Proteostasis and Inflammation: New Insights and Therapeutic Strategies in Neurodegeneration

June 4

Tuesday, 12:30 pm

Weekly Colloquium

Billings Building
Rosedale Conference Room

Speaker: Li Gan, Ph.D.
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Host: Gary Gibson, Ph.D.

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Abstract

The fast progress in human genetics reveals common molecular mechanisms in aging-related neurodegenerative diseases, such as Alzheimer's disease (AD) and Frontotemporal Dementia (FTD). I will focus the discussion on two converging pathways linking AD and FTD, including innate immunity and proteostasis. In human iPSC and mouse models of disease, our research employs a combination of in vitro and in vivo approaches, such as genomic and proteomic approaches, electrophysiology, and behavioral tests. I will discuss our recent work on identification of key pathways in microglia-mediated neuronal injury and novel mechanisms regulating homeostasis of tau, a key pathogen in AD and FTD. I will also discuss how dysregulated innate immune response contributes to proteostasis malfunction.

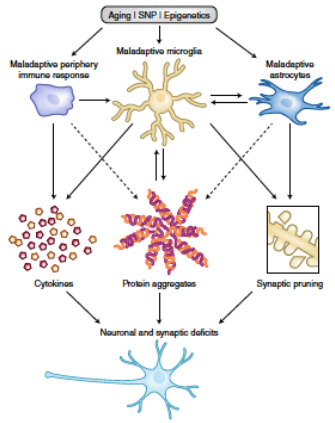

Fig. 3 | Innate immune pathways in neurodegenerative diseases. A maladaptive innate immune response has emerged as a critical driving force in the pathogenesis of many neurodegenerative diseases. SNPs on many disease-associate genes induce maladaptive innate immune responses that are also associated with aging and epigenetic changes. Microglia, the resident immune cells in the brain, engage in cross-talk with astroglia and are modulated by peripheral immune system. Maladaptive microglia could damage neuronal circuits due to dysfunction in their detection or response to homeostasis imbalance, resulting in accumulation of protein aggregates, in concert with astroglia and possibly the peripheral immune system. Microglia could also cause neuronal and network dysfunction by altering cytokine signaling and synaptic pruning, independently of their effects on protein aggregates.

1. Proximal recolonization by self-renewing microglia re-establishes microglial homeostasis in the adult mouse brain. Zhan L, Krabbe G, Du F, Jones I, Reichert MC, Telpoukhovskaia M, Kodama L, Wang C, Cho SH, Sayed F, Li Y, Le D, Zhou Y, Shen Y, West B, Gan L. PLoS Biol. 2019 Feb 8;17(2):e3000134. doi: 10.1371/journal.pbio.3000134. eCollection 2019 Feb.
2. Converging pathways in neurodegeneration, from genetics to mechanisms. Gan L, Cookson MR, Petrucelli L, La Spada AR. Nat Neurosci. 2018 Oct;21(10):1300-1309. doi: 10.1038/s41593-018-0237-7. Epub 2018 Sep 26. Review. PMID: 30258237
3. Differential effects of partial and complete loss of TREM2 on microglial injury response and tauopathy. Sayed FA, Telpoukhovskaia M, Kodama L, Li Y, Zhou Y, Le D, Hauduc A, Ludwig C, Gao F, Clelland C, Zhan L, Cooper YA, Davalos D, Akassoglou K, Coppola G, Gan L. Proc Natl Acad Sci U S A. 2018 Oct 2;115(40):10172-10177. doi: 10.1073/pnas.1811411115. Epub 2018 Sep 19. PMID:30232263

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