THE ROLE OF SERINE/THREONINE PROTEIN KINASES OF MYCOBACTERIUM TUBERCULOSIS IN DISEASE MANAGEMENT

Abstract

Mycobacterium tuberculosis, which causes TB, is a serious global health problem. Protein kinases are essential for controlling many cellular functions, including the induction of immune response to pathogens. Now a day TB strains that are getting more and more drug resistant is a significant public health concern. The physiological function of the kinases may help to comprehend the signalling networks underlying the TB infection. Finding novel pharmacological targets that are crucial for the in vivo bacterial survival and persistence is essential for treating TB successfully. In M. tuberculosis, phosphorylation-based signalling cascades that are controlled by serine/threonine protein kinases and phosphatases that are similar to those found in eukaryotes translate extracellular cues into cellular responses that lead to the pathogen's proliferation, persistence, and disease. The M. tuberculosis genome encodes two-component systems, 11 Serine Threonine Protein Kinases (STPKs), 1 Ser/Thr phosphatase, 1 Tyrosine Kinase, and 2 Tyrosine Phosphates regulate the signalling pathways in MTB. By examining these molecules' potential as targets for therapeutic intervention and the management of diseases, these studies will close a knowledge gap.

Keywords: Mycobacterium, Kinase, Phosphatase, Phagolysosome, Pathogenicity.

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I. INTRODUCTION

The main processes by which signals are converted into cellular responses are protein phosphorylation and dephosphorylation. Post translational modification is a known method used by mycobacteria to convert extracellular signals into different biological activities[1]. As kinase regulation is commonly linked to illness, drug development programmes have suggested kinases as targets to modify and regulate cellular processes[2]. The Serine/threonine protein kinases and two-component systems are both used by mycobacteria for signal transduction. Sequence investigation of the *M. tuberculosis* genome identified 11 two-component systems and 11 serine/threonine protein kinases that are similar to those found in eukaryotes[1; 3; 4]. Therefore, in contrast to other bacterial species with comparable genome sizes, mycobacterial genomes include an unusually large number of serine/threonine protein kinases and a comparatively low number of two-component systems. Serine/threonine kinases range in number from four in *Mycobacterium leprae* to 24 in *Mycobacterium marinum*, it should be emphasised.

Intriguingly, *M. leprae* differs from *M. tuberculosis* in that it has a lower G+C content and a 26% smaller genome[3]. In addition, compared to *M. tuberculosis*, which has more than 90% protein-coding genes, only around 50% of the genome's sequences code for proteins; the other sequences are either regulatory or cover pseudogenes. The significant gene degradation in *M. leprae* shows that only a small subset of the pathogenicity-related genes was maintained by this mycobacterial species. As a result, the four serine/threonine kinase genes that are still found in its genome are considered to be essential and likely perform critical physiological roles[3].

Nine of the 11 kinases found in the *M. tuberculosis* genome are conventional receptor-like kinases with a transmembrane domain, whereas two of these kinases, protein kinase G and protein kinase K, are projected to be cytosolic[3]. The receptor kinases may be divided into the three groups viz,PknA/PknB/PknL (Group1), PknD/PknE/PknH (Group2), and PknF/PknI/PknJ (Group3) based on how similar their amino acid sequences are as shown in figure 1[1; 5]. All mycobacterial serine/threonine kinases are members of the Protein Kinase N2 family, which is most closely related to eukaryotic serine/threonine kinases[3; 6]. They all include eleven conserved domains that are indicative of Hanks-type kinases[7; 8].

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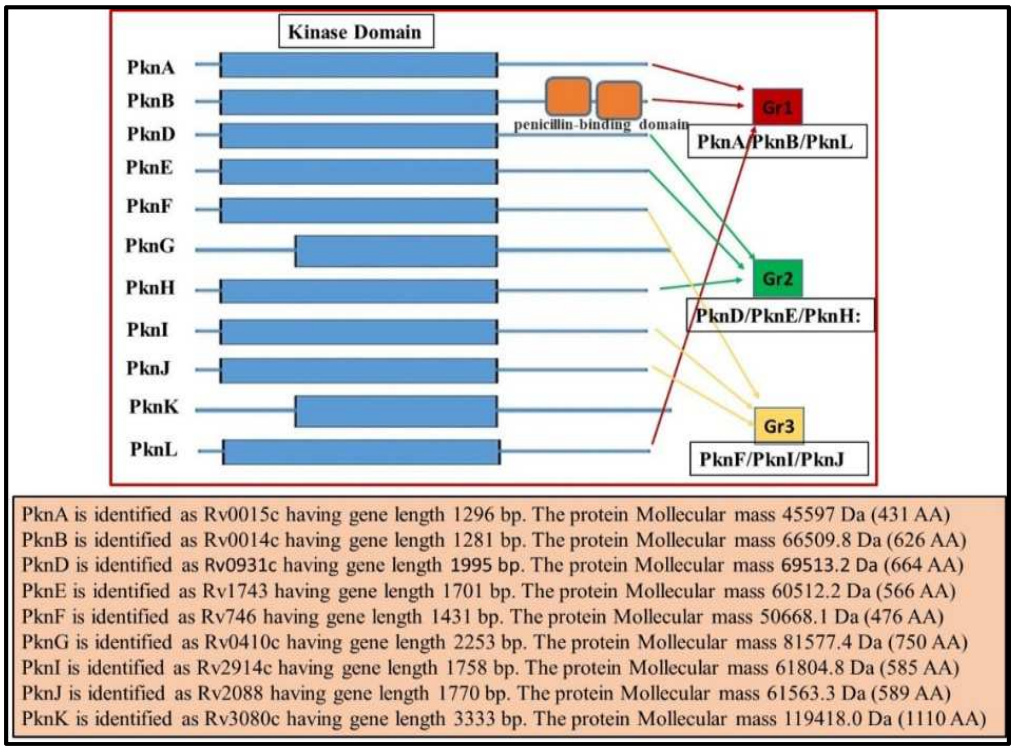

Figure 1: The eleven Ser/Thr protein kinases of MTB are divided into three groups (Gr1, Gr2&Gr3) the kinase and transmembrane domains are designated differently as seen above. The auto phosphorylation is necessary for their activation before the subsequent phosphorylation process in intracellular kinases. The gene and protein characteristics of the eukaryotic Ser/Thr kinase are described above.

There are two types of mycobacteria: pathogenic (*Mycobacterium tuberculosis* H37v, *Mycobacterium bovis*), with a generation period of 18–24 hours, and non-pathogenic (*Mycobacterium smegmatis* (MS)), with a creation time of 3–4 hours.The pathogenicity of MTB was widely dispersed in many animals with several types of MTB strains, of which BCG is one and is usually employed as a vaccine in humans[9]. Mycobacteria's non-pathogenic strain is commonly used as a model strain in studies on TB. Compared to MTB, the MS genome is more complicated. Except few, all serine/threonine kinases are lacking from the MS strain but present in the MTB. The MTB occupies the lung tissue as a potential location for infection in humans because it requires an aerobic environment for development and reproduction. By increasing the amplification of immunological cascades inside the cell, the host cell stimulated phagosome maturation for the killing and removal of such pathogens as in Fig. 2[7].

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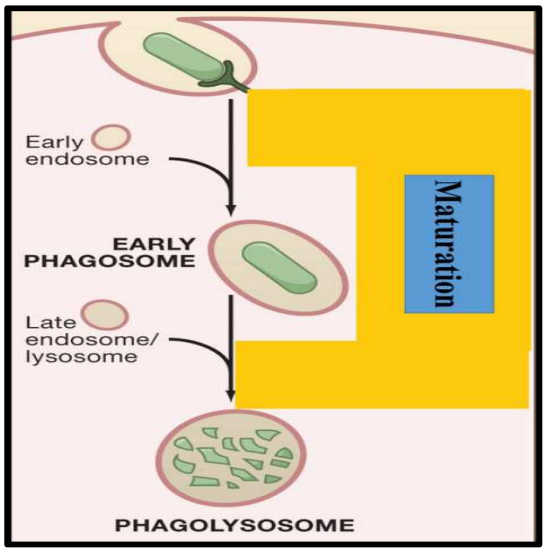

Figure 2: Maturation of phagosome containing MTB.

Sphingosine kinase and/or phospholipase C (PLC) are activated by receptors that interact with the bacterium or chemicals on its surface, increasing the quantity of cytosolic free calcium ions (Ca2+). Early phagosomes are created when nascent phagosomes fuse with early endosomes, while phagolysosomes are created when late endosomes and lysosomes combine. Elevated Ca2+ is assumed to be needed for the last stage. The bacteria are eliminated by lysosomal enzymes in the phagolysosome[7].

II. FUNCTIONAL IMPORTANCE OF SER/THR PROTEIN KINASES:

All species of mycobacteria have PknA, PknB, PknG, and PknL, indicating that these kinases play significant roles in regulating fundamental elements of mycobacterial physiology, however PknA and PknB are essential for MTB[10]. The other STPKs most likely play more specialised regulatory roles in infection.PknD has been associated with central nervous system tuberculosis and plays a significant role in phosphate transport in MTB. A pknD deletion strain was shown to be incapable of invading the central nervous system during a screen for genes necessary for *M. tuberculosis* infection[11]. PknG, a virulence factor, inhibited phagosome-lysosome fusion by controlling host signalling after being released into the phagosome of macrophages[12]**.** PknJ is important in controlling the growth and survival of mycobacteria[13]. Furthermore, The PknG, PknA and PknB is most important serine threonine protein kinase which can be used as a key molecule to control MTB infection.

The PknB is an essential gene of mycobacterium so researcher screened the inhibitors for binding with PknB and induction of toxicity insight the cell viz, MRT67127, MRT67153, MRT68667, MRT68606 etc. Similarly, triazolylmethoxychalcones, flavanones and 2-aminopyrimidines as inhibitors of mycobacterial FAS-II and PknG[14; 15]. We can also approach by receptor tyrosine kinase inhibitors as host-directed antimicrobials which may be effective for mycobacterium elimination[16]. The tyrosine kinase inhibitor dasatinib reducesthe growth of intracellularMycobacterium tuberculosis. Therefore, one major host defence mechanism of macrophages againstMTBis the acidification of lysosomes in which

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the mycobacte-ria reside. The tyrosine kinase regulates the acidification process insight the cell and the investigation was demonstrated using the tyrosine kinase inhibitors viz, imatinib, nilotinib anddasatinib[17].

III. CONCLUSION

We are focused on the MTB Ser/Thr protein kinases in this article. The roles of protein phosphorylation and de-phosphorylation insight the cell to control the mycobacterial cell envelope, metabolic activity, and pathogenic activity of MTB are thoroughly outlined. The novel findings addressing the activation and control of *M. tuberculosis* kinases and phosphatases are among the prospective methods for developing disease-controlling medications. In the therapy of the illness, kinase inhibitors are crucial for the activity and control of MTB infection. The researcher is aiming to discriminate between host and parasite kinase for the prospective treatment in order to specifically create medications and cure illness.

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