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Serial Review: Redox Signaling in Immune Function and Cellular Responses in Lung Injury and Diseases
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Heat shock response and acute lung injury ☆

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Abstract

All cells respond to stress through the activation of primitive, evolutionarily conserved genetic programs that maintain homeostasis and assure cell survival. Stress adaptation, which is known in the literature by a myriad of terms, including tolerance, desensitization, conditioning, and reprogramming, is a common paradigm found throughout nature, in which a primary exposure of a cell or organism to a stressful stimulus (e.g., heat) results in an adaptive response by which a second exposure to the same stimulus produces a minimal response. More interesting is the phenomenon of cross-tolerance, by which a primary exposure to a stressful stimulus results in an adaptive response whereby the cell or organism is resistant to a subsequent stress that is different from the initial stress (i.e., exposure to heat stress leading to resistance to oxidant stress). The heat shock response is one of the more commonly described examples of stress adaptation and is characterized by the rapid expression of a unique group of proteins collectively known as *heat shock proteins* (also commonly referred to as *stress proteins*). The expression of heat shock proteins is well described in both whole lungs and in specific lung cells from a variety of species and in response to a variety of stressors. More importantly, in vitro data, as well as data from various animal models of acute lung injury, demonstrate that heat shock proteins, especially Hsp27, Hsp32, Hsp60, and Hsp70 have an important cytoprotective role during lung inflammation and injury.

Contents

Abbreviations: CLP, cecal ligation and puncture; ER, endoplasmic reticulum; HO, heme oxygenase; HSFs, heat shock factors; Hsp, heat shock protein; IKK, IκB kinase; IL, interleukin; I/R, ischemia–reperfusion; MAPK, mitogen-activated protein kinase; MKP-1, mitogen-activated protein kinase phosphatase-1; TLR, Toll-like receptor; TNF, tumor necrosis factor.

☆ This article is part of a series of reviews on "Redox signaling in immune function and cellular responses in lung injury and diseases". The full list of papers may be found on the home page of the journal.

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That which drug fails to cure, the scalpel can cure. That which the scalpel fails to cure, heat can cure. If the heat cannot cure, it must be determined to be incurable.

Hippocrates

Introduction

Ferruccio Ritossa unintentionally observed a novel hyperthermia-dependent puffing pattern in the giant chromosomes from the salivary glands of *Drosophila melanogaster* in 1962 [1]. By chance occurrence, a colleague accidentally increased the temperature of one of the incubators in which he kept his specimens and the following morning Ritossa discovered a new puffing pattern that had not been there on the previous day. Realizing the mistake, Ritossa conducted additional, properly controlled experiments, and subsequently linked this new chromosomal puffing pattern with the expression of a specific group of proteins that he fittingly called *heat shock proteins* [1,2]. Notably, the editors of one of the more reputable scientific journals at the time rejected his manuscript, describing the findings as irrelevant and unimportant. Fortunately, investigations into this new area continued and since that time, there has been growing interest in what is now commonly referred to as the *heat shock response*. Fig. 1.

The heat shock response is characterized by the rapid expression of a unique set of proteins collectively known as *heat shock proteins* [3–5]. These highly conserved proteins have been identified in virtually all eukaryotic and prokaryotic species examined to date. While classically described as a response to thermal stress (hence the term *heat shock response*) [1,6], heat shock proteins can be induced by a wide variety of nonthermal stressors and pharmacological agents (Table 1). For this reason, the terms *stress response* and *stress proteins* may be more appropriate, though these terms will be used interchangeably throughout the remainder of the present discussion. Whether induced by thermal or nonthermal stress, the stress response confers protection against subsequent and otherwise lethal hyperthermia, a phenomenon that is referred to as *thermotolerance* [6,7]. Perhaps more interesting from a clinical standpoint is the phenomenon of cross-tolerance, whereby induction of the stress response confers protection against nonthermal cytotoxic stimuli. For example, in vitro experiments have demonstrated that induction of the stress response protects endothelial cells against endotoxin-mediated apoptosis [8]. Other examples include stress response-dependent protection against nitric oxide [9], peroxynitrite [10], and hydrogen peroxide [11]. In vivo, induction of the stress response protects animals against endotoxemia/sepsis [12,13], acute lung injury [14,15], and ischemia–reperfusion (I/R) injury [15].

The structure, mode of regulation, and function of stress proteins are highly conserved among different species, with well-described bacterial homologs of mammalian stress

Table 1
Inducers of the stress response

Type of stress	Agent	Comments
Environmental	Temperature	
	Heavy metals	Cadmium, zinc
	Ethanol	
	Oxygen radicals	
Metabolic	Hyperosmolality	
	Glucose starvation	
	Tunicamycin	
	Calcium ionophores	
	Amino acid analogs	
Clinical	Ischemia/reperfusion	Reperfusion seems to be the limiting factor
	Shock	
	Anoxia	
	Endotoxin	
Pharmacologic	Sodium arsenite	Used extensively in vitro and in vivo
	Herbimycin A	Tyrosine kinase inhibitor
	Geldanamycin	Tyrosine kinase inhibitor and HSP90 inhibitor
	Prostaglandin A1	Other prostaglandins are also active
	Dexamethasone	
	Aspirin	Lowers temperature threshold for HSP induction
	Nonsteroidal anti-inflammatory drugs	Lowers temperature threshold for HSP induction
	Pyrrolidine dithiocarbamate	Antioxidant; inhibitor of NFκB
	Diethyldithiocarbamate	
	Bimoclomol	Hydroxylamine derivative, nontoxic
	Serine protease inhibitors	Concomitant inhibition of NF-κB
	Curcumin	Major constituent of tumeric; anti-inflammatory
	Glutamine	Clinically applicable amino acid
	Geranylgeranylacetone	Antiulcerative agent

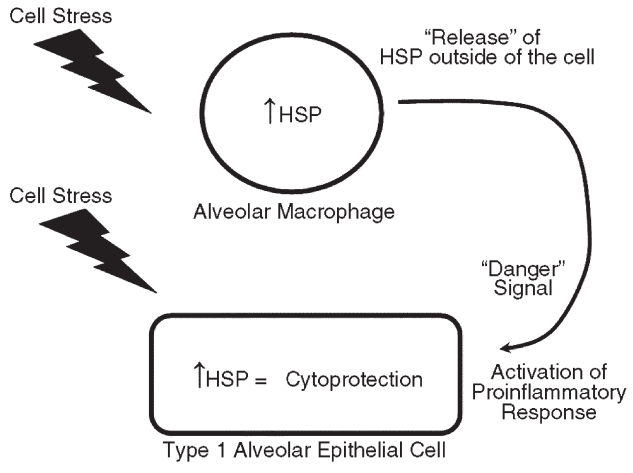

Fig. 1. Potential roles of heat shock proteins (HSP) in acute lung injury. The expression of heat shock proteins in both alveolar macrophages and airway and alveolar epithelial cells is upregulated in response to a myriad of cell stressors, including LPS, free radicals, thermal stress, and hypoxia. Increased expression of heat shock proteins results in a cytoprotective response in these cell types. Release of heat shock proteins (by an as yet unidentified mechanism) may serve as a "danger signal" to activate the inflammatory response in surrounding cells.