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Review

The virus-induced HSPs regulate the apoptosis of operatus APCs that results in autoimmunity, not in homeostasis

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ABSTRACT

The viruses are salient in the roles of environmental factors that trigger autoimmunity. The virus realizes its effects by the power of its induction of heat shock proteins (HSPs) as well as by the viral IE-axis-mediated conversion of organ epithelial cells into virgin de novo professional antigen-presenting cells (APCs). The HSP is the accomplished operator in homeostasis by the logic of it being the regulator of apoptosis. That HSP which regulates and controls different points in the pathways of apoptosis is rationally propitious as both HSP and apoptosis are highly conserved in multicellular organisms. By virtue of its regulation of apoptosis, the HSP is also involved in human autoimmunity and this involvement is tripartite: (i) adornment of viral IE-axis-generated virgin de novo professional APCs with HSP-induced co-stimulatory molecules which transform these otherwise epithelial cells to achieve the status of fledged competent antigen-presenters, the operatus APCs, which are liable to apoptosis that becomes the initiator of organ damages that can culminate in the autoimmune syndrome(s); apoptosis is a routine fate that befalls all APCs following their antigen presentation; (ii) molecular mimicry mechanism: epitopes on the HSP may be mistaken for viral peptides and be presented by operatus APCs to autoreactive TCRs resulting in the apoptosis of the operatus APCs; and (iii) regulation of MHC class II-DR-mediated apoptosis of operatus APCs which can ultimately consequent in organ-specific autoimmune syndromes. We should remember, however, that Nature's intended purpose for the apoptosis of the professional APCs is benevolence: as a principal regulator of homeostasis. It is only from the apoptosis of our postulated operatus APCs that the apoptotic consequence can be deleterious, an autoimmune syndrome(s). The transformation of virgin de novo professional APCs to operatus APCs mirrors the maturation of DCs, through their acquisition of HSP-induced co-stimulatory molecules; and what happens to mature DCs as antigen-presenters that ends in homeostasis is replicated by what happens to operatus APCs that ends instead in autoimmune syndromes (Fig. 1).

Contents

1. Introduction

An autoimmune disease (AD) (exemplified by type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis,

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etc.) is a state of health which results from an aberrant immune response in which an individual's protective immune system (B- and T-cells) that is normally designed and geared to recognize and destroy invading foreign bodies such as infectious agents (viruses, bacteria and other forms of pathogens) instead fails to distinguish self-antigens and proceeds to attack and destroy the host's body cells, tissues and organs. All autoimmune diseases are genetically founded. However, individuals may be properly genetically primed but it still requires the intervention of environmental factors, particularly the viruses, to trigger the onset of these diseases [1–11]. The virus realizes its effects through the power of its induction of HSPs as well as by the viral IE-axis-mediated conversion of organ epithelial cells into competent antigen-presenters that would suffer apoptosis on antigen-presentation. Accumulative apoptosis can lead to organ damage resulting in autoimmune syndromes.

1.1. Heat shock proteins (HSPs)

The heat shock proteins form an evolutionarily well preserved family of regulatory proteins that act as molecular chaperones which refold misfolded proteins, assist in the elimination of irreversibly damaged proteins, and maintain the cell cycle, cellular proliferation and cytoprotection to rescue cells from apoptosis [12–14]. These protein molecules are characterized according to their sizes into five major classes of families: HSP70, HSP27, HSP60, HSP90, and HSP100 (Table 1) [15,16]. HSPs can be normally produced constitutively, but their synthesis, regulated at the transcriptional level by the heat shock factor-1 (HSF-1) is rapidly up-regulated in response to various stressors: elevated temperature, glucose deprivation, microbial (e.g. virus) infection and cancer [15,17]. The regulatory role of HSPs depends on their ability to interact with proteins or polypeptide substrates [18]. The regulation is controlled by a reaction cycle of ATP binding, hydrolysis and nucleotide exchange to mediate a series of rapid association–dissociation cycles between the HSP protein and its target polypeptides [19]. Another characteristic of the HSPs is that they tend to oligomerize (a non-covalent combination), form chaperone complexes with each other and act in conjunction with co-chaperones which are smaller chaperone protein molecules [BAG-1, CHIP (c-terminal HSP90 interacting protein), HSP40, Hip (HSc70 interacting protein), Hop (HSP70–HSP90 organizing protein) and p23 (a 23-kDa co-chaperone of HSP90)] [20,21]. These co-chaperones catalyze the interconversion between the ATP and ADP states.

One of the most important functions of the HSPs is the regulation of apoptosis. HSPs mediate the inhibition of apoptosis through inhibition of caspase activation. They can inhibit the activity of pro-apoptotic Bcl-2 family proteins to prevent permeabilization of the outer mitochondrial membrane and release of apoptogenic factors into the cytosol. HSP70 has been reported to block apoptosis by binding apoptosis protease activating factor-1 (Apaf-1) thereby preventing constitution of the apoptosome (the Apaf-1/cytochrome C/caspase-9 activation complex) [22–24]. Such disruption of apoptosome formation represents a mechanism by which HSPs can prevent caspase activation and induction of apoptosis. Several signaling cascades involved in the regulation of key elements within the apoptotic cascade are also subject to modulation by HSPs, including those involving JNK, NF-kB and AKT [15]. It has also been observed that HSPs might also modify apoptotic signaling down-stream of mitochondria [25]. Thus they have been seen to inhibit apoptosis by interfering with AIF which is a caspase-independent death effector that, like cytochrome C, is released from mitochondria early in the apoptotic process [22]. Finally, it is pertinent to inject at this juncture the peculiarity of HSPs: they are pleiotropic and display a dichotomy of functional facets, witnessed by the documentation that the pro-apoptotic role in normal state gets balanced and usually overcome by the HSP-induced cytoprotection [26,27].

The HSPs play a role in the induction of autoimmunity. They are highly conserved among diverse groups of microbial agents and mammals, exhibited by the observation of conserved amino acid sequence between human and microbial HSPs [28,29]. Owing to this conserved nature, mammalian HSPs may become targets of immune response and the T cells primed against microbial HSPs may be autoreactive and recognize epitopes on the human HSPs [29]. This is molecular mimicry which becomes amplified by the enhanced expression of HSPs under stress resulting in the unmasking of previously hidden antigenic determinants that can initiate and perpetuate autoimmune reactivity. Experimental and clinical observations have confirmed that HSPs are involved in the regulation of some autoimmune diseases (autoimmune arthritis, type 1 diabetes, atherosclerosis and multiple sclerosis) [28,30–34]. Finally, the HSP chaperone-polypeptide complexes have been shown to be highly immunogenic [35].

Table 1
Major heat shock proteins.
Adopted from Sreedhar AS and Csermely P [12].

HSP	Co-chaperones or isoforms	Expression	Localization
HSP27	Various isoforms	Constitutive/inducible	Cytoplasm/nucleus
HSP60	HSP60/HSP10-cyt	Constitutive/inducible	Cytoplasm
	HSP60/HSP10-mito	Constitutive	Mitochondria
HSP70	HSP70	Constitutive/inducible	Cytoplasm/nucleus
	HSP70.1	Constitutive/inducible	Cytoplasm
	HSP70.2	Constitutive	Cytoplasm
	HSP.3	Constitutive	Cytoplasm
	HSP70	Constitutive/inducible	Mitochondria
	Grp75	Constitutive	ER/cytoplasm
	Grp78	Constitutive/inducible	ER/cytoplasm
	HSP105	Constitutive	Cytoplasm/nucleus
HSP90	HSP90-alpha	Constitutive/inducible	Cytoplasm/nucleus
	HSP90-beta	Constitutive/inducible	Cytoplasm/nucleus
	HSP90-N	Constitutive/inducible	Cytoplasm/nucleus
	HSP75/TRAP-1	Constitutive/inducible	Mitochondria

1.2. The antigen-presenting cells (APCs)

The APCs are specialized white blood cells that are in the fore-front to fight off foreign substances (e.g. bacteria and viruses) that gain entrance to the body. There are two types of APCs: the professional APCs (B cells, macrophages and dendritic cells (DCs)) express MHC class II molecules; and the non-professional APCs (epithelial and all other cell types) express MHC class I molecules on their surfaces. For relevance with our intended exposé, our review will limit coverage to the professional APCs, in particular, to the DCs which are key components of innate and adaptive immune responses. Following a foreign pathogen invasion of the body, the DC engulfs the antigen, the enzymes inside the APC break down the antigen into smaller particles (peptides). These processed peptides enter a vesicle containing the MHC class II molecules that combine with the peptides to form complexes which are then transported to the surface of the APC. The complex forms epitopes which the CD4+ T-cell receptor (TCR) recognizes and binds to. Once the TCR binds to the MHCII:peptide complex, the APC sends out an additional co-stimulatory signal to activate the CD4+ T-cell which then performs immune protection function.

For the APCs to take part in immune regulation they must first be activated. The HSPs constitute the internal endogenous signals that activate the DCs [36]. They stimulate the macrophages to secrete cytokines which induce up-regulated expression of antigen-presenting and co-stimulatory molecules on the immature DCs as the maturation process of these APCs [37]. The co-stimulatory molecules include members of the B7 family, the TNF family and the intracellular adhesion molecules which are critical to the activation of the T cells. CD91 receptor is pivotal in regulating HSP-mediated co-stimulation; HSPs utilize CD91 to transmit signals to APCs [38]. The stimulation of co-stimulatory molecules proceeds through the NF-kB signaling pathway.