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Cellular stress response and pulmonary inflammation

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Abstract

Innate immunity as the first line of the immune system, provides initial protection against various pathogens and infections. Recent studies suggest a link between cell stress response and immune response upon exogenous insults in the lung. The key proteins in cellular stress responses were demonstrated to be involved in the activation and regulation of the immune signaling pathways. Further research on the function of these stress proteins in innate immunity defenses, particularly in pulmonary diseases and inflammation may help to clarify the disease pathogenesis and provide potential therapeutic treatments for various infectious and inflammatory lung diseases.

Keywords: Innate immune response; Immune signaling; Oxidative stress; ER stress; Heat shock

1. Introduction

The human immune system consists of the innate immune system and the adaptive system. Innate immunity serves as the first line of the immune system which provides initial protection against various pathogens and infections. Innate immune responses are mediated by pattern-recognition receptors (PRRs) that recognize molecular structures that are broadly shared by pathogens, known as pathogen-associated molecular patterns (PAMPs), resulting in expression of microbicidal effectors and inflammatory mediators against the pathogens [1,2]. Epithelia of the human body form interfaces between the internal milieu and the external environment. In the respiratory tract, the epithelium acts as a mechanical barrier to prevent infections and pollutants, and participates in the critical innate immune response through secreting immune effectors such as mucin, antimicrobial peptides and reactive oxygen species (ROS) to attack invading microbes. Airway epithelial cells can also act as mediators connecting innate and adaptive immunity by producing various cytokines and chemokines [3,4].

The altered airway environment resulting from infection and inflammation can have a great impact over pulmonary cells. Stressed cells may respond in a variety of ways called cellular stress response, such as heat shock response, unfolded protein response, and oxidative stress. The response helps a cell to defend against and recover from insults. For example, heat shock response or the unfolded protein response mediates an increase in chaperone protein activity which enhances the protein folding capacity of cells to counteract stress and maintain cell survival [5]. However, if the stimulus is too strong and cells are unable to cope up, then cell death signaling pathways may be activated to cause tissue injury and diseases.

Recent studies suggest a link between cell stress response and immune activation [4]. The key proteins in cellular stress responses were shown to interact with signaling intermediates involved in the activation of innate immune responses. The effect of such regulation may influence the inflammatory response of the immune system during infection and disease. The goal of this review is to describe pulmonary cellular stress response and its relationship with the immune system.

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2. Innate immune system in airway

Cells of the innate immune system, including phagocytes, dendritic cells and epithelial cells can express microbial PRRs like Toll like receptors (TLRs), nod-like receptor (NLRs), and RIG-I-like receptors (RLRs) which can recognize PAMPs of bacterial and viral pathogens [6]. Common airway pathogens such as virus (e.g. influenza viruses, rhinovirus, and respiratory syncytial virus) and bacteria (e.g. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, and *Klebsiella pneumonia*) are detected through the presence of PAMPs on epithelial cell surface [7].

The main receptors of pulmonary cells are TLRs and RLRs. Respiratory epithelia express various kinds of TLRs at the cell surface and endosomes. TLRs have extracellular ligand-binding domains consisting of 19–25 contiguous copies of a motif called leucine-rich repeats (LRRs) and a conserved stretch of 200 amino acids in their cytoplasmic region called toll/interleukin-1 receptor homology (TIR)domains, that mediates recruitment of signaling components [6,8]. To date, 10 and 12 functional TLRs have been identified in human and mouse, respectively. Each TLR recognizes a unique kind of molecular pattern, including peptidoglycans, bacterial lipopolysaccharide (LPS), lipoteichoic acid, lipoproteins, lipopeptides, fungal zymosan, bacterial flagellin, single- or double-stranded RNA, and CpG DNA [9].

TLR signaling can be divided into two distinct intracellular pathways: the MyD88 (myeloid differentiation primary-response protein 88) dependent pathway, which is used by all TLRs except TLR3, and the MyD88-independent pathway [7,10]. In the MyD88-dependent pathway (Figs. 1 and 2), activation of a TLR and subsequent signaling through MyD88 initiates an extensive signal transduction cascade that proceeds through a number of kinases and transcription factors, leading to activation of nuclear factor-κB (NF-κB) and (Activator protein-1)AP-1. The transcription factors NF-κB and AP-1 can promote expression of pro-inflammatory cytokine genes and chemokines, such as TNF-α, IL-6, IL-8, MCP-1, and MIP-1 [11–13]. The MyD88-independent pathway (Fig. 2) is mediated by other adaptor molecules: MyD88 adaptor-like; also known as Tir domain-containing adaptor protein [TIRAP]; TIR domain containing adaptor inducing IFN-β (TRIF or TICAM-1]), Trif-related adaptor molecule (TRAM) and sterile α- and HEAT-Armadillo motifs (SARM) [14–18]. TLR2 and TLR4 use TIRAP as an additional adaptor to recruit MyD88. TRAM acts as a bridge between TLR4 and TRIF. TLR3 and TLR4 use TRIF to activate NF-κB and IRF3 to induce the expression of inflammatory cytokine and type I IFN which is essential to viral infection clearance.

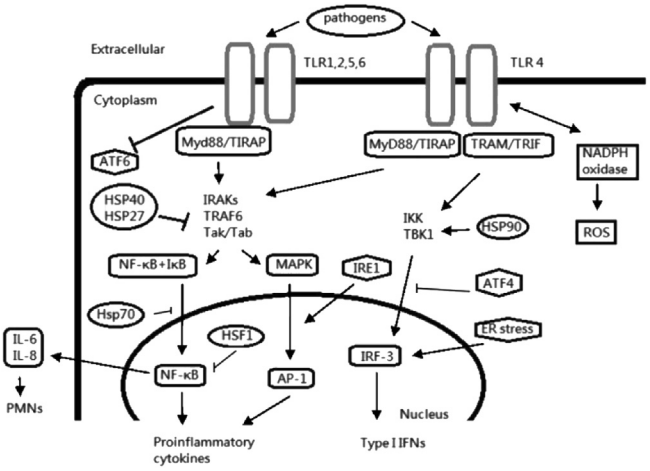

Fig. 1. Cell surface TLR signaling pathways. TLR1, 2, 4, 5, 6 initiates the MyD88-dependent signaling pathway, which results in activation of the transcription factors NF-κB and AP-1. The TLR4 pathway results in expression of type I IFNs mediated by IRF3. Key proteins of cellular stress response involved in these signaling pathways are illustrated. ⊥: Inhibition, ↑: Stimulation.

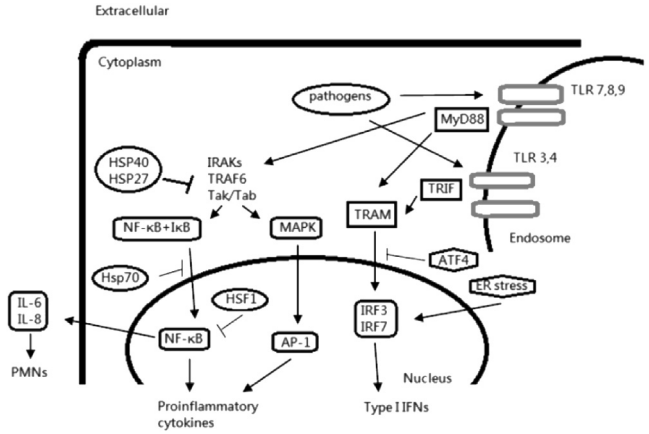

Fig. 2. Endosomal TLR signaling pathways. TLR7,8,9 initiates the MyD88-dependent signaling pathway, which results in activation of the transcription factors NF-κB, AP-1 and expression of type I IFNs. TLR3,4 initiates the MyD88-independent signaling pathway and results in expression of type I IFNs. Key proteins of cellular stress response involved in these signaling pathways are illustrated. ⊥: Inhibition, ↑: Stimulation.

In addition to TLRs, cytoplasmic PRRs play a central role in pathogen recognition and activation of immune responses (Fig. 3). RLRs are viral sensors and NLRs are intracellular sensors of pathogens and cell injuries [19–21]. RLRs include RIG-I, MDA5, and LGP2 are RNA helicases which can detect viral nucleic acids and activate IRF3 and 7, leading to type I IFN production. NADPH oxidase and ROS are essential for this RLR-mediated pathway [22]. NLRs, including Nod1 and -2, which recognize bacterial peptidoglycan and interact with the receptor interacting serine-threonine protein kinase 2 (RIPK2, also known RIP2) to induce NF-κB and mitogen-activated protein kinase (MAPK) signaling. NLRPs are another subfamily of NLRs that recognize bacterial DNA, toxins, and double-stranded RNA. NLRP assemble large protein complexes known as inflammasomes, which activate the inflammatory caspase, caspase-1, that processes the pro-forms of interleukin-1β (IL-1β) and IL-18, two crucial pro-inflammatory cytokines [23,24].

3. Cell stress response

The cellular stress response is a reaction to changes or fluctuations of extracellular conditions, which damage the structure and function of macromolecules [25]. Different