Experimental Neurology xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Commentary

Commentary: Progressive inflammation as a contributing factor to early development of Parkinson's disease☆

Suraj Pradhan, Katrin Andreasson*

Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA

ARTICLE INFO

Article history:
Received 28 September 2012
Revised 8 December 2012
Accepted 13 December 2012
Available online xxxx

Keywords:
α-synuclein
Parkinson's disease
Inflammation
Microglia

ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder with three cardinal features of pathology: 1. Aggregation of α-synuclein into intraneuronal structures called Lewy bodies and Lewy neurites. 2. Dysregulated immune activation in the substantia nigra (SN). 3. Degeneration of dopaminergic neurons in the nigrostriatal circuit. The largely correlative nature of evidence in humans has precluded a decisive verdict on the relationship between α-synuclein pathology, inflammation, and neuronal damage. Furthermore, it is unclear whether inflammation plays a role in the early prodromal stages of PD before neuronal damage has occurred and Parkinsonian motor symptoms become apparent. To gain insight into the interaction between the inflammatory response and the development of neuronal pathology in PD, Watson et al. characterized neuroinflammation in a wild-type α-synuclein overexpressing mouse model of prodromal PD. They demonstrate, for the first time, the existence of early and sustained microglial mediated innate inflammation that precedes damage to the nigrostriatal circuit. Additionally they observe the spread of inflammation from the striatum to the SN. This study suggests that early dysregulated inflammation may contribute to progressive nigrostriatal pathology in PD, although the initiating factor that triggers the inflammatory response remains elusive. The novel concept of an early inflammatory response in the development of PD has important implications for preventive and therapeutic strategies for PD.

Chronic inflammation is a prominent feature of many neurodegenerative disorders (Glass et al., 2010), however its pathophysiologic role in the development of PD has only recently become a focus of investigation (Fellner et al., 2011). CNS inflammation was first observed in post-mortem brain samples from PD patients by McGeer et al. (1988), where microglia expressing the activated immune cell marker MHC-II were identified in the SN (McGeer et al., 1988). More recently, PET imaging has confirmed the widespread activation of microglia in the midbrain (Ouchi et al., 2005) as well as brain stem, striatum, cingulate gyrus, and neocortex of PD patients (Gerhard et al., 2006). Interestingly, microglial activation in the midbrain was positively correlated with motor symptom severity in early PD and negatively correlated with dopaminergic (DA) fiber density in the striatum (Ouchi et al., 2009). Damage to the nigrostriatal DA circuit is a hallmark of PD, yet it is unclear whether inflammation plays a role in the degeneration of SN DA neurons and subsequent progression of the disease process. Several observational studies offer clues supporting a contribution of inflammation to disease pathogenesis. Polymorphisms in genes encoding for the immune molecule tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and human leukocyte antigen (HLA) are associated with a higher risk of developing PD (Ahmed et al., 2012; Bialecka et al., 2008; Hamza et al., 2010; Wahner et al., 2007). Regular use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly ibuprofen, is associated with a significantly lower risk of developing PD (Gagne and Power, 2010; Gao et al., 2011; Rees et al., 2011; Samii et al., 2009), although some studies present conflicting results (Becker et al., 2011; Driver et al., 2011). Furthermore, infections with certain viruses or bacteria or exposure to pesticides in the environment seem to modify the disease risk for PD later in life (Brown et al., 2006; Jang et al., 2009a,b; Lopez-Alberola et al., 2009; Nielsen et al., 2012; Reid et al., 2001; van der Mark et al., 2012). These observations suggest that inflammation may play a detrimental role in the etiology of this progressive disorder (Long-Smith et al., 2009; Lucin and Wyss-Coray, 2009; Phani et al., 2012). However, no study has conclusively demonstrated the existence of neuroinflammation in the early prodromal stages of PD. In this issue of Experimental Neurology, Watson et al. demonstrate for the first time the onset and progression of early microglial inflammation that precedes nigrostriatal synaptic injury in a genetic model of PD (Fig. 1).

Role of microglia in PD

Microglia are the resident immune cells of the CNS and can mediate either beneficial or toxic inflammatory functions (Ransohoff and Perry, 2009). In the healthy brain, microglia exist in a resting state with a

☆ This work was supported by the National Science Foundation (SP), 1F31NS074712 (SP), and RO1AG030209 (KA). The authors thank Holden Brown for assistance with graphics.

* Corresponding author at: Stanford University School of Medicine, 1201 Welch Road, MSLS P210, Stanford, CA 94305, USA.
E-mail address: kandreas@stanford.edu (K. Andreasson).

0014-4886/$ – see front matter © 2012 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.expneurol.2012.12.008

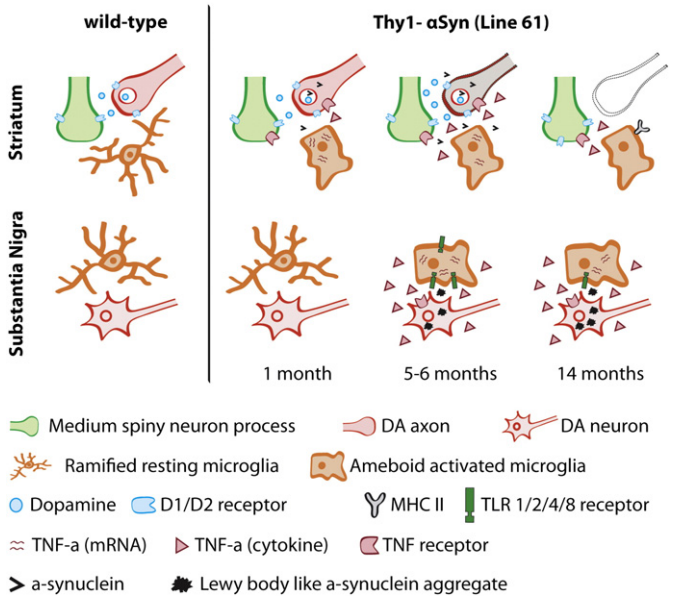

Fig. 1. Spatiotemporal progression of inflammation in Line 61 mice. Early and sustained microglial activation precedes the loss of DA terminals in the striatum. Inflammation spreads to the SN paralleling the appearance of α-synuclein aggregates, but does not lead to DA neuron loss. Structures are not to scale.

ramified morphology, extending their processes to sample the tissue environment for signs of distress. Neuronal injury leads to the release of immunogenic molecules that cause microglia to adopt an ameboid morphology and display a classically or alternatively activated phenotype depending on environmental context (Lucin and Wyss-Coray, 2009). Activation states of microglia can be divided broadly in two classes, M1 and M2, although there can be overlap between these two classes. Classically activated (M1) microglia serve a "killing" function by producing damaging reactive oxygen species (ROS) and reactive nitrogen species (RNS), and secreting pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, interferon gamma (IFN-γ) that bind to neuronal receptors and initiate cell death pathways. Alternatively activated (M2) microglia serve a "repair" function by downregulating production of these toxic factors and upregulating production of anti-inflammatory cytokines such as IL-10, and growth factors including transforming growth factor beta (TGF-β). M2 microglia also engage in phagocytosis of debris left by dying neurons and exhibit increased levels of cell surface scavenger receptors involved in the phagocytic machinery (Colton, 2009). Evidence for both M1 and M2 activated microglia has been found in PD. Post-mortem studies of PD patients have demonstrated increased levels of TNF-α, IL-6, and IL-1β in the striatum (Mogi et al., 1994a,b) and M1 microglia producing TNF-α and NO in the SN (Boka et al., 1994; Hunot et al., 1996). Resulting oxidative damage was evident in the form of increased protein carbonylation (Alam et al., 1997a,b), membrane lipid peroxidation (Dexter et al., 1994), oxidative DNA damage (Alam et al., 1997a,b), and decreased levels of the antioxidant enzyme glutathione peroxidase in the SN (Lange et al., 1992). Moreover, intra- and extraneuronal aggregates of α-synuclein were densely surrounded by activated glia in the SN of PD brains (McGeer et al., 1988; Yamada et al., 1992). On the other hand, M2 microglia expressing the phagocytic markers CD64 and CD68 persisted in the SN along with α-synuclein deposits (Croisier et al., 2005; Orr et al., 2005) suggesting that they may be actively phagocytosing α-synuclein. In vitro experiments have demonstrated that neither lipopolysaccharide (LPS) nor α-synuclein are directly toxic to primary mesencephalic neurons in the absence of microglia, suggesting that microglial inflammation and oxidative stress contribute to non-cell-autonomous injury to DA neurons in the SN of PD patients (Zhang et al., 2005). However, evidence supporting a role for neurotoxic or neuroprotective microglia in human PD has been correlative, and the fundamental question of whether neuroinflammation promotes neuronal injury or occurs as a result of neuronal injury remains unclear.

Animal models of neurotoxin induced Parkinsonism

The earliest Parkinsonian models employed neurotoxins to mimic the motor deficits that are a characteristic feature of human PD. In 1968, injection of the DA analog, 6-hydroxydopamine (6-OHDA), into the nigrostriatal pathway was shown to selectively kill DA neurons in the SN and reproduce behavioral symptoms resulting from degeneration of the basal ganglia motor circuitry (Ungerstedt, 1968). 15 years later another neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), was found to cause severe and selective loss of DA neurons in the SN and bradykinesia in humans (Langston et al., 1983), primates (Burns et al., 1983), and mice (Heikkila et al., 1984). Other environmental toxins including rotenone and paraquat led to SN DA neurodegeneration but have been challenged by variability in behavioral deficits between studies (Bove and Perier, 2012). Importantly, SN microglial activation is seen within 24 h of MPTP administration and precedes DA neuron death in MPTP (Liberatore et al., 1999), 6-OHDA (Marinova-Mutafchieva et al., 2009), paraquat (Purisai et al., 2007), and rotenone models (Sherer et al., 2003). Blocking microglial activation rescues DA neurons, although it is not clear whether neuronal death is prevented or simply delayed (Wu et al., 2002, 2003). Nevertheless, research on these neurotoxin models implicates the role of neuroinflammation in potentiating acute injury to DA neurons in models that are distinct from overexpression of α-synuclein.

Role of α-synuclein in PD and in development of prodromal PD

PD is a multi-system neurodegenerative disorder that affects many circuits outside of the nigrostriatal system. Genetic mouse models have been developed to mimic the progressive and widespread α-synuclein pathology of human PD. α-synuclein was the first gene to be associated with PD (Polymeropoulos et al., 1997), and encodes a protein that is highly enriched in presynaptic terminals and regulates vesicle exocytosis and synapse maintenance (Burre et al., 2010; Chandra et al., 2005; Lotharius and Brundin, 2002). It is also the predominant component of PD-associated intraneuronal Lewy bodies (Spillantini et al., 1997). Dominantly inherited mutations in the α-synuclein locus including A53T, A30P, and E46K cause familial early-onset PD. Further studies have revealed associations with the dominant LRRK2 mutation and autosomal-recessive Parkin, PINK-1, and DJ-1 mutations. Mouse models of familial PD expressing these mutant human proteins show varying degrees of α-synuclein accumulation, neurodegeneration, and behavioral changes and have greatly enhanced our understanding of the disease mechanisms (Dawson et al., 2010). However, only around 5% of PD cases are genetically inherited whereas the remaining 95% are sporadic and not caused by any known mutations. Interestingly, polymorphisms in the promoter of the α-synuclein gene are risk factors for developing PD (Farrer et al., 2001; Pals et al., 2004). α-synuclein gene dosage in humans affects the age of onset and severity of PD and triplications at the α-synuclein locus lead to PD (Chartier-Harlin et al., 2004; Ibanez et al., 2004; Singleton et al., 2003). Moreover, age-related increases in α-synuclein protein levels are correlated with sub-threshold decreases of the DA neuron marker tyrosine hydroxylase (TH) in the SN from healthy human and monkey brains (Chu and Kordower, 2007). This suggests that expression levels of α-synuclein may influence the development of sporadic PD. Several wild-type α-synuclein overexpressor (ASO) models, including the Line 61 mice studied by Watson et al., were developed to better model the etiology of sporadic PD. Line 61 mice use the Thy1 promoter to broadly overexpress full-length wild-type human α-synuclein in neurons throughout the brain, a distribution similar to that seen in human PD (Chesselet et al., 2012; Rockenstein et

Please cite this article as: Pradhan, S., Andreasson, K., Commentary: Progressive inflammation as a contributing factor to early development of Parkinson's disease, Exp. Neurol. (2012), http://dx.doi.org/10.1016/j.expneurol.2012.12.008