

Alzheimer's disease

The Role of Heat-Shock Proteins (HSPs) in Alzheimer's disease

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Despite considerable research progress made in Chemistry, Biology and Medicine, neurodegenerative diseases affect more and more people in the ageing population and remain a real therapeutic challenge. Nevertheless, advances made in this field allow us to better understand the molecular mechanisms responsible for these disorders and the key-role of conformational changes (change in the shape) of some proteins.

Alzheimer's disease (AD) is an irreversible, progressive and fatal neurodegenerative brain disease resulting in progressive memory and cognitive impairment, which impacts all facets of an AD patient's life. Two characteristic neuropathological structures define AD, extracellular amyloid deposits and neurofibrillary tangles (NFTs) in the senile plaques in the cerebral cortexⁱ. The presence of these insoluble proteins almost invariably leads to the loss of function and death of the cells in which they form. Amyloid plaques build up between nerve cells. They contain deposits of a neurotoxic protein fragment called amyloid-beta peptide ($A\beta$). NFTs form inside dying cells and are twisted filaments derived from the aggregation of hyperphosphorylated forms of the tau protein (τ).

$A\beta$, a peptide of 40/42 amino acid residues, is generated by the cleavage of β -amyloid precursor protein (APP), an integral membrane glycoprotein expressed in many tissues and concentrated in the synapses of neurons. Thus, it is believed that APP plays a central role in AD pathogenesis and holds a central role in AD research. APP was also the first gene in which mutations associated with inherited AD were found. Although the molecular details of the generation of amyloid- β protein from APP are being unravelled, the actual physiological functions of APP are far from clear. New evidence suggests that the C-terminal end of APP may have multiple biological activities, ranging from axonal transport to nuclear signalling. Neurons that degenerate in the brains of persons with AD accumulate APP, which is thought to negatively affect mitochondrial function and cellular homeostasis. Because proteins that enter mitochondria require assistance from chaperone proteins, it is hypothesized that heat-shock proteins (HSPs) help accumulate APP in mitochondria.

Over the past few years, a great deal of attention has been focused on a family of cellular proteins, which act as molecular chaperones and guide the normal folding of intracellular proteins into their native conformations and transport of proteins between or into cell organelles. Chaperones are usually referred to either as heat shock proteins (HSPs), if they respond to heat shock, or glucose regulated proteins (GRPs), if they respond to metabolic stress, such as glucose insufficiency. HSPs are a group of proteins present in all living cells, which have evolved to cope with the potential for proteins to become unstable or denatured when stressed, thereby acting as a defence against protein damageⁱⁱ.

Evidence in the literature suggests protein quality control mechanisms involving the HSP family of molecular chaperones become impaired with aging and contribute to a variety of neurodegenerative diseases. Through their role in protein folding, aggregation and degradation, HSPs are involved in the development of age-related disorders. They are also associated with mature proteins that have an unfolded structure (and become prone to aggregation) due to an environmental insult such as heat shock.

While many mechanisms have been suggested to explain the starting point of AD, it is clear that neurons first fail in function and then die from lack of ability to compensate multiple metabolic

stresses arising from overproduction and/or failure to clear neurotoxic amyloidogenic proteins. One promising role for HSPs in this process is to accelerate A β removal. When clearance mechanisms become overwhelmed, A β oligomers form insoluble fibrils that are deposited as amorphous inclusions that can include HSPs. Elevated levels of HSP27 and HSP70 protect neurons from the cytotoxic effects of protein aggregates. HSP levels are lower in the brains of AD patientsⁱⁱⁱ. Thus, if levels of HSP27 or HSP70 can be increased to higher levels by drug or supplement administration, increased levels of HSPs may be a therapy for neurological diseases.

References

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