Baker's yeast to study Parkinson's Disease

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INTRODUCTION

Parkinson's disease (PD)

- PD is the second most common neurodegenerative disorder.
- PD affects around 1% of the world-wide population over 60 years of age and 4% in those above 80 years.
- Symptoms:

Resting tremor

Muscle rigidity

Bradykinesia

Postural instability

Its cause remains unclear:

- Sporadic
  - 90% of PD cases
- **Genetic**
  - **10% of PD cases**

- Pathology: selective and progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies (mainly α-synuclein).
- Only symptomatic treatment: dopamine substituents (L-dopa).

Yeast

- *Saccharomyces cerevisiae*: yeast most commonly used.

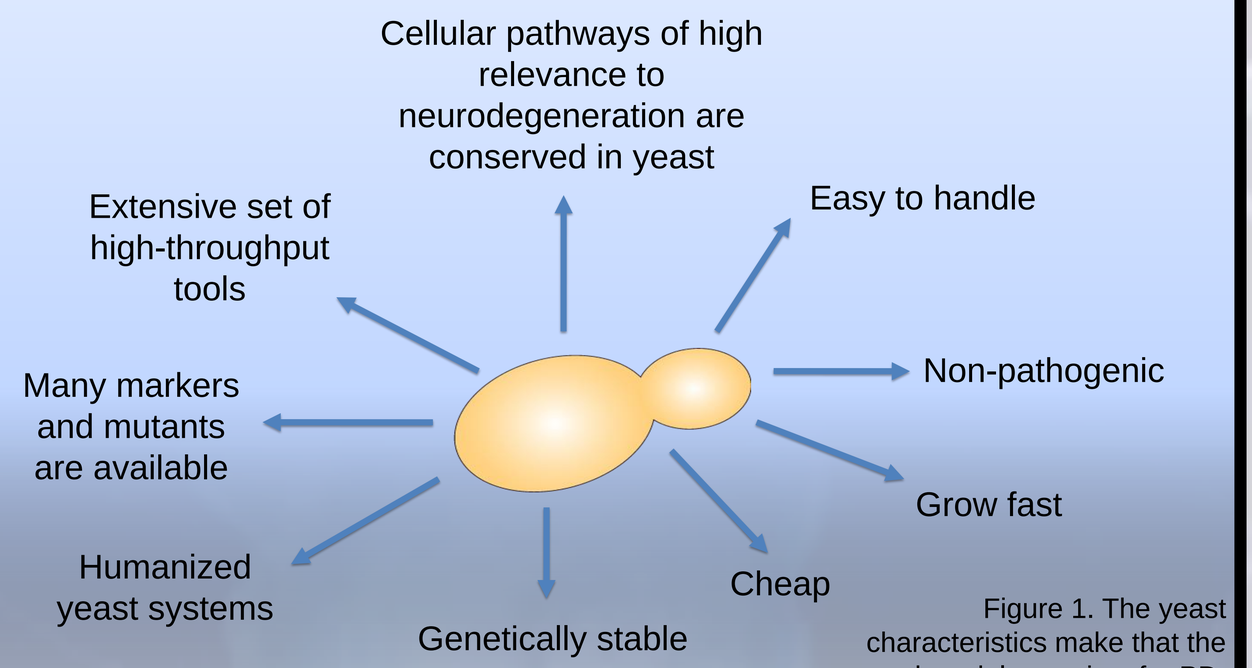

Figure 1. The yeast characteristics make that the good model organism for PD.

WHAT HAS BEEN ACHIEVED?

Genetics of Parkinson's disease

At present 18 genetic loci (designated PARK1-18) have been associated with the development of PD (Table 1).

Table 1. Description of PARK loci, corresponding gene, map positions, main function and inheritance pattern.

PARK loci	Gene	Map Position	Function	Inheritance
PARK1/4	α-synuclein (SNCA)	4q21	Synaptic vesicle formation / membrane fusion	AD
PARK2	Parkin	6q25.2-q27	E3 ubiquitin ligase	AR
PARK3	SPR?	2p13	Unknown	AD with reduced penetrance
PARK5	UCHL-1	4p14	Hydrolyze small C-terminal adducts of ubiquitin	AD
PARK6	PINK1	1p35-p36	Mitochondrial Kinase	AR
PARK7	DJ-1	1p36	Cystein protease/redox-regulated chaperone	AR
PARK8	LRRK2	12q12	Kinase/GTPase activity	AD
PARK9	ATP13A2	1p36	Lysosomal ATPase	AR
PARK10	Unknown	1p32	Unknown	Unclear
PARK11	GIGYF2	2q36-q37	Unknown	AD
PARK12	Unknown	Xq21-q25	Unknown	Unclear
PARK13	Omi/HTRA2	2p13	Serine protease+	AD?
PARK14	PLA2G6	22q13.1	Phospolipid remodelling	AR
PARK15	FBX07	22q12-q13	E3 ubiquitin protein ligase subunit	AR
PARK16	Unknown	1q32	Unknown	Unclear
PARK17	VPS35	16q11.2	Subunit of the retromer complex	AD
PARK18	EIF4G1	3q27.1	Unknown	AD

** AD: autosomal dominant; AR: autosomal recessive.*

Mechanisms of neurodegeneration

There are different mechanisms involved in neurodegeneration of Parkinson's disease, such as mitochondrial dysfunction, oxidative stress, altered proteolysis (proteasomal and lysosomal), inflammatory change and excitotoxic mechanisms (Figure 2).

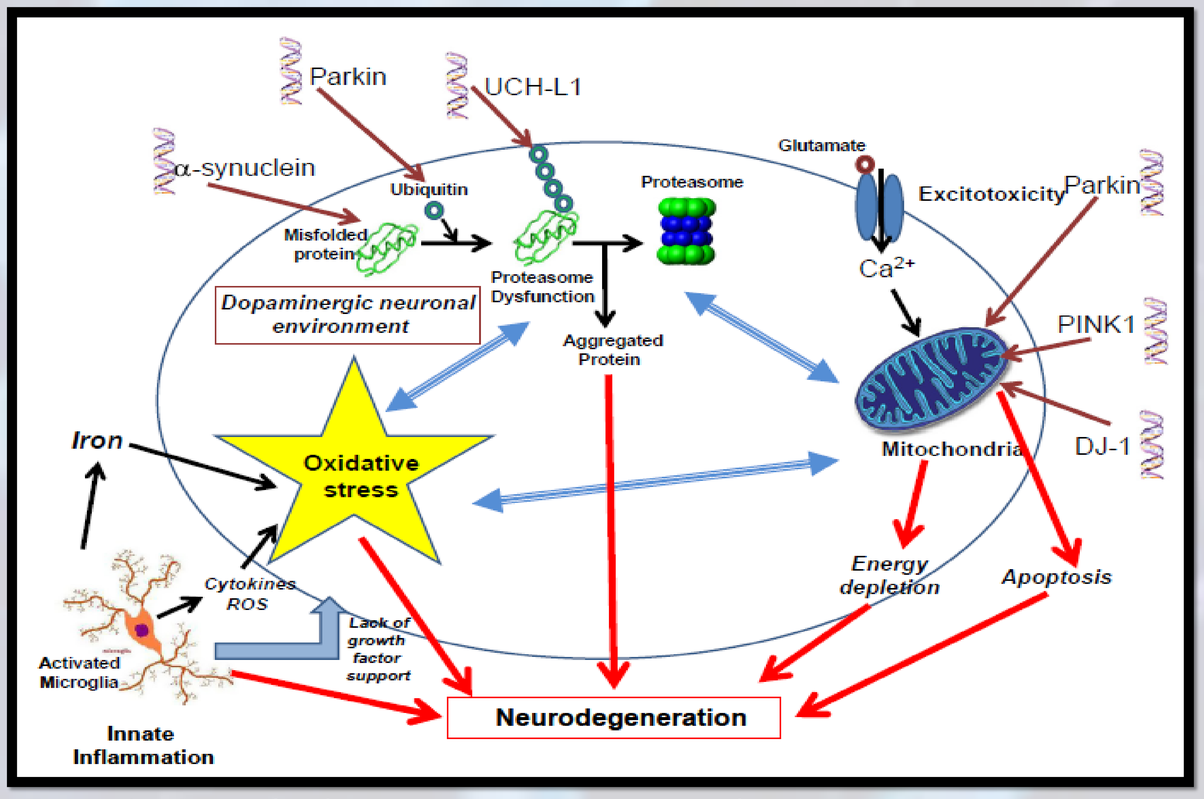

Figure 2. Key molecular mechanisms that are widely accepted to contribute to the neurodegenerative process in PD. Double helix structures identify some of the common gene mutations found in familial PD and brown arrows indicate where the altered protein may interfere with cell function and overlap with known mechanisms of cell death in PD. Blue double-headed arrows indicate molecular mechanisms that may not only be toxic in their own right but importantly may also influence other molecular mechanisms known to be features in PD. ROS, reactive oxygen species [1].

CONCLUSIONS

- Several research groups have developed great expertise in uncovering the cellular aspects of α-synuclein toxicity using humanized yeast models.
- Yeast is a simple unicellular organism that has preserved many of the complex processes that occur in neuronal cells. Thus, yeast constitutes a powerful system to investigate the molecular basis underlying neurodegenerative disorders, such as PD.
- Yeast models strongly contributed to our current knowledge of the genes and pathways involved in the most prominent human neurodegenerative diseases, as demonstrated by their subsequent validation in higher eukaryotic models.
- Yeast models may facilitate strategies aimed to identify therapeutics for treating PD.

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