Neuroscience 302 (2015) 47–58

REVIEW

THE RELATION BETWEEN α-SYNUCLEIN AND MICROGLIA IN PARKINSON'S DISEASE: RECENT DEVELOPMENTS

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Abstract—Recent research suggests a complex role for microglia not only in Parkinson's disease but in other disorders involving alpha-synuclein aggregation, such as multiple system atrophy. In these neurodegenerative processes, the activation of microglia is a common pathological finding, which disturbs the homeostasis of the neuronal environment otherwise maintained, among others, by microglia. The term activation comprises any deviation from what otherwise is considered normal microglia status, including cellular abundance, morphology or protein expression. The microglial response during disease will sustain survival or otherwise promote cell degeneration. The novel concepts of alpha-synuclein being released and uptaken by neighboring cells, and their importance in disease progression, positions microglia as the main cell that can clear and handle alpha-synuclein efficiently. Microglia's behavior will therefore be a determinant on the disease's progression. For this reason we believe that the better understanding of microglia's response to alpha-synuclein pathological accumulation across brain areas and disease stages is essential to develop novel therapeutic tools for Parkinson's disease and other alpha-synucleinopathies. In this review we will revise the most recent findings and developments with regard to alpha-synuclein and microglia in Parkinson's disease.

This article is part of a Special Issue entitled: Inflammation in Nervous System Disorders.

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Abbreviations: CSF, cerebrospinal fluid; FcgR, Fc gamma receptors; HO-1, heme oxygenase-1; IgG, immunoglobulin G; LPS, lipopolysaccharide; Nrf2, NF-E2-related factor 2; PD, Parkinson's disease; PET, positron emission tomography; rAAV, recombinant adeno-associated viral vectors; RAGE, receptor for advanced glycation end-products; TLR, Toll like receptor; TNFa, tumor necrosis factor alpha.

http://dx.doi.org/10.1016/j.neuroscience.2015.02.008
0306-4522/

Key words: microglia, alpha-synuclein, neuroinflammation, Parkinson's disease, TLR.

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INTRODUCTION

Parkinson's disease (PD) is mainly characterized by the loss of dopaminergic neurons in the substantia nigra and the appearance of aggregated alpha-synuclein in Lewy bodies. It is now evident that alpha-synuclein plays a central role in the disease: Not only it is the main component of Lewy bodies and Lewy neurites found in all PD patients (Spillantini et al., 1997), but some forms of familial PD are related to point mutations in the alpha-synuclein gene, SNCA (Polymeropoulos et al., 1997; Kruger et al., 1998; Zarranz et al., 2004; Lesage et al., 2013; Proukakis et al., 2013), or even triplication of the gene (Ross et al., 2008), indicating that an excessive amount of the normal protein can also cause PD. The concept of PD as a multifactorial and complex disease is sustained by the Braak hypothesis, which based on their observations of alpha-synuclein pathology in PD patients' brains at different stages of the disease, suggests that brain pathology may start in the olfactory nucleus and several dorsal motor nuclei, and progresses as alpha-synuclein pathology spreads upward into the midbrain and the cortex (Braak et al., 2003). This has given rise to the proposal of PD pathology starting somewhere outside the brain, where the nervous system is in close contact with the exterior environment: i.e. the digestive system or the olfactory mucosa. Specific insults will initiate the aggregation of alpha-synuclein in those areas, leading to

the spreading of alpha-synuclein pathology in a prion-like manner to higher neuronal structures. Indeed alpha-synuclein can be released both in monomeric and aggregated form, and can be uptaken by neighboring cells, resulting, in rodents, to such proposed prion-like spreading (for a review (Steiner et al., 2011; Olanow and Brundin, 2013). Therefore, it is of special interest to elucidate the effect of extracellular alpha-synuclein, as well as its clearance or degradation in the extracellular milieu. A recent work approaching the prion-like spreading of intra-cerebral injections of aggregated alpha-synuclein, has shown that at the site of injection, as long as 4 months later, there exists a robust astro- and microgliosis, and the presence of intracellular inclusions of alpha-synuclein in astroglia and microglia; supporting an important role of glia in the clearance of alpha-synuclein (Sacino et al., 2014). It should be noted that three different enzymes have been shown to degrade extracellular alpha-synuclein: Plasmin (Kim et al., 2012), metalloproteinase (Sung et al., 2005) and neurosin (Tatebe et al., 2010), which can be of relevance in future therapies. However, understanding the mechanisms underlining alpha-synuclein cellular uptake and degradation, as well as alpha-synuclein's effect in glial cells is also of crucial importance.

MICROGLIA AN IMPORTANT TEAM PLAYER

Among the many factors related to PD pathology, microglia and neuroinflammation have gained the great attention during the last years, and it has been suggested that the immune system plays an active part in the symptoms and progression of the disease (Doorn et al., 2012; Blandini, 2013). Further supporting this, epidemiological studies have shown that the use of non-aspirin NSAIDs decreases the risk to develop PD (Rees et al., 2011). In parallel, the investigation of alpha-synuclein's role in PD has added several highly relevant pieces of evidence regarding the neuroinflammatory process occurring in PD. First: Extracellular alpha-synuclein is most efficiently cleared by microglia (Lee et al., 2008); second, the efficiency of this process seems to depend on the activation state of microglia and on whether alpha-synuclein is in monomeric or oligomeric form (Lee et al., 2008; Park et al., 2008) (although other labs have not confirmed such observation, see below). Lastly, alpha-synuclein, especially if aggregated, can lead to pro-inflammatory activation of microglia (we will review this further herein).

Microglia in the CNS form a heterogeneous population and local cues in healthy humans are enough to induce variances in the expression of surface markers between microglia in different areas of the brain (de Haas et al., 2008). Such cues can be the result of neuronal activity, neurotransmitter release and neuronal plasticity, since microglia possess neurotransmitter receptors and is involved in the removal of synapses (Neumann, 2001; Farber et al., 2005; Phani et al., 2012). Microglial changes in the brain are a complex event and the result of not only neuronal changes, but also of the microglia's interaction with other immune cells; therefore a more integrated immune response is bound to be mounted in the patients. Indeed, changes in cytokine composition in serum from PD patients, as well as alterations in different immune populations, support this integrative concept (previously reviewed in (Kannarkat et al., 2013; Sanchez-Guajardo et al., 2013). In this review we would like to bring forward the most novel findings with respect to microglia's interaction with alpha-synuclein in PD. It is our belief, that there is robust evidence now of the active role of microglia in alpha-synuclein-related neurodegeneration in PD and a more intense focus on the physiological responses of the microglia to alpha-synuclein pathology/neurodegeneration should be undertaken.

MICROGLIOSIS IN PD AND ITS RELATION TO ALPHA-SYNUCLEIN PATHOLOGY

Since the first report showing activation of microglia in PD postmortem brains (McGeer et al., 1988) numerous other studies have been published describing microglial changes, so called ''microgliosis,'' in humans, as well as in PD animal models (Long-Smith et al., 2009; Halliday and Stevens, 2011). The postmortem observations have been confirmed by *in vivo* positron emission tomography (PET) imaging studies of microglial activation, by means of administration of the peripheral benzodiazepine receptor (PBR/TSPO) binding ligand [11C]-(R) PK11195. This ligand gives normally a low signal in the brain coming mainly from ependymal walls, choroid plexus and the olfactory bulb. But its signal is increased upon neuronal injury due to up-regulation of the TSPO in microglial cells (Weissman and Raveh, 2003). The use of this ligand revealed microglial activation in midbrain and putamen of PD patients (Ouchi et al., 2005; Bartels et al., 2010). Other areas are also highlighted in PET, such as pons and cortex (Gerhard et al., 2006). These and other studies, have confirmed that microgliosis is not only related to those areas with neuronal death, but rather to the appearance of alpha-synuclein pathology, supporting activated microglia as a sensitive index of neuropathological changes (Imamura et al., 2003). Furthermore these studies suggest that microglia activation is an early event in PD and that they remain activated through the disease duration (reviewed by Politis et al., 2012). However, we believe the microglia response will differ as the disease progresses, as they will respond to neuronal changes such as alpha-synuclein modification, differences in neurotransmitters release and neuronal death. In fact, we have shown in an alpha-synuclein model of PD both in rodents and primates, that the microglia response is early, preceding cell death, but not static (Sanchez-Guajardo et al., 2010; Barkholt et al., 2012). Also *in vitro* microglia's response to alpha-synuclein is complex, with both pro and anti-inflammatory profiles co-existing in parallel (Reynolds et al., 2008b). Further supporting of a mixed population, alpha-synuclein can not only induce pro-inflammatory signals in glia, such as NFκB but also at long-term anti-inflammatory signals via NF-E2-related factor 2 (Nrf2) (Lastres-Becker et al., 2012). Moreover, it has been shown that change of cytokine profiles in PD patients is also region specific, supporting a complex and anatomical microglia response