Innate Immune Pattern Recognition Receptors Connect Genomic Instability with Neurodegeneration

Awardee: Mark W. Albers
Award: New Innovator Award
Awardee Institution: Massachusetts General Hospital

The sequences of genomes present in individual cortical neurons from the same human vary significantly, and the degree of structural mosaicism in genomes increases with aging, which is a critical risk factor for neurodegenerative disease. We hypothesized that the *intrinsic* induction of innate immune signaling cascades in neurons arising from sporadic genomic lesions, such as expanded nucleotide repeats, e.g. *C9orf72*, or monoallelic genomic inversions introduced during repair of double stranded DNA breaks, is an unrecognized mechanism of neurodegeneration.

Olfactory sensory neurons (OSNs) are an excellent model system because they naturally undergo degeneration and regeneration, they are susceptible to degeneration in Alzheimer's disease (AD), and they are arrayed in an orderly anatomy that is genetic tractable, afforded by many genes that are specifically expressed in OSNs. We developed mouse models to elucidate mechanisms of neurodegeneration by overexpressing isoforms of the human amyloid precursor protein (hAPP) exclusively in OSNs. In two novel lines— Nd1 conditionally expressing a pathogenic mutation of hAPP, and Nd2 conditionally expressing a non-pathogenic mutation of hAPP—we find marked neurodegeneration that is dependent on transgene expression, but not the levels of APP or Aβ. RNA-seq of sorted OSNs from the Nd1 line revealed a robust induction (>10x) of a network of genes that comprise an innate immune-mediated signal transduction cascade. RNA fluorescent *in situ* hybridization affirmed that this pathway is markedly induced in OSNs in both the Nd1 and Nd2 lines. Importantly, these innate immune genes remain at basal levels in parallel mouse lines that express the same isoforms of hAPP at the same levels but do not exhibit the neurodegenerative phenotype. Suppression of the expression of either the Nd1 or Nd2 transgene reverses the expression of the innate immune pathway and the neurodegenerative phenotype. A known trigger of innate immune signaling pathways is engagement of dsRNA by pattern recognition receptors (PRRs). Our preliminary data reveal complex chromosomal rearrangements, including inversions, in the Nd1 line and the association of dsRNA expressed from the Nd1 transgene bound to a PRR, the myeloma differentiation antigen 5. Moreover, we found dsRNA arising from the hexanucleotide expansion in *C9orf72* in brains from patients with frontotemporal dementia and ALS, and we found induction of PRRs in *C9orf72* expanded and AD human brains. We suggest that genomic lesions that elicit dsRNAs can mimic viral infections and activate innate immune signaling pathways in neurons to trigger neurodegenerative disease in humans.

Funding NIH DP2 OD006662, Lefler Foundation, Wilkens Foundation