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Emerging New Aspects of Toll like Receptor-2 during *Mycobacterium tuberculosis* Pathogenesis

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Summary

Now in these days, Tuberculosis is emerging as a great threat to mankind due to its multi or extensively drug resistance forms. One third of human population is infected with this deadly disease [1]. It is also declared as a global emergency by WHO (World Health Organization) because *M. tuberculosis* (Mtb) have very effective strategy to survive inside the host [2]. *M. tuberculosis* infects alveolar macrophage through its various adhesion molecules and modulates host immune system. The first line of innate defence mechanism provided by host is to recognize Mtb by immune cells like macrophages and dendritic cells [3]. These cells recognize Mtb through its various surface receptors which are known as pattern recognition receptors (PRR). One set of major PRR are Toll like Receptors (TLR) which include TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, TLR12, and TLR13 but TLR12 and TLR13 are not found in humans. Each TLR are bound to specific ligands present in the surface of microbes and initiate specific immune response [4].

Here we are emphasizing on TLR2 which is also named as CD282 (Cluster of Differentiation 282) and it is identified by various Mtb cell wall fractions like lipoarabinomannan, mycolylarabinogalactan-peptidoglycan complex etc. [5]. TLR2 signalling cascade initiate antimicrobial action in infected macrophages and has a potential to control inflammation during chronic infection. Besides interaction with various ligands of Mtb cell wall components, TLR2 also plays role in entry of Mtb into macrophages with the interaction of PE_PGRS33 family protein [6]. PE_PGRS (Polymorphic GC repetitive sequences) are unique family proteins of Mtb genome which contain 63 members, exact role of each is still unknown but it is presumed that they are involved in immunopathogenesis of TB [7,8]. In a recent study it has been shown that TLR2 is required to mediate entry of Mtb into macrophage through PE_PGRS33, as PGRS has a fix domain within 140 and 260 amino acids, which interact with TLR2 and it will initiate the PI3K signalling. In the absence of PE_PGRS33 Mtb has an impaired ability to enter into macrophage [6].

In another experiment it has been shown that Rv3628 of Mtb genome, which is soluble inorganic pyrophosphates, can be used

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as vaccine target due to its ability to interact with dendritic cells and initiate the secretion of various cytokine and chemokine [9]. This alteration in immune response is generated by Rv3628 through binding to TLR2 and trigger downstream signalling cascade of MAPK, MyD88 and NF- κ B and enhances Th-1 formation [9].

Cholesterol oxidase (ChoD) is another virulent factor of Mtb which effects macrophage, but its role is still unclear. To investigate its impact on macrophage another bacterial ChoD from *Nocardia erythropolis* is used, which is 70% similar to Mtb enzyme [10]. ChoD is known to function in both pathogenic and non-pathogenic forms of bacteria but in a different way, as in non-pathogenic bacteria it is used to degrade cholesterol and in pathogenic bacteria it is used to alter the membranous structure and infect the host [11]. ChoD interact with macrophages via TLR2 binding sites and initiate MAPK pathway to enhance secretion of IL-10 [10].

TLR2 is also important to control inflammation during Mtb infection to uphold control on bacterial replication and maintain

recruitment of Foxp3+ Tregs (T regulatory cells) to the lungs. In a recent research on TLR2 knockout mice some observations are made, like pulmonary granuloma structure is interrupted in the absence of TLR2 during chronic Mtb infection, also the number of CD4+Foxp3+ Tregs cells are decreased in lungs due to the absence of TLR2. It is due to the absence of the availability of signalling cascade which is generated by TLR2 [12].

Recently it has been proved that TLR2 and NKp44 which are specific receptors expressed only on activated NK cells, are identified to be involved in initiating cytotoxic activity against infected cells during Mtb infection. It has been demonstrated that extracted NK cells from healthy donor can respond right away to *Mycobacteria bovis* Bacillus Calmette Guerin (BCG) through TLR2 [13].

Nkp44 and TLR2 interact with different cell wall component of Mtb and initiate activation of NK cells. TLR2 binds with peptidoglycan component of Mtb cell wall and play primary role in initiating activation of NK cells of host and stimulate production of IFN- γ while NKp44 interact with other membranous component maintaining NK cell activation [14].

Mtb has a several mechanism to dodge its damage by phagolysosomes for its successful replication and growth. During infection Mtb move out from phagosome, in the cytosol of dendritic cells which facilitates by ESAT6 and a gene located in RD-1 (Region of Difference-1), conferring its safe environment to survive by altering TLR2 signalling. Lately it has been described that TLR2 and MyD88 signalling pathways play crucial role in confining to Mtb within phagosome. As mutant strain of ESAT6 and RD-1 of Mtb can translocate in cytosol only in TLR2 deficient mice which proves that TLR2 signalling cascade is important to retain Mtb within phagolysosome [15].

One of the major consequences during Mtb infection is stimulation of apoptosis and necrosis in host macrophages.

Apoptosis seems to be beneficial to host rather necrosis is beneficial to bacilli growth and progression [16]. Mycobacteria are rich in lipoproteins, which are post-translationally modified proteins, deliberated to be potent immune-modulatory [17]. In recent findings, 19KDa of lipoprotein of Mtb (P19) is effective immunomodifier and associated to cell wall, which stimulate phagocytosis of bacilli due to its adhesive nature [18]. P19 also plays crucial role in persuading apoptosis in macrophages through TLR2 dependent JAK (Janus Kinase) pathway [19], as by blocking of TLR2 with anti-TLR2 which inhibits the process of apoptosis in THP-1 cells [20]. Virulent Mtb like lipoproteins factors stimulates maturation of DCs through TLR2 and TLR4 signalling pathway. Cell death due to necrosis is a main factor in granuloma formation, tissue damage and transmission of bacilli [21].

In this way we can conclude that in various other TLR's, TLR2 is the only receptor so far known to form heterodimers with other TLR's (those are TLR1 and TLR6) and various other non TLR molecule which allows it to recognize a wide variety of PAMPs (Pathogen associated molecular patterns). TLR2 also plays a central role in apoptosis through JAK pathway which is induced by lipoproteins of bacilli; in turn inhibition of antigen presentation in infected macrophages. Role of TLR2 in necrosis is still doubtful and needed to be evaluated. TLR2 play important role in defence against Microbial infection. It has several crucial other function during Mtb infection rather than only work as a PRR molecule of host immune cells. This needs more extended research to know the other signalling aspects of TLR2 while it interacts with other virulent factors of Mtb.

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