Ferroptosis and cell death mechanisms in Parkinson's disease

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Abbreviations

6-OHDA: 6-hydroxydopamine, 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, LB: Lewy body, LC3: protein light chain 3, LIP: labile iron pool, 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: Tumour necrosis factor α, TRADD: tumor necrosis factor type 1-associated death domain protein.

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.

Keywords

Alpha-synuclein, cell death, ferroptosis, Parkinson's disease

Introduction

Parkinson's disease (PD) affects multiple systems of the body, causing gastrointestinal (Edwards et al., 1991), olfactory (Ansari and Johnson, 1975), sympathetic (Goldstein et al., 2002; Li et al., 2002) and central nervous system deficits (Fearnley and Lees, 1991; Nakano and Hirano, 1984; Rinne et al., 1989b; Zarow et al., 2003). 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; Rinne et al., 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.

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; Braak et al., 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.

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), iron elevation and lipid peroxidation (Yang et al., 2014). These features of ferroptosis are also pathogenic changes observed in PD, including 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; Dexter et al., 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., 2014; Ayton et al., 2013; Lei et al., 2015; Lei et al., 2012) and in a phase II clinical trial (Devos et al., 2014a). 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 understanding the potential role of the newly identified cell death pathway, ferroptosis, in PD.

Apoptotic cell death mechanisms

Intrinsic caspase-dependent apoptosis

Intrinsic apoptosis pathways are triggered by an intracellular cell stress signal that results in either a caspase-dependent or caspase-independent cell death cascade (Kroemer et al., 2007). Apoptotic cell death pathways have three key stages: the induction phase, in which various stress signals trigger signal transduction pathways, the effector phase, in which multiple stimuli-mediated pathways converge and signal cell death rather than cell survival, and the degradation phase, in which cell structures are destroyed (Kroemer et al., 1995). Internal cell stress signals that activate the induction phase of intrinsic apoptosis include DNA damage (Tamura et al., 1995), oxidative stress (Hockenbery et al., 1993), excitotoxicity (Zeron et al., 2004) and other intracellular stressors. The induction phase then triggers either caspase-dependent or -independent apoptosis.

The effector phase of caspase-dependent intrinsic apoptosis involves stress signal-mediated binding between one of the pro-apoptotic Bcl-2 family proteins, such as Bak or Bax (Wei et al., 2001), and either tumour suppressor protein p53 (Leu et al., 2004) or an anti-apoptotic Bcl-2 protein (Chittenden et al., 1995). As the ratio between Bak or Bax and each of these proteins increases, binding events induce an apoptotic signal (Leu et al., 2004; Oltvai et al., 1993; Raisova et al., 2001). Bak and Bax induce the formation of a pore in the outer mitochondrial membrane (Kushnareva et al., 2012; Kuwana et al., 2002; Martinou and Green, 2001; Wei et al., 2001), also known as mitochondrial outer membrane permeabilisation (MOMP) (Goldstein et al., 2000). Cytochrome C is released from the mitochondria following MOMP (Goldstein et al., 2000), and binds to apoptosis protease activation factor 1 to form a multimeric complex called an apoptosome, which interacts with procaspase 9 to produce caspase 9 (Zou et al., 1999). Caspase 9 activates downstream effector caspases such as caspase 3, which are molecules that initiate the degradation phase of apoptosis (Slee et al., 2001). The consequent destruction of cellular structures

includes chromatin condensation, nuclear fragmentation and cell shrinkage (Kroemer et al., 2007).

Intrinsic caspase-dependent apoptosis is a cell death pathway that has been linked to PD in humans and cell models. Post-mortem studies revealed that nigral dopaminergic neurons expressing caspase-3 are more likely to undergo cell death in PD than cells that fail to express caspase-3 (Hartmann et al., 2000). Nigral dopaminergic neurons of post-mortem late-onset PD brains also expressed caspase-9 and caspase-8 at a greater frequency than in brains of age-matched controls (Viswanath et al., 2001). Furthermore, when compared to control patients post-mortem, PD patients had a greater proportion of nigral neurons containing activated caspase-3 (Hartmann et al., 2000; Tatton, 2000), Bax (Tatton, 2000) and MOMP regulator glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Tarze et al., 2007; Tatton, 2000).

PD toxin models also demonstrate several signs of intrinsic caspase-dependent apoptosis in the SN. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) are two toxins commonly administered to animals to induce PD-like nigral neurodegeneration and motor deficits (Schober, 2004). Administration of MPTP to WT mice induced cytochrome C release and consequent caspase-9, caspase-3 and caspase-8 activation in the SN (Viswanath et al., 2001). Furthermore, treatment of cultured dopaminergic neurons with 1-methyl-4-phenylpyridinium (MPP+), the MPTP metabolite that induces toxicity in the brain, resulted in activation of caspase-9 and caspase-8, and cell death that was rescued by caspase-9 inhibition (Viswanath et al., 2001). High levels of pro-apoptotic protein Bax have also been identified in SN neurons in WT mice, and were further increased following MPTP administration (Bove et al., 2014; Vila et al., 2001). The involvement of Bax in MPTP-induced cell death was further demonstrated by the resistance of Bax KO mice to MPTP-induced nigral neurodegeneration (Vila et al., 2001), and the rescue of lysosomal deficits and nigral neurodegeneration by Bax channel inhibition (Bove et al., 2014). Furthermore, the broad-spectrum caspase inhibitor Q-VD-OPH significantly rescued depletion of SNpc dopaminergic neurons and striatal dopamine following MPTP injection in mice (Yang et al., 2004). This strengthens the hypothesis that MPTP-induced neurodegeneration in mice is mediated by intrinsic caspase-dependent apoptosis. Apoptotic markers have also been identified in 6-OHDA models. Stereotaxic injection of 6-OHDA into rats induced shrunken nuclei (He et al., 2000) and chromatin condensation in the SN (He et al., 2000; Marti et al., 2002) . p53 and Bax expression levels were also elevated in response to 6-OHDA treatment *in vitro* (Blum et al., 1997), which suggests that intrinsic apoptosis is a likely feature of multiple PD models.

αsyn has also been linked to intrinsic caspase-dependent apoptosis. Mice overexpressing A53T mutant αsyn developed αsyn aggregates accompanied by mitochondrial DNA damage, which is a known inducer of apoptosis (Martin et al., 2006). Affected neuronal regions also expressed activated caspase-3 and p53 (Martin et al., 2006). Mutant A30P αsyn-expressing cells were also more susceptible to caspase-9 and caspase-3 dependent apoptosis than cells expressing WT αsyn (Tanaka et al., 2001). Upon exposure to neuronally secreted αsyn, αsyn -overexpressing rat primary cortical neurons showed an increase in caspase-3 levels and nuclear fragmentation (Desplats et al., 2009). The binding of αsyn to the neuronal dopamine transporter caused an increase in dopamine uptake and induced apoptotic-like morphological changes *in vitro*, which could suggest a mechanism by which αsyn induces apoptotic stress signals (Lee et al., 2001).

Intrinsic caspase-independent apoptosis

Intrinsic caspase-independent apoptosis is a pathway that cannot be rescued by caspase inhibition (Kroemer et al., 2009), and involves the release of molecules from the mitochondria in response to MOMP, such as apoptosis-inducing factor (AIF) (Susin et al., 1999) and endonuclease G (EndoG) (Li et al., 2001), which act on the nucleus to cause chromatin condensation, DNA fragmentation and DNA loss (Li et al., 2001; Susin et al., 1999). In a study of PD brain tissue, EndoG was present in significantly more nigral nuclei than age-matched healthy controls (Buttner et al., 2013). Furthermore, EndoG depletion ameliorates αsyn toxicity in cultured cells, directly implicating this molecule in αsyn-mediated cell death (Buttner et al., 2013). AIF expression was upregulated in cells treated with MPP+, while siRNA knockdown of AIF protected against MPP+ mediated cell death (Liou et al., 2005). However, despite these data, there is far more evidence to suggest that caspase-dependent apoptosis contributes to neurodegeneration in PD.

Extrinsic apoptosis

Extrinsic apoptotic pathways are triggered by an extracellular binding event between a ligand and either a death-domain receptor (DR) or dependence receptor, which induces a stress signal and activates an intracellular cell death cascade (Galluzzi et al., 2012). Dependence receptor-mediated extrinsic apoptosis is not well characterised, but is described as the activation of the effector caspase cascade in response to deprivation of a particular ligand at a dependence receptor (Galluzzi et al., 2012). DR-mediated apoptosis involves the release of specific ligands in response to cellular stress. Tumour necrosis factor α (TNFα) (Hsu et al., 1995) and FAS ligand (Brunner et al., 1995) are just two examples of molecules that bind to extracellular DR. TNFα binding to TNFαR induces recruitment of signalling molecules TNF-receptor type 1-associated death domain protein (TRADD) and consequently kinase receptor interacting protein 1 (RIP-1) to the tail of the cytoplasmic domain (Hsu et al., 1996a). Once a complex is formed, TNF receptor-associated factor 2 can interact with the N-terminal of TRADD to induce the anti-apoptotic NFκβ pathway (Hsu et al., 1996b; Hsu et al., 1995), while Fas-associated protein with death domain (FADD) can interact with the death domain of TRADD to induce a pro-apoptotic pathway via caspase-8 activation (Hsu et al., 1996b; Wang et al., 2008). Caspase-8 triggers a cascade of caspase-dependent pathways and downstream cleavage and activation of effectors such as the pro-apoptotic Bcl2-interacting protein BID (Li et al., 1998), which then induce the intrinsic caspase-dependent apoptotic pathway. Cells in which NFκβ signalling is inhibited are more susceptible to TNFα-induced apoptosis (Van Antwerp et al., 1996), and downregulation of this signalling pathway likely increases the susceptibility to apoptosis (He and Ting, 2002; Kelliher et al., 1998).

Several human and animal studies demonstrated evidence of a role for extrinsic apoptosis in Parkinsonian neuronal cell death. TNFα levels are elevated in the striatum and cerebrospinal fluid (CSF) of PD patients (Mogi et al., 1994), and knockout of TNF receptors in mice protected against MPTP neurotoxicity in SN dopaminergic neurons (Sriram et al., 2002). Furthermore, TNFα mRNA is upregulated in the striatum of mice overexpressing A53T and A30P αsyn (Su et al., 2009). Since several steps of the intrinsic caspase-dependent apoptotic pathway are also common to extrinsic apoptosis, it could be argued that evidence in humans, animal and cell models of PD point towards extrinsic apoptosis as the most likely apoptotic pathway contributing to PD neurodegeneration.

However, while based on this evidence targeting apoptosis might seem a promising strategy for disease-modification in PD, apoptosis also plays an essential role in preventing the survival of damaged and potentially mutated cells that could induce diseases such as cancer

(Yin et al., 1997). Therefore, pharmacologically targeting such a widespread and critical pathway has the potential to induce oncogenesis and other damage in cells throughout the body. Indeed, the addition of a broad-spectrum caspase inhibitor, z-VAD-fmk, in an MPP+ culture model signalled a change from apoptotic to necrotic cell death (Hartmann et al., 2001), despite evidence that caspase-8 was contributing to neurotoxicity. Identifying targets further upstream of apoptosis in PD will likely yield more promising disease-modifying.

Anoikis

Anoikis is a cell death mechanism which occurs when the integrin-mediated interaction between a cell and the extracellular matrix (ECM) is disrupted, causing cells to no longer be anchored to the ECM, and apoptosis to be triggered (Frisch and Francis, 1994). While the mechanism by which anoikis is triggered is still being investigated, several pro-apoptotic pathways have been implicated. Following epithelial cell detachment from the ECM, Bcl-2 transcription was reduced, which caused increased activation of the Jun-N Terminal Kinase pathway, and ultimately apoptosis (Frisch et al., 1996). Epithelial cell detachment also caused inhibition of phosphoinositide 3-kinase (PI3K) activity (Khwaja et al., 1997), which is a pro-apoptotic cellular event (Almeida et al., 2005; Hussain et al., 2006; Shimamura et al., 2003). A study of endothelial cell detachment indicated that activation of the FAS pathway disrupted cell anchorage to the ECM, and possibly triggered anoikis in these cells (Aoudjit and Vuori, 2001).

There are several studies linking anoikis to cell death in PD. Detachment of endothelial cells from ECM causes elevation of mitochondrial reactive oxygen species (ROS), a known feature of PD, which modulates anoikis by activating the Jun-N Terminal Kinase pathway and increasing caspase-3 activity (Li et al., 1999). While anoikis has predominantly been studied in epithelial (Frisch and Francis, 1994; Frisch et al., 1996; Khwaja et al., 1997) and endothelial (Aoudjit and Vuori, 2001; Li et al., 1999) cells, which require tightly-regulated integrin binding to ECM in order to function, anoikis can also occur within neurons, the key cell type susceptible to cell death in PD. Rat primary hippocampal neurons bound to a laminin (integrin-binding ligand) surface were resistant to glutamate-induced apoptosis when compared to neurons cultured on a poly lysine surface due to reduced activation of PI3K pathway (Gary and Mattson, 2001). Neurons cultured on poly lysine that were treated with an integrin-binding peptide showed a significant rescue of cell death (Gary and Mattson, 2001), indicating that anoikis was the cell death pathway observed in these neurons.

An integrated pathways analysis of PD GWAS and protein expression profiles indicated that focal adhesion pathways were the second most over-represented pathway in PD (Edwards et al., 2011). Additionally, cultured neurons undergoing αsyn-mediated cell death showed reduced attachment to the culture surface, while overexpression of Bcl-2 protected against αsyn toxicity (Saha et al., 2000). Further study of anoikis, including PD toxin models *in vivo*, is needed to determine whether anoikis is a significant contributor to PD neurodegeneration.

Autophagic cell death

Autophagic cell death is defined as any mechanism mediated by autophagy in which cell death can be prevented by chemically or genetically inhibiting autophagy (Galluzzi et al., 2012). Autophagy involves the sequestration of organelles within a double membranous vesicle known as an autophagosome, which is directed to lysosomes for degradation of its contents (Klionsky and Emr, 2000). Each of the five major steps of autophagy, induction of autophagy, autophagosome formation, autophagosome docking, lysosomal fusion and autophagic breakdown, are tightly regulated processes (Klionsky and Emr, 2000). Autophagosome formation can occur via suppression of mammalian target of rapamycin

(mTOR) kinase (Boland et al., 2008), or via an mTOR-independent mechanism, such as Ca^{2+}/calpain- and inositol-dependent signalling pathways (Sarkar et al., 2005; Williams et al., 2008). Microtubule associated protein light chain 3 (LC3)-II levels are consequently increased (Boland et al., 2008), and accumulate on the autophagosomal membrane as autophagy progresses (Kabeya et al., 2000). Sequestration of organelles and cytoplasm into an autophagosome is mediated by the covalent binding, or conjugation, of two different Atg proteins, Atg5 and Atg12 (Mizushima et al., 1998). An autophagosome then docks and fuses to the lysosomal membrane, and its contents undergo lysosomal degradation (Klionsky and Emr, 2000). However, further research is required to distinguish physiological autophagy in cells from autophagy-mediated cell death.

It is unknown whether autophagy contributes to cell death in PD. Morphological indications of autophagic cell death were identified in several melanised nigral dopaminergic neurons of PD patients (Anglade et al., 1997), and a post-mortem study of PD patients identified LC3-II expression in 80% of nigral LBs, and LC3-II upregulation in the SNpc, indicating an increase in autophagosome formation (Dehay et al., 2010). Furthermore, lysosomal markers were significantly reduced in the nigra (Chu et al., 2009; Dehay et al., 2010), with the most pronounced depletion of lysosomes in neurons containing αsyn inclusions (Chu et al., 2009). Depletion of lysosomes and a consequent increase in autophagosome formation has also been identified as a feature of nigral dopaminergic neurodegeneration in an MPTP-mouse model (Dehay et al., 2010). Taken together, this indicates that an increase in autophagosome formation and a depletion of lysosomes are likely features of the PD nigra, indicating an impairment in the autophagy-lysosome pathway.

Loss of function of several genes that have familial PD-associated mutations, such as DJ-1 and ATP13A2, have been implicated in impaired lysosome function and autophagy *in vitro* (Dehay et al., 2012; Gusdon et al., 2012; Krebiehl et al., 2010). Immortalised mouse DJ-1 fibroblasts showed signs of lysosomal dysfunction and reduced basal levels of autophagy (Krebiehl et al., 2010), which suggests that loss of DJ-1 function would similarly impair autophagy and lysosomal function in humans. Over 90% of nigral LBs contain ATP13A2 (Dehay et al., 2012), and surviving SNpc neurons express elevated ATP13A2 mRNA levels in the PD brain when compared with age-matched controls post-mortem (Ramirez et al., 2006). ATP13A2 mutations in PD-derived fibroblasts showed impaired lysosome function, while ATP13A2 knockdown resulted in cell death that was exacerbated by administration with lysosomal inhibitors, chloroquine and ammonium chloride (Dehay et al., 2012), which could indicate ATP13A2 loss of function in PD contributes to impaired autophagy. ATP13A2 knockdown also resulted in accumulation of endogenous αsyn, and toxicity due to loss of ATP13A2 was exacerbated by αsyn overexpression (Dehay et al., 2012). An increase in ATP13A2 levels in cultured neuroblastomas caused an increase in endogenous αsyn exported via exosomes (Kong et al., 2014). Interestingly, a mutant form of a lysosomal enzyme, cathepsin D, resulted in accumulation of endogenous αsyn (Crabtree et al., 2014), and cathepsin D overexpression decreased αsyn aggregation and protected against toxicity due to mutant A53T and A30P αsyn *in vitro* (Qiao et al., 2008).

A role for αsyn in autophagy or mediating autophagic cell death is not yet clear. Multiple studies indicate that mutant αsyn may inhibit chaperone-mediated autophagy (Cuervo et al., 2004; Martinez-Vicente et al., 2008; Xilouri et al., 2009), macroautophagy (Winslow et al., 2010) and mitophagy (Chinta et al., 2010) *in vitro*, and that impairment in autophagocytic breakdown of mutant αsyn contributes to neurotoxicity (Xilouri et al., 2009). Cellular overexpression of WT and mutant A53T αsyn caused a reduction in LC3-II levels (Song et al., 2014), while αsyn oligomeric accumulation, impaired lysosomal degradation and cell death arising from WT αsyn overexpression was reduced with administration of an

autophagy activator, trehalose (Hollerhage et al., 2014). Trehalose, which causes an upregulation in autophagosome formation when administered to cells (Casarejos et al., 2011), also rescued cellular accumulation of αsyn aggregates (Casarejos et al., 2011), and disaggregated A53T fibrils and prevented its aggregation when co-incubated (Yu et al., 2012).

Genetic, pathological and toxicology evidence link elevated autophagosome formation and lysosomal dysfunction to PD. While accumulation of autophagosomes could indicate that autophagic cell death is a key feature in PD neurodegeneration, it could also be a sign of dysfunction in the ability of lysosomes to fuse and degrade the contents of autophagosomes. Indeed, there is evidence to suggest that lysosomal degradation precedes an increase in autophagosomes *in vitro* in a PD toxin model (Dehay et al., 2010). Therefore, further evidence is needed to determine whether autophagic cell death is a significant contributed to Parkinsonian neurodegeneration, or whether impairments in autophagy are a pathological step that contributes to another cell death pathway.

Necrotic cell death pathways

Necrosis

Necrosis is a cell death cascade that lacks the morphological and biochemical components of apoptosis and autophagic cell death, and which often is caused by or leads to inflammation due to pathological cell loss (Galluzzi et al., 2007). Necrosis has also been characterised as RIP-1 dependent and activated by a receptor or in response to cellular damage (Golstein and Kroemer, 2007). Cyclophilin D, a mitochondrial matrix protein which regulates the permeability of the mitochondrial membrane (Nakagawa et al., 2005; Thomas et al., 2012), induces Ca^{2+} accumulation and ROS production in response, and is followed by calpain- and cathepsin-mediated proteolysis (Golstein and Kroemer, 2007). Necrotic morphological features include mitochondrial swelling and perinuclear clustering, lysosomal rupture and ultimately plasma membrane rupture (Golstein and Kroemer, 2007). However, cyclophilin D is considered the best biochemical marker distinguishing necrotic from apoptotic cell death (Thomas et al., 2012).

Mice deficient in cyclophilin D are less susceptible to mitochondrial damage, membrane depolarisation and ROS generation in nigral dopaminergic neurons following acute MPTP administration (Thomas et al., 2012). Induction of A53T mutant αsyn expression in cultured cells primarily induced apoptotic morphological changes, with necrotic morphological changes identified in only 3-5% of cells (Smith et al., 2005). However, there is as yet limited data on necrosis in PD-affected human tissue, or PD models.

Necroptosis (regulated necrosis)

Necroptosis describes a mechanism of regulated necrosis that occurs in the absence of apoptosis signals. Necroptosis is activated by ischemic injury or TNFα, which binds to a DR to induce RIP-1-mediated mitochondrial dysfunction, cytoplasmic membrane disruption and loss of autophagic clearance of cellular debris (Degterev et al., 2005). NMDA-mediated excitotoxicity, which has been implicated in PD neurodegeneration (Beal, 1998), was rescued *in vitro* by the necroptosis inhibitor, nectrostatin-1 (Li et al., 2008). This suggests that excitotoxicity is a downstream consequence of necroptotic cell death. Accumulation of intracellular Ca^{2+} also caused necroptosis in human neuroblastomas *in vitro* (Nomura et al., 2014), which is important because Ca^{2+} signalling has been identified as one of the most overrepresented pathways in gene and protein expression studies of PD (Edwards et al., 2011).

As previously mentioned, TNFα is extensively implicated in PD pathogenesis, which strengthens the evidence for the involvement of necroptosis in PD (Mogi et al., 1994; Sriram et al., 2002; Su et al., 2009). Necrostatin-1 also rescued 6-OHDA toxicity in cultured cells, causing stabilisation of mitochondrial membrane potential and inhibition of autophagy (Wu et al., 2015). Another inhibitor of necroptosis, curcumin, rescued toxicity due to ferrous chloride overload in primary cortical neurons, and reduced RIP-1 expression levels (Dai et al., 2013), providing another potential pathway by which iron exerts toxicity in PD. Taken together, there are several links that could identify necroptosis as a potential candidate for nigral cell death in PD.

Other cell death pathways

Parthanatos

Parthanatos is a caspase-independent cell death pathway that involves activation of the enzyme poly(ADP-ribose) polymerase 1 (PARP-1) in response to strand breaks in DNA (David et al., 2009). PARP-1 activation triggers post-translational NAD^+-dependent polymerisation of ADP-ribose (PAR), and the newly formed PAR polymer interacts with chromatin-associated proteins to mediate repair of DNA damage (Ame et al., 2004). Over activation of PARP-1 leads to a pathological depletion of NAD^+ and ATP (Gaal, 1987), and an accumulation of the PAR polymer, which triggers the release of AIF (Yu et al., 2006). A binding event between PAR and AIF is required for AIF to translocate to the nucleus and initiate parthanatos in cells (Wang et al., 2011).

Several studies have implicated parthanatos in PD. An *in vivo* study showed that MPTP administration in WT mice increased expression of PARP in nigral dopaminergic neurons (Mandir et al., 1999), while PARP KO mice were protected against MPTP toxicity, suggesting that PARP over-activation is a mediator of MPTP-neurotoxicity. Treatment of mice with a PARP inhibitor rescued MPTP-induced reduction of striatal ATP and NAD^+ levels (Cosi and Marien, 1999). Furthermore, several PARP inhibitors significantly protected MPTP-induced striatal dopamine depletion in both cultured rat primary dopaminergic neurons (Outeiro et al., 2007) and in WT mice (Cosi et al., 1996), further implicating parthanatos in MPTP-neurotoxicity. Neuronal nitric oxide synthase (nNOS) KO mice showed no signs of striatal ADP-ribose polymerisation following MPTP administration when compared with WT (Mandir et al., 1999), suggesting that MPTP-induced PARP activation and consequent ADP-ribose polymerisation is likely dependent on NO-induced DNA damage. Since nigral NO levels are significantly increased in PD (Ayton, 2015; Hunot et al., 1996) this strengthens the evidence for parthanatos as a cell death pathway by which nigral dopaminergic neurons are selectively depleted in the disease.

PARP-1 inhibition has also rescued αsyn-induced neurotoxicity in transfected cells *in vitro* (Outeiro et al., 2007), indicating that pharmacologically inhibiting PARP could be a promising therapeutic strategy for targeting αsyn toxicity in addition to preventing dopaminergic neuron depletion. Overexpression of AIMP2, a substrate of the PD-implicated parkin gene, caused overactivation of PARP-1 and cell death in SH-SY5Y cells due to direct association of AIMP2 with the nucleus (Lee et al., 2015). AIMP2 overexpressing mice showed increased PARP-1 activation and increased nigral dopaminergic neuron depletion and motor deficits when compared to WT mice, which was rescued by administering a PARP-1 inhibitor (Lee et al., 2015). This is particularly relevant, as AIMP2 has not only been identified in LBs in sporadic PD (Corti et al., 2003), but also accumulates in the SN (Corti et al., 2003) and striatum (Corti et al., 2003; Ko et al., 2010) of PD patients. Taken together, these data support the hypothesis that parthanatos is a cell death pathway involved in PD. However, further investigation is needed into whether PARP inhibition is a valid therapeutic strategy for PD in

humans, as long-term side effects have been hypothesised to accompany treatment with this class of drugs (Graziani and Szabo, 2005).

Pyroptosis

Pyroptosis, a caspase-1 dependent cell death mechanism that was first shown in macrophages (Brennan and Cookson, 2000; Fink et al., 2008) and dendritic cells (Fink et al., 2008), causes DNA cleavage, activation of cytokines and consequently, cell lysis in response to pathogenic bacteria. Cell exposure to a pathogen triggers the activation of an inflammasome complex consisting of caspase-1, NLRP3, and other innate immune response mediators (Martinon et al., 2002). The inflammasome activates caspase-1 and consequently induces the pyroptotic cell death cascade (Fink et al., 2008; Martinon et al., 2002). While originally identified as an innate immune response to presentation of pathogenic organisms, pyroptosis has since been found to occur in response to presentation of other cellular stressors, including the neurodegenerative proteins amyloid-beta (Tan et al., 2014) and fibrillary αsyn (Codolo et al., 2013) in cultured cortical neurons and monocytes, respectively.

This is particularly relevant to PD, as IL-1β levels are significantly increased in the CSF of PD patients when compared to healthy controls (Blum-Degen et al., 1995). In a 6-OHDA model, increased IL-1β expression in the rat SN induced progressive loss of dopaminergic neurons and motor impairment (Ferrari et al., 2006) and increased the susceptibility of dopaminergic neurons to cell death (Koprich et al., 2008). αsyn fibrils have also been shown to interact with toll-like receptor 2 to activate NLRP3 inflammasomes in a ROS-independent mechanism and consequently release IL-1β cytokines in cultured monocytes (Codolo et al., 2013). Furthermore, aggregated αsyn induces release of NO and upregulation of toll-like receptor and IL-1β expression via microglial activation (Beraud et al., 2011), a process which has been pathogenically linked to αsyn toxicity in dopaminergic neurons *in vitro* (Zhang et al., 2005). Therefore, there have been several links established between inflammation, αsyn and PD that could implicate pyroptosis as a cell death pathway contributing to neurodegeneration in PD. However, further research is required to determine whether pyroptosis can occur within dopaminergic neurons and other neurons affected in PD, or whether the cytokine release from this cell death mechanism triggers activation of another cell death cascade within neurons.

Mitotic catastrophe

Mitotic catastrophe is a cell death mechanism that occurs as a result of disrupted mitosis. Despite debate in the literature, a popular definition is that mitotic catastrophe occurs due to defective chromosomal segregation or a failure of other mitotic processes, leading to an arrest of mitosis and consequent cell death cascade (Galluzzi et al., 2012). While no articles have implicated mitotic catastrophe in human PD, αsyn over-expression increased the number of cells in the S phase of mitosis *in vitro*, elevated proliferation rate and phosphorylation of ERK1 and ERK2, which are signalling molecules involved in cell proliferation (Lee et al., 2003). Furthermore, αsyn overexpression induced elevated expression of the mitotic molecule cyclin B, which is accumulated in the nucleus immediately prior to a cell undergoing mitosis (Gallant and Nigg, 1992), which was also found to be upregulated in αsyn positive LBs in PD post-mortem brains (Lee et al., 2003). This could indicate that αsyn contributes to neurodegeneration in PD by altering ERK-dependent regulation of the cell cycle.

Since neurons are post-mitotic, under physiological conditions activation of the cell cycle would not occur, and aberrantly triggering the cell cycle in differentiated neurons could therefore lead to mitotic catastrophe. Interestingly, cyclin B2 expression was significantly

upregulated in cultured sympathetic neurons in response to dopamine exposure (Shirvan et al., 1997), which could suggest that dopaminergic neurons might be more susceptible to mitotic catastrophe. However, more research is required to determine whether mitotic catastrophe is a likely contributor to neurodegeneration in PD.

Ferroptosis- a possible cell death pathway in PD

Ferroptosis is a recently identified caspase-independent, iron-dependent cell death pathway that is in the early stages of characterisation (Dixon et al., 2012). Key features of ferroptosis include depletion of GSH, lipid peroxidation, and distinct morphological changes, including shrunken mitochondria, chromatin condensation, cytoplasmic swelling and plasma membrane rupture (Dixon et al., 2012).

Ferroptosis can be induced *in vitro* by administration of the small molecule erastin, which inhibits the xCT cystine/glutamate antiporter and consequently prevents cystine uptake into a cell and causes ferroptotic cell death via a MEK-dependent signalling pathway **(Figure 1)** (Dixon et al., 2012). Cystine is converted to cysteine within the cell, which is a rate-limiting precursor of glutathione synthesis. Decreased cystine uptake when xCT is inhibited leads to lower levels of GSH synthesis (Bannai, 1986; Yang et al., 2014). GSH is consumed by glutathione peroxidases such as GPX4 (Yang et al., 2014), which detoxifies hydrogen peroxide on phospholipid membranes (Ursini and Bindoli, 1987). A second inducer of ferroptosis, RSL3, causes ferroptosis by binding and inactivating GPX4 (Yang et al., 2014). Therefore, both erastin and RSL3 administration induce lipid peroxidation and ROS generation, which contributes to ferroptotic cell death (Dixon et al., 2012; Yang et al., 2014).

GSH is also the natural ligand for ferrous iron in the LIP (Hider and Kong, 2011). The LIP is an exchangeable pool of loosely ligated iron within neurons. GSH binding to iron in the LIP prevents ferrous iron being oxidised, which (1) maintains solubility of iron (ferric iron is highly insoluble) and (2) prevents ferrous iron acting as a catalyst for the production of the potent oxidant, the hydroxyl radical, from physiologically available hydrogen peroxide. Exhaustion of GSH liberates iron to generate hydroxyl radicals, and induce the lipid peroxidation observed in ferroptosis.

Erastin-induced ferroptosis is rescued by iron chelation (Dixon et al., 2012; Torii et al., 2016; Yang and Stockwell, 2008), indicating that iron is a necessary mediator of the cell death pathway. Cells susceptible to ferroptosis have upregulated transferrin receptor 1 (TfR1), which is required to form a complex with transferrin for iron uptake, and downregulated expression of ferritin (Yang and Stockwell, 2008), which is involved in intracellular iron storage. This likely results in a propensity of these cells towards iron elevation. Autophagy has also been implicated in ferroptosis, since lysosomal inhibitors were found to reduce ferroptosis by reducing TfR1 iron uptake, autophagic degradation of ferritin and ROS generation (Torii et al., 2016). Furthermore, knockdown of two genes involved in autophagosome formation, Atg5 and Atg7, reduced iron accumulation and lipid peroxidation after erastin-administration (Hou et al., 2016). Increasing the expression of a receptor required for autophagic breakdown of ferritin, NCOA4, caused elevation of iron levels while lowering GSH, and consequently induced lipid peroxidation and increased erastin-mediated cell death (Hou et al., 2016). Conversely, NCOA4 knockdown reversed these effects (Hou et al., 2016). Therefore, autophagy is likely an upstream mediator of iron elevation in ferroptosis.

Agents shown to inhibit ferroptosis include ferrostatin-1 (Do Van et al., 2016), deferiprone (Do Van et al., 2016), NAC (Do Van et al., 2016) and liproxstatin-1 (Friedmann Angeli et al., 2014). Ferrostatin-1 and liproxstatin-1 prevent ferroptosis by inhibiting lipid peroxidation

(Friedmann Angeli et al., 2014; Skouta et al., 2014). The iron chelator deferiprone rescues ferroptotic cell death by preventing iron accumulation (Do Van et al., 2016), while NAC protects against ferroptosis by elevating intracellular GSH levels (Yang et al., 2014).

Investigating key components of the ferroptotic cell death pathway reveals several mediators previously implicated in PD pathogenesis. Iron accumulation is a feature of the SN in PD (Ayton and Lei, 2014; Dexter et al., 1991; Dexter et al., 1989b; Good et al., 1992; Hirsch et al., 1991; Lei et al., 2012; Sofic et al., 1988). As a strong reducing agent, iron produces hydroxyl radicals (Bilinski et al., 1985), and induces oxidation of dopamine (Linert et al., 1996), which likely contributes to an oxidative environment that increases loss of nigral dopaminergic neurons in PD (Jenner et al., 1992). Furthermore, genetic disorders that result in brain iron dyshomeostasis often cause parkinsonism (Costello et al., 2004; Miyajima et al., 2003; Nielsen et al., 1995), demonstrating a clear potential for iron elevation that occurs in PD to contribute to PD pathogenesis.

Mutations in several proteins related to iron uptake and export have been linked to PD. Mutant forms of transferrin, a critical protein for neuronal iron uptake, are associated with increased susceptibility to PD (Borie et al., 2002; Rhodes et al., 2014). This could suggest that the iron uptake mechanism is overactive in these patients resulting in increased neuronal iron accumulation. Conversely, mutations in TfR2 (Rhodes et al., 2014) were associated with a protective effect in PD, potentially due to a reduction in functional iron uptake and consequently lowering the risk of iron elevation. Neuronal iron export occurs via a transmembrane ion channel, ferroportin (Donovan et al., 2005), and the AD-implicated amyloid precursor protein (APP) stabilises ferroportin expression on the membrane to promote iron efflux (Duce et al., 2010), while loss of APP membrane function results in impaired iron efflux and consequent neuronal iron retention (Lei et al., 2012). Ceruloplasmin (CP) enables iron export by converting Fe^{2+} to Fe^{3+} (Osaki et al., 1966), which is then bound to and removed by transferrin. Several rare variants of APP predispose individuals to PD (Schulte et al., 2015), and examination of several studies of familial AD indicate APP mutations are associated with parkinsonism (Edwards-Lee et al., 2005; Rosenberg et al., 2000), and LB formation (Halliday et al., 1997; Rosenberg et al., 2000). Similarly, several point mutations in the CP-encoding gene are significantly associated with PD (Hochstrasser et al., 2004), and parkinsonism (Kohno et al., 2000; Miyajima et al., 2003), indicating that CP-mediated iron homeostasis mechanisms are also likely involved in PD pathogenesis. A significant depletion of APP expression levels in the independent of cell loss and an 80% decrease in CP activity in the PD nigra further ties deficits in iron export to the disease, resulting in iron accumulation (Ayton et al., 2013; Ayton et al., 2015b).

Recent evidence suggests that iron is a tractable therapeutic target for PD. Treatment of cell culture and MPTP mouse models with the iron chelator, deferiprone, reduces oxidative stress and increases dopamine availability, with consequent improvements in existing motor symptoms and reduced deterioration of motor function (Devos et al., 2012). Deferiprone treatment also slowed progression of motor deficits and reduced existing motor symptoms in early stage PD patients over an 18-month period in a small group of PD patients (Devos et al., 2014a). Replication of this result in a phase III trial would make deferiprone the first successful disease-modifying therapy for PD, which points to a critical role for iron in disease-causative mechanisms.

Oxidative stress is also extensively implicated in PD. Lipid peroxidation is elevated in the substantia nigra in PD (Dexter et al., 1989a) and increases nigral neurodegeneration (Dexter et al., 1986), and pronounced decrease of nigral reduced glutathione levels is likely an early event in PD pathogenesis (Jenner et al., 1992). Coupled with the observation that human PD

patients treated with deferiprone showed an increase in CSF glutathione peroxidase activity in addition to reduced motor impairment over 6 months (Devos et al., 2014b), both GSH expression levels and glutathione peroxidase activity are likely mediators of cell death in PD. Furthermore, the GSH synthesis precursor, NAC, improved PD neurodegeneration in a recent phase II clinical trial (Monti et al., 2016), however, a much larger clinical trial is required to confirm this improvement in motor symptoms. αsyn can directly interact with mitochondrial membrane to induce elevated nitric oxide and Ca^{2+} levels, and oxidative stress (Parihar et al., 2008). While we are not aware of any studies that have explored whether αsyn is involved in ferroptotic cell death, ferroptosis is a strong candidate for a cell death pathway contributing to PD neurodegeneration, as it involves several cellular events that are common to the PD brain and *in vivo* models.

While the rationale for the involvement of ferroptosis in PD is strong, only one paper has investigated ferroptosis directly in relation to PD cell death mechanisms thus far. A human dopaminergic neuronal precursor derived cell line, LUHMES cells, were identified as uniquely sensitive to ferroptosis, and exhibited several features of ferroptosis when treated with erastin, including pronounced MEK-dependent cell death following activation of PKCα, and significantly reduced total glutathione levels (Do Van et al., 2016). Erastin-induced toxicity was rescued with administration of the previously identified ferroptosis inhibitors, iron chelator deferiprone and NAC, while apoptosis and autophagy inhibitors failed to rescue toxicity. Furthermore, dopamine toxicity in LUHMES cells could be rescued by ferroptosis inhibitors and increased dopamine expression exacerbated erastin toxicity, suggesting that dopaminergic neurons could be inherently susceptible to ferroptosis. This could explain why the enrichment of both iron and dopamine in neurons increases vulnerability toward PD neurodegeneration (Hare, 2014). Organotypic slice cultures treated with erastin caused significant cell loss in the striatum, a region affected by neurodegeneration in PD, while administration of MPP+ induced toxicity that could be rescued by ferroptosis inhibitors (Hare, 2014). Coupled with the observation that injecting mice with ferrostatin-1 24 hours prior to MPTP treatment could significantly rescue behavioural impairment and neuron loss (Hare, 2014), this suggests that the mechanism by which common PD toxins cause neurodegeneration in animal models could be ferroptosis.

Conclusion

This review has described the currently recognised neuronal cell death pathways, and their potential links to PD. Multiple pathways are likely to be involved in Parkinsonian neurodegeneration; the pathways that have the most support as candidates for PD-specific cell death appear to be intrinsic and extrinsic caspase-dependent apoptosis, and autophagic cell death, which have been studied extensively for several decades in regards to PD. Ferroptosis is a new cell death pathway that has only recently been investigated in PD, but there is a strong rationale for involvement of this pathway in the disease. Several ferroptosis inhibitors, such as deferiprone, ferrostatin-1, and NAC have already been identified, with both deferiprone and NAC being well tolerated in humans and showing promise for PD patients in early trials. Future research should focus on ascertaining the involvement of αsyn in ferroptosis and the contribution of ferroptotic cell death in PD, in order to determine whether pharmacologically targeting this pathway could be a promising disease-modifying strategy for patients. Finally, iron accumulation is also a common feature of other neurodegenerative diseases including Alzheimer's and Huntington's diseases (Ayton et al., 2015a; Bartzokis et al., 1999), and therefore, ferroptosis inhibitors could have broad-acting benefits in other neurodegenerative diseases where there are currently no disease modifying therapies.

Conflicts of interest

The authors declare no conflicts of interest.

Figure Legend

Figure 1. Links between ferroptosis and Parkinson's disease. Evidence supporting pathological involvement of ferroptosis in humans (blue circles), and evidence suggesting pharmacological modulators of ferroptosis could be beneficial in PD (purple circles). Blue: (1) transferrin (Tf)- mutations increase susceptibility (Borie et al., 2002; Rhodes et al., 2014); (2) ceruloplasmin (CP)- mutations increase susceptibility (Rhodes et al., 2014); (3) amyloid precursor protein (APP)- mutations increase susceptibility, expression levels reduced in PD (Ayton et al., 2015b; Schulte et al., 2015); (4) reduced-glutathione- nigral depletion (Jenner et al., 1992); (5) ferrous iron (Fe(II))- nigral elevation (Ayton and Lei, (2014); Dexter et al., 1991; Dexter et al., 1989b; Good et al., 1992; Hirsch et al., 1991; Lei et al., 2012; Sofic et al., 1988); (6) lipid peroxidation- nigral elevation (Dexter et al., 1989a, Dexter et al., 1986). Purple: (1) deferiprone (DFP)- motor improvement in phase II clinical trial. (Devos et al., 2014b), (2) N-acetylcysteine (NAC)- mild motor improvement in phase II clinical trial (Monti et al., 2016).

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