Molecular Mechanism of Parkinson's Disease

Jongkyeong Chung, Ph.D.

Department of Biological Sciences, KAIST, Taejon 305-701, Korea

Parkinson's disease is characterized by motor disturbances and dopaminergic neurodegeneration. *parkin* and *PINK1*, two most critical Parkinson's disease-associated genes, have been intensively studied to address the underlying molecular pathogenesis of the disease, but our understanding still remains unclear. Through generation and characterization of *Drosophila* mutants for *PINK1*, we show that *PINK1* is required for mitochondrial integrity and function in both indirect flight muscles and dopaminergic neurons. Surprisingly, we find that *PINK1* mutants share striking phenotypic similarities with *parkin* mutants. Indeed, transgenic expression of *parkin* dramatically ameliorates all *PINK1* loss-of-function phenotypes, but not *vice versa*, implicating that Parkin acts downstream of PINK1 in maintaining mitochondrial integrity and function in both muscles and dopaminergic neurons. With the establishment of the PINK1-Parkin pathway, we are trying to further investigate the detailed molecular relationship between PINK1 and Parkin using both mammalian dopaminergic neuronal cells for biochemical analysis and Drosophila model animal for genetic analysis. We believe that elucidating the molecular function of Parkinson's disease-associated genes will be of big help for the ultimate understanding of the pathogenic mechanism of this disease and also for the development of effective drugs for Parkinson's disease.

KAIST

Molecular mechanism of Parkinson's disease

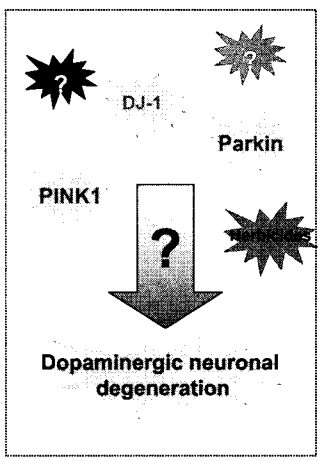
Jongkyeong Chung, Ph.D.

Dept. of Biological Sciences
KAIST

KAIST

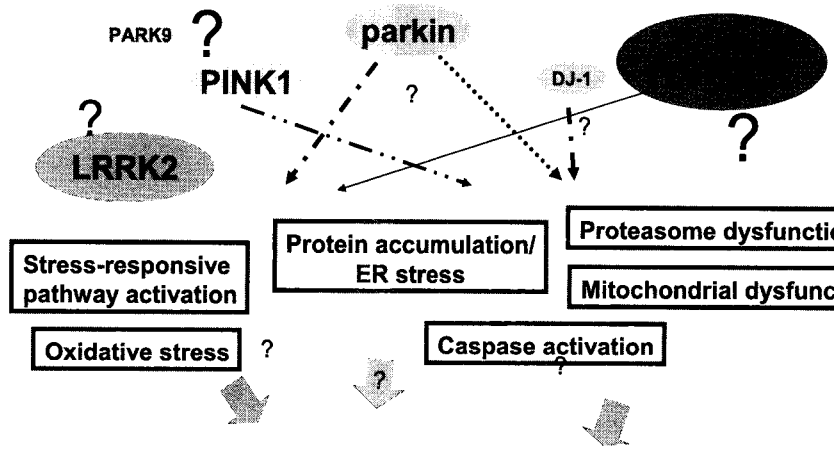
Parkinson's disease (PD)

- Human population genetics is very slow & laborious
- Mouse system is not appropriate for PD studies
- Culture cells don't accurately reflect *in vivo* biology



KAIST

What is the pathological mechanism leading to PD?

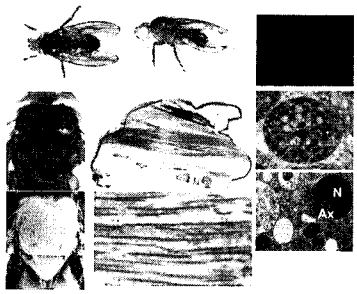


Parkinson's Disease

KAIST

High phenotypic similarity between *PINK1* and *parkin* mutants

PINK1 **mutant**

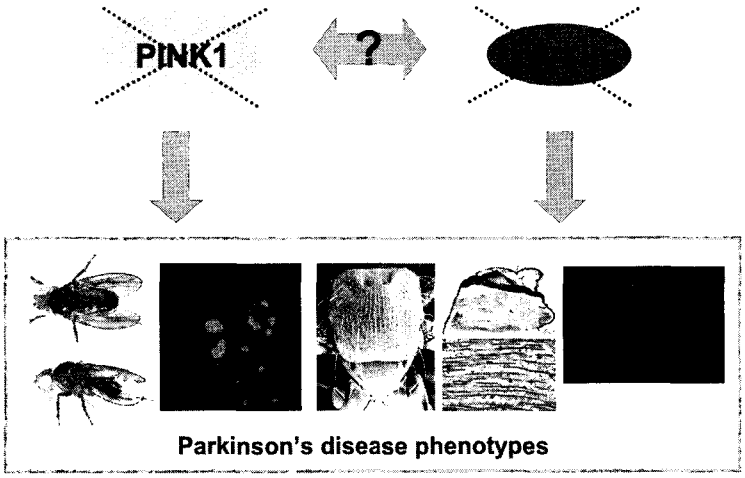


VS

Parkin **mutant**

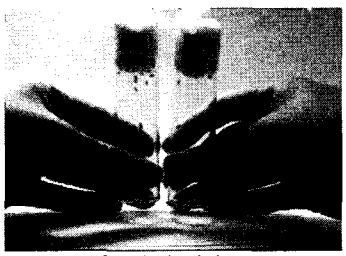
KAIST

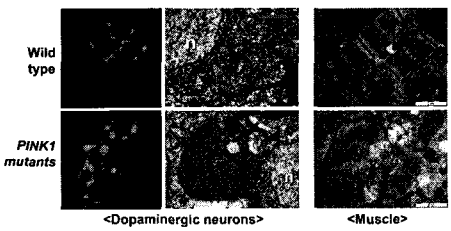
PINK1 and Parkin in a common pathological mechanism...?



KAIST

In vivo functions of PINK1 and Parkin





<Current model of PD pathogenesis>