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The Development of Novel Drug to Treat Tuberculosis Disease

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Abstract

One important agenda in the sustainable development goals is the eradication of infectious diseases such as tuberculosis. Targeting tuberculosis is not as easy as it is said, because the bacterium that causes this disease, *Mycobacterium tuberculosis*, seems to have its own agenda to become an eternal enemy of civilization. Prevention of TB disease established by BCG vaccination is only effective in preventing TB for children. At the later stage, these bacteria can still infect humans in adulthood. Treatment strategy for TB patients has been implemented with DOTS, but the success of this strategy requires carefulness and discipline of medical staff and patients. This curative strategy also continues to experience problems with the emergence of Mtb strains that are resistant to multiple antibiotics (MDR) and extremely resistant drug resistant (XDR). In addition to these problems, attention also needs to be focused on latent tuberculosis infection (LTBI). The current estimation by WHO suggests that a quarter of the human population may be latently infected with Mtb, and about ten percent of this number will develop active TB. The present understanding of the mechanism by which Mtb is capable of infecting humans in latent fashion provides strategy to deal with Mtb, i.e. by blocking Mtb's proteins that contribute to latent tuberculosis infection. In this minireview, Mtb proteins involved in latent tuberculosis infection and the opportunity to develop TB novel drugs based on the inhibition of these proteins are presented.

Keywords: *Sustainable Development Goal, latent tuberculosis, novel drugs, protein inhibition*

Mycobacterium tuberculosis (Mtb) bacteria, the causative agent of TB cases are estimated to infect a quarter of world population[1]. Although not all infections develop into TB cases, the number of TB cases is still top killer with 10 million cases and responsible for 1.7 Million deaths annually [2].

Of equal important, latent Mtb infection also need more attention, since it is not clear when and how infected persons will develop TB case. Our present knowledge in latent Mtb infection is also limited to the identification of some virulence factors from Mtb that related to latent Mtb infection. However, the mechanism by which those virulence factors develop latent infection is not fully understood. At molecular point of view, it is important to reveal the interaction of those virulence factors with molecules of host cells. In other words, which molecules of host cells are affected by Mtb's virulence factors. The answer of this question is the key to handle the latent infection.

A deeper understanding of biochemical properties of Mtb virulence factors will provide novel ways to combat Mtb, i.e. sequestration or inhibition of Mtb virulence factors may lead us to prevent latent Mtb infection.

Attempt to combat TB has been undertaken through different strategies. Prevention by vaccination has long been accepted. To date, only BCG vaccine is recommended, even though its efficacy is questioned, especially against new Mtb strains and complication with HIV/AIDS [2]. Several new vaccine candidates are in clinical phase. Nevertheless, real brand new vaccine than can be worldwide accepted still needs a long way to be materialized [3].

Annual new TB cases have lead to a significant mortality rate. This figure is worsened by antibiotic resistant bacteria (MDR and XDR strains). Another combat area against TB is latent Mtb infection. To deal with this matter, a detail understanding of the development of latent infection is necessary.

The ability of Mtb to enter dormant phase within its host (macrophage) cells stems from several modulator proteins being secreted by the bacteria to the host cytoplasm. They reroute phagosome maturation process which otherwise will provide a harsh environment for the bacteria that rapidly degrading the invading bacteria.

Phagosome maturation

At the beginning of Mtb infection, Mtb cells are engulfed by macrophage cells,-cells that involve in defense system-. This process in known as phagocytosis, where a micro environment is limited by a double layer membrane called phagosome. Phagosomes subsequentially undergo several maturation process initiated by fusion with early endosome, late endosome and lysosome (Desjardins, 1994) that produce early, intermediate and mature phagolysosome, respectively. Each steps is characterized by the

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presence of specific markers. Phagolysosome is a membrane –limited structure whose lumen is acidic (pH 4.5) and gain plethora of hydrolases/proteases from lysosome that are able to degrade bacteria, including Mtb.

Modulators or Effectors that inhibit phagosome maturation

A number of mechanisms have been proposed to explain the process by which Mtb modulate defence system of macrophage which eventually end up with persistence of the bacteria. To name a few of them are PknG, PtpA and PtpB proteins.

Protein kinase G (PknG)

PknG is the only hydrophilic kinase of the whole genome of all Mycobacterium strains. This highlights the importance of this protein. This protein is reported to be essential for the persistence of Mtb in vivo, but not in vitro [4]. PknG is believed to be an important mediator in the inhibition of phagosome maturation, as shown by deletion of pkng gene result in the inability of the bacteria to prevent phagosome maturation and the bacteria subsequently degraded by macrophage. It is suggested that PknG modulate a yet to determine host protein that essential for phagosome-lysosome fusion even [5].

Protein fosfatase A (PtpA) and Protein phosphatase B (PtpB)

PtpA and PtpB are two tyrosine phosphatases of Mtb. Recent studies shows the likely that host vacuolar sorting protein VPS33B is substrate of PtpA [6] and PtpA dephosphorylation of VPS33B inactivates this host protein, leading to inhibition of phagosome–lysosome fusion. PtpA also inhibits phagosome maturation by binding to sub unit H of V-ATPase, an event that prevent acidification of phagolysosome [7].

PtpB is also known to responsibles for successful latent infection development and its interaction with host protein is not fully understood. Hence, one of the goals in the proposed project is to reveal the detail of interaction of PtpB with host protein. Knowing that both tyrosine phosphatases are important for latent infection, many researches have directed to find inhibitor of those phosphatases. In our preliminary works, we have been able to show that unconventional eicosenoic acid derivatives are able to inhibit PtpA.

In addition to PknG, PtpA and PtpB, several modulator proteins have also been reported, such as lipoamide dehydrogenase C (PpdC), lipoarabinomanan (LAM), PknF [7] and SapM [8]. The fact many modulator proteins involved in the survival mechanism of Mtb underlines that the development of latent infection is a complex even and is still an interesting challenge.

Referring to the above status of global tuberculosis research, especially in dealing with latent tuberculosis (LTBI) it is proposed in the future to do works on:

1. establishing interaction of Mtb modulator proteins with host protein, by using several methods, i.e. pull-down assay, yeast two hybrid screening, immunoprecipitation/co-immunoprecipitation, as well as by bioinformatics
2. finding specific inhibitors Mtb protein that prevent it elimitation from body, such as done for PtpA and PtpB. We propose that pevention of latent Mtb infection could be achieved by inhibiting the activity of secreted Mtb phosphatase. This objective is could be achieved in combination with other treatment for LTBI.

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