Neurochemistry International 104 (2017) 34–48

Contents lists available at ScienceDirect

Neurochemistry International

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

Ferroptosis and cell death mechanisms in Parkinson's disease

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ARTICLE INFO

Article history:
Received 2 November 2016
Received in revised form
18 December 2016
Accepted 6 January 2017
Available online 9 January 2017

Keywords:
Alpha-synuclein
Cell death
Ferroptosis
Parkinson's disease

ABSTRACT

Symptoms of Parkinson's disease arise due to neuronal loss in multiple brain regions, especially dopaminergic neurons in the substantia nigra pars compacta. Current therapies aim to restore dopamine levels in the brain, but while these provide symptomatic benefit, they do not prevent ongoing neurodegeneration. Preventing neuronal death is a major strategy for disease-modifying therapies; however, while many pathogenic factors have been identified, it is currently unknown how neurons die in the disease. Ferroptosis, a recently identified iron-dependent cell death pathway, involves several molecular events that have previously been implicated in PD. This review will discuss ferroptosis and other cell death pathways implicated in PD neurodegeneration, with a focus on the potential to therapeutically target these pathways to slow the progression of this disease.

Contents

Abbreviations: 6-OHDA, 6-hydroxydopamine; ACSL4, acyl-CoA synthetase long-chain family member 4; AIF, apoptosis-inducing factor; APP, amyloid precursor protein; αsyn, alpha-synuclein; CSF, cerebrospinal fluid; CP, ceruloplasmin; DR, death-domain receptor; ECM, extracellular matrix; EndoG, Endonuclease G; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GSH, reduced-glutathione; GWAS, genome-wide association study; IRE, iron response element; LB, Lewy body; LC3, protein light chain 3; LIP, labile iron pool; LPCAT3, lysophosphatidylcholine acyltransferase 3; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MOMP, mitochondrial outer membrane permeabilisation; mTOR, mammalian target of rapamycin; NAC, *N*-acetylcysteine; NOS, nitric oxide synthase; PAR, polymerisation of ADP-ribose; PARP-1, poly(ADP-ribose) polymerase 1; PI3K, phosphoinositide 3-kinase; PD, Parkinson's disease; RIP-1, receptor interacting protein 1; ROS, reactive oxygen species; SN, substantia nigra; SNpc, substantia nigra pars compacta; TfR, transferrin receptor; TNFα, Tumor necrosis factor α; TRADD, tumor necrosis factor type 1-associated death domain protein.

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http://dx.doi.org/10.1016/j.neuint.2017.01.004
0197-0186/

1. Introduction

1.1. Parkinson's disease

Parkinson's disease (PD) is typified by death of neurons in the substantia nigra pars compacta (SNpc), which is a region of the basal ganglia that regulates execution and control of motor function, cause rigidity, tremor and other motor symptoms that typify the disease (Fearnley and Lees, 1991; Rinne et al., 1989b). While other regions of pronounced cell loss include the locus coeruleus (Zarow et al., 2003) and nucleus basalis of Meynert (Nakano and Hirano, 1984), there is a strong correlation between the loss of nigral dopaminergic neurons and motor impairment in PD patients (Rinne et al., 1989a, 1989b). Treatment with levodopa elevates striatal dopamine levels that are depleted by SNpc neurodegeneration in PD, however levodopa and other dopamine-based therapies only partially relieve motor symptoms during the early stages of the disease and have no effect on disease progression (Ahlskog and Muenter, 2001; Marsden and Parkes, 1977; Miyawaki et al., 1997). Unfortunately no disease-modifying therapies for PD have yet been identified, and the search for a drug that slows or prevents the death of neurons in the PD brain is a priority. While there are many pathogenic factors implicated in PD, including the protein alpha-synuclein (αsyn) (Baba et al., 1998; Edwards et al., 2010; Pankratz et al., 2009; Satake et al., 2009; Simon-Sanchez et al., 2009; Spillantini et al., 1997), it is currently unknown how these cause or contribute to neuronal death.

1.2. Alpha-synuclein in Parkinson's disease

Multiple genetic loci and mutations have been identified as disease-causative or risk factors for idiopathic or familial PD, however, several genetic studies, including multiple genome-wide association studies (GWAS), have identified SNCA, the αsyn-encoding gene, as one of the strongest independent genetic risk loci for developing idiopathic and familial forms of PD (Edwards et al., 2010; Pankratz et al., 2009; Satake et al., 2009; Simon-Sanchez et al., 2009). Affected members of families identified with the SNCA point mutations A53T (Polymeropoulos et al., 1997), A30P (Kruger et al., 1998), E46K (Zarranz et al., 2004), H50Q (Appel-Cresswell et al., 2013; Proukakis et al., 2013), and G51D (Lesage et al., 2013) exhibit early-onset PD. Duplication (Ikeuchi et al., 2008; Obi et al., 2008) and triplication (Fuchs et al., 2007; Singleton et al., 2003) of the SNCA locus also causes familial PD, which further implicates αsyn as an important mediator of Parkinsonian neurodegeneration.

Intraneuronal Lewy bodies (LB), of which insoluble αsyn fibrils are the major protein component (Baba et al., 1998; Spillantini et al., 1997), are a pathological feature of the SN in the majority of PD cases (Gibb and Lees, 1988; Hughes et al., 1992; Spillantini et al., 1997). The formation of these fibrils follows the conversion of monomeric to oligomeric αsyn (Baba et al., 1998; Giasson et al., 2001), which has been identified as a neurotoxic species *in vivo* (Winner et al., 2011). Striatal injection of exogenously aggregated αsyn into non-transgenic mice induced LB-like deposits and loss of dopaminergic neurons in the SN and Parkinsonian behavioural deficits (Luk et al., 2012). Multiple studies involving different injection sites have since demonstrated that aggregated αsyn is inherently pathogenic (Masuda-Suzukake et al., 2013; Sacino et al., 2014), which supports the hypothesis that αsyn pathology spreads around the brain in stages that correlate with symptom development in patients (Braak et al., 2003, 2004). Therefore, it appears that there is a causal link between αsyn and Parkinsonian neurodegeneration. However, the mechanisms underlying how this protein causes cell death in PD are undefined, and the identification of these cellular processes could lead to a novel therapeutic target to slow PD progression.

2. Cell death mechanisms of Parkinsonian neurodegeneration

There are multiple cell death mechanisms implicated in PD pathogenesis, and a newly identified pathway referred to as ferroptosis has also recently been linked to PD (Do Van et al., 2016). Ferroptosis is an iron-dependent cell death pathway that involves depletion of intracellular reduced-glutathione (GSH) levels (Bannai, 1986; Yang et al., 2014) (the major antioxidant of neurons and natural ligand for iron in the 'labile iron pool' (LIP)) (Hider and Kong, 2011), and lipid peroxidation (Yang et al., 2014). GSH depletion leads to an increase in the labile iron pool (Kaur et al., 2009), which increases the cellular availability of iron as a catalyst for ferroptosis. These features of ferroptosis are also pathogenic changes observed in PD, including the increased availability of catalytic iron via nigral iron elevation (Lei et al., 2012; Mastroberardino et al., 2009; Mochizuki et al., 1994), GSH depletion (Sian et al., 1994; Sofic et al., 1992), lipid peroxidation (Dexter et al., 1986, 1989a) and elevated reactive oxygen species (ROS) generation (Cassarino et al., 1997; Jenner et al., 1992; Sousa et al., 2003; Sriram et al., 1997). Treatments that protect against ferroptosis have shown therapeutic potential in PD. *N*-acetylcysteine (NAC; precursor to GSH synthesis) treatment rescued neurodegeneration in PD mouse models (Park et al., 2004; Perry et al., 1985) and conferred mild motor improvement in an early clinical trial of PD patients (Monti et al., 2016). Iron chelators also have been shown to ameliorate motor symptoms in multiple animal models of PD (Ayton, 2015; Ayton et al., 2013, 2014; Lei et al., 2015; Lei et al., 2012) and in a phase II clinical trial (Devos et al., 2014). Early work has shown that specific ferroptosis inhibitors, such as ferrostatin-1, are beneficial in PD models (Do Van et al., 2016), which suggests that they hold promise for the human condition. In this review, the cell death mechanisms implicated in Parkinsonian neurodegeneration will be discussed as a background to