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REVIEW

The endoplasmic reticulum stress response: A link with tuberculosis?

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SUMMARY

Tuberculosis (TB) remains a major cause of mortality and morbidity in the worldwide. The endoplasmic-reticulum stress (ERS) response constitutes a cellular process that is triggered by mycobacterial infection that disturbs the folding of proteins in the endoplasmic reticulum (ER). The unfolded protein response (UPR) is induced to suspend the synthesis of early proteins and reduce the accumulation of unfolded- or misfolded proteins in the ER restoring normal physiological cell function. Prolonged or uncontrolled ERS leads to the activation of three signaling pathways (IRE1, PERK and ATF6) which directs the cell towards apoptosis. The absence of this process facilitates spread of the mycobacteria within the body. We summarize here recent advances in understanding the signaling pathway diversity governing ERS in relation to TB.

Contents

1. Introduction

It is more than one hundred years since *Mycobacterium tuberculosis* (Mtb) was first characterized by Robert Koch. Tuberculosis (TB) remains one of the most serious global diseases affecting man, preferentially affecting aged individuals or those affected by the human immunodeficiency virus (HIV). More than 9 million new cases were reported in 2013 with 1.5 million deaths in the world. Multi-drug resistance is a particularly intractable problem with an estimated 480,000 new cases and 210,000 deaths in 2013, of which 9.0% were reported in some countries to be infected with extensively drug resistant (XDR) strains [1].

Mtb is highly adapted to the human host and has multiple mechanisms to resist the host immune response after entry primarily through the respiratory tract. Failure of the immune

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response to clear infection results in death of individual cells. Interestingly, cell death is a double-edged sword in the competition between host and pathogen. Necrosis favors the spread of Mtb, whereas, by contrast, apoptosis facilitates controlling the infection [2]. Bacterial killing by infected cells is mediated by the production of cytokines and intracellular enzymes which also results in autophagy. Macrophages are the major host cell type infected by Mtb. In earlier studies, Mtb is considered to resident in phagosomal compartments which immediately fuse with lysosomes after entering into the cells. Phagolysosome fusion offers an acidic environment rich in hydrolytic enzymes that degrade and kill bacteria. Whereas, in recent studies, Mtb surprisingly translocate from phagolysosomes into the cytosol in nonapoptotic cells, but not for *M. bovis* BCG or in heat-killed mycobacteria due to the virulent strains secreting mycobacterial gene products the 10-kDa culture filtrate protein (CFP-10) and the 6-kDa early secreted antigenic target (ESAT-6) which have cytolytic ability [3–5]. Cytosolic Mtb has been reported to induce type I Interferons (IFNs) and to activate autophage via the stimulator of interferon gene (STING) pathway [6]. As known, STING locates in the endoplasmic reticulum (ER) membrane. Infection of macrophages by the virulent H37Rv and attenuated H37Ra strains results in increases in the amount of rough- (RER) and smooth- (SER) endoplasmic reticulum respectively [7].

ER is not only the major site of folding and transportation of proteins after synthesis, but also the major storage site of intracellular Ca^{2+} and of synthesis of cholesterol steroids and many lipids. Mycobacterial infection results in loss of Ca^{2+} from the ER and an increase in the intracellular redox state which results in accumulation of unfolded or misfolded proteins in the ER resulting

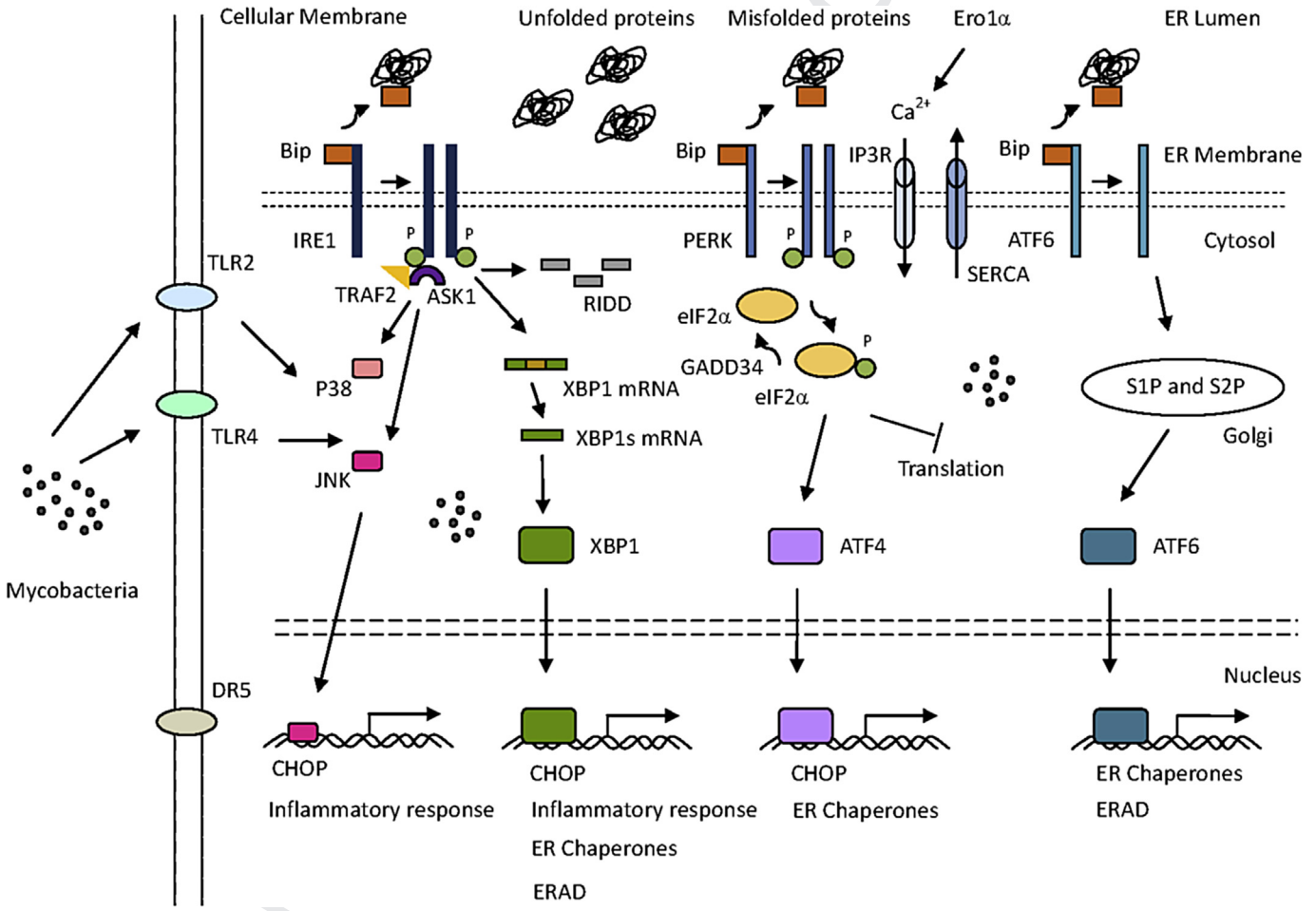

Figure 1. Cellular responses to endoplasmic reticulum stress induced by mycobacteria. Under normal physiological conditions, inactive Bip binds to the lumen domain of three kinds of transmembrane protein: inositol-requiring kinase/endoribonuclease 1 (IRE1), protein kinase activated by double-stranded RNA (PKR)-like ER kinase (PERK) and activating transcription actor 6 (ATF6). The accumulation of unfolded or misfolded proteins in the ER resulting in ER stress (ERS) when the cells are infected by Mtb or antigen proteins like ESAT-6. The Bip from IRE1, PERK and ATF6 is then able to bind unfolded-or misfolded proteins. The luminal domain of dissociated IRE1α forms homodimers in the ER membrane, while the cytosolic domain of IRE1α auto-phosphorylates to stimulate the kinase and RNase activities and to splice XBP-1 mRNA which binds to the UPR element (UPRE) and to the ER stress-response elements I and II (ERSE-I and ERSE-II) in the promoter regions of target genes. IRE1 can also recruit TRAF2 and ASK1, leading to down-stream activation of JNK and p38 MAPK when the cells are infected by *M. kansasii* or the Mtb 38 kDa antigen, then activates CHOP and other apoptotic transcription factors. In addition, the Mtb 38 kDa antigen can activate MAPK phosphorylation in both a TLR2-and TLR4-dependent manner. Regulated IRE1-dependent decay of mRNA (RIDD) has been shown to reduce ER localized mRNAs after Mtb infection. Activated PERK undergoes oligomerization and trans-autophosphorylation when the cells are infected by Mtb or antigen proteins like ESAT-6. PERK phosphorylates Ser51 of the alpha subunit of eukaryotic translation initiation factor 2 (eIF2α) which selectively induces the expression of activating transcription factor 4 (ATF4) mRNA which can induce transcription of some ER chaperone proteins and UPR-related transcription factor genes. CHOP can activate DNA damage-inducible transcript 34 (GADD34) which promotes the dephosphorylation of eIF2α, leading to the recovery of protein translation after ESAT-6 stimulation. The 38 kDa antigen induces the production of ROS and the subsequent ERS via ERO1α which regulates $Ca2^{+}$ fluxes through inositol 1,4,5-triphate receptor (IP3R) and Sarco-endoplasmic Reticulum Calcium Atpase (SERCA). ATF6 is released from Bip for trafficking to the Golgi apparatus where it is sequentially cleaved to a 50 kD active fragment including the N-terminal by site 1 and site 2 proteases at the transmembrane site. ATF6 then translocates to the nucleus to promote transcription of the ERSE-I, ERSE- II, UPR element (UPRE) and cAMP response element (CRE) genes. Unlike PERK and IRE1, nothing is known about the interaction between mycobacteria and the ATF6 pathway.

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