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Review

Assuming the role of mitochondria in mycobacterial infection

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ABSTRACT

Tuberculosis is one of the leading causes of death by *Mycobacterium tuberculosis* (*Mtb*) affecting millions of people worldwide. *Mycobacterium* species enter host macrophages during infection and target various cellular organelles and their function for their own benefit. Mitochondria appear to be among the important targets for bacterial pathogens. *Mtb* and other pathogenic bacteria secrete various proteins that initiate structural changes in mitochondria to modulate its function. Additionally, virulent mycobacteria interfere with the balance between pro- and anti-apoptotic factors to inhibit apoptosis and, in later stages, promote necrosis. Furthermore, mitochondria perform multiple biological functions in the cell, and the inhibition of these functions by bacterial proteins promotes *Mtb* survival, growth, and successful infection.

Contents

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Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*Mtb*) continues to be a major cause of morbidity and mortality throughout the world. Despite the availability of various effective drugs and Bacillus Calmette–Guérin (BCG) vaccines, TB-control programs have failed to reduce this problem in most parts of the world. In 2013, it was estimated that approximately one-third of the world population was asymptomatically infected with *Mtb*, of which nine million people developed TB and 1.5 million died from this deadly disease, including one-fourth who were human immunodeficiency virus (HIV)-positive [1]. Emergence of new resistant strains, such as multidrug-resistant and extensively drug-resistant strains, as well as other complicating factors, such as HIV coinfection, has posed an extra burden on TB-control programs [2]. Therefore, there is an urgent need to find new mycobacterial targets to allow for the development of drugs against this deadly disease.

Mtb is the causal organism of TB that engulfs host macrophages through various available phagocytic receptors, of which the complement of mannose receptors are the most prevalent [3,4]. Virulent *Mtb* has adapted itself to enable its survival in the host macrophage by utilizing various strategies, such as preventing the fusion of phagosomes with lysosomes, restriction to phagosomal acidification, and targeting cellular organelles, such as mitochondria, to disturb the balance of pro- and anti-apoptotic factors in order to escape the immune response [5]. Mitochondria are double-membrane-bound organelles that have evolved from an endosymbiotic proteobacterium and perform various biological functions, such as adenosine triphosphate (ATP) synthesis, ion homeostasis, biosynthesis of fatty acids, calcium storage, iron-sulfur-cluster biogenesis, and regulation of cell-death pathways. Due to the multiple and diverse roles of mitochondria, it is an attractive target organelle for bacterial pathogens. Therefore, one could hypothesize that interference with mitochondrial functions would be useful to pathogens for establishment of successful infection.

Mtb and apoptosis

Apoptosis is an evolutionarily preserved mechanism for cell self-destruction, and it plays an important role in many physiological processes, such as morphogenetic changes in embryonic development, aging, and homeostatic maintenance [6]. Most pathological conditions are linked to the misregulation of programmed cell death, with examples involving neurodegenerative diseases, cardiovascular diseases, cancers, and acquired immune deficiency syndrome [7,8]. Apoptosis induction in response to viral infection is also well established. Many viral pathogens are known to encode genes whose products inhibit host cell death to provide a suitable niche for viral replication and survival [9,10]. Apoptosis is an innate cellular defense mechanism that is usually initiated under stress conditions. Pathogenic bacteria have evolved various strategies to target host cells to either to inhibit apoptosis for their survival and growth or promote apoptosis. Virulent strains of *Mtb* inhibit apoptosis in macrophages through upregulation of antiapoptotic proteins, such as B-cell lymphoma (Bcl)-2 and Mcl-1, through destruction of mitochondrial transmembrane potential and by depletion of cytochrome c [11–13].

In addition to *Mtb*, other pathogenic bacteria of the mycobacterium species include *Mycobacterium leprae*, which causes leprosy and induces apoptosis through upregulation of Mcl-1 expression and downregulation of the Bcl-2-associated death promoter and Bcl-2 homologous antagonist/killer (Bak) proteins [12], wild-type *Mycobacterium bovis*, which induces low levels of apoptosis by increasing production of interleukin-10 and Bcl-2 and reduces production of tumor necrosis factor (TNF)-α [14]. TNF-α production is critical for the induction of apoptosis in mycobacteria-infected macrophages [15]. Other bacteria known to induce apoptosis include *Pseudomonas aeruginosa*, *Escherichia coli*, *Listeria monocytogenes*, *Neisseriae* spp., *Yersinia pseudotuberculosis*, *Yersinia pestis*, *Yersinia enterocolitica*, *Salmonella typhimurium*, and *Shigella Flexneri* [16].

Mtb infection predominantly leads to necrosis, a form of cell death characterized by plasma-membrane disruption that differs from apoptosis, where the integrity of the plasma membrane is preserved. *Mtb* induces necrosis to evade host defenses and to exit macrophages in order to disseminate to and infect surrounding cells. H37Rv, a pathogenic strain of mycobacterium, promotes necrosis by inducing substantial alterations to mitochondrial transmembrane potential [17]. A recent study reported that *Mtb* PPE68 and Rv2626c genes encoded proteins involved in aiding bacterial escape from host macrophages by promoting necrosis. Deletion of the Rv2626c gene resulted in decreased necrosis induction, while overexpression promoted significant necrosis [18]. However, there is limited information available regarding the mechanism used by bacteria to promote necrosis.

Mitochondrial roles in induction of apoptosis and necrosis

Mitochondrion plays a key role in the regulation of apoptotic cell death [8]. These organelles are not only involved in intrinsic cell-death pathways, but they are also involved in extrinsic cell-death pathways in some cell types. Intrinsic mitochondria-mediated cell death differs from extrinsic cell-death pathways in how it is elicited in the presence of various stressors associated with the intracellular environment, such as DNA damage, microbial infection, and oxidative stress. In contrast, the extrinsic pathway is initiated by extracellular cell-death signals. In response to specific apoptotic stimuli, mitochondria release the proapoptotic factor cytochrome c and apoptosis inducing factor (AIF). Cytochrome c associates with a scaffold protein, apoptotic protease activating factor-1, to drive the assembly of a supramolecular complex known as the apoptosome, which leads to the activation of caspase cascades that lead to cell death [19]. X-linked inhibitor of apoptosis protein possesses caspase-inhibitory activity, which is counteracted by second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein, a mitochondrion-derived activator of caspases [20]. However, some factors, such as AIF, can

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