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Update in neurosciences

Protein folding and misfolding in the neurodegenerative disorders: A review

Le repliement de protéine normal et erroné dans les maladies neurodégénératives : une mise au point

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ABSTRACT

Protein misfolding is an intrinsic aspect of normal folding within the complex cellular environment. Its effects are minimized in living system by the action of a range of protective mechanisms including molecular chaperones and quality control systems. According to the current growing research, protein misfolding is a recognized key feature of most neurodegenerative diseases. Extensive biochemical, neuropathological, and genetic evidence suggest that the cerebral accumulation of amyloid fibrils is the central event in the pathogenesis of neurodegenerative disorders. In the first part of this review we have discussed the general course of action of folding and misfolding of the proteins. Later part of this review gives an outline regarding the role of protein misfolding in the molecular and cellular mechanisms in the pathogenesis of Alzheimer's and Parkinson along with their treatment possibilities. Finally, we have mentioned about the recent findings in neurodegenerative diseases.

RÉSUMÉ

Le repliement de protéine erroné est un aspect intrinsèque du processus normal du repliement de protéine intervenant au sein de l'environnement complexe des cellules. Dans l'organisme vivant, les effets du repliement erroné sont minimisés par l'action de plusieurs mécanismes protecteurs comme les protéines chaperons et les systèmes de contrôle de qualité. Selon les résultats de la recherche récente, le repliement de protéine erroné apparaît comme l'élément clé de la plupart des maladies neurodégénératives. Les abondantes données biochimiques, neuropathologiques et génétiques suggèrent que l'accumulation cérébrale de fibrilles amyloïdes est un événement central dans la pathogénèse des

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maladies neurodégénératives. Dans la première partie de cette mise au point, nous examinons le processus général de repliement et de repliement erroné. La deuxième partie présente un résumé du rôle du repliement erroné dans les mécanismes pathogéniques moléculaires et cellulaires des maladies d'Alzheimer et de Parkinson, ainsi que des possibilités thérapeutiques. Enfin, nous mentionnons les récents résultats avec les maladies neurodégénératives.

1. Introduction

Alzheimer disease (AD) and Parkinson disease (PD) are the most frequent neurological disorders and causes of dementia in elderly people (over 60 years old) [1]. They lead to progressive disability and decreased quality of life and are associated mainly with age-related changes, such as the high production of free oxygen radicals which damage the cell components including the DNA, or a decreased enzymatic activity which lead to accumulation of abnormal proteins in the brain cells [2,3]. Both of these disorders are protein misfolding diseases, which are caused by the presence and accumulation of abnormal proteins, and are associated with cell dysfunctions [4]. Protein folding is an intrinsic feature of normal folding within the complex cellular environment, and its effects are minimized in living systems by the action of a range of protective mechanisms, including molecular chaperons and quality control system of cell (Fig. 1) [5]. Cellular protein quality control relies on three separate yet interrelated strategies whereby misfolded proteins can either be refolded, degraded, or delivered to distinct quality control compartments that sequester potentially harmful misfolded species [6]. In all the tissues, the majority of intracellular proteins are degraded by ubiquitin–proteosome pathway (UPP). The protein degradation by UPP involves two sucessive steps:

- tagging of substrate by covalent attachment of ubiquitin molecules;

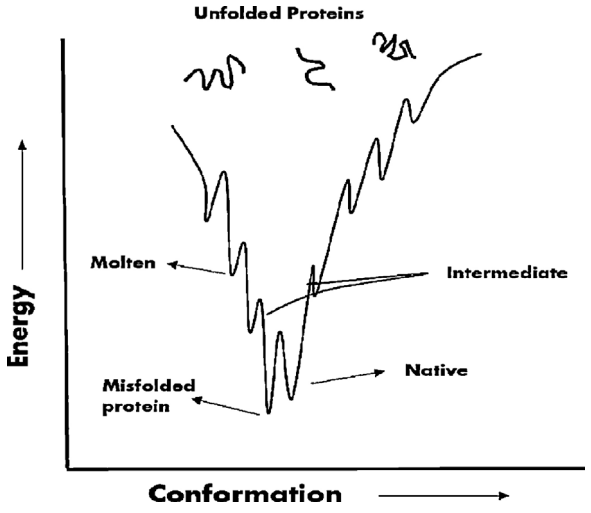

Fig. 1 – Protein folding funnel. The protein folding funnel is based on the concept of minimizing free energy and gives an explanation for how proteins fold in to their native structure.

- degradation of tagged proteins in to small peptide by 26s proteosome complex with release of free and reusable ubiquitin [7,8].

Fig. 2 illustrates about the fate of misfolded proteins toward the pathogenicity of neurodegenerative diseases [9]. Along with the ubiquitin degradation pathway misfolded aggregated proteins can also be degraded by a seprate autophagy pathway that involves an ultimate delivery to the lysosome [10]. Autophagy is a nonspecific bulk degradation pathway that was initially described for long lived cytoplasmic proteins and demanded organelles. Additionally, protein inclusions may enhance the efficiency of aggregate clearance, presumably by facilitating interactions with lysosomal and autophagic pathways [11]. When a protein is unable to fold correctly upon synthesis or misfolds at a later stage in its cellular life time, it can no longer fulfill its biological functions [12]. The folding of most newly synthesized proteins in the cell requires the interaction of a variety of protein co-factors known as molecular chaperones. These are set of proteins that link with unfolded polypeptides thereby preventing aggregation and prolific folding in an ATP-dependent manner [13]. Unfolded and misfolded polypeptides have a tendency to form a variety of aggregate, including the highly ordered and kinetically stable amyloid fibrils. These aggregates signify a generic form of structure resulting from the innate polymer properties of polypeptide chain, and their formation is associated with a wide range of debilitating human diseases [14]. Current knowledge interplay between different forms of protein structure and their generic distinctiveness provides a platform for rational therapeutic intervention designed to prevent and to treat this whole family of diseases [5]. It is well recognized that protein misfolding diseases (PMD's) also known as 'conformational diseases' are caused by the misfolding of proteins into intermolecular β sheet aggregation [15]. Such conformation is stabilized by intermolecular interactions, leads to formation of oligomers, protofibrils and fibrils, which then accumulate as amyloid deposits in affected tissues. Aggregates of prion protein (PrPSc) in prion diseases, amyloid-beta (Aβ) in the Alzheimer's disease (AD), islet amyloid polypeptide (IAPP) in type 2 diabetes (T2D) or serum amyloid A (SAA) in secondary amyloidosis accumulate extracellularly [13,15]. Further, misfolded aggregates that accumulate intracellularly, are alpha-synuclein (α-syn) in Parkinson disease (PD), superoxide dismutase (SOD) in amyotrophic lateral sclerosis (ALS), tau in Tauropathies and huntingtin (Htt) in Huntington disease (HD) [13]. In AD, a small protein fragment called Aβ accumulates initially in the hippocampus, disturbing the complex neural networks of this brain region, resulting in cell death and loss of memory function [16]. They are generated from smaller, less ordered protein clumps called