, warehousing, technological infrastructure, and human resources. By examining the financial interactions of these organizations, the study aims to reveal how each company effectively controls costs amidst the competitive environment of supply chain management.

The findings offer significant insights into the financial outcomes and expense distribution strategies used by prominent firms in the industry, which can act as benchmarks for other enterprises seeking to enhance their supply chain management operations.

Literature Review

The SCM process encompasses various stages, including procurement, production, transportation, warehousing, and delivery. Financial costs associated with SCM generally include transportation, warehousing, technology infrastructure, and human resources. As noted by Christopher [1], logistics and distribution represent significant portions of the overall supply chain expenses, particularly within the e-commerce and FMCG sectors. Moreover, companies frequently allocate resources towards technology and personnel to retain a competitive edge. Supply chain expenses differ across industries such as logistics, retail, and food delivery, influenced by their complexity and operational needs [2]. Amazon's SCM strategy relies on an extensive global network of suppliers, fulfilment centers, and distribution channels. According to a KPMG report (2020), Amazon's supply chain heavily depends on technological investments, with considerable spending on infrastructure, fulfillment operations, and delivery systems. In Amazon’s financial disclosures, costs linked to fulfillment, technology infrastructure, and fulfillment center operations have been consistently increasing over the years (Amazon Annual Report, 2022). Researchers have observed that Amazon’s focus on automation and AI has enhanced inventory management efficiency, though this comes alongside significant technological expenditures [3]. For example, Amazon’s operating costs for fulfillment and technology surged from $58 billion in 2020 to $84 billion in 2022, underscoring the company's continuous investment in its supply chain infrastructure. Blue Dart, a prominent player in the logistics field, operates in a market where supply chain management expenses are primarily associated with transportation and warehousing. As indicated by Trivedi and Bajaj [4], the main cost drivers for Blue Dart include

fuel, fleet maintenance, and delivery network management. While Amazon operates an expansive fulfillment infrastructure, Blue Dart concentrates on enhancing transportation efficiency and optimizing warehousing. Based on their financial data (Blue Dart Annual Report, 2022), it is evident that Blue Dart's logistics-related costs, encompassing depreciation and finance charges, constitute a significant part of their overall expenses. Their strategy of reducing transportation costs through optimized routing and effective fleet management has been crucial in sustaining a competitive advantage in the logistics sector. Swiggy, functioning within the food delivery domain, encounters distinctive supply chain management challenges compared to Amazon and Blue Dart. As discussed by Sharma and Agarwal (2020, food delivery services are heavily dependent on delivery personnel and real-time technology for tracking orders. Swiggy's investment in human resources and technology infrastructure is substantial, alongside significant costs related to packaging and delivery. Data from Swiggy's financial reports (Swiggy Annual Report, 2022) reveal that labour costs and employee benefits have risen markedly as the company expands its network of delivery personnel. Additionally, Swiggy is dedicated to enhancing its technology platform to improve delivery times and customer experience. Research conducted by Ravi et al. (2020) points out that Swiggy's notable expenditures on "other expenses," which include marketing, technology, and customer acquisition, signify its efforts to scale quickly in a fiercely competitive food delivery landscape. The comparative examination of Amazon, Swiggy, and Blue Dart highlights significant disparities in their SCM strategies and the distribution of financial resources. Amazon, given its extensive global presence, emphasizes investments in fulfillment infrastructure and technology. Conversely, Swiggy prioritizes human resources and technological investments focused on optimizing delivery networks, while Blue Dart allocates the majority of its financial resources to transportation and logistics. According to Mentzer [5], efficient management of supply chain costs hinges on aligning financial strategies with fundamental operational functions, and each of these companies has customized its financial priorities accordingly.

Additionally, the increasing expenses in technology and human resources for all three companies highlight a trend in the supply chain management (SCM) industry, where embracing digital transformation and optimizing labour has become crucial for minimizing operational inefficiencies. Specifically, the food delivery industry, represented by Swiggy, encounters cost challenges related to labour and logistics technology—issues that Amazon and Blue Dart are less affected by [6]. The heightened dependence on technology to enhance supply chains is clear in all three firms. Amazon utilizes automation and AI within its warehouses, Blue Dart emphasizes route optimization technology, and Swiggy employs a real-time tracking system, showcasing the vital role technology has in controlling financial costs. As noted by Hopp and Spearman [7] investing in technology may lead to substantial long-term savings, despite the initial financial outlay being significant.

Research Methodology

To fulfil the goals of this study, a detailed qualitative and quantitative approach has been utilized. The research relies on secondary information obtained from publicly accessible financial statements, annual reports, and industry literature related to Amazon, Swiggy, and Blue Dart.

The methodology is organized as follows:

1. **Data Gathering:** Financial information for Amazon, Swiggy, and Blue Dart over the past three years was collected from their respective annual reports, investor presentations, and audited financial documents. Additional insights into the industry were obtained from market research publications and financial analysis tools.

2. **Analysis of Expense Categories:** Critical expense categories within the supply chain, including logistics expenses, technology infrastructure, warehousing, and human resources, were identified and evaluated. Emphasis was placed on cost trends, variations, and any significant changes in expense distribution over time.

3. **Comparative Evaluation:** The financial data from each company was compared concerning their operational costs, concentrating on common operating expenses. Metrics such as operating margin, asset turnover, and return on investment (ROI) were also computed to evaluate the financial effectiveness of supply chain spending. These comparisons are interpreted strategically rather than as exact operational benchmarks, given the differences in business models and sectoral contexts.

4. **Interpretation and Insights:** The results were analyzed within the framework of each company's business model and supply chain strategies. This comparative method aids in grasping the financial priorities of these firms and how they align their expenditures to further operational goals.

This paper focuses on the operating expense segment of the income statement for Amazon, Blue Dart, and Swiggy for the years 2020, 2021, and 2022.

Limitations of the Study

This study relies exclusively on secondary data obtained from publicly available annual reports, audited financial statements, and investor disclosures. While these sources ensure reliability and transparency, they often aggregate cost items into broad accounting categories. As a result, some supply chain cost components such as last-mile delivery expenses, reverse logistics, and micro-level warehousing efficiencies cannot be fully isolated.

The analysis also focuses primarily on financial cost metrics and does not incorporate non-financial operational performance indicators such as delivery lead times, inventory turnover, order accuracy, or service quality levels. Although these indicators are critical for evaluating supply chain effectiveness, consistent and comparable disclosures were not publicly available for all three firms.

The study period (2020–2022) coincides with the COVID-19 pandemic, which caused abnormal operational disruptions, demand fluctuations, and regulatory

constraints. Therefore, certain cost variations may reflect short-term crisis responses rather than stable long-term strategic patterns.

Furthermore, the three firms operate under fundamentally different business models — Amazon's infrastructure-intensive global e-commerce operations, Swiggy's hyper-local on-demand delivery network, and Blue Dart's premium logistics services. Hence, the comparative analysis emphasizes strategic cost allocation patterns rather than strict numerical equivalence across companies.

Table 1: Amazon — Operating Expenses (2020–2022)

Amazon			
	2020	2021	2022
Operating Expenses:			
Cost of sales	$233,307	$272,344	$288,831
Fulfillment	58,517	75,111	84,299
Technology and Content	42,704	56,052	73,213
Marketing	22,008	32,551	42,238
General and Administrative	6668	8,823	11,891
other operating expenses, net	75	62	1,263
Total operating expenses	$363,165	$444,943	$501,735

Source: based on Amazon Annual Reports (2020–2022).

Table 2: Blue Dart — Financial Summary (2020–2022)

Blue Dart			
Particulars	Mar-20	Mar-21	Mar-22
Income from Operations	3,16,639	3,27,970	5,17,222
Other Income	1401	1266	5054
Total Income	318040	329236	522276
Total Expenditure	297855	290307	453996
Profit before Exceptional Items, Depreciation, Interest and Tax	20185	38929	68280
Depreciation	15280	20067	16664
Finance Cost	3214	3172	1742
Profit Before Exceptional Items and Tax	1691	15690	49874
Exceptional Items	6411	2585	0
Profit/(Loss) Before Tax	4720	13105	49,874
Income Tax expenses	891	3474	13230

Source: based on Blue Dart Annual Reports (2020–2022).

Table 3: Swiggy — Income and Expenses (2020–2022)

Swiggy			Rs in millions
	year ended March 31, 2020	year ended March 31, 2021	year ended March 31, 2022
Income			
Revenue from operations	32,875	20,080	35,571
other income	2,610	1,370	4,891
Total income	35,485	21,450	40,462
Expenses			
Cost of operations	26,176	2,812	
Cost of material consumed	1,489	379	511
purchases of stock-in-trade	224	82	6
Changes in inventories of stock-in-trade	128	114	14
Employee benefits expense	11,565	9,353	14,706
Finance costs	758	714	411
Depreciation and amortisation expense	1,951	2,029	1,214
other expenses	30,112	17,622	50,547
Total Expenses	72,147	33,105	67,409

Source: based on Swiggy Annual Reports (2020–2022).

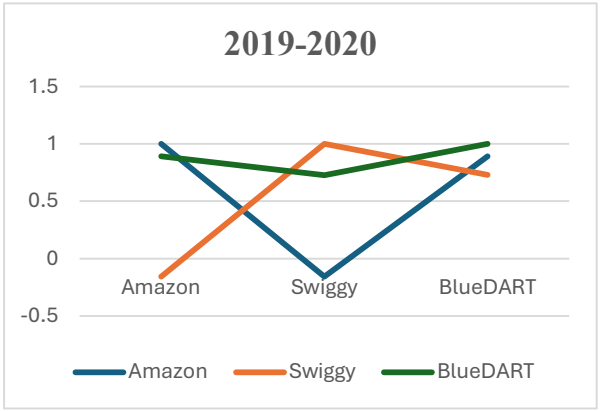

Figure. 1 Correlation curve for 2019–2020

Source: Authors' own analysis based on Amazon, Swiggy, and Blue Dart annual reports (2020).

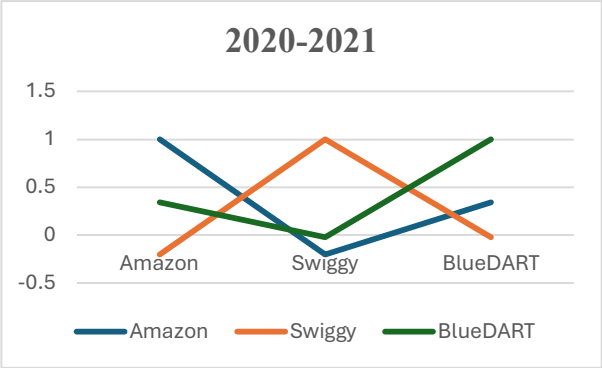

Figure 2. Correlation curve for 2020–2021

Source: Authors' own analysis based on Amazon, Swiggy, and Blue Dart annual reports (2021).

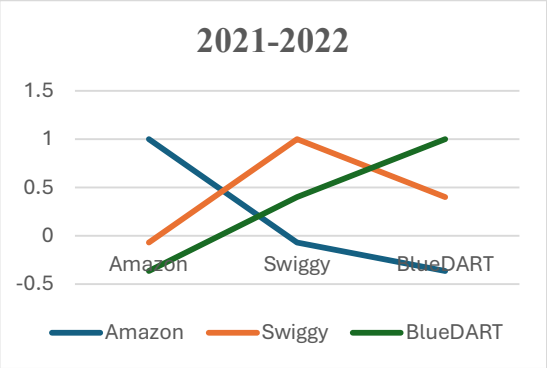

Figure 3 Correlation curve for 2021–2022

Source: Authors' own analysis based on Amazon, Swiggy, and Blue Dart annual reports (2022).

Key Findings:

From the three curves, it is evident that Swiggy has a similar trend from 2019-2022 whereas Amazon and BlueDART show a different trend during the 2019-2022. This is due to the fact that the three companies operate in different sectors in operation and logistics industry. Amazon and BlueDART are FMCG sector whereas Swiggy come in food sector companies.

The shift or trend is shifted during the COVID-19 situation.

Conclusion

Based on the correlation data spanning three years, it is evident that Amazon, Swiggy, and BlueDart exhibit varying relationships that mirror their different methodologies in handling supply chain costs and expenditures. Initially, Amazon and BlueDart demonstrated a strong alignment, but this connection has diminished in recent years. The correlation of Swiggy with both Amazon and BlueDart has varied, indicating possible changes in business strategies, such as Swiggy's heightened emphasis on technological innovations or collaborations. Essentially, the correlation analysis highlights the distinct strategies these companies implement within the larger supply chain management framework, with their financial tactics and operational models adapting to both internal dynamics and external influences. The instances of weak or negative correlations further emphasize the unique business models and market environments in which each company operates, illustrating that each organization's expense management is distinctly customized to meet its individual business requirements and competitive challenges. The findings should therefore be interpreted as strategic financial insights rather than precise operational benchmarks. Nonetheless, the analysis offers meaningful guidance on how different supply chain-dependent firms align financial investments with their

competitive priorities under dynamic conditions.

Conflict of Interest: There is no conflict to declare.

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ALK Kinase Mutagenesis in Non-small Cell Lung Cancer

Soma Garani[1*] and Ahana Chakraborty[2]

[1] *WBUAFS, Kolkata, West Bengal*
[2] *AIIMS, Jodhpur, Rajasthan*

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[*]*Corresponding author:* *somagofficial@gmail.com*

Abstract

Lung cancer is a leading cause of mortality worldwide, accounting for approximately 18% of global cancer deaths and representing a significant public health burden, particularly in countries with high smoking rates and pollution. This review examines the critical role of anaplastic lymphoma kinase (ALK) in non-small cell lung cancer (NSCLC) and explores how ALK mutagenesis analysis is a therapeutic strategy for this malignancy. ALK gene rearrangements, occurring in 3–7% of NSCLC cases, most commonly result in the EML4-ALK fusion protein, which drives uncontrolled cancer cell proliferation through constitutive activation of downstream signaling pathways including PI3K/AKT, RAS/MAPK, JAK/STAT, and PLCγ. The discovery of these molecular alterations has revolutionized lung cancer treatment, enabling the development of targeted ALK inhibitors ranging from first-generation drugs like crizotinib to advanced third-generation inhibitors such as lorlatinib. However, acquired resistance through secondary ALK mutations and bypass signalling pathways remains a significant clinical challenge. This study focuses on ALK protein mutagenesis analysis as a cornerstone of precision oncology. By systematically characterizing resistance mutations such as L1196M, G1269A, F1174L, and G1202R, we can predict treatment failure, guide therapeutic selection, and design next-generation inhibitors with improved efficacy. Through techniques such as site-directed mutagenesis, CRISPR-Cas9 gene editing, and structure-based drug design supported by crystallographic studies, researchers are developing more potent compounds tailored to mutant ALK protein conformations. Our research aims to advance personalized medicine by integrating molecular diagnostics, real-time mutation monitoring, and adaptive treatment strategies. Understanding the complex interplay between ALK mutagenesis and therapeutic response will enable clinicians to overcome resistance mechanisms, optimize combination therapies, and ultimately improve survival outcomes for ALK-positive lung cancer patient. This approach represents a critical step toward transforming lung cancer from a uniformly fatal disease to a manageable chronic condition through precision-targeted interventions.

Keywords: Anaplastic Lymphoma Kinase (ALK), Non-Small Cell Lung Cancer (NSCLC), ALK Mutagenesis Analysis, Targeted Therapy and Drug Resistance, Precision Oncology

1. Introduction

Lung cancer is one of the most common and deadliest forms of cancer globally. It ranks second when it comes to death due to cancer. It occurs when abnormal cells in the lung grow uncontrollably, often forming tumours that interfere with lung function. The two main types are **non-small cell lung cancer (NSCLC)**, which accounts for approximately 85% of cases, and **small cell lung cancer (SCLC)**, which is more aggressive and rapidly spreading. The primary causes include long-term smoking, exposure to environmental pollutants, and genetic mutations. Lung cancer often remains asymptomatic in its early stages, leading to late diagnosis and poor prognosis in many cases. NSCLC predominantly occurs in individuals who are passive smokers, but SCLC is seen in active smokers mainly. The former rises mainly due to adenocarcinoma, that is, cancer or hyperproliferation of glandular cells. Men mostly die due to lung cancer, and this incidence is mounting day-by-day.

1.1 World Disease Percentage

Lung cancer is a leading cause of cancer-related deaths worldwide. According to the World Health Organization (WHO), lung cancer accounts for about **11.4% of all diagnosed cancers globally** and nearly **18% of all cancer deaths**. It is more prevalent in countries with high rates of smoking, industrial pollution, and aging populations. Despite advances in cancer treatment, the five-year survival rate for lung cancer remains relatively low, emphasizing the need for early diagnosis and innovative therapeutic strategies.

1.2 Percentage in India

In India, lung cancer represents a significant public health concern. It is the second most common cancer in men and the fifth in women. The incidence rate is estimated to be around 6.9 per 100,000 individuals, and it contributes to about **8.1% of all cancer-related deaths** in the country. The increasing prevalence of smoking, especially among males, along with rising air pollution in urban centres, has led to a notable rise in lung cancer cases. Moreover, awareness, early screening, and access to modern treatments remain limited in many parts of the country, contributing to higher mortality rates.

1.3 Mode of Action of Lung Cancer

The development of lung cancer begins at the cellular level, where genetic and environmental factors cause mutations in DNA. These mutations disrupt the normal cell cycle, leading to uncontrolled growth and the formation of tumours. Key mechanisms include:

A. **Oncogene activation**: Gain-of - function mutation of genes like EGFR, KRAS, and ALK are frequently mutated or overexpressed, leading to excessive cell proliferation.

B. Tumour suppressor gene inactivation: Loss or mutation of genes like TP53 removes the natural checks on cell division.

C. Angiogenesis: Tumours stimulate the growth of new blood vessels to supply nutrients, allowing them to grow and spread.

D. Metastasis: Cancer cells can break away from the original tumour, travel through the blood or lymph, and form new tumours in other organs.

These molecular changes are complex and often involve multiple pathways, making treatment a challenge, especially in advanced stages.

Table 1: Country-wise ALK Mutagenesis Type and Prevalence in Lung Cancer (2020-2025)

Country/Region	ALK Prevalence (%)	Predominant ALK Mutation/Fusion Type	Most Common Cancer Subtype	Patient Demographics	Effects on Treatment Outcomes	Reference
United States	4.3-5.0%	EML4-ALK fusion (most common); L1196M, G1202R resistance mutations	Adenocarcinoma (predominant)	Younger patients (18-44 yrs: 16.2%); Asian Americans: 6.3%; Non-smokers	High response to crizotinib (60%); Median survival 6.8 years with targeted therapy	Allen et al., 2020; Desai et al., 2021
China	5.1-5.8%	EML4-ALK fusion (81.5%); KIF5B-ALK (1.5%); Resistance: L1196M, G1269A, G1202R	Invasive mucinous adenocarcinoma and acinar subtype	Predominantly non-smokers; Younger age (median 52 years); Female predominance	Excellent response to 1st gen TKIs; Resistance develops within 11-14 months; 2nd/3rd gen inhibitors extend PFS	Tarigopula et al., 2020; Zaric et al., 2016
Taiwan	5.73%	EML4-ALK fusion	Adenocarcinoma (71% EGFR+)	Non-smokers; Asian ethnicity; Younger patients	High response rate; Better PFS with alectinib vs crizotinib; Overall favorable prognosis	Lin et al., 2025
Japan	4-5%	EML4-ALK fusion variants (V1, V3a/b predominant)	Adenocarcinoma	Non-smokers; Younger median age	Superior outcomes with 2nd gen ALK-TKIs (alectinib); Lower CNS metastasis with early treatment	Multiple studies 2020-2023
South Korea	5-6%	EML4-ALK fusion; Secondary mutations after treatment	Adenocarcinoma	Never-smokers; Female predominance	High initial response; Sequential therapy with multiple generations of ALK-TKIs improves OS	Tarigopula et al., 2020
India	2.7-3.0%	EML4-ALK fusion; Limited data on specific resistance mutations	Adenocarcinoma (81.9%)	Peak age 36-50 years; Both smokers and non-smokers	Response similar to global data but limited access to newer TKIs affects outcomes	Tarigopula et al., 2020
Europe (Overall)	3.7-4.9%	EML4-ALK fusion; G1202R and L1196M resistance mutations	Adenocarcinoma	Younger patients; Non-smokers; No significant gender difference	Good response to ALK-TKIs; Access to 3rd gen inhibitors (lorlatinib) improves resistant cases	Multiple European studies 2020-2024
Eastern Europe (Serbia)	5.1%	EML4-ALK fusion (acinar subtype correlation)	Acinar subtype of adenocarcinoma	Caucasian population; Similar demographics to Western Europe	Comparable outcomes to Western populations with appropriate therapy	Zaric et al., 2016
Middle East & North Africa (MENA)	8.7% (range: 2.2-19.6%)	EML4-ALK fusion; Limited mutation profiling data	Adenocarcinoma	Younger age; Non-smokers; No EGFR co-mutation	Variable outcomes due to testing availability; Egypt highest (19.6%), Lebanon lowest (2.2%)	AlJassim et al., 2025
Saudi Arabia	3-5%	EML4-ALK fusion	Adenocarcinoma	Mixed smoking history	Limited data on outcomes; Testing increasingly available	AlJassim et al., 2025
Egypt	19.6%	EML4-ALK fusion	Adenocarcinoma	Predominantly younger patients	Higher prevalence may indicate population-specific factors; Good response to available TKIs	Al-Shamsi et al., 2021
Lebanon	2.2%	EML4-ALK fusion	Adenocarcinoma	Mixed demographics	Lower prevalence similar to Western populations	Al-Shamsi et al., 2021
Kuwait, Bahrain, UAE	3-8%	EML4-ALK fusion; BRAF testing recent	Adenocarcinoma	Younger age; Non-smokers	Routine testing now standard; Good access to targeted therapies	AlJassim et al., 2025
Levant Region (Lebanon, Jordan, Iraq)	3-5%	EML4-ALK translocation by FISH	Adenocarcinoma	Mean age 63.4 years; 66% male	Limited access to newer ALK-TKIs; Primarily crizotinib available	Multiple studies 2017-2025
Latin America (Overall)	3.7-9.5%	EML4-ALK fusion	Adenocarcinoma	Mixed ethnicity; Genetic ancestry influences frequency	Chile: 3.7%; Costa Rica: 9.5%; Variable access to testing and treatment	Laguna et al., 2024
Brazil	5-7%	EML4-ALK fusion; KRAS mutations (24.2%)	Adenocarcinoma	Admixed population; Variable smoking history	Outcomes depend on access to molecular testing and targeted therapies	Laguna et al., 2024
Argentina	6-8%	EML4-ALK fusion; KRAS mutations (23%)	Adenocarcinoma	Similar to Brazil	Limited molecular testing in practice; Most patients managed without mutation data	Laguna et al., 2024

1.4 Role of Alk on Lung Cancer

The anaplastic lymphoma kinase (ALK) gene plays a crucial role in a subset of non-small cell lung cancer (NSCLC). The kinase is encoded by the ALK gene located on chromosome 2, particularly on the 2p23 region. In about 3–7% of NSCLC patients, a chromosomal rearrangement causes the gene to fuse with another gene, most commonly EML4. This fusion leads to the production of a constantly active ALK fusion protein, which drives cancer cell growth, division, and survival. The discovery of rearrangements has had a major impact on the treatment of lung cancer. ALK-positive patients often respond well to targeted therapies, particularly ALK inhibitors such as crizotinib, ceritinib, alectinib, and newer third-generation drugs like lorlatinib. These treatments specifically block the activity of the ALK protein, significantly slowing disease progression and improving survival rates.

1.5 Our Aim to Cure Lung Cancer by Alk Protein Mutagenesis Analysis

Our research is focused on understanding and combating lung cancer through ALK protein mutagenesis analysis. This involves studying how specific mutations in the ALK gene affect its structure and function, as well as its interaction with targeted drugs. By identifying mutations that lead to drug resistance or hyperactivity of the protein, we can design more effective, next-generation inhibitors.

This approach allows us to:

- Predict resistance mutations that may emerge during treatment.
- Develop personalized therapies tailored to individual mutation profiles.
- Enhance drug design by understanding the molecular structure of mutant ALK proteins.
- Improve long-term outcomes for ALK-positive lung cancer patients.

Through this focused analysis, we aim to advance precision medicine strategies and move closer to curing ALK-driven lung cancer.

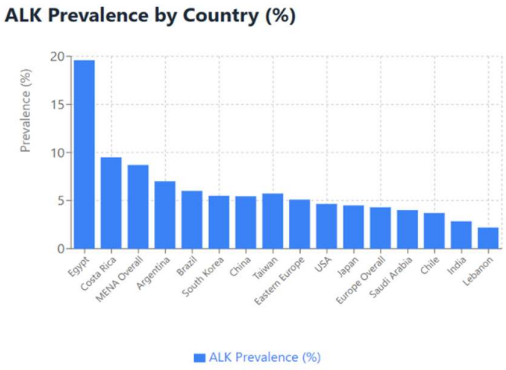

Figure. 1 ALK mutation rate country wise

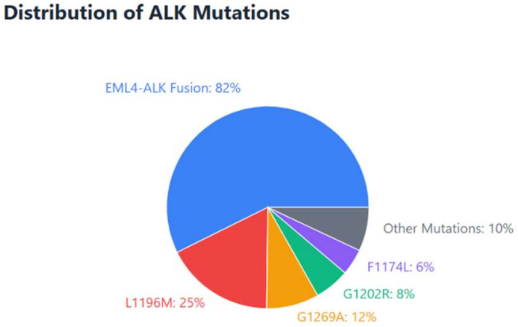

Figure 2. Distribution of ALK mutation

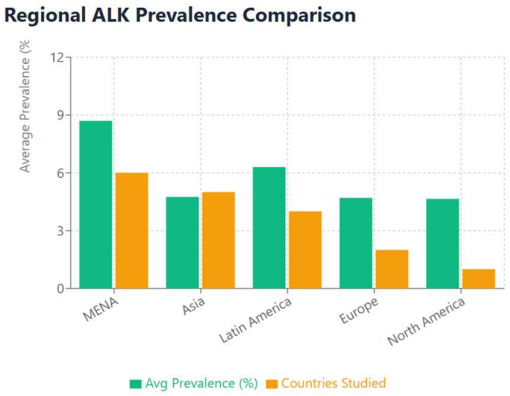

Figure.3. Comparison of ALK mutation

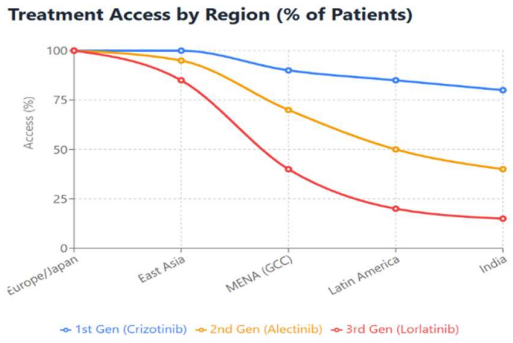

Figure 4. Treatment access by region

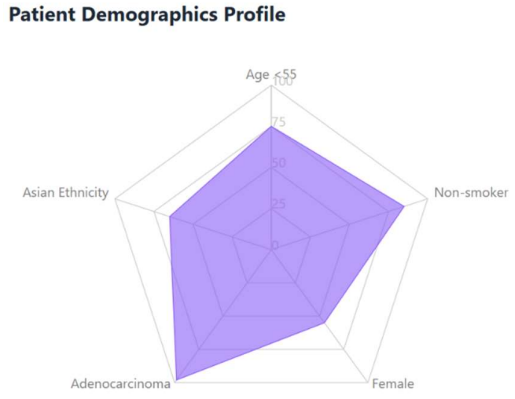

Figure 5. Patient demographic profile

2. Lung Cancer Effects on Physiology

Lung cancer significantly impacts the human body, not only due to the presence of malignant cells in the lungs but also through its systemic effects on various physiological systems. As the disease progresses, it disrupts normal lung function, impairs oxygen delivery, alters metabolism, and weakens the immune system. These physiological disruptions can lead to serious complications and ultimately affect the entire body. The most immediate and profound effect of lung cancer is on the respiratory system. Tumours can grow within lung tissue or bronchial passages, leading to obstruction of airways, causing shortness of breath (Dyspnea), wheezing, and persistent coughing. There is diminished gas exchange, where oxygen intake and carbon dioxide removal become less efficient due to the destruction of alveoli and capillaries. Pleural effusion is the buildup of fluid between the lungs and chest wall, which compresses the lungs and makes breathing more difficult. Haemoptysis (coughing up blood), often a result of tumour invasion into blood vessels. These issues cause a chronic lack of oxygen (hypoxia), which affects nearly all other body systems.

Lung cancer weakens the immune system, both directly and through treatments like chemotherapy and radiation. The tumour itself can suppress immune responses by releasing immunosuppressive signals, allowing it to grow unchecked. Cancer also spreads via the lymphatic system, affecting lymph nodes and reducing the body's ability to fight infections. As lung cancer progresses, it can lead to muscle wasting (cachexia), characterized by severe weight loss, fatigue, and loss of muscle mass. Metastasis to bones is common, causing bone pain, fractures, and elevated calcium levels in the blood (hypercalcemia), which can lead to confusion, kidney issues, and muscle weakness.

The cardiovascular system is indirectly affected by lung cancer. Hypoxia forces the heart to work harder to deliver oxygen to

tissues, potentially leading to tachycardia and high blood pressure as compensatory mechanisms. There is failure of right-side of the heart due to high pressure in the lungs from blocked blood vessels or a tumour mass. Anaemia, either from chronic disease or cancer-related bleeding, can further reduce the oxygen-carrying capacity of the blood. In advanced stages, cancer cells may enter the bloodstream and metastasize to distant organs, further complicating physiological functions. Lung cancer can spread to the liver, impairing its function and leading to symptoms like jaundice, fluid accumulation (ascites), and liver failure. Additionally, nausea, vomiting, and loss of appetite are common—partly from the cancer itself and partly from side effects of treatment—further reducing nutritional status and overall health. Hence, it disrupts vital physiological systems through direct tumour growth, metastasis, and the body's response to chronic illness. Understanding these effects is critical for managing symptoms, improving quality of life, and guiding treatment strategies.

3. Alk Expression and Signalling Pathway

The Anaplastic Lymphoma Kinase (ALK) is a receptor tyrosine kinase (RTK) that plays a crucial role in the development of the nervous system. While ALK expression is typically low or absent in healthy adult tissues, its abnormal activation through mutations, gene rearrangements, or amplification has been strongly associated with several cancers, including non-small cell lung cancer (NSCLC), anaplastic large cell lymphoma (ALCL), and neuroblastoma. In normal physiology, ALK is expressed predominantly in embryonic neural tissues, where it helps regulate cell growth, differentiation, and survival. In adults, its expression is minimal, but in cancers, ALK can become abnormally activated through mechanisms such as Gene fusion, point mutations and duplications. The most common mechanism in NSCLC, where ALK fuses with another gene, most frequently is EML4 (Echinoderm Microtubule-associated protein-Like 4). This results in the EML4-ALK fusion protein, which is constitutively active and no longer regulated by normal cellular mechanisms. Point mutations are found in neuroblastoma and other cancers, which cause abnormal activation of the ALK protein. An increase in the number of copies of the ALK gene can lead to overexpression of the protein. These alterations result in continuous signalling through downstream pathways that promote cancer cell proliferation and survival.

When ALK is abnormally activated, either by mutation or gene fusion, it triggers a cascade of downstream signalling pathways that are vital for cell survival, proliferation, and resistance to apoptosis. The major downstream pathways activated by ALK include:

A. PI3K/AKT Pathway:

The phosphoinositide 3-kinase (PI3K)/AKT signalling cascade plays a major role in promoting cell growth, metabolism, and survival. When ALK is activated, it recruits PI3K, which in turn activates AKT. This pathway inhibits apoptosis and promotes resistance to chemotherapy, making the cancer more aggressive.

B. RAS/MAPK Pathway:

This pathway is involved in cell proliferation and differentiation. Activated ALK stimulates RAS, which then activates the RAF-MEK-ERK kinase cascade. Continuous stimulation of this pathway leads to uncontrolled cell division, a hallmark of cancer.

C. JAK/STAT Pathway:

ALK also activates the Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway, particularly STAT3. This results in the transcription of genes that promote cell survival, proliferation, and immune evasion.

D. PLCγ Pathway:

Activation of phospholipase C gamma (PLCγ) leads to the production of diacylglycerol (DAG) and inositol triphosphate (IP3), which increase intracellular calcium levels and activate protein kinase C (PKC). This contributes to changes in cell adhesion and motility, enhancing the potential for metastasis.

Understanding ALK signalling is crucial in modern oncology as it would help us find which pathway or molecules to target for controlling cancer progression.

4. Therapeutic Use of Alk Mutagenesis

The discovery of ALK rearrangements in NSCLC has revolutionized treatment, allowing for targeted therapy using ALK inhibitors like crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib. These drugs specifically block ALK's kinase activity, shutting down the aberrant signaling pathways and slowing tumour growth. The first breakthrough in ALK-targeted therapy came with the development of **Crizotinib**, a first-generation ALK inhibitor. It specifically targets ALK fusion proteins in ALK-positive NSCLC and blocks their activity. However, over time, many patients develop resistance due to additional mutations in the ALK gene, such as **L1196M, G1269A, and F1174L**. These mutations change the ALK protein's shape, reducing drug binding and allowing the cancer to progress. However, resistance often develops through secondary mutations in ALK or activation of bypass pathways. **Gatekeeper mutations** (e.g., L1196M) introduce steric hindrance at the ATP-binding site, as a consequence, the first-generation inhibitors lose potency. **Solvent-front mutations** (e.g., G1202R) alter the entrance to the ATP pocket rendering most second-gen inhibitors are ineffective; third-gen inhibitors can accommodate these changes. **Macrocyclic design** (third-gen) locks inhibitors into conformations that avoid clashes and stabilize inactive kinase, leading to a broad resistance coverage.

Ceritinib has shown efficacy in preclinical studies and phase 1 trials, inhibiting ALK secondary mutations during crizotinib therapy. In one phase 1 study involving 114 NSCLC patients, the overall response rate was 58%, with notable responses in patients with ALK gene amplification or mutations. Another phase 1 study yielded a response rate of 55% among 20 patients. The ASCEND-1 trial, which included 246 ALK-rearranged NSCLC patients, reported an overall response rate of 72% in ALK inhibitor-naïve patients and 56% in those pretreated. Additionally, the ongoing ASCEND-2 study reported a response rate of 38.6% in 140 ALK-rearranged NSCLC patients who had failed prior treatments (Holla et al.,2017).

Ongoing research into the structure and mutagenesis of ALK is helping to develop next-generation inhibitors and combination therapies to overcome resistance. To overcome this, second- and third-generation ALK inhibitors were developed such as Ceritinib and Alectinib. They are second-generation inhibitors that target both wild-type and mutated forms of ALK. Brigatinib is effective against a wider range of resistance mutations. Lorlatinib is a third-generation inhibitor designed to overcome nearly all known resistance mutations, including those that cause

resistance to second-generation drugs. The development of these drugs is directly linked to the study of ALK mutagenesis, demonstrating how therapeutic research is driven by mutation profiling. First-generation inhibitors, such as Crizotinib, primarily target the ATP-binding site of wild-type ALK, forming hydrogen bonds with the hinge region of the kinase domain. However, their binding affinity is often compromised by gatekeeper mutations (e.g., L1196M) that sterically hinder inhibitor interaction. Second-generation inhibitors, including Ceritinib and Alectinib, exhibit enhanced potency and selectivity by adopting a more flexible binding mode, allowing them to accommodate several resistance mutations. Third-generation inhibitors, exemplified by Lorlatinib, incorporate structural modifications that enable binding to both the wild-type and highly resistant ALK mutants, such as G1202R, by stabilizing the kinase in a specific inactive conformation and avoiding steric clashes. These mechanistic insights provide a structural rationale for the stepwise development of ALK inhibitors and their ability to overcome acquired resistance in non-small cell lung cancer.

Despite the success of ALK inhibitors, acquired resistance remains a major challenge. Resistance can develop through secondary mutations in ALK that reduce drug efficacy and activation of bypass signalling pathways, such as EGFR, MET, or KRAS. Phenotypic transformation (e.g., transformation from NSCLC to small-cell lung cancer) is another way of developing resistance.

Through **mutagenesis analysis**, researchers can identify these resistance mechanisms at the molecular level. By sequencing tumour DNA from patients who relapse after therapy, clinicians can detect new ALK mutations and adjust treatment accordingly. For instance, if a patient develops the **G1202R mutation**, they may respond better to Lorlatinib than to earlier inhibitors.

This kind of real-time monitoring and adaptive treatment strategy — also called precision oncology — relies heavily on understanding and tracking ALK mutagenesis over the course of the disease.

In the lab, ALK mutagenesis is used to model drug resistance and discover new inhibitors. Techniques like site-directed mutagenesis and CRISPR-Cas9 gene editing allow scientists to artificially introduce specific mutations into cancer cell lines or animal models. These models help to understand how each mutation affects drug sensitivity, predict how resistance may develop in patients and design inhibitors that fit the altered structure of mutant ALK proteins. This has led to a structure-based drug design approach, where inhibitors are tailored to the 3D conformation of ALK with specific mutations. Structural studies, often supported by cryo-electron microscopy or X-ray crystallography, guide medicinal chemists in developing next-generation compounds.

Studies of ALK mutagenesis in non-small cell lung cancer employ a combination of genetic, biochemical, cellular, and computational approaches to comprehensively analyze the functional and therapeutic consequences of specific mutations. Site-directed mutagenesis is frequently used to introduce precise point mutations or small insertions/deletions into ALK cDNA, typically via PCR-based methods or commercial mutagenesis kits. The resulting constructs are transfected into cell lines, and successful mutation is confirmed by sequencing, while expression and activity are validated through

immunoblotting and kinase assays. CRISPR-Cas9 gene editing enables the introduction of mutations directly into the endogenous ALK locus in cells or animal models, preserving native regulatory contexts. Following CRISPR modification, genomic sequencing, protein expression analysis, and functional assays—including proliferation, apoptosis, and drug response studies—are performed to evaluate the effects of the mutations in physiologically relevant settings. Complementing these approaches, overexpression systems allow controlled comparison between wild-type and mutant ALK, while in vitro kinase assays with purified recombinant proteins directly measure catalytic activity and inhibitor sensitivity, isolating kinase-intrinsic effects from cellular context. Structural modeling and molecular dynamics simulations provide mechanistic insights, revealing how specific mutations alter the ATP-binding pocket, affect inhibitor binding, and confer resistance. High-throughput mutagenesis and screening approaches, such as saturation mutagenesis libraries, further enable systematic identification of resistance hotspots and unexpected mutations that impact inhibitor efficacy. By integrating these methodologies, researchers can dissect the molecular mechanisms underlying ALK activation, mutation-driven drug resistance, and therapeutic response, providing a detailed framework for the rational design and optimization of next-generation ALK inhibitors.

The therapeutic use of ALK mutagenesis has already improved survival and quality of life in many cancer patients. It plays a central role in

A. **Molecular diagnostics**: Testing for ALK rearrangements and mutations guides treatment decisions.

B. **Treatment selection**: Patients receive therapies best suited to their mutation profile.

Table 2: ALK Mutations and Their Effects on Lung Cancer Treatment

Generation	Inhibitor	Target (WT / Mutants)	Molecular Mechanism / Resistance Overcoming
First	Crizotinib	WT ALK; some activity vs L1196M (limited)	Binds the ATP-binding site of ALK kinase, forming hydrogen bonds with hinge region residues. Gatekeeper mutation L1196M introduces steric hindrance, reducing binding affinity and leading to resistance.
	Ceritinib	WT ALK	Similar ATP-competitive binding; more potent than crizotinib, but less effective against solvent-front mutations like G1202R.
Second	Alectinib	WT ALK, L1196M, C1156Y, F1174C, others	Flexible binding to ATP pocket allows accommodation of bulky gatekeeper and adjacent mutations. Hydrophobic interactions with αC-helix and hinge region stabilize binding despite mutations.
	Brigatinib	WT ALK, L1196M, G1269A, F1174C	Binds ATP pocket with extended substituents to avoid steric clashes from gatekeeper mutations; hydrogen bonding network allows activity against solvent-front and αC-helix mutations.
	Ceritinib (later considered second-gen)	WT ALK, L1196M, G1269A	Similar to alectinib; improved interactions with hydrophobic pocket reduce sensitivity to gatekeeper mutations.
Third	Lorlatinib	WT ALK; resistant mutants including G1202R, L1196M, F1174C, I1171N	Stabilizes ALK in inactive DFG-out conformation, avoiding steric hindrance from gatekeeper and solvent-front mutations. Overcomes almost all clinically relevant resistance mutations.
	Ensartinib	WT ALK; many resistant mutants (L1196M, G1269A, F1174C)	Designed to maintain hydrogen bonding and hydrophobic contacts even in the presence of bulky substitutions in the ATP-binding pocket; flexible binding mode allows activity against multiple mutation classes.

C. **Monitoring disease progression**: Repeating genetic tests during and after treatment helps detect emerging resistance.

D. **Personalized medicine**: ALK mutagenesis allows for highly individualized treatment planning, reducing trial-and-error approaches. Looking ahead, combining ALK inhibitors with agents targeting parallel pathways, immunotherapies, or chemotherapy may improve outcomes further. Ongoing studies continue to investigate novel mutations, combination strategies, and biomarkers of response to optimize ALK-targeted therapy.

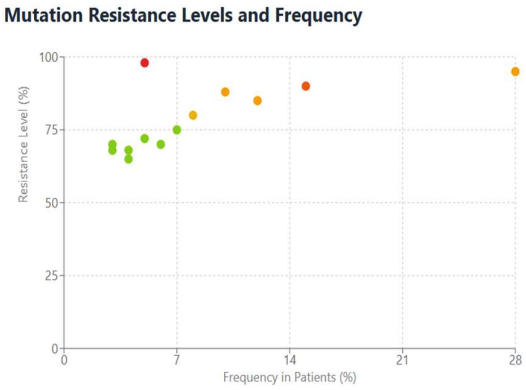

Figure. 6 Mutation resistance level and frequency

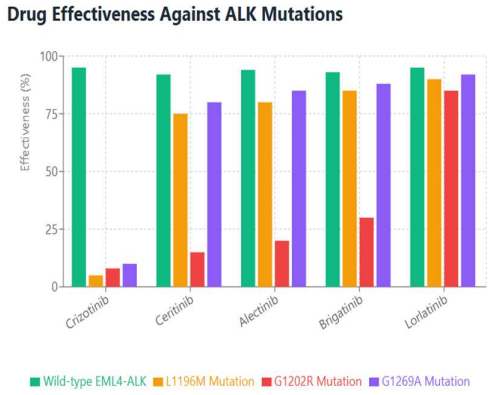

Figure 7. Drug effectiveness against ALK mutation

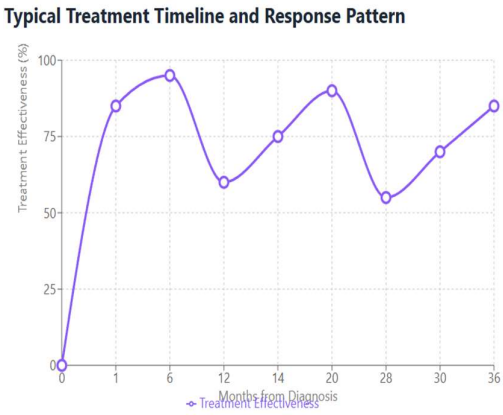

Figure 8. Treatment response pattern

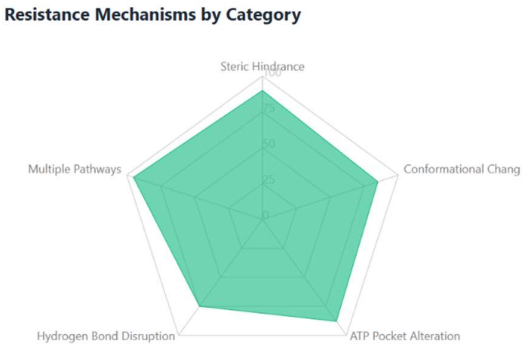

Figure 9. Resistance mechanism by category

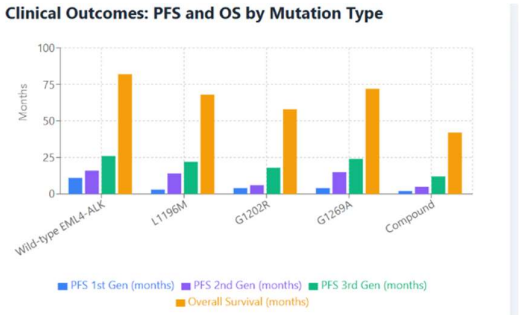

Figure 10. Clinical outcome

Table 3. Overcoming resistance in tabular form

Mutation	Location	Generation of Inhibitor Affected	Mechanism of Resistance	Clinical Effect	Effective Treatment	Reference
L1196M	Kinase domain (gatekeeper position)	First-generation (Crizotinib)	Steric hindrance blocks drug binding to ATP pocket	High resistance to crizotinib; disease progression	Ceritinib, Alectinib, Brigatinib	Choi et al., 2010; Katayama et al., 2012
G1269A	Kinase domain	First-generation (Crizotinib)	Conformational change reduces drug affinity	Moderate to high resistance; reduced progression-free survival	Ceritinib, Alectinib, Lorlatinib	Doebele et al., 2012
F1174L	Kinase domain	First-generation (Crizotinib)	Altered ATP-binding pocket structure	High resistance; associated with aggressive disease	Ceritinib, Brigatinib, Lorlatinib	Choi et al., 2010
G1202R	Kinase domain (solvent front)	First and Second-generation	Steric clash and altered hydrogen bonding	Resistance to both crizotinib and second-gen inhibitors	Lorlatinib (third-generation)	Katayama et al., 2012; Shaw et al., 2020
L1152R	Kinase domain	First-generation	Disrupts drug binding interface	Moderate resistance	Alectinib, Brigatinib	Doebele et al., 2012
C1156Y	Kinase domain	First-generation	Alters ATP pocket configuration	Moderate to high resistance	Ceritinib, Lorlatinib	Katayama et al., 2012
I1171T/N/S	Kinase domain	First and some second-generation	Changes hydrophobic interactions	Variable resistance depending on substitution	Brigatinib, Lorlatinib	Lin et al., 2017
V1180L	Kinase domain	First-generation	Structural alteration of binding pocket	Moderate resistance	Alectinib, Brigatinib	Doebele et al., 2012
F1245C	Kinase domain	First-generation	Reduces drug binding affinity	Moderate resistance	Second and third-generation inhibitors	Katayama et al., 2012
S1206Y	Kinase domain	First-generation	Conformational change in ATP pocket	Moderate resistance	Ceritinib, Alectinib	Lin et al., 2017
D1203N	Kinase domain	First-generation	Disrupts critical hydrogen bonds	Moderate resistance	Second-generation inhibitors	Doebele et al., 2012
E1210K	Kinase domain	First-generation	Electrostatic repulsion affects drug binding	Moderate resistance	Alectinib, Brigatinib	Lin et al., 2017
Compound Mutations (e.g., G1202R + L1196M)	Multiple positions	Second and third-generation	Multiple resistance mechanisms acting synergistically	Extreme resistance; very poor prognosis	Limited options; experimental compounds	Shaw et al., 2020
EML4-ALK (wild-type fusion)	Chromosomal rearrangement (2p23)	Drug-sensitive	Constitutive kinase activation without secondary mutations	Excellent initial response to ALK inhibitors	Crizotinib, Alectinib (first-line)	Soda et al., 2007; Solomon et al., 2014

Benefits of ALK Mutagenesis Analysis in Lung Cancer

1. Precision Medicine and Personalized Treatment

ALK mutagenesis analysis enables clinicians to tailor treatment strategies based on individual patient mutation profiles (Lin et al., 2017). By identifying specific ALK gene rearrangements and mutations, oncologists can select the most effective targeted inhibitor, moving away from the traditional trial-and-error approach and significantly improving treatment outcomes.

2. Early Detection of Drug Resistance

Through continuous molecular monitoring, resistance mutations can be detected before clinical relapse becomes apparent (Katayama et al., 2012). This early detection allows for timely adjustment of therapeutic strategies, such as switching to more potent third-generation inhibitors like lorlatinib when secondary mutations emerge, thereby extending progression-free survival (Shaw et al., 2020).

3. Development of Next-Generation Inhibitors

Understanding the structural and functional consequences of specific ALK mutations guides the design of novel inhibitors (Choi et al., 2010). Structure-based drug design, informed by crystallographic studies of mutant ALK proteins, has already led to the development of increasingly effective drugs that can overcome resistance mechanisms (Lin et al., 2017).

3.1 Fourth-Generation ALK Inhibitors

TPX-0131 (Zotizalkib)

TPX-0131 is a compact macrocyclic molecule designed to fit within the ATP-binding boundary to inhibit ALK fusion proteins, with superior potency against the G1202. TPX-0131 is potent against the G1202R/L1196M compound mutation in cell proliferation assays with an IC50 of 0.7 nmol/L, while other ALK inhibitors had modest to no measurable (Murray et al., 2021). Against the L1196M gatekeeper mutation, TPX-0131 is 76-fold more potent than lorlatinib and 11- to 550-fold more potent than first- and second-generation inhibitors (Murray et al., 2021). Following repeat oral administration to rats, brain levels of TPX-0131 were approximately 66% of those observed in plasma (Murray et al., 2021).TPX-0131 is currently being studied in the phase I/II FORGE-1 trial, with the phase I portion determining safety, tolerability, pharmacokinetics, and recommended phase 2 dose, while the phase II portion will include patients with advanced ALK-positive NSCLC who have received fewer than three prior lines of ALK TKI therapy (Desai & Lovly, 2023).

3.2.NVL-655 (Neladalkib)

NVL-655 is a novel ALK inhibitor designed to have activity against single and compound ALK mutations while sparing TRKB, with in vitro data showing single digit nanomolar efficacy against G1202R, G1202R/L1196M, G1202R/G1269A, and G1202R/L1198F (Desai & Lovly, 2023).

3.3. Proteolysis-Targeting Chimeras (PROTACs)

Novel strategies including development of fourth-generation macrocyclic TKIs and proteolysis targeting chimeras are currently under development to overcome compound mutations that represent an area of major unmet need for patients whose disease progresses on lorlatinib (Desai & Lovly, 2023).

3.4.Antibody-Drug Conjugates (ADCs)

For patients who develop tumor progression due to off-target ALK-

independent resistance, options may include combination therapies targeting ALK and other downstream or parallel pathways, novel antibody drug conjugates, or combinations of ALK inhibitors with chemotherapy and immunotherapy (Desai & Lovly, 2023). ADCs are a hybrid molecule that combines biologics, made up of an antibody scaffold covalently connected by a chemical linker with small molecular payloads, combining the principles of both chemotherapy and immunotherapy (Khan et al., 2023). While ALK-targeted ADCs remain largely in preclinical development, this approach offers a mechanism distinct from kinase inhibition.

3.5. Combination Strategies

To enhance ADC efficacy, they are increasingly being combined with other therapeutic strategies, including immune checkpoint inhibitors, chemotherapy, small-molecule inhibitors, anti-angiogenic agents, and CAR-T cell therapies, with these combination therapies aiming to overcome resistance mechanisms, improve tumor targeting, and boost immune responses (Mao et al., 2025). The single-arm pilot study ALKTERNATE investigated fixed alternating cycles of lorlatinib intercalated with crizotinib in individuals resistant to second-generation ALK inhibitors, revealing safety, feasibility, and effectiveness with a median time-to-treatment failure of 10 months (Itchins et al., 2024).

4. Improved Survival Rates and Quality of Life

ALK-targeted therapies have dramatically improved outcomes for ALK-positive NSCLC patients compared to traditional chemotherapy (Solomon et al., 2014; Peters et al., 2017). The five-year survival rate for these patients has increased substantially, and targeted inhibitors generally cause fewer side effects than conventional treatments, preserving patient quality of life (Costa et al., 2015).

5. Advancement of Cancer Biology Knowledge

Studying ALK mutagenesis deepens our understanding of cancer signaling pathways, including PI3K/AKT, RAS/MAPK, JAK/STAT, and PLCγ cascades (Hallberg & Palmer, 2013). This knowledge extends beyond lung cancer and contributes to therapeutic strategies for other ALK-driven malignancies such as anaplastic large cell lymphoma and neuroblastoma (Morris et al., 1994).

6. Cost-Effectiveness in the Long Term

Although molecular testing and targeted therapies are initially expensive, personalized treatment reduces unnecessary exposure to ineffective drugs, minimizes hospitalizations due to treatment-related complications, and ultimately proves more cost-effective than traditional approaches with poorer outcomes.

7. Foundation for Combination Therapies

Mutagenesis analysis reveals bypass resistance mechanisms involving alternative pathways like EGFR, MET, or KRAS (Doebele et al., 2012; Yasuda et al., 2012). This insight enables the rational design of combination therapies that simultaneously target multiple pathways, potentially preventing or delaying resistance development.

Challenges of ALK Mutagenesis Analysis in Lung Cancer

1. Emergence of Multiple Resistance Mechanisms

Cancer cells can develop resistance through various mechanisms including secondary ALK mutations, activation of bypass signaling pathways, and phenotypic transformation (such as conversion to small cell lung cancer) (Katayama et al., 2012; Doebele et al., 2012). Managing these diverse resistance patterns requires continuous monitoring and increasingly complex treatment strategies.

2. Limited Accessibility and High Costs

Advanced molecular testing, including next-generation sequencing and mutation profiling, remains expensive and inaccessible in many regions, particularly in developing countries like India where awareness and access to modern diagnostics are limited (Indian Council of Medical Research, 2023). This creates disparities in treatment outcomes between different socioeconomic groups and geographic regions.

3. Tumour Heterogeneity

Lung tumours often contain multiple clonal populations with different mutations. A single biopsy may not capture the full mutational landscape, leading to incomplete treatment planning. Spatial and temporal heterogeneity means that mutations present at diagnosis may differ from those at relapse (Lin et al., 2017).

4. Technical Complexity and Expertise Requirements

Conducting mutagenesis analysis requires sophisticated laboratory techniques such as CRISPR-Cas9 gene editing, site-directed mutagenesis, cryo-electron microscopy, and X-ray crystallography. These methods demand specialized equipment, highly trained personnel, and substantial infrastructure investment.

5. Time Lag in Mutation Detection

Current diagnostic approaches often identify resistance mutations only after clinical progression becomes evident (Katayama et al., 2012). Real-time monitoring technologies are still evolving, and the delay between mutation emergence and detection can allow resistant clones to expand, limiting treatment options.

6. Incomplete Understanding of All Mutations

While major resistance mutations like L1196M, G1269A, and G1202R are well-characterized (Choi et al., 2010), rare or novel mutations continue to emerge. The clinical significance and optimal treatment approaches for these uncommon variants remain uncertain, complicating treatment decisions.

7. Drug Development Lag

Despite rapid progress, the development of new inhibitors to overcome emerging resistance mutations takes years (Camidge et al., 2018). Regulatory approval processes, clinical trials, and manufacturing scale-up mean that patients may develop resistance faster than new drugs become available.

8. Sample Acquisition Challenges

Obtaining adequate tumour tissue for comprehensive mutation analysis can be difficult, especially for repeated biopsies during disease monitoring. Liquid biopsies using circulating tumour DNA show promise but are not yet standardized or universally available, and their sensitivity varies.

9. Limited Applicability

ALK rearrangements occur in only 3–7% of NSCLC patients (Soda et al., 2007), meaning this approach benefits a relatively small subset of lung cancer cases. The majority of patients with other driver

mutations or no identified targetable alterations cannot benefit from ALK-specific therapies.

10. Psychosocial and Ethical Considerations

Continuous genetic monitoring and the possibility of developing untreatable resistance mutations can cause significant psychological distress for patients. Additionally, questions arise regarding informed consent, data privacy, and equitable access to precision medicine technologies.

Conclusion

While ALK mutagenesis analysis represents a significant advancement in lung cancer treatment with clear benefits in survival and quality of life (Solomon et al., 2014; Peters et al., 2017), addressing the challenges of accessibility, cost, tumour complexity, and evolving resistance mechanisms remains critical. Future research must focus on developing more affordable diagnostic tools, improving real-time monitoring capabilities, accelerating drug development pipelines, and ensuring equitable access to precision oncology worldwide (Lin et al., 2017; Shaw et al., 2020).

Conflict of interest

There is no conflict of interest among the authors of the manuscript

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Bio-Memristors: The Convergence of Biological Computation and Artificial Cognition

Saanvi Suri and Nitish Saini*

DPS International, Golf Course Extension Road, Sector 50, Gurgaon 12200, India

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**Corresponding author: nitish2593@gmail.com*

Abstract

The ever-growing demands of AI and data-driven computing expose the inefficiencies of conventional CMOS, HPC, and AI workloads (GPUs & TPUs), which suffer from the von Neumann bottleneck. Bio-memristors offer a transformative alternative, merging memory and computation for real-time, energy-efficient processing. Inspired by synaptic plasticity, they utilize Electrochemical Metallization (ECM) and Valence Change Mechanism (VCM) for adaptive, multi-level conductance, key to neuromorphic computing. Recent advances in biomaterial-based memristors—incorporating plantderived cellulose nanofibers, saccharide-based electrolytes, DNA-based switching, and protein-assisted charge transport—enhance sustainability and biocompatibility while replicating parallel processing and in-memory computing. Additionally, quantum conductance effects enable ultra-precise, low-power synaptic modulation, further bridging artificial and biological intelligence. This review explores memristor evolution, key switching mechanisms, and bio-inspired designs, categorizing bio-memristors based on their resistive switching behavior and highlighting applications in neuromorphic AI, neuroprosthetics, and energy-efficient IoT. Finally, it addresses challenges in scalability, integration, and ethical considerations, paving the way for computing systems that learn and evolve like the human brain.

Keywords: Bio-memristors, neuromorphic computing, synaptic plasticity, in-memory computing, resistive switching, biomaterials, quantum conductance

1. Introduction

The 21st century finds evidence of an unprecedented data explosion, with artificial intelligence (AI), quantum physics, and neuromorphic engineering transforming the underpinnings of computation. However traditional complementary metal-oxide-semiconductor (CMOS) circuits, high-performance computing (HPC), and AI computations based on Graphics Processing Units (GPUs) and Tensor Processing Units (TPUs) remain limited by the von Neumann bottleneck. Isolation between processing and memory results in high energy consumption, low bandwidth, and high latency, rendering real-time intelligent processing a continuous challenge [1].

In addition, the production of electronic chips to drive the Internet of Things (IoT), artificial intelligence, and fifth-generation mobile networks has grown exponentially, resulting in an increase in e-waste by many times.[2] The lifespan of electromagnetic products decreases. Global electronic waste will increase by 21% in 5 years, but its disposal through recycling does not match this rate [2]. Conventional semiconductor-based products are based on nonrenewable energy and toxic materials, such as toxic compounds and heavy metals, whose passing into the earth, water, and air causes pollution of natural ecosystems [3]. With the increasing computational requirements due to AI, cloud computing, and IoT, its ecological footprint has become unsustainable.

The hour of need is unmistakably obvious: we need to create a device that's environmentally friendly and brain-like in its computation. The human brain works with unparalleled efficiency, carrying out trillions of calculations each second and using only a mere 20 watts of energy [4]. Evolution has developed biological intelligence through dynamic self-tuning neural networks constantly changing, learning, and memorizing with breathtaking accuracy. The failure of contemporary computing to match this biological efficiency leaves us with a profound and existential question: Can nature provide a roadmap to the future of computing?

Thus, by eliminating energy-intensive data shuttling associated with von Neumann architectures, memristors—electronic devices that combine memory and processing—provide a paradigm shift in computing [5]. Memristors, initially proposed by Leon Chua in 1971 and experimentally demonstrated by HP Labs in 2008, enable in-memory computing, considerably reducing computational overhead and energy consumption by processing data directly inside the storage unit [6]. They are also excellent candidates for neuromorphic computing, machine learning accelerations, and edge AI, where speed, energy efficiency, and real-time adaptability are paramount because of their resistive switching nature, controlled by charge transport and ion migration [7].

Yet, memristors are limited by those very materials that endow them with their valuable characteristics. Sequential and parallel processing to achieve brain-like computing is hampered by standard memristors based on inorganic metal oxides such as titanium dioxide or hafnium oxide. The rigid and crystalline nature of these oxides lacks biological plasticity to adapt to synapses [8]. The usual stochastic variability, limited

tunability, and non-ideal switching of these inorganic materials restrict their usability in large-scale neuromorphic networks [9]. On the contrary, neurons modulate their synaptic weights dynamically through biochemical cascades.

In addition to computational limitations, the widespread deployment of memristive devices is constrained by fundamental issues of stability, reliability, and reproducibility [10]. Inorganic memristors frequently suffer from cycle-to-cycle and device-to-device variability arising from stochastic filament formation, uncontrolled ion migration, and interfacial defects. These effects lead to resistance drift, limited endurance, and poor retention, particularly under prolonged operation and large switching cycles. Moreover, the requirement for precise control over nanoscale conductive pathways makes large-area integration and uniform fabrication challenging.

To bridge this gap between artificial and biological intelligence, bio-memristors emerge as a revolutionary alternative**?** The flexible, dynamic biomolecules such as proteins, polypeptides, and even DNA utilized by the bio-memristors, as opposed to their rigid, inorganic based counterparts, enable synapse-like plasticity and authentic parallel and sequential processing of information similar to what the human brain accomplishes [11]. Their prospect of neuromorphic computing as well as real-time artificial intelligence applications are augmented by their ability to induce continuous, low-energy ionic modulations, simulating the biological learning process [12].

Aside from functionality, bio-memristors redefine sustainability. They cut down dramatically on the consumption of rare earth metals as well as toxic chemicals since they comprise renewable and biodegradable materials, reducing production costs and environmental harm [13]. Secondly, low power consumption matches necessities of large-scale, green computing with increasing AI loads and pervasive edge devices [14]. Bio-memristors harness the precision of electronics with the flexibility of biology to deliver a smarter and greener computing future [15].

This paper discusses recent progress in memristor technology, with an emphasis on its development toward bio memristors for use in neuromorphic hardware systems. It evaluates different biomolecules as active switching layers in bio memristors, ranging from proteins, DNA, those derived from plants, polymers, and saccharides, focusing on their neuromorphic
applications.

2.Memristors

A memristor is a two-terminal device composed of a thin functional layer situated between two electrodes [16]. It stores data through the internal rearrangement of charged particles within this layer, allowing it to stabilize in various resistance states based on different external inputs [17]. Akin to a biological synapse, the top and bottom electrodes act as pre- and postsynaptic neurons, respectively, allowing charged particles to move from one electrode to another through conduction filament via quantum tunnelling. These electrodes are linked by a distinctive synaptic weight that

enables the memristor to process information similarly to the human brain [18].

A memristor processes digital and analog signals in real time by adjusting its resistance states through the rearrangement of charged particles when voltage is applied [19]. This allows it to store and transmit information efficiently, enabling both binary data representation and continuous resistance changes for analogue signals [20].

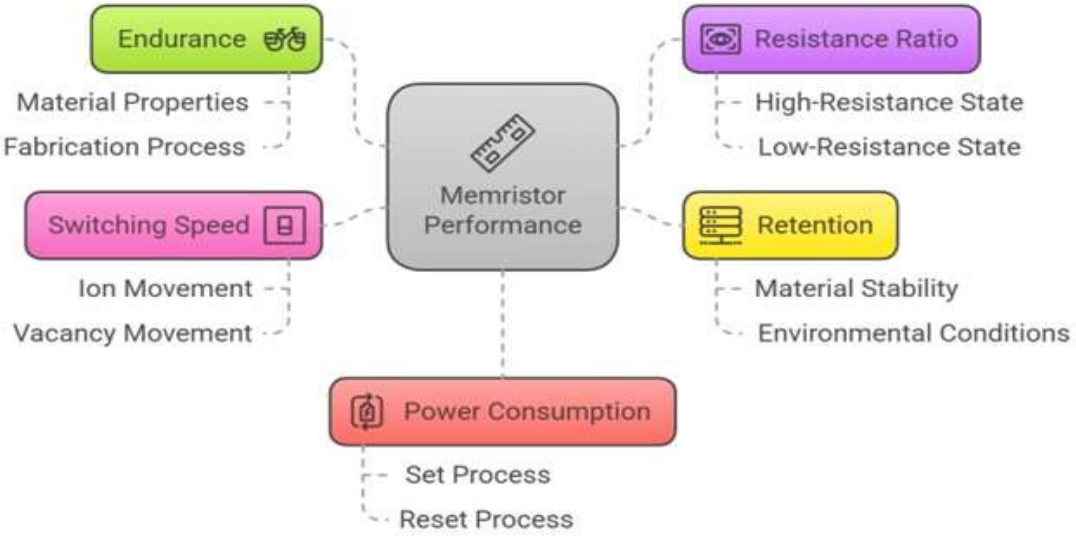

Figure 1. Overview of Critical Performance Parameters in Memristor Technology for Neuromorphic and Computing Applications.

The analog and digital memristors are distinguished by their switching properties [21]. Analog memristors exhibit a gradual, tunable change in resistance, making them ideal for modulation of synaptic weight in neuromorphic networks, as opposed to digital memristors which switch between discrete resistance states, typically classified as the low resistance state (LRS) and the High Resistance State (HRS) [22]. The transition from HRS to LRS is referred to as the set process, while the reverse transition from LRS to HRS is known as the reset Process [23].

These switching characteristics determine the key performance parameters of the memristors, including the switching speed, endurance, resistance ratio, retention, and power consumption.

Endurance: Device endurance depends on its stability across several cycles of switching. Memristor endurance is characterized by its ability to withstand a certain number of set/reset cycles prior to degradation. The endurance of a memristor depends on intrinsic characteristics such as material and fabrication process variations, as well as extrinsic characteristics such as electrical stress due to circuit operation. Conversion between LRS and HRS involves applying a signal with correct polarity, either creating or breaking down the conduction filament, thus changing the resistance state of the device. The number of times this cycling can withstand until permanent breakdown characterizes its endurance property. A high endurance level is crucial in memory

applications, where repeated read and write operations should not fail.[?]

Resistance Ratio: The resistance ratio refers to the ratio between device resistance in high-resistance state (HRS) and low-resistance state (LRS). The higher the resistance ratio, the greater the clarity of state differentiation, with higher ease in differentiating among memory states. The differentiation is very important in order to achieve high accuracy in data storage as well as in execution of logical operations. The higher resistance ratio decreases read errors, increases signal-to-noise ratio, and enables more efficient multi-level cell (MLC) storage, with intermediate resistance used to store multiple bits of data into each memristor [24].

Retention: Retention describes the memristor's property of preserving its resistance state (LRS or HSR) with no power applied over a period of time. The retention time over which a memristor can store a state is measured by observing the resistance drift under zero-bias conditions [25]. Long retention times are specifically crucial in non-volatile memory as data needs to stay stable even when turned off. Retention also depends upon stability of materials, defect migration, and external environment, with designs aiming to achieve optimum retention times equal to years or even decades to compete with conventional flash memory [26].

Switching speed: The switching speed of a memristor refers to how long it takes to switch between LRS and HRS [27]. It is regulated by charged species (ions or vacancy) movement in the functional layer. The set process creates a conductive path, whereas the reset process disturbs it. Higher switching speeds improve high-speed computing and memory performance, but high speeds beyond certain levels may lead to structural instability, cutting down on endurance [28].

Power Consumption: On application of a voltage, the device runs at a certain level of power as measured by the setting or resetting process. The level of power at which the device becomes set or reset represents the energy needed to create or destroy a state in the device [29].

3. Bio-inspired memristors

Bio-memristors are a category of memristive devices based on biological or bio-mimetic materials, including proteins, DNA, polysaccharides, and other biomolecules, used to realize electrical resistance switching [30]. As opposed to traditional metal-oxide memristors, based on inorganic materials, bio-memristors take advantage of electrochemical and ionic characteristics of biomolecules to provide memory and processing operations. Development was based on investigation into using biocompatible and renewable substitutes for neuromorphic computing [31].

Theoretical basics of bio-memristors date back to research on conduction in biological systems as well as in organic electronics. The earliest of theories backing bio-memristors come from Leon Chua's memristor hypothesis (1971), where it was hypothesized that a memoryresistor was possible. This was followed by Strukov et al.'s (2008) first experimental evidence of a memristor in nanoscale [32].

Recent advances in materials science, including protein-based resistive switching (e.g., silk fibroin and ferritin), showed the potential of energy-efficient and biocompatible computing with bio-memristors [33]. With these advancements, bio-memristors are well-placed as a prime enabling technology in bridging artificial intelligence with green electronics [34].

3.1 Biological Inspiration Behind Bio-Memristors

The efficiency and adaptability of the human brain have long inspired researchers in the pursuit of next-generation computing architectures [35]. Unlike traditional digital systems, which rely on rigid logic gates and fixed memory-storage separation, the brain exhibits highly efficient, parallel, and self-learning capabilities due to its synaptic network. The foundation of this adaptability lies in synaptic plasticity, a biological mechanism that allows neurons to modify their connectivity based on activity patterns. Bio-memristors are designed to emulate these biological processes, offering a hardware-based alternative to artificial synapses, capable of adaptive learning, real-time information processing, and ultra-low power consumption [36].

3.1.1 Synaptic Plasticity and Biological Learning Mechanisms

Synaptic plasticity is the brain's ability to strengthen or weaken neuronal connections in response to stimuli, forming the basis of learning and memory. This adaptability occurs through two primary mechanisms:

- **Short-Term Plasticity (STP):** Temporary changes in synaptic strength, occurring over milliseconds to minutes. STP is responsible for transient information retention and immediate neural responses.
- **Long-Term Plasticity (LTP & LTD):** More permanent modifications in synaptic weight, occurring over minutes to hours, enabling long-term learning and memory formation.
  - **Long-Term Potentiation (LTP):** Strengthening of synaptic connections after repeated activation [37].
  - **Long-Term Depression (LTD):** Weakening of synapses when activity decreases, optimizing neural efficiency [38].

These mechanisms ensure that frequently used neural pathways become stronger, while less used connections weaken or disappear, allowing for adaptive and efficient memory storage.

In computational terms, this behaviour is crucial for neuromorphic computing, where systems must dynamically adjust their memory states based on past inputs without explicit reprogramming [39].

Essentially, synaptic plasticity in bio-memristors is analogous to the adaptive learning processes of the human brain. These devices emulate synaptic plasticity by modulating their resistive states in response to electrical stimuli. Instead of fixed ON/OFF states like conventional transistors, bio-memristors exhibit gradual, analog-like conductance changes, closely mirroring biological synapses [40]. Their resistance is altered through mechanisms such as ion migration, redox reactions, and charge

trapping, allowing them to mimic STP and LTP/LTD in the following ways:

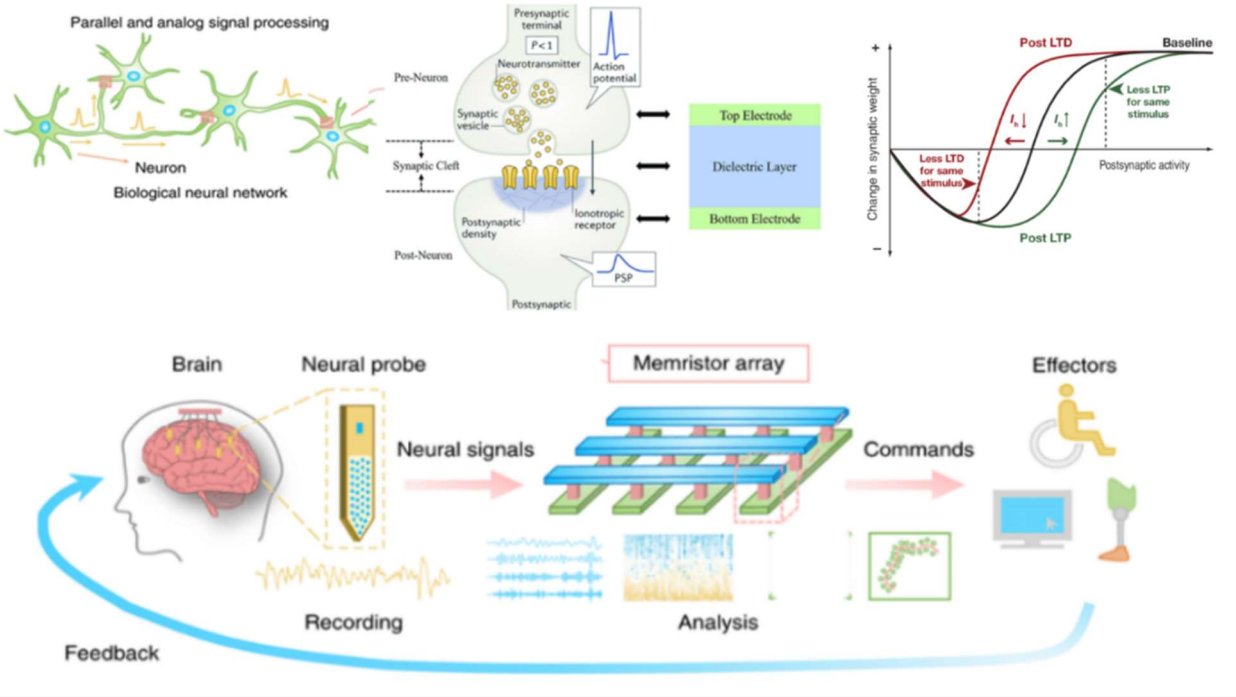

Figure 2. This schematic illustrates bio-memristors mimicking synaptic plasticity for neuromorphic systems. (Top left) Biological neural networks process signals via synapses. (Top middle) A synapse and its bio-memristor equivalent, featuring electrodes and a dielectric layer. (Top right) A synaptic plasticity curve showing LTP and LTD, essential for learning. (Bottom) A neuromorphic interface using neural signals and memristors for adaptive control of prosthetics and interfaces.

- **Short-Term Memory (STP in Bio-Memristors):**

- Low-amplitude voltage pulses induce transient resistive changes, similar to neurotransmitter release in biological synapses.
- Resistance gradually returns to its original state, mimicking the short-lived memory retention seen in neural circuits.
- Used for temporary buffering of information and rapid signal processing [41].

- **Long-Term Memory (LTP & LTD in Bio-Memristors):**

- Higher or repeated voltage stimuli induce cumulative and lasting changes in resistance, akin to synaptic weight adjustments in long-term memory formation [42].
- Just like in biological neurons, the ”stronger” or ”weaker” connections persist, allowing information to be retained over extended periods.
- Essential for learning-based AI systems, neuromorphic processors, and real-time decision-making applications.

These characteristics position bio-memristors as a hardware-based alternative

to software trained artificial neural networks, enabling real-time learning and cognitive processing with significantly lower energy consumption [43].

3.1.2 Neurotransmitter-Like Switching in Resistive Memory

Biological synapses are based on neurotransmitters—chemical messengers like glutamate and acetylcholine—to change synapse strength [44]. Neurotransmitters interact with postsynaptic neuron receptors, controlling ion channel function, changing electrical conductivity, and facilitating proper signal transfer. Drawing an analogy, bio-memristors depend on neurotransmitter-like mechanisms like ion transport, redox processes, and molecular switching to change resistance states [45].

Proton-conducting biomemristors function by harnessing cation chelation and ion transport mechanisms in protein or biopolymer films [46]. Hydrogen-bond networks or amino acid residues present in such films can conduct protons by the proton hopping mechanism, whereby protons are passed between sites. Cationic chelation in addition stabilizes intermediate transport states and thereby increases the mobility of protons [47]. Dynamic transport of ions leads to resistance modulation, simulating ionic currents in biological systems' synaptic clefts. Through these mechanisms, these devices mimic synaptic plasticity, facilitating information processing and storage [48]. Ultra-low power operation modes and biocompatibility make them excellent candidates for usage in biocompatible electronics, especially wearable and implantable medical devices. The systems are going to change the integration of electronic and biological interfaces forever [49].

Moreover, one of the major phenomena accountable for switching in oxide-based biomemristors is oxygen vacancy migration. It refers to the movement of oxygen vacancies in the active region of the device under an applied electrical field. Oxygen vacancies are lattice defects and are charge carriers. They are accountable for interfacial modulation. Redistribution of oxygen vacancies between interlayers in the material changes local electronic structure, and this changes device's conductivity [50]. The

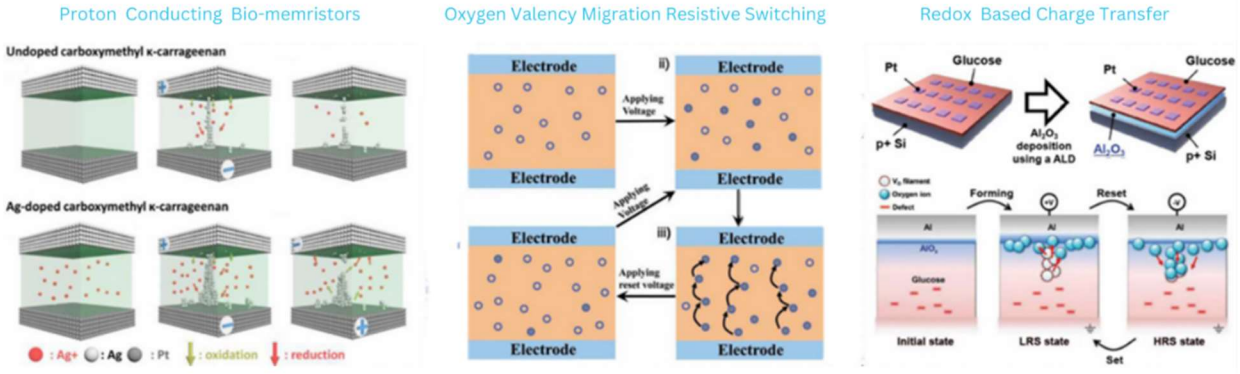

Figure 3. Overview of emerging resistive switching mechanisms in bio-inspired and oxide-based memristors: (Left) Proton-conducting bio-memristors using carboxymethyl κcarrageenan, (Middle) Oxygen valency migration-driven resistive switching, and (Right) Redox-based charge transfer in glucose-assisted memristors.

modulation is similar to biological synaptic plasticity, where neurotransmitters and ions regulate synaptic strength. Oxygen vacancy migration also creates or dissolves conducting filaments, and this offers another mechanism of controlling resistance. Devices based on these are especially valuable in nonvolatile memory, where data are stored even in the absence of supply of power, and in neuromorphic computing, where device's adaptive characteristics are exploited to simulate brain-like processing [51].

Redox-mediated charge transfer represents another vital mechanism, with redox transformations between organic molecules or bio-inspired molecules initiating changes in conductance. Redox processes are characterized by electron transfer, resulting in valence state switching of the active material [52]. For example, an increase in oxidation state provides higher conductivity, and reduction provides lower conductivity. The redox reaction dynamics underlies filament growth, or paths of high-conductance, inside the material. The

Table 1. Representative biomaterial-based memristors categorized by material class (protein, DNA, plant, and saccharide), device architecture, dominant switching mechanism, and key performance metrics including ON/OFF ratio, endurance (cycle number), and retention time

Material	Device Structure	Mechanism	OFF/ON Ratio	Cycle Number	Retention (s)
Protein Based Memristors					
Ferritin	Au/Ferritin/Au	Charge trapping	$\sim 10^4$	$> 10^5$	$\sim 10^7$
Silk fibroin	ITO/Silk fibroin/Ag	Proton conduction	$\sim 10^3$	$> 10^4$	$\sim 10^5$
Egg albumen (EA)	Ag/EA/Ag	Ionic transport	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Hybrid EA-protein	Au/EA-protein/Ag	Mixed valence	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Catalase enzyme	Pt/Catalase/Ti	Charge tuning	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Lysozyme enzyme	Au/Lysozyme/Ag	Proton hopping	$\sim 10^3$	$> 10^5$	$\sim 10^8$
Peroxidase-functionalized	Ag/Peroxidase/Au	Biochemical redox	$\sim 10^4$	$> 10^5$	$\sim 10^8$
Bacteriorhodopsin	ITO/Bacteriorhodopsin/Ag	Photo-driven switching	$\sim 10^3$	$> 10^4$	$\sim 10^6$
Genetically modified bacteriorhodopsin	Au/GM Bacteriorhodopsin/Ag	Optoelectronic response	$> 10^4$	$> 10^5$	$\sim 10^7$
Prion-like protein	Au/Prion-like protein/Ag	Conformational change	$> 10^2$	$> 10^4$	$\sim 10^6$
Amyloid fibril	Pt/Amyloid fibril/Au	Electron tunneling	$> 10^3$	$> 10^5$	$\sim 10^7$
Hemoglobin	ITO/Hemoglobin/Ag	Charge transport	$> 10^3$	$> 10^5$	$\sim 10^7$
DNA Based Memristors					
DNA-templated Au nanowires	Au/DNA-Au nanowires/Au	Electron transport	$\sim 10^4$	$> 10^5$	$\sim 10^8$
Metal-ion-doped DNA	Pt/DNA-Metal ion/Ag	Redox	$\sim 10^3$	$> 10^4$	$\sim 10^7$
G-quadruplex DNA	Au/G4-DNA/Au	Charge transport	$\sim 10^3$	$\sim 10^4$	$\sim 10^6$
DNA-intercalator	Ag/DNA-Intercalator/Ag	Charge transfer	$\sim 10^4$	$> 10^5$	$\sim 10^7$
DNA origami	ITO/DNA Origami/Ag	Programmable resistance	$\sim 10^3$	$\sim 10^5$	$\sim 10^7$
Silver-ion DNA conduction	Ag/DNA-Ag^+/Ag	Ion transport	$\sim 10^3$	$\sim 10^4$	$\sim 10^7$
Copper-doped DNA	Cu/DNA-Cu^{2+}/Ag	Conductive filaments	$\sim 10^4$	$\sim 10^5$	$\sim 10^7$
Graphene-DNA hybrid	Graphene/DNA/Ag	Charge trapping	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Plant Based Memristors					
CNF-based	ITO/CNF/Ag	Ionic transport	$\sim 10^3$	$\sim 10^4$	$\sim 10^7$
CNC-based	Pt/CNC/Au	Dielectric polarization	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Bacterial cellulose	Ag/Bacterial Cellulose/Ag	Ionic drift	$\sim 10^3$	$\sim 10^5$	$\sim 10^7$
CMC-doped	Au/CMC/Ag	Redox	$\sim 10^4$	$> 10^5$	$\sim 10^8$
Cellulose acetate	ITO/Cellulose Acetate/Ag	Resistive switching	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Lignin-carbon nanodot	Au/Lignin-CND/Au	Conductive pathways	$\sim 10^4$	$> 10^5$	$\sim 10^7$
Lignosulfonate	Pt/Lignosulfonate/Ag	Proton hopping	$\sim 10^3$	$\sim 10^4$	$\sim 10^7$
Polydopamine-lignin	Ag/PD-Lignin/Ag	Electron tunneling	$\sim 10^3$	$\sim 10^5$	$\sim 10^7$
Enzymatically processed lignin	ITO/Lignin/Ag	Redox modulation	$\sim 10^3$	$\sim 10^4$	$\sim 10^7$
Saccharide Based Memristors					
Starch-AgNP	Ag/Starch-AgNP/Ag	Charge trapping	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Corn starch	ITO/Corn Starch/Ag	Ionic conduction	$\sim 10^3$	$\sim 10^4$	$\sim 10^6$
CNF-doped starch	Au/Starch-CNF/Ag	Electron hopping	$\sim 10^4$	$\sim 10^5$	$\sim 10^7$
Metal oxide-starch	Pt/Starch-MO/Ag	Conductive filaments	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Hydrogel starch	Au/Starch-Hydrogel/Ag	Ionic drift	$\sim 10^3$	$\sim 10^4$	$\sim 10^6$
Chitosan	Ag/Chitosan/Ag	Ion diffusion	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Xanthan gum	Au/Xanthan/Ag	Ionic migration	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Alginate	Pt/Alginate/Ag	Biodegradable switching	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Potato starch composite	ITO/Potato-Starch/Ag	Resistive switching	$\sim 10^4$	$\sim 10^5$	$\sim 10^7$
Gelatin-starch blend	Au/Starch-Gelatin/Ag	Electron transport	$\sim 10^3$	$> 10^4$	$\sim 10^7$
Carrageenan-based starch	Pt/Starch-Carrageenan/Ag	Ionic redistribution	$\sim 10^3$	$\sim 10^4$	$\sim 10^6$

filaments facilitate regulated and reversible resistance adjustability, replicating biological synapse's chemical communication processes. The end product is an architecture with multi-level storage, with different resistance state correspondence to respective quantities of stored data. The high densities of these devices and their energy consumption result in them being suited to high-density storage as well as energy-efficient computing architectures [53].

3.3 Bio-molecules for active switching layers in bio-memristors

Bio-materials and bio-inspired materials are pivotal to bio-memristors due to their provision of biocompatibility, elasticity, and energy-efficient switching characteristics. They comprise protein-based systems (e.g., silk proteins, bacteriorhodopsin), conducting architectures based on DNA and peptides, and tunable electronic property organic polymers [54]. Their ability to self-assemble naturally and transport ions allows them to exhibit synaptic-like characteristics, rendering them suitable for neuromorphic applications. Bio-hybrid composites also provide stability and high conductivity, leading towards environmentally friendly, next-generation memory and computation technologies [55].

3.3.1 Protein-Based Memristors

Protein-based memristors are revolutionizing the next-generation memory device paradigm by providing inherent charge transport mechanisms, spontaneous assembly properties, and adjustable resistive switching. Unlike rigid silicon-based architectures, these biomolecular components provide flexible, dynamic, and biocompatible information processing and are therefore extremely promising for environmentally friendly and neuromorphic electronics [56]. One of the key advancements here is the ability of some

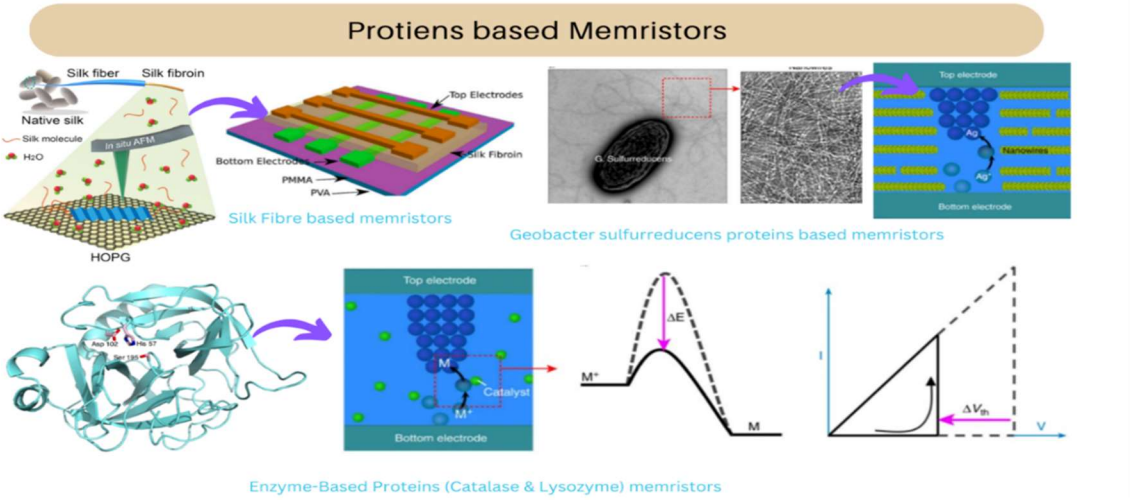

Figure 4. Overview of Protein-Based Memristors: Silk fiber-based memristors (top left) utilize silk fibroin for resistive switching. Geobacter sulfurreducens protein-based memristors (top right) leverage conductive bacterial nanowires for charge transport. Enzyme-based memristors (bottom) incorporate catalase and lysozyme to enable ionic modulation and resistive switching, demonstrating the potential of biological materials in neuromorphic computing.

proteins to enable redox reactions and ionic transport and perform resistive switching at the nanoscale. Geobacter sulfurreducens proteins, for instance, enable electron transfer and filament stabilization, accelerating synapse-like conductivity [57]. In ferritin, an iron-storage protein, there are multi-level states of resistivity, allowing high-density encoding of memory through charge trapping. Recent research has shown that programmable resistance changes are possible by altering the oxidation state of ferritin, opening up the possibility of nonvolatile energy-efficient memory systems [58].

Besides metal interactions, biopolymer protein silk fibroin from Bombyx mori has demonstrated enormous potential toward flexible, transparent, and biodegradable memristors and opening the way toward wearable and bio-integrated computing [59]. Further, egg albumen (EA) is also gaining popularity due to cost and stable switching performance. In an interesting turn of events, researchers at the National University of Singapore recently found that they can create stable nanoscale conducting filaments using a hybrid EA-protein network, significantly enhancing endurance and reliability compared to regular organic memristors [60]. One of the emerging frontiers of protein-based memristors includes the study of charge dynamics enabled by enzymes. Proteins from enzymes like catalase and lysozyme introduce biochemical tunability to memristor operations [61]. For example, catalase was shown to catalyze hydrogen peroxide degradation while tuning local charge distribution, effectively regulating resistive states. In one foundational study, scientists created a peroxidase-functionalized memristor that is capable of responding to extrinsic biochemical signals, paving the way toward neuromorphic circuits that can dynamically adapt to biological environments [62]. In addition, bacteriorhodopsin, a photoreceptor protein, is demonstrated to display photoresponsive resistive switching, and this makes it possible to develop optically driven memory architectures [63]. Synthetic biology advancements enabled the genetic modulation of bacteriorhodopsin's chromophore dynamics, and this can be programmed through pulses of light to develop memristors [64]. This innovation opens up possibilities of energy-efficient, optogenetically driven neuromorphic computing. One of the fronts that remain untouched is the use of prion-like proteins, having the shared ability to alter their shape. MIT scientists recently examined the potential of using prion domains in artificial peptides and discovered that their metastable states can be exploited to store multi-bit memory [65]. The observation that prion-like sequences can be made to exhibit controllable resistive switching reveals an entire class of bioelectronic devices that can store information in protein folding states [66]. Using protein conformation dynamics and biochemical reactivity, researchers are extending the boundaries of molecular-scale memory, bridging the gap between organic intelligence and artificial computation. The application of protein-based memristors to neuromorphic circuits, brain-machine interfaces, and self-learning AI hardware is a paradigm-changing step toward bio-inspired computing paradigms as efficient and

adaptive as those of nature [67]. As the technology progresses, the potential of self-assembling, self-healing, and even selfevolving memristor networks may revolutionize the boundaries of artificial intelligence and sustainable electronics [68].

3.3.2 DNA and Peptide-Based Memristors

DNA and peptides, the biological building blocks, are emerging as flexible platforms for biomemristors, offering an unparalleled combination of molecular recognition, self-assembly, and tunable conductivity [69]. Relative to conventional inorganic compounds, these biomolecules offer nanoscale charge transport with high accuracy, utilizing their structural pliability and chemical programmability toward next-generation memory [70]. One of the most promising aspects of DNA-based memristors is their ability to facilitate electron and ion transport by means of π-stacking interactions and metal-ion doping. Using conductive metal nanoparticles or intercalating redox-active molecules, DNA strands can be induced to exhibit resistive switching behavior, mimicking synaptic plasticity [71]. In addition, G-quadruplex DNA

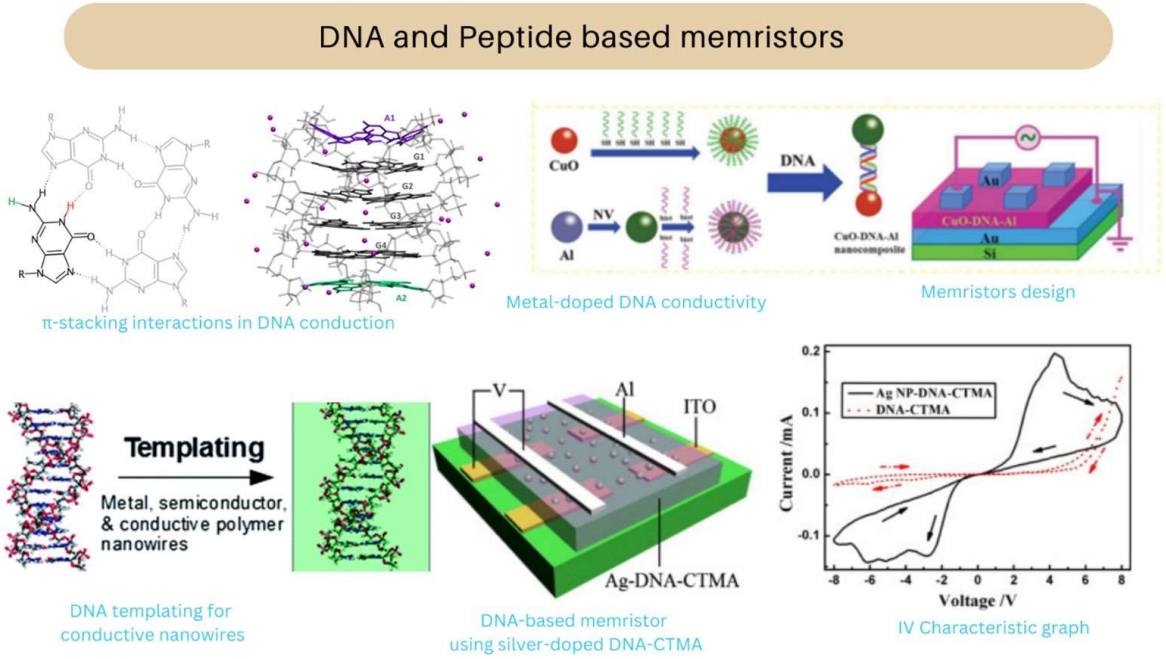

Figure 5. Concepts in DNA and Peptide-Based Memristors: π-stacking interactions in DNA facilitate conduction (top left), while metal-doped DNA enhances electrical properties (top center). Memristor design using DNA nanocomposites (top right) demonstrates practical applications. DNA templating enables the formation of conductive nanowires (bottom left), and silver-doped DNA-CTMA is used in memristor fabrication (bottom center). The IV characteristic graph (bottom right) illustrates the electrical behaviour of DNA-based memristors, highlighting their resistive switching capabilities.

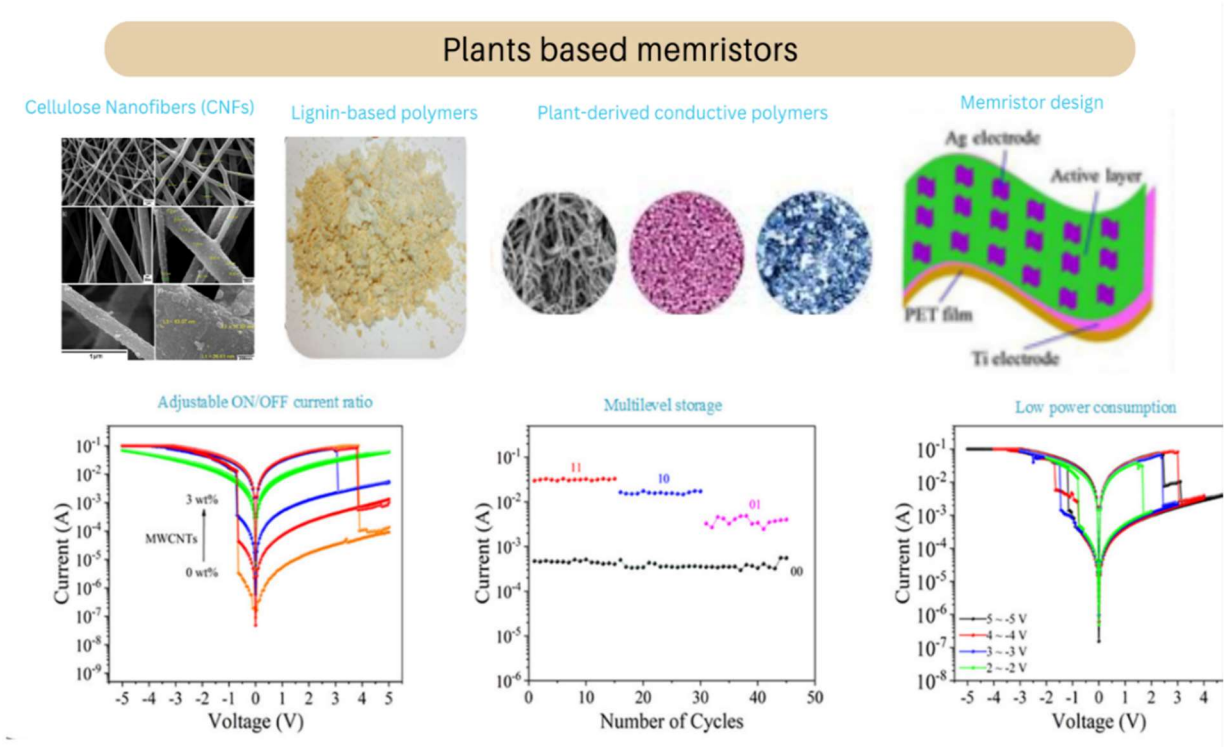

Figure 6. Cellulose nanofibers (CNFs) (top left), lignin-based polymers (top center), and plant-derived conductive polymers (top right) serve as bio-materials for resistive switching applications. A flexible memristor design (top far right demonstrates the integration of this materials [80]. The bottom graphs illustrate key performance characteristics: adjustable ON/OFF current ratio (bottom left), multilevel data storage (bottom center), and low power consumption (bottom right), showcasing the potential of plant-based materials for sustainable and efficient memory devices.[81]

architectures, distinguished by high electrical conductivity and stability, are examined as natural templates for multi-state storage and neuromorphic processing. Such biomolecules, when paired with structural versatility, provide prospects for ultra-low-power, adaptive, and biodegradable computing systems [72]. Groundbreaking research has confirmed the revolutionary promise of DNA-based memristors. Scientists at Chalmers University of Technology (Sweden) synthesized DNA-templated arrays of gold nanowires, having precise resistive switching through π-stacking interactions and stable electron transport [73]. Scientists at Tel Aviv University studied metal-ion-doped DNA strands, and metal ions including silver and copper ions facilitated improved charge transport, an alternative contender for ultra-lowpower neuromorphic circuits [74]. Stanford University advancements focused on G-quadruplex

DNA devices, where DNA architectures folded create natural conductivity, enabling multi-level states of resistance to be stored, perfect for high-density memory [75]. Parallel to this, researchers at the National University of Singapore (NUS) incorporated redox-active intercalators into DNA to achieve stable switching by charge transfer mechanisms that are reminiscent of enzymatic reactions. Concurrently, MIT researchers created programmable DNA

origami memristors by exploiting the structural programmability of DNA to construct nanoscale architectures that modulate resistive states directly and provide unmatched control over memory behavior [76]. Besides DNA, peptides are also possible bio-memristor prospects. Scientists at ETH Zurich were able to successfully demonstrate peptide-based conducting films that display adaptive electrical properties reminiscent of those observed in synaptic plasticity. Amyloid fibrils and silk fibroin peptides, among several others, are among those that have demonstrated high potential to enable flexible, biodegradable, and transparent wearable and implantable devices [77]. Embracing sequence-directed self-organization, charge transport by π-stacking and metal-ion coordination, and structural dynamics of DNA and peptides, bio-memristors provide a paradigm shift in memory technology [78]. Their integration into neuromorphic hardware, bio-sensing platforms, and in vivo memory systems is a revolutionary step toward computing architectures compatible with biological environments. Bridging the gap between organic intelligence and artificial computation, these advancements demonstrate the feasibility of an adaptive, sustainable future of electronics [79].

3.3.3 Plant-Based Memristors

Plant-based composites and bio-hybrid polymers are some of the advanced next-generation memristor technologies that take advantage of the biocompatibility, structural variability, and environmental friendliness of plant-based materials,[82] Through the use of naturally occurring organic components whose electronic properties are controllable, these materials offer an alternative to the use of conventional synthetic and inorganic semiconductors, particularly where applications require flexible, low-power, and biodegradable memory devices.

With environmental concerns and energy consumption on the rise, eco-friendly neuromorphic computing systems are increasingly being made possible by plant-based memristors [83]. Among all the cellulosic polymers, cellulose stands out due to its mechanical strength, high dielectric strength, and tunable ionic conductivity [84]. There are several forms of cellulose that were examined as potential applications when it comes to resistive switching devices, and these are cellulose nanofibers (CNFs), cellulose nanocrystals (CNCs), and bacterial cellulose (BC). They are all nanostructured materials that are extremely flexible and are therefore best suited to wearable computing systems and flexible electronics [85]. One of the main mechanisms of cellulose-based memristors is the use of intrinsic hydroxyl (-OH) groups to facilitate hydrogen bonding and redox interactions, important for resistive switching behavior [86]. Recently, it was demonstrated that cellulose nanofibers, when functionalized by conducting nanoparticles, are capable of exhibiting stable bipolar resistive switching, indicative of their application potential as low-power memory. Additionally, bacterial cellulose, having its highly interconnected and porous network of nanofibers, presents an ionic transport scaffold, facilitating better tunability of switching properties [87]. Derivatives of cellulose, carboxymethyl

cellulose (CMC), and cellulose acetate, among others, have been studied because they show improved conductivity and structural stability. Doping cellulose with conducting bio-based fillers like tannins, flavonoids, or even graphene analogs from plants has been demonstrated to significantly improve its electronic properties [88]. A recent breakthrough along these directions was the application of blends of CNC along with conducting plant extracts to fabricate ultra-low switching voltage memristive films, paving the way to energy-efficient neuromorphic hardware [89]. One of the aromatic complex polymers found within the cell wall of plants is lignin, another possible candidate for bio-based memristors. Unlike cellulose, whose primary role is structural support, lignin is redox active due to the presence of numerous phenolic and quinone functional groups. Such functional moieties are able to support charge transfer reactions, enabling non-volatile memory storage with enhanced environmental stability [90].

Recent studies on lignin electronics demonstrated that carbon nanodots from lignin are functional additives that can be utilized to increase conductivity and optimize switching performance of organic memristors. Experiments confirmed that lignosulfonates, soluble lignin derivatives, can be incorporated into bio-composite films to enable controlled resistive switching through proton-coupled electron transfer [91]. A breakthrough experiment here was the blending of lignin and conducting polymer from plants, including polydopamine, and this achieved stable memory storage up to thousands of switching cycles, an important step toward practical applications [92]. Furthermore, enzymatically processed lignin was also explored as a bio-template semiconductor wherein redox cycling generates reversible resistance changes. Lignin-polyphenol conjugates were also successfully engineered by scientists to exhibit multi-state resistive switching, an essential property of artificial synapses in neuromorphic computing [93]. Such advancements are crucial toward the development of bio-memristors capable of mimicking human brain synaptic plasticity. Aside from cellulose and lignin, polyphenols from plants, flavonoids, and tannins are also being considered due to their electronic properties. These naturally occurring molecules commonly found in tea, cocoa, and grapes possess redox properties that are ideal for use in resistive switching devices. Researchers were able to create bio-memristors from catechin-functionalized nanocellulose films and prove the existence of multi-level states of resistance that are crucial to high-end memory architectures [93]. One of the innovative solutions is the use of plant-based conducting biopolymers like melanin, a naturally found pigment in various plants. Melanin is intrinsically electronically conducting and possesses proton mobility, and hence it is one of the best candidate materials for memristor applications. Research on melanin-coated cellulose membranes demonstrated their ability to be used as low-power, biodegradable electronic memories, opening up further possibilities of eco-friendly computing material. Cellulosebased materials, including cellulose nanofibers (CNFs), cellulose nanocrystals (CNCs), and bacterial cellulose (BC), exhibit excellent

mechanical flexibility, high dielectric strength, and tunable ionic conductivity [94]. Their intrinsic hydroxyl groups facilitate hydrogen bonding and redox interactions, enabling resistive switching behaviour crucial for neuromorphic significant advantages over traditional synthetic and inorganic semiconductors, particularly for applications in low-power, flexible, and biodegradable memory devices computing [95]. Modified cellulose derivatives, such as carboxymethyl cellulose (CMC) and cellulose acetate, further enhance conductivity and structural stability, expanding their applicability in flexible memory architectures.

3.3.3 Saccharide-Based Memristors

Saccharide-based memristors have immense brain-like computing potential brain-like computing because of their tunable resistive switching mechanisms, biocompatibility, and flexibility. Being naturally occurring polysaccharides, these compounds already possess inherent ionic conductivity, structural plasticity, and suitability to incorporate conductive fillers to augment charge transport [96]. They are attractive candidates for applications in neuromorphic computing, flexible electronics, and green memory storage due to their potential to achieve ion transport and electrochemical redox processes. Natural polysaccharide

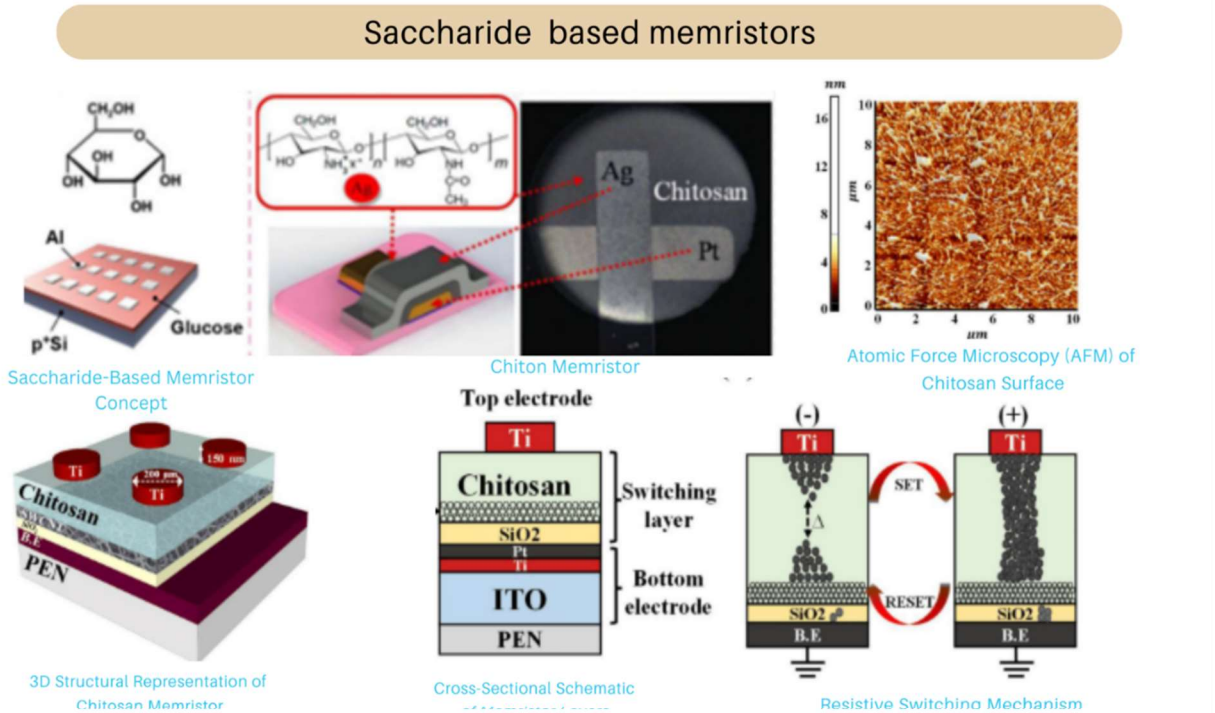

Figure 7. Chitosan-based materials (top left) serve as the active layer for resistive switching, with a detailed device structure (top center) and surface morphology analysis (top right). A flexible memristor design (top far right) demonstrates the integration of these bio-materials. The bottom section presents key performance metrics: tunable ON/OFF current ratio (bottom left), multilevel data storage capability (bottom center), and energy-efficient switching behavior (bottom right), highlighting the potential of saccharide-based memristors for sustainable memory applications.

starch, comprising amylose and amylopectin, has demonstrated great promise in resistive

switching because of its semi-crystalline nature, high dielectrics, and property to establish stable ionic networks. Through the addition of conducting fillers like carbon nanofibers (CNFs), graphene oxide, or metal nanoparticles, scientists have successfully used starch-based composites to achieve tunable resistance states with characteristics similar to synaptic plasticity [97]. Researchers at Tsinghua University made a major breakthrough with starch-based memristive films after doping starch with silver nanoparticles (AgNPs). The composite architecture allowed metal filament formation under applied voltages, causing non-volatile resistive switching and more than two memory states [98]. The fact that starch is bio-derived also allowed it to exhibit biodegradability, a quality well suited to transient electronics and environmentally friendly computing systems. Additionally, corn starch-based memristors, created in Zhejiang University, had humidity-sensitive conductivity, enabling tunable switching characteristics depending on environmental humidity levels. The property is very desirable in sensor applications and bio-interfacing systems where external stimuli are used to modulate the performance of a memristor [99]. The hydrogel-forming property of starch also offers a path towards flexible and stretchable electronic device design with preserved functionality under mechanical stress conditions. Chitosan, a chitin-derived biopolymer, represents another saccharide-based material with immense potential to exhibit memristive characteristics. Chitosan, with its proton-conducting nature and metal cation chelating ability, exhibits memristors based on chitosan with mechanisms of operation based on ionic migration, rendering them appropriate for applications in neurosynaptic and neuromorphic circuits and also in sensors [100]. Researchers at Yonsei University created resistive memory devices based on chitosan, where an analogue memory function was observed with the polymer matrix facilitating the creation and destruction of mobile silver- or copper-based conductive filaments. Chitosan-based memristors are also investigated as low-power, biocompatible computing platforms due to their proton transport functionality, with them proving to be well-suited as implantable neural interfaces as a result of this property [101]. More recent breakthroughs with saccharide-based memristors went beyond starch and chitosan to incorporate cellulose, another ubiquitous polysaccharide with remarkable mechanical resistance and stability. Researchers in Cambridge created cellulose nanofiber-based memristors using gold nanoclusters to improve charge transport and storage characteristics [102]. The memristors showed multilevel resistive switching, opening up high-density energy-saving memory arrays. Moreover, a pioneering technique at MIT used xanthan gum, a viscoelastic exopolysaccharide, to create self-healable memristors. Ionic liquid electrolytes were incorporated into xanthan gum matrices to achieve dynamic resistive switching with recovery after mechanical deformation, presenting opportunities for self-healable, long-lasting electronics [103].

3.4 Neuromorphic Application of Bio-memristors

Bio-memristors represent a paradigm shift in neuromorphic engineering and biomedical technology, leveraging intrinsic biocompatibility and ionic dynamics to emulate the core functions of biological synapses. In neuroprosthetics and brain-machine interfaces (BMIs), these devices can mediate communication between artificial circuits and living neural networks, enabling adaptive connectivity across damaged pathways to restore motor or sensory function in patients with paralysis or neurotrauma [104]. Their analog, stochastic, and activity-dependent conductance modulation mirrors synaptic plasticity, supporting real-time, bidirectional interaction between neurons and prosthetic devices, and allowing more naturalistic control of prosthetic limbs, exoskeletons, and sensory substitution systems [105].

Beyond BMIs, bio-memristors hold transformative potential for bioelectronic therapeutics. Implantable or wearable neuromodulation devices incorporating bio-memristors could provide closed-loop, adaptive stimulation for neurodegenerative diseases such as Parkinson's and Alzheimer's [106]. Unlike conventional rigid stimulation protocols, bio-memristor-based systems can dynamically modulate electrical patterns in response to neural activity, enhancing efficacy while minimizing side effects. Their long-term, non-volatile information storage at the ionic level further enables learning-enabled implants that adapt autonomously to disease progression or patient-specific neural signatures.

At the molecular and cellular scale, bio-memristors offer new avenues in biosensing. By transducing biochemical signals into modifiable electrical states, they can detect enzymatic reactions, metabolite fluctuations, or neurotransmitter concentrations with high temporal resolution [107]. Integrated into implantable or wearable platforms, these devices enable continuous monitoring of biomarkers such as glucose, cardiac metabolites, or amyloid-beta levels, providing immediate feedback or triggering autonomous therapeutic interventions [108]. Their low-energy, non-volatile operation makes them ideal for self-powered, real-time diagnostic systems.

In neuromorphic computing, bio-memristors support short- and long-term synaptic plasticity, spike-timing-dependent plasticity (STDP), and homeostatic scaling, making them suitable for in-memory computing, online learning, and energy-efficient pattern recognition. They can power cognitive neuroprosthetics that learn patient-specific neural patterns to improve rehabilitation after stroke or traumatic brain injury, serve as hybrid bio-electronic chips for low-power AI and pattern recognition, enable dynamic sensory encoding in artificial vision, audition, or tactile feedback systems, and facilitate smart pharmacological interfaces that modulate drug delivery or neuromodulation in real time, effectively merging diagnostics, computing, and therapy.

Despite their promise, the long-term deployment of bio-memristors in biomedical systems remains constrained by challenges in material stability, reproducibility, and degradation under physiological conditions.

Biomaterials used in memristive devices—such as proteins, polysaccharides, and biopolymers—are susceptible to hydration-driven structural rearrangements, ionic drift, enzymatic degradation, and fatigue over repeated switching cycles, which can lead to variability in conductance states and device-to-device inconsistency. Ensuring stable synaptic emulation over clinically relevant timescales therefore requires precise control over material composition, encapsulation strategies, and interface engineering to mitigate degradation while preserving biofunctionality. Addressing these limitations is critical for translating bio-memristors from proof-of-concept demonstrations to reliable, implantable neuromorphic systems.

4. Conclusion

In conclusion, this review assesses biomaterial-based memristors from an angle that focuses on their neuromorphic functionality, rather than attempting to classify them from an analogy-based comparison between biological systems and memristors. In theory, further developments from memristor-based systems towards utilizing biomaterials for neuromorphics opens doors for exploring ionic transport properties, redox processes, or biomaterial-based molecular conformation dynamics based on biological systems for systematic control of analog or stochastic resistive switching at lower voltages.

A function-based classification system of bio-memristors, which includes plant-derived polymers, proteins, nucleic acids, and saccharide biomolecules, is proposed to overcome the current disjointed state of the literature. By using a classification system, a wide range of bio-memristors with different chemistries are easily compared by correlating the physicochemical properties, which include ion mobility, hydrated transport, redox reversibility, and biomolecule flexibility, with the performance properties, which include endurance, resistance ratio, retention, switching times, and power dissipation. Based on the comparison with traditional inorganic memristors, the biomaterial devices have been shown to have lower operation voltages and better analog characteristics, although with the trade-offs in long-term endurance and reproducibility.

Importantly, the use of biomaterials in this regard enables additional functionality that transcends computation. Owing to their biocompatibility, ionic-electronic coupling in the absence of external stimuli, stochasticity inherent in the material's underlying processes and properties, and the flexibility of the material that makes possible the analogue representation of weights bio-memristors present a paradigmatic shift in neuroprosthetic interfaces and nanobiosensing applications.

Conflict of Interest: There is no conflict to declare.

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Variations of Mitochondria in Nervous System Disorders

Shipra Sharma*

IFTM University, Lodhipur Rajput, Moradabad 244001

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**Corresponding author: shipgenet@gmail.com, shipra.sharma@iftmuniversity.ac.in*

Abstract

Mitochondria, often referred to as the powerhouse of the cell, predominantly influence highly energy-dependent organs such as the brain, heart, and skeletal muscles. Consequently, mitochondrial disorders are commonly classified as encephalocardiomyopathies. These disorders typically involve multiple organ systems, with neurological dysfunction being one of the most prominent clinical features. The interplay between mitochondrial DNA and nuclear DNA adds another layer of complexity to understanding and diagnosing mitochondrial disorders. Furthermore, clinical heterogeneity—where a single mutation may lead to diverse phenotypes and similar phenotypes with various mutations may arise from different genetic defects—significantly complicates diagnosis. Another major challenge arises from the highly polymorphic nature of the mitochondrial genome, largely attributed to its exposure to a highly oxidative environment. As a result, distinguishing pathogenic or deleterious variants from benign polymorphisms becomes difficult, necessitating the use of specific criteria and computational prediction algorithms. Despite these challenges, substantial progress has been made in recent years. An increasing number of nuclear genes associated with mitochondrial dysfunction have been identified, enriching our understanding of disease mechanisms. The advent of next-generation sequencing (NGS) has further accelerated the field by enabling comprehensive analysis of both mitochondrial and nuclear genomes in a single workflow. This review focuses on the role of mitochondrial polymorphisms in the pathogenesis of major neurological disorders. Recent advancements in genetics and genomics are significantly improving our understanding of mitochondrial disease complexity and are paving the way for more accurate diagnosis and potential therapeutic strategies.

Keywords: mitochondria, variation, parkinson, oxidative stress

Introduction

Mitochondria are known as the power house of cell, their disorders are collectively called encephalocardiomyopathies as they affect most energy dependent organs like brain, heart and muscles. Mitochondria consist of its own circular DNA which is eubacterial in origin [1]. Mitochondria present in multiple copies in the cell and their number can vary depending on the tissue type. Ever since mitochondrial genome sequenced [2], and first pathogenic mutation was identified [3], many mitochondrial variations have been implicated in various disorders [4-6]. Highly oxidative environment of mitochondria, favors the accumulation of variations [7,8]. Both mutated and wild type copies of mitochondrial DNA are present in the cell. State of presence of both mutated and normal copy in the cell is known as heteroplasmy. Ratio of normal to mutated mitochondrial DNA or percent of heteroplasmy (a state where both mutated and wild type mtDNA exists) decides the manifestation of disease. That particular ratio is known as threshold. After crossing a threshold disease gets manifested. Percent heteroplasmy is responsible for variable expressivity in mitochondrial disease. Heteroplasmy varies among different tissues within the same individual i.e 5.1% in red bone marrow, 62% in the bladder for mutation (m.16093T>C) in non coding regulatory region in a study [9]. Similarly, in a preprint study it was shown that heteroplamy was significantly higher in neurons in comparison to muscles [10]. There are examples of certain homoplasmic mutations causing the disease with variable expressivity. To explain this variable expressivity due to homoplasmic mutation two locus hypothesis is suggested where a nuclear gene is acting as modifier in addition to mitochondrial counterpart. Many more nuclear genes are being discovered. These nuclear genes have been modelled in various model organisms including yeast, zebra fish. This review focuses on mitochondrial mutations in relation to neurological disorders. All kinds of mutations e.g. insertions, deletions, rearrangements and point mutations have been reported in various neurological disorders including Alzheimer, Ataxia, Wilson's disease etc. These mutations show variable expressivity, genetic and clinical heterogeneity, a hallmark of mitochondrial disorders. Furthermore, oxidative stress due to mitochondrial dysfunction is a reason for neuronal death in several neurological disorders. Oxidative damage acts in age dependent manner. This age related damage is more in mitochondrial DNA rather than nuclear DNA.

Mitochondrial genome: The double stranded and circular mitochondrial genome is of eubacterial origin, comprising, 16569 bps[2]. Thirteen polypeptides involved in oxidative phosphorylation (OXPHOS), two ribosomal RNAs (rRNAs) and 22 transfer RNAs (tRNAs) that are required for protein synthesis inside mitochondria are encoded by mitochondrial genome[2,](Fig 1). Besides 13 polypeptides, several nuclear encoded proteins are involved for the functioning complex mitochondrial machinery. Mitochondrial genome is haploid, maternally inherited and traditionally thought not to recombine but recent evidence suggest low-frequency

recombination does occur [11,12]. Mitochondrial genome shows codon bias.

Dual genetic control: Variable penetrance is a hallmark feature of mitochondrial disorders which can easily be explained by hetroplasmy. There are certain homoplasmic mutations showing variable penetrance pointing towards the presence of other locus acting as modifier. For example A1555G in 12SrRNA gene implicated in sensorineural hearing loss and A4300G in the $tRNA^{ile}$ involved in maternally inherited hypertrophic cardiomyopathy [13,14]. In addition to playing as modifier, a lot of nuclear gene codes of protein which are essential for mitochondrial functioning. Mitochondria imports around 1500 nuclear encoded protein for its functioning. Out of all, most of the mutations are reported in polymerase gamma. Many complementation studies using cybrids and yeast as a model system shows nuclear – mitochondrial interactions. Nuclear–mitochondrial DNA cross talk can be seen in SNHL (Sensorineural Hearing Loss), where *Saccharomyces cerevisiae* is taken as a model system. Yeast cells harbouring the paramomycin resistance P^R 454 mutation, produce phenotype deficient in respiration only in the presence of a nuclear mutation. This nuclear mutation is present in two highly conserved genes, MTO1 and MSS1 and this paramomycin resistance P^R 454 mutation was homologous to the human mitochondrial A1555G mutation [13]. These nuclear genes probably are required to run translational and the splicing mechanisms optimally. Human homologs of these genes are present but no mutation has been reported in them. These nuclear genes involved in the translational machinery, are thought to be conserved as A1555G, corresponding mutation in human, falls in the highly conserved region of 12S rRNA therefore, can be considered as potential modifier [15]

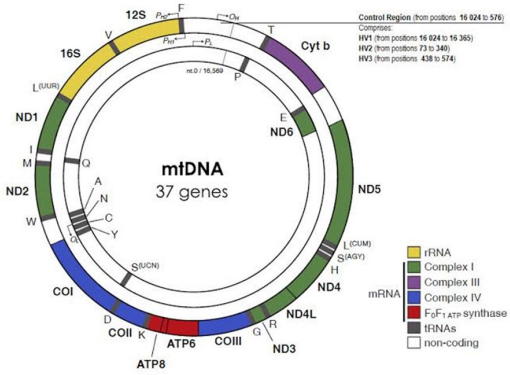


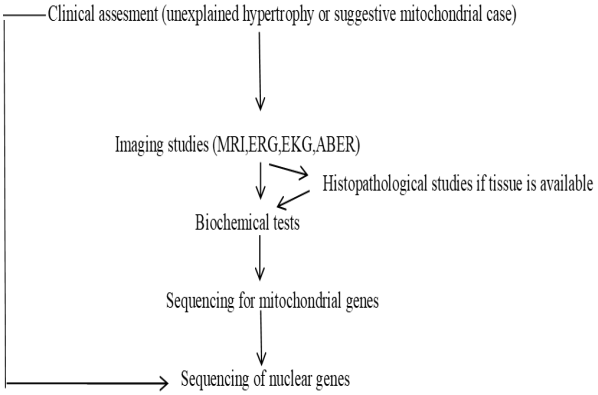
Figure 1 Organization of mitochondrial genome. Reproduced from: Amorim A, Fernandes T, Taveira N. Mitochondrial DNA in human identification: a review. PeerJ. 2019;7:e7314

Heterogeneity in disease presentation: Number of mitochondria varies from 500 to 2000 per cell. Mitochondrion follows the rule of population genetics rather following the mendalian genetics [16]. It is maternally inherited, with rare recombination events. Since recombination is very rare then a question arises what is the genesis of mitochondrial variations? One of the reasons of variations of mitochondria is highly oxidative environment. These variations inherit in different inheritance pattern. Some are sporadic and some are familial. Moreover, mitochondrial disorders show clinical and genetic heterogeneity. There are different mutations which produces identical phenotype known as genetic heterogeneity and also there are mutations where a single mutation producing different phenotypes.

For example, Defect in ATPase 6 gene lead to clinically indistinguishable Leigh syndrome. On the other hand, in case of clinical heterogeneity same genetic defect can results in multiple clinical phenocopies for example classical MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes), with CPEO, or with deafness and diabetes are the result of one A3243G mutation that is present in mitochondial $tRNALeu^{(UUR)}$ gene. Different clinical presentations in different children of same mother of A3243G mutation can be explained by bottleneck effect (a process where there is a sharp reduction in the mt DNA copies during oogenesis followed by random drift and amplification in mature oocytes resulting in a shift in the percentage of mutant mtDNA from mother to offsprings). Interestingly, sometimes mitochondrial mutations affect multiple organs (Leigh syndrome) whereas in few cases it affect specific organs only e.g. Leber Hereditary Optic Neuropathy (LHON) and aminoglycoside induced deafness [17]. Due to clinical and genetic heterogeneity mitochondrial variations are difficult to prioritize. Moreover, polymorphic nature of mitochondrial genome and variations accumulated due to oxidative environment adds the complexity. Following criterion can be adopted to prioritize the variations.

- Mutation would be novel and not reported in normal individuals
- Base change / variation must occur at a site which is evolutionary conserved. For example in protein coding regions, certain regions of ribosomal or t RNAs and few functionally important regions of D loop. The idea is any change in these conserved region is likely to be deleterious. For protein coding genes the misssense mutation has higher chances of being deleterious. However, a synonymous change can also lead to a reduced expression of the gene.
- Heteroplasmic status of the variation
- For various clinical presentations with different clinical severity, segregation of mutation or mutation load differs i.e severely affected person has high heteroplasmy while normal or asymptomatic individual will has low level of heteroplasmy.
- The mutation segregates biochemically with the disease.

Diagnosing mitochondrial disease is a complex, requiring a multidisciplinary approach combining clinical history, physical exams, biochemical tests (like lactate/pyruvate levels, amino/organic acids), specialized imaging (MRI, EKG), and ultimately definitive genetic testing (mtDNA/nDNA sequencing) to find mutations, often supported by muscle biopsies to assess mitochondrial function directly, because symptoms mimic many other conditions and affect multiple organs. At DNA level genetic heterogeneity of mitochondrial diseases becomes a challenge in diagnosing the disease. No single test confirms the disease therefore a integrative approach should be adopted. (Fig.2)



MRI -Magnetic Resonance Imaging

ERG - Electroretinogram

EKG - Electrokardiogram

ABER – Abduction and External Rota

Figure 2 Schematic diagram showing diagnosis of mitochondrial disorders.

Mitochondrial haplogrups

Mitochondrial genome is haploid, maternally inherited with rare recombinational events. Consequently, it evolves due to accumulation of sequential mutations along different lineages and therefore, all the variations in a lineage remain associated with each other. Based upon the frequency of common variants, the normal mitochondrial genomes can be subdivided into distinct genetic groups (haplogroups). These haplogroups have been defined on the basis of existence of restriction site polymorphisms, which are nothing but single nucleotide polymorphisms in the mtDNA sequences. Study of haplogroups from all over the world suggests one common ancestor of Homo Sapiens which is African in origin. Majority of the reported mutations in mitochondrial genome in modern human populations have occurred on pre-existing haplogroups. Therefore, in addition to be used in phylogenetic studies, it has been shown that certain haplogroups confer disease susceptibility whereas some are protective. For example, there are three main mtDNA mutations are found for LHON out of which two i.e T14484C in the ND6 gene and G11778A in the ND4 gene are associated with haplogroup J, a haplogroup which occur 15% in northern Europeans. It has been suggested that increased penetrance of these two mutations is due to haplogrpoup J [18]. LHON affects males only. The possible explanation of sex bias in LHON is nuclear locus such as PRICKLE3, located on X-chr acting as modifier, altering the clinical severity of LHON mtDNA mutations [19]. Similarly haplogroup J and K are reported to have protective effect to Parkinson disease in European population [20]. Besides disease predisposition, mitochondrial polymorphisms have also been shown to be associated with adaptation to cold climates. This is because, variations in respiratory complexes leading to tightly coupled complexes would generate more energy, a condition advantageous in tropics whereas uncoupled complexes would generate more heat, a condition advantageous in cold climate [21].

Mitochondrial polymorphisms in neurological disorders: Since brain metabolism is one of the high energy requiring processes, therefore role of mitochondria in neurological disorders cannot be ignored. Mitochondrial dysfunction has been reported in many neurological disorders. Key mechanisms involved in these disorders are impaired ATP production, oxidative stress, point

mutations and deletions, calcium dysregulation, apoptosis and defective mitochondrial dynamics (fission, fusion and mitophagy).

Epilepsy: In an epidemiological study by Gourie-Devi [22], epilepsy was the most prevalent neurological disorder especially in rural India. Epilepsy is a common manifestation of the MERRF syndrome, MELAS and POLG associated disorders [23]. Mitochondrial disorders are progressive therefore leading to worsening the symptoms. Several different mtDNA mutations have been identified for epilepsy. Among several mutations for MERRF, very first report was of m.8344A>G mutation present in the tRNA gene of mitochondria coding for lysine [24]. Two more mutations i.e m.8356T>C and m.8361G>A in the same tRNA gene reported to cause same clinical syndrome. There are several other mitochondrial mutations resulting in clinical syndromes with myoclonic epilepsy along with cardiomyopathy or diabetes mellitus. Furthermore, MERRF and MELAS presents the overlapping symptoms showing phenotypic variability characteristic of mitochondrial disorders and poor phenotype–genotype correlation. MELAS is a rare genetic disorder primarily defined by lactic acidosis i.e the accumulation of lactic acid in blood that results in vomiting, stroke-like episodes and temporary muscle weakness (SLEs) [25, 26]. Several different mtDNA mutations, can cause MELAS out of which m.3243A>G in the MTTL1 is a cardinal mutation[27]. This mutation can result mainly in MELAS, CEPO (Chronic Progresive External Opthalmoplagia & MIDD(Maternally Inherited Deafness and Diabetes) along with some additional symptoms [28]. Epilepsy is a presenting symptom in 65% of Mitochondrial spinocerebellar ataxia and epilepsy (MSCAE) patients [29]. This early age onset disorder is characterized by spinocerebellar ataxia, peripheral neuropathy, and epilepsy. MSCAE is different from MELAS in the sense that sensorineural deafness is rare and acute liver necrosis is common in it. MSCAE is caused by the recessive mutations in the catalytic subunit of POLG gene out of them two are very imp i.e the c.1399G>A correspond to p.A467T and the c.2243G>C correspond to p.W748S [30]. A recent study also warrants screening of PolG in epileptic cases [31].

Parkinson disease (PD): Parkinson disease is a progressive neurological disorder characterized by selective degeneration of dopaminergic neurons in substantia nigra [MIM#605909]. Mitochondrial involvement in PD has been documented in several studies but results of these studies are not consistent. A variation at position A10398G was reported in many studies altering the susceptibility towards PD in individual. In some studies this polymorphism is conferring protection to PD while in few studies not [20, 32]. Table 1 [20, 33-41]

Table 1 Effect of polymorphism A10398G on risk of PD in different studies.

S.N	Study	Population	Risk for PD	Odd ratio
1	Huerta C (2007)	Spanish	Protective	0.52(0.34-0.81)
2	Huerta C (2005)	Spanish	Decrease	0.53(0.33-0.86)
3	Vander Walt JM(2003)	Europian	Protective	0.53(0.39-0.73)
4	Chu Q (2015)	Chinese	Increase	1.30 (0.95-1.76)
5	D. Otaegui(2004)	Spanish	No correlation	
6	Clark J (2011)	Caucasian	Inversely associated	1.4-2.0
7	Chen CM (2007) A10398G with in a haplotype	Taiwanese	Decrease	0.44(0.24-1.80)
8	Latsoudis H(2008)	Cretan	No correlation	
9	Liou et al(2016)	Cybrid cells	Resistance against PD	.50(.33-.28)
10	Simon DK (2010)	Non-Hispanic Caucasians	No correlation	

A study in European population reveals that this variation was significantly associated with decreased risk of PD in haplotype J & K. Protective effect was stronger in women(P=.009) than among men(P=.04). A recent meta-analysis suggests that A10398G was not significantly associated with Asian population (G Vs A: OR=1.090, 95%CI=0.939-1.284, P=0.242) while it is protective in Caucasian population (G Vs A: OR=.699, 95%CI=0.546-.895, P=0.005).Reason of these conflicting results can be small sample size or population stratification in case control studies which give false association between gene marker and disease, therefore selection of ethnically matched control and cases are warranted. SNP A10398G results in threonine to alanine amino acid change which is a non-conservative change in the ND3 subunit of complex I. SNPA10398G may act as a surrogate marker for a causative variation present in other mitochondrial gene. One probable reason to explain the protective effect of this polymorphism is the decreased ROS production by complex I is associated with increased oxidative stress, eventually resulting in degeneration of neurons [32].

Alzheimer disease (AD): AD is characterized by the selective loss of neurons of hippocampus or cerebral cortex.AD brain shows the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles of hypophosphorylated tau protein. AD inherits in autosomal dominant fashion which is approximately 5% of all cases. Fifty percent of them has mutations in one of the three genes ie. amyloid precursor protein (APP), presenilin1 (PSEN1) or presenilin 2 (PSEN2) are found. Remaining cases are sporadic. Only one genetic factor is known for sporadic AD is APOE genotype. Variation A433G in this gene has been reported in AD and PD as well in many studies. Mitochondrial haplogroups have been reported to influence AD risk. Haplogroup K and U may modulate the susceptibility to AD by neutralising the effect of APOE4 genotype [42]. However haplogroup K is not associated with decreased risk of AD according to Vander Walt 2004. They also demonstrated that males belonging to haplogroup U and carrying the 10398 A allele showed a increased risk of AD compared to males with G allele. With the same haplogroup U, polymorphism 12308G and 7028 T were associated with decreased risk of AD. Haplogroup U showed the gender dependent risk reported in many studies., e.g this haplogroup was less frequent among male centenarian (4%) than among control males (23%) ans more frequent in AD males (13.3%), as compared to age-matched controls (6.8%) [43-45]. In a study in Han Chinese population haplogroup B5 confers genetic susceptibility to AD and its effect was most likely mediated by ancient variation m8584G>A [46]. While the interaction between the APOE -ϵ4 genotype mtDNA haplogrops has been investigated in multiple studies, there is no consensus on validation by genome-wide association studies (GWAS). Effect of various haplogroups on neurological disorders are compiled in Table 2 [20, 42-49].

Table 2: Effect of haplogroups on neurological disorders in different populations.

S.N.	Study	Haplogroup	Ethnicity	Risk for disease
1	Soini HK(2013)	U5a1(m.15218A>G)	Finnish	Increased risk for epilepsy
2	Van Der Walt(2003)	J and K(A10398G)	European	Decrease risk for PD
3	Carrieri, G (2001)	K	European	No effect on the risk for AD
4	Van Der Walt(2004)	U	Caucasians	Increase risk in males, decrease risk in females in AD
5	De Benedictis G (2000a)	J	Italian	Associated with longevity
6	De Benedictis G (2000)	U	Italian	Associated with longevity
7	Bi, R (2015)	B5	Han Chinese	Suceptible for AD
8	Takasaki S(2009)	M7b2, B4e, B5b	Japanese	Associated with PD
9	Takasaki S(2008)	G2a	Japanese	Associated with AD

Somatic mutations: Mitochondrial genome acquires mutation at higher rate than nucleus due to mitochondrial oxidative environment. These acquired mutations are termed as somatic mutations. Somatic mutations have been reported in various neurodegenerative diseases like Parkinson [50], Huntington [51] and Alzheimer [52] AD. Coskun et al identified T414G, T414C and T477C mutations in control region which were exclusive to AD patients. Out of these three, 65% of examined AD brains had T414 mutations. Few mutations were common between AD and control brains both but more prevalent in AD brains. Moreover these were growing in percentage with the increase in age in comparison to controls. These mutations were heteroplasmic (70-80% hetroplasmy) [53].

Few common mutations in mitochondrial and nuclear genomes are listed in Table 3 [32, 54-60].

Table 3: Important mitochondrial polymorphisms in neurological disorders

Disease	Gene	Mutation	Ref
Mutations in proteins encoded by mitochondrial genome			
NARP (Neuropathy, Ataxia and Retinitis Pigmentosa)	ATPase 6	T899C	Majendar et al 1997
Parkinsonism, deafness and neuropathy	12S RNA	T1095C	Thygarajajan D et al 2000
MELAS	$tRNA^{leu}$	A3243G	Kaufman et al 2004
Parkinson	ND3 subunit of Complex I	A10398G	Hua F et al 2017
Mutations in nuclear encoded mitochondrial proteins			
Alzheimer	Apolipoprotein E	Genotypeε3/ε3	LiuM et 2014
Alzheimer and other neurodegenerative diseases	Apolipoprotein E	e 2 genotype	Goldberg, T.E. et al 2020
Epilepsy	PolG	G1399A(p.A467T), G2243C(p.w748S), G2542A(p.G848S)	Anagnostou EM et al 2016
Infantile onset spinocerebellar ataxia	Twinkle	C1472T A1708G	Nikali K et al 2005

Oxidative stress and neurodegenerative disorders

One of the common mechanisms in neurological disorders is oxidative stress due to mitochondrial dysfunction. Oxidative stress is defined as a disequilibrium between production and accumulation of reactive oxygen species (ROS) and ability of cell to detoxify these reactive products. Mitochondria is major source of ROS. These ROS are produced as a result of defective electron transport chain (complex I and complex III are the major site of ROS production) due to mutation in mitochondrial DNA. Excessive ROS generation disrupts mitochondrial function through multiple mechanisms. It initiates lipid peroxidation and oxidizes amino acids, thereby compromising the electron transport chain and reducing ATP synthesis. ROS also induces DNA strand

breaks, leading to the accumulation of harmful mutations [61]. In addition, it alters the permeability of the inner mitochondrial membrane by promoting the formation of the mitochondrial permeability transition pore (mPTP) [62], and triggers calcium release from the endoplasmic reticulum [63]. Persistent calcium overload enhances superoxide production, creating a self-amplifying cycle that activates signaling pathways such as CaMKII, causes osmotic imbalance, and culminates in swelling and rupture of the outer mitochondrial membrane. These events ultimately drive programmed or unregulated cell death via apoptosis or necrosis [64]. The damaged cells are subsequently eliminated through autophagy.

Oxidative stress and Alzheimer disease (AD)

In a recent study sodium dismutase; a marker for oxidative stress was found elevated in the patients of AD and MCI (mild cognitive impairment) with ApoE polymorphism [65]. A case control study of postmortem brain samples of AD subjects showed increased levels of protein oxidation product (carbonyl) and decreased glutamine synthetase activity in age matched control and AD groups but more profound in AD brains [66].This decreased enzyme activity led to decreased clearance of glutamate, eventually, increase in glutamate toxicity or excitotoxicity in which neurons are killed by overstimulating glutamate receptor like NMDA, causing massive calcium influx, leading to mitochondrial damage, induce oxidative stress(ROS) and activation of destructive enzymes, triggering cell death by both necrosis and apoptosis a common mechanism in Huntington, Alzheimer and ALS(Amyotrophic Lateral Sclerosis) which may lead to cell death [67]. Another study suggests involvement of glycated tau protein in inducing oxidative stress found in neurofibrillary tangles in sporadic AD [68]. Different studies revealed that AβP can generate free radical peptide and produce ROS [69]. Deficiency of cytochrome oxidase, a marker for ROS and reduced expression of mitochondrial Cox1 and Cox 3 subunits have also been observed in AD brains [70].

Oxidative stress and Parkinson disease (PD)

Parkinson is the second most degenerative neurological disorder after Alzheimer. PD and AD shows overlapping symptoms thus suggesting a common etiological mechanism [61]. Mutations in mitochondrial (12S RNA) and nuclear genes (PINK1, PARK2, PARK6, alpha-synuclein &DJ-1) have been shown to be associated with PD [71]. These mutations in these genes make cell susceptible to oxidative stress, one of proposed mechanism for nigrostriatal loss (loss of dopamine neuron in nigrostriatal pathway). This has been corroborated by several studies [72-75]. Activity of complex I and ubiquinone was found reduced in the brain of PD patients which may lead to neurodegeneration [76-78]. Moreover, downregulation of mitochondrial encoded genes in expression studies of dopaminergic neurons of PD patients, thereby further strengthening of

the idea of mitochondrial dysfunction in this disease [79].

Oxidative stress and Amyotrophic lateral sclerosis (ALS)

It has been shown that in ALS or more commonly Charcot disease, oxidative stress play an important role in loss of motor neurons and mitochondrial dysfunction leading to neurodegeneration. People have shown that loss of super oxide dismutase (SOD) activity results in the loss of motor neurons in spinal cord [80]. This can be increased by reduced glutamate transport and situation can be improved by supplementing antioxidants showing that there is involvement of free radicals. Mutant SOD gene in transgenic mice has shown to induce symptoms corresponding to human ALS [81].

Recent advances in mitochondrial genetics:

Disease management of mitochondria can be done either by (a) replacing defective mitochondria or (b) manipulating the mitochondrial genome. A recently emerged technique involves selection of preimplantation embryos with low mutation load. This is an IVF based technique known as preimplantation genetic diagnosis (PGD). PGD fails when mother is homoplasmic for the mutation or fails to produce embryo of low mutation load. There are reports of PGD in case of alzhiemer and other neurological disorders [82, 83]. Mitochondrial donation (MD) techniques also hold potential includes mitochondrial spindle transfer (MST), pronuclear transfer (PNT), polar body transfer and genetic transfer. Out of these MST and PNT most extensively studied MD techniques (Fig3,4) [84]. Both of these techniques involves the removal of nuclear material from patient and donor oocytes either pre or post fertilization. Now the nuclear material from patient oocyte is transferred to donor oocyte resulting in the reconstruction of oocyte or zygote that contains nuclear material of patient and normal mitochondria from donor. There are ethical and regulatory considerations for Mitochondrial Donation (MD) center on safety, "three-parent" identity(refers to an infant born from mother, father and donor. Since contribution of mitochondria is only 37 genes, about 0.1% of the total genome, so it does not affect much on appearance of baby), germline modification, donor consent/rights, equity of access, and regulatory clarity on parenthood, requiring robust oversight like the UK's Human Fertilization and Embryology Authority (HFEA), balancing reproductive freedom against long-term health risks, ensuring donor anonymity or identity access, and addressing societal views on genetic contribution. Key issues involve the permanence of germline changes, ensuring informed consent for donors and recipients, defining parental roles, and managing potential "slippery slope" arguments toward broader genetic editing.

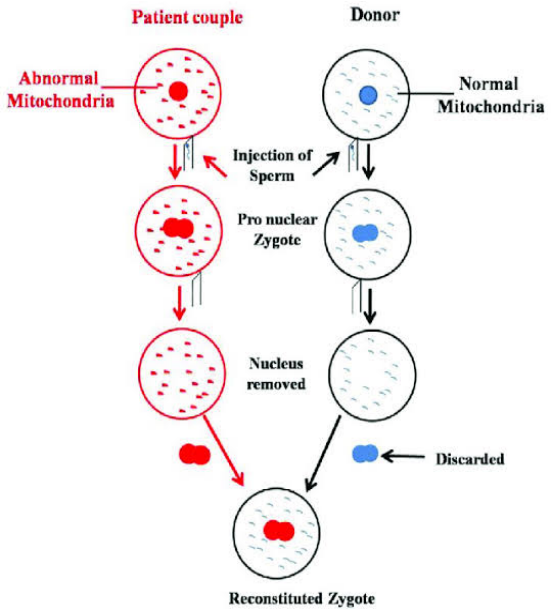


Figure 3: Pronuclear Transfer Technique of mitochondrial donation

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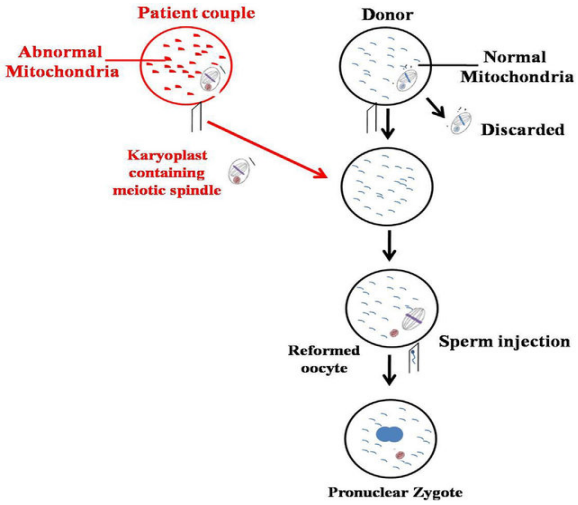

Figure 4 Pronuclear Transfer Technique of mitochondrial donation

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Another approach involves altering mitochondrial heteroplasmy. This can be achieved by many ways like selectively inhibiting the mutant mitochondrial DNA replication, destruction of mutant mt DNA by restriction endonucleases and by gene editing.

With the advent of next generation sequencing (NGS), mitochondrial science witnesses a major change in diagnosis and theraputics as well. NGS enables detection of even low hetroplasmy, therefore, helping in diagnosis [85]. It will reduce the need for an invasive muscle biopsy especially in disorders involving coding sequences however muscle biopsy remains the "gold standard" for certain biochemical assays that NGS can not replace. Furthermore, comprehensive information of disease target enables the formation of homogenous cohorts of patients for clinical trial, therefore, aiding in intervention.

Conclusion:

Mitochondrial disorders represent one of the most challenging disease categories to diagnose and manage due to their clinical complexity and genetic variability. Since mitochondria play essential roles in cellular energy production and apoptosis, they have become a central focus for research on neurological disorders. Numerous mitochondrial polymorphisms have been identified, some directly implicated in disease pathogenesis, while others are associated with altered disease susceptibility. The advent of next-generation sequencing (NGS) has transformed the diagnostic landscape,

enabling accurate detection even with small sample sizes and facilitating the discovery of rare mitochondrial disorders. Additionally, NGS allows rapid analysis of both mitochondrial and nuclear genomes, offering precise and sensitive detection of heteroplasmy. With ongoing advancements in genetic and genomic technologies, significant improvements in the diagnosis and treatment of mitochondrial disorders are expected in the future.

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