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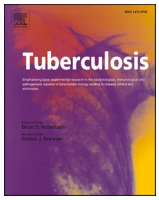

Review

Macrophage activation highlight an important role for NER proteins in the survival, latency and multiplication of *Mycobacterium tuberculosis*

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ABSTRACT

Nucleotide excision repair (NER) is one of the most extensively studied DNA repair processes in both prokaryotes and eukaryotes. The NER pathway is a highly conserved, ATP-dependent multi-step process involving several proteins/enzymes that function in a concerted manner to recognize and excise a wide spectrum of helix-distorting DNA lesions and bulky adducts by nuclease cleavage on either side of the damaged bases. As such, the NER pathway of *Mycobacterium tuberculosis* (Mtb) is essential for its survival within the hostile environment of macrophages and disease progression. This review focuses on present published knowledge about the crucial roles of Mtb NER proteins in the survival and multiplication of the pathogen within the macrophages and as potential targets for drug discovery.

1. Introduction

Tuberculosis (TB) is a contagious, airborne infectious disease caused by the bacillus *Mycobacterium tuberculosis* (Mtb), which continues to be a major cause of morbidity and mortality mainly due to limited therapeutic options. This is further accentuated by world-wide emergence of multidrug-resistant strains of Mtb. Although it primarily affects the respiratory system, it also affects other parts of the body. A recent estimate (2021) from the World Health Organization indicate that full death toll associated directly or indirectly with the Mtb accounts for 10.6 million people [1]. Considering the socioeconomic impacts of the COVID-19 pandemic, the report also highlights the setbacks in measures taken to achieve the sustainable development goals over the recent years for the eradication of this dreadly disease [1]. Under the current scenario, contemplating about this worldwide concern, research breakthroughs related to new vaccine/advance diagnose development and intense investigations are urgently required to rapidly reduce the TB incidence worldwide.

Consistent with many other pathogenic bacteria, several processes, such as multiplication, transmission, adaptation to humans, and virulence of Mtb hinges on its physiological condition and the environment [2]. There has been significant progress over the last decades in our understanding of Mtb biology in the context of the human immune response. Despite the generation of robust host immune responses, Mtb subverts the host immune system to establish a chronic infection [3]. There are many excellent reviews that cover immune evasion mechanisms adopted by Mtb [4–8]; however, the potential role of the nucleotide excision repair (NER) pathway in the context of activated macrophages has not been reviewed. In this review, we describe and discuss the current knowledge about the crucial roles of Mtb NER proteins in the survival and multiplication of the pathogen within the macrophages and their potential as therapeutic targets.

1.1. Activation of the host cell by host-pathogen interaction

The cell envelope of Mtb is a very impermeable intricate structure composed of a capsule, outer membrane (mycomembrane), arabinogalactan layer, peptidoglycan layer and an inner plasma membrane [9]. Specifically, the outer membrane contains mycolic acids, glycolipid trehalose 6,6′ dimycolate (TDM) and various other lipids such as phthiocerol dimycocerosates (DIM/PDIM), diacyltrehalose (DAT) and polyacyltrehalose (PAT). Additionally, it contains mannosyl-phosphatidyl-myo-inositol-based glycolipids (PIM) and lipoglycans such as lipomannan (LM) and lipoarabinomannan (LAM) in the cell coat and outer or inner plasma membrane [7,10]. As such, tremendous attention has been paid to the research on mycobacterial cell envelope because the components of cell envelope play a crucial role in mycobacterial adherence and invasion of host cells [11,12]. Host cells interact with Mtb by recognizing pathogen-associated molecular patterns (PAMPs) present on the bacterial surface through the pattern recognition receptors (PRRs) of the host cell. Currently identified PRR

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