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Modeling disease of the peripheral nervous system

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Functional and molecular aspects of human genetic disease can be recapitulated *in vitro* using patient-specific pluripotent stem cells (PSCs). Familial Dysautonomia (FD) is a debilitating developmental and degenerative disorder that primarily affects derivatives of the neural crest (NC), such as the peripheral nervous system (PNS). For unknown reasons, FD patients present with mild or severe disease despite carrying the identical, homozygous point mutation in *IKBKAP*. We present *in vitro* phenotypes at various stages of development that capture severe and mild FD in human PSC-derived cellular lineages. Patient-specific cells only from severe but not mild FD display an impaired capacity of developing into NC derivatives, such as autonomic and sensory neurons, thus they have neurodevelopmental defects. Interestingly, however, both severe and mild FD cells show defects in peripheral neuron survival, indicating neurodegeneration as the primary culprit in mild FD. Importantly, we found that neuronal degeneration in mild FD can be halted by treatment with candidate therapeutic compounds kinetin and SKF-86466. Genetic rescue of the FD mutation in severe FD iPSCs reversed NC, but not sensory neuron lineage phenotypes, implicating that the known FD mutation does not account for all symptoms. Employing whole-exome sequencing (WES), we identified candidate mutations that were only found in severe but not mild FD patients, providing evidence that FD may constitute two genetic sub-diseases. Our study demonstrates that human PSC-based disease modeling is sensitive in recapitulating disease severity and paves the road for applications in personalized medicine. Using a chemical screen, we identified a compound that could rescue severe FD defects. This further paves the way towards future treatments tailored more specifically towards individual patients.

Biography

Nadja Zeltner has received her PhD from Ichan School of Medicine at Mount Sinai in New York and has completed her Post-doctoral studies from Dr. Lorenz Studer's laboratory at Memorial Sloan Kettering Cancer Center in New York. Her research focuses on disease modeling using human pluripotent stem cells with particular focus on the peripheral nervous system (PNS). Her ultimate goal is employing this technology to further understand PNS disorders that will lead to the development of novel drugs and therapeutics. She has started her own research group at the Center of Molecular Medicine at the University of Georgia.

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