SCIENTIFC PUBLICATIONS

1. **MIOST CITED PAPERS** **Source: *Google Scholar***

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Abstracts

1. The Molecular Bases of Alzheimer's Disease and Other Neurodegenerative Disorders.

Alzheimer's disease, the cause of one of the most common types of dementia, is a brain disorder affecting the elderly and is characterized by the formation of two main protein aggregates: senile plaques and neurofibrillary tangles, which are involved in the process leading to progressive neuronal degeneration and death. Neurodegeneration in Alzheimer's disease is a pathologic condition of cells rather than an accelerated way of aging. The senile plaques are generated by a deposition in the human brain of fibrils of the β-amyloid peptide (Aβ), a fragment derived from the proteolytic processing of the amyloid precursor protein (APP). Tau protein is the major component of paired helical filaments (PHFs), which form a compact filamentous network described as neurofibrillary tangles (NFTs). Experiments with hippocampal cells in culture have indicated a relationship between fibrillary amyloid and the cascade of molecular signals that trigger tau hyperphosphorylations. Two main protein kinases have been shown to be involved in anomalous tau phosphorylations: the cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3β. Cdk5 plays a critical role in brain development and is associated with neurogenesis as revealed by studies in brain cells in culture and neuroblastoma cells. Deregulation of this protein kinase as induced by extracellular amyloid loading results in tau hyperphosphorylations, thus triggering a sequence of molecular events that lead to neuronal degeneration. Inhibitors of Cdk5 and GSK3β and antisense oligonucleotides exert protection against neuronal death. On the other hand, there is cumulative evidence from studies in cultured brain cells and on brains that oxidative stress constitutes a main factor in the modification of normal signaling pathways in neuronal cells, leading to biochemical and structural abnormalities and neurodegeneration as related to the pathogenesis of Alzheimer's disease.
This review is focused on the main protein aggregates responsible for neuronal death in both sporadic and familial forms of Alzheimer's disease, as well as on the alterations in the normal signaling pathways of functional neurons directly involved in neurodegeneration. The analysis is extended to the action of neuroprotective factors including selective inhibitors of tau phosphorylating protein kinases, estrogens, and antioxidants among other molecules that apparently prevent neuronal degeneration.

2. Role of microtubule-associated proteins in the control of microtubule assembly.

In eukaryotic cells, microtubules, actin, and intermediate filaments interact to form the cytoskeletal network involved in determination of cell architecture, intracellular transport, modulation of surface receptors, mitosis, cell motility, and differentiation. Cytoskeletal organization and dynamics depend on protein self-associations and interactions with regulatory elements such as microtubule-associated proteins (MAPs). The MAP family includes large proteins like MAP-1A, MAP-1B, MAP-1C, MAP-2, and MAP-4 and smaller components like tau and MAP-2C. This review focuses on relevant aspects of MAP function, with emphasis on their roles in modulating cytoskeletal interactions. In this context, MAP expression mechanisms and posttranslational modifications are also discussed. Microtubule-associated proteins have a rather widespread distribution among cells, but certain MAPs have been identified in specific cell types. Within single neurons, MAP-2 is dendritic while tau is

preferentially an axonal protein. Their expression is developmentally regulated. Even though MAPs share a capacity to interact with the COOH-terminal tubulin domain, stabilize microtubules, and link them with other cytoskeletal polymers, they exhibit structural differences. However, MAP-2, MAP-4, and tau have common repetitive microtubule-binding motifs. Microtubule-associated proteins not only control cytoskeletal integrity, but they also appear to interact with highly structural elements of cells. Molecular biological approaches permitted localization of new MAPs in cultured mammalian cells and invertebrate organisms and other microtubule-interacting proteins that exhibit transient interactions with microtubules. The structural/functional aspects of several new MAP-like proteins in centrosomes and the mitotic spindle, functionally implicated in cell cycle events, are also analyzed.

3. Neuroinflammation: implications for the pathogenesis and molecular diagnosis of Alzheimer's disease.

During the past few years, an increasing set of evidence has supported the major role of deregulation of the interaction patterns between glial cells and neurons in the pathway toward neuronal degeneration. Neurons and glial cells, together with brain vessels, constitute an integrated system for brain function. Inflammation is a process related with the onset of several neurodegenerative disorders, including Alzheimer's disease (AD). Several hypotheses have been postulated to explain the pathogenesis of AD, but none provides insight into the early events that trigger metabolic and cellular alterations in neuronal degeneration.

The amyloid hypothesis was sustained on the basis that Aβ-peptide deposition into senile plaques is responsible for neurodegeneration. However, recent findings point to Aβ oligomers as responsible for synaptic impairment in neuronal degeneration. Amyloid is only one among many other major factors affecting the quality of neuronal cells. Another explanation derives from the tau hypothesis, supported by the observations that tau hyperphosphorylations constitute a common feature of most of the altered signaling pathways in degenerating neurons. Altered tau patterns have been detected in the cerebrospinal fluids of AD patients, and a close correlation was observed between the levels of hyperphosphorylated tau isoforms and the degree of cognitive impairment. On the other hand, the anomalous effects of cytokines and trophic factors share in common the activation of tau hyperphosphorylation patterns. In this context, a neuroimmunological approach to AD becomes relevant. When glial cells that normally provide neurotrophic factors essential for neurogenesis are activated by a set of stressing events, they overproduce cytokines and NGF, thus triggering altered signaling patterns in the etiopathogenesis of AD. A solid set of discoveries has strengthened the idea that altered patterns in the glia-neuron interactions constitute early molecular events within the cascade of cellular signals that lead to neurodegeneration in AD. A direct correlation has been established between the Aβ-induced neurodegeneration and cytokine production and its subsequent release. In effect, neuroinflammation is responsible for an abnormal secretion of proinflammatory cytokines that trigger signaling pathways that activate brain tau hyperphosphorylation in residues that are not modified under normal physiological conditions. Other cytokines such as IL-3 and TNF-α seem to display neuroprotective activities. Elucidation of the events that control the transitions from neuroprotection to neurodegeneration should be a critical point toward elucidation of AD pathogenesis.

4. Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches.

Alzheimer disease (AD) is the most common cause of dementia in people over 60 years old. The molecular and cellular alterations that trigger this disease are still diffuse, one of the reasons for the delay in finding an effective treatment. In the search for new targets to search for novel therapeutic avenues, clinical studies in patients who used anti-inflammatory drugs indicating a lower incidence of AD have been of value to support the neuroinflammatory hypothesis of the neurodegenerative processes and the role of innate immunity in this disease.

Neuroinflammation appears to occur as a consequence of a series of damage signals, including trauma, infection, oxidative agents, redox iron, oligomers of t and b-amyloid, etc. In this context, our theory of Neuroimmunomodulation focus on the link between neuronal damage and brain inflammatory process, mediated by the progressive activation of astrocytes and microglial cells with the consequent overproduction of proinflammatory agents. Here, we discuss about the role of microglial and astrocytic cells, the principal agents in neuroinflammation process, in the development of neurodegenerative diseases such as AD. In this context, we also evaluated the potential relevance of natural anti-inflammatory components, which include curcumin and the novel *Andean Compound*, as agents for AD prevention and as a coadjuvant for AD treatments.

5. Inhibition of tau phosphorylating protein kinase cdk5 prevents β-amyloid-induced neuronal death.

The key target of this study was the tau protein kinase II system (TPK II) involving the catalytic subunit cdk5 and the regulatory component p35. TPK II is one of the tau phosphorylating systems in neuronal cells, thus regulating its functions in the cytoskeletal dynamics and the extension of neuronal processes. This research led to demonstration that the treatment of rat hippocampal cells in culture with fibrillary beta-amyloid (Abeta) results in a significant increase of the cdk5 enzymatic activity. Interestingly, the data also showed that the neurotoxic effect of 1-20 microM Abeta on primary cultures markedly diminished with co-incubation of hippocampal cells with the amyloid fibers plus the cdk5 inhibitor butyrolactone I. This inhibitor protected brain cells against Abeta-induced cell death in a concentration dependent fashion. Moreover, death was also prevented by a cdk5 antisense probe, but not by an oligonucleotide with a random sequence. The cdk5 antisense also reduced neuronal expression of cdk5 compared with the random oligonucleotide. The studies indicate that cdk5 plays a major role in the molecular path leading to the neurodegenerative process triggered by the amyloid fibers in primary cultures of rat hippocampal neurons. These findings are of interest in the context of the pathogenesis of Alzheimer's disease.

6. Controlled proteolysis of tubulin by subtilisin: localization of the site for MAP2 interactions.

The treatment of tubulin with subtilisin resulted in a significant decrease in the ability of tubulin to assemble. The addition of taxol reduced the effect of subtilisin on the assembly of digested protein. Limited proteolysis of tubulin by subtilisin affected simultaneously both α- and β-subunits, and it resulted in the appearance of two major cleavage fragments (32 and 20 kilodaltons) or an alternative pattern yielding two fragments (48 and 4 kilodaltons). The smallest peptide (4 kilodaltons) and also the 20-kilodalton fragment are localized in the C-terminal region of the tubulin α-subunit. Digested tubulin can assemble into sheet-shaped polymers, which cannot incorporate MAP_2. On the other hand, the isolated C-terminal fragments can bind to MAP_2. These
results suggest that the carboxyl-terminal domain of the tubulin molecule is the site for the MAP_2 interaction.

7. Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway.

Inflammation is a process that has been actively related with the onset of several neurodegenerative disorders including Alzheimer disease (AD). However, the precise implications of inflammatory response for neurodegeneration have not been elucidated. A current hypothesis considers that extracellular insults to neurons could trigger the production of inflammatory cytokines by astrocytes and microglia. These cytokines, namely, interleukin (IL)-1h, TNFα, and IL-6, could affect the normal behaviour of neuronal cells. In the present study, we describe the effect of the administration at physiologic doses of one of these

cytokines, IL-6, to hippocampal neurons, on the protein kinase pathways as well as on the tau phosphorylation patterns. IL-6-treated neurons exhibited an increase in the amount of anomalously hyperphosphorylated tau protein in epitopes dependent on proline-directed protein kinases (PDPKs). On the basis of our data, the observed increase of tau epitopes of Alzheimer type is explained by an increase of intraneuronal levels of p35 activator and in the activity of the protein kinase cdk5 in response to this cytokine. Further confirmation of cdk5 involvement in this process was based on the findings that inhibition of the kinase activity with butyrolactone-I prevents the appearance of tau of Alzheimer type in IL-6-treated neurons. Additional studies suggest that an increase of cdk5 activity could be mediated by a known signaling cascade described for IL-6 function, namely, the MAPK–p38 signaling pathway. Stimulation of the IL-6 pathway appears to increase the tau epitopes of Alzheimer type, as demonstrated in studies with specific inhibitors. These results support the findings of a pathologic role for IL-6 in the neuroinflammatory response as related with the pathogenesis of neuronal degeneration.

8. Insulin resistance and Alzheimer's disease: molecular links & clinical implications.

Hyperinsulinemia as well as type II diabetes mellitus are among the risk factors for Alzheimer´s disease (AD). However, the molecular and cellular basis that link insulin resistance disorders and diabetes with AD are far from clear. Here, we discuss the potential molecular mechanisms that may explain the participation of these metabolic disorders in the pathogenesis of AD. The human brain uses glucose as a primary fuel; insulin secreted by the pancreas cross the blood brain barrier (BBB), reaching neurons and glial cells, and exerts a region-specific effect on glucose metabolism. Glucose homeostasis is critical for energy generation, neuronal maintenance, neurogenesis, neurotransmitter regulation, cell survival and synaptic plasticity. It also plays a key role in cognitive function. In an insulin resistance condition, there is a reduced sensitivity to insulin resulting in hyperinsulinemia; this condition persists for several years before becoming full blown diabetes. Toxic levels of insulin negatively influence neuronal function and survival, and elevation of peripheral insulin concentration acutely increases its cerebrospinal fluid (CSF) concentration. Peripheral hyperinsulinemia correlates with an abnormal removal of the amyloid beta peptide (Aβ) and an increase of tau hyperphosphorylation as a result of augmented cdk5 and GSK3β activities. This leads to cellular cascades that trigger a neurodegenerative phenotype and decline in cognitive function. Chronic peripheral hyperinsulinemia results in a reduction of insulin transport across the BBB and a reduced insulin signaling in brain, altering all of insulin’s actions, including its anti-apoptotic effect. However, the increase in brain insulin levels resulting from its peripheral administration at optimal doses has shown a cognition enhancing effect in patient with AD. Some drugs utilized in type II diabetes mellitus reduce cognitive impairment associated with AD. The link between insulin resistance and neurodegeneration and AD, and the possible therapeutic targets in preventing the insulin-resistance disorders are analyzed.

9. Involvement of the carboxyl-terminal domain of tubulin in the regulation of its assembly.

Limited proteolysis of phosphocellulose-purified tubulin with subtilisin resulted in cleavage of both alpha and beta tubulin subunits, with the formation of two major fragments (S alpha, and S beta, 48 kDa) and a small peptide (4 kDa) containing the carboxyl-terminal region of tubulin. Interestingly, tubulin cleaved under the present conditions showed an increased ability to assemble into large polymers in the absence of MAPs and under conditions that do not promote assembly of undigested tubulin--i.e., low magnesium concentrations and the absence of taxol and polyalcohols. The critical concentrations for the subtilisin-cleaved tubulin assembly was similar to that of MAPs-promoted tubulin assembly. Assembly product from subtilisin-cleaved tubulin consisted mainly of protofilament bundles, hooked polymer, and open tubules, structures showing equatorial and longitudinal spacings of 50 and 40 A, respectively. The existence of junctions between polymer walls indicates that the carboxyl-

terminal removal facilitates polymer-polymer interactions. These results, together with previous studies on the involvement of the carboxyl-terminal domain of tubulin in its interaction with MAP-2, suggest a regulatory role for this domain in tubulin assembly. Thus, in general terms the tubulin molecule can be analyzed as a protein containing two essential domains with functional significance, one domain playing a major role in self-association and the other (the carboxyl-terminal moiety) playing a regulatory role in modulating the interactions responsible for self-association.

10. The Revitalized Tau Hypothesis on Alzheimer's Disease.

Many hypotheses have been raised regarding the pathophysiology of Alzheimer's disease (AD). Because amyloid beta peptide (Aβ) deposition in senile plaques appears as a late, nonspecific event, recent evidence points to tau phosphorylation and aggregation as the final common pathway in this multifactorial disease. Current approaches that provide evidence in favor of neuroimmunomodulation in AD and the roles of tau pathological modifications and aggregation into oligomers and filamentous forms are presented. We propose an integrative model on the pathogenesis of AD that includes several damage signals such as Aβ oligomers, oxygen free radicals, iron overload, homocysteine, cholesterol and LDL species. These activate microglia cells, releasing proinflammatory cytokines and producing neuronal degeneration and tau pathological modifications. Altered and aggregated forms of tau appear to act as a toxic stimuli contributing to neurodegeneration. Recent findings provide further support to the central role of tau in the pathogenesis of AD, so this protein has turned into a diagnostic and therapeutic target for this disease.

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