Learning for Life Week 6 Summary 10-31-18

Topic: Neurodegenerative Diseases: Alzheimer's and Parkinson's

Speakers: D. James Surmeier PhD and Robert Vassar PhD

When diseases have treatments that only modify symptoms but don't actually modify the course and prognosis of the disease, it is critical to understand the underlying biological mechanisms in order to identify more advanced treatments. Today we heard from two scientists who are doing exactly that in their study of Parkinson's and Alzheimer's disease.

Translational research takes what we learn in the laboratory setting and applies it to the clinical setting. Northwestern is at the forefront of this kind of research and is the lead investigative institution in the largest multi-center NIH funded trial to understand the underlying mechanisms and identify novel treatments for patients with Parkinson's disease (PD). Jim Surmeier's lab has laid the foundational scientific understanding for the clinical questions being addressed in this trial by neurologist, Dr. Tanya Simuni. Parkinson's disease is the second most common neurodegenerative disease following Alzheimer's, with a rising prevalence in the world. At this point we have no cure or disease modifying therapy; we only have the same treatments that have been available for at least 50 years, and these only moderately control symptoms. The biggest risk factor for Parkinson's disease is age, but genes and environmental toxins also play a role.

The brains of patients with PD show a characteristic pathologic pattern. They have an accumulation of Lewy bodies or intracellular garbage aggregates. They also demonstrate neuronal degeneration (death of neurons) in distinctive locations in the brain, particularly the substantia nigra where many neurons secrete dopamine. The loss of dopaminergic neurons results in the characteristic symptoms of PD. Both Lewy Body deposition and neuronal degeneration are progressive, involving more of the brain as the disease evolves. Jim's work centers around the critical question: How do we use the patterns of neurodegeneration and Lewy Body deposition to understand the causes of the disease?

The dopaminergic neurons are located in a part of the brain called the basal ganglia which we can consider to be the brain's "advice center". It helps us choose the right actions in the right context without thinking and serves a critical function in the individual's response to a threatening situation (for example, escaping from a tiger). Any disruption in this important part of the brain slows us down and inhibits movement. Dopaminergic neurons are constantly active, watching for threats and opportunities. Think of them as the brain's "sentinels". Unfortunately, this constant neuronal activity comes at a bioenergetic cost. The energy for the cells to function and secrete dopamine is generated in a part of the cell called the mitochondria. This process results in an accumulation of free radicals which are toxic to the cell, accumulate in Lewy Bodies and cause the cell to degenerate faster. Mitochondrial energy production is stimulated by the presence of calcium. So, the constant activity of the dopaminergic neurons in the basal ganglia keeps the brain ready to respond to any situation or threat, but as society has evolved, the constant threats have diminished, and maybe we don't need to be quite

as “ready” to flee from a tiger. What if we could diminish the dopaminergic activity in the basal ganglia, thereby requiring less cellular energy production and subsequently fewer toxic byproducts that result in neuronal destruction? If we can inhibit the calcium required by the mitochondria for energy production, maybe we can slow down the progression of Parkinson’s disease by sparing the dopaminergic neurons. The phase 3 trial referred to above is looking specifically at this possibility. PD patients are being treated with isradipine, a calcium channel blocking drug that has been used in the treatment of high blood pressure in the past. Results may be available as early as next spring. This is a perfect example of how a deep understanding of the underlying pathophysiology of the brain in Parkinson’s disease, allowed investigators to identify a therapeutic target. Now, fingers crossed.

Alzheimer’s disease is the most prevalent neurodegenerative disease, and its incidence is rising as our population ages. Like Parkinson’s, we have no cure or disease modifying treatment, and we need to better understand the underlying biology before we can hope to identify preventive or curative treatments.

In Alzheimer’s disease (AD), there is increased atrophy, neurodegeneration, inflammation and a buildup of amyloid plaques and neurofibrillary tangles in the brain. A-beta is a protein that is made by neurons. Its function is yet unknown and the brain has processes by which it is degraded and washed out. As we age, there is an imbalance between A-Beta’s production and its clearance resulting in a build-up and aggregation of this protein called an amyloid plaque. In addition to the increased number of amyloid plaques in the brain of a patient with AD, there are neurofibrillary tangles which are a by-product of the inflammation that is produced when the brain works to clear the amyloid. Another protein produced by the brain is called the Tau protein. In patients with AD, this protein is abnormal and becomes “sticky”, also contributing to the characteristic neurofibrillary tangles. If we look at PET scans of patients with Alzheimer’s, we can see the excess Tau protein and amyloid even years before the onset of symptoms.

Bob described what is known about the risk factors for AD. Unlike Parkinson’s disease, genetics seems to play a more significant role in the development of AD. Many genes have been implicated, but the most common is called APOE4. Carrying two copies of this gene increases an individual’s risk for AD significantly. These genes are involved in the production and clearance of the A-Beta protein. In addition to genetic factors, environmental and cardiovascular risk factors are also important. Increased age, head trauma and lower education all are risk factors, as are high blood pressure, diabetes and high cholesterol. Exercise, social/intellectual stimulation and a Mediterranean diet can reduce risk.

If we can understand why the A-beta builds up or why the Tau protein is abnormal in the brains of patients with Alzheimer’s disease, we might be able to develop more effective treatments targeted at this critical underlying pathology. Bob shared the work that his lab is doing involving an enzyme called BACE 1. This enzyme is involved in the production of A-beta and subsequently amyloid. If one were to block the enzyme, the production of amyloid would go down. Bob’s team has genetically engineered a mouse that does not make the BACE 1 enzyme (Remember the mouse brain is very similar to the human brain, so it is an excellent experimental model for studying neurological disease). In this mouse and its offspring, amyloid plaque does not develop. We know that BACE 1 levels are nearly two times higher in the brains with AD than in normal brains but we don’t truly understand its function.

We count on the work that Bob and other investigators are doing to understand the pathology in Alzheimer’s disease at a molecular level. This will then lead to the development and trial of novel

therapies. In the meantime, we can exercise, eat well and remain intellectually stimulated to reduce our risk.

Take Home Points:

1. It is critical to understand the underlying biological mechanisms in neurodegenerative diseases before we can develop effective, disease modifying treatments.
2. The identification of calcium as a target for inhibition in Parkinson's disease is based on the work of Jim Surmeier and has led to Northwestern's leading role in a multi-center clinical trial investigating a calcium channel blocker, isradipine.
3. Alzheimer's is a complex disease involving many genetic and environmental factors.
4. Work at Northwestern is investigating the production of amyloid protein in an effort to reduce its toxic impact on the brain in AD patients.