

Toward Precision Medicine, November 7, 2016: Jessica Young, PhD., Assistant Professor, UW Department of Pathology/ ADRC Affiliate Member. *Probing cellular mechanisms of sporadic Alzheimer's disease risk using patient stem cells*

Abstract

Jessica Young's talk focused on the use of patient-derived stem cells to elucidate cellular mechanisms of sporadic AD risk (SAD). Human induced pluripotent stem cell (hiPSC) technology is a powerful method to ask how individual genetic background contributes to risk of complex disease, like SAD. hiPSCs are generated from reprogramming adult somatic cells (like skin cells) to an embryonic-like state. These cells can then be differentiated into disease relevant cell types such as neurons or glial cells in order to study SAD and other neurodegenerative disorders. Young described her investigation into how genes associated with increased risk of SAD in a population might show cellular phenotypes in neurons grown in the laboratory. In particular, she focuses on the SORL1 gene, which encodes a protein called SORLA that is involved in sorting and trafficking the amyloid precursor protein (APP) in neurons and contributes to regulating the generation of Amyloid beta (Ab). She used a cohort of patient cells and found that if she genotyped them for AD risk variants in SORL1, the pattern was indicative of a larger population. She then generated hiPSCs from these patients and derived purified neurons for analysis of SORL1 gene expression and Ab production. The results demonstrated that hiPSC-derived neurons from individuals with SAD genetic risk variants in the SORL1 gene showed a reduced response to SORLA expression induction and higher levels of Ab than neurons from individuals with protective variants. Her future work focuses on SORLA and other endocytic receptors to try to determine the function of AD risk variants in this important cellular pathway. She will do this by looking at both patient derived stem cells from ADRC participants, as well as introducing or correcting the genetic variant using genome-editing technology.

Group Discussion

Jessica Young's talk sparked a group discussion over the complex genetics and heterogeneity of AD and what different phenotypes could be documented with stem cell technology. One major point of discussion centered on how to determine if a risk variant is causative. Some variants identified by GWAS studies may not actually be a causative variant, but rather a marker of a large region of DNA that may harbor pathogenic variants. This fact could be an important consideration in the choice of risk factors to pursue in precision-medicine oriented stem cell studies.

Young noted that the discussion informed her, as a cell biologist, as to what she can expect from her samples from ADRC participants and how many genetic backgrounds to examine to achieve meaningful results. She reinforced her main idea that a model of individuals' cellular phenotypes will help predict which genotypes might be more relevant for particular clinical trials. Perhaps, some in the group suggested, they could achieve this goal even before the field arrives at a full scientific understanding of risk factor mechanisms.

Young and Dirk Keene also talked about their new ADRC collaboration to collect leptomeningeal cells from the brains of every ADRC participants at autopsy, and then differentiate them into neurons. They hope to create a bank of patient-derived neurons, each accompanied by a confirmed post-mortem neuropathological diagnosis and personal clinical record. The group came to the consensus that the combination of stem cell and gene editing technology has the potential to answer many of the unsolved questions in variation in AD pathogenesis across individuals.