Progress in Neurobiology 92 (2010) 184–211

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Heat shock proteins: Cellular and molecular mechanisms in the central nervous system

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ARTICLE INFO

Article history:
Received 9 March 2010
Received in revised form 23 May 2010
Accepted 27 May 2010

Keywords:
Heat shock protein
Synaptic transmission
Protein degradation
Cell death
Cerebral ischemia
Parkinson's disease
Huntington's disease
Alzheimer's disease
Prion
Charcot–Marie–Tooth

ABSTRACT

Emerging evidence indicates that heat shock proteins (HSPs) are critical regulators in normal neural physiological function as well as in cell stress responses. The functions of HSPs represent an enormous and diverse range of cellular activities, far beyond the originally identified roles in protein folding and chaperoning. HSPs are now understood to be involved in processes such as synaptic transmission, autophagy, ER stress response, protein kinase and cell death signaling. In addition, manipulation of HSPs has robust effects on the fate of cells in neurological injury and disease states. The ongoing exploration of multiple HSP superfamilies has underscored the pluripotent nature of HSPs in the cellular context, and has demanded the recent revamping of the nomenclature referring to these families to reflect a re-organization based on structure and function. In keeping with this re-organization, we first discuss the HSP superfamilies in terms of protein structure, regulation, expression and distribution in the brain. We then explore major cellular functions of HSPs that are relevant to neural physiological states, and from there we discuss known and proposed HSP impacts on major neurological disease states. This review article presents a three-part discussion on the array of HSP families relevant to neuronal tissue, their cellular functions, and the exploration of therapeutic targets of these proteins in the context of neurological diseases.

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Abbreviations: AChR, acetylcholine receptor; AD, Alzheimer's disease; AIF, apoptosis-inducing factor; APP, amyloid precursor protein; ARE, AU-rich elements; CHIP, C-terminal HSP-interacting protein; CMA, chaperone-mediated autophagy; CMT, Charcot–Marie–Tooth; dHMN, distal hereditary motor neuropathy; ERAD, endoplasmic reticulum-associated degradation; GA, geldanamycin; G/F, glycine/phenylalanine; HD, Huntington's disease; Hip, heat shock factor interacting protein; Hop, heat shock factor organizing protein; HSE, heat shock element; HSF, heat shock factor; HSP, heat shock protein; HSR, heat shock response; KA, kainic acid; LAMP2A, lysosome-associated membrane protein 2; MCAO, middle cerebral artery occlusion; mtUPR, mitochondrial unfolded protein response; NEF, nucleotide exchange factor; NMJ, neuromuscular junction; PD, Parkinson's disease; PERK, PKR-like ER kinase; polyQ, polyglutamine; PP5, protein phosphatase 5; PPD, polypeptide domain; PS1, presenilin-1; ROS, reactive oxygen species; SCA, spinocerebellar ataxia; SNARE, soluble NSF attachment protein receptors; TIM, translocase of inner membrane; TOM, translocase of outer membrane; TPR, tetratricopeptide repeats; TSE, transmissible spongiform encephalopathies; UPR, unfolded protein response.

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0301-0082/$ – see front matter. Published by Elsevier Ltd.
doi:10.1016/j.pneurobio.2010.05.002

1. Introduction

Critical functions and neuroprotective properties of heat shock proteins (HSPs) in the brain have been explored for several decades, yet studies of the precise mechanistic control and function of HSPs continue to yield new surprises. Moreover, the HSP superfamily of proteins includes a multitude of subgroups and closely related members. The emerging literature related to HSP functions in protein management and cell death, in particular within the neuronal context, creates a focal point for reviewing the newfound roles of HSPs in the central nervous system.

In this review, we will (1) strive to apply current nomenclature to a review of previously published literature, (2) highlight important recent advances in the regulation of HSP function, (3) illustrate relevant physiological roles of HSPs in the context of the brain, and (4) describe the alteration of HSP function by neuropathological conditions, and thus explore the therapeutic potential of HSPs in the context of neuropathology.

1.1. Nomenclature

The overall understanding of heat shock proteins in terms of gene organization, phylogenic branching of protein families and regulation has expanded dramatically in the past several years. While multiple review articles underscore the relevance of HSPs in neurological stress conditions, the rapid growth in knowledge of specific chaperone subtypes creates a need for continued review of new data and incorporation of changes in terminology.

The original discovery that heat-inducible (and constitutive) chaperone proteins function in the folding of proteins to correct native structures was an exciting leap in the understanding of protein–protein interactions. However, the molecular tools available at the time precluded a detailed analysis of full gene sequences, specific function and/or regulation, or the development of antibodies able to differentiate between highly homologous members. In the ensuing 40 years of research devoted to HSPs, more than 80 chaperones grouped into several distinctive functional families have been discovered. Many of these family members were not previously dissociated from each other; thus, the literature dating within even recent years can be somewhat nebulous in terms of the specific family members.

In the present review, we will attempt to bring up to date advances in the regulation and function of HSPs in the neuronal context, and we will try to evaluate the roles of specific family members in light of experimental findings (Table 1). In order to minimize confusion, we will adhere to the recently proposed

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