

PROJECT SUMMARY (See instructions):

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity. Every year there are millions of TBI cases involving car accidents, contact sports, and military duty. TBI is characterized as a head injury that causes contusion, hemorrhage, or diffuse axonal injury, and individuals that survive suffer from a variety of cognitive and behavioral deficits. This injury, whether acute or repetitive, can trigger multiple molecular and cellular alterations that can be life-threatening to neuronal cells such as excitotoxicity, Ca^{2+} overload, oxidative stress, inflammation, and more. In addition to these deleterious effects, epidemiological studies have demonstrated that TBI is a significant risk factor for Alzheimer's disease (AD), the most common form of dementia in the elderly population and one of the leading problems of public health. Though AD affects the elderly population (65 and up), certain risk factors, such as TBI, can accelerate its development. AD is characterized by the progressive formation of extracellular amyloid plaques, intracellular neurofibrillary tangles, synaptic alterations, neuronal loss, brain inflammation, and cognitive impairment.

This proposal entitled "Traumatic Brain Injury promotes Alzheimer's disease through seed formation" focuses on elucidating the molecular mechanism by which TBI is associated to the development of AD. Our overarching hypothesis is that TBI induces the formation of the first misfolded oligomeric seeds composed of either or both amyloid-beta and Tau protein, which then spread the pathology throughout the brain by a prion-like mechanism to result in the development of AD. In this project we will test this hypothesis using various transgenic mice models of AD subjected to experimentally induced TBI. We will carefully analyze the pathological changes in the brain at various time points after TBI. The plan is to observe the localized appearance of misfolded protein aggregates soon after TBI which then spread along neuroanatomical connections to compromise the entire brain, leading to the onset of clinical alterations. We will also study the biochemical, structural and biological characteristics of misfolded aggregated seeds produced by the TBI event, particularly to assess whether they are capable to nucleate the polymerization of protein aggregates in vitro and in vivo.

The findings obtained in this project may provide a mechanistic explanation for the epidemiological link between TBI and AD and may open up a new area of research that we will aggressively pursue through application for external funding. Furthermore, our results may open novel strategies for therapeutic intervention to either minimize the initial alterations produced by TBI or to block the spreading of the pathology that will subsequently lead to neurodegeneration.

RELEVANCE (See instructions):

Alzheimer's disease is the most common form of dementia in late life and is currently one of the largest problems of public health. One the best documented risk factors for AD is traumatic brain injury. In this application we propose to study the molecular basis of this linkage under the hypothesis that TBI induces the formation of the first protein misfolding events in the brain that then spread the pathology, leading to the onset of the disease. Our results may help to understand the pathogenesis of a large proportion of AD cases and may uncover novel strategies for intervention.

This project emerges through the collaboration of two established scientists located at UT Health Science Center at Houston: Dr Pramod Dash a worldwide recognized expert in traumatic brain injury, who has available all the models, resources and expertise to study the cellular and molecular biology of TBI and Dr Claudio Soto, an expert in neurodegenerative diseases associated to the cerebral accumulation of misfolded protein aggregates, who has been working for the past two decades on the molecular basis of Alzheimer's disease and related brain disorders.