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Review Article

Systems Biology and Bioinformatics Approaches to Investigate Innate Dysregulation in Neurodegenerative Diseases

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ABSTRACT

In neurodegenerative diseases, activation of the innate immunity system plays an important pathogenicmechanism(3). The dysfunction of the nervous system leads to neurodegenerative disorders. Parkinson's disease (PD), motor neuron diseases (MND), multiple system atrophy (MSA), Alzheimer'sdisease (AD), and frontotemporal dementia (FTD) are amongst some most studied neurodegenerative disorders (NDDs). These disorders happen due to the progressive deterioration of neurons especiallypresent in the brain, which leads to a variety of symptoms, including cognitive failure, motorweakening, and deviations in behaviour. Recent experimental and clinical studies have shown that innate immune activation and neuroinflammation are significant hallmarks of neurodegenerativeprocesses which also contribute to the development of neurodegenerative disorders with itscharacterization. The multidisciplinary approach can be used to understand the complex relationshipbetween innate immunity and neurodegeneration. System biology and bioinformatics play a verycrucial role in understanding the connection between the nervous system and immunology, especially inthe case of neurodegenerative disorders. This interdisciplinary approach integrates computationalbiology, system biology, artificial intelligence, and machine learning to understand the disordermechanism, identifying biomarkers and potential treatment strategies for neurodegeneration. In thisreview article, we are going to overview the innate immune system and how its dysregulation plays acrucial role in neurodegenerative disorders. Also, the importance of system biology andbioinformaticsin Neuro-immunology.

KEYWORDS

• Innate immunity • Immune system • Neurodegenerative disorders • Neuro-immunology • Bioinformatics • System biology • Artificial intelligence and machine learning

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INTRODUCTION

Innate immunity is the first response of our body against harmful foreign substances. Certain cells in the immune system destroy foreign substances such as bacteria or viruses that try to enter the body. Innate immunity is a non-selective and non-specific defence system. It includes the physical barriers such as skin (epidermis and Dermis), mucous membranes found in respiratory, gastrointestinal and urogenital tracts, and Lacrimal secretions and chemical barriers like lysozyme, defensins, lactoferrin and Cathelicidins. Reflexes like coughing, sneezing and Peristalsis are also part of innate immunity system.(1) Innate immunity plays an important role in different disorders ranging from protecting the body against pathogens like SARS-CoV-2 and mycobacterium tuberculosis to contributing to disease progression by chronic inflammation such as in the case of Autoimmune diseases like rheumatoid arthritis[2]. In neurodegenerative diseases, activation of the innate immunity system plays an important pathogenic mechanism[3]. The dysfunction of the nervous system leads toneurodegenerative disorders. Parkinson's disease (PD), motor neuron diseases (MND), multiple systematrophy (MSA), Alzheimer's disease (AD), and frontotemporal dementia (FTD) are amongst some popular types of NDDs. These disorders happen due to the progressive deterioration of neurons especially presentin the brain, which leads to a variety of symptoms, including cognitive failure, motor weakening, and deviations in behaviour[4]. It affects more than 1.7% of the global population. The neurodegeneration is characterized by neuronal death, synaptic dysfunction and neuroinflammation. Recent experimental and clinical studies have shown that innate immune activation and neuroinflammation are significant hallmarks of neurodegenerative processes which also contribute to the development of neurodegenerative disorders with its characterization[5]. The neuronal damage is caused due to the overactivation of the microglial cells, the resident innate immune cells of the brain. The progression of the disease is sustained due to the release of pro-inflammatory cytokines like IL-1β and TNF-α[6].

System biology and bioinformatics play a very crucial role in understanding the connection between the nervous system and immunology, especially in the case of neurodegenerative disorders[7]. This interdisciplinary approach integrates computational biology, system biology, artificial intelligence, and machine learning to understand the disorder mechanism, identifying biomarkers and potential treatment strategies for neurodegeneration[8]. System biology plays a pivotal role in understanding immune-neural interactions. Microglial cells play their role in chronic inflammation commonly seen in Alzheimer's and Parkinson's disorders[9]. This microglial cell signaling pathways are mapped with the help of system biology. Microglial cells are the primary immune cells of the central nervous system (CNS) and are crucial for innate immune response. They act as a first-line defence in the case of neuroinflammation and microinjury.[10] These cells express TLRs (TLR2, TLR4 etc.) and they are involved in recognizing pathogen-associated molecular patterns (PAMPs)[11]. Computational tools also analyze cytokine networks and how they impact neurodegeneration. The network biology reveals that TNF-α, IL-1β and IFN-γ play ley role in neuroinflammation in neurodegenerative disorders[12]. Moreover, bioinformatics tools help in virtual screening and molecular docking of potential drug candidates that cause immune responses during neurodegeneration and prevent neuronal damage. Also, it helps in optimizing therapies for different neurodegenerative disorders that involve autoimmune neuroinflammation such as Alzheimer's, Parkinson's and Amyotrophic lateral sclerosis (ALS)[14]. In this review article, we are going to overview the innate immune system and how its dysregulation plays a crucial role in neurodegenerative disorders. Also, the importance of system biology and bioinformatics in Neuro-immunology[13].

Innate Immune Dysregulation in Neurodegenerative Disorders.

Innate immune dysregulation plays a crucial role in the pathogenesis of several neurodegenerative disorders such as Alzheimer's disorder (AD), Parkinson's Disorder (PD), and Multiple Sclerosis (MS). In Alzheimer's disorder, the dysregulation mechanism includes chronic microglial activation with impaired β-amyloid clearance and release of excessive cytokines[15]. IL-6, IL-1β, TNF-α and complement system are

mediators involved in it. The accumulation of β-amyloid and tau hyperphosphorylation can lead to memory decline and eventually permanent memory loss[16]. In Parkinson's, there is a microglial activation trigger due to aggregation of α-Synuclein. Inflammasome, NLRP3, IL-6 and TNF-α are the mediators involved in the progression of disorders[17]. This eventually leads to the degeneration of dopaminergic neurons in the substantia nigra and motor impairment[18]. In the case of Multiple Sclerosis, there is dysregulation in the infiltration of peripheral immune cells and breakdown of the Blood-brain barrier which leads to chronic inflammation. The mediators of multiple sclerosis are macrophages, TLRs, IL-1β, and IFN-γ. This can eventually lead to demyelination, neurodegeneration, axonal loss and deficit of motor.[19] In Amyotrophic Lateral Sclerosis (ALS) there is excitotoxicity of excessive glutamate, dysregulation of astrocytes and microglia and oxidative stress and the mediator molecules include the IL-6, TLR4, TNF-α and mutations of SOD1. In this disorder, there is degeneration of motor neurons and paralysis with respiratory failure in extreme cases[20]. Huntington's disease (HD) can lead to an overactive innate immune response caused by the mutant Huntington gene (mHTT) which causes an increase in inflammatory cytokines. Complement cascades are potent mediators with IL-6, TNF-α and activation of NF-κB. Neuronal apoptosis and cognitive decline with mitochondrial dysfunctions are the consequences of Huntington's disease[21].

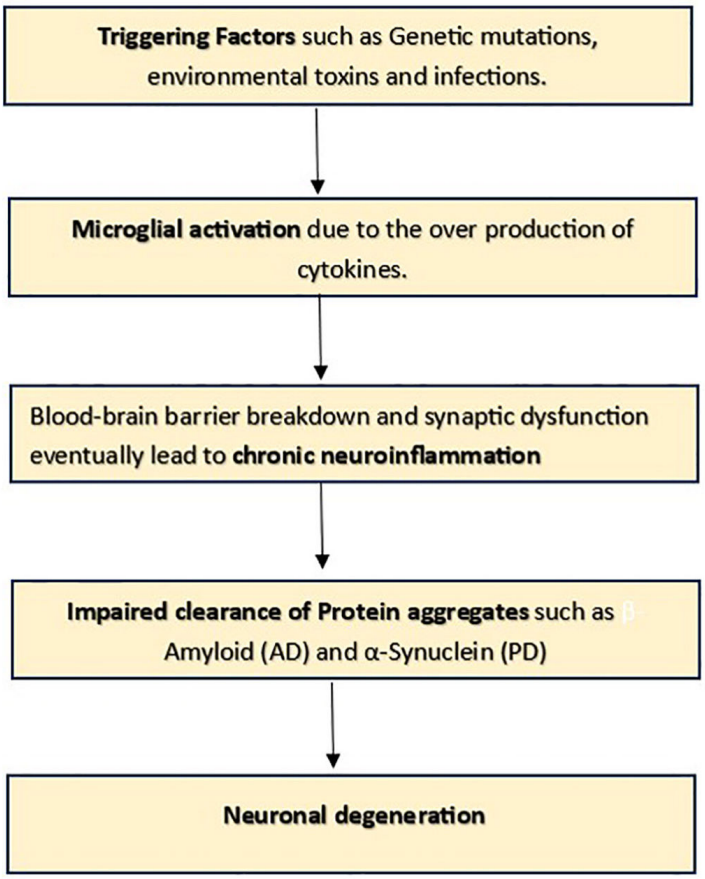


Figure 1: The flowchart of innate immune dysregulation in Neurodegenerative disorders

The dysregulation of the innate immune system in Neurodegenerative disorders begins with the trigger of factors such as ageing, infections, genetic mutations and environmental factors. This can trigger activation of Microglial leading to overproduction of cytokines which eventually causes Blood-Brain Barrier breakdown responsible for chronic neuroinflammation. Then there is impaired clearance of protein aggregates like β-Amyloid (AD) andα-Synuclein (PD). This causes Neuronal degeneration signified by motor impairment and cognitive decline[22].

System Biology Approach to study Innate Immune Dysregulation in Neurodegenerative Disorders

In recent studies, it has been found that the integrative system biology approach can be utilized to understand the mechanism of the disorders and identify Hub genes and potent biomarkers of complex immune dysregulation in neurodegenerative disorders. This can also help to develop target therapies for neurodegeneration. System biology combines multi-omics data such as genomics, proteomics, transcriptomics and metabolomics with computational biology to identify potent interactions between neurodegeneration and the innate immune system[23].

Multi-Omics Integration

Genomics and Epigenomics studies involve the identification of mutations in key genes, such as LRRK2 in Parkinson's and TREM2 in Alzheimer's, which affect the innate immune system. Transcriptomics and proteomics help identify the differentially expressed proteins and genes involved in neuroinflammation. Metabolomics can track the metabolic changes during the activation of chronic immunity.[24]

Computational Network Modeling

Protein-protein networks can be used to analyze the molecular interactions among the mediators, cytokines, neuronal aggregates and microglial proteins. Furthermore, AI-ML (Artificial intelligence and Machine learning) can be used to predict the progression of disease and potential drug targets using large datasets.[25]

Discovery of Biomarkers and Drug Target Identification

The early detection biomarkers related to immune dysregulation can be identified using the analysis of differential gene expression. Neuroprotective compounds can be found using molecular docking and Virtual screening of potential drugs against the targets involved in immune pathways of neuronal degeneration.[26]

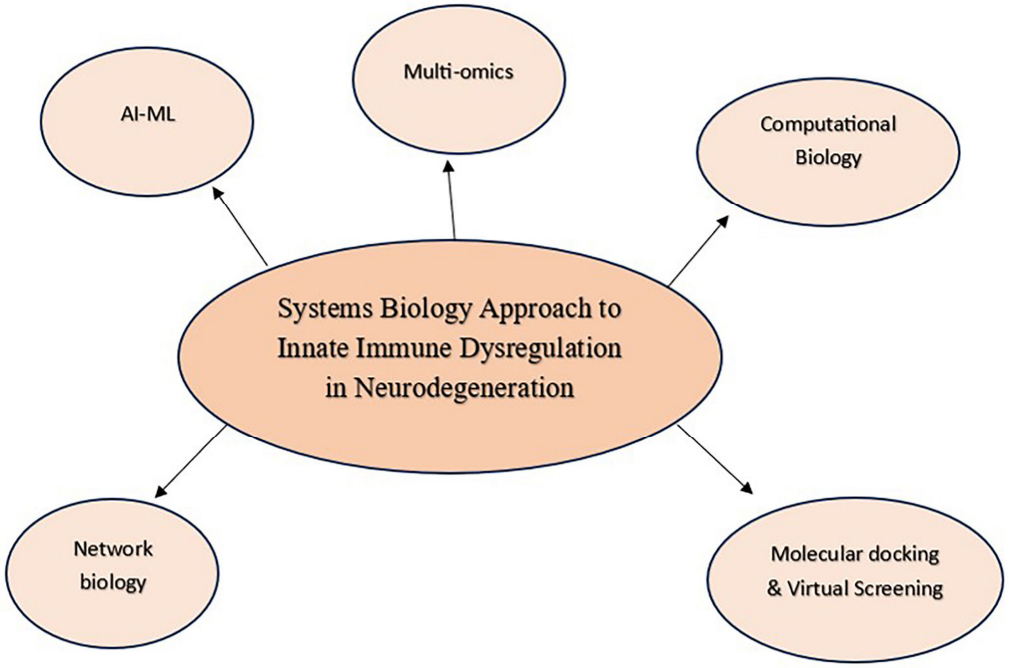


Figure 2: Integrating different system biology approaches including multi-omics, computational biology, AI-ML, Network biology, molecular docking & virtual screening

Computational modelling of Immune response in the central nervous system

Computational modelling of the immune responses in the central nervous system (CNS) is a multidisciplinary field that helps to integrate neurological science and immunology neurological science with mathematical modelling. It aids in understanding the relations between neural components and immune cells. The computational models can be utilised to analyze the progression of disease and the

response of therapies in neuroinflammatory disorders such as Parkinsons and Alzheimer's. These models are utilized for an improved understanding of T-cell interactions and blood-brain permeability.[27]

Moreover, Ordinary Differential equation (ODE) models are used in describing the active interactions amongst immune components with the help of differential equations. These are used for modelling cytokines production and feedback mechanisms in the central nervous system.

The multi-scale models are used in studying the systemic effects of immune components on CNS function. It deals with the analysis of CNS inflammation and immune effects at each level including the molecular level which deals with the signalling pathways such as JAK-STAT, cellular level including migration of immune cells and tissue levels including the integrity of brain-specific immune tissues[28].

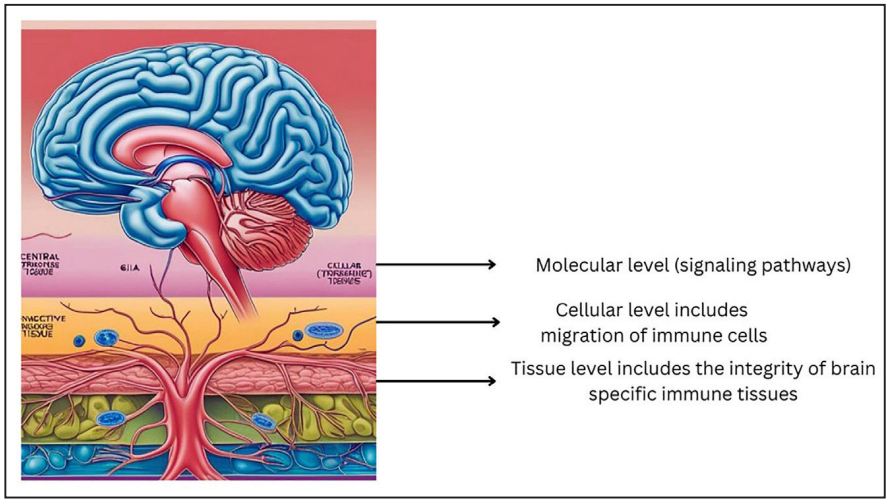


Figure 3: A multi-layered visualization of the immune response during CNS inflammation

AI-ML for the prediction of CNS immune response

The large transcriptomics and proteomics datasets are used to predict the immune responses during Neurodegeneration with the help of Machine learning models. Also, it can help to analyze the patient data and identify novel therapeutic targets.

The workflow of this includes the data input of large data sets such as those of Transcriptomics and Proteomics. Then features like immunological biomarkers are extracted. The AI models are trained by the use of neural networks and decision trees. Finally, the disease progression is predicted and the potential therapies and their targets are identified[(29)].

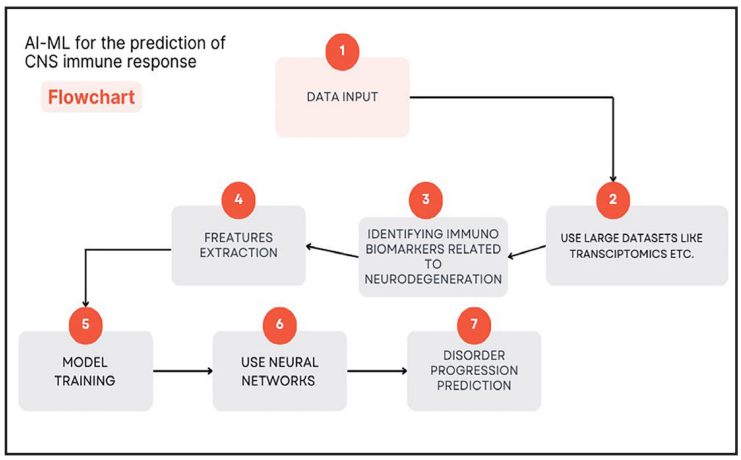


Figure 4: A pipeline flowchart of the workflow predicting the Immune response of CNS

CONCLUSION

The innate immune regulation in the central nervous system is unique as well as complex due to the specialized immune cells including microglial and astrocytes that reside over there. [30] Moreover, the dynamic nature of microglial activation makes it hard to identify and define biomarkers with a static nature. The multi-omics data sets like metabolomics, transcriptomics, genomics, epigenomics and proteomics are very large and it becomes difficult to integrate them. The heterogeneity of the obtained data formats further complexes this process. There is a lack of a gold standard neuroinflammatory stimulating models which makes it hard to predict real-time immune responses. There is very limited data on longitudinal patients most of the data are extracted from post-mortem or late-stage disease samples because of which early immune alterations are missing. Still, AI-ML is not of high quality which is needed for this purpose. There is a requirement for advances in AI-ML to improve the prediction of neuroimmune dysfunction. The spatial multi-layered omics approach is required to understand the immune cell interactions at each level. Moreover, the integration of neuroimmune data repositories around the world is required to enhance the reproducibility of the results. Targeted immunotherapies can be developed using computational drug screening. Dysregulated immune genes can be manipulated using CRISPR-based genome editing in patients. Though system biology has advanced the understanding of innate immune dysregulation in neurodegeneration, still there are challenges in data integration and further advancements in multi-omics and AI-ML models are required to pave the way for better knowledge of neuroimmunology and novel therapeutic interventions[31].

Conflict of Interest: Nil

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