The Role of Misfolded Proteins in Neurodegenerative Diseases

An Essay

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قَالُوا سُبْحَانَكَ
لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
a. صدق الله العظيم
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List of Abbreviations

α	Alpha
β	Beta
γ	Gamma
α-syn	α-synculein
17AAG.....	17-allylamino-17-demethoxy geldanamycin
Aβ.....	Beta-amyloid
AA	Amino acid
ABri	British amyloid peptide
AD	Alzheimer's disease
ADan.....	Danish amyloid peptide
AIF	Apoptosis inducing factor
ALS	Amyotrophic lateral sclerosis
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
AR	Androgen receptor
ATP	Adenosine triphosphatases
BACE.....	Beta secretase
Ca^{+2}	Ionized Calcium
Cdk	Cyclin-dependent protein kinase
CFTR.....	Cystic fibrosis conductance regulator

CIDNP	Chemically induced nuclear polarization
CJD	Creutzfeld-Jackob disease
DMSO.....	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DRPLA.....	Dentatorubral pallidolysian atrophy
ER	Endoplasmic reticulum
ERAD	Endoplasmic-reticulum associated degradation
ERK	Extracellular regulated kinase
FAD	Familial Alzehimer's disease
FBD.....	Familial British Dementia
FDD	Familial Danish Dementia
FFI	Fatal familial insomnia
FTDP-17.....	Frontotemporal dementia with Parkinsonism-17
GPI.....	Glycophosphatidylinositol
GRP	Glucose-regulated protein
GSK	Glycogen synthease kinase
GSS	Gerstmann-straussler-scheinker syndrome
HD.....	Huntington's disease
HDX.....	Hydrogen/deuterium exchange
HIBM.....	Hereditary inclusion body myopathy
HRP	Heat shock responsive protein
HSC 70 …….	Heat shock cognate 70

HSEs	Heat shock elements
HSF1.....	Heat shock transcription factor 1
HSP.....	Heat shock protein
HSR	Heat shock response
Ig	Immunoglobulin
JNK.....	c-jun N-terminal kinase
KDa……..	Kilo Dalton
LAMP.....	Lysosomal associated membrane protein
LDL	Low density lipoprotein
MAP.....	Mitogen activated protein
MAPK	Mitogen-activated protein kinase
MSA.....	Multiple system atrophy
NAC.....	Non A beta component
NFT's.....	Neurofibrillary tangles
NMDA	N-methyl-D-aspartate
NMR.....	Nuclear magnetic resonance
NO.....	Nitric oxide
NSAID	Non-steroidal-anti-inflammatory drugs
PABP2	Poly (A) binding protein 2
PD	Parkinson's disease
PK	Protein kinase-k
PrDs.....	Prion related disorders

PrP^c	Cellular prion protein
PrP^{sc}	Prion protein scrapie
PS	Presenilin
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SBMA	Spinal & bullar muscular atrophy
SCA.....	Spinocerebellar ataxias
sHSPs.....	Small heat shock proteins
SIBM	Sporadic inclusion body myositis
SOD	Superoxide dismutases
UPR	Unfolded protein response
vCJD.....	Variant Creutzfeld-Jackob disease

Introduction

A growing numbers of neurodegenerative diseases are associated nowadays with the expression of misfolded proteins. As known that protein molecules are responsible for almost all biological functions in the cell. In order to fulfill their various biological roles, these chain-like molecules must fold into precise three-dimensional shapes ***(Hartl, 2010).***

The order of the amino acids determines the *primary* structure of the protein by creating a unique polypeptide chain, which is relatively flexible. Protein folding is the process by which the newly synthesized protein molecule folds into its unique, three- dimensional structure as polypeptides can fold into three *secondary* elements: the alpha-helix and the beta-sheet, which determine the three-dimensional structure of the protein, and the random coil. The *tertiary* structure refers to the distribution of the alpha-helices, beta-sheets and random coils in the protein, where in these elements are folded into a compact conformation stabilized by hydrogen bonds or ionic interaction. To become functional, the protein has to be packed into its particular *native* conformation. In the cell, a variety of proteins named chaperones assist the newly synthesized

polypeptide to attain its native conformation ***(Bryngelson et al., 1995; Herczenik and Gebbink, 2008).***

Polypeptides and proteins may undergo misfolding processes resulting in aggregates: oligomers and fibrils possessing toxic properties. Genetic mutations are the main cause for protein misfolding in rare families, but the majority of patients have sporadic forms possibly related to environmental factors that results in the unfolding of the proteins which have a tendency to aggregate. Recent studies suggest that generation of excessive nitric oxide (NO) and reactive oxygen species (ROS), in part due to overactivity of the N-methyl-D-aspartate (NMDA) - subtype of glutamate receptor, can mediate protein misfolding in the absence of genetic predisposition ***(Nelson et al., 2005; Nakamura and Lipton*, 2009*).***

Protein aggregation can result in several neurodegenerative diseases such as: Alzheimer's disease (deposits of amyloid beta and tau), Parkinson's disease (deposits of alpha synculein), Myotonic Dystrophies, Inclusion-Body Myositis and Prion related Disorders (PrDs) which also known as Transmissible spongiform encephalopathies (deposits of prion protein) ***(Matus et al., 2011).***

Recent findings provide new concepts for inhibition of protein aggregation and its proinflammatory and cytotoxic effects. The main approaches fall into the following categories: Small compounds that inhibit aggregation; such as 2,4-dinitrophenol, di- and tri substituted aromatic molecules, Immunotherapy (antibody therapy and vaccination), and Compounds that interfere with amyloid-cell or amyloid-protein interactions ***(Verdier and Penke, 2006; Herczenik and Gebbink, 2008).***

Some recent studies proposed that molecular chaperones are neuroprotective because of their ability to modulate the earliest aberrant protein interactions as they may convert toxic conformations of misfolded proteins to nontoxic forms that can be tolerated by cells, also they prevent the formation of toxic pre-fibrillar intermediates, or accelerate their conversion to nontoxic amorphous aggregates that can be turned over more easily by the proteolytic machinery ***(Muchowski et al., 2002).***

Aim of the Work

To Review:

1- Why and how proteins are misfolded.

2- The role of misfolded proteins in pathogenesis of neuro-degenerative diseases.

3- Recent diagnostic procedures and therapies for neuro-degenerative diseases.

4- Future prospect of neurodegenerative disease' therapy.

For better understanding, diagnosis and therapy of neurodegenerative diseases.

Chapter (1):

Proteins: Structure and Folding Process

Proteins are essential elements for life. They are building blocks of all organisms and the operators of cellular functions. Humans produce a repertoire of at least 30,000 different proteins, each with a different role. The function of a protein can only be interpreted from its structure. The nervous system is a network of cells, and the peculiar functional properties of these cells can be derived from the properties and interactions of their proteins. Proteins are involved in all stages of neural activity. Those embedded wholly or partly in membranes regulate the transport of ions and molecules as a means of signal exchange with other cells and the external medium. Some of them have enzymatic functions to catalyze the chemical processes essential for function ***(Makhatadze and Privalov, 1995; Baldwin, 2007)***.

The structure of proteins

Proteins are molecules composed of an amino acid chain, in which each amino acid is connected to the next one by a peptide bond. Proteins are very diverse and vary in size from small peptides to large multimers. The variation