Alzheimer's disease: The Silver Tsunami of the Twenty First Century

Alzheimer's disease (hereafter AD), a disease with no absolute cure to date, is the second leading cause of death in United States and is aptly called the "Silver Tsunami of the Twenty First Century". As per National Institute of Aging (NIA), deaths from AD increased 68 percent between 2000 and 2010, while deaths from other major diseases, including the number one cause of death (heart disease), decreased. So far AD, the most common form of dementia in older people, has affected nearly 21 million people globally and their numbers are increasing. Dementia represents a variety of diseases and conditions that develop when neurons (nerve cells) in the brain die. The death of neurons causes changes in memory, behavior and ability to think clearly and finally leads to death. Many gene mutations responsible for AD have been identified[1-4], but we do not yet understand how these mutations trigger signaling pathways to activate cell death and lead to AD pathology.

Accumulation of amyloid-plaques comprising of human amyloid-beta 42 (Aß42) protein coincides with AD related neurodegeneration. However, the mechanisms that trigger the progression of AD remain unclear[5]. A major focus in AD research has been to reduce the levels of Aβ42 protein in neurons with the ultimate goal of preventing its accumulation. Clinical trials largely aimed at removing Aß42 plaques have not been effective. Thus, understanding the mechanisms of regulation of Aß42 protein accumulation, and the signaling pathways (e.g., cell death) that trigger neuronal cell death due to Aβ42 accumulation can generate important insights into AD pathobiology. These insights should lead to a cure or better therapeutic strategies for this disease. Several vertebrate (*e.g.*, mouse) and invertebrate models for AD have been successfully developed to understand how Aβ42 containing plaques can induce death of neurons. The underlying signaling mechanisms may shed light on the genes/pathways involved in the neurodegenerative process.

We have employed fruit fly *Drosophila melanogaster*, an excellent disease model organism to model AD[6]. Fruit flies are an excellent model because of their large repository of mutant flies available and other powerful genetic tools. Remarkably, the genetic makeup of fruit fly brains is similar to humans. We have been able to produce high levels of human Aß42 in the developing fly retina that mimics AD-like neuropathology and death of photoreceptor neurons (eye-specific nerve cells) due to activation of cell death pathways[2]. This model can be tested by unbiased genetic and chemical screens to find chemical inhibitors and genetic modifiers of Aß42-mediated neuronal death. The novelty of our approach lies in its simplicity and specificity for isolating a set of functionally relevant genes, biomarkers and compounds that can block Aß42-mediated neurodegeneration. Such discoveries will contribute to our knowledge of the progression of AD and lead to treatments and potential cures.

The modularity of our proposed approach results in two prong effort in understanding the genetic basis of AD, identifying the biomarker for early detection and then chemical inhibitors to block the onset of Aß42 mediated neurodegeneration. Our long term goal is to use our *Drosophila* eye model of AD to (1) develop sensors for measuring the neurotoxic response of Aß42 accumulation, (2) to identify chemical inhibitors of Aß42 mediated neurotoxicity using chemical screens. Findings from ours studies can be directly applied to other preclinical models, and tested for diagnostic or therapeutic value.

References:

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