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DJ-1, PINK1 and their effects on Mitochondrial Pathways

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Abstract

Genetic forms of parkinsonism are interesting for two particular reasons. First, finding a gene identifies a cause for a disease that would otherwise be unexplained. Second, finding several genes for the same disorder allows us to reconstruct molecular pathways that, in the example of Parkinson's disease, are associated with the survival of dopamine neurons in the substantia nigra. Two rare causes of parkinsonism, DJ-1 and PINK1, are associated with mitochondria. This organelle has long been linked with Parkinson's disease, and recent results are starting to show how mutations impact mitochondrial function. In this short review, I will discuss how we can use some of this information to understand why it is that neurons become dysfunctional in PD.

Introduction

A major advance in understanding the etiology of Parkinson's disease (PD) has been the identification of genes that cause syndromes that overlap with the sporadic disorder. A general schematic, discussed elsewhere ^{1, 2}, is that the dominant genes (α -synuclein and LRRK2) are informative about cell loss in the various regions of the brain that are affected in PD and about the formation of Lewy bodies, pathological hallmarks of sporadic PD. In contrast, recessive genes tell us something about cell loss in the substantia nigra and may or may not be informative about Lewy body formation.

Here, I will discuss the two least frequent genes for parkinsonism, DJ-1 and PINK1. Both of these are recessive disorders, meaning that a patient will have inherited a loss of function allele from each of their parents. Because the genetics of the diseases impacts how we might design experiments to probe the functions of these proteins, I will briefly outline what is known about DJ-1 and PINK1 mutations.

DJ-1 and PINK1 as rare recessive genes for parkinsonism

Many articles about PD start off by saying how common it is. Although true, this misses the point that there is some pleasure to be had in deliberately working on unusual diseases, so long as the biology is interesting. However, it is important to understand just how rare the recessive mutations in DJ-1 and PINK1 are. For DJ-1, Bonifati et al reported four affected patients in a Dutch family with a genomic deletion and three affected patients in an Italian family with an L166P point mutation ³. Subsequent studies have identified one case with M26I ⁴, two siblings with E64D ⁵, one case with A104T ⁶, one case with D149A ⁴ and three patients with E163K mutations ⁷ for a total of less than 20 patients. To put this in context, there were about 200 primary papers published on DJ-1 in Pubmed by the end of 2007, suggesting that there more people working on the biology of DJ-1 than have a DJ-1 mutation.

Mutations in PINK1 are a little more common, but still fairly rare. Some surveys suggest that PINK1 mutations account for 1–8% of early onset parkinsonism ⁸, but this phenotype

accounts for only a small fraction of all PD, so on a population basis, PINK1 accounts for less than 1% of all PD. There is some controversy about whether having a single, heterozygous, PINK1 mutation contributes to the lifetime risk of PD (see 9), but even if this were true, the frequency of PINK1 mutations would still be low.

Why is this important in understanding the biology of DJ-1 and PINK1? First, it limits our information of the phenotypes associated with these mutations. For example, the expression of disease in DJ-1 cases is variable: E163K is associated with amyotrophy where others are pure parkinsonian disorders. Second, there are no *post-mortem* brain samples from patients with DJ-1 or PINK1 mutations, which means that we cannot yet estimate the severity of neuronal loss or whether they have Lewy bodies. There are brain samples from cases with heterozygous PINK1 mutations but these could be rare non-pathogenic variants in sporadic PD brains.

What is clear is that both DJ-1 and PINK1 cases have mild parkinsonism that responds well to L-DOPA and have positron emission tomography imaging results consistent with loss of striatal dopamine 10, 11. Hence it seems reasonable to assume that the pathological substrate of the disease in these cases is a loss of nigral in the presence of an intact striatum. Therefore, in the experiments reviewed below, we can infer that DJ-1 and PINK1 are associated with cellular pathways relevant to neuronal viability.

DJ-1 and oxidative stress

DJ-1 is part of a large family of that is conserved across many species 12, 13. The crystal structure of DJ-1 reveals a small compact protein with a single folded domain 14. DJ-1 forms a strong dimer with much of the protein buried in a hydrophobic region between two monomers and some mutations disrupt this structure. For example, the L166P mutation 3 is in the middle of an α -helix near the dimer interface and acts to break this helix and destabilize the protein, leading to an effective knockout of the protein 15–19. This result clearly identifies mutations in DJ-1 as loss of function, but does not explain how all mutations work as some are quite stable 20. Therefore, some mutations must disrupt another key aspect of DJ-1 function.

The logical next question in understanding pathogenesis, therefore, is what is function of DJ-1? Over the past few years DJ-1 has been suggested to have several possible functions but a consistent finding is that it responds to oxidative stress, causing the isoelectric point (pI) to shift towards more acidic values 21, 22. The sulfhydryl group of an absolutely conserved cysteine residue (C106 in human DJ-1) reacts with reactive oxygen species to form a cysteine sulfinic acid 23–28. The modification occurs at lower levels of oxidative stress than modifications at other residues and is stabilized by interactions with nearby residues. What is interesting is that this cysteine is required for the ability of DJ-1 to protect against oxidative stress in vitro 28, 29 and in vivo 30 as replacement with Alanine (or other residues) removes the protective abilities of DJ-1.

This observation suggests that DJ-1 has a ‘signaling’ role in coordinating cellular responses to oxidative stress. The problem is that there is little agreement on what DJ-1 actually does within the cell. DJ-1 is reported to; affect ras-dependent transformation 31; control fertility 32; modulate androgen-receptor signaling via sumoylation 33, 34 and possibly through histone deacetylation 35; act as a protein chaperone 36; act as a protease 18, 37; affect transcription 38 including that of tyrosine hydroxylase 39; alter dopamine receptor signaling 40; suppress apoptosis via an interaction with kinases 41, 42 and/or suppression of the phosphatase PTEN 43; alter p53 signaling 44–46; alter Akt1 function 47; upregulate glutathione synthesis or heat shock proteins 48; stabilize antioxidant transcription factors 49; interact with PINK1 50 and parkin 51; and act similar to a peroxiredoxin 24.

The above list raises the question of how this small protein manages to do all of these different things. Probably the easiest way to resolve this problem is to suggest that there is a simple, single activity that explains them all. If there is a theme in the above observations it is of altered cell signaling pathways. Binding of DJ-1 to DNA directly or as part of a protein complex might be an obvious link, although it is interesting that DJ-1 was first cloned as an RNA interactor 52 suggesting that this nucleic acid may be important. A role for DJ-1 in modulating gene expression under oxidative conditions was suggested by Bonifati et al 3 but much work is needed to confirm or refute this idea.

The other major theme about DJ-1 function from many of the above studies is a potential role in nuclear to mitochondrial communication. DJ-1 is protective against, amongst other things, mitochondrial stressors both in vitro 28, 29, 53 and in vivo 45, 54–58. A portion of DJ-1 is present in mitochondria in cells 3, 20, 28, 59 and in brain 60. Quite why DJ-1 associates with mitochondria is unclear, but it is likely to have some functional role. Although further work is therefore needed on this subject, this leads nicely to the discussion of a more clearly mitochondrial protein, PINK1.

PINK1 – a “mitochondrial” kinase

Although the structure of PINK1 has not been solved, the primary sequence has several distinct features. At the N-terminus is a mitochondrial targeting sequence that is sufficient to direct proteins to the organelle 61, 62. Following this is a short hydrophobic sequence then a kinase region –whether this is a single independently folded protein sequence (and therefore a domain in the strict sense) is unclear. Finally, there is a C-terminal extension that can be inhibitory 61 or stimulatory for kinase activity 63 depending on whether the recombinant enzyme is purified from bacteria or insect cells respectively. These results suggest that PINK1 is post-translationally modified in a way that modulates the effect of the C-terminal region.

These and other results confirm that PINK1 is an active kinase 61, 63–66. As for DJ-1, a subset of mutations destabilize the protein 66. Together with the recessive nature of the disease, likely indicates that PINK1 mutations cause a loss of kinase function within the cell. In support of this idea, PINK1 can protect cells against apoptotic or mitochondrial stressors but not if an artificial kinase dead version is used 67.

PINK1 may also play a role in maintenance of mitochondrial function *in vivo* as *Drosophila* where the PINK1 homologue has been deleted show apoptotic muscle loss and fertility defects that are related to mitochondrial morphology 68–71. Interestingly, these effects can be rescued by reexpressing fly or human PINK1, suggesting functional conservation across species, or by parkin, suggesting that the two genes form a functional pathway. Although PINK1 knockout mice do not show obvious mitochondrial damage 72, fibroblasts from human patients show subtle morphological defects that can be exacerbated by stress and rescued by parkin 73. Such defects are reminiscent of mitochondrial fragmentation seen under conditions of excess fission, although it has not been proven that fission plays a role in PINK1 or parkin deficiency.

If we are to understand why PINK1 affects mitochondria, then the most important piece of information is to identify its kinase substrate(s). The mitochondrial chaperone TRAP1 has been proposed as a relevant substrate in one study 64. Very recently, the mitochondrial protease and inhibitor of apoptosis, Omi, has been suggested to be phosphorylated in a PINK1-dependent manner although whether it is a direct PINK1 substrate is unclear. Therefore, at this stage, there is a sense that the problem of understanding PINK1 deficiency is a tractable one, the molecular details of the process are still to be worked out.

A small difficulty with the above idea is that it isn't actually clear how much PINK1 is mitochondrial. Work from several groups now has suggested that at least a portion of PINK1 is cytoplasmic 66, 74, 75. This is supported indirectly by observations that PINK1 can be present in Lewy bodies 76, 77 or in cellular structures where proteins are degraded called aggresomes 62. These observations may be unimportant – perhaps PINK1 is simply shuttled to the cytoplasm for degradation, which might occur more rapidly than normal if the protein is overexpressed in model systems. But they might also be a clue that some important functions of PINK1 may be related to the outside face of the mitochondria and not to its inner workings.

Summary

The many studies discussed here point generally to an important role in mitochondria for understanding recessive parkinsonism. Because both DJ-1 and PINK1 seem to be signaling molecules of sorts, we can infer that their role is to control mitochondrial function under a range of circumstances that include oxidative or other stressors to which nigral neurons might be selectively vulnerable. At this juncture, it would be premature to say that the problem is solved, but it would certainly seem to be solvable.

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