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Review

Genetics and iron in the systems biology of Parkinson's disease and some related disorders

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ABSTRACT

The systems biology approach to complex diseases recognises that a potentially large number of biochemical network elements may be involved in disease progression, especially where positive feedback loops can be identified. Most of these network elements will be encoded by genes, for which different alleles may affect the network(s) differentially. A primary requirement is therefore to determine the relevant gene-network relationships. A corollary of this is that identification of the network should thereby allow one to 'explain' or account for any genetic associations.

We apply this approach to Parkinson's disease, a disease characterised by apoptotic death of neurons of the substantia nigra, and coupled significantly to a derangement of iron metabolism. We thereby account for the involvement of various genes and biochemical pathways associated with Parkinsonism, including seemingly unconnected ones involving iron, α-synuclein, parkin, mitochondrial respiration and biology, ceramide production, lysosome biology, Lewy body formation, and so on. Although such an analysis necessarily recognises that there is no unitary 'cause' of Parkinson's, it also recognises that each of the elements contributing can or does effectively converge on a particular mode of apoptotic cell death in dopaminergic neurons, often involving iron-mediated hydroxyl radical formation.

Overall, the systems biology approach allows us to propose at least one coherent synthesis of the rather disparate literature surrounding the aetiology of Parkinson's disease, and thereby to suggest some (synergistic) targets for ameliorating the disease and its progression.

1. Introduction

As with all traits, especially if the phenotype is heterogenous and ambiguous (Yang et al., 2010), sporadic idiopathic Parkinson's disease (PD) (OMIM entry #168600) is recognised as a complex multifactorial disease, most likely with a variety of subforms with variable contributions of genetic susceptibility and environmental factors (Jellinger, 2012; Winklhofer and Haass, 2010) At the cellular level the main manifestation responsible for the disease-characterizing motor features is a progressive degeneration and loss of preferential dopaminergic neurons containing neuromelanin in the substantia nigra (SN) (Gibb, 1992; Kastner et al., 1992) and the production of intracytoplasmic inclusions of protein/lipid aggregates called Lewy bodies (LB). At the clinical or physiological level the disease is characterised by a variety of motor (bradykinesia, rigidity, tremor, postural instability) and non-motor symptoms (hyposmia, autonomic dysfunction, REM sleep behaviour disorder, depression, cognitive decline and others) (Chaudhuri and Schapira, 2009; Maetzler et al., 2009; Singh et al., 2007).

Given that the existence of neurodegeneration in PD is not in doubt, and that it affects many parts of the central and peripheral nervous system (Braak et al., 2003; Wakabayashi et al., 2010), the main questions to be asked are

(i) Why is neurodegeneration especially prevalent and harmful in the substantia nigra?, and

Abbreviations: LB, Lewy body; PD, Parkinson's disease; SN, substantia nigra; ROS, reactive oxygen species; IRE/IRP, iron responsive element/iron responsive protein; NBIA, neurodegeneration with brain iron accumulation; KRS, Kufor-Rakeb syndrome; LRRK2, leucine rich repeat kinase 2; GBA, Glucocerebrosidase; INAD, infantile neuroaxonal dystrophy; AD, Alzheimer's disease; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; AP, amyloid plaque; MRI, magnetic resonance imaging; TCS, transcranial sonography.

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(ii) What is the actual mechanism of this neurodegeneration?

Although, by definition, PD shares neurodegenerative properties with other neurodegenerative diseases such as Alzheimer's, Huntington's and Friedreich's Ataxia, we shall seek here to confine our attention mainly to PD.

Until recently the vast majority of PD cases have been regarded as sporadic (90–95%), and familial cases were attributed to only 5–10% (Jomova et al., 2010a). However, this view reflects only part of the genetic input to the disease. Due to new, high-throughput technologies our knowledge of the genetic contribution to PD is increasing rapidly. As with many other disorders (Manolio et al., 2009), the genetic underpinnings of this neurodegenerative disorder are no longer seen only in a mono-causal or Mendelian way, as so far known from the monogenic forms of PD in which rare variants account only for a small overall effect or frequency of cases. Rather, low-frequency variants with intermediate effects (for example GBA mutations) or common variants as implicated by GWAS studies (loci include for example SNCA and MAPT) (Nalls et al., 2011) lead to a different (and improved) understanding of the pathophysiology of the disease. However, the influence of low-frequency and common variants to the final onset of PD is less penetrant and, more importantly, probably quite distinctly influenced by other genetic, environmental (McCulloch et al., 2008) and possibly further factors. Hence, for the understanding of pathophysiological pathways it is still wise first to consider monogenic forms, in which specific cascades can be followed more easily. Therefore, with regard to PD, we will focus in the following on the genes known to be involved in monogenic forms of PD, usually referred to as PARK genes, which are listed in Table 1.

However, there is an additional crucial factor for which there is no direct genetic basis, and that is the metal iron (in various forms). A very large literature [e.g. (Barnham and Bush, 2008; Boelmans et al., 2012; Bolognin et al., 2009b; Crichton et al., 2011; Dexter et al., 1989; Galazka-Friedman et al., 2012; Jomova et al., 2010a; Kell, 2009b, 2010b; Mochizuki and Yasuda, 2012; Nunez et al., 2012; Perez et al., 2008; Rhodes and Ritz, 2008; Schneider and Bhatia, 2012; Schneider et al., 2012; Sian-Hulsmann et al., 2011, 2010; Snyder and Connor, 2009; Thompson et al., 2001; Zecca et al., 2004)] strongly indicates that the metal iron, when unliganded and in various ionic forms, is intimately (Dröge, 2002) involved in the aetiology of PD, albeit that the molecular mechanisms and the degree of this contribution still need to be elucidated in detail.

The chief underlying basis for this is that hydrogen peroxide and superoxide are both produced by mitochondria in very large amounts [e.g. (Adam-Vizi, 2005; Adam-Vizi and Chinopoulos, 2006; Barja, 1999; Fato et al., 2008a; Orrenius et al., 2007; Raha and Robinson, 2001; Turrens, 2003)], and can react with iron when it is in unliganded or poorly liganded forms. The chemistry of the Fenton (Wardman and Candeias, 1996) (Eq. (1)) and Haber–Weiss (Kehrer, 2000) (Eq. (2)) reactions is as follows:

$$Fe(II) + H_2O_2 \rightarrow Fe(III) + OH^- + OH^{\cdot} \quad (1)$$

$$O_2^{\cdot-} + Fe(III) \rightarrow O_2 + Fe(II) \quad (2)$$

Together they allow iron to act catalytically to produce hydroxyl radicals ($OH^{\cdot}$), the most damaging of the reactive oxygen species (Halliwell and Gutteridge, 2006) as they can react in nanoseconds with essentially any molecules to which they are adjacent. Additionally, reactive nitrogen species can be formed by reactions involving NO, to produce the similarly very reactive peroxynitryl radical (Ebadi et al., 2005b; Ebadi and Sharma, 2006; Kell, 2009b, 2010b). We use the term 'iron' to mean iron of any valency or degree of liganding unless specified.

Iron content in the most vulnerable brain region of PD, the SN, is higher than in most other regions of the brain, even under physiological conditions (Hallgren and Sourander, 1958; Riederer et al., 1989). The process of neurodegeneration may thus be accelerated by increased levels of iron, especially Fe(II) reacting with H_2O_2 to form $^{\cdot}OH$ via the Fenton reaction and favouring a greater turnover of the Haber–Weiss cycle which leads to an amplification of oxidative stress (Gerlach et al., 1994; Riederer and Youdim, 1993) with subsequent cell death (Youdim et al., 1991). Iron can also react with dopamine directly in the dopaminergic neurons of the SN to form a toxic complex (Arreguin et al., 2009; Paris et al., 2005) that itself probably catalyses hydroxyl formation. The general abundance of iron in the SN is probably sufficient to account for the selectivity of neurodegeneration, i.e. the first question. Additionally, neuromelanin, also especially localised in the dopaminergic neurons of the SN, is known to be an excellent binder of metal ions, in particular iron, thereby contributing to the iron load of the SN (Ben-Shachar et al., 1991).

The selective increase of total iron content and iron(III) in the SN of PD patients has been demonstrated both biochemically and histochemically (Dexter et al., 1989; Riederer et al., 1989, 1992; Sofic et al., 1988, 1991). Moreover, increased iron levels of the SN in PD have also been demonstrated *in vivo* using magnetic resonance imaging (MRI) (Martin, 2009; Rossi et al., 2010; Zhang et al., 2010) and transcranial sonography (TCS) (Becker et al., 1995; Berg et al., 2001, 2002; Götz et al., 2004; Walter et al., 2002).

Importantly, in PD animal models, chelation of iron has been shown to be effective in delaying or preventing neurodegeneration by reducing the amount of iron which contributes to oxidative stress (Kaur et al., 2003), indicating possible therapeutic strategies (Jomova and Valko, 2011a; Van der Schyf et al., 2006; Whitnall and Richardson, 2006).

The term 'systems biology' describes an approach to understanding biology that places emphasis on the interactions between the components known via molecular biology, rather than on the components themselves (Hood, 2003; Ideker et al., 2001; Kitano, 2002).

Because there are so many genes that are known to have a potential contribution to PD in any individual case (e.g. (Antony et al., 2011; Houlden and Singleton, 2012), such problems are properly to be seen as problems of systems biology (Kell and Knowles, 2006; Kell, 2009b, 2010b) for which a suitably annotated network model may be used to encapsulate our understanding (Herrgård et al., 2008; Kell, 2007; Kell and Mendes, 2008). The systems or network view explains straightforwardly the complexity of the system and how so many genes (or biochemical network elements) can be operative in the same pathological process, and whether they are 'upstream' or 'downstream' in a particular cascade or network. For instance, if we require sources of unliganded iron and of (su)peroxide to produce hydroxyl radicals, then anything that can increase one or more of these will appear to be (and will be) a contributing causative factor of PD. The first step, then, is to find out who the actors are and how they interact (Herrgård et al., 2008; Kell and Knowles, 2006). We note in particular here the existence of two very useful systems biology models of iron metabolism (Hower et al. 2009; Chifman et al. 2012).

The logic underpinning such an analysis could be as follows:

1. Both genetic and non-genetic factors influence the development of PD. Despite so-called 'monogenic' forms, no one step alone explains the entire system, and 'iron' is a noteworthy non-genetic factor.
2. When we know the full biochemical network(s) involved, and thereby the systems biology of disease progression, we ought to be able to explain 'a lot', or at least the major

Table 1
Known genes and loci of familial and sporadic cases of PD.

Locus	Gene	Chromosome	Gene product	Inheritance	Cellular or phenotypic effects of mutations	Known molecular interaction with iron?
PARK1	*SNCA*	4q21–23	α-Synuclein (pointmutation)	AD	Nigral degeneration with Lewy bodies	Yes, several, including binding
PARK2	*Parkin*	6q25.2–27	E3 ubiquitin protein ligase	AR	Nigral degeneration without Lewy bodies	Indirect via regulation of DMT1
PARK3	*Unknown*	2p13	?	AD	Nigral degeneration with Lewy bodies	?
PARK4	*SNCA*	4p14–16.3	α-Synuclein (duplication or triplication)	AD	Nigral degeneration with Lewy bodies	Yes, several, including binding
PARK5	*UCHL1*	4p14	Ubiquitin carboxyterminal hydrolase L1	AD	No known pathology	?
PARK6	*PINK1*	1p35–36	PTEN-induced mitochondrial serine/ threonine kinase	AR	Nigral degeneration with Lewy bodies	Not as yet
PARK7	*DJ-1*	1p36	Redox-dependent molecular chaperone in mitochondria	AR	No pathology reported	Not as yet
PARK8	*LRRK2*	12p11.2-q13.1	Leucine-rich repeat-containing kinase	AD	Variable α-synuclein and tau pathology	Not in detail (possibly indirect via interaction with Parkin)
PARK9	*ATP13A2*	1p36	Neuronal P-type ATPase	AR	Pallidopyramidal degeneration	Not as yet
PARK10	*Unknown*	1p32	?	?	No pathology reported	?
PARK11	*GIGYF2*	2q36–37	Regulation of tyrosine kinase receptor signalling?	AD	No pathology reported	?
PARK12	*Unknown*	Xq21–25	?	X-linked	No pathology reported	?
PARK13	*Omi/ HTRA2*	2p12	Mitochondrial serine protease	sporadic	No pathology reported	None direct
PARK14	*PLA2G6*	22q13.1	Phospholipase A2	AR	Spheroid body accumulation, Lewy body formation	Not as yet.
PARK15	*FBXO7*	22q12–13	E3 ubiquitin protein ligase	?	Parkinsonism and pyramidal tract signs	?
PARK16	*Unknown*	1q32	?	?	?	?
PARK17	*VPS35*	16q12	Vacuolar protein sorting 35	AD	No pathology reported	Not as yet.
PARK18	*EIF4G1*	3q26-q28	Eukaryotic translation initiation factor 4 gamma 1	AD	α-Synuclein type	Not as yet.
	GBA	1q21	Lysosomal glucocerebrosidase	sporadic	Nigral degeneration with Lewy bodies	Not as yet.
	DMT1 (SLC11A2)	12q13	Proton-coupled divalent metal ion transporter (solute carrier family 11, member 2)			
	SCARB2	Position 77418010 in NCBI build 36.3	Lysosomal integral membrane protein type 2 (LIMP-2); trafficking of GBA to lysosome	?	?	?
	SREBF1/ RAI1	Position 17655826 in NCBI Build 36.3	?	?	?	?

features, of the disease, including accounting for the genetic data (in that the pertinent genes should encode for or influence the relevant biochemical networks).

3. A detailed survey of the literature illustrates the (numerous) main processes involved in the (apoptotic) cell death characteristic of SN neurones in PD. Here, we seek to include all main processes known to us.
4. Consequently, the (systems biology) model that we provide can give a reasonable explanation of the (partial) contribution of the various genes that have been identified to be involved in the progression of PD and where appropriate in their interaction with iron.

As mentioned above, so-called monogenic forms of PD are of importance as they allow one to study the effects of a particularly pathogenic mutation or allele and to model its contribution to the pathogenesis of the progressive neurodegenerative process. Notably, indices of increased iron content are present not only in sporadic PD, but also in monogenic variants of PD (Schweitzer et al., 2007b). Knowledge about the interaction of the pathways affected in monogenic PD may therefore contribute to the understanding of the role of iron in the pathogenesis of PD. Recently, Lv et.al indicated that increased iron levels in chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated PD mice correlate with the selective nigral dopaminergic neuron degeneration in Parkinson's disease (Lv et al., 2011). Given that inhibition of complex I and iron accumulation are important aspects of idiopathic PD, one study from the group of Nunez may be of relevance for a better understanding of the pathophysiology. They analyzed iron-sulfur (Fe–S) clusters as small inorganic cofactors present in numerous proteins. These clusters are synthesized in the mitochondria and are involved in many biological processes. By artificial inhibition of complex I the group of Nunez found a reduction in cytoplasmic aconitase activity associated with an increase in iron regulatory protein (IRP) mRNA binding activity. Additionally, the cytoplasmic labile iron pool was also elevated (Mena et al., 2011). They therefore hypothesise that Fe–S cluster inhibition could result in a false iron deficiency signal as it is known that IRP activity regulates the expression of iron import in a post-transcriptional manner.

Moreover, there are several iron-accumulating disorders that primarily affect the basal ganglia leading to a phenotype dominated by extrapyramidal symptoms including parkinsonism. As in some of these disorders specific mutations and consecutively affected pathways are also known, these disorders constitute another interesting group that may help in the understanding of the pathogenic role of iron in parkinsonism.

In the following we shall therefore seek to combine knowledge derived from genetic studies and from pathological cascades

induced by iron in a systems biological approach to account for the complexity of the pathogenesis of PD, at least in part.

2. Positive feedback and autocatalysis in cell death

In general terms, evolution has selected the topologies of biochemical networks for robustness, since any single-point-failure of the system is likely to be selected against [e.g. (Bornholdt and Sneppen, 2000; Kitano, 2004; Shinar and Feinberg, 2010; Stelling et al., 2004; van Nimwegen et al., 1999; von Dassow et al., 2000; Wagner, 2005)]. There are at least two consequences:

- The first is that in order to drive a cell towards death often quite overwhelming stresses have to be applied, acting at multiple points. This is also why multiple reactions have to be affected to raise biochemical fluxes for increasing the rate of production of substances of interest in biotechnology, as in (Butelli et al., 2008; Park et al., 2007), and why the most effective pharmaceutical drugs (have to) act at multiple points (Besnard et al., 2012; Hopkins et al., 2006; Hopkins, 2008; Lehár et al., 2007; Lehár et al., 2008; Small et al., 2011).
- The second consequence is that one means by which to have major effects on a biochemical network is to have a positive feedback such that a toxin, for example unliganded iron or the hydroxyl radical, reacts with the system to cause yet further production of unliganded iron or the hydroxyl radical, and so on. This runaway kind of reaction is clearly capable of overwhelming any kinds of robust defences (Kell, 2010b).

A particularly nice example involving unliganded iron and hydroxyl radical provides exactly the explanation of why bactericidal antibiotics differ mechanistically from those that are merely bacteriostatic (Dwyer et al., 2009; Kell, 2010b; Kohanski et al., 2007).

In the present article we shall bring together the evidence that there is an autocatalytic interplay between biochemical events in the lysosome and in mitochondria that lie at the heart of the neurodegeneration occurring in Parkinson's disease. Cocktails of substances affecting multiple relevant targets may thus offer the best therapeutic options. A 'mind map' of the review is given at Fig. 1, and the relevant literature review extends to June 2012.

3. Mechanisms of cell death

To answer the second question above, the mechanisms of neuronal cell death accompanying Parkinson's, requires recognition that cells tend to die either by necrosis or by apoptosis (Kostrzewa, 2000), and there is considerable evidence that neuronal cell death during PD is essentially apoptotic in nature [e.g. (Blum et al., 2001; Burke, 2007; France-Lanord et al., 1997b; Hartley et al., 1994; Jenner and Olanow, 2006; Lev et al., 2003; Maruyama et al., 2002; Novikova et al., 2006; Petit et al., 2005; Shi et al., 2010; Tatton et al., 2003; Vila and Perier, 2008; Vila et al., 2008; Xu et al., 2005b; Yacoubian and Standaert, 2009; Yasuda and Mochizuki, 2010; Zhu et al., 2010)]. This is not necessarily surprising in view of the extensive evidence for mitochondrial dysfunction in PD, that we shall come to.

4. Apoptosis, mitochondria, lysosomes and 'ceramide'

In apoptosis (Kerr et al., 1972) (Fig. 2), the best known version of 'programmed cell death' (Burke, 2007), cells exposed to various stresses, such as oxidative stress mediated by inflammatory cytokines, undergo a regulated demise involving the release of cytochrome c from mitochondria and the activation of various proteases (caspases) that cause cellular degradation. A variety of toxins that cause mitochondrial dysregulation can also thereby affect Parkinson-like syndromes.

One mechanism contributing to oxidative stress in PD involves an impairment of mitochondrial function, especially of complex I activity (Bové et al., 2005; Danielson et al., 2011; Dawson and Dawson, 2003; Fato et al., 2008b; Henchcliffe and Beal, 2008; Perier et al., 2007; Schapira et al., 1989; Schapira, 2007; Sterky et al., 2012; Winklhofer and Haass, 2010), increased excitotoxicity, altered calcium homeostasis (Lang, 2007; Maetzler et al., 2007) and other factors. The involvement of aberrant complex I activity is especially interesting, as both rotenone and $MPTP^+$, inhibitors of complex I, can induce Parkinson-like symptoms [e.g. (Drechsel and Patel, 2008; Miller et al., 2009; Sherer et al., 2002; Sterky et al., 2012; Terzioglu and Galter, 2008)]. It is of interest that rotenone can also lead to selective uncoupling in complex I (Phillips and Kell, 1982), with presumed increased scope for (su)peroxide production. ROSs can also be induced by the interaction of inhibitors with complex III [e.g. (Therade-Matharan et al., 2005)].

A particularly interesting relationship here is that between 'ceramide' and mitochondria-induced apoptosis. Ceramide is a generic term used to describe a sphingolipid [see (Heavner et al., 2012) for the relevant biochemical networks] composed of sphingosine amide linked by N-acylation to a fatty acid. Thus C16-ceramide, a typical ceramide found in mammalian cells, involves a fatty acyl chain with 16 carbons (palmitate). What has become clear over some 20 years [e.g. (Birbes et al., 2002; Colombini, 2010; Degli Esposti and McLennan, 1998; France-Lanord et al., 1997a; Jana et al., 2009; Levenson et al., 2004b; Siskind, 2005)] is that while such ceramides cannot themselves cross cell membranes, they are capable of effecting pore formation in the mitochondrial outer membrane, thereby allowing cytochrome c to diffuse into the cytoplasm, and of interacting with the mitochondrial respiratory chain (Di Paola et al., 2000). Both of these activities thus contribute to the induction of apoptosis.

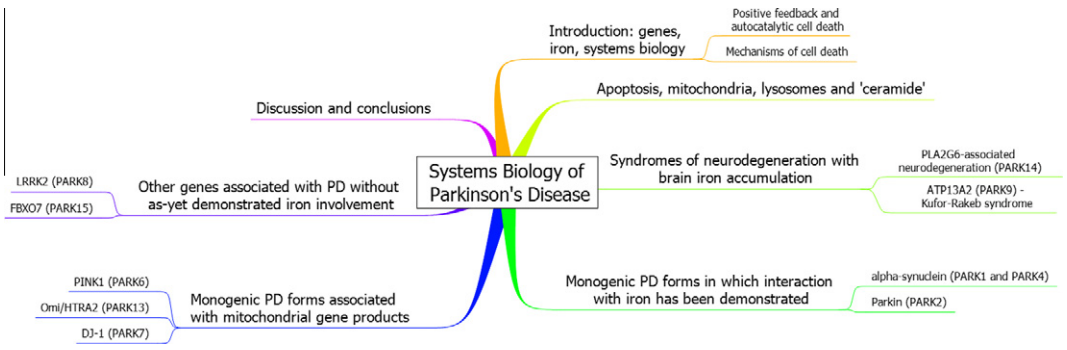

Fig. 1. A 'mind map' summarising the various sections in the review. To read this start at "12 o'clock" and read clockwise.

Thus in summary, a variety of potential pathways exist for the induction of apoptosis in dopaminergic neurons of the SN.

Lysosomes also play an important role and free iron in lysosomes and permeabilization of lysosomal membranes are an important inducer of oxidative stress (Dusek et al., 2012). They induce ferritin with concomitant mitochondrial damage (Ghosh et al., 2011) and ultimately apoptosis. Lysosomes thereby contribute directly to neurodegeneration by the ectopic release of lysosomal proteases into the cytoplasm. Lysosomal breakdown and AP accumulation also occurred in PD brain samples, where LB were strongly immunoreactive for AP markers (Dehay et al., 2010). Cells prevent apoptosis by binding reactive iron to heavy-chain (H)-ferritin, which can incorporate lysosomal iron into ferritin molecules (Persson, 2005).

In the following we shall review the existing knowledge of the contribution of iron in different monogenic forms of PD and other monogenic disorders accumulating iron in the basal ganglia with a clinical presentation that includes Parkinsonism. We begin with the syndromes of neurodegeneration with brain iron accumulation (NBIA) (Schneider et al., 2012), for which the link to iron metabolism is rather overt, followed by the more clinically pure parkinsonian and other seemingly more complicated disorders. Our aim is to understand better the ways in which iron affects different pathways that finally accumulate in the clinical picture of Parkinsonism.

5. Syndromes of neurodegeneration with brain iron accumulation (NBIA): Complicated forms of Parkinsonism bridging the gap to PD

5.1. PLA2G6-associated neurodegeneration (PARK14)

A group of disorders characterized by prominent iron accumulation in the basal ganglia has been described, and referred to collectively as syndromes of neurodegeneration with brain iron accumulation. One of the core syndromes is, besides pantothenate kinase-associated neurodegeneration, PLA2G6-associated neurodegeneration (PLAN) (Hayflick, 2003, 2006; McNeill, 2012; Schneider et al., 2012). The PLA2G6 gene is located on chromosome 22; the encoded protein, iPLA2 beta is a group VIA calcium-independent phospholipase A2 and is an 85- to 88-kDa cytoplasmic PLA2 whose amino acid sequence includes eight N-terminal ankyrin repeats, a caspase-3 cleavage site, relevant to the apoptotic mechanism – see above, an ATP-binding domain, a serine lipase consensus sequence (GXSXG), a bipartite nuclear localization sequence, and a C-terminal calmodulin-binding domain (Ma and Turk, 2001). iPLA2 beta hydrolyzes the sn-2 acyl chain of phospholipids, generating free fatty acids and lysophospholipids and is suggested to play important roles in remodeling of membrane phospholipids, signal transduction, cell proliferation, and apoptosis.

The clinical phenotype associated with *PLA2G6* mutations is variable. On the one hand it may present as infantile neuroaxonal dystrophy (INAD) or, on the other hand, when onset is later, with complicated dystonia parkinsonism (Schneider and Bhatia, 2010a). In the adult-onset cases, parkinsonism was characterized by the presence of tremor including a pill-rolling rest component, rigidity, and severe bradykinesia with a good response to levodopa (Paisan-Ruiz et al., 2009). However, there was early development of dyskinesias. Cerebellar signs and sensory abnormalities which are often prominent in the early childhood variant were absent. Recently, Engel and colleagues (Engel et al., 2010) presented functional studies correlating genetic alterations with the different clinical presentations. They showed that mutations associated with INAD/NBIA result in loss of enzyme activity, with mutant proteins exhibiting less than 20% of the specific activity of the wild type protein in both lysophospholipase and phospholipase assays, which predicts accumulation of PLA2G6 phospholipid substrates. In contrast, mutations associated with dystonia-parkinsonism did not impair catalytic activity which may explain the relatively milder phenotype and absence of iron accumulation in at least some cases.

PLAN belongs to the group of neuroaxonal dystrophies, the characteristic histological hallmark feature of which are spheroid bodies (dystrophic neuroaxonal swellings) that are observed throughout the peripheral and central nervous system. A core component of neuroaxonal spheroids is tubulovesicular membrane accumulation which may be explained by the role of PLA2G6 in phospholipid homeostasis and may explain the axonal accumulation of membranes in neuroaxonal spheroids (Engel et al., 2010).The findings are in line with findings from animal studies (Wada et al., 2009) where spheroids strongly stained ubiquitin positive in a mouse model (Malik et al., 2008).

Abnormal iron is found, in classical INAD, mainly in the globus pallidus and sometimes, in the more atypical cases, in the SN (Gregory et al., 2009; Paisán-Ruiz et al., 2010b). However, as mentioned above, genetically-proven cases without observable iron deposition have been reported (Paisan-Ruiz et al., 2009). Widespread presence of α-synuclein-positive LB pathology, which was particularly severe in the neocortex has also been reported as representing a link between PLA2G6 and parkinsonian disorders. The LB pathology spread corresponded to Braak stage 6 and was that of the ‘‘diffuse neocortical type’’ (Paisán-Ruiz et al., 2010b). In view of the role of α synuclein in regulating fatty acid metabolism, Engel et al. (2010) proposed that this may be the pathophysiological link between PLA2G6 mutations and α-synuclein accumulation. A link between fat metabolism and iron accumulation has also been observed for a number of other, related disorders (Kell, 2009a).

Accumulation of hyperphosphorylated tau in both cellular processes as threads and neuronal perikarya as pretangles and neurofibrillary tangles has also been reported (Paisán-Ruiz et al., 2010b). Tau involvement tended to be less in late-onset cases (Kruer et al., 2010; Schneider and Bhatia, 2010b).

The lysosome is the site of most labile iron in the cell [e.g. (Dusek et al., 2012; Fakih et al., 2008, 2009; Gorria et al., 2008; Kurz et al., 2004, 2007, 2008a,b; Persson, 2005; Sahoo et al., 2012; Tenopoulou et al., 2007; Terman et al., 2006; Yu et al., 2003)]. Thus it is reasonable that lysosomal destabilization by impaired PLA2G6 activity might results in iron release inducing apoptotic processes.

5.2. ATP13A2 (PARK9) – Kufor Rakeb syndrome

Mutations in the neuronal P-type ATPase gene cause an autosomal recessive form of early-onset, often complicated form of parkinsonism (Dusek et al., 2012; Ramirez et al., 2006). Recently, Schneider et al. (Schneider et al., 2010; Schneider and Bhatia, 2012) reported the presence of iron accumulation in the putamen and caudate nuclei as demonstrated by T2*-weighted MRI in a Pakistani patient homozygous for a novel ATP13A2 mutation (Paisán-Ruiz et al., 2010a). Similarly, in a Chilean family with genetically-proven Kufor Rakeb syndrome (KRS) one of the compound heterozygous mutation carriers showed iron deposition in the basal ganglia in addition to severe global brain atrophy (Brüggemann et al., 2010). How far the SN is also affected by the iron accumulation remains as yet unclear.

In contrast to other forms of PD, one study reported a lack of hyperechogenicity in the SN (which is thought to be a sign for increased SN iron content (Brüggemann et al., 2010). This may argue for a different underlying pathophysiology compared with other monogenic forms of parkinsonism and idiopathic PD. Kufor-Rakeb syndrome belongs to the syndromes of neurodegeneration

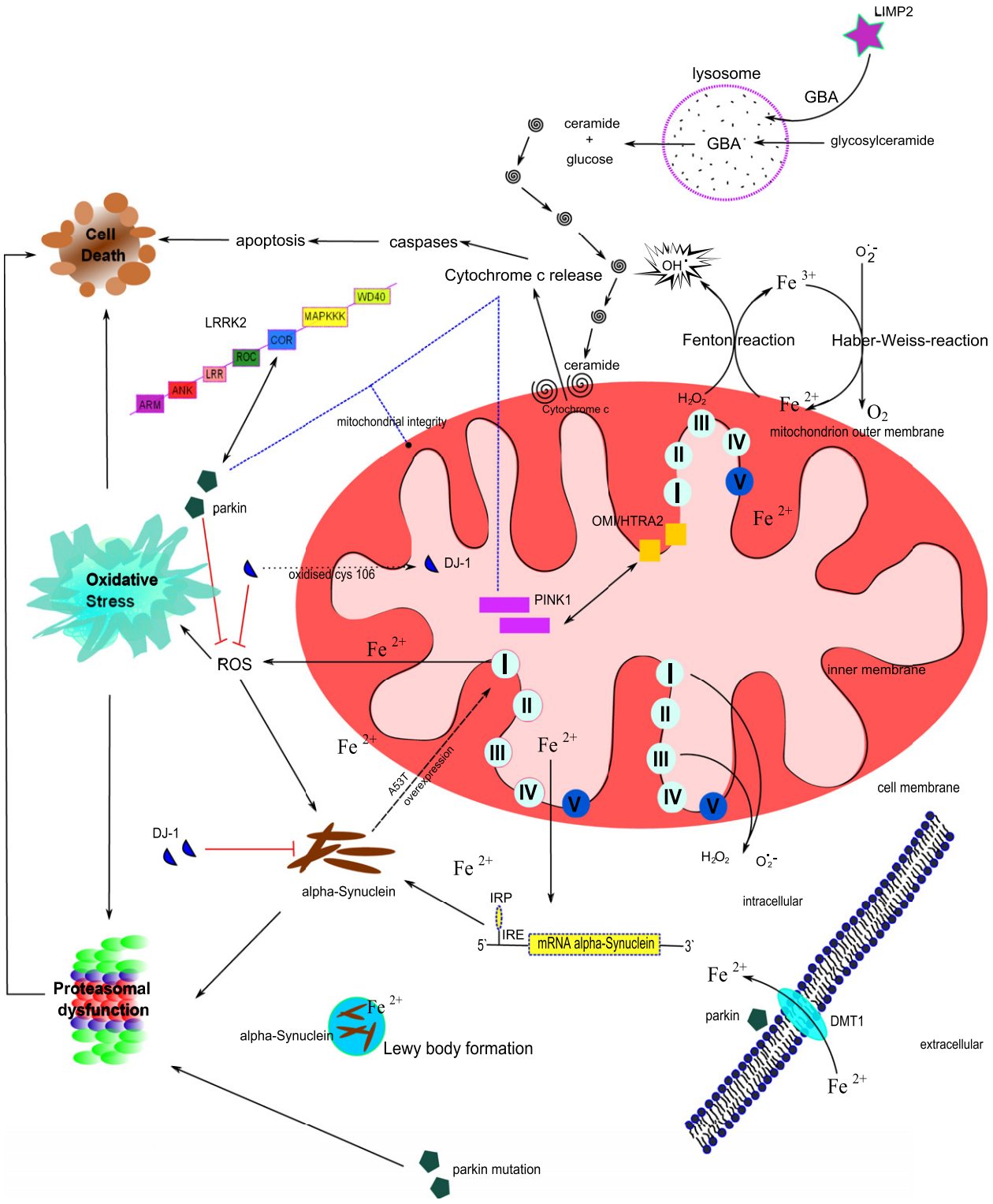

Fig. 2. Interactions between mitochondria, lysosomes, iron and apopotosis in the systems biology of Parkinson's disease. The figure illustrates much of what we know about the aetiology of Parkinson's disease, showing in particularly the interplay between mitochondria and lysosomes during the apoptotic cell death that characterises the death of neurons in the substantia nigra that is the hallmark of PD. The role and location in the network of a variety of gene products known to be involved in PD neurodegeneration is also illustrated. Because the nature of many of the interactions is still not known we have decided not to use the Systems Biology Graphical Notation for these (Le Novère et al., 2009).

with brain iron accumulation (NBIA) (Brüggemann et al., 2010; Schneider et al., 2010) and classification of KRS as NBIA type 3 has been proposed (Schneider et al., 2010).

The 26 kb-spanning gene contains 29 exons and encodes a lysosomal 5 P-type ATPase. While postmortem studies of human Kufor Rakeb disease are lacking, nerve biopsy revealed cytoplasmic membrane-bound, irregular, and occasionally folded inclusions within Schwann cells, perineurial and epineurial cells (Paisán-Ruiz et al., 2010a). More recently, post-mortem pathological examination in patients with ATP13A2 mutations, clinically presenting

with neuronal ceroid lipofuscinosis showed abundant neuronal and glial lipofuscinosis involving the cortex, basal nuclei, cerebellum, but sparing the white matter, with whorled lamellar inclusions typical of NCL in electron microscopy. Lipofuscin deposits were confirmed in the retina (Bras et al., 2012).

Functional studies showed mutant ATP13A2 was retained in the endoplasmic reticulum, and there was premature degradation by the proteasomal, but not the lysosomal, pathways which may contribute to the aetiology (Park et al., 2011). The exact molecular link to iron remains unknown.

5.3. Pantothenate kinase-associated neurodegeneration

Mutations in the PANK2 cause pantothenate kinase-associated neurodegeneration, the most common cause of NBIA. There are links to PLA2G6-associated neurodegeneration both clinically, on imaging grounds and pathologically, in that both are characterized by iron accumulation and are classified as neuroaxonal dystrophies. In PKAN, iron accumulation is present in the globus pallidus, both as ferric iron (Fe^{3+}; the paramagnetic form putatively associated with MRI hypointensity) but to a lesser degree also ferrous iron (Kruer et al., 2011). Diffuse iron-staining of the neuropil (“iron dust”) may be present. However, this NBIA syndrome is not classified as a PARK disorder, nor considered a major cause of parkinsonism. Instead patients typically present with early onset dystonia with pyramidal signs (Hayflick, 2003). Thus, for reasons of focus, PKAN will not be further discussed here.

6. Monogenic PD forms, in which interaction with iron has been demonstrated

6.1. α-Synuclein (PARK1 and PARK4)

The first gene product described to be associated with familial PD was α-synuclein (Polymeropoulos et al., 1997), encoded by the SNCA gene (Xia et al., 2001). Synucleins are proteins which occur abundantly in the brain (Goedert, 2001). Of these, α-synuclein is a cytoplasmic lipid binding protein considered to be involved in storage and regulation of neurotransmitters as well as in synaptic vesicle recycling (Lotharius and Brundin, 2002; Vekrellis et al., 2004). α-Synuclein is also the main component of LB, the classic pathological intraneural inclusions in PD, and may itself be oxidatively modified (Double et al., 2008). LBs contain nearly 80 other proteins (Licker et al., 2009), amongst others ubiquitin (Kuzuhara et al., 1988), proteasome subunits (Ii et al., 1997), heat shock proteins (Auluck et al., 2002) and neurofilaments (Galvin et al., 1997). LBs are found not only in idiopathic PD but also in most monogenic forms of PD (Duda et al., 2002; Spillantini et al., 1998). In fact, LBs are abundantly present in the SN where iron accumulation also occurs (Li et al., 2010a; Spillantini et al., 1997). In addition, ferrous (Fe(II)) and ferric iron (Fe(III)) are found to be present in LBs (Peng et al., 2010b) as well as in many other amyloid structures (Das et al., 2010; Singh et al., 2010). There seem to be different types of interaction of α-synuclein and iron – all leading to increased toxicity.

First, a possible interaction of iron and α-synuclein has been demonstrated by treating SK-N-SH, a neuroblastoma cell line, cells with different iron concentrations, which lead to ferric iron-induced α-synuclein aggregation (Li et al., 2010a). More generally, ferric iron may itself catalyse the formation of α-synuclein oligomers (Brown, 2009; Hillmer et al., 2010; Peng et al., 2010b).

Second, it has been shown, that α-synuclein is especially vulnerable to changes in iron concentration as the 5′-untranslated region of α-synuclein mRNA contains an element predicted to represent an iron responsive element (IRE) (Friedlich et al., 2007). Therefore, it has been suggested that iron might regulate α-synuclein aggregation via the iron responsive element/iron regulatory protein system (IRE/IRP).

Third, Li et al. observed an upregulation of the mRNA level of α-synuclein as well as an increase of its aggregation in SK-N-SH cells after previous knockdown of the IRP (Li et al., 2010b). This overexpression in turn seems to not only have an effect on α-synuclein aggregation but also on the toxicity of iron: Studies in SK-N-SH neuroblastoma cells overexpressing the wildtype α-synuclein have shown an enhanced toxic effect of ferric iron, a decrease in cell viability and mitochondrial membrane energisation and an increase in intracellular ROS (He et al., 1996). Additionally, by silencing the expression of α-synuclein, iron-induced toxicity could be attenuated to some extent (He et al., 1996). According to these findings, it seems likely that α-synuclein aggregation may increase the toxicity of iron in SK-N-SH neuroblastoma cells.

Fourth, SH-SY5Y cells stably expressing the divalent metal ion transporter 1 (DMT1) show a dramatic enhancement of Fe^{2+} uptake into the cells. In combination with mutant A53T α-synuclein the Fe^{2+}-mediated toxicity was much more aggravated. Interestingly, this phenomenon seems to occur as a result of excessive autophagic activity and not because of an apoptotic process (Chew et al., 2011).

Fifth, the group of Brown (Davies et al., 2011) provided evidence that α-synuclein is able to function as a cellular ferrireductase, reducing iron(III) to iron(II). By overexpressing α-synuclein in human neural cell lines, a significant increase in ferrireductase activity and therefore in iron(II) concentration could be demonstrated in comparison to cells normally expressing the protein. Moreover, they suggest that iron binding of α-synuclein could be important for the normal protein activity.

Sixth, there also seems to be a possible and interesting link between α-synuclein expression and mitochondrial dysfunction: overexpression of wildtype α-synuclein has been shown to decrease mitochondrial complex I activity and led to increased ROS production in human fetal dopaminergic primary neuronal cells (Devi et al., 2008).

Finally, findings from cell-culture experiments are supported by animal studies. Transgenic mice expressing the A53T mutation in the α-synuclein gene and exposed to paraquat develop a progressive age-related enhancement of dopaminergic neurodegeneration after oral intake of increased amounts of iron in the neonatal period (Peng et al., 2010a).

6.2. Parkin (PARK2)

Mutations in the parkin gene cause autosomal recessive juvenile PD (Kitada et al., 1998). To date more than 100 pathogenic mutations within the parkin gene have been identified resulting in a loss of function (Hardy et al., 2009; Hardy, 2010; Nuytemans et al., 2010). An inactivation of parkin is also thought to play a role in sporadic PD (Pilsl and Winklhofer, 2012).

A decade ago the group of Hirsch identified via immunohistochemical studies the expression of parkin in neuronal perikarya and processes. Additionally, it was found in glial and blood vessels in the human brain (Zarate-Lagunes et al., 2001). In the physiological state, parkin has been proposed to have a wide neuroprotective capacity (Winklhofer and Haass, 2010), amongst others protection of cells against proteasome inhibition, mitochondrial dysfunction, endoplasmic reticulum stress and excitotoxicity [for review see (Moore, 2006; Winklhofer, 2007)]. Parkin functions as an E3 ubiquitin ligase, which subsequently polyubiquitinates its protein substrates, thus targeting them for degradation by the 26S proteasomal complex (Moore, 2006).

An inactivation of parkin due to its misfolding as a consequence of severe stress (oxidative, nitrosative or dopamine) has been

identified in brains of sporadic PD patients (Chung et al., 2004; LaVoie et al., 2005, 2007; Schlehe et al., 2008; Wang et al., 2005; Winklhofer et al., 2003; Wong et al., 2007; Yao et al., 2004).

In brains of PD patients and animal disease models, parkin was found to be S-nitrosylated. S-nitrosylated proteins show concomitant effects on neurodegeneration (Gu et al., 2010). This alteration evidently stimulates the E3 ligase activity of Parkin, which has been hypothesized to lead to an autoubiquitination with subsequent inhibition of its activity (Lim et al., 2002; Lipton et al., 2005).

The interaction of Parkin with iron metabolism has also been investigated. Parkin plays a key role (Roth et al., 2010) in the regulation of metal transport via proteasomal degradation of the 1B isoforms of divalent metal ion transporter 1 (DMT1). The latter is the major transport protein responsible for the uptake of iron into mammalian cells and of iron exit from endosomes (Garrick et al., 2012), and is also present in the brain (Salazar et al., 2008b). There exist four major mRNA isoforms resulting in four protein isoforms, 1A versus 1B and +IRE versus −IRE isoform. The first 1A and 1B isoforms describe just the different transcription start points and the +IRE/−IRE isoforms reflect the presence or absence of an iron responsive element in the 3′ region of the mRNA. Consistent with earlier experiments (Roth et al., 2010), the group of Garrick demonstrated that the regulation of DMT1 by proteasomal degradation due to parkin is isoform specific. While 1A DMT1 seems to be unaffected by parkin, the 1B DMT1 isoform can be a target for the E3-ligase (Garrick et al., 2012). Relevance to PD from these findings can be derived from the fact that the group of Hirsch demonstrated recently an increase in the expression of DMT1 in the SN of PD patients (Salazar et al., 2008a). The effects of parkin mutations on 1B isoforms ubiquitination have not yet been studied, although further evidence for the importance of DMT1 is that a mutation in DMT1 that impairs iron transport may be protective in rodents against the parkinsonism-inducing neurotoxins MPTP and 6-hydroxydopamine (6-OHDA) (Salazar et al., 2008a).

It is therefore tempting to speculate that changes in DMT1 regulation results in alterations of iron transport in specific brain regions with possible subsequent enhancement of oxidative stress. However, SNP analysis in the DMT1 gene in Han Chinese population failed to find any significant association between the tested genotypes, alleles or mutation and PD (He et al., 2011).

Besides the DMT1 regulation other lines of evidence indicate a possibly important interaction of parkin and iron: experiments with Drosophila also demonstrate an important function of parkin in protection against redox-active metals and pesticides. Flies mutant for parkin showed an extended lifespan through sequestration of redox active metals and an enhancement of anti-oxidative pathways (Saini et al., 2010).

7. Monogenic forms associated with mitochondrial gene products which act in the same pathway as parkin and for which so far no direct interaction with iron has been shown

Because mitochondria are normally the main cellular source of the less toxic (than ·OH) reactive oxygen species peroxide and superoxide, anything that disrupts mitochondria could in principle lead to an increase in (su)peroxide production. This in turn, if free iron is available, can produce the hydroxyl radical and thereby even liberate more iron from mitochondrial components such as Fe–S centres (Kell, 2010a). In this sense, any role of iron in effecting neurodegeneration might be anticipated to be rather secondary for these mitochondrially acting gene products.

7.1. Pink1 (PARK6)

PINK1 (PTEN-induced putative kinase) encodes a mitochondrial targeted serine/threonine kinase and is another cause of autosomal recessive, early-onset Parkinsonism (Pilsl and Winklhofer, 2012; Valente et al., 2004). It has been demonstrated that PINK1 and Parkin act in a common molecular signalling pathway in which Parkin acts downstream of PINK1 to protect mitochondrial integrity. Both interact with components responsible for fission and fusion of the mitochondria (Clark et al., 2006; Park et al., 2006; Poole et al., 2008; Yang et al., 2008). PINK1 is necessary for long term survival and mitochondrial function in human dopaminergic neurons (Wood-Kaczmar et al., 2008). Silencing PINK1 in SH-SY5Y cells led to an increase in mitochondrial dysfunction and oxidative stress (Gegg et al., 2009; Vos et al., 2012).

No association of iron-induced oxidative stress and PINK1 function has been described so far, although patients carrying a PINK1 mutation displayed a significantly larger area of SN echogenicity (a marker for increased tissue iron content in PD) than did healthy controls assessed with transcranial ultrasound (Schweitzer et al., 2007a). Because of this indirect evidence, and due to the neuroprotective function of PINK1 and its mitochondrial localisation an interaction with iron and subsequent enhancement of oxidative stress may be anticipated and deserves further investigation, particularly with regard to detecting (su)peroxide production (Davey and Kell, 1996), a possibility made more plausible by the recent findings with vitamin K_2 (Vos et al., 2012). PINK1 dysfunction does lead to the production of Lewy bodies (Samaranch et al., 2010).

7.2. Omi/HTRA2 (PARK13)

Omi/HTRA2 functions as a serine protease and contains an N-terminal mitochondrial targeting sequence. Therefore it is also linked to the group of proteins responsible for mitochondrial dysfunction and neurodegeneration (Strauss et al., 2005). Mutations in the Omi/HTRA2 gene inactivate its protease activity and have been identified as a high risk factor for the development of PD (Strauss et al., 2005). HtrA2 interacts with PINK1 and both are components of the same stress-sensing pathway. It is suggested that PINK1-dependent phosphorylation of HtrA2 might modulate its proteolytic activity, thereby contributing to an increased resistance of cells to mitochondrial stress (Plun-Favreau et al., 2007). So far no interaction of HtrA2 and iron has been shown, but because of its mitochondrial localization and relationship to PINK1, similar conclusions apply.

7.3. DJ-1 (PARK7)

DJ-1 mutations are less prevalent causes of autosomal recessively inherited PD (Bonifati et al., 2003) than are PINK-1 mutations. Physiologically, DJ-1 displays various functions: it is a redox-dependent molecular chaperone with neuroprotective functions and inhibits, amongst others, α-synuclein aggregate formation (Shendelman et al., 2004). Therefore, the oxidation state of DJ-1 plays an important role, in view of its chaperone function (Zhou et al., 2006). Moreover, it has been shown that cysteine 106 of DJ-1 is essential for its neuroprotective activity (Canet-Avilés et al., 2004; Taira et al., 2004; Waak et al., 2009; Yokota et al., 2003). Localization studies described DJ-1 in different compartments of the cell, including cytoplasm, mitochondria and also the nucleus. Notably, under oxidative stress an enhancement of the mitochondrial localization is observed (Lev et al., 2008; Li et al., 2005; Miller et al., 2003). DJ-1 has also been found to be present in LBs [for review see (Licker et al., 2009)]. Under conditions of oxidative stress DJ-1 is converted into an acidic variant allowing a reaction with ROS and favouring a localization in the mitochondria. Specifically, this oxidation of a cysteine in position 106 of the DJ-1 peptide is necessary for mitochondrial targeting and protection against oxidation-induced cell death (Canet-Avilés et al., 2004).

Recently, DJ-1 has been observed to play a critical role in mitochondrial homeostasis, evidenced by a loss of DJ-1 leading to impairment of mitochondrial respiration, reduced mitochondrial membrane energisation and an increase in intramitochondrial reactive oxygen species (Krebiehl et al., 2010). DJ-1 is also known to be protective against neuronal apoptosis (Xu et al., 2005a).

In spite of all this evidence for involvement in oxidative stress, similar to PINK1 and Omi/HTRA2, no direct relationship between iron metabolism and DJ-1 has been demonstrated, yet.

8. Other genes associated with PD with possible but so far not demonstrated links to iron homeostasis

8.1. LRRK2 (PARK8)

A rather common cause of autosomal dominantly inherited monogenic PD is represented by mutations in the LRRK2 gene (PARK8), mapped to chromosome 12p11.2-q13.1, which are located all over the coding sequence. The LRRK2 gene encodes a large multidomain protein (280 kDa) containing an armadillo (ARM) domain, an ankyrin (ANK) domain, leucine-rich repeats (LRR), Ras of complex proteins (ROC), C-terminal of ROC (COR), mitogen-activated protein kinase kinase kinase (MAPKKK) and a WD40 repeat domain (Kumari and Tan, 2009; Shen, 2004; Zimprich et al., 2004). It is expressed in many regions of the central nervous system, e.g. cerebellum, spinal cord and also in the SN as well as in other organs (Paisán-Ruíz et al., 2004; Zimprich et al., 2004). Localisation studies describe LRRK2 to be predominantly present in the cytoplasm, but also existing in the mitochondrial outer membrane (Smith et al., 2005; West et al., 2005), additionally associated with the plasma membrane, lipid rafts, synaptic vesicles, the Golgi apparatus and a cytoskeleton protein microtubule (Biskup et al., 2006; Hatano et al., 2007). Importantly, as reviewed by Ghandi et al. (Gandhi et al., 2009), LRRK2 is suggested to be localised to LBs in human PD brains.

Within the LRRK2 gene many variations (point mutations) of unknown significance have been identified in almost all domains (Chung et al., 2011). At the moment eight proven pathogenic mutations are known [reviewed in (Kumari and Tan, 2009)]. One common mutation, G2019S, can be found in both familial and sporadic cases of PD (Di Fonzo et al., 2005; Gilks et al., 2005; Nichols et al., 2005). This mutation is located within the kinase domain and considered to be associated with increased kinase activity (Greggio et al., 2006; Jaleel et al., 2007; West et al., 2005). In SH-SY5Y cells and primary neurons derived from mouse, neuronal degeneration and toxicity could be observed as a result of this increased kinase activity of the mutant G2019S LRRK2 (Smith et al., 2005, 2006). Inhibiting LRRK2 kinase activity may offer neuroprotection (Liu et al., 2011). Interestingly, LRRK2 (wildtype and mutated) seem to interact with parkin as demonstrated (Smith et al., 2005) in HEK cells. The RING2 domain of parkin seems to be primarily responsible for this interaction with LRRK2. Because of this interaction and the fact that parkin plays a key role (Roth et al., 2010) in the regulation of metal transportation, an indirect interaction of LRRK2 with iron homeostasis is at least feasible.

The mitochondrial "membrane potential", better described as "membrane energisation" (Kell, 1992), and the total intracellular ATP levels have been shown to be decreased in G2019S mutation carriers (Mortiboys et al., 2010). Additionally, the same group revealed an elongation of the mitochondria in mutation carriers as well as an increase in its interconnectivity. Summarising these results, fibroblasts from mutation carriers for the G2019S mutation displayed an impairment of its mitochondrial function and morphology.

Another fact to mention is the age-dependency of penetrance of the G2019S mutation. The international LRRK2 consortium estimates the risk of PD for a person carrying the LRRK2 G2019S mutation to be about 28% at the age of 59 years, 51% at 69 years, and 74% at 79 years (Healy et al., 2008). Obviously for any individual this is a function of the rest of their "genetic make-up" and its interaction with environmental (lifestyle) stimuli. This necessarily begs the question of why (mechanistically) some very old carriers remain free of disease.

To date, no studies showing direct interactions of LRRK2 with iron seem to have been published. However, increased tissue iron levels of the SN have also been demonstrated for LRRK2-associated PD by transcranial sonography (Schweitzer et al., 2007a,b; Brockmann et al., 2010), so it may be possible that Parkinson's disease resulting from a variation in the LRRK2 allele does have an impact on the acceleration of neurodegeneration via increased iron levels and concomitant oxidative stress. However, this interaction may be less strong and detrimental than the one in idiopathic PD (Schweitzer et al., 2007a).

8.2. Glucocerebrosidase (GBA)

So far, heterozygous GBA mutations are the most common genetic risk factor for PD (Lesage and Brice, 2009; Nichols et al., 2009). The human Glucocerebrosidase (GBA) gene is located on chromosome 1q21 and encodes for a lysosomal enzyme, that hydrolyses the beta-glycosidic linkage of glycosylceramides, which are present in the plasma membrane of mammalian cells and originate from ceramides and glucose [reviewed in (Bras and Singleton, 2009)]. Mutations in the GBA gene cause a lysosomal storage disorder named Gaucher disease (with accumulation of glucocerebroside in lysosomes of mononuclear phagocytes (Grabowski, 2008). If only one GBA allele is affected a strong association with Parkinsonism is found (combined odds ratio of 5.43 to 6.98 compared to controls) (Bras and Singleton, 2009; Goker-Alpan et al., 2004; Sidransky et al., 2009a,b).

Lwin et al. first reported (Lwin et al., 2004) this increased prevalence of mutations in *GBA* among patients with Parkinson's disease and a lot of studies have confirmed and extended this observation, e.g. (Aharon-Peretz et al., 2005; Clark et al., 2005, 2007; Eblan et al., 2006; Sato et al., 2005; Toft et al., 2006).

Interestingly, Ron et al. observed in cell culture experiments that mutant GBA interacts with parkin (Ron et al., 2010). Additionally, they demonstrated that parkin promotes the accumulation of mutant GBA in aggresome like structures. The authors therefore hypothesise an involvement of parkin in mutant GBA degradation, leading to a time-dependent accumulation of its natural substrates.

Recently, overexpression of GBA mutants has been shown to be able to raise human α-synuclein levels significantly in both cell culture and in vivo (Cullen et al., 2011) without alteration of the GBA activity in a dose- and time-dependent manner.

Notably, in the autosomal recessive Gaucher disease (GD) a dysregulation in iron metabolism (Schiano et al., 1993; Stein et al., 2010; Weisberger et al., 2004) is well established, with (for example) an impressive elevation of serum ferritin in GD 1 (Stein et al., 2010). It is highly significant that the lysosome is the chief site of labile iron in the cell. This raises the question whether heterozygous GBA mutation carriers affected by Parkinsonism also show imbalances in iron homeostasis.

It would thus be logical (Kell, 2010a) to seek (and expect to find) a direct association with iron-mediated neurodegeneration in this form of PD, although none has as yet apparently been described.

8.3. FBXO7 (PARK15)

Mutations in the FBXO7 gene causing parkinsonism complicated by pyramidal features have recently been reported in an Iranian family with homozygous mutations (Shojaee et al., 2008).

Patients with heterozygous mutations associated with a milder phenotype were subsequently also described (Di Fonzo et al., 2009). The locus was assigned as the PARK15 locus.

FBXO7 has been characterized as a member of the FBXO family and is a component of modular E3 ubiquitin protein ligases (see also PARK2/ parkin) that play a role in phosphorylation-dependent ubiquitination (Jin et al., 2004). There is yet no overt link to iron.

Finally, a recent and extensive genome-wide association study (Do et al., 2011) has identified some novel genetic loci (including SCARB2 and SREBF1/RAI1) associated with Parkinson's disease, but not yet accorded PARK gene status. We have included them in Table 1.

9. Discussion

There is accumulating evidence that PD is best seen as a multifactorial, systems biology problem. This may be one reason why searches for unitary causes of PD have largely not been successful. Nonetheless, a variety of causes may converge on a more or less unitary mechanism (Kell, 2010b), which is certainly involved in many cases, and that is the autocatalytic production of the hydroxyl radical and other related toxicants catalysed by unliganded iron.

Not least from genome-wide association studies, a number of PARK genes have clearly been identified via alleles that have 'extreme' effects on function and thereby allow them to be observed as a 'monogenic' contributor to one or more forms of PD.

Here we thus reviewed functions of the known genes and proteins that are associated with Parkinsonism and Parkinson's disease with regard to their link to iron metabolism, trying to incorporate current understanding into a more holistic perspective. As shown above, knowledge about the role of iron in Parkinsonism ranges from a rather overt, even likely causative role to cases with no known direct association at all. Between these extremes there are 'monogenic' forms of PD in which iron may play a contributory role in the neurodegenerative process. This becomes especially obvious in the regulation of α-synuclein aggregation via an iron regulatory protein system and the fact that LBs, which are one of the hallmark features of PD, contain α-synuclein and iron. Therefore, iron may in the future, with further insights into this field, prove to be one of the key connecting links between the various forms of PD. Recently, Lei et al. published observations from tau-knockout mice developing amongst others an iron accumulation, loss of neurons in the SN and parkinsonism. By treating mice with an oral iron chelator, clioquinol, these symptoms could be prevented. These data suggest that there might be a contribution of tau to the toxic neuronal iron accumulation in PD (Lei et al., 2012).

However, despite the voluminous evidence that iron may damage tissue either directly or by changing the cellular environment so that it is more susceptible to toxins, it is also possible that iron deposition is in part a consequence of axonal disruption (Stankiewicz et al., 2007), as part of an autocatalytic feedback mechanism.

The understanding of the role of iron has implications for the development of therapies. It is thus interesting to follow the current literature reporting results from trials with iron chelation agents (Ward et al., 2012) as potential treatments for PD and related disorders, but also for example Alzheimer's disease (AD). The first successful demonstration of the utility of iron chelators in slowing the progression of AD is more than 20 years old (Crapper McLachlan et al., 1991)! While there have been some promising results in cell cultures [e.g. (Avramovich-Tirosh et al., 2007; Chao et al., 2010; Gaeta et al., 2011; Mercer et al., 2005; Wu et al., 2010; Xu et al., 2008)] and animal models (Adlard et al., 2008; Bolognin et al., 2009a; Bowern et al., 1984; Cheng et al., 2008; Dexter et al., 2011; Ebadi et al., 2002, 2005a; Gal et al., 2009; Kooncumchoo et al., 2006, 2012; Lan and Jiang, 1997; Levenson, 2003; Levenson et al., 2004a; Levites et al., 2001; Mounsey and Teismann, 2012; Mu et al., 2011; Perez et al., 2008; Saini et al., 2010; Shachar et al., 2004; Shi et al., 2010; Ward et al., 2012; Zhang et al., 2005, 2012), a resurgence of pre-clinical and clinical trials in humans is only just beginning to show positive results (Weinreb et al., 2009) and there has not yet been a clear correlation between a reduction of iron seen via neuroimaging and clinical benefit or the lack thereof. It should be noted that most chelators are not specific to a single metal (Hider et al., 2011), such that they may alter the distribution of multiple metals in the brain with possible unknown effects following long-term use (Gh Popescu and Nichol, 2010). There are also issues connected with getting such drugs to their actual sites of action (Dobson and Kell, 2008; Kell et al., 2011, 2012). Hopefully with further research into this area, whether with dietary (often polyphenolic) or pharmacological chelators, the effectiveness of the chelators can be increased in the near future, making them a secure and useful treatment option. Further study of natural, polyphenolic, dietary iron chelators seems especially warranted (Di Giovanni, 2009; di Matteo et al., 2009; Guo et al., 2007; Jomova et al., 2010b; Jomova and Valko, 2011b; Kell, 2009a, 2010a; Levites et al., 2001; Mak, 2012; Mandel et al., 2008; Mandel and Youdim, 2012; Ortega-Arellano et al., 2011; Perron and Brumaghim, 2009; Tan et al., 2008; Tanaka et al., 2011; Weinreb et al., 2004). Of course, many of these polyphenolic chelators are also (recognised as) anti-oxidants (Aquilano et al., 2008; Du et al., 2012; Gogoi et al., 2011; Kell, 2009b, 2010a; Oshiro et al., 2011; Pandey et al., 2012; Reale et al., 2012; Uttara et al., 2009; Wang et al., 2012; Zbarsky et al., 2005), albeit some anti-oxidants (such as various cysteine derivatives (Napolitano et al., 2011) are not known to be chelators. On synergistic grounds alone (e.g. (Koutsoukas et al., 2011; Lehar et al., 2009; Small et al., 2011; Xie et al., 2012; Zhao et al., 2011; Zimmermann et al., 2007) one might suggest that the combination of anti-oxidants and iron chelators will prove especially effective.

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