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Toll-like receptors in lymphoid malignancies: Double-edged sword

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Abstract

Toll-like receptors (TLRs) are the best characterized pattern recognition receptors (PRRs), which play an essential role in the recognition of invading pathogens via specific microbial molecular motifs, comprising a bridge between the innate and adaptive immune responses. Toll-like receptors expression is determined in both normal immune cells and malignant cells, with a distinctive pattern compared to each

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other, rendering them plausible targets for cancer therapy. Improved molecular profiling of lymphoid malignancies may give new insights into pathogenesis of these cancers and pave the way for novel therapeutic agents, including TLR agonists. In the current review, we summarize the immunopathogenic roles of TLRs in B cell and T cell lymphomas, acute lymphoblastic leukemia, multiple myeloma, and chronic lymphocytic leukemia, as well as the results of studies on TLR ligands and their future implications to manage these hematologic malignancies.

Keywords: Toll-like receptors; Pattern recognition receptors; Lymphoma; Leukemia

1. Introduction

Toll-like receptors, the best characterized pattern recognition receptors (PRRs), are one of the components of the innate immunity, able to recognize conserved molecular structures of pathogens called pathogen-associated molecular patterns (PAPMs) [1–4]. These mammalian homologues of drosophila Toll proteins include a total of 11 human TLRs, detecting a wide domain of ligands from microbial patterns to endogenous and synthetic ligands [5].

The engagement of TLRs by pathogenic components culminate in the induction of interferons (IFNs), proinflammatory cytokines (IL-1, IL-6, and TNF-α), and chemokines (which orchestrate innate immunity), and upregulation of costimulatory molecules (which promote adaptive T-cell-mediated immunity) [6]. Nuclear factor-kappaB (NF-κB) is a transcription factor that can be considered as the isthmus of TLRs signaling hourglass [7–9]. Activation of the TLRs leads not only to the induction of innate immune responses but also to the development of antigen specific adaptive immunity through activating the antigen-presenting cells (APCs) [10–12]. Most experimental models have shown that TLR agonists conduct adaptive immunity toward a predominantly T-helper1 (Th1) mode, required for efficient tumor clearance [13].

In attempt to determine the contributing roles of individual TLRs in the pathogenesis of infections, allergic diseases, autoimmune disorders, and cancers; extensive experimental studies have been described in the medical literature. Recent advances in TLR-related research have set the stage for potential therapeutic exploitation against diseases, such as lymphoid malignancies [2,14–20].

The natural immune response to the lymphoid malignancies is not optimal per se, because of weak immunogenicity of lymphoid tumor cells, a substantial misfortune due to the escape of tumor cells from the numerous activated tumor-reactive cytotoxic T cells [19]. Targeting the TLRs is a rationale for producing more efficient immune response. To date, few but remarkable investigations have been managed with regard to employing TLRs in lymphoid malignancies, required to be systematically reviewed. This review is composed of three sections. In Section 1, the structure and biological functions of TLRs will be reviewed. In the second section the signaling pathway of TLRs will be briefly discussed. Then in the third section we systematically collect the recent evidence of human trials with regard to therapeutic roles of TLRs' agonists in the field of these hematologic malignancies: (1) B cell and T cell lymphomas, (2) acute lymphoblastic leukemia, (3) multiple myeloma, and (4) chronic lymphocytic leukemia.

2. TLR structure and ligands

TLRs are type 1 integral membrane glycoproteins characterized by an *ectodomain* (extracellular *N*-terminal domain of approximately 16–28 leucine-rich repeats responsible for ligand binding and discrimination, obtaining a sufficient immune response to TLR agonists) and a *cytoplasmic domain* (homologous to the cytoplasmic portion of the IL-1 receptor family, also known as TIR domain) [2,5,6]. Eleven human TLRs and thirteen mouse TLRs have been discovered up to now and each of these TLRs seem to response to distinct class of either PAMPs or non-pathogenic ligands (synthetic and endogenous molecular patterns). Studies of the molecular structure of TLR ectodomains and their ligand complexes have predicted that a vast variety of ligands can be sensed through the TLRs inducing the activation of TLR signaling. Moreover, diverse dimerization of TLRs enables them in more efficient pattern recognition; examples include: the TLR3 homodimer (recognizes double-stranded RNA); TLR1–TLR2 heterodimer (discriminates triacylatedlipopeptides); TLR2–TLR6 heterodimer (discriminates diacylatedlipopeptides); TLR4-MD-2 and TLR4-CD14 heterotetramer (recognize lipopolysaccharides from Gram-negative bacteria) [2,5,6]. Although human TLR10 can be heterodimerized with TLR2 and TLR1, a true ligand for these heterodimers remains masked. Based on the literature, we can categorize the TLR ligands into these groups: (1) exogenous ligands, (2) endogenous ligands, (3) synthetic analogs, and (4) fully synthetic small molecules. Detailed list of already discovered TLR agonists is well described in previous reviews [2,21,22].

Given the location of TLRs, a group of them including TLR3, TLR7, TLR8, and TLR9, are not expressed on the cell membrane; however, they are present within one or more endosomal compartments and can sense nucleic acids [2,23]. Since this subset of TLRs (especially TLR7 and TLR9) is more involved in different aspects of hematologic malignancies discussed below, we provide a brief review of their structure and ligands. Also, Table 1 displays a comprehensive compilation of TLR ligands.

TLR3 has been demonstrated to recognize viral dsRNA and the dsRNA mimic polyriboinosinic polyribocytidylic