Oxidation of the amyloid beta peptide and implications in the etiology of Alzheimer’s Disease

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Oxidation of the amyloid beta peptide and implications in the etiology of Alzheimer's Disease

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Research Abstract

Alzheimer’s disease (AD) is the leading cause of dementia in the elderly, by striking 1 over 20 in the World. A defining feature in AD is the post-mortem observation of proteinaceaous plaques, mainly composed of the amyloid-beta peptide (Aß), along with metal ions such as copper, iron or zinc. Aß is found aggregated as amyloid fibrils in the plaques of AD brains, but is present as soluble monomer in healthy subjects. Thus, aggregation of Aß is a critical step and intermediates (often called oligomers) seem to be the most toxic species, reported to mediate

oxidative stress by production of reactive oxygen species (ROS). The redox active metal ions (Cu, Fe) are pivotal in the production and defense of ROS (like NADPH oxidase and SOD, respectively), and loosely bound Fe and Cu can catalyze efficiently the generation of ROS. Indeed, in AD more loosely bound Cu and Fe have been detected and there is a large body of evidence that Cu bound to Aß is part if this Cu pool. Cu can also influence the aggregation of Aß. Thus, the complexes formed between metal ions and Aß might be the cross point of ROS production and Aß aggregation linked to Aß-induced toxicity in AD. Their study appears as particularly promising in understanding the mechanisms of AD development in brain.
The project AlzABox aims at studying the relation between metal-induced oxidative stress in AD, the resulting oxidative damages on the Aß peptide and their consequences on the main mechanisms involved in AD etiology, i.e. aggregation, ROS production and cell toxicity. For this purpose, an interdisciplinary approach, at the frontier between chemistry and biology, is proposed to be developed for i) deeply characterizing the metal-induced oxidative modification undergone by the Aß peptide for in vitro and in vivo model systems, ii) understanding the consequences of Aß oxidation regarding the aggregation mechanism, the coordination of metal ions, the metal-induced ROS production and the cell toxicity, iii) establishing biologically relevant mechanisms of oxidation that might be involved in AD development. Mass spectrometric-based analytical methodologies (coupled to chromatography, high resolution), coordination chemistry, cell and living systems biology are among the disciplines that will be implemented to gain knowledge at the molecular level and ensure the biological relevance, for the success of the project.
The novel and original approach developed in the project AlzABox will first lead to improve the knowledge on the oxidative modification undergone by the Aß peptide, submitted to oxidative stress conditions: identification of the oxidized amino acid residues, nature of the chemical modification, preferential amino acid residues targeted by the ROS attack and time-dependency of oxidation, primary events of the oxidation process that impact the Aß sequence, nature of oxidation as the function of the initial aggregation state of the Aß peptide (monomers, oligomers, amorphous aggregates, fibrils)… Then, by putting in perspective the study of the coordination of metal ions (Cu+, Cu2+, Zn2+) to the Aß oxidized species and the propensity of these latter to aggregate, produce ROS or be toxic for cell, a comprehensive mechanism should emerge regarding the deleterious impact of Aß oxidation towards neurons. Comparison with the Aß oxidized species as characterized in the brain of transgenic AD mice, at different levels of AD development, and in the post-mortem brain samples from AD patients will ascertain the biological relevance of the results.
Finally, by gaining significant insights into the mechanisms of Aß oxidation, their consequences on aggregation, ROS production, metal ion binding and cell toxicity, the project AlzABox should contribute significantly to improve the knowledge on the AD pathology and further open ways to the development of of novel therapeutic strategies, targeting the early stages of AD.

Further information available at:

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