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Review

The clearance of misfolded proteins in neurodegenerative diseases by zinc metalloproteases: An inorganic perspective

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ABSTRACT

In recent years there has been a wide interest toward zinc metalloproteases involved in neurodegenerative diseases. Enzymes such as matrix metalloproteases, neprilysin, insulin degrading enzyme, etc. play a pivotal role in the homeostasis of peptides and proteins whose accumulation and fibrillation seem to be the major cause for the development of such diseases. It is also well known that chemical factors such as oxidative stress, small molecules and metal ions are able to significantly affect the activity of the above mentioned metalloproteases and therefore, very recently, many research groups have been focused on studying the interaction between those chemical factors and some of the enzymes involved in neurodegenerative diseases. Particularly, metal ions can play various roles (catalytic, structural, allosteric) in enzymes and both the coordination environment as well as the specific metal ion involved, determine the particular function of a metalloprotease.

In this article, chemical factors which modulate the activity of zinc metalloproteases involved in neurodegenerative diseases are examined together with recently proposed therapeutic routes related to them. Moreover, two of the most used experimental techniques applied for studying such modulation are also reviewed.

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1. Introduction

Different neurodegenerative diseases (NDs) show very different symptoms, but a common feature shared by almost all NDs is the alteration of the structure and/or aggregation properties of specific proteins, that lead to their abnormal deposition. Misfolding of these proteins not only results in a loss of their physiological function but also may lead to their intra- or extra- cellular accumulation [1]. Many NDs such as Alzheimer's disease (AD) and Parkinson disease (PD) are considered a widespread plague around the world and their impact on modern society is expected to increase in the near future [2,3]. For this reason, the scientific community, from chemists to doctors, is investing a large amount of time and money in trying to understand the molecular mechanisms involved in NDs and to find possible therapeutic treatments. In this perspective, a well-trodden path in scientific research has been the study of the possible chemical factors which might cause the aggregation of the specific proteins that seem to be the major culprit of NDs. Particular attention has been given to the investigation of all the polymorphic fibril structures of aggregating proteins and the way they considerably vary upon the chemical environment found during the aggregation process [4,5]. Many environmental factors such as small molecules [6], oxidative stress [7,8], metal ions [9,10] and pH [11] seem to largely affect the oligomeric/aggregated forms of the proteins whose aggregation is considered the main cause of NDs.

However, in physiological conditions, each disease related protein has a specific function and its turnover is finely regulated by a perfect balance between production, secretion and clearance [12–15]. An imbalance of this turnover causes a dyshomeostasis of the protein which eventually provokes the onset of the disease. For this reason, the hypothesis according to which the onset of NDs could be due, partially or totally, to a dysfunction of one or more of the many clearance mechanisms of the disease related proteins is attracting a lot of attention [16–19]. Indeed, degradation of proteins involved in NDs occurs through many different routes [20–25] and therefore it is very difficult to define the failure of which molecular mechanism of protein degradation might be responsible for the onset of NDs [26]. Furthermore, specific chemical conditions occurring during protein degradation may produce biologically active catabolites whose function is different from that of the whole protein from which they are generated [20,27,28].

In this scenario, degradation by zinc metalloproteases (ZnMPs) is considered a very important pathway for the maintenance of the homeostasis of proteins majorly involved in NDs [29–32]. However, there are several ways by which ZnMPs activity can be regulated: transcriptional regulation [33]; ex vivo gene delivery [34]; cleavage of prodomain [35]; allosteric modulation [36–38]; compartmentalization [39]; complex formation [40]; oxidative stress [41–43]; interaction with cations [44–47] and anions [48]. All these different modulation mechanisms of ZnMPs activity may occur simultaneously *in vivo* and this contributes to make the comprehension of the molecular mechanisms at the base of NDs a very challenging task.

MPs comprise about 34% of all proteases and, besides being implicated in NDs, are involved in several different processes as diverse as embryonic development, reproduction, cancer, bone formation, etc. ZnMPs are a large part of the MPs and have been classified into distinct families on the basis of sequence of the zinc binding site and/or of structural similarities. There are at least four families of identified ZnMPs: zincins, inverzincin, carboxypeptidase and DD-carboxypeptidase [49]. Although the presence of coordinated Zn^{2+} is a common feature of all the ZnMPs, the sequence motifs involved in coordinating this metal ion are different in each of the above listed families. Therefore, even if all proteases universally seem to recognize beta-strands in their active sites [50], differences in the structure of ZnMPs make each enzyme specialized in a specific function. Moreover, the variability of the Zn coordination site, as well as of the overall enzyme structure, makes the various ZnMPs susceptible to a plethora of modulatory mechanisms by various chemical factors. Particularly, in this review we will focus on the ZnMPs involved with the most common and widespread NDs, summarizing and discussing the chemical factors (small molecules, oxidative stress and metal ions) that modulate their enzyme activity.

2. Brief overview of neurodegenerative diseases

It is possible to group different pathologies under the same name of NDs as they show the common feature of progressive loss of structure or function of neurons and many similarities on a subcellular level that relate these diseases to one another. There are many analogies between different NDs but atypical protein assemblies as well as induced cell death seem to be the two mostly shared features. For this reason, most NDs are considered protein aggregation diseases and, in the following subsections, a brief overview of three widespread NDs will be given (AD, PD and prion diseases).

2.1. Alzheimer's disease

The two main histopathological observables for AD are the extracellular deposits of fibrillar Aβ peptides and the intraneuronal fibrillar tangles consisting of twisted strands of hyperphosphorylated tau protein [51]. Tau is a highly soluble microtubule-associated protein which is principally found in neurons rather than non-neuronal cells. One of tau's main functions is to modulate the stability of axonal microtubules and its increased insolubility and impaired clearance due to hyperphosphorylation causes damage much before the filamentous aggregates develop [52]. Indeed, even an altered subcellular localization of the tau protein results in its interaction with other cellular proteins with which it would otherwise either not interact or to a less extent, thereby impairing their physiological functions [53]. Therefore, as aberrant tau phosphorylation is acknowledged to be a key disease process that influences tau structure, distribution and function in neurons, therapeutic strategies aimed at targeting tau phosphorylation have been recently proposed [54]. Particularly, rational approaches targeting neurofibrillary degeneration include inhibition of one or more tau protein kinases, activation of tau phosphatases, elevation of beta-N-acetylglucosamine modification of tau through inhibition of beta-N-acetylglucosaminidase or increase in brain glucose uptake, and promotion of the clearance of the abnormally hyperphosphorylated tau via autophagy or ubiquitin proteasome system [55].

Deposited fibrillar Aβ peptides are often referred to as senile plaques and, although they have been considered a hallmark of AD, it is now well known that about 20–40% of unaffected elderly individuals also possess them, as revealed by post-mortem diagnosis [56]. For this reason, it would be misleading to assert that these are the only significant pathological changes occurring in the AD brain besides deposition of hyperphosphorylated tau. Indeed, numerous other structural and functional alterations such as inflammatory responses and oxidative stress also occur [57]. Moreover, although Aβ peptide was first identified as a component of extracellular amyloid plaques in the mid-1980s, nowadays the existence of intracellular Aβ has also been ascertained [58]. Despite the lack of knowledge regarding the precise cause of Aβ dyshomeostasis and the experimental efforts aimed to study a peptide so difficult to be handled and analyzed [59,60], Aβ peptide is universally considered to play a pivotal role in AD [61]. For this reason, many studies have been trying to identify the biomolecular mechanisms