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Review

Molecular chaperones and neuronal proteostasis

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ABSTRACT

Protein homeostasis (proteostasis) is essential for maintaining the functionality of the proteome. The disruption of proteostasis, due to genetic mutations or an age-related decline, leads to aberrantly folded proteins that typically lose their function. The accumulation of misfolded and aggregated protein is also cytotoxic and has been implicated in the pathogenesis of neurodegenerative diseases. Neurons have developed an intrinsic protein quality control network, of which molecular chaperones are an essential component. Molecular chaperones function to promote efficient folding and target misfolded proteins for refolding or degradation. Increasing molecular chaperone expression can suppress protein aggregation and toxicity in numerous models of neurodegenerative disease; therefore, molecular chaperones are considered exciting therapeutic targets. Furthermore, mutations in several chaperones cause inherited neurodegenerative diseases. In this review, we focus on the importance of molecular chaperones in neurodegenerative diseases, and discuss the advances in understanding their protective mechanisms.

Contents

Abbreviations: 17-AAG, 17-allylamino-17-demethoxygeldanamycin; 17-DMAG, 17-dimethylamino-ethylamino-17-demethoxygeldanamycin; Aβ, amyloid beta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; α-syn, α-synuclein; CMT2, Charcot–Marie–Tooth type 2; dHMN, distal hereditary motor neuropathies; DRP1, dynamin-related protein 1; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; GF, glycine-phenylalanine; HD, Huntington's disease; HPD, histidine–proline–aspartate; Hsps, heat shock proteins; Htt, huntingtin; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NBD, nucleotide binding domain; NEFs, nucleotide exchange factors; PD, Parkinson's disease; polyQ, polyglutamine; p-tau, hyperphosphorylated tau; Rho, rhodopsin; RP, retinitis pigmentosa; SBD, substrate binding domain; SOD1, Cu/Zn superoxide dismutase 1; TDP-43, transactive response DNA binding protein 43 kDa; UIMs, ubiquitin interacting motifs.

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1. Introduction

Proteins must fold to their native state in order to achieve functionality. However, in the crowded cellular environment, and under environmental and physiological stress conditions such as heat, oxidative stress and inflammation, proteins are susceptible to the formation of non-native interactions that can lead to protein misfolding and aggregation. The accumulation of misfolded and aggregated protein is considered toxic to the cell and is implicated in numerous diseases such as type 2 diabetes, cardiovascular disease and neurodegenerative diseases. Cells have therefore developed an intrinsic network of protein quality control machinery that functions to balance protein folding, misfolding, aggregation and degradation, thereby maintaining protein homeostasis (proteostasis) and the functionality of the proteome. The protein quality control machinery includes molecular chaperones, which act as the first line of defence and participate in the refolding or, alternatively, the degradation of misfolded proteins. Their role in maintaining proteostasis in neurons, which are post-mitotic cells that are particularly vulnerable to protein aggregation, is the subject of this review.

2. Molecular chaperones

Molecular chaperones are defined as proteins that interact with, stabilize or assist another protein to gain its native and functionally active conformation, without being present in the final structure [1]. Members of the molecular chaperone family are often referred to as heat-shock proteins (Hsps) due to their upregulation under stress conditions that typically destabilize proteins, such as elevated temperature and oxidative stress. Molecular chaperones are often classified according to their molecular weight and members include Hsp90, Hsp70, Hsp60, Hsp40 (DnaJ) and the small Hsps. Molecular chaperones display large functional diversity and in addition to their fundamental roles in *de novo* folding, and the refolding of misfolded protein, chaperones also regulate critical cellular processes such as protein trafficking, protein degradation and macromolecular complex assembly [2].

2.1. Hsp90 (HSPC) family

Hsp90 is an ATP-dependent chaperone that functions in the activation and stabilization of client proteins; including protein kinases, cell cycle regulators, cell surface receptors and transcription factors. Therefore, Hsp90 plays a critical role in cellular processes including signal transduction, cell cycle progression, apoptosis and protein degradation [3]. The activation of Hsp90 clients is driven by a cycle of substrate binding and release mediated by a series of conformational changes in the chaperone and an ATP-induced transition between an open and a closed conformation. Hsp90 exists as a homodimer, with each subunit consisting of three domains; an N-terminal ATP-binding domain (N-domain), a middle domain that binds the substrate (M-domain) and a C-terminal dimerization domain (C-domain). In the absence of nucleotide Hsp90 adopts a V-shaped open conformation. The binding of ATP to the N-domain induces a conformational change that closes a lid over the nucleotide binding pocket. Following lid closure, the N-domains dimerise, forming a compact structure with a closed conformation. The formation of the closed dimer induces ATP hydrolysis, subsequently promoting the N-domains to dissociate and the return of Hsp90 to the open conformation, with the release of the substrate [4].

The reaction cycle of Hsp90 is regulated by various co-chaperones. The co-chaperones exhibit specific binding preferences for different Hsp90 conformations and affect different stages of the cycle, such as client binding and ATP hydrolysis. Co-chaperones therefore usually co-operate in a sequential cycle to facilitate the maturation of Hsp90 clients.

2.2. Hsp70 (HSPA) family

Hsp70 functions in a wide array of cellular processes including the folding of newly synthesized protein, the refolding of misfolded and aggregated protein, transport of proteins across membranes, and protein degradation [3]. These functions rely on the ability of Hsp70 to interact with hydrophobic stretches exposed in client proteins and subsequently undergo an ATP-dependent cycle of substrate binding and release. Hsp70 is composed of a N-terminal ATPase domain (NBD) and a C-terminal substrate binding domain (SBD), divided into subdomains that form a hydrophobic binding pocket and a lid [2]. The NBD and SBD are connected by a flexible linker that enables the NBD to allosterically control the conformation of the SBD. In the ATP-bound state the binding pocket and lid are in an open conformation. The SBD has a low substrate affinity and fast substrate exchange rates. The hydrolysis of ATP to ADP drives the SBD into a high affinity state for substrate binding through the closing of the lid, enabling stable binding of the client protein. The release of ADP and the rebinding of ATP triggers the opening of the lid and the subsequent unloading of the bound substrate.

The Hsp70 reaction cycle contains two rate limiting steps, ATP hydrolysis, due to low basal ATPase activity, and ADP dissociation, due to the high levels of cytoplasmic ATP under physiological conditions. Therefore, Hsp70 requires the action of co-chaperones to facilitate the reaction cycle between ATP and ADP bound states. The ATPase activity of Hsp70 is stimulated by members of the DnaJ (Hsp40) family via their conserved J domain [5]. The dissociation of ADP requires the opening of the nucleotide binding cleft, a process catalyzed by a range of nucleotide exchange factors (NEFs), including the Hsp70-like Hsp110 proteins, HspBP1, SIL1 and BAG family [6].

2.3. DnaJ (Hsp40) family

As mentioned above, members of the DnaJ family (also referred to as Hsp40) are important regulators of Hsp70 activity by stimulating ATP hydrolysis. All DnaJ proteins contain a J domain, a conserved region of 70 amino acids that folds into four α-helices. Helix II and helix III form an antiparallel two-helix bundle, with a loop connecting the two helices containing a histidine–proline–aspartate (HPD) motif. The HPD motif is critical for lowering the activation energy of ATP hydrolysis [7].

The human genome encodes 49 DnaJ proteins, which can be divided into three classes according to their domain composition [8]. Class I (DNAJA) proteins share all domains present in the *Escherichia coli* DnaJ protein, with an N-terminal J domain, a glycine-phenylalanine (GF) rich region, a zinc binding domain and a C-terminal domain. Class II (DNAJB) proteins contain an N-terminal J domain and a GF rich region, whereas class III (DNAJC) proteins share only the J domain. The diversification of domains outside the

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