Pathogenesis of Parkinson’s Disease

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Parkinson’s Disease

- Most common chronic progressive neurologic disorders affecting 3% of the population over the age of 65
- Disease mechanism(s) are poorly understood
- Neuronal vulnerability is controlled by many factors
  - Involve expression levels of proteins, signaling molecules, neuronal protein dysfunction, and oxidative stress

Risk Factors

- **Age**
  - Most patients diagnosed are at least 60 years old

- **Sex: Males**
  - Men are 1.5 times more likely to get the disease
  - Speculation that estrogen protects against PD
Risk Factors

- **Genetic factors:**
  - 10 mutations in 6 genes correlated with disease to date
  - Those with an affected 1st degree relative have a 2-3 fold increased risk of developing Parkinson's, as compared to the general population

- **Environmental factors:**
  - Rural living, well water, herbicide/pesticide (rotenone, paraquat) use, and exposure to metals
  - Biproduct of a synthetic heroin, MPTP, can cause immediate and permanent parkinsonism if injected

http://www.pdf.org/AboutPD/causes.cfm
http://www.parkinson.org/site/pp.asp?c=9dJFJLPwB&b=71117
Clinical Features

- Signs & symptoms:
  - Tremor, rigidity, bradykinesia, and postural instability
  - Small, cramped handwriting, stiff facial expression, shuffling walk, muffled speech, depression

- Death occurs on average a decade after initial symptom onset
  - Complications from immobility
  - Dysphagia: impaired ability to swallow

S. Gandhi et al. Human Molecular Genetics 14 (2005) 2749-2755
Neuronal Pathology

- Loss of pigmented neurons in the substantia nigra pars compacta (SNc) of the midbrain.

http://www.hcnr.med.harvard.edu/visitorInfo/parkinsons.php

http://www.nottingham.ac.uk/pathology/lewy/lewyinfo.html
Some Factors Involved with Dopaminergic Degeneration in PD

- Oxidative stress
- Glia and brain inflammation
- Mitochondrial dysfunction
- Molecular pathogenesis
  - Protein aggregation:
    - α-synuclein
    - Lewy bodies

Molecular Pathogenesis

- Many neurodegenerative disease share common pathogenic process
  - 2 Stages:
    - Protein aggregation
    - Cellular response to these abnormal proteins

S. Gandhi et al. *Human Molecular Genetics* 2005 (14) 2749-2755
Protein Aggregation: β-synuclein

- Highly expressed in brain tissues and is primarily localized at the presynaptic terminals of neurons
- Normally aids brain function, possibly by helping cells communicate with one another
- Soluble & unfolded protein in its native state
- NAC region prone to aggregate especially under oxidative stress forming protofibril & ultimately fibrils
- Two mutations, A53P and A30P, have been identified in families with early-onset familial Parkinson's disease

S. Gandhi et al. Human Molecular Genetics 2005 (14) 2749-2755
M.G. Spillantini et al., Nature 1997 (388) 839
S.M. Park et al., Blood 2002 (1000) 2506
Mark R. Cookson Annual Reviews Biochem. 74 (2005) 29-52
Protein Aggregation: Lewy Bodies

- Abnormal intracytoplasmic filamentous aggregates of \( \alpha \)-synuclein

- First appear in lower brainstem
  - As disease worsens, Lewy bodies appear higher in the brainstem, then substantia nigra, eventually cerebral cortex

- Presence in the brain disrupts the brain's normal functioning, interrupting the action of the important chemical messengers

Cellular Response to Protein Aggregation: Ubiquitin Protease System

- Normal function: degrade abnormal proteins
- First evidence that UPS’ role in Parkinson’s disease was the identification of the parkin gene (most numerous in early onset parkinsonism)
- Neuronal degeneration may be caused by a deficiency in UPS as well as mutations in parkin gene & deficits in the proteasome


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T. Dawson et al. Science 2003 (302) 819-822
Complex I of Mitochondria

- Largest enzyme of the oxidative phosphorylation system, composed of at least 46 subunits
- Catalyses 1\textsuperscript{st} step in mitochondrial electron transport chain
- Electrons from the oxidation of NADH convert oxygen to water
Mitochondrial Damage

- 30% decrease in complex I activity in PD

- Inhibition of complex I causes:
  - Depletion of ATP & all ATP dependent cellular processes
  - Generation of free radicals that cause oxidative stress

S. Gandhi et al. Human Molecular Genetics 2005 (14) 2749-2755
DJ-1 Gene

- Plays important role in neuroprotection against oxidative stress
- Mutation causes autosomal recessive parkinsonism
- Study of SNc of mice treated with MPTP revealed significant increase in DJ-1

S. Gandhi et al. Human Molecular Genetics 2005 (14) 2749-2755
J. Choi et al. Journal of Biological Chemistry 2006 (281) 10816-10824
PINK1 Gene

- Normally has neuroprotective properties against variety of cellular stresses

- Mutation G309D in PINK1 causes loss of neuroprotective properties (this mutation is found within certain families with PD)

S. Gandhi et al. *Human Molecular Genetics* 2005 (14) 2749-2755
Mitochondrial Damage

- What else causes mitochondrial damage? NITRIC OXIDE

- Cells are able to withstand some increase in NO concentration

- Once threshold is reached $\rightarrow$ limited resistance to NO $\rightarrow$ irreversible damage to mitochondria

F. Antunes et al. *Biochimica et Biophysica Acta* 2002 (1556) 233-238
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Glia & Brain Inflammation

- Normal functions of microglia:
  - Compose 5-20% of brain depending on region
  - Play a role in tissue repair & cellular homeostasis
  - Activated microglia → immune function, destroy invading microorganisms, fight infections


www.powmri.edu.au/.../pdda/pdrd/cellular/ipd.htm
Resting Microglia

Tissue necrosis stimulus

Activated Microglia:
undergo hypertrophy & hyperplasia

Chronically Activated Microglia:
Seen in paretic neurosyphilis

Rounded Macrophage

http://www.urmc.rochester.edu/neuroslides/slide004.html
Microglia in PD

- Activated microglia present in proximity to damaged neurons
- Microglia in SNc is highly activated in PD, mostly by:
  - Cytokines: TNF-α, IL-1β, INF-γ
  - Induction of MHC-I
  - iNOS
- In PD, microglia activation has detrimental effects

Experimental Evidence

- In an *in vitro* study, activated microglia released not only TNF-α, IL-1β, INF-γ but also O$_2^-$, H$_2$O$_2$, and NO.

  Found that activated microglia released 3-4-fold more ROS (H$_2$O$_2$ and NO more than O$_2^-$).

  Through the release of ROS, dopaminergic cells were severely injured.

Le et al. *The Journal of Neuroscience* 2001 (21) 8447-8465
Nitric Oxide Synthase: 3 Types

1. **Neuronal NOS:**
   - Found in neurons
   - Major isoform present in brain

2. **Endothelial NOS:**
   - Found only in some regions of the brain & endothelial lining of blood vessels

3. **Inducible NOS (iNOS):**
   - Normally absent or minimally expressed
   - In pathological conditions, increase in iNOS expression increases brain glial cells & macrophages
   - Considerable amounts of iNOS expression in SNc was found in post-mortem brain sample of PD patients

Experimental Evidence

- Administered MPTP to mice
  - Cause severe and irreversible PD like syndromes
- In comparison to control, MPTP mice showed a 250% increase of microglial iNOS expression by 24 hours
- iNOS deficient mice were more resistant to MPTP
NO Damage

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Oxidative Stress

Abnormal increase in the production of ROS might tilt the balance b/t production & elimination leading to enhanced oxidative stress.

Destructive condition resulting from insufficient scavenging of ROS that are generated by biochemical reactions.

J. Lotharius et al. Nature Reviews 2002 (3) 932-942
Oxidative Stress

- Clear evidence of oxidative stress in postmortem PD brain:
  - Increased lipid peroxidation & malondialdehyde levels (metabolite of lipid peroxidases)
  - Increased iron concentration in SNc has been implicated in the progressive dopaminergic neuronal degeneration
    - Fenton Reaction:
      $$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^-$$

Source of Oxygen Free Radicals

- **Neuromelanin**
  - Present in large amt in SNc
  - Normally protects neurons from oxidative stress
  - When neurons die, neuromelanin released causes microglia to produce toxic substances

Oxidative Stress: Glutathione

- Major antioxidant in cellular defense against oxidative stress from \( \text{H}_2\text{O}_2 \)

Levels of total glutathione & glutathione peroxidase in the SNc in PD is decreased

Oxidative Stress: Superoxide Dismutase

- Superoxide dismutase (SOD) were found to be overexpressed as an adaptive response to the increase in superoxide formation.
- Increase in SOD/glutathione peroxidase ratio could result in the accumulation of H$_2$O$_2$.
- Give rise to hydroxyl radicals by Fenton Rxn promoted by Fe overload in SNc.

http://www.sigmaaldrich.com/Area_of_Interest/Biochemicals/Enzyme_Explorer/Cell_Signaling_Enzymes/Superoxide_Dismutase.html
Treatments: Carbidopa/Levodopa (Sinemet®)

- Available since 1960s
- Natural amino acid that is converted to dopamine in the brain
- Commonly prescribed with benserazide or carbidopa (a decarboxylase inhibitor), which prevent peripheral conversion of L-Dopa to dopamine → decreasing associated side effects

http://www.pdf.org
Treatments: Dopamine Agonists

- Bromocriptine, Pergolide
- Drugs that stimulate dopamine receptors
- Brain "thinks" it is receiving dopamine

http://www.pdf.org
Treatments: Anticholinergics

- Oldest class of medications available
- Lack of dopamine to balance out acetylcholine causes tremor, stiffness in muscles
- Anticholinergics balance out the production of dopamine and acetylcholine reduce tremor or rigidity
- Can be taken alone or in combination with levodopa

http://www.parkinson.org
www.parkinsonsinfocom
Treatments: MAO-B inhibitors

- Blocks enzyme & slows the breakdown of dopamine in the brain
Treatments: Gene Therapy

- Insertion of the genes into an individual's cells and tissues to treat a disease

- Implant cells genetically modified to express tyrosine hydroxylase

- Transplant fetal neurons into PD patients
  - Neurons extended axons to striatum
  - Allowed patients to stop L-dopa treatments

- Transplant non-neuronal cells genetically modified \textit{in vitro} to express tyrosine hydroxylase being studied


www.wikipedia.com

Treatments: Deep Brain Stimulation

- Good for patients with:
  - Uncontrollable tremor for which medications have not been effective
  - Patients with symptoms that are well treated with medications but who experience severe motor fluctuations
- Implant electrodes into subthalamus of brain
- Activation of these electrodes results in alleviation of dystonia or dyskinesias

http://www.neuro.jhmi.edu/dbs/
Treatments: Deep Brain Stimulation

- Electrodes are connected by wires to a type of pacemaker device, impulse generator (IPG), implanted under the skin of the chest.

- Once activated, the device sends continuous electrical pulses to the target areas in the brain, blocking the impulses that cause tremors.

http://www.medicinenet.com/deep_brain_stimulation/article.htm
Conclusion

- Pathogenesis still not fully understood
- PD patients have selective degeneration of neurons in the SNc accompanied by:
  - Oxidative stress
  - Microglial activation
  - Mitochondrial dysfunction
  - Abnormal protein aggregation
- Treatments are available to alleviate the symptoms associated with PD