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Parkinson's Disease and Cancer: The Unexplored Connection

By Ken Garber

It's hard to imagine two diseases more different than Parkinson's and cancer. Parkinson's disease, a progressive neurological disease that causes tremors, muscular rigidity, and loss of motor function, happens when neurons that release the neurotransmitter dopamine die in the tiny substantia nigra region of the brain. In cancer, cell death fails to occur.

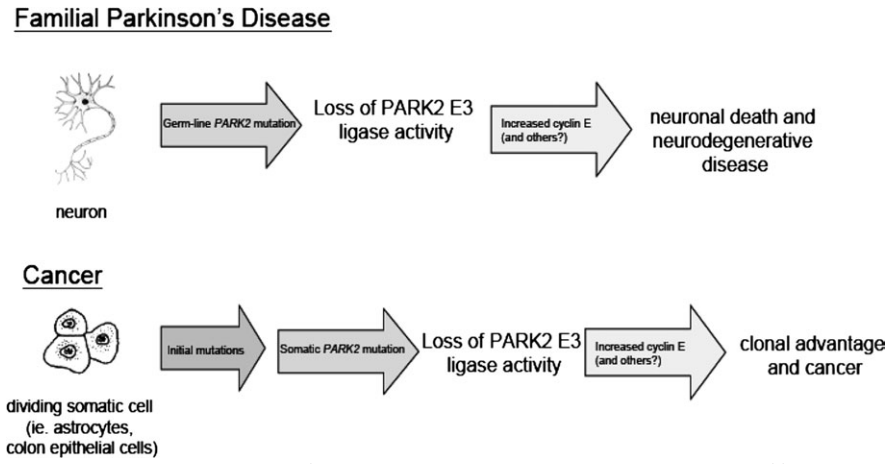
But a November 2009 online report in *Nature Genetics* identifying Parkin (also known as PARK2) as a tumor suppressor gene was just the latest-discovered link between the two diseases; Parkin mutations cause up to half of early-onset hereditary cases of Parkinson's disease. Another early-onset Parkinson's gene, DJ-1, has been implicated in cancer, and a third gene, LRRK2, has features that strongly hint at cancerlike effects. Epidemiological studies show that Parkinson's patients have less risk of most cancers but increased risk for some. These mysterious connections have raised hopes that studying the biology of one disease will lead to treatments for the other. Such research, barely begun, could eventually solve the mystery and explain what dead neurons have in common with cells that refuse to die.

Neuron Protector and Tumor Suppressor

In the 1980s researchers began reporting that Parkinson's patients had an overall decreased incidence of cancer, with some important exceptions, mainly melanoma. One 8,000-patient registry study in Denmark

showed that people with Parkinson's disease had a twofold-increased risk of melanoma; other studies have reached similar conclusions.

"Clearly melanoma is increased in patients with Parkinson's disease," said Joseph Jankovic, M.D., a neurologist and Parkinson's researcher at the Baylor College of Medicine in Houston. "Also, breast cancer seems to be increased in patients with Parkinson's disease . . . there is a huge body of epidemiological data to support these conclusions."



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Live or let die: Mutations in Parkin (PARK2) lead to opposite fates in Parkinson's disease and cancer.

Reasons for these associations remain unknown, but new discoveries in the genetics of Parkinson's disease are providing clues. Over the last dozen years, five genes have been definitively identified that cause hereditary Parkinson's disease, about 6%–8% of all Parkinson's cases in North American whites. Three of these genes are recessive and two are dominant, and their role in Parkinson's disease pathogenesis is hotly debated. But all have appeared in the cancer literature. "Whenever one of these new [Parkinson's] genes pops up, we always look at what has been done with these genes, and inevitably these genes have some link to various kinds of cancer," said Andrew West, Ph.D., a Parkinson's researcher at the University of Alabama at Birmingham.

Parkin provides the closest link. In 1998 a Japanese group found that Parkin mutations cause juvenile Parkinson's disease, and it has since emerged as the most frequent cause of early-onset disease. The gene codes for a ubiquitin ligase, one of a family of enzymes that tags proteins for degradation in the proteasome, the multienzyme complex that destroys the cell's discarded proteins. (Whether loss of ligase function causes Parkinson's disease in these families remains controversial.)

In cancer, Parkin was already a suspected tumor suppressor gene because it resides on the long arm of chromosome 6, a segment of which has long been known to be altered or deleted in a wide variety of human cancers. In their recent *Nature Genetics* article, a group led by Timothy Chan, M.D., Ph.D., at the Memorial Sloan–Kettering Cancer Center in New York sealed the case. Chan reported frequent copy number loss on chromosome 6q restricted to the Parkin gene in human cancer samples, especially colon cancer and glioblastoma. Sequencing the gene in more than 200 human tumors, Chan's group discovered Parkin cancer mutations for the first time in several glioblastomas and lung cancers. Introduction of the mutant gene into cancer cell lines promoted cell growth, whereas the wild-type gene reduced it. "This established without a shadow of a doubt that Parkin is a tumor suppressor," said John Staropoli, M.D., Ph.D., a pathologist at Massachusetts General Hospital in Boston.

Novel tumor suppressor genes pop up all the time, but two factors lend Parkin special importance. First, Parkin loss or mutation is found in an unusually large number of tumor types. "It might play a role in nearly all cancers . . . along the lines of p53," speculated Staropoli.

And Parkin's role as a ubiquitin ligase may be directly relevant not just to these cancers but also to Parkinson's disease. Chan's group found, in cell lines, that the Parkin cancer mutations interfered with the protein's ability to ubiquitinate (by attaching small ubiquitin proteins as tags) and to degrade cyclin E, a critical component of the cell cycle. Cyclin E levels went up, and the cells began cycling and dividing faster. Chan speculates that, in Parkinson's disease, similar Parkin mutations lead to cyclin E buildup, which causes dopaminergic neurons to try to divide—a catastrophic development in these cells. "Because they're terminally differentiated, they cannot divide, and then they die," he said.

Divide and Conquer, or Die Trying

In 2003 Staropoli had reported cyclin E accumulation in Parkin-deficient primary neurons and speculated that loss of Parkin caused dopaminergic neurons to reenter the cell cycle and die. But other ideas about Parkin loss in Parkinson's disease eclipsed the cyclin E story. The other theories ranged from wholesale derangement of protein degradation—a cellular "garbage strike"—to the excessive buildup of the neurotransmitter glutamate at the synapse, or excitotoxicity, leading to cell death, to the autoconsumption of mitochondria, known as mitophagy. But the Chan study, together with two other reports last year, reaffirms cyclin E as a major suspect.

"I do feel a certain amount of vindication," said Staropoli. He and Chan didn't rule out other mechanisms of cell death from Parkin loss, but Staropoli speculated that they might converge downstream, all leading to the kick-starting of the cell cycle in neurons followed by cell death. "Maybe cyclin E or another cell cycle regulatory protein is at the nexus of this converging pathway," Staropoli said.

The Parkin story is one example of how cancer research can inform the Parkinson's debate. But the debate continues, because Parkin might work differently in the context

of dividing epithelial cells in cancer than in the postmitotic neurons of Parkinson's patients. "Neurons that try to reenter the cell cycle may end up going through a cell death pathway—that's been suspected for decades," said West. "The question is, how are these neurons dying in Parkinson's disease? We don't know the answer." Studying the brains of people with advanced Parkinson's disease with substantial neurodegeneration is problematic, because the dead neurons that may be most informative are gone. "With cancer research you have the cells that you're interested in," noted West. "In Parkinson's disease we have to study ghosts."

In both diseases "the cell cycle is being engaged in an aberrant manner," observed Chan. "Gaining insight into the function of Parkin in cancer may potentially identify novel targets of therapy that may be useful in both cases." Chan's lab is now looking for Parkin loss in other cancer types, screening for other ubiquitination targets of Parkin, and crossing Parkin-knockout mice with mice lacking other tumor suppressor genes to work out the exact role that Parkin plays in cancer.

LRRKing in the Wings

The other Parkinson's gene solidly linked to cancer is DJ-1. DJ-1 was cloned in 1997 as an oncogene, and 6 years later the mutant form was found to cause early-onset Parkinson's disease in families, although it's much rarer than Parkin. The role of DJ-1, a molecular chaperone and sensor of oxidative

stress, remains obscure in Parkinson's disease, but University of Toronto cancer researcher Tak Mak, Ph.D., has found that it downregulates the tumor suppressor PTEN. It also stabilizes HIF-1α, a key regulator of cellular responses to hypoxia that accumulates in tumors with low oxygen levels. High expression of DJ-1 has been found in many cancers. Mak, at the International Conference on Molecular Targets and Cancer Therapeutics in Boston in November, speculated that loss of DJ-1 could be killing neurons in Parkinson's disease, whereas too much DJ-1 was keeping cells alive in cancer. "On one hand you could have Parkinson's [disease] due to excess cell death," he said. "On the other hand you could have cancer, perhaps due to lack of cell death." Working out details of the pathways altered by excess DJ-1 in cancer could shed light on the gene's role in Parkinson's disease.

The most exciting Parkinson's gene is LRRK2. In 2004 two multinational groups found that dominantly inherited mutations in this gene cause typical Parkinson's disease. Then came the surprising discovery that in two populations, Ashkenazi Jews and Arab Berbers in North Africa, the gene accounts for 30% or more of all Parkinson's cases. "We didn't think a gene like LRRK2 could exist—nobody did," said West. "That a gene could be responsible for 30% of late-onset [Parkinson's disease], that wasn't supposed to be possible."

So far LRRK2 links to cancer are only indirect and suggestive. Like many key cancer genes, LRRK2 codes for a kinase—it can transfer a phosphate group from ATP to a downstream substrate to activate it. And, like the ras oncogene, it is also a GTPase, in that it can bind either of the guanine nucleotides, GDP or GTP; such binding determines its activation state and its ability to send an excitatory signal to downstream targets. LRRK2 is the only known protein (besides LRRK1) to have both a kinase domain and a ras-like GTPase domain. (This finding has made it an attractive drug target in Parkinson's disease, because there are multiple places for small-molecule compounds to bind.) LRRK2 may function in the mitogen-activated protein kinase pathway, which is important for cell survival. One more cancerlike feature is the most common Parkinson's-related LRRK2 protein alteration: It's in the same structural position as the alteration in BRAF kinase that drives about half of all cases of malignant melanoma.

Whether LRRK2 has anything to do with melanoma or any other cancer is unknown. But because so many Ashkenazi Jews and Arab Berbers with Parkinson's disease have the gene, large epidemiological studies looking at cancer incidence are now under way. For example, Jankovic and colleague Rivka Inzelberg, M.D., of Tel Aviv University in Israel are completing a large study looking at cancer in Israeli Ashkenazi Jews who carry the mutant LRRK2 gene. "There is some speculation that there is going to be a strong link between cancer and LRRK2 mutations in this population," said West.

Mostly, the Parkinson's–cancer story remains to be written. The association is firm, but mechanistic findings are sketchy, largely speculative and sometimes contradictory. "You're not going to build a unified hypothesis to describe the link without understanding the specific biochemical . . . mechanisms," said West. Other researchers agree the knowledge gaps are wide but inviting. "There are a lot of interesting hints and clues," said Jankovic. "And I think we just need to connect the dots."

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