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Review Article

Parkinson's Disease-Overview

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Abstract

Parkinson's disease one of the most complex neurological disorder. The disease risk and progression are due to common genetic variants. Approximately 6.2 million cases are reported each year according to the statistics published in 2015 whereas it is expected that this number will be twice by 2040. There are two types of Parkinson's disease, familial Parkinson's disease, and sporadic Parkinson's disease. The disease is characterized by the presence of Lewy bodies. Adult age increases the risk of Parkinson's disease. In this review, we provide an overview of the disease pathology of Lewy bodies in the occurrence of Parkinson's disease, in vitro studies to determine the role of iPSCs in treatment of Parkinson's disease, in vivo studies to determine the role of animal model in studying disease modeling, and future prospective how single-cell RNA sequencing technology is a major advancement in studying and find the treatment for Parkinson's disease.

Keywords: Parkinson's disease; Lewy pathology; In vivo transplantation; Healthcare

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Introduction

Parkinson's disease (PD) is referred as one of the complex neurodegenerative disorders [1]. The disease risk and gradual progression is due to some well-studied common genetic variants [2]. Early onset or atypical symptoms are often caused due to mutations in genes associated with the disease [2]. Rise in Parkinson's disease is becoming a serious healthcare issue globally. It is expected that by the year 2040 prevalence of will double from 6.2 million cases reported in 2015 [3, 4]. Parkinson's disease is a progressive movement disorder although the non-motor related symptoms exist [5]. A long phase of Parkinson's disease has features that include anosmia, constipation, and sleep disturbance.

Increased age act as a greatest risk factor in the occurrence of the disease [6]. Fasting and physical exercise has been demonstrated to reduce symptoms and increase cognition [7, 8]. Genetic risk of Parkinson's disease is divided into two categories [9]. Risk factors associated with monogenic or familial Parkinson's disease known as uncommon DNA variants. While the later one is identified in apparently sporadic Parkinson's disease these are more common and are smaller effect variants [10].

Parkinson's disease Pathology

The main pathological characteristic of Parkinson's disease is the occurrence of Lewy bodies (LB) and dementia with Lewy bodies discovered more than hundred years ago [11, 12]. The major component of LB and Lewy neuritis (LN) is an abnormal folded protein, α-synuclein (αSyn) [13]. Through light microscopy the morphology of LB is determined. The morphology of Lewy bodies depends on their location in the brain [14, 15]. LN's morphology is like αSyn immunohistochemical profile in neuronal cell bodies, but different in brainstem and sub cortical brain regions [16]. The occurrence and role of Lewy pathology in neural degeneration is still vague [17]. The current research from the literature suggests that first abnormal oligomers are formed by intraneural αSyn that is induced by the extracellular αSyn aggregates and then transformed into amyloid fibrils [18]. Transmission electron microscopy (TEM) conducted on the resin-embedded post-mortem brain tissues of patients demonstrated the ultrastructure of LB [19, 20, 21].

Another hypothesis stated in literature about pathology of PD states the staging system based upon four stages [22]. The initial stage is where olfactory bulb is affected [23]. Stage IIa is brainstem predominant and stage IIb is limbic predominant [24]. Following this stage these two distinct pathways join into stage III in which both the areas are affected [25]. In the last stage, neocortical areas are affected. Pathological stages correlate with loss of neuron as well as cognitive and motor symptoms [26]. The biomedical imaging of the brain of PD patients demonstrates that the atrophy in the human brain shows a common trend based on the neuronal connectivity, and therefore, this atrophy links with the symptoms of the disease [27].

In vitro (cell-based) studies

The complex human brain remains a challenge. Neurite dysfunction and apoptosis are some of the disease phenotypes recapitulated from the PD patients by the generation of human iPSCs-derived DA neuron [28]. Such in-vitro model systems can be used to determine whether there is defect in neuronal axonal length [29, 30] or nuclear size [31] or even be used for drug assessment [32]. In-vitro model could be brought closer to the in-vivo situation by co-culturing of neurons along with astrocytes or microglia [33]. However, certain nuclear proteins play an important role in the efficiency of neuronal generation and substrate adhesion [34, 35]. Current advancement by the developed of 3D culture system which is also known as

'Organoids' reveals new possibilities for PD disease treatment based upon iPSCs. Pluripotent stem cells possess the ability to self-organize, which forms the basis of human brain organoid culture. [36].

During embryonic development, single cell iPSCs can differentiate into embryoid bodies representing the three germ layers [37]. The differentiation of the outer layer to ectodermal fate is done by culturing in minimal medium. Implanting these structures in extracellular matrices facilitates neuroepithelium outgrowth by acting as a support in the formation of neural tube [17]. Subsequently, 3D culture system provide numerous opportunities for disease modeling of human degeneration in specific brain region such as SN in Parkinson's disease [38].

In vivo (animal model) studies

Researchers have implemented the principles observed during embryonic development of neurons to the differentiation of dopaminergic neurons derived from pluripotent stem cells [39]. First step in the differentiation protocol involves the utilization of either feeder cells or astrocytes along with the activation of genes responsible for upregulating different signaling pathways [40]. Upon in vivo transplantation, there was lack of expression of markers for FOXA2 and LMX1A, but the neurons did not survival well after transplantation [41]. Signaling pathways such as WNT, SHH, and FGF regulates the development while floor plate cells give rise to DA neurons. Several in vivo studies conducted experiments on zebrafish to determine the expression of TH to evaluate the integrity of dopaminergic system [40]. These experiments would enable researchers to discovery biomarkers to detect the disease ahead of time [42]. The proteomics of zebrafish is conserved which permits the use of other biomarkers of different species. When these biomarkers are tested on zebrafish, they provide similar results of reactivity. By inhibiting the expression of protein to dopaminergic neurons will maintain the pathological mechanism while decreasing the lethality [40].

Future Outlook for Parkinson's disease

Single-cell RNA sequencing is merged along morphological characterization, tracing of lineage, functional analysis to collect detailed catalog of neuronal subtypes which are molecularly distinct and factors contributing to the development and functioning of human brain [43]. There are three types of scRNAseq techniques for neurodegenerative disorders such as spatial transcriptomics, cell barcoding and patch-seq. Spatial transcriptomics would help us to understand the functionality of single cell in unique spatial architecture in samples of brain tissues [44]. It is one of the most advanced technology that is based upon the assumptions to define specific cell type functions, determining the location without disturbing the cell-cell communication as well as intracellular regulation [41]. Cell barcoding helps in the reconstruction of the phylogenetic tree that precisely points out sister cells from each division. It is important to conduct the single-cell analysis of electrically dysfunctional neurons to study the etiology of neurodegenerative disorders

[43]. Single-cell Patch seq is a technique that can link molecular features of different neurons with their physiological role and function in human brain. This technology is an important advancement towards postulating high-resolution analysis of cells and specifically neurons that are either lost or is not determined when using traditional scRNA-seq [44].

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