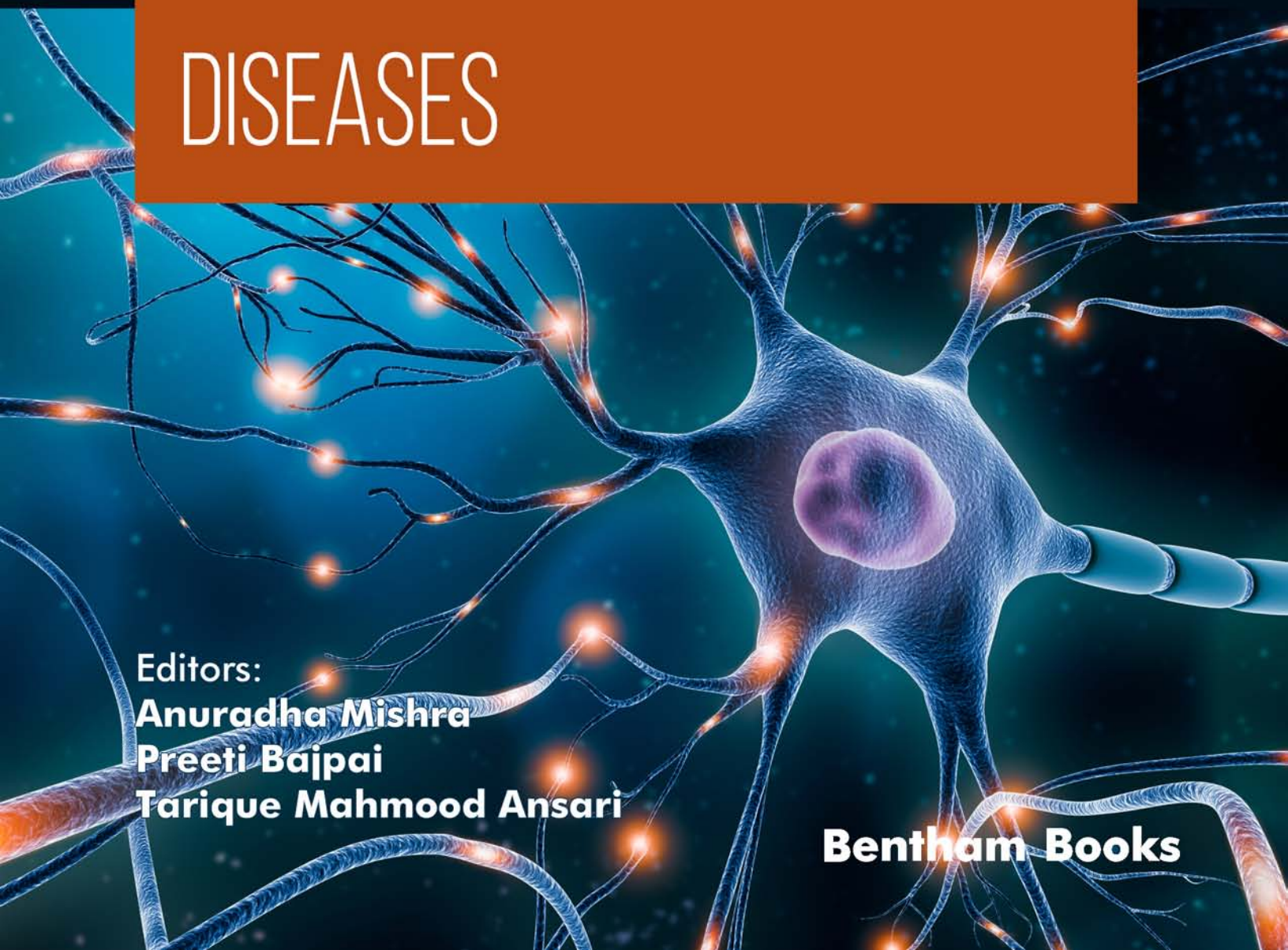
ADVANCES IN DIAGNOSTICS AND IMMUNOTHERAPEUTICS FOR NEURODEGENERATIVE DISEASES



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Advances in Diagnostics and Immunotherapeutics for Neurodegenerative Diseases

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FOREWORD

Neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis, are debilitating disorders that affect millions of people worldwide. These conditions are characterized by the progressive loss of function and death of neurons, resulting in a wide range of symptoms, including memory loss, motor impairment, and cognitive decline. Despite extensive research, there is currently no cure for most neurodegenerative conditions, and existing treatments only offer limited symptom relief.

However, there is a ray of hope. In recent years, significant advances have been made in the field of neurodegenerative research, particularly in the areas of diagnostics and immunotherapy. These advances have led to the development of novel diagnostic tools that allow for earlier and more accurate diagnosis of these conditions, as well as promising immunotherapeutic approaches that target the underlying pathologies of these diseases.

This book, Advances in Diagnostic and Immunotherapeutic Approaches for Neurodegenerative Conditions, provides a comprehensive overview of these recent advances, highlighting the most promising developments and providing insights into future directions for research and treatment.

The book focuses on advances in diagnostics, covering topics such as biomarkers for early detection, imaging techniques for improved diagnosis, and the role of genetics in neurodegenerative conditions. The authors explore the potential of these diagnostic tools to enhance early detection and diagnosis, which is crucial for the development of effective treatments, and immunotherapeutic approaches, including novel strategies for targeting misfolded proteins and inflammatory pathways, as well as the use of stem cells and gene therapy. The authors explore the potential of these approaches to slow or even reverse the progression of neurodegenerative conditions, offering hope for the development of effective disease-modifying treatments.

The final section of the book examines the challenges and opportunities presented by these recent advances, exploring topics such as ethical considerations in the development and implementation of these approaches, the potential impact on healthcare systems, and the need for collaboration between researchers, clinicians, and patients.

This book is an essential resource for researchers, clinicians, and students in the fields of neurology, neuroscience, and immunology, as well as for anyone interested in the latest developments in the diagnosis and treatment of neurodegenerative conditions.

Overall, the book “Advances in Diagnostic and Immunotherapeutic Approaches for Neurodegenerative Conditions” represents an important contribution to the field of neurodegenerative research, offering a roadmap for the development of more effective diagnostic and therapeutic approaches, and providing hope for a brighter future for those living with these conditions.

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PREFACE

In the intricate landscape of neuroscience, the journey to understanding and combating neurodegenerative conditions has been both challenging and inspiring. "Advances in Diagnostic and Immunotherapeutic Approaches for Neurodegenerative Conditions" endeavors to capture the remarkable strides made in recent years, offering readers a panoramic view of the cutting-edge research shaping the future of neurodegenerative disease management.

Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), represent a complex and multifaceted challenge. These conditions not only affect the individuals diagnosed but also reverberate through families, communities, and healthcare systems worldwide. With the aging population on the rise, the imperative to develop effective diagnostic tools and therapeutic strategies has never been more pressing.

This comprehensive book aims to provide readers with a panoramic view of the latest advancements in diagnostic methodologies, from cutting-edge imaging technologies and biomarker identification to sophisticated genetic profiling techniques. By illuminating these breakthroughs, we strive to enhance our understanding of disease mechanisms, enabling earlier detection, more accurate diagnosis, and personalized treatment approaches.

The latter sections of the book are dedicated to exploring the burgeoning field of immunotherapeutic interventions. Here, we delve into the exciting potential of harnessing the body's immune system to target and combat neurodegenerative processes. The latter chapters in this section showcase the transformative power of immunotherapy in reshaping our approach to treating neurodegenerative conditions.

However, this volume is not merely a compilation of scientific achievements; it is a call to action. By highlighting the most promising developments and discussing the challenges that remain, we hope to inspire collaboration and innovation across disciplines. The complex nature of neurodegenerative research necessitates a multidisciplinary approach, where insights from neuroscience, immunology, genetics, and computational biology converge to drive progress.

As you navigate through the pages of "Advances in Diagnostic and Immunotherapeutic Approaches for Neurodegenerative Conditions," you will encounter the dedication, perseverance, and vision of the scientists, clinicians, and researchers who are leading the charge against neurodegeneration. Their pioneering work, presented here in detail, offers a compelling narrative of hope, resilience, and the relentless pursuit of scientific excellence.

We invite you to embark on this enlightening journey with us, as we explore the present landscape and envision a brighter, healthier future for those affected by neurodegenerative conditions.

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INTRODUCTION

In this book, various categories of neurodegenerative conditions are discussed, along with their pathological origins, which include genetic and epigenetic factors, and different therapies such as synthetic drugs, biologicals, and repurposed drugs. The book is divided into three segments.

The first segment covers different categories of neurodegenerative conditions (NDC) and their pathological states of origin. It delves into neuroinflammation and its role in causing Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and more. Furthermore, it covers how such inflammatory responses can be held responsible for the generation of NDC. Interestingly, it also sheds light on how such inflammatory pathways open the door to impending therapy and next-generation drug development. This segment also covers immunomodulation associated with degenerative Huntington's disease. The second segment focuses on gut microbiota and their impact on the genesis of brain disorders. It discusses the interplay between gut microbiota and neurodegeneration. The third segment discusses epigenetics and its potential role in intervening in neurodegeneration. Finally, the book explores the use of repurposed drugs in treating NDDs.

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CHAPTER 1

A Systematic Review of Neurodegenerative Diseases: Etiology, Clinical Symptoms, Pathogenesis, and Future Developments

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Abstract: Neurodegenerative diseases (NDDs) are nervous system disorders that impact around 30 million people globally. Loss of brain tissue is a hallmark symptom of NDDs. Amyotrophic lateral sclerosis (ALS), frontotemporal dementia, Parkinson's disease, Alzheimer's disease, and Huntington's disease are among the NDDs caused by protein misfolding and inappropriate processing of proteins. In addition, neurodegeneration has also been linked to oxidative stress, mitochondrial malfunction, and/or environmental variables strongly correlated with aging. Significant evidence has been obtained after years of intensive research that shows these factors have a crucial role in the etiology of prevalent neurodegenerative disorders. Many clues have been identified regarding neurodegenerative illnesses, but the complexities of these conditions still make them difficult to understand. This chapter presents a more straightforward explanation to help individuals better understand NDDs, their etiology, clinical symptoms, and pathogenesis

Keywords: Ageing, Neurodegenerative diseases, Neurodegenerative disorders, Neurodegeneration, Parkinson's disease.

INTRODUCTION

There is an immediate danger to human health from neurodegenerative illnesses. The ageing of the population has led to an increase in cases of neurodegenerative illnesses such as Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral

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sclerosis (ALS), frontotemporal dementia, and spinocerebellar ataxias. The pathophysiology of these conditions is quite diverse; some of them manifest in memory and cognitive decline, while others manifest in difficulties with locomotion, speech, and respiration [1, 2]. Just to name a few, there are (a) Aberrant protein dynamics with faulty protein aggregation and degradation, (b) Oxidative stress and the formation of free radicals, (c) Poor bioenergetics and dysfunctional mitochondria, and (d) Exposure to pesticides and metal toxicity (Fig. **1**). In addition, despite extensive research efforts, the pathophysiology of these proteinopathies remains unclear, making it difficult to identify effective therapeutic drug targets. However, neuroscientists have capitalized on their comprehension of the primary etiology of these disorders to study applications with the aim of producing recently developed new therapeutics for these diseases. Even though every disease has a unique molecular mechanism and set of clinical symptoms, certain common pathways may be identified in various pathogenic cascades. These include oxidative stress and free radical production, metal dyshomeostasis, mitochondrial dysfunction, protein misfolding and aggregation, and phosphorylation impairment, all occurring concurrently.

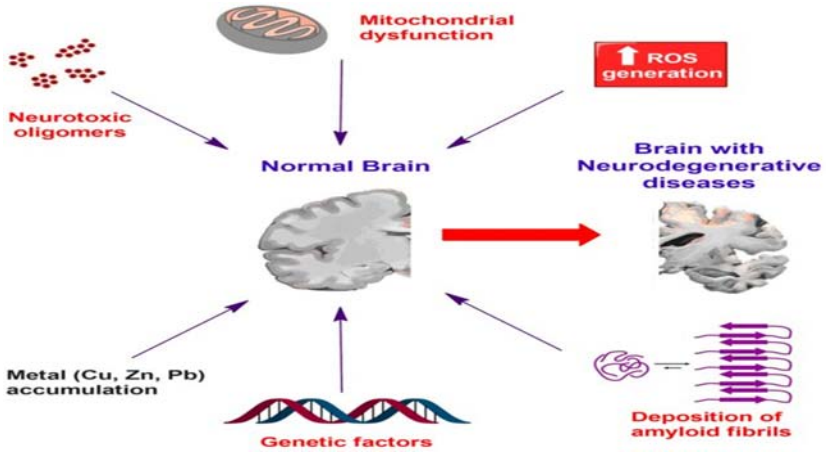

Fig. (1). Different factors responsible for the precipitation of neurodegenerative disorders [7].

With remarkable progress in genome sequencing technology, we can now read individual genomes and get insight into the origins of both common and unusual genetic illnesses, although Deoxyribonucleic acid (DNA) sequence variants are common, it is not yet known which ones are harmful and only cause a slight change in gene function [3]. Human genome sequencing has led to the identification of candidate gene variants, the effects of which may be evaluated using model animals. A cure for spinal muscular atrophy (SMA) is an inspiring example of scientific advancement. Mutations causing loss of function in the

survival motor neuron (SMN1) gene result in SMA, the most common inherited cause of infant mortality. On the heels of ground-breaking research into the molecular basis of the disease and the development of animal models, antisense oligonucleotides (ASOs) are currently being tested in human trials as a therapy option to correct a splicing error and restore functional SMN protein. Researchers verified the promising findings in animal model systems in two clinical trials, including children with SMA. After the approval by the Food Drug Administration (FDA) of the ASO medication at the year's end, it became the first disease-modifying therapy for SMA and a comparison was made between infants who did not receive the medication with those who showed significant gains in motor ability. This is a big win for patients, their loved ones, and the model systems [4].

The healing path forward in the fight against neurodegenerative diseases is now clear. Scientists studying this field are fortunate to be doing their work during such an intriguing and productive time [5, 6]. The primary target of neurodegeneration, which has a multifactorial aetiology, is the neurons in the human brain. This disorder is linked to the gradual loss of brain tissues, which results in the death of neurons. It is directly related to ageing, and one of its primary characteristics is the degeneration of proteins, which leads to the buildup of inclusion bodies and insoluble deposits in different parts of the brain. Neurotoxic oligomers, oxidative stress, neuroinflammation, mitochondrial dysfunction, calcium dysregulation, deficiencies in axonal transport, metal buildup, amyloid deposition, and DNA damage are only a few other factors that have been associated with neurodegeneration (Fig. **1**). Through a variety of pathways, including apoptosis, necrosis, autophagy, and parthanatos, programmed cell death eventually results from the persistence of these conditions overwhelming self-defense mechanisms.

Parkinson’s Disease

Neurodegenerative diseases include Parkinson's. When substantia nigra neurons die, movement issues occur. The substantia nigra contains many neurons that produce dopamine. Substantia nigra neurons release dopamine to connect with movement-producing brain regions like the frontal lobe and basal ganglia. Ganglia are neuron clusters. Basal ganglia are neuronal groupings in the brain's core. Neuronal loss in the substantia nigra causes stumbling and trembling in persons with this condition. They have trouble initiating and maintaining movement [7].

CHAPTER 2

Neuro-inflammatory Responses in Alzheimer's v/s Parkinson's Diseases

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Abstract: Neurodegenerative diseases are a heterogeneous group of disorders and are the leading cause of morbidity and disability. These are described by the progressive degeneration of the neurons and impaired function of the central nervous system. Prevailing neurodegenerative diseases in the world include Alzheimer's disease and Parkinson's disease and reports predict that on average, the prevalence of both diseases will double in a span of the next twenty years. Pieces of evidence showed that the immune system is profoundly involved in brain development, maintenance, and repair as well as in damage, therefore, may provide a wide scope to focus on the neuroinflammation-based therapeutic approaches. In this chapter, the various neuroinflammatory responses will be discussed during the onset and progression of both Alzheimer's and Parkinson's disease pathologies. We will be focusing on both central and peripheral inflammatory responses and their consideration for disease diagnosis and therapeutics.

Keywords: Alzheimer's disease, Disorders, Neuroinflammation, Parkinson's, Pathologies.

INTRODUCTION

Inflammation is a crucial physiological event in response to infection, injury, and trauma. An effective inflammatory response mechanism eradicates invading pathogens and initiates cellular healing. Neuroinflammatory responses particularly involve the inflammatory responses of cells available in the brain and spinal cord. Such inflammatory responses are mediated by the production of cytokines (IL-1β, TNFα, and IL-6), chemokines (CCL5, CCL2, CXCL1), reactive oxygen species, and secondary messengers (NO and prostaglandins). These mediators are mostly produced by glial cells of the brain (microglia and

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astrocytes), endothelial cells, and peripheral-derived immune cells which collectively may execute various immune, physiological, biochemical, and psychological responses [1, 2]. In such a framework, the inflammation can be noticed as an intricated series of localized immune responses that collectively serve to deal with various menaces to the brain microenvironment. In most neurodegenerative diseases, inflammatory responses are unavoidable and significantly contribute to disease onset and progression. The observed neuroinflammatory responses may be the initiators or the consequences of the dying neurons however, the sequential events are still not known. In the central nervous system (CNS), the resident glial cells (microglia and astrocytes) play a crucial role in the neuroinflammatory responses during disease conditions, and among these, microglial cells have more deleterious effects as these are the phagocytic cells of the brain. On the contrary, the astrocytes protect the neurons by facilitating their antioxidant defenses through the glutathione pool. Astrocytes also provide metabolic support to neurons and constitute the only energy reservoir for neurons as neurons cannot store glycogen [3]. Astrocytes also contribute to the maintenance of brain homeostasis including various aspects like ion concentration, pH of brain environment, and neurotransmitter concentrations in synaptic interstitial fluid. The tripartite synapse which comprises both presynaptic and postsynaptic neurons along with astrocyte contribution is the best example of a close functional association of neurons and astrocyte's physiology [4, 5].

Microglial cells are brain resident M1 type phagocytic cells, which are actively involved in the maintenance of the brain microenvironment. Resting microglia represent ramified morphology and small while activated microglia represent ameboidic morphology have a retracted process and are comparatively big. In physiological conditions, the resting microglia and neurons communicate optimally and regulate the behavior and brain physiology mostly through CX3CL1 (fractalkine receptor) secreted from the neurons and its receptor located on microglial cells (CX3CR1) [6]. The interaction of Fractalkine and CX3CR1 initiates the signaling pathway which modulates the microglial activation in a broad spectrum. In both Alzheimer's and Parkinson's disease, the disruption of this interaction has been reported suggesting its active involvement in brain pathology [6, 7]. Though a contradictory report by Lee et al. (2010) has shown that the deficiency of receptor CX3CR1 decreases the microglia activation as well as declines the production of proinflammatory molecules (IL-1β, TNF-α, monocyte chemoattractant protein 1 (MCP-1 or CCL2) and enhances its phagocytic activity which contributes to the reduction of β-amyloid protein accumulation [8]. Therefore, this suggests that both neurotoxic and neuroprotective actions of these signaling pathways are dependent on the disease stage, pathological context, and the stimuli that activate microglial cells in the CNS microenvironment. However, the reports suggest the critical role of both

microglial and astrocyte cells in the maintenance of physiological as well as pathological conditions by executing neuroinflammatory responses during injury or diseased conditions. In the next sections, we will discuss neuroinflammatory responses reported in the pathologies of Alzheimer's and Parkinson's disease.

INFLAMMATORY RESPONSES IN ALZHEIMER'S DISEASE

Astrocytes and microglia are the primary immune responses involved in the pathological process of AD [9]. The Aβ toxicity can be propagated by the microglia and astrocytes. Aβ aggregates can release cytokines, chemokines, nitric oxides, and ROS that contribute to neuronal death [10]. Aggregates of Aβ activate the microglia and it became referred to as disease-associated microglia that release several inflammatory factors. The activation of microglia was mainly due to the binding of Aβ on RAGE, nucleotide-binding oligomerization domain-like receptor (NLRs), and TLR 4 receptors that activate transcriptional factors such as NF-κB, AP-1, c-AMP response element-binding protein and interferon regulating families. The activated microglia in turn play a role in the progression of AD [11]. The observed augmented immunoreactivity of microglia vicinal to Aβ plaques toward cytokines and chemokine receptors has been reported [12]. Along with microglial cells, astrocytes maintain homeostasis and provide growth factors to neurons. In AD condition, the astrocyte undergoes morphological and functional changes which make it a reactive astrocyte. These reactive astrocytes have increased expression of glial fibrillary acidic protein (GFAP) and have been found in the vicinity of Aβ plaque [13]. Astrocytes can also sense the Aβ aggregates in a TLR/RAGE-dependent manner and produce neurotoxic factors (IL1 β, TNF-α, IFNγ, IL6) [14].

In AD patients, IL-1 promotes the synthesis of inflammation-associated factors such as S100β in astrocytes. Another report states that in Aβ diffuse deposits, IL-1 initiates dystrophic neurite formation and increases IL-1 level in AD patients promoting p38-MAP kinase activity, which leads to tau hyperphosphorylation [15]. It has also been emphasized that blocking of IL-1β signaling decreases the GSK-3β activity and promotes neurogenesis through the Wnt/β-catenin pathway. Another report showed that cytokine IL-6 induces tau phosphorylation through cdk5/p35 pathway deregulation that leads to the formation of neurofibrillary tangles. Overexpression of IL-6 was observed in the brain of two hAPP transgenic models (TgCRND8 and Tg2576) that lead to significant gliosis that could promote Aβ elimination in early stages of the disease by upregulating microglial phagocytic marker [16]. It has been reported that TGF-β, a cytokine with anti-apoptotic function may promote neuronal survival [17]. In AD patients, the augmented level of TGF-β1 was observed and it has been hypothesized that TGF-β1 overexpression induces amyloidogenesis in the cerebral vasculature and

CHAPTER 3

Immunopathogenesis of Alzheimer's disease, Parkinson's Disease, and other Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases are categorized mostly by protein deposits or known hereditary mechanisms, despite recent studies showing overlap and intra-individual variations in these symptoms. A synergistic interaction between pathological proteins advises extensive pathogenic pathways. Animal models and other studies have uncovered the fundamental mechanisms underlying neurodegeneration and cell death, opening up new avenues for future prevention and therapy plans. A multidomain therapy approach that emphasizes the underlying reasons why diseases alike Parkinson's, Alzheimer's, *etc*. occur. Neurodegenerative diseases like Parkinson's disease (PD) and Alzheimer's disease (AD) are becoming far more common in the Western world. Neuronal inflammation, gut microbiota, extracellular misfolded protein accumulation, hallmarks of various neurodegenerative nephropathies, and failure of the systemic and cerebral immune systems are some of the elements that affect the immunopathogenesis of neurodegenerative diseases. Deficits in the ubiquitin proteasome autophagy system, abnormal protein dynamics brought on by oxidative stress and free radical formation, mitochondrial dysfunction, impaired bioenergetics, neurotrophins dysfunction, "neuroinflammatory" processes, and (secondary) distractions of neuronal Golgi apparatus and axonal passage are some of the fundamental mechanisms that contribute to immunopathogenesis. Long-term cooperation between these interconnected systems results in programmed cell death. In this review, we discussed every idea and hypothesis that have been put up on the pathophysiology of neurodegenerative disorders.

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Keywords: Amyloid, Alzheimer's disease, Gut microbiome, Mitochondrial abnormalities, Neuroinflammation, Neuronal dysfunction/death, Oxidative stress, Pathogenic factors, Retinopathies'.

INTRODUCTION

Ageing is the key factor of NDD, it constitutes a significant source of impairment and has contributed to a rise in interest in the immunopathological processes underlying neurodegenerative disorders. It has been revealed that ischemia, neurodegenerative diseases, immune-mediated disorders, infections, and trauma all have immunologically active central nervous systems (CNS). It frequently has the potential to harm neurons. Even though not all immune reactions in the CNS are negative, many of them promote repair and regeneration. The microglia have two distinct roles in neurodegeneration: they both harm and protect brain homeostasis. T cells, like microglia, can benefit patients improve from neurodegenerative illnesses, albeit it is unknown exactly how T cells are able to do this. Complex interactions have been revealed by thorough investigations of the neuroimmune interaction at the cellular and molecular levels, indicating that immune cells emit both neurotoxic and neuroprotective chemicals. The role of immune responses in neurodegenerative ailments is discussed, as is the hazy distinction between pathogenic and immunological responses associated with repair. To harness favorable responses for therapeutic treatments, a deeper knowledge of this dynamic will be required [1 - 3]. According to studies, the occurrence of Parkinson's disease (PD) and Alzheimer's disease (AD) has dramatically grown over the past few decades in the western world. As a result, numerous attempts at neuroprotective treatments have been undertaken or are currently being made. Ageing is accelerated by a number of co-factors, which are related to the beginning of PD and AD [4 - 6]. As an illustration, the metabolic syndrome (MetS), which can bestudied further, also encompasses neurodegenerative conditions that are considered by the loss of neurons and the formation of amyloid beta. One of the key diseases in the setting of MetS is obesity, a prevalent inflammatory condition that has been demonstrated to harm the cardiovascular system and neurological system (neurodegeneration) (atherosclerosis and myocardial infarction) 2012 [7]. Traditional cytokines such as tumor necrosis factor (TNF), IL-6, interleukin (IL)-1, and monocyte chemoattractant protein-1 are released by immune cells or adipocytes in obese people [8]. In addition to boosting innate immunity and directing the adaptive immune response toward the T helper cell (h), one route of inflammation, two so-called adipokines produced by adipocytes, visfatin and leptin, assist in maintaining the inflammatory state [9]. The primary pathways are involved in the immunopathogenesis of NDD. We addressed every theory and hypothesis on the

pathophysiology of neurodegenerative illnesses that has been put out in this review.

Worldwide Data of AD

The World Health Organization estimates that 35.6 million people worldwide suffer from Alzheimer's disease. By 2030, data could increase to 65.6 million [10]. In India, 1.8 million people had dementia in 2005, and that number is likely to rise to 8 million in the following 30 years. Because the population in countries like the United States is getting older, the number of Alzheimer's sufferers will grow in the coming years [11]. According to an age-related factor, dementia and Alzheimer's disease affect 3% of those aged 65 and older, 17% of those aged 75 to 84, and 32% of those aged 85 and older. In the United States, AD and dementia will affect 5.8 million people by 2020. By 2025, there will be 7.1 million additional Alzheimer's patients in the US [12].

Pathophysiology of Immunopathogenic Neurodegenerative Disease Hypotheses

The majority of the newly hypothesized pathogenic pathways are based on the amyloid cascade theory and the tau hyperphosphorylation theory. Inflammation, oxidative stress, amyloid (A), Tau, cholinergic neuron damage, and other factors are all proposed for Alzheimer's disease, which can be characterized by changes in the ventricular regions of the brain (Fig. **1**). Numerous efforts to develop anti-NDD and AD drugs have been made on the basis of these thoughts. Here are a few theories about how immunopathogenesis occurs.

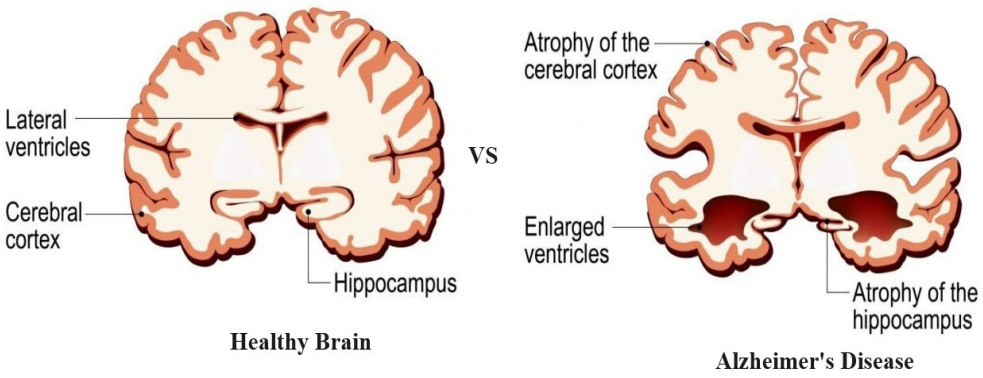

Fig. (1). Anatomical difference between Healthy brain V/S Alzheimer's brain.

CHAPTER 4

Immunobiology and Immunotherapies in Huntington's Disease

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Abstract: Huntington's disease (HD) is a progressive neurodegenerative complication of the brain that causes uncontrolled choreatic movements, memory loss, abnormal motor function, emotional changes, and a decline in cognition as well as an inability to perform daily routine tasks. The development of advanced techniques, including genetics, molecular biology, and genetic engineering, is beginning to discover an anomalous role of immune modulatory molecules in HD onset and pathophysiological complications. However, the role of immunoregulatory molecules, which are the key chemical messengers that mediate intracellular communication to regulate cellular and nuclear functions in HD pathogenesis, is still being unexplored. Here we present recent immunological association studies on HD and emerging mechanisms for the immunotherapies implicated in HD pathogenesis. The implications of immunotherapies are very critical under both healthy and HD disease conditions. Recently, research work has established new functional aspects of their pathways. Moreover, we propose future directions for immune-related research in HD pathogenesis and potential therapeutic approaches for immune-related therapies.

Keywords: Combination therapy, Huntington's disease, Immunotherapy, Immunomodulatory drugs, Neurodegeneration.

INTRODUCTION

Huntington's disease (HD) is a progressive neurodegenerative complication of the central nervous system (CNS) marked with indecisive choreatic movements, behavioral and psychiatric disturbances, emotional and behavioral changes, along with the deterioration of cognition. Further, HD is an autosomal dominant inherited disease that transfers the mutated genes to offspring, and many individuals are born with the defective gene that favors HD. Unfortunately, the initial signs and symptoms of HD generally do not show up straight away. In this

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connection, a line of research reports indicates that juvenile HD is enormously rare, and the majority of subjects start showing signs and symptoms of HD between the ages of 30 and 50 and gradually, the disease progresses differently depending on the pathophysiological conditions of the patient with time. Based on the disease progression rate, HD complications could eventually cause many deleterious physiological difficulties and make life worse over time. Specifically, subjects with HD suffer from weak muscles, chorea, or jerky muscular movements, difficulty swallowing, speaking abnormalities, irregular saccadic eye movements, insomnia, narcolepsy, depression, and difficulties with self-control.

Many studies have reported that HD develops from unusual gene patterns in the DNA, specifically by a genetic mutation in the cytosine-adenine-guanine (CAG) trinucleotide repeat expansion on the short arm of chromosome 4p16.3 in the huntingtin gene (HTT), that extends the polyglutamine tract at the huntingtin protein's N-terminus, encoding an elongated polyglutamine tract within the N-terminal of the huntingtin protein (Htt). Basically, the HTT gene has 10 to 35 repetitions in the DNA segment; however, in subjects with HD, it contains 36 to 120 repetitions. Further, if an individual retains between 30 and 36 repetitions of HTT, they could be asymptomatic. Since the individual has observed more than 40 HTT repetitions, it is quite likely that they will get HD [1]. More importantly, those subjects who carry the HTT gene, subsequently suffer from HD, while the gene's sequence mutates, the Htt protein misfolds, the abnormal protein aggregates in the brain tissues, and HD symptoms gradually manifest.

IMMUNE SYSTEM AND BRAIN

In the past decade, researchers have reported that the job of protecting the brain is not as simple and thought to be an immunologically restricted organ with an inability to generate humoral as well as cellular immune responses. However, it is interesting to note that the brain and immune system are tightly intertwined, and its protection measures possess gateways and gaps, and its confined borders are booming with an active resident of immune cells, known as microglia. In a normal, healthy brain, the resident macrophages in the CNS, known as microglial cells, are at a dormant stage. Activation of microglial cells increases the expression of their cell surface antigens and triggers the release of proinflammatory mediators like IL-6, IL-12, and TNF-α [2]. A crucial aspect of secretions of these proinflammatory mediators causes interaction between the nearby microglial cells, astrocyte cells, T cells, neuron cells, and myeloid progenitor cells [3].

Immune System and HD brain

The immune response in brain tissues can be triggered by the existence of any pathological lesion within the brain caused by either internal or external factors. Abnormal immune responses to the aberrant protein folding as well as aggregates in neuronal compartments promote neuroinflammation, and are present in the majority of neurodegenerative disorders, including HD, and lead to neuronal degeneration. Moreover, the mHtt clumps are observed in HD subjects, which are coherent with some other neurodegenerative disorders. Neostriatal atrophy is a prominent characteristic in HD brains that indicates severe neurodegeneration in the neostriatum, notably in the putamen and caudate. However, protein aggregation in the brain tissues triggers apoptosis, which damages neurons, and subsequently, the production of apoptotic bodies can trigger microglia activation in the CNS innate immune system. The fact that the carriers of the gene do not show the typical signs and symptoms of typical HD subjects offers vital hints to the evolution and consequences of HD in this correlation, where the progression of HD is yet unknown. These facts, however, also reveal that mHtt protein aggregation provokes activated microglia to accumulate in the striatum, leading to early neuronal dysfunction, significantly increasing pathogenic extra synaptic N-methyl-D-aspartate receptor (NMDAR) signalling, decreased synaptic connectivity, and a loss of brain-derived neurotrophic factor [4].

Mechanisms of Neurodegeneration in HD

Over the past two decades, several *in vitro*, *in vivo*, and postmortem studies have been carried out to comprehend the processes by which the mHTT gene exerts its adverse effects on HD subject's brain tissue. The deleterious pathological processes in the HD brain include but are not restricted to, NMDAR-mediated excitotoxicity, dopaminergic-based dysfunction, mitochondrial dysfunction, oxidative-nitrosative stress, dysregulated autophagy, abnormal protein aggregates, disruption of gene transcription, and also the loss of trophic support. Recent advances in genetic, biochemical, molecular, histopathological, and mechanistic evidence showed immune pathway dysregulation in HD pathogenesis, with alterations in cytokine signalling, immune cell proliferation/migration, changed phagocytosis, and reactive gliosis as common characteristics of HD. Moreover, studies have reported that the pathological signature of HD proteinopathies is chronic immune activation, encompassing innate and adaptive immune responses Fig. (**1**) [5]. Over the past decade, studies have reported a significant connection between pathogenic misfolded protein aggregation and immune activation in the HD brain. Peripheral immune cells as well as brain-resident cells both have high levels of mHTT gene expression, which caused inflammatory mediators' stimulation for these cells [6]. The secretion of proinflammatory cytokines,

CHAPTER 5

Introduction to Gut Microbiota and their Effects on Various Brain Disorders

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Abstract: Human gut microbiota (GM) research has emerged as one of the most promising fields in recent years. Moreover, a major area of interest is the connection between GM and several human disorders. Numerous recent studies have demonstrated the vital roles that the gut microbiome plays in human physiology and pathology. Additionally, microbiome-based medicines have been used to cure illnesses. In biomedical research, aging and neurodegenerative conditions such as Alzheimer's and Parkinson's disease have also attracted a lot of attention. To explore the potential pathogenic or therapeutic impacts of GM in diseases, several researchers have examined the connections between these factors. Numerous biologically active chemicals produced by microbiota have an impact on neurochemistry *via* neuroendocrine, immunological, and metabolic pathways. Gastrointestinal functional disturbances can manifest well in advance of the onset of neurodegenerative disorders. Furthermore, recent advancements in both preclinical and clinical research have indicated that the composition of the GM assumes a significant role in governing the dynamic interplay between the gut-brain axis, potentially bearing relevance to the etiology of neurodegenerative maladies. This chapter focuses on the relationship between the microbiota and neurodegeneration, as well as the pertinent mechanisms, present applications, and potential future prospects for microbiome-based therapy.

Keywords: Amyotrophic Lateral Sclerosis, Alzheimer's, Huntington’s Disease, Intestinal Microbiome, Microbiota, Neurodegeneration, Parkinson's.

INTRODUCTION

The word “microbiota” refers to the symbiotic bacteria, archaea, fungi, protozoa, and viruses that coexist with humans and populate their bodies. These structured communities of microbes live in our digestive, respiratory, urogenital, skin, and oral systems. The GM contains roughly 1000 different species of bacteria, 99% of

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which are exclusively anaerobic. It is the most densely populated microbiome. A wide range of metabolic processes and activities, including antimicrobial defense, immunomodulation, control of the host epigenetic machinery, and food and drug metabolism, are covered by integrated microbiome products [1, 2]. The GM might be thought of as an additional organ as a result of all these abilities. There are hundreds of commensal species in the oral cavity, the majority of which are facultative anaerobes or aerobes. This makes the oral cavity's microbiota the second most diverse microbial community in the body which plays a significant role in shielding the body from the spread of microorganisms that cause illness [3]. In the realm of scientific inquiry, several factors, such as the administration of drugs like antibiotics, dietary patterns, living conditions, and chronological age, stand out as noteworthy variables capable of exerting influence over the equilibrium of the microbiota. Initially considered devoid of microbial presence at birth, the human gastrointestinal tract and oral cavity rapidly undergo colonization by bacteria, culminating in the attainment of an "adult-like" microbial composition at approximately one year of age. Subsequently, throughout the period of adulthood, both microbiotas demonstrate a relatively stable configuration. Nevertheless, advancing age introduces discernible alterations in these microbial communities, manifesting as an augmented prevalence of *Lactobacilli, Staphylococci,* and yeasts within the oral cavity, whereas a reduced prevalence of *Firmicutes, Bifidobacteria,* and *Bacteroidetes* within the gut [4, 5].

The microbiome affects the brain through various pathways. The gut-brain axis, which largely consists of neuroendocrine, neuronal, endocrine, and immunological signaling pathways, is a two-way functional communication network between the brain and the intestine. Through these routes, the metabolites of the GM, including short-chain fatty acids, gamma-aminobutyric acid (GABA), serotonin, kynurenines, norepinephrine, and histamine, among others, control a number of cerebral physiological functions. In response to signals from the dysbiosis of the intestinal microbiome, the brain experiences low-grade inflammation, increased oxidative stress, disturbed energy metabolism, and accelerated cellular senescence, which all contribute to the degenerative processes of neurodegeneration as shown in Fig. (**1**) [6 - 8]. The vagus nerve, which connects the central nervous system (CNS) and the enteric nervous system directly, is an example of a well-studied method [9]. Additionally, bacteria affect the immune system's growth and control, which may change how the immune and CNS systems interact. Additionally, bacteria release metabolites and neuroactive chemicals that could travel through the bloodstream to the brain. Short-chain fatty acids, such as butyrate, which are fermentation products obtained from the diet and important for microglia homeostasis, serve as an illustration of this. Furthermore, the microbiota produces and secretes substances (such as neurotoxins, neurotransmitters, lipopolysaccharides, and amyloids) that can harm

the CNS's neurochemistry, causing amyloidosis, synucleinopathies, and tauopathies, which in turn aid in the onset and/or progression of neurodegenerative diseases [10]. The quality of life of patients with neurodegenerative disorders can be significantly improved by early diagnosis, monitoring, and treatment of unpleasant gastrointestinal symptoms, including normalization of the microbiota [11, 12].

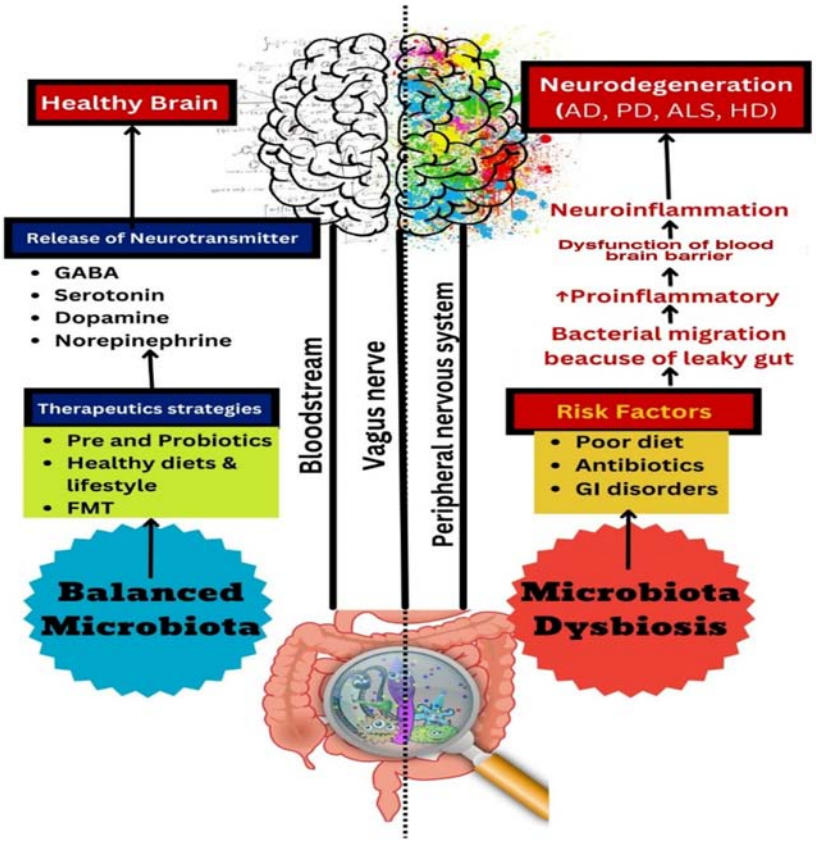

Fig. (1). Role of microbiota in pathogenesis of neurodegeneration.

Currently, research is being conducted on the use of probiotics and dietary supplements for the prevention and potential therapy of CNS diseases that can restore normal neuroendocrine, neuroimmune, and humoral systems [13]. The impact of probiotic microorganisms is extremely varied and can take the form of any or all of the following: probiotics positively modulate immunity to infectious diseases; they are involved in the synthesis of several essential vitamins, particularly vitamins B and K; synthesize significant metabolites for the host

CHAPTER 6

Interplay Between Gut-microbiota and Neurodegeneration

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Abstract: Introduction: The body of scientific evidence linking the microbiome to many diseases has grown dramatically over the past several years; neurological diseases have also shown a similar tendency. As a result, the gut-brain axis theory as well as the notion that there could be a connection between the gut microbiome and several CNS-related disorders whose pathophysiology is still not known have both emerged.

Development: We look at the role played by gut microbiomes in the gut-brain axis as well as the neurological conditions neuromyelitis optica, Alzheimer's, amyotrophic lateral sclerosis, Parkinson's, and multiple sclerosis, where changes in the gut microbiota have been linked to human studies.

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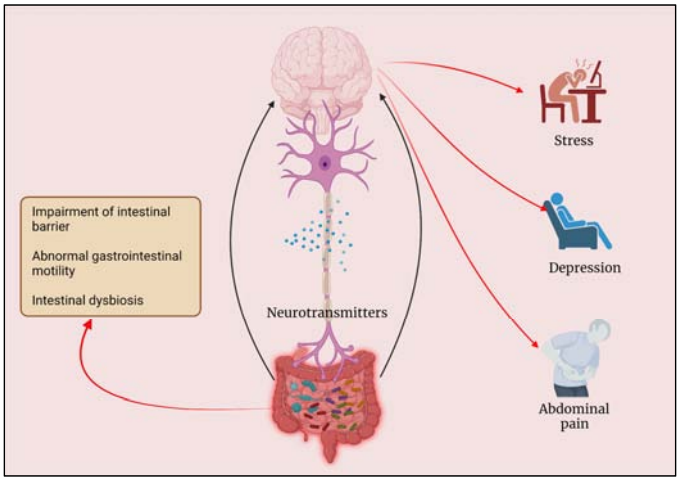
Conclusions: The amount of data connecting gut microbiota to different neurological illnesses has significantly increased. Today, there is no longer any doubt that the gut microbiota of the host influences brain function. This review assembles a sizable body of credible research that is essential in emphasizing the crucial role of microbiota colonization in neurodevelopment and how changes in microbiota dynamics might have an age-dependent effect on brain function.



Keywords: Gut microbiota, Neurodegenerative disorders, Oxidative stress.

INTRODUCTION

The gut-brain axis (GBA) is an extensive network of interactions between the brain and the gut microbiome. The maintenance of the body's overall homeostasis depends on the GBA, which includes multiple biological systems [1]. Signals are sent from the stomach to the central nervous system (CNS) and vice versa *via* either direct channels involving the autonomic nervous system or indirect pathways utilizing metabolites and chemical transmitters [2]. The makeup of the gut microbiota can affect each of these interactions, which can change. In recent times, the GBA has gathered attention because of its newly discovered potential in regulating health and related diseases as well as its key potential value as a therapeutic target. The gut microbiota has an impact on a variety of elements of brain function and development, including permeability, myelination, neurogenesis, and blood-brain barrier (BBB) formation [3 - 5]. The pathogenesis of several brain disorders, including neurodegenerative diseases (ND), may involve GBA disruption [6, 7]. The possibility that the gut microbiota has a role in the progression of inflammation and degeneration in the central nervous system, but still the subject of much discussion. In this review, a summary of the available research on the function that the gut microbiota plays in neurodegenerative

diseases is provided, with a particular focus on the current and prospective GBA-targeting therapy approaches. However, with the increase in people's age, the prevalence of NDs rises, placing a heavier cost on society [8, 9]. Unfortunately, despite numerous current clinical trials, there is no effective treatment for these disorders due to their uncertain origin and the intricacy of the nervous system. The gut contains a variety of microbes known as the gut microbiota, which are found in numerous ecological niches and include archaea, viruses, bacteria, and different eukaryotic species including fungi and protozoa [10]. Numerous aspects of the host's physiology, such as nutrient metabolism, infection prevention, the immune system, and neuron growth are significantly affected by the gut microbiome [11]. The gut microbiota is adapting to a new environment as a result of industrial growth, urbanization, and advancements in food and medical technologies [12]. Given that it plays a crucial role in NDs and in regulating the central nervous system's tissue-resident immune cells' development, proliferation, maturation, and activation, the significance of gut microbiota has recently come to light [13]. Through the use of neurotransmitters and other metabolites, the gut-brain axis contributes to the bidirectional [14, 15] link between the gut microbiome and the brain [16, 17]. We list the potential pathogenic functions of the microbiota in NDs in this review.

GUT MICROBIOTA

The host and the diverse, dynamic bacteria that make up the gut microbiota form a symbiotic connection. The metabolic interactions and activities of the gut microbiomes affect normal physiology and the host's susceptibility to diseases [18]. Individual differences and diversity at the bacterial strain level are caused by variations in gut pH, immunological factors, and digesting enzymes [19]. Additionally, each person is home to a unique microbial community that contributes to the establishment of a durable and stable condition. In the mucosa of an adult gut, Bacteroidetes and Firmicutes prevail in terms of number over Actinobacteria, Proteobacteria, and Verrucomicrobia [20, 21]. By secreting microbial substances including lipids, vitamins, and vital amino acids, the gut microbiota has the potential to have a direct impact on human health [22]. These variables may influence the gut-microbiota *via* neuronal, endocrine, and immunological signaling pathways, which may then affect physiological processes such as the development of the neurological system as we age and the function of the GIT (gastrointestinal tract) [23, 24].

Gut Microbiota and Neurodegenerative Disease: A Correlation

The gut microbiome is thought to be crucial for controlling human behavior, myelination, neurogenesis, and activation of microglial cells in the brain, as well

CHAPTER 7

Epigenetic Regulation of Microglia: Plausible Mechanism and Interventional Approaches in Neurodegeneration

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Abstract: Microglia, the brain resident macrophages perform a wide range of functions ranging from brain development, equilibrium, maintenance in the brain microenvironment, injury repair and the preservation of neuronal networks. Cellular elasticity is a prerequisite for the multi-dimensional tasks performed by microglia. Epigenetic modulations are critically involved in altering gene expression finely coordinating with the phenotypic plasticity in microglia. Any change in its tuning favors the inflammatory state of the brain, which leads to detrimental effects on the nervous system. The present review offers an insightful exploration into the origin of microglia, shedding light on its vital functions and the intricate mechanisms that govern the epigenetic modification of microglia in neurodegenerative disorders. Furthermore, it explores potential avenues for mitigating these diseases.

Keywords: Histone acetylation, Histone methylation, Microglia, Neurodegenerative disorders.

INTRODUCTION

Neuroinflammation stands as a central feature in the landscape of neurodegenerative diseases, with its roots traced back to a cast of inflammatory actors including cytokines, chemokines, reactive oxygen species, and other messengers of inflammation. This ensemble of troublemakers is predominantly dispatched into action by the brain's immune sentinels, microglial cells, and astrocytes. When these resident cells engage with pro-inflammatory agents and cytokines like TNF-alpha, IFNγ, IL1, and IL-6, a symphony of responses is set in motion [1].

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Microglial cells, armed with Pattern Recognition Receptors, form ligand-receptor complexes that trigger a cascade of signals, ultimately leading to the production of neurotoxic substances that pave the way for neurodegenerative disorders. The relentless bombardment of these stimuli instigates both physical and functional transformations in microglia, further fuelling the flames of neurodegeneration. These microglial cells, functioning as the brain's resident macrophages, possess a repertoire of genes responsible for maintaining the brain's well-being and safeguarding against threats. Any external stimulus that disrupts their housekeeping and protective functions throws them into disarray, setting the stage for neuroinflammation. Fortunately, immune checkpoints like Trem2, chemokine CX3CR1, and the progranulin pathways regulate this neuroinflammation and manage scavenger receptor pathways. However, interference with these regulatory mechanisms can tip the balance, resulting in microglial dysfunction and neuronal harm [2].

The cascade of these events eventually leads to the progression of debilitating diseases such as Parkinson's disease, presenile dementia, prion disease, amyotrophic lateral sclerosis, dementia, autism spectrum disorder, Huntington's disease, and chronic traumatic encephalopathy. Consequently, curbing inflammatory responses by maintaining regulatory control over microglial activation or inducing a switch in their phenotype emerges as a promising avenue for identifying therapeutic targets and designing interventions against neurodegenerative diseases.

Furthermore, the interplay between epigenetic alterations and a broad spectrum of ailments, including neurodegenerative disorders, cancers, and autoimmune conditions, has been extensively documented. Research spanning the past two decades has shed light on the critical role of epigenetic modifications in shaping the physiological and phenotypic behaviours of microglia. This knowledge underscores the potential for manipulating epigenetic changes to develop effective preventive and therapeutic approaches against these diseases. Consequently, this chapter aims to delve into the origin and functions of microglia while unravelling the intricate mechanisms behind epigenetic modifications, offering valuable insights for future research and therapeutic interventions.

Origin of Microglia

Microglial cells, approximately 10-15% of the cells in the central nervous system (CNS), play a crucial role as mononuclear phagocytic cells [3]. They contribute to neuronal circuits during development and a state of equilibrium in the brain. Recent fate-mapping studies have illuminated the origin of microglia, suggesting

that they originate from progenitor cells possessing erythromyeloid characteristics within the yolk sac. These cells then migrate to the brain around embryonic days 9.5 to 10.5 [4]. Despite these insights, the exact origin of microglia continues to be a subject of exploration. Pioneering research conducted by Cuadros *et al*. in 1993, which involved experiments on chick embryos, initially proposed that microglial cells derive from the embryonic yolk sac [5]. In a quest to examine the necessity of a blood supply for the infiltration of primordial myeloid cells during development, a research group conducted experiments involving the fusion of chick embryos with quail yolk sacs. Remarkably, their findings provided evidence suggesting that blood supply may not be indispensable for the invasion of these cells. Furthermore, in 1999, Alliot *et al*. bolstered this hypothesis by demonstrating the presence of microglia precursors in the yolk sac [6]. Nevertheless, while these discoveries yielded valuable insights into the temporal and spatial distribution of microglia cells during embryonic development, they fell short of definitively resolving the issue of microglial origin.

Moreover, some researchers have suggested that the precursors of microglia originate from the neuroectoderm and/or mesoderm present in the developing brain [7]. The majority (approximately 95%) of microglial cell formation occurs after the development of the blood-brain barrier. The microglial population in the brain is maintained through the local proliferation of progenitor cells. Another hypothesis proposes that bone marrow stem cells (BMSC) present in the bloodstream infiltrate the brain and differentiate into microglial cells [7]. Additionally, a different group of researchers have observed that during injury, monocyte cells of bone marrow origin are predominantly found in the brain [8].

Definitive evidence regarding the origin of microglia from the embryonic yolk sac has been established through the research conducted by Ganzhou *et al*. [9]. They employed a meticulous approach, crossing ROSA26 floxed reporter mice with tamoxifen-inducible Cre recombinase-expressing mice under the control of the yolk sac-specific Runx1 promoter (Runt-related transcription factor 1).

Activating the Runx1-driven Cre recombinase at various stages of embryonic development through tamoxifen induction led the researchers to trace the fate of cells derived from the yolk sac. The findings conclusively demonstrated that microglial progenitor cells originate from the yolk sac and subsequently migrate into the brain through the bloodstream.

A separate study conducted by Schulz *et al*. in 2012, provided further affirmation of microglial derivation from the yolk sac. The research group reported that the transcription factor MYB which plays a key role in haematopoiesis, is not essen-

CHAPTER 8

Epigenetics as Diagnostic and Therapeutic Tool in Neurodegenerative Disorders

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Abstract: Epigenetics is a field that is concerned with the investigation of heritable modifications in gene expression that transpire without DNA sequence alterations, thereby establishing a connection between the genome and its surroundings. Epigenetics simply analyzes gene expression amendment beyond variation to the DNA sequence. The gradual accumulation of epigenetic changes over the course of an individual's life span may contribute to neurodegeneration. This chapter deals with epigenetic alteration, which affects the progress of neurodegeneration with age. Epigenetic regulation, encompassing DNA methylation and histone modification, has been implicated in the anomalous alterations in gene expression that occur during the progression of neurodegeneration. The concept of epigenetics is useful to synthesize novel medications to target these disorders. In recent times, a plethora of epigenetics-based medications have been developed for the treatment of neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's. Due to a major lack of early screening processes that allow therapeutic agents to be distributed to afflicted neurons paramount to cell death, many neurological conditions have severely restricted options for treatment. Significant progress has been seen in neurodegenerative disease biomarkers. These biomarkers have been unfortunate, due to substantial disparities amidst the tissues acclimated to source biomarkers and biomarkers of disease. Neurodegeneration may be exacerbated by epigenetic changes that develop gradually. Epigenetic biomarkers could aid in the diagnosis, and monitoring, of neurodegenerative diseases.

Keywords: Diagnosis, Epigenetics, Neurodegenerative disorders, Treatment.

INTRODUCTION

Neurodegenerative disorders pose an enormous challenge and represent some of the most severe health problems that societies will face around the world. These are progressive and incurable conditions, which arise from the continuous degene-

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ration and death of nerve cells. A majority of these disorders become more prevalent with age, such as Alzheimer's and Parkinson's disease. The burden of these diseases is increasing at an alarming, with incalculable costs both in terms of human and economic resources. According to a comprehensive study by the World Health Organization, the World Bank, and the Harvard School of Public Health (the Global Burden of Disease Study), neurodegenerative diseases such as dementia rank eighth in terms of disease burden in developed regions in 2030. Neurodegenerative diseases are anticipated to become the second most prevalent cause of mortality across the globe by the year 2030, surpassing cancer. It is important to emphasize that these predictions are not definite, however, the amalgamation of these projections with the present situation undeniably confirms that the public apprehension regarding neurodegenerative disorders is escalating [1].

Neurodegenerative disorders have both genetic and environmental factors. The largest proportion arises due to the complex interplay between these factors. As a result, it is difficult to delineate specific risk factors, useful biomarkers, potential new therapeutic targets and agents, and even a definite diagnosis. The pathological characteristics of the brain during the process of neurodegeneration exhibit significant overlap among different types of neurodegenerative cognitive and motor impairment, adding to the complexity of diagnosis and treatment. The correlation between pathological findings and clinical findings is not always straightforward. Extensive neuropathology does not necessarily indicate severely impaired neurological function, nor does minor pathology necessarily mean only mild neurological function impairment. The reason for this is that neuropathological processes may not be the cause of the underlying disease at early stages, but may simply be a reflection of fundamental disease processes that are yet to be understood in most neurodegenerative disorders. However, as the disease progresses, neuropathological changes are likely to contribute to disease progression in a positive feedback loop [2].

Currently, a clear diagnostic test that can identify the presence, or absence of a neurodegenerative disease does not exist. The diagnosis of an individual is dependent on the clinical evaluation of their symptoms and specific neuroimaging characteristics, a process that can take numerous years to complete. However, there are certain exceptions to this, such as monogenic diseases like Huntington's disease (HD), where the diagnosis can be confirmed through a specific genetic test. Thus, the development of an accurate diagnostic test for neurodegenerative diseases is a pressing need in the field of medicine.

Neurodegenerative diseases have complex underlying mechanisms that are not yet fully understood. A significant number of these diseases are characterized by the

aggregation of intracellular proteins, but it is unknown whether this is a primary mechanism or a consequence of another disturbed cell function. The potential mechanisms of neurodegeneration are numerous and varied, including primary effects of protein homeostasis, disrupted protein degradation, gene expression, transcriptional regulation, and mitochondrial dysfunction. Consequently, there is an urgent need to further explore the pathophysiology of these diseases to improve early diagnosis and develop disease-modifying treatments that can reduce their impact on patients' lives [2].

EARLY DIAGNOSIS AND TREATMENT

The schedule of administering drugs governs the therapeutic effectiveness in neurodegenerative diseases. Folate optimizes cognitive problems in people with moderate Alzheimer's disease [3], but not in people with severe Alzheimer's disease [4]. Recognizing the importance of prompt medical approaches, early diagnosis of neurodegenerative diseases could significantly improve drug efficacy. Thus, early symptoms of neurodegenerative disorders, nascent disease-associated neural features, are therefore examined with great attention [5].

Neurons in early-stage Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, and dendrite anomalies triggered by the disease can be linked to structural changes in the dendritic cytoskeleton [6, 7]. Impeded axonal transport has been seen in Alzheimer's disease in fruit flies [8], mice [9, 10], fruit fly model [11, 12], and squid [13].

A significant proportion of neurological diseases are linked to mitochondrial dysfunctions such as respiratory, trafficking, inter-organelle communication, and quality control issues [14]. A broad range of anomalous neural features observed in neurodegenerative disorders imply that unusual changes in cell functions eventuate all through the framework [15]. More pertinently, even though they appear early, these system-wide atypical alterations have the potential to be utilized as initial neurodegenerative disease markers.

NEURODEGENERATIVE DISORDERS AND EPIGENETIC ALTERATION

One probable explanation for such change is epigenetic alteration. Epigenetic modification, characterised by modifications in the gene expression that eventuate unvarying changes in the intrinsic nucleotide sequence [16], has been linked to neurodegenerative disorders. Drugs that reinstate neuropathological disease-associated epigenetic modifications have been evinced in Alzheimer’s disease (AD) [17], Parkinson's disease (PD) [18], and Huntington's disease (HD) models to reduce disease toxicity [19, 20]. Recently, significant efforts have been made

CHAPTER 9

Current Therapeutic Options and Repurposed Drugs for Neurodegeneration

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Abstract: Neurodegenerative diseases are a vast collection of neurological disorders with various clinical and pathological manifestations that impact particular subsets of neurons in distinct functional anatomic systems; they begin for unexplained reasons and advance inexorably. Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Huntington's disease, Friedreich ataxia, and Spinal muscular atrophy are the major neurodegenerative diseases. The prevalence and incidence of these diseases rise dramatically with age; thus, the number of cases is expected to increase for the foreseeable future as life spans in many countries continue to increase. Although there are several medicines currently approved for managing neurodegenerative disorders, a large majority of them only help with associated symptoms. The limitations of pharmacotherapy in these disorders have led to an urgent shift towards the development of novel compounds, interventions, and methods that target shared features across the spectrum of neurodegenerative diseases. Drug repurposing is a novel strategy where existing drugs that have already been approved as safe in patients for the management of certain diseases are redeployed to treat other, unindicated diseases. In this chapter, we have covered the current therapeutic options and drugs that can be repurposed or have the potential to be repurposed for the management of various neurodegenerative diseases.

Keywords: Amyotrophic lateral sclerosis, Friedreich ataxia, Huntington's disease, Spinal muscular atrophy.

INTRODUCTION

Neurodegenerative disease is a ubiquitous term encompassing a variety of conditions causing impairment and death of the neurons. These conditions are

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frequently persistent, and deadly and impact basic functionalities. Protein aggregation, a high load of reactive oxygen species, the subsequent accumulation of inflammatory processes and oxidative stress in the central nervous system (CNS), abnormal ubiquitination, neurotransmitter depletion, or insufficient biosynthesis are all important precipitating factors in neurodegenerative diseases. Whilst humungous research is aimed at finding the cure for these neurodegenerative diseases, there is a huge gap between the understanding of underlying molecular pathways involved in their pathophysiology and actual targets available for developing potential drug candidates against them. Pre-clinical and clinical studies of novel drugs for neurodegenerative diseases face major challenges such as inadequate disease characterization, unavailability of appropriate translational animal models, and reliable biological markers that could help in the realistic prediction of disease progression rate in single patients. Alzheimer's disease (AD), Parkinson's disease (PD), Friedreich ataxia (FA), Spinal muscular atrophy (SMA), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS) are some of those neurodegenerative disorders that still await the safer and effective therapies that will aim at removing the underlying cause and not just symptomatic relief with minimal adverse effects.

Drug Repurposing

The discovery of new drug molecules is time-consuming and costly with very low success rates. Drug repositioning which means finding new uses for known drugs, is one of the modern and most cost-effective approaches to drug development, with a history of current drug use [1]. Based on the data about the quantity and quality of the biological, pharmacological, toxicological, physicochemical, and pharmacokinetic properties of drug particles, the strategies employed in drug repurposing can be classified into three categories: target-oriented, drug-oriented, target-oriented, and disease/therapy-oriented [2]. Drug repositioning can be observed as a response to the elusive output of neurodegeneration drug discovery, as an arrangement to reduce the time development, and affordable therapy to gain the improved request and unfilled requisite of individuals suffering from neurodegeneration.

The preference and the main driver for the potential interest in drug repurposing over conventional drug discovery is a smaller number of new chemical entities that clear all phases of clinical trials, a huge number of unaddressed diseases, very high costs, and extended timelines involved in the research and development, increase in the regulatory demands, expiry of patents, and mounting competition of branded medicines with generics. Given this challenging scenario, drug repurposing is considered a propitious option to address these unmet needs. Over the last few decades, drug repurposing has evolved as a master plan to search for

newer uses for existing drugs not only by serendipity but by using more advanced and intricate computational tools. On-target and off-target approaches are mainly used in the pursuit of repositioning drugs.

ALZHEIMER'S DISEASE (AD)

AD is the leading prevalent factor of dementia among old age people. It is an age-related, incurable neurodegenerative, and progressive condition characterized by memory and cognitive deterioration [3]. The disorder frequently begins with the short-term loss of memory and continues to include language impairments, confusion, changes in mood, and behavioral concerns (sleep changes, agitation, psychosis). The disorder eventually leads to loss of physiological functions and, lastly, death [4]. Based on the core pathophysiology of AD, current research suggests that the primary histological lesions of AD are intra-cellular Tau neurofibrillary tangles and extracellular amyloid plaques. According to the "amyloid hypothesis," the brain's generation of amyloid-beta (Aβ) initiates a chain reaction that results in the clinical presentation of AD. The amyloid cascade, which causes neurotoxicity, is triggered by the production of amyloid oligomers [5]. There are presently no approved medicines that tackle the pathophysiology of AD directly. Existing therapies are symptomatic, aiming to improve cognitive function through two distinct mechanisms: agonism and antagonism of the cholinergic system and N-methyl-D-aspartate receptor (NMDA-receptor) [4].

There is a clear need for new drugs or therapies since the benefits provided by current treatments for AD are optimum (Fig. **1**). The current treatments for AD are only symptomatic which suffer from many limitations. The present treatments display dose-related side effects like diarrhea, vomiting, abdominal cramps, bradycardia, nausea, and higher syncope rates [6]. Disease management is expensive in low-income countries. Another challenge is getting the drug over the blood-brain barrier, which is now the only available treatment option [7]. Confusion, dizziness, and headache were the supreme adverse events in memantine trials [8].

This figure provides an overview of the multifaceted landscape of current drug treatments for AD. From acetylcholinesterase (AChE) inhibitors to NMDA receptor modulators and emerging experimental therapies. These approaches aimed at managing the complex symptoms and underlying pathology of AD, offering hope for improved cognitive function and quality of life for affected individuals.

SUBJECT INDEX

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"WISDOM IS NOT A PRODUCT OF SCHOOLING BUT THE LIFELONG ATTEMPT TO ACQUIRE IT "

Albert Einstein

Anuradha Mishra

Anuradha Mishra is presently working as professor & Director, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Lucknow. She has rich experience on pharmacological screening of drugs for various disorders like neurodegenerative, gastric ulcers, cancer, etc. She has 18 years of teaching and research experience. She has published 72 research papers in National and International journals. She has published 2 books with International Publishers. She has received research grants from CST-UP. She has published various book chapters including Springer publishers. Currently she is involved in targeting brain and neurological disorders and possible therapeutic or preventive approaches to reduce the disease advancement. She supervised 10 PhD and 20 PG scholars so far.

Preeti Bajpai

Preeti Bajpai is presently working as Associate Professor in the Department of Zoology, Mahatma Gandhi Central University, Motihari, Bihar. Dr. Bajpai is a goal-oriented professional with more than 20 years of spearheaded academic and research experience on immunological aspects of vector borne parasite diseases, metabolic and neurological disorders. Moreover her lab has been actively involved in designing novel immunomodulators of synthetic or natural origin drug and vaccine delivery nano vehicles as an ameliorative approach towards disease. Her research work has been acclaimed by DST, SERB and ICMR in the form of extramural grant of more than 2.5 crores. Dr. Bajpai has 70 research articles in International journals of high repute, 11 book chapters with International publishers and nine national and International awards to her credits. Furthermore, she has also supervised more than 15 PhD scholars and 100 post graduate dissertations. Her current research work spheres around the exploration of epigenetic factors regulating immunological pathways in neurodegenerative disorders.

Tarique Mahmood Ansari

Tarique Mahmood Ansari is a Professor in the Department of Pharmacy, Integral University, Lucknow having more than 15 years of Experience in Teaching, Research & Pharmaceutical Industry. His subject and field of technical / Research expertise are Pharmacological screening of herbal drugs & formulations, cardiovascular diseases, Dyslipidemia, Diabetes and Obesity and Advance cardiovascular pharmacology. He is Principal Investigator (PI) of an EMR project sanctioned by Ministry of AYUSH, Govt. of India. He Supervised around 50 M. Pharm. Dissertation work as Supervisor/ co-supervisor and 6 Ph.D. Research scholars and 8 Ph.D. Research scholars are enrolled. He has Published more than 100 Research/Review papers and more than 50 Abstracts in various International / National journals of high repute with a cumulative impact factor of more than 60. He has Participated in more than 70 International / National conferences as Delegate/ Key person/ Organizing Committee member. He has been Awarded by Many Government and Non-Government Bodies like Ministry of Ayush, Prisal Foundation, Apti, Ad Scientific Indexing, Benthem Science.