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AREVIEW

# Protein misfolding and neurodegenerative disease

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**ABSTRACT**

Many chronic neurodegenerative disorders diseases and systemic amyloidosis, are thought to arise from the misfolding and aggregation of an underlying protein. Recent findings strongly support this hypothesis and have increased our understanding of the molecular mechanism of protein conformational disorders. Genetic mutations are the root cause for protein misfolding in rare families, but the majority of patients have variable forms possibly related to environmental factors. Diverse human disorders, including several neurodegenerative. Nanoneuro medicine which means the development of small drug formulations for the diagnosis and treatment of degenerative, inflammatory, infectious, vascular, addictive, behavioral and metabolic disorders of the nervous system, will provide a focus for each of the scientific sessions marked due to deposits of misfolded or aggregated proteins.

**Key Words :** Protein misfolding, Neurodegenerative diseases, Alzheimer's disease, Nanotechnology, Amyloid

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Protein misfolding and deposition of protein aggregates in tissues are the main cause of almost twenty five neurodegenerative diseases known today. These diseases are termed as protein aggregation diseases or amyloid diseases and are mostly incurable. These include Alzheimers disease (AD), type 2 diabetes (T2D) and the transmissible spongiform encephalopathies (TSEs). Despite their different pathologies, etiologies and diverse disease specific factors and the fact that each of these diseases is characterized by tissue deposition of a different protein, it appears that they might have in common certain basic molecular mechanisms. Uncovering the principles of protein misfolding, aggregation and associated cell degeneration at the molecular and cellular levels is thus, still a great challenge in biochemical and biomedical research. Progress in this direction will assist in both elucidating the molecular basis of disease pathogenesis and developing novel therapeutic and diagnostic strategies.

## Protein folding problem :

One of the predominant product of gene expression is protein synthesis which contribute significantly to the shape and functionality of the cell. The expression of proteome has an important role in the health of individual cells and the lifespan of the organism. In addition to cell type and tissue specific regulation of protein expression, maintenance of the proteome depends on efficient protein

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folding homeostasis or proteostasis, that monitors and ensures folding, assembly and targeting of newly synthesized proteins, repair of damaged proteins and clearance. Proteotoxic conditions arise by external stresses or as a byproduct of normal cellular metabolic and signaling events during development and aging (Table 1). This is in addition to the intrinsic variation in the proteome due to polymorphisms which is further exacerbated by random errors that can occur at every step of protein biogenesis. These factors contribute to a flux of metastable proteins that are at risk for misfolding and aggregation (Rutherford and Lindquist, 1998 and Stevens and Argon, 1999).

In healthy young cells, these processes are balanced by the concerted action of molecular chaperones, detoxifying enzymes, degradation machinery and adaptive stress responses (Michels *et al*., 1997). In aging and disease, damaged proteins accumulate, leading to both loss of function and gain of function toxicity as these homeostatic mechanisms fail and contribute to pathology.

**Protein damage: oxidative modifications :**

According to the 'free radical theory'(Harman, 1956) and the 'oxidative stress theory' (Sohal and Weindruch, 1996) of aging postulate that aging and many age related diseases may be attributed to the generation of oxygen free radicals and reactive oxygen and nitrogen species (ROS and RNS), in excess of cellular antioxidants, resulting in oxidative damage to DNA, lipids and proteins. Many evidences has connected the aging associated diseases, including atherosclerosis, arthritis, muscular dystrophy, cataracts, pulmonary dysfunction, neurological disorders and cancer with oxidative damage (Stadtman and Oliver, 1991). The decrease in glutamine synthetase activity was found to distinguish the brains of Alzheimer disease (AD) patients from age matched individuals, leading to the conclusion that Alzheimer disease may represent a specific brain vulnerability to age related oxidation. In addition to oxygen radicals, glucose, galactose, fructose and many glycolytic intermediates participate in non-enzymatic protein glycosylation (glycation) and glycoxidation, contributing to age related protein modifications. Some glycolytic intermediates can generate methylglyoxal (MG), which is a highly reactive glycating agent (Ahmed *et al.,* 2005) leading to the formation of advanced glycation end products (AGEs), that has been implicated in age-related diseases, including Alzheimer's disease and complications associated with diabetes (Kuhla *et al*., 2007). A decrease in circulating glucose and reduction of methylglyoxal, resulting from dietary restriction or fasting, may explain some of the health improving effects of these treatments (Hipkiss, 2006).

In addition to functional inactivation of proteins, free radicals can have a local effect on charged side chains or cause cleavage of the polypeptide backbone, leading to a spectrum of consequences, from complete unfolding to local conformational changes (Stadtman, 1993) to

**Table 1 : Factors responsible for protein folding**

| | | |
|---|---|---|
| Human body activities | Neurotransmission | |
| | Respiration, Glycolysis | |
| | Burst of protein synthesis (differentiation) | |
| | Signaling | |
| Stressors | Hormonal imbalance(thyroid and growth hormone), emotional/ psychological stress | |
| | Pathophysiological state (fever, inflammation, infection, hypoxia, reperfusion, etc) | |
| | Nutrient intake imbalance | |
| | Amino acid analogues ( including food sources- Azetidine, Canavanine | |
| | Aberrant physiological conditions (oxidation, osmolarity, pH) | |
| | Antibiotic and anti- inflammatory drugs (puromycin, tetracycline, NSAID, indomethacin) | |
| | Trauma, injury | |
| | Anesthetic | |
| | Alcohols, nicotine | |
| | Environmental stressors (heavy metals, arsenates, pesticides, mutagens, irritants, etc.) | |
| Mutations, | Protein conformation | Protein misfolding |
| Polymorphisms, Mistranslation | Subunit stoichiometry | |
| | Protein stability | |
| Damaged / mutated chaperones | Protein misfolding | |

targeting for disposal.

**Alzheimer's disease :**

Alzheimer's disease (AD) is a devastating, fatal, neurological disorder with no known cause and no cure. The common cause of dementia in the geriatric (old age) population (Masters *et al.*, 2006) is Alzheimer's disease (AD). It is primarily a disease of old age and it has become a very serious problem with the general life-expectancy gradually increasing. Patients with AD experience an impaired cognition ranging from an insidious impairment of episodic memory at the onset to an eventual dementia syndrome. The latter is a severe impairment or loss of intellectual capacity and function including deficits in attention, in memory, in thinking, in reasoning and in language skills. Moreover, accompanied with the dementia syndrome is usually the inability of the patient to perform "motor functions" and "alterations of personality" (Mattson, 2004). On the average, the patient dies nine years after the AD diagnosis (Citron, 2002).The afflicted person suffers progressive loss of memory and thinking ability, mood swings, personality changes and loss of independence. Physically, AD is characterized by massive loss of neurons and disruption of synaptic function throughout the brain, beginning in the hippocampus, an area of the cortex that plays a key role in formation of new memories.

**Cell biology of Alzheimer's disease :**

AD brains show intracellular neurofibrillary tangles, which contain hyperphosphorylated tau and extracellular plaques, which contain Aβ (amyloid β-peptide).These aggregates may consist of oligomeric complexes of non-native secondary structures and demonstrate poor solubility in aqueous or detergent solvent. Other disorders manifesting protein aggregation include Huntington's disease (a poly Q disorder), amyotrophic lateral sclerosis (ALS) and prion disease (Ciechanover and Brundin, 2003). The aforementioned disorders are also termed ''conformational diseases'' because of the emergence of protein aggregation in the brain. An additional feature of most neurodegenerative diseases is excessive generation of reactive nitrogen species and reactive oxygen species which can contribute to neuronal cell injury and death (Lin and Beal 2006 and Barnham *et al.*, 2004).

While many intra and extra-cellular molecules may participate in neuronal injury, accumulation of nitrosative stress due to excessive generation of nitric oxide (NO) appears to be a potential factor contributing to neuronal cell damage and death (Beal, 2001).

A well established model for NO production entails a central role of the N-methyl-D-aspartate (NMDA)-type glutamate receptors in nervous system. Excessive activation of NMDA receptors drives $Ca^{2+}$influx, which in turn activates neuronal NO synthase (nNOS) as well as the generation of ROS (Bredt *et al*., 1991).

Accumulating evidence suggests that NO can mediate both protective and neurotoxic effects by reacting with cysteine residues of target proteins to form S-nitrosothiols (SNOs), a process termed S-nitrosylation because of its effects on the chemical biology of protein function. Importantly, normal mitochondrial respiration may also generate free radicals, principally ROS and one such molecule, superoxide anion ($O^{2-}$), reacts rapidly with free radical NO to form the very toxic product peroxynitrite ($ONOO^-$). Importantly, protein aggregation can result from either a rare mutation in the disease related gene encoding the protein or posttranslational changes to the protein engendered by nitrosative oxidative stress, which may well account for the more common sporadic cases of the disease (Zhang and Kaufman, 2006). Therefore, a key theme of this article is the hypothesis that nitrosative and oxidative stress contribute to protein misfolding in the brains of the majority of neurodegenerative patients.

**Role of nanotechnology :**

Recently the emerging field of nanotechnology has promised new techniques to solve some of the AD challenges. Nanotechnology refers to the techniques of designing and manufacturing nanosize (1–100 nm) structures through controlled positional and/or self-assembly of atoms and molecules. Nanoparticles are expected to bring about a revolution for the inhibition of protein and peptide aggregation – a process related to several "misfolding diseases." Proteins are important biological macromolecules that are fundamental to the proper functioning of cells and organisms; therefore, the impact of nanoparticles in living organisms at the protein level is a critical issue that is attracting increasing attention from researchers. Protein and peptide aggregation into characteristic amyloid fibrils is a major cause of various neurodegenerative diseases like Alzheimer's, Parkinson, Creutzfeldt–Jakob disease, and others (Burke *et al.*, 2013). The complete cure of AD may become feasible

by a combination of nanotechnology and some other novel approaches, like stem cell technology.

*Nanodiagnostics for Alzheimer's disease* :

Presently, the prevailing common aim in the AD community is early detection for more timely and effective treatment of the disease. An ideal diagnostic tool for AD must have more than 80 per cent sensitivity and specificity for early diagnosis of AD and ruling out other differential diagnosis. In addition, it must be reliable, reproducible, simple to perform, inexpensive and noninvasive (Sunderland *et al.*, 2006).

*Disease therapy through nanotechnology* :

Presently there exist no therapeutic methods available for curing AD (Mattson, 2004). The cure for AD would require therapeutics that will cease the disease progress and will reverse its resultant damages. Today, common medications for AD are symptomatic and aim at the disrupted neurotransmission between the degenerated neurons. Examples of such medications are acetylcholine esterase inhibitors, including tacrine, donepezil, rivastigmine and galantamine (Masters *et al.*, 2006).

Presently there are the following five molecular mechanistic therapeutic approaches under investigation (*i*). Inhibition of Aβ production; (*ii*). Inhibition of Aβ oligomerization, (*iii*). Anti-inflammation, (*iv*). Cholesterol homeostasis modulating; and (*v*). Metal chelation. The advances in nanotechnology are adding further opportunities for the AD therapy. Generally, the focus of the nanotechnology therapeutic approaches for every disease have been on drug discovery and monitoring (Jain, 2005 ), controlled release of therapeutic agents (Muller-Schultea and Schmitz- Rode, 2006) and targeted drug delivery. The later is the most researched one, and it is especially prerequisite for reaching stronger therapeutic effects with the least amount of side effects. However, the potential capabilities of nanoparticles and nanodevices, including their controllable size and suspend ability (based on modifiability of the nanoparticles outer layer), multi-functionality and remote controlled functionality (McNeil, 2005).

There are many challenges regarding the biocompatibility of nanoparticles and nanodevices especially in a complex biological systems. Nanotechnology can be used as the basis of new tools for early detection of AD. With further research, mechanistic therapeutic approaches could gradually complement the above mentioned approaches. Design of each mechanistic therapeutic is for targeting a different stages of the neurodegenerative diseases pathogenetic process and, therefore, help to cease the progress of the disease.

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