

27th International conference on

Neurology and Cognitive Neuroscience

October 18-19, 2018 | Warsaw, Poland



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The neuroimmunology of Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease, characterized by behavioral disorders, loss of memory and cognitive impairment. AD represents around 12% of people over 65 worldwide. Cumulative evidence shows that innate immunity participates in the pathogenesis of AD. According to our theory of neuroimmunomodulation, microglial activation by the so called "damaged signals" triggers alterations in the cross-talks between microglia and neuronal cells, involving a cascade of pathological events leading to tau hyperphosphorylation and oligomerization, associated with cognitive impairment. This activation depends on the type and intensity of the stimulus. Generation of NF- κ B occurs, promoting the expression and release of proinflammatory cytokines IL1 β , IL-6, IL-12, IFN γ and tumor necrosis factor TNF α . As a consequence, short-lived cytotoxic factors, such as superoxide radicals, nitric oxide and ROS are released. Pathological tau hyperphosphorylations by p35 Cdk5 complex reduce tau-microtubule interactions, downregulating tau activity in stabilizing microtubules. In AD, a persistently active microglial condition seems to generate neuronal damage, with a consequent neuronal death, causing the release of pathological tau toward the extracellular environment. Released tau would subsequently cause reactivation of microglial cells, thus promoting a feedback mechanism and generating a continuous neuronal damage. However, from the pathophysiological point of view, AD is significantly more complex than just inducing a loss of memory. In fact, alterations in the dopaminergic pathway together with serotonin depletion in the elderly lead to late onset depressive phenomena according with recent evidences. These events seem to occur together with neuroimmunomodulatory changes responsible for a final tau oligomerization in the course of neurofibrillary tangles formation. This means that both affective disorders and mood changes are followed by neuroinflammatory processes that lead to intraneuronal alterations that lead to cognitive impairment. We integrate the cellular basis for the functional connections between emotional and cognitive phenomena and their pathological alterations in AD, underlying possible mechanisms for the role of consciousness. The previously summarized mechanisms could explain the onset of AD, opening a new projection to research on therapeutic agents that could modulate the interactions between tau and microglial cells.

Biography

Ricardo B Maccioni is a Professor of Neurology at the Medical School, and Professor of Neurosciences at University of Chile. He also serves as the Director of the Laboratory of Molecular Neurosciences, Scientific Director of the International Center for Biomedicine (ICC) and Senior Investigator of the Brain/Mind Program in Chile. He has served as an Associate Professor at the University of Colorado, Medical School, USA. He has completed his Doctoral degree in 1975, and was a Postdoctoral Fellow in the National Institutes of Health at the University of Colorado, Health Sciences Center and a Visiting Scholar at the Max Plank Institute for Biophysics in Germany. On the basis of these and numerous other findings, he is considered among the leading investigators in Alzheimer's disease. He is co-author with George Perry of the recent book "Current Hypotheses and Research Milestones in Alzheimer's Disease", among other 10 books in this medical field. He has made outstanding achievements in the training of 59 young scientists. He is the author of 146 publications in high-impact journals and 18 patents.

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