The Brazilian Journal of
INFECTIOUS DISEASES

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Review Article

TLR2 and TLR4 mediated host immune responses in major infectious diseases: a review

Suprabhat Mukherjee[1], *Subhajit Karmakar*[1], *Santi Prasad Sinha Babu*[*]

Parasitology Laboratory, Department of Zoology (Centre for Advanced Studies), Visva-Bharati University, Santiniketan, India

ARTICLE INFO

Article history:
Received 31 August 2015
Accepted 16 October 2015
Available online 14 January 2016

Keywords:
Toll like receptor (TLR)
Trypanosomiasis
Malaria
Filariasis

ABSTRACT

During the course of evolution, multicellular organisms have been orchestrated with an efficient and versatile immune system to counteract diverse group of pathogenic organisms. Pathogen recognition is considered as the most critical step behind eliciting adequate immune response during an infection. Hitherto Toll-like receptors (TLRs), especially the surface ones viz. TLR2 and TLR4 have gained immense importance due to their extreme ability of identifying distinct molecular patterns from invading pathogens. These pattern recognition receptors (PRRs) not only act as innate sensor but also shape and bridge innate and adaptive immune responses. In addition, they also play a pivotal role in regulating the balance between Th1 and Th2 type of response essential for the survivability of the host. In this work, major achievements rather findings made on the typical signalling and immunopathological attributes of TLR2 and TLR4 mediated host response against the major infectious diseases have been reviewed. Infectious diseases like tuberculosis, trypanosomiasis, malaria, and filariasis are still posing myriad threat to mankind. Furthermore, increasing resistance of the causative organisms against available therapeutics is also an emerging problem. Thus, stimulation of host immune response with TLR2 and TLR4 agonist can be the option of choice to treat such diseases in future.

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Introduction

Antimicrobial inflammatory response primarily onsets through initial sensing of distinct pathogen associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) of hosts. These receptors serve as crucial innate PRRs that sense microbial or endogenous products released from damaged or dying cells and trigger innate immunity through the activation of intracellular signal transduction pathways.[1] Amongst the innate immune PRRs, Toll-like receptors (TLRs) have the unique capacity to sense the initial infection and are the most potent inducers of the inflammatory responses.[1] Depending on their cellular localization or respective PAMPs they identify, TLRs can be divided into two sub groups such as transmembrane (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11) and intracellular (TLR3, TLR7, TLR8, and TLR9).[1] These evolutionary conserved type-I transmembrane proteins (TLRs) can recognize ligand from almost all types of pathogenic organisms including viruses, bacteria, fungi, protozoa,

* *Corresponding author.*
E-mail address: spsinhababu@gmail.com (S.P.S. Babu).
[1] These authors contributed equally to this work.
http://dx.doi.org/10.1016/j.bjid.2015.10.011
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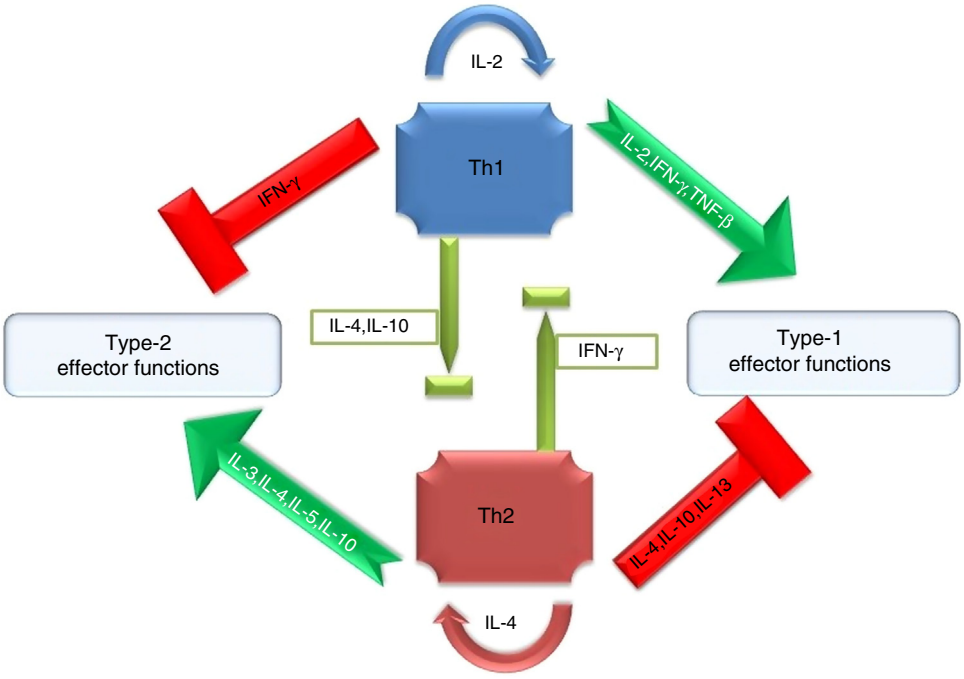

Fig. 1 – Cytokine mediated proinflammatory (Th1) or anti-inflammatory (Th2) polarization of immune cells.

helminths, etc. Structurally, TLRs located on cell membranes possesses an extracellular domain containing leucine-rich repeats that recognize distinct PAMPs and a toll-interleukin 1 (IL-1) receptor (TIR) domain required for downstream signalling that guides activation of transcription factor nuclear factor-κB (NF-κB) for inducing pro-inflammatory cytokines and chemokines as well as the up-regulation of co-stimulatory molecules on antigen presenting cells, such as macrophages (MΦs) and dendritic cells (DCs) that in turn sensitize T-cell activation. Inflammation signalled from TLR is a protective measure of the host body to ensure removal of detrimental threats posed by infectious agents as well as to accelerate the healing process. However, the Th1 biased inflammatory consequences orchestrated by TLRs not only involve in eliminating pathogenic infections but also can induce fatal pathological outcomes like septic shock (Fig. 1). Similarly, pathogen modulated TLR signalling develops a Th2 based response beneficial for the pathogen i.e. disease progression (Fig. 1). Thus, an adequate balance between pro- and anti-inflammatory immune responses is of immense importance to restore the normal physiological conditions of the host body during and after a pathogenic infection.[2] Herein, major research findings exploring the role of TLR2 and TLR4 in the induction of host immunity against major parasitic diseases such as tuberculosis, leishmaniasis, malaria, trypanosomiasis, and filariasis have been reviewed.

Immunobiology of TLR2 and 4

Since their discovery, TLR2 and 4 have gained much attention due to their extreme ability of identifying diversified array of pathogenic ligands.[1] Alike *Drosophila* protein 'Toll', mammalian TLR2/4 possesses a cytosolic IL-1 receptor homolog domain but heterologous extracellular leucine-rich repeats.[3] Interestingly, the mode of signalling is highly similar for e.g. transcription factor 'Dorsal' activated by Toll pathway in *Drosophila* is a functional homologue of NF-κB.[4] The mode of activation of NF-κB or Dorsal also share high degree of similarity in terms of signalling intermediates like protein kinases such as 'Pelle' of *Drosophila*[5,6] and mammalian IL-1 receptor-associated kinase.[7] A comparative homology in the signal pathway transduced by *Drosophila* 'Toll' and mammalian "TLR" have been depicted in Fig. 2.

The functional features of "Toll signaling" are primarily different from insect to mammals. As obvious, 'Toll' receptors in insect (*Drosophila*) perform developmental roles primarily but it serves as innate immune receptor majorly in mammals. The proteins involved in the dorso-ventral polarity also play crucial role in the antimicrobial response in the fly as well.[8] Interestingly, intermediates of dorso-ventral polarity determining 'Toll' pathway of insect share high degree of homology with vertebrate TLRs (specifically TLR4) that performs pattern recognition.[8] Thus, the functional ancestry between development and immune pathway has been emerged as a major question. In particular, the discovery of immune function of 'Toll' in *Drosophila* also suggested towards the fact that the immune function of the Toll gene product was not adapted by the higher animals rather it can be revealed that the coordination and integration and/or cross talk between the intermediates of 'Toll signaling' has been improved with the increase in complexity among animals most likely during the course of evolution.[8] In addition, unrelenting selective pressure exerted by the rapidly evolving pathogenic organism also contributed in this adaptive evolution of 'Toll' receptor.[8] Particularly for TLR4, evolution of the gene (mostly due to mutation) led to differential expression of TLR4 with different affinity and specificity to its PAMP[8] which may be the reason behind

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