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Minding Cancer's Own Business: Parkinson's Disease and Malignancy

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It is a man's own mind, not his enemy or foe, that lures him to evil ways. Buddha

That cancer and neurodegenerative disorders are related is increasingly evident, providing a rapidly expanding area for investigation¹. The relationship between Parkinson's disease (PD) and cancer is particularly complex. A wealth of epidemiologic data suggests reduced risk of some cancers, and increased risk of others, in patients with PD¹. The study by P-C Yang/C-H Lin, and colleagues² suggests a remarkable increase in cancer risk in PD patients in an East Asian population that is genetically more homogeneous than previously studied western populations. From the Taiwan National Health Insurance Research Database, these investigators drew a sample of 62,023 patients from 2004–2010, with PD diagnosed and followed up until 2012. They found a hazard ratio (HR) of 1.58 (95% CI, 1.50–1.65, $p < 0.001$) for all cancers, which was also statistically significant in 16/19 individual cancers (other than breast, ovarian, or thyroid cancers). These HRs were significant in malignant brain tumors, gastrointestinal tract cancers, some hormone-related cancers, urinary tract cancers, in melanoma as well as other skin cancers. Unlike previous studies, no inverse associations were found between PD and the development of cancer.

Now why should this be? What is the possible linkage between PD and subsequent cancer? We must of course consider methodological issues. Both PD and cancer are disorders of aging, and likely to co-occur as individuals grow older; these investigators indeed found that the associations were strongest in the oldest age stratum. The data were not prospectively gathered, so possibilities such as length bias and survival bias could not be accounted for. The data on both PD and cancer were obtained from medical records where the possibility of diagnostic misclassification cannot be ruled out. Additional data on risk factors such as smoking and pesticide exposure evidently could not be obtained from the database. Having duly acknowledged these limitations, the authors draw our attention to possible ethnic, genetic, and environmental factors which might be distributed differently in Taiwan than in

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previously studied regions. Whether PD increases cancer directly, or whether they share common antecedents or mechanisms, cannot be discerned from this study.

Other than pesticide exposure, the established etiologic factors for Parkinson's disease include several familial syndromes associated with mutations or allelic variants in PARK2, LRRK2, and DJ-1, and mitochondrial DNA damage³. Indeed, DNA damage is associated with both oxidative stress and mitochondrial defects. Mitochondria generate the requisite adenosine triphosphate (ATP) through oxidative phosphorylation within the electron transport chain, and serve as buffering sites for endoplasmic reticulum control of cytosolic calcium concentration. They generate important cellular intermediates such as nucleotides and amino acids, as well as Fe/S clusters. They contribute to programmed cell death or apoptosis through intrinsic (p53-dependent), extrinsic (TNF family receptor dependent), and cytolytic (mediated by NK and T cells) pathways. The major opposition to apoptotic death is autophagy or 'programmed cell survival.' Autophagic processes clear protein aggregates, intracellular viruses, and effete mitochondria, and are critically important for normal functioning of both post-mitotic neuronal cells and proliferating epithelial cells that give rise to most cancers.

Mitochondria are also the major cellular sources of reactive oxygen species (ROS). It remains unknown how substantia nigra neurons, responsible for the production of dopaminergic signals, respond to mitochondrial defects. Conversely, we also do not know which of the underlying nuclear- encoded genes have their functions altered and are thus not 'matched' appropriately with the maternal inherited mitochondrial genes. The PTEN-induced kinase 1 (PINK1), linked to PD and an example of a nuclear-encoded gene⁴, is localized to both cytosolic and mitochondrial compartments. PINK1 regulates mitochondrial homeostasis and dendritic morphogenesis, presumably in both central and peripheral neurons. Peripheral neurons innervate sites of both chronic inflammation and emergent cancers. This direct role of local neuronal influences on cancer development has been best studied in the setting of prostate and pancreatic cancer and is an exciting area of inquiry. Indeed, mitochondrial dysfunction is well identified in both neurodegenerative diseases and cancer.⁵

Our work⁶ suggests another possible linkage. Clearance of defective mitochondria, through a form of autophagy known as mitophagy, enables quality control of these important organelles. New rounds of mitochondrial biogenesis are promoted by clearance of ROS-generating mitochondria disabling further mutagenesis, likely important in PD and certainly in cancer. We believe that the nuclear protein high mobility group box 1 (HMGB1) is central to the emergence of cancers in the setting of chronic stress. We also believe HMGB1 is likely important in both compartments, given its ability to promote both nuclear and mitochondrial DNA repair. It binds to alpha synuclein, which is implicated in PD, serving as an important intermediary between nuclear and mitochondrial functions. HMGB1 promotes autophagy; its loss or diminution may promote disordered cellular homeostasis associated with both PD and cancer.

Indeed our cells are of two minds, with both a nuclear genome (20,000 genes) and a mitochondrial genome (only 37 genes). Interestingly, the mitochondrial genome represents

4% of the total cellular DNA residing in thousands of copies as mitochondrial nucleoids within a single cell. Thus, at a broader, more important level, it may be that the precise nuclear- encoded or mitochondrial-encoded genes in themselves are not sufficient to cause disease. Rather, how well they function and ‘match’ each other may be the critical factor for both PD and its unusual linkage to cancer.

Having now established that these complex diseases (PD and cancer) are linked, the way appears clear for careful and systematic analysis of both the intrinsic differences in cell biology as well as extrinsic factors found in the environment that link them. This should enable a more ‘mindful’ approach to their etiology, focusing on both of these critical genomes residing within a cell and the interactions between them.

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