DJ-1, a possible therapeutic target against Parkinson's disease

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Aims

- Introduce Parkinson's disease (PD) and the DJ-1 protein and gene
- Study the links between PD, oxidative stress and protein aggregation
- Recognize the role of DJ-1 on oxidative stress and protein aggregation
- Identify mutations and damage in DJ-1 as cause and risk factors for PD

References

[1] Wilson M.A. et al (2003): *The 1.1 Å resolution crystal structure of DJ-1, the protein mutated in autosomal recessive Parkinson's disease*. Proc Natl Acad Sci USA 100:9256-9261

[2] Adapted from Vicenzo Bonifati (2003): *Autosomal recessive, early-onset Parkinson's disease, Chapter 1: Introduction*; printed by Optima Grafische Communicatie, Rotterdam

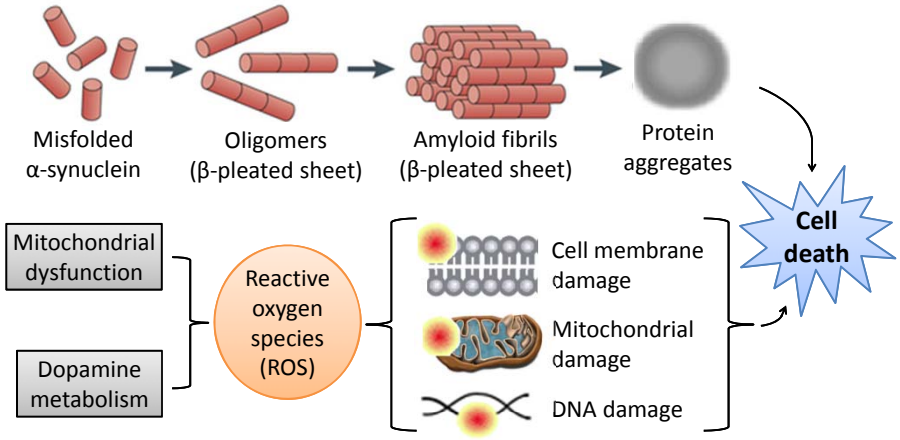
[3] Adapted from Toyoda Y. et al (2014): *Products of the Parkinson's disease-related glyoxalase DJ-1, D-lactate and glycolate, support mitochondrial membrane potential and neuronal survival*. Biology Open 3:777-784

[4] Adapted from Marc C. Meulener et al (2006): Mutational analysis of DJ-1 in Drosophila implicates functional inactivation by oxidative damage and aging. Proc Natl Acad Sci USA 103:12517-12522.

1 Parkinson's disease

- Parkinson's disease (PD) is the second most common neurodegenerative disorder nowadays
- It consists on dopaminergic neurons cell death through apoptosis
- Patients struggle to start and control voluntary movements
  - Sporadic PD ⟶ Multifactorial disease
  - Familiar PD ⟶ Genetic disease
- Protein aggregation (mainly α-synuclein) and oxidative stress are key factors in pathology development of PD

2 Protein aggregation and oxidative stress



3 The DJ-1 gene and protein

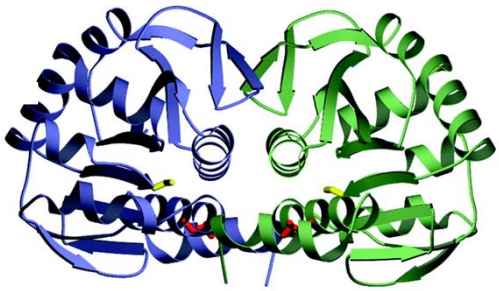


Figure 1. Ribbon diagram of the DJ-1 homodimer[1]

- DJ-1 is a 189 amino acid protein, highly expressed in brain as a 40 kDa homodimer
- It has an α/β sandwich folding belonging to the PfpI Cysteine proteases family, but spatially distorted catalytic amino acids make it lose protease activity.
- DJ-1 gene location: PARK7 *locus*, short arm of chromosome 1
- It is 24 kb long and has 8 exons, being exon 1 alternatively spliced

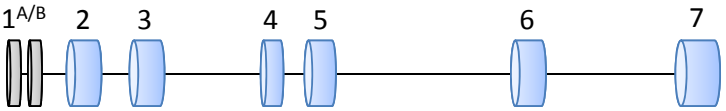
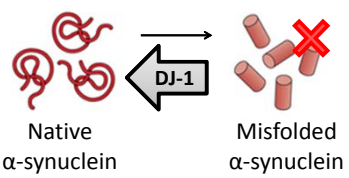


Figure 2. Structure of the DJ-1 gene[2]

4 DJ-1's functions on oxidative stress and protein aggregation

1. Antioxidant: DJ-1 scanvenges ROS by oxidizing itself
2. Glyoxalase: DJ-1 detoxifies aggressive products of energetic metabolism and stabilizes mitochondria
3. Chaperone: DJ-1 prevents α-syn misfolding and aggregation



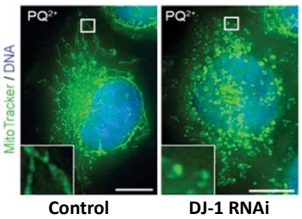
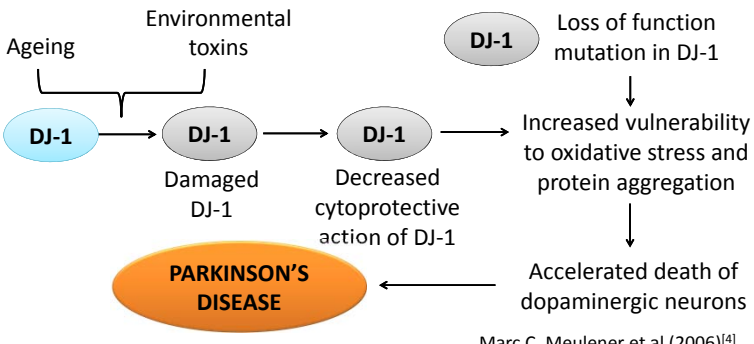


Figure 3. Mitochondria of paraquat (PQ^{2+}) treated HeLa cells. PQ^{2+} is a mitochondrial toxin, capable of inducing Parkinsonism.[3]

5 DJ-1 and Parkinson's disease

- Loss of function mutations in DJ-1 cause early onset autosomal recessive Parkinson's disease.
- DJ-1 is altered in sporadic Parkinson's disease patients



Marc C. Meulener et al (2006)[4]

Conclusions

- DJ-1 loss of function results in Parkinson's disease because dopaminergic cells become very sensitive to oxidative stress insults and protein aggregation.
- DJ-1 may be a therapeutic target against Parkinson's disease. However, further research on its therapeutic potential is needed.