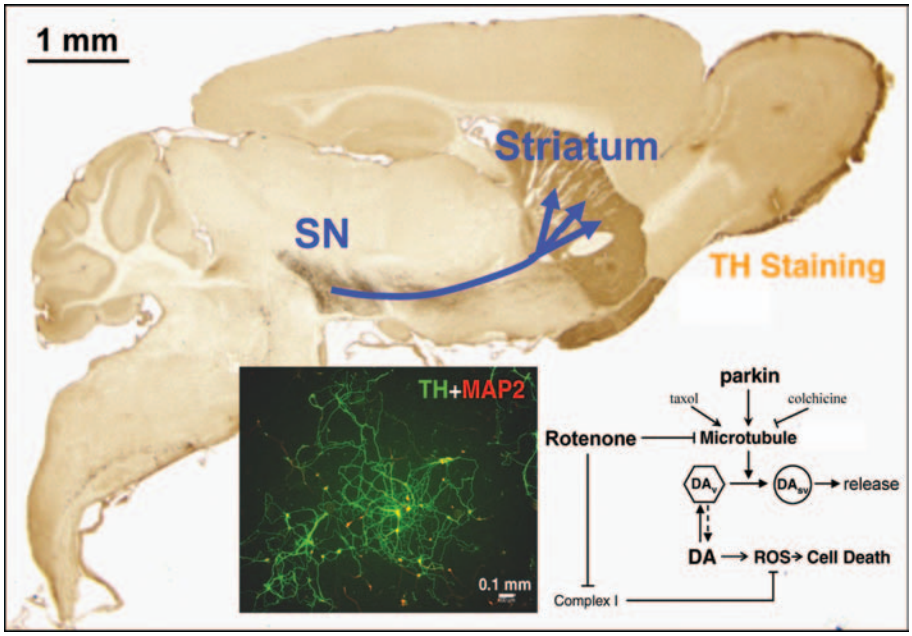
Parkinson's Disease: Shootout at the Microtubule Corral?

Parkinson's disease (PD) was named for English physician James Parkinson, who in 1817 first described the "shaking palsy" now recognized as a progressive neurodegenerative disease. Parkinson's is caused by the selective death of neurons that produce dopamine, a chemical required by brain circuits that control body movement. Parkinson's affects about 500,000 mostly older Americans, with 50,000 new cases diagnosed each year. Familial and young-onset cases of PD are linked to mutations in "parkin," a gene on chromosome 6. The parkin protein is a type of enzyme known as an E3 ubiquitin ligase, which targets ('tags') specific proteins for degradation within cells.

Mutations in parkin (and other less-understood genes) clearly create a "predisposition" for PD. However the question of what actually triggers pathology in dopamine-producing neurons is highly controversial, and may hinge on a delicate balance between genetics, environmental insults, oxidative stress and cell aging. For example, the agricultural pesticide rotenone can produce "Parkinson-like" symptoms in laboratory animals, but rotenone exposure is clearly not the sole cause of PD in humans. Jian Feng, a researcher at the State University of New York at Buffalo, wondered if the damage caused by rotenone might somehow involve parkin.

To understand how rotenone kills dopamine-producing cells, Feng's lab first treated neuronal cultures from embryonic rat brains with the drug. Interestingly, rotenone selectively destroyed only dopamine-producing neurons, and spared other types of neurons. Rotenone has two known targets in cells: mitochondria (the cell's 'power plants') and microtubules, which are highways for intracellular transport. Rotenone inhibits mitochondrial complex I, resulting in a cascade of highly-toxic free radicals. By depolymerizing microtubules, rotenone halts the movement of intracellular transport vesicles, including dopamine-containing vesicles, which then leak their contents into the cytosol. The spilled dopamine oxides generate even more free radicals. Free radicals can damage tubulin, the protein building blocks of microtubules. In neurons that do not produce dopamine, the chemicals transported along microtubules are not toxic. Thus, the selective vulnerability of dopamine-producing neurons to rotenone seems to lie in the vulnerability of their microtubule highways and the toxicity of their unique dopamine cargo. Further supporting this idea, the microtubule-stabilizing drug taxol substantially protects neurons against rotenone toxicity.

How does parkin fit this picture? Feng's group found that parkin helps destroy unpolymerized tubulin. They speculate that this activity is normally beneficial, because it helps dispose of free radical-damaged tubulin. Supporting this idea, when Feng and colleagues over-expressed normal parkin, it protected dopamine-producing neurons against rotenone. In contrast, parkin mutants that had lost their enzymatic activity, and were unable to 'tag' tubulin for destruction, failed to protect cells from rotenone. Thus, it appears that the survival of dopamine-producing neurons requires constant vigilance by parkin, which helps 'keep the tracks clear' by getting rid of damaged tubulin. This role, and neuronal survival, is challenged by rotenone, a prominent environmental factor linked to PD, which raises the levels of both unpolymerized and free-radical-damaged tubulin. In this fight, mutated parkin apparently arrives unarmed.



In this rat brain section, dopamine-producing (DA) neurons in the substantia nigra (SN) extend long axons to the striatum. Parkinson's is linked to degeneration of these neurons, which could be caused by environmental toxins and/or genetic mutations. By inhibiting mitochondrial complex I and depolymerizing microtubules, rotenone produced significantly more reactive oxygen species (ROS) in dopamine neurons than in other types of neurons, which may explain the selective toxicity of rotenone. Parkin protected against rotenone toxicity through its actions on tubulin, the building blocks of microtubules.

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Rotenone and Parkin Act Antagonistically on Microtubules to Affect the Survival of Dopaminergic Neurons, Y. Ren, W. Liu, H. Jiang, J. Feng; Physiology and Biophysics, State University of New York at Buffalo, Buffalo, NY.

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