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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.

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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

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