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ISSN: 2329-8847
Journal of Aging Science

Commentary

Implications of Heat Shock Proteins in Alzheimer's Disease

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DESCRIPTION

Most Age-related neurodegenerative diseases are hallmarked by the existence of pathological protein depositions in the brain, for example, extracellular plaques and neurofibrillary tangles in Alzheimer's disease. Furthermore, aging and neuro-degeneration in Alzheimer's disease are often accompanied by a functionally impaired Ubiquitin-Proteasome System (UPS) that may be both a cause and one of the detrimental consequences of the aggregation. Synaptic plasticity is affected n Alzheimer's disease and involved metabolism of at least 5%-8% of brain proteins each day. As stated, central to PQC (Protein Quality Control) are HSPs (Heat Shock Proteins) that interact with mis or unfolded proteins. They generally bind to exposed hydrophobic, aggregation prone regions, preventing their self-association and aggregation. Whilst the best-known outcome of such interaction is that chaperone next assists in the refolding of its bound client protein, HSPs also can assist in supporting its client's proteosomal or autophagosomal degradation. In addition, HSPs can assist in the disassembly of protein complexes and provide the driving force for translocation of proteins across membranes. From gene transcription to posttranslational modification, several quality checks are essential before a protein is ready for biological action, locally or distantly *via* axonal transport in neurons. The accurate folding and control over levels of many proteins must be tightly regulated both spatially and temporally. To achieve this, the cell possesses a network of different protein quality control systems for co-translational protein folding *via* molecular chaperons, as the first line of defense against protein misfolding and aggregation. Subsequently, accurate protein degradation, encompassing the ubiquitin-proteasome system and the autophagosomal-lysosomal system is the second line defense. Recent data also suggest an additional protein quality control pathway in which misfolded proteins are excreted actively after encapsulation at the endoplasmic reticulum, a process dubbed Misfolded Associated Protein Secretion. In each of the protein quality control systems, an array of Heat Shock Proteins (HSPs) are required to chaperone and direct substrates toward their correct fate and to avoid off-pathway reactions that might lead to harmful accumulations of protein aggregates. Recent studies focused on the cross-talk between the UPS and the HSPs, concepts that are in line with the current idea that Alzheimer's disease is in an asymptomatic cellular phase long before it can be translated into clinically relevant conservation and interventions. As stated before, recent data suggest an additional PQC pathway in which misfolded proteins are excreted actively after encapsulation at the endoplasmic reticulum, a process dubbed MAPS (Microtubule-Associated Proteins). This process was dependent on an ER-resident ubiquitin-specific protease, USP19, which originally was shown to function in ER-associated proteosomal degradation. The catalytic domain of USP19 was found to possess an unprecedented chaperone activity, allowing recruitment of misfolded protein to the Endoplasmic Reticulum (ER) surface. Deubiquitinated cargos are then encapsulated into ER-associated late endosomes and secreted to the cell exterior. The action of USP19 was found to be independent of its interaction with HSP90, with whom it normally partners in the process of ER-associated proteosomal degradation. In a recent research, extracellular release of neurodegenerative-associated proteins was also found to be a regulated process, operating likely under conditions of compromised intracellular PQC. Finally a recent study on *C. elegans* showed that adult neurons extrude large membrane-surrounded vesicles, termed exospheres. This effect was likewise augmented upon decline in intercellular PQC capacity as well as by compressed mitochondrial functioning. Although each of these export mechanisms may provide a level of cytoprotection, this type of secretion may also contribute to the prion like propagation of Aβ or tau and therefore may be a target for inhibition to halt disease progression. These studies also further underscore the importance of maintaining an optimal intracellular PQC to prevent neurodegenerative diseases and brain aging. Protein homeostasis is crucial for the proper function of cells and maintaining an optimally functioning PQC network is therefore essential to prevent neuronal degeneration.

CONCLUSION

Most facets of PQC erode during aging and this may be a central factor in the onset or progression of Alzheimer's disease.

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Received: 10-Oct-2022, Manuscript No. JASC-22-18939; **Editor assigned:** 13-Oct-2022, Pre QC No. JASC-22-18939 (PQ); **Reviewed:** 27-Oct-2022, QC No JASC-22-18939; **Revised:** 03-Nov-2022, Manuscript No. JASC-22-18939 (R); **Published:** 11-Nov-2022, DOI: 10.35248/2329-8847.22.10.292.

Citation: White C (2022) Implications of Heat Shock Proteins in Alzheimer's Disease. J Aging Sci. 10:292.

Conversely, potentiating PQC in various ways may help to delay the disease onset, either directly *via* various means of chaperoning Aβ or tau monomers or aggregates or indirectly by maintaining normal PQC and preventing aggregate release and propagation. A summary of possible actions of HSP in the pathogenesis of Alzheimer's disease is provided as a result of the research in the recent years. Simultaneously, improving UPS efficiency *via* autophagic activities is an option. Alternatively, reducing the burden on the PQC, e.g., by preventing accumulation of other misfolded proteins in general or even specific ones like UBB+1 could also help to delay a disruption in protein homeostasis. However as many of these processes are promiscuous, interference with their global activity may come with too many negative tradeoffs. They may also only be effective transiently due to auto regulatory feedback loops or epigenetic changes, as observed when trying to boost HSF-1 actively by HSP90 inhibition. Therefore, specific targeting of cochaperons or UBB+1 or their transcripts may be an option.

Interestingly, significant decrease in the levels of H2S in response to HH was reproducibly observed. H2S augmentation was found to prevent hypobaric hypoxia induced endothelial and glial activation as indicated by expression of sICAM in plasma samples and GFAP in brain sections. In striking contrast to the animals exposed to HH without NaHS an H2S donor, the Laminin-Aqp signals perfectly localized in the brain sections of animals receiving NaHS, prior to HH. We thus inferred that NaHS-mediated maintenance of H_2S levels prevented HH-induced loss of Glio-Vascular homeostasis. Taken together, our work resolved origin/nature of injury during hypobaric hypoxia. It revealed early glio-vascular unit dysfunction, which progesses to perturb the neurovascular unit and secondary neuronal loss with neuro-pathophysiological effects during Hypogonadotropic hypogonadism (HH). In addition, the role of H2S signaling in preservation of brain vascular homeostasis under HH condition was observed.