LBRN

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Keynote Talk : January 28th, 2022 : 1:10 – 2:00 PM

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Redundancy and Resiliency Signalling for Neuronal Longevity Counteracts Alzheimer's Onset.

The onset of neurodegenerative diseases reflects a failure of neuronal cell survival. It is in a way an inability to succesful aging, that is to be able to live over nine decades without neuropathologies. Neurodegeneration activates detrimental events, including inflammation that leads to progressive cognitive decline (e.g., dementia, as in Alzheimer's disease (AD)) and sight failure (blindness, as in age-related macular degeneration (AMD)). We have identified novel mediators, the elovanoids (ELVs), that control the unfolding of neuroinflammation, restore homeostasis and function. ELVs are 32C and 34C,n-3 stereospecific dihydroxylated molecules derived from Very Long Chain Polyunsaturated Fatty Acids,n-3 (VLC-PUFA). I will discuss recent results that demonstrate that the targets of ELVs include senescence gene programming, signaling proteins, microglia, Tau phosphorylation, Tau missorting, Netosis, and telomerase activation.

In both brain and retina interdependent cellular systems, neurons-glia (astrocytes and microglia) and retinal pigment epithelial cells-photoreceptor cells (a differentiated neuron) sustain homeostasis. A proof of principle of the bioactivity of lipid mediators yielded our recent unexpected discovery that intranasally delivered lipid mediators are directly associated with rescuing working memory deficits and other homeostatic changes in a mouse model of AD. We also found that insufficiencies of the biosynthetic ELVs pathway in the hippocampus of a knock-in of amyloid precursor protein (APP) and in the 5XFAD model that the ELV and the neuroprotectin D1 (NPD1) pathway are downregulated, preceding neuronal cell loss. Furthermore, ELVs protect human neurons/astrocytes in cultures from oligomeric Aβ (OAβ) peptide-mediated toxicity and arrest senescence gene programming expression, including SASP secretome. In AMD, OAβ sets inflammatory events in motion that contribute to photoreceptors cell death. ELVs prevented OAβ-induced changes in the expression of genes engaged in senescence, inflammation, autophagy, extracellular matrix remodeling, and AMD. MALDI molecular imaging of early and advanced AMD human retinas showed decreased PC-VLC-PUFAs in macula cone photoreceptor cells. Overall, we find decreased DHA retention, VLC-PUFA formation and ELVs/NPD1 synthesis in AMD and in AD models. Thus, multiple disrupturing mechanisms that lead to the onset and progression of AD and the dry-form AMD are targeted in a redundant fashion by ELVs and related lipid mediators. Thus, they uncover fundamental events in the biology of aging ,represent biomarkers of prodromal disease stages and open avenues of therapeutic exploration.