Abstract for Talk

Title: A *Drosophila* model of HSAN-1 - Of wrong connections, neurodegeneration and protein aggregation

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A challenging question in biomedical research is how early neurodevelopmental defects can lead to subsequent neurodegeneration in adult human patients and how this neuronal dysfunction and loss can be prevented. The disorder HSAN-1 (*Hereditary sensory and autonomic neuropathy type 1*) is associated with severe sensory impairment, reduction or loss of temperature sensation and degeneration of peripheral neurons. It has been linked to mutations in the evolutionary conserved serine palmitoyltransferase (SPT), a key-enzyme of sphingolipid biosynthesis. However, the cellular mechanisms underlying the neuronal defects are so far unknown. In a forward genetic screen for regulators of *Drosophila* brain circuit development, we have identified SPT mutations that lead to axonal mistargeting phenotypes in the *Drosophila* brain. These defects are associated with a severe aggregation of the cell recognition molecule Dscam. Further analysis revealed that the *SPT* mutant phenotypes result from defects in the compartment-specific localization of axonal and dendritic Dscam isoforms during neuronal growth. Expression of SPT transgenes which carry HSAN-1 associated mutations also result in the formation of Dscam aggregates and axonal phenotypes, indicating a causal link between developmental protein sorting defects and neuronal dysfunction in the mature nervous system.