Chapter 9

Parkinson's Disease Involving Glial Cell Dysfunction

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ABSTRACT

It is well known that the decline in the viability of dopamine neurons slowly leads to the appearance of various symptoms characteristic of Parkinson's disease (PD). These symptoms depend mainly on dysfunction of nigrostriatal dopaminergic denervation. The cause of neuronal death has not yet been elucidated, although there are several hypotheses suggesting different factors that may trigger it. One possible mechanism of neurodegeneration is the establishment of chronic inflammation in the central nervous system, where glial cells are key regulators of inflammatory responses. They also play a phagocytic role, engulfing synapses, apoptotic cells, cellular debris and released toxic proteins. An imbalance in the activation of these cells can lead to an overproduction of cytotoxic factors, which contribute to the death of dopamine neurons. As PD involves not only the loss of dopamine neurons, but also the dysfunction of glial cells, whose loss or excessive activation can contribute to neuronal death, there is a need to better understand the role of these cells in PD in order to develop effective therapies.

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting around 10 million people worldwide (Pringsheim et al., 2014). Clinically, PD is diagnosed by the recognition of cardinal symptoms of the motor system, such as resting tremor, bradykinesia, muscle rigidity and postural instability (Kim et al., 2011). Motor disorders are due to the progressive degradation of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and striatum along the nigrostriatal pathway (Langston, 2006; Lees et al., 2009). Although less studied than motor symptoms, a number of studies show that non-motor symptoms of PD play an important role in predicting the emergence of clinical motor symptoms in PD (Dujardin et al., 1999; Weintraub & Burn, 2011).

There have been no substantial changes in the treatment pathway for PD in recent years, and the gold standard treatment has been levodopa since its inception in the early 1960s (Witt & Fahn, 2016). However, it is important to note that levodopa is only beneficial in the early stages of the disease, as continued use can lead to undesirable side effects such as dyskinesia, dependence and depression (Jankovic & Aguilar, 2008; Jimenez-Shahed et al., 2016). Dopamine agonists and inhibitors of dopamine-degrading enzymes have been used as alternative means of controlling or delaying the progression of PD, but with little efficacy in the advanced stages of the disease (Dextera & Jenner, 2013; Rascol et al., 2003). In addition, for people with significant motor difficulties, surgical procedures such as deep brain stimulation of the medial globus pallidus, subthalamic nucleus and pedunculopontine nucleus have been used (Okun, 2012). Stem cell-based methods of treating PD have been presented as a new treatment pathway. These procedures are being further investigated to establish their efficacy in the treatment of PD patients. Several types of stem cells have been studied and have shown promise for the treatment of PD (Goodarzi et al., 2015.; Zhang et al., 2017), including embryonic stem cells (ESCs) (Brederlau et al., 2006), neural stem cells (NSCs) (Daadi et al., 2012), mesenchymal stem cells (MSCs) (Z. Zhang et al., 2008) and induced pluripotent stem cells (iPSCs) (Savchenko et al., 2018).

Glial cells have recently emerged as a promising source for the development of therapeutic approaches for neurodegenerative diseases such as PD (Bradl & Lassmann, 2010; J. Wang et al., 2013). It remains unclear whether glial cells play a role in the development of PD or whether they represent a viable therapeutic option. Indeed, previous research has emphasised a dual function, indicating that glial cells may switch from a neuroprotective to a neurodegenerative profile throughout the development and progression of PD, although this remains to be proven (De Miranda et al., 2018; Yue et al., 2018).

This chapter will attempt to review what is currently known about several glial cell types. It will also identify their important tasks in healthy brains and in brains affected by PD, and determine whether these glial cells play a role in the onset and progression of PD, and whether they are possible therapeutic targets and agents for the treatment of the disease.

THE GLIAL SYSTEM: ROLES AND FUNCTIONS

In terms of cellular diversity, the CNS is made up of several cell types in addition to neurons, namely glial cells, whose function has not been well understood. For many years, these glial cells were considered only as support cells maintaining the viability of neurons. From the point of view of cellular and functional diversity, glial cells are superior to neurons (Fields et al., 2014), and are divided mainly into three essential groups: astrocytes, microglia and oligodendrocytes, whose cells can regulate neuronal

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