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Review

Glia and alpha-synuclein in neurodegeneration: A complex interaction

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ABSTRACT

α-Synucleinopathies (ASP) comprise adult-onset, progressive neurodegenerative disorders such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) that are characterized by α-synuclein (AS) aggregates in neurons or glia. PD and DLB feature neuronal AS-positive inclusions termed Lewy bodies (LB) whereas glial cytoplasmic inclusions (GCIs, Papp–Lantos bodies) are recognized as the defining hallmark of MSA. Furthermore, AS-positive cytoplasmic aggregates may also be seen in astroglial cells of PD/DLB and MSA brains. The glial AS-inclusions appear to trigger reduced trophic support resulting in neuronal loss. Moreover, microgliosis and astrogliosis can be found throughout the neurodegenerative brain and both are key players in the initiation and progression of ASP. In this review, we will highlight AS-dependent alterations of glial function and their impact on neuronal vulnerability thereby providing a detailed summary on the multifaceted role of glia in ASP.

Contents

Introduction

α-Synucleinopathies (ASP) are progressive, adult-onset neurodegenerative diseases that include Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) (Spillantini and Goedert, 2000; Goedert, 2001; Beyer and Ariza, 2007). The main pathological hallmark of these diseases is the occurrence of hyperphosphorylated, misfolded and fibrillized α-synuclein (AS)-positive inclusions throughout the central nervous system (CNS) (Fujiwara et al., 2002; Uversky, 2008; Vilar et al., 2008). In PD and DLB, neurons are the main cell type displaying cytoplasmic AS-positive aggregations which are called Lewy bodies (LB) and Lewy neurites (LN) (Baba et al., 1998; Beyer and Ariza, 2007), whereas in MSA, these inclusions predominantly develop in oligodendroglia and are therefore named glial cytoplasmic inclusions (GCIs, Papp–Lantos bodies) (Spillantini et al., 1998; Dickson et al., 1999; Hasegawa et al.,

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2004; Song et al., 2009; Fellner et al., 2011; Fellner and Stefanova, 2013). Furthermore, PD and DLB show AS depositions in astrocytes and oligodendrocytes (Wakabayashi et al., 2000; Braak et al., 2007; Song et al., 2009). Wenning and Jellinger described AS-positive deposits in astroglial cells in MSA (Wenning and Jellinger, 2005), however they appear to be less prominent and sometimes absent (Song et al., 2009) compared to neuronal and oligodendroglial inclusion pathology. AS aggregation in astroglial cells and its relevance to disease initiation and progression require further attention in MSA.

The brain protein AS is predominantly located in presynaptic terminals of neurons in the hippocampus, striatum, thalamus, cerebellum and neocortex (Iwai et al., 1995; Norris et al., 2004). AS belongs to a family of three distinct genes, including *SNCA*, *SNCB* and *SNCG* (α-, β- and γ-synuclein) and is composed of 140 amino-acids (Dev et al., 2003; Eriksen et al., 2003). Although the precise function of the protein is not solved yet, the importance of AS in folding and refolding of synaptic proteins has been proven (Chandra et al., 2005). Moreover, AS directly interacts with phospholipid vesicle membranes suggesting an important regulatory role in both inhibitory and facilitatory transmitter releases (Auluck et al., 2010) (Abeliovich et al., 2000; Cabin et al., 2002; Gitler and Shorter, 2007).

The development of the AS-positive GCI, LB and LN has not been completely elucidated yet. However, different studies demonstrated that AS overexpression impairs macroautophagy suggesting that reduced AS clearance is involved in the generation of AS inclusions in DLB and PD (Winslow et al., 2010; Xilouri and Stefanis, 2011). Furthermore, alterations in the autophagosomal proteins in MSA brains and the participation of macroautophagy in the MSA pathogenesis have been suggested (Tanji et al., 2011; Schwarz et al., 2012). Post-translational modifications of AS, such as ubiquitination, nitration and phosphorylation may promote pathological inclusion formation and enhance disease progression (Giasson et al., 2000; Tofaris et al., 2003; Xilouri and Stefanis, 2011). Moreover, Ozawa et al. showed a connection between neuronal cell loss, aggregation of AS and disease severity in MSA (Ozawa et al., 2004). Prion-like cell-to-cell propagation of AS has been suggested a crucial contributor to neurodegeneration and therefore to the progression of ASP (Desplats et al., 2009; Lee et al., 2010; Hansen et al., 2011; Reyes et al., 2014).

Glial cells are important in supporting neuronal survival, synaptic functions and local immunity (Webster and Astrom, 2009; Hauser and Cookson, 2011). However, glial cells might be crucial for the initiation and progression of different neurodegenerative diseases, including ASP (Gerhard et al., 2003, 2006; Fellner et al., 2011; Halliday and Stevens, 2011). Due to various stimuli, e.g. infection or injury, astroglial and microglial cells get activated (Nimmerjahn et al., 2005; Wilhelmsson et al., 2006). Neurons may benefit from activated microglia and astroglia due to the release of trophic factors or the clearance of damaged cells by microglia (Liberto et al., 2004; van Rossum and Hanisch, 2004; Nimmerjahn et al., 2005; Wilhelmsson et al., 2006).

Especially in neurodegenerative diseases microglia and astroglia can get over activated resulting in reactive microgliosis and astrogliosis. It was described that astroglial cells can activate microglial cells (Gu et al., 2010; Halliday and Stevens, 2011; Schmidt et al., 2011), or vice versa microglial activation can induce astrogliosis (Balasingam et al., 1996; Hanisch, 2002; Rohl et al., 2007). Reactive gliosis might induce neurotoxicity, perturbation of the neuronal network, and maladaptive plasticity and further lead to tissue damage (Papa et al., 2014). Moreover, it was demonstrated that neuronal cells have the ability to release excessive AS leading to the activation of an inflammatory response in microglia (Lee et al., 2010; Kim et al., 2013). Furthermore, the before mentioned prion-like spreading of pathological AS (Luk et al., 2009; Hansen et al., 2011; Masuda-Suzukake et al., 2013; Watts et al., 2013) could be a possible mechanism of AS aggregation in ASP and further cause activation of microglia and astroglia. Aggregated AS was shown to induce reactive microgliosis resulting in dopaminergic cell death (Zhang et al., 2005). Glial overactivation results in the release of (pro)-inflammatory cytokines, nitric oxide (NO) and reactive oxygen species (ROS) (Neumann et al., 2002; Deshpande et al., 2005; Mizuno et al., 2005; Zhang et al., 2005; Qian and Flood, 2008; Dean et al., 2010; Lee et al., 2010; Qian et al., 2010).

Besides, oligodendroglial cells that are exposed to oxidative stress and cytokines present with cellular dysfunction, demyelination and cell death, as well as reduced trophic support which consequently affects neuronal survival (Thorburne and Juurlink, 1996; Jurewicz et al., 2005).

This review summarizes the main features of ASP and the involvement of glial cells regarding the initiation and progression of these neurodegenerative diseases. We will discuss the main changes of glial cells during disease initiation and progression.

Glia in PD and DLB

PD and DLB are common neurodegenerative diseases in the population over the age of 65. About 3% of the general population develops PD after the age of 65, whereas about 20% of all diagnosed dementia patients have DLB (McKeith, 2004; Dorsey et al., 2007). In both disorders movement and cognition, as well as mood and autonomic function are severely affected. Diagnosis to distinguish PD and DLB is very difficult, because of the overlap of symptoms and signs (Henchcliffe et al., 2011). In search for new biomarkers different factors were examined in the cerebrospinal fluid (CSF) of PD and DLB patients in comparison with Alzheimer disease (AD) patients and controls. Nagatsu and colleagues described elevated levels of pro-inflammatory cytokines such as Interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6, as well as decreased levels of neurotrophins such as brain-derived neurotrophic factor (BDNF) in the ventricular or lumbar CSF of PD patients (Nagatsu and Sawada, 2005). Moreover, elevated levels of the astroglial protein glial fibrillary acidic protein (GFAP), as well as the neurofilament light protein (NFL), which is used as a marker of neuronal damage, and AS were found in the CSF of PD patients (Constantinescu et al., 2010; Gao et al., 2014). Different studies could show that CSF AS levels are lower in PD and DLB compared to AD patients and controls (Mollenhauer et al., 2008; Wennstrom et al., 2013). Additionally, Wennstrom and colleagues described a decrease of neurosin, an AS degrading protease, in the CSF of patients with PD and DLB (Wennstrom et al., 2013). Furthermore, it was suggested that an altered ratio of phosphorylated AS CSF levels might serve as a biomarker to distinguish PD from controls (Foulds et al., 2011).

Both diseases feature LB consisting of aggregated AS as a hallmark lesion of degenerating neurons. PD patients show enhanced neuronal loss in the substantia nigra (SN) compared to DLB patients (Tsuboi and Dickson, 2005). Immunohistochemical studies showed a significantly higher amount of amyloid plaques in the putamen and caudate nucleus and more severe tau pathology in DLB compared to PD brains. Additionally, Jellinger and Attems suggested an elevated level of AS-lesions in DLB compared to PD (Jellinger and Attems, 2006). The accumulation of AS is increased with the occurrence of point mutations or duplications as well as triplications of the SNCA gene (Polymeropoulos et al., 1997; Singleton et al., 2003; Zarranz et al., 2004; Nishioka et al., 2006). Recent studies confirmed the association between PD and both SNCA single nucleotide polymorphisms (SNPs) and the H1 haplotype of microtubule-associated protein tau (MAPT) (Edwards et al., 2010; Elbaz et al., 2011; Trotta et al., 2012). Other genetic risk factors in the development of PD include leucine-rich repeat kinase 2 (LRRK2), the human leukocyte antigen (HLA) region and DJ-1 (Bonifati et al., 2003; Zimprich et al., 2004; Simon-Sanchez et al., 2009; Hamza et al., 2010). Genetic observations show also overlaps between PD and DLB. Mutations in the genes encoding AS (El-Agnaf et al., 1998; Ibanez et al., 2004), LRRK (Zimprich et al., 2004) and glucocerebrosidase (Goker-Alpan et al., 2006) were found in some DLB patients. However, also sporadic PD and DLB cases occur suggesting that genetic

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