Parkinsons's Disease: New Perspectives

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What are the "unmet needs" for neurodegenerative diseases?

- Definition of the NDD, e.g. PD
- Understanding the pathogenesis
- Identifying a potential target for intervention

Clinical definition of PD

An adult-onset, progressive, predominantly motor disorder

- **Combining 2 or more of the following:**
  - **Bradykinesia**
  - **Rest tremor**
  - **Limb rigidity**
  - **Postural instability**
- **Marked and sustained response to levodopa**

Non-motor manifestations

- Seborrheic dermatitis
- Sensory complaints
- Premorbid personality
- Olfactory dysfunction
- Constipation
- Depression
- REM–sleep behavior disorder

Definition of parkinsonian syndromes – Lumping or splitting?

Clinical subtypes of Parkinson's disease

- Tremor predominant
- Akinetic-rigid type
- Postural Instability Gait Disorder
- Lower body parkinsonism

Genes associated with PD

Table 1 Reported familial PARK loci

Locus	Region	Gene	Age-at-onset	Inheritance
PARK1/4	**4q21**	**SNCA**		**AD**
PARK2	**6q26**	**PRKN**	**Early-onset**	**AR**
PARK3	2p13	–		AD
PARK5	4p13	UCH-L1		AD
PARK6	**1p36.12**	**PINK1**	**Early-onset**	**AR**
PARK7	**1p36.23**	**DJ-1**	**Early-onset**	**AR**
PARK8	**12p12**	**LRRK2**		**AD**
PARK9	**1p36.13**	**ATP13A2**	**Early-onset**	**AR**
PARK10	1p32	–		–
PARK11	2q37.1	–		AD
PARK12	Xq21-q25	–		X-linked
PARK13	2p13.1	–		AD
PARK14	**22q13.1**	**PLA2G6**	**Early-onset**	**AR**
PARK15	**22q12.3**	**FBXO7**	**Early-onset**	**AR**
PARK16	1q32	–		–
PARK17	**16q11.2**	**VPS35**		**AD**
PARK18	3q27.1	EIF4G1		AD

PARK loci is the traditional nomenclature used to specify a chromosomal region that was linked with a specific parkinsonism phenotype. This system, however, is becoming outdated as classical linkage studies will most likely be replaced with next-generation sequencing technologies, and to date genome-wide association regions have not been designated as PARK loci. Those genes highlighted in bold are those confirmed to be a cause of PD and early-onset parkinsonism

AD autosomal dominant; *AR* autosomal recessive

Several genetic mutations account for some PD cases

However,

most cases are sporadic

Environmental factors associated with PD

Presumed PD-associated factors

Causative

- Age
- Male gender
- Toxin exposure
- Head trauma

Protective

- Uric acid
- Smoking
- Caffeine
- NSAID

This means that there is phenotypic convergence, where the same clinical manifestations result from different etiologies

PD, a multifactorial disease

- A complex progressive neurodegenerative disorder characterized by brain atrophy and deposits of synuclein
- Caused by a heterogeneous combination of environmental and genetic factors

PD – one disease or many?

Clinical, pathological and genetic heterogeneity

Even the pathological definition is insufficient

J Neural Transm (1999) [Suppl] 56: 107–111

Parkinson's disease: one disease entity or many?

A. D. Korczyn

Sieratzki Chair of Neurology, Sackler Faculty of Medicine, Tel-Aviv University, Israel

Summary. Although most neurologists accept that Parkinson's disease (PD) is a unique disorder, we still lack a valid biological tool and therefore depend primarily on clinical examination in diagnosis. The distinction between PD and other parkinsonian syndromes is discussed.

How can biomarkers help?

Focus on dopamine as a central moleculer involved in neurodegeneration

Modern understanding of the pathophysiology of PD

- Discovering the depigmentation of the SN
- Identification of dopamine as neurotransmitter
- Mapping dopaminergic pathways in the brain, particularly the nigrostriatal tract
- Realization of dopamine loss in PD
- Demonstration in animals that dopamine depletion produces parkinsonism (6-OH-DA, reserpine)
- Substitution therapy with dl-dopa, then levodopa, then levodopa + DDCI, then bromocryptine
- Identification of dopamine receptor subtypes
- Synthesis of selective D_2 agonists.

Yet, no biomarker emerged for PD which is related to dopamine

The first genetic mutation discovered in familial parkinsonism in the α-synuclein gene, established PD as being essentially a synucleinopathy

Synuclein as a biomarker?

Omics Sciences

- Genomic
- Transcriptomics
- Proteomics
- Metabolomics

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Is Parkinson's disease a disease?

What is a disease?

Is hepatic cirrohosis a disease?

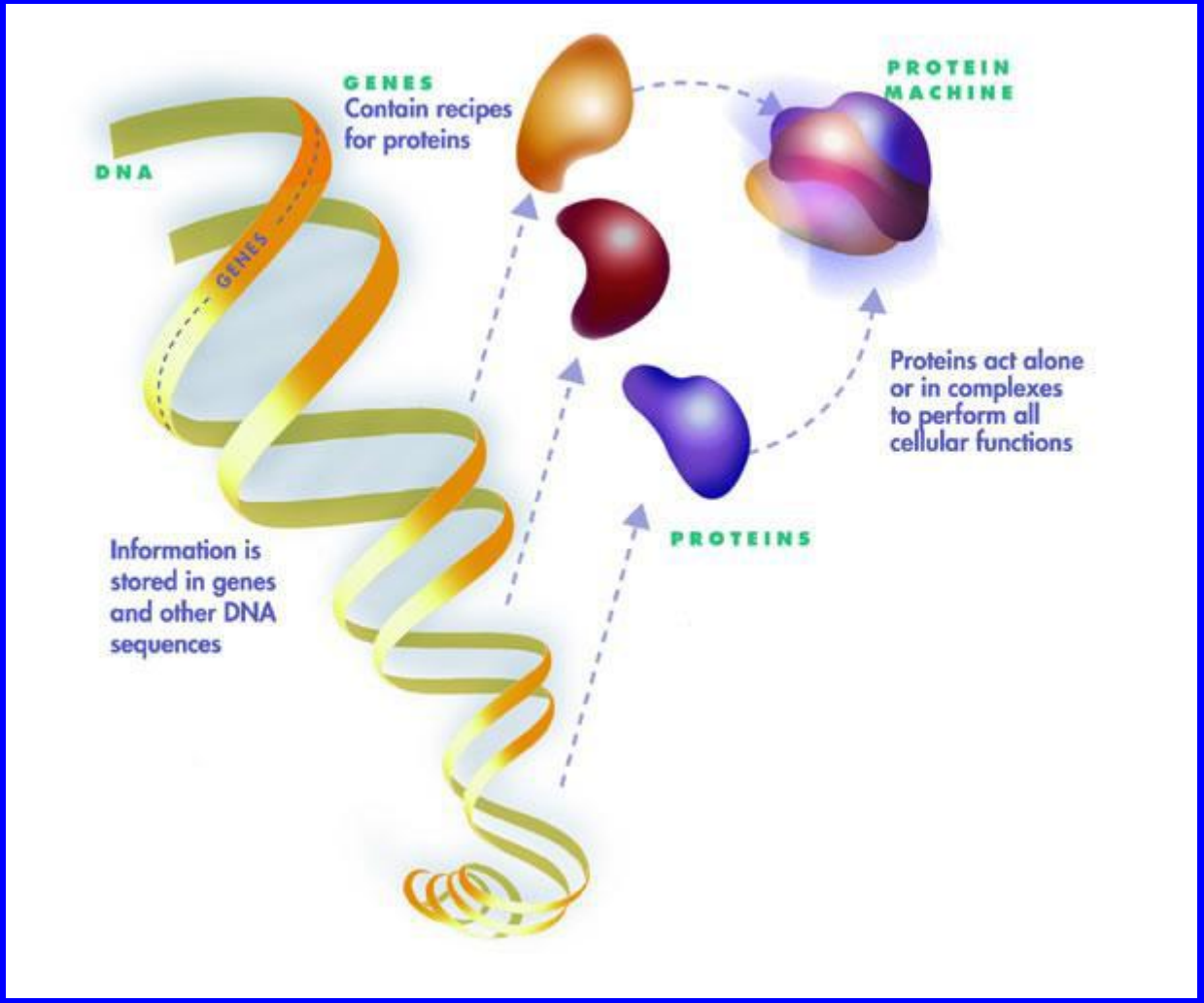
Is hepatic cirrhosis a disease?

- Alcohol abuse
- Viral hepatitis
- Bilharziasis
- Primary biliary cirrhosis
- Autoimmune hepatitis
- Cardiac failure
- Wilson's disease

What is a disease?

'Disease' **is an abstract concept encompassing the underlying process, with a common etiology, pathogenesis, evolution and pathology**

Genes, proteins, and molecular machines



Epigenomics

- The genetic programming that occurs predominantly as a consequence of DNA methylation
- The molecular underpinning of this regulation involves the methylation of cytosine and is maintained by a family of DNA methyltransferases
- Actively transcribed genes are usually in an unmethylated state, whereas genes that are silenced are heavily methylated

PD, a multifactorial disease

- A complex progressive neurodegenerative disorder characterized by brain atrophy and deposits of synuclein
- Caused by a heterogeneous combination of environmental and genetic factors
- Because of its complexity and etiological heterogeneity it is not a “disease” in the classical sense

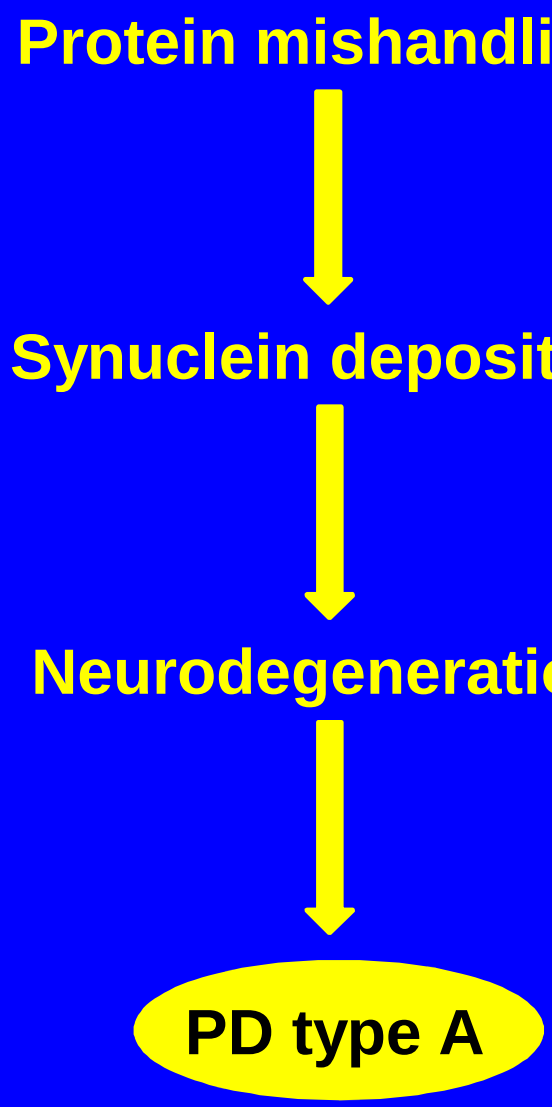
MicroRNAs (miRNAs)

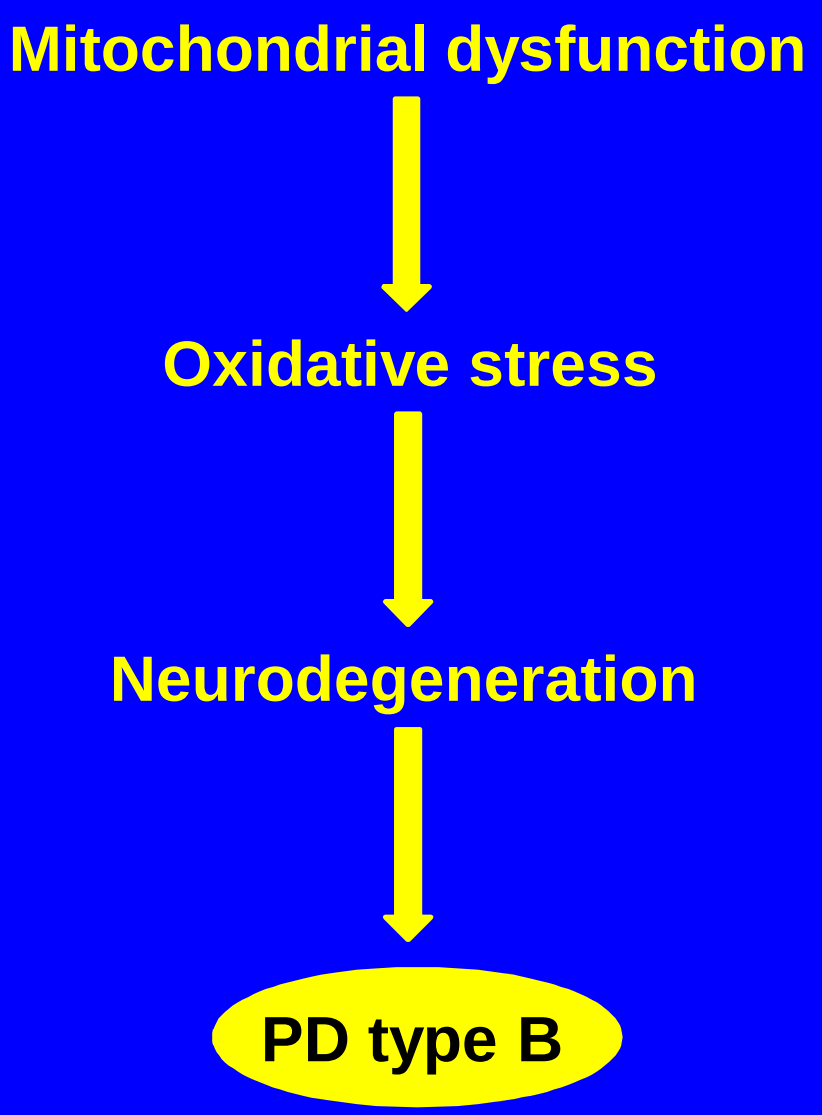
- **Small, noncoding single stranded RNA molecules of about 20-25 nucleotides (nt) tat originate from a 70-100 nt hairpinprecursor (pre-miRNA)**
- **Regulate eukaryotic gene expression at the post-transcriptional level by binding to the 3' untranslated region (UTR) of their target mRNAs and leading to a decrease of the target protein by either degradation of the mRNA or translational repression.**
- **miRNAs are abundant in the brain where they have crucial roles in development and synaptic plasticity.**
- **Certain miRNAs are differentially expressed in the human brain and regulate the expression of genes implicated in specific neurodegenerative diseases**

Genes associated with PD: A second look

The genes can be grouped according to presumed effects:

- Mitochondrial dysfunction
- Protein handling
- Neuro immuno-inflammation
- Lysosomal dysfunction


Protein mishandling
Synuclein deposition
Neurodegeneration
PD type A


Mitochondrial dysfunction
Oxidative stress
Neurodegeneration
PD type B

Cochrane Database Syst Rev., 2011

Coenzyme Q10 for Parkinson's disease

Liu J, Wang L, Zhan SY, Xia Y

REVIEW

CNS Neuroscience & Therapeutics

Pharmacological Therapy in Parkinson's Disease: Focus on Neuroprotection

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Keywords
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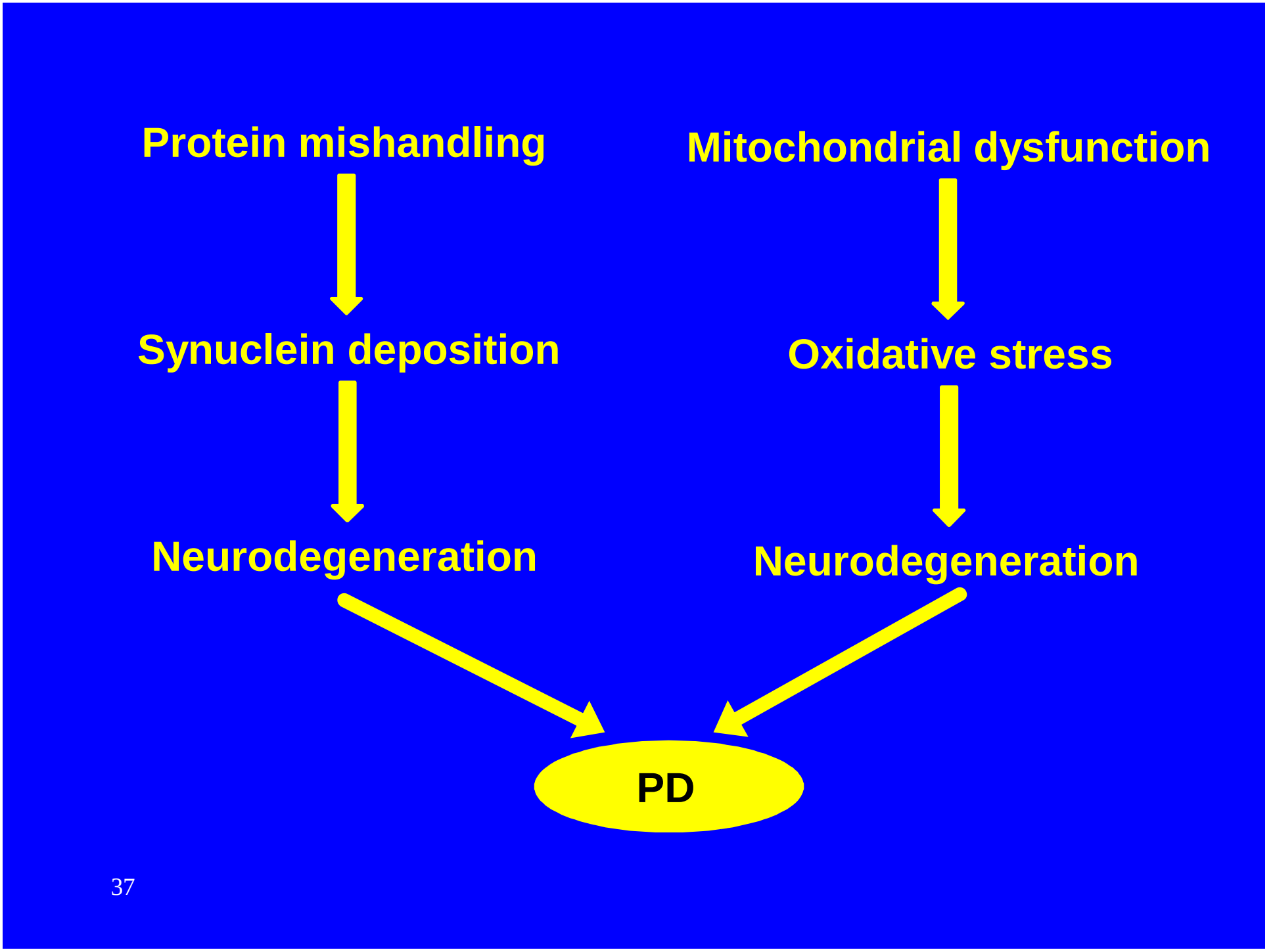
Although the number of available therapeutic approaches in Parkinson's disease (PD) is steadily increasing the search for effective neuroprotective agent is continuing. Such research is directed at influencing the key steps in the pathomechanism: the mitochondrial dysfunction, the oxidative stress, the neuroinflammatory processes and the final common apoptotic pathway. Earlier-developed symptomatic therapies were implicated to be neuroprotective, and promising novel disease modifying approaches were brought into the focus of interest. The current review presents a survey of our current knowledge relating to the pathomechanism of PD and discusses the putative neuroprotective therapy.


Protein mishandling
Synuclein deposition
Neurodegeneration
Mitochondrial dysfunction
Oxidative stress
Neurodegeneration
PD

Making a diagnosis of PD is like making a diagnosis of stroke

The next stage is to identify the etiology or pathogenesis

- PAF
- Mitral valve lesion
- CADASIL/Fabry etc
- Atherosclerosis

Take home message

- **PD is a syndrome, not a disease**
- **The clinical syndrome is the result of phenotypic convergence**
- **PD is the result of a hetergeneous combination of several genetic and environmental factors**
- **Several metabolic abnormalities likely exist in PD patients**
- **Identification of these processes and the patients having them is the basis of developing future DMDs**

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SAVE THE DATES

A major complicating factor

Genetic – phenotypic discrepancies

Vascular Parkinsonism

Assumption

Sporadic PD follows the same pathologic roadmap as the monogenic familial disease