Iron and Parkinson’s Disease

It has long been known that patients with Parkinson’s Disease (PD) generally present with excess iron in the substantia niagra of the brain, a region involved in reward, addiction, and movement. However, the mechanism of pathology associated with elevated iron levels neurons of PD patients has been unclear. Research published by Dr. Julie Andersen and colleagues of the Buck Institute for Research on Aging has recently shed light upon this unknown mechanism. Their recent findings suggest that abnormally high concentrations of iron cause dysfunction of the lysosome, a cellular substructure involved in recycling of damaged proteins. This impairment allows additional iron to enter neurons and cause deleterious oxidative stress.

Autophagy is the process whereby damaged intracellular compartments and proteins are degraded into their constituent parts. These components are then recycled for the biosynthesis of new cellular macromolecules. Lysosomes are crucial to proper cellular autophagy. Disruption of lysosomal function results in stagnated autophagy and the accumulation of damaged proteins within the cell. This dysfunctional autophagy has been associated with a variety of diseases, including PD. Autophagy prevents the accumulation of reactive oxygen species and reactive nitrogen species, both oxidative stressors to the cell.

According to Dr. Andersen, “It’s recently been realized that one of the most important functions of the lysosome is to store iron in a place in the cell where it is not accessible to participate in toxic oxidative stress-producing reactions. Now we have demonstrated that a mutation in a lysosomal gene results in the toxic release of iron into the cell resulting in neuronal cell death.”

The work was led by Dr. Subramanian Rajogopalan, first author on the paper published in the last issue of the Journal of Neuroscience. They found that decreasing the expression of the ATP13A2 gene, implicated in an early-onset form of PD known as Kufor-Rakeb syndrome, resulted in an inability of the lysosome to maintain iron homeostasis. ATP13A2 is regulated by a class of enzymes known as prolyl hydroxylase domain proteins (PHDs) that have been shown to have neuroprotective effects in vitro and in vivo models of PD.

Intracellular levels of iron are tightly regulated in a complex metabolic pathway. Iron import refers to the process by which cells take up iron via endocytosis. Alternatively, iron in its reduced state may enter the cell through the plasma membrane via cation importers. Iron typically has a concentration of 0.001mM within the cell. Iron export is thought to be handled by the protein ferroportin, the only known iron exporter.
“The issue with iron chelation [the bonding of ions and molecules to iron] is that it’s a sledge hammer — it pulls iron from the cells indiscriminately and iron is needed throughout the body for many biological functions,” said Dr. Andersen. “Now we have a more specific target that we can hit with a smaller hammer, which could allow us to selectively impact iron toxicity within the affected neurons.”

This recent work has shed light upon a potential link between the longstanding observation of excess iron in brains of PD patients and neurodegeneration. Future work for the Anderson lab includes investigation of therapeutic agents that have the potential to prevent brain metal toxicity.