Pharmacology & Therapeutics 138 (2013) 441–451

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: M. Belvisi

Toll-like receptors as therapeutic targets for autoimmune connective tissue diseases

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ARTICLE INFO

Keywords:
Toll-like receptor
Autoimmune diseases
Inflammation
Small molecule modulator
Drug discovery

ABSTRACT

Autoimmune connective tissue diseases (ACTDs) are a family of consistent systemic autoimmune inflammatory disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc) and Sjögren's syndrome (SS). IL-1R-like receptors (TLRs) are located on various cellular membranes and sense exogenous and endogenous danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), playing a critical role in innate immune responses. During the past decade, the investigation of TLRs in inflammatory autoimmune diseases has been fruitful. In this report, we review the significant biochemical, physiological and pathological studies of the key functions of TLRs in ACTDs. Several proteins in the TLR signaling pathways (e.g., IKK-2 and MyD88) have been identified as potential therapeutic targets for the treatment of ACTDs. Antibodies, oligodeoxyribonucleotides (ODNs) and small molecular inhibitors (SMIs) have been tested to modulate TLR signaling. Some drug-like SMIs of TLR signaling, such as RDP58, ST2825, ML120B and PHA-408, have demonstrated remarkable potential, with promising safety and efficacy profiles, which should warrant further clinical investigation. Nonetheless, one should bear in mind that all TLRs exert both protective and pathogenic functions; the function of TLR4 in inflammatory bowel disease represents such an example. Therefore, an important aspect of TLR modulator development involves the identification of a balance between the suppression of disease-inducing inflammation, while retaining the beneficiary host immune response.

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Abbreviations: ACTDs, autoimmune connective tissue diseases; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SSc, systemic sclerosis; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; TLRs, IL-1R-like receptors; DAMPs, danger-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; MyD88, myeloid differentiation primary response gene 88; TRIF, Toll/IL-1R (TIR) domain-containing adapter-inducing interferon-β; SARM, sterile α- and armadillo-motif-containing protein; TIRAP, TIR domain-containing adaptor protein; MAL, MyD88 adaptor-like protein; TRAM, TRIF-related adaptor molecule; TRAF, tumor necrosis factor receptor-associated factor; TBK1, TRAF family member-associated NF-κB activator (TANK)-binding kinase 1; RIP1, receptor-interacting protein 1; IRAK, IL-1R-associated kinase; TAK1, transforming growth factor β-activated kinase 1; TAB, TAK1-binding protein; NF-κB, nuclear factor-κB; IKK, inhibitor of NF-κB kinase; IκB, inhibitor of NF-κB; TNF, tumor necrosis factor; IRF, interferon regulatory factor; IFN, interferon; mDCs, myeloid dendritic cells; MKK, mitogen-activated protein kinase kinase; JNK, JUN N-terminal kinase; LPS, lipopolysaccharide; MD-2, myeloid differentiation protein 2; HMGB1, high mobility group box 1; FcγRs, Fc γ receptors; RAGE, receptor for advanced glycation end products; APCs, antigen-presenting cells; dsDNA, double-stranded DNA; poly(I:C), polyinosinic/polycytidylic acid; BCR, B cell receptor; PBMCs, peripheral blood mononuclear cells; IRF7, interferon regulatory factor 7; PAD, peptidyl arginine deiminase; ACPA, anti-citrullinated peptide antibodies; IRGs, interferon responsive genes; SGECs, salivary gland epithelial cells; SMIs, small molecule inhibitors; STAT3, signal transducer and activator of transcription 3; AID, activation-induced cytidine deaminase;; ODNs, oligodeoxyribonucleotides; MMP-9, matrix metalloproteinase-9; ML, mycobacterial lipomannans; IBD, inflammatory bowel disease.

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0163-7258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2013.03.003

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1. Introduction

Autoimmune connective tissue diseases (ACTDs) are characterized by the spontaneous stimulation of the immune system with the production of autoantibodies, which are specific for self-components in the nucleus and cytoplasm, often macromolecular complexes of proteins and nucleic acids. ACTDs can affect any connective tissue of the human body via inflammation or destruction. Possible causes of ACTDs include genetic (Romano et al., 2011; Chai et al., 2012), hormonal (Jacobson et al., 1997; Luppi, 2003) and environmental factors (Arnson et al., 2010); genetic factors may predispose an individual to the development of ACTDs. The classic ACTDs include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), Sjögren's syndrome (SS) and mixed connective tissue disease (MCTD) (Diamond & Lipsky, 2008).

Toll-like receptors (TLRs) are a family of evolutionarily conserved innate immune receptors that play a crucial role in the first-line defense against foreign agents. These protein receptors are characterized by their ability to respond to invading pathogens promptly by recognizing particular TLR ligands, including flagellin and lipopolysaccharide (LPS) of bacteria, nucleic acids derived from viruses and zymosan of fungi (Takeuchi et al., 2002). These ligands can activate dendritic cells (DCs), macrophages, B cells, T cells and other antigen-presenting cells (APCs). These immunocompetent cells express different subsets of TLRs (Table 1) and TLR activation allows for the effective presentation of microbial antigens to cells of the adaptive immune system. However, recent findings have also revealed that TLRs recognize and respond to endogenous ligands produced during infection or damage (Okamura et al., 2001; Smiley et al., 2001; Asea et al., 2002; Termeer et al., 2002; Vabulas et al., 2002; Park et al., 2004; Brentano et al., 2005; Vollmer et al., 2005; Yasuda et al., 2009) (Table 2). The identification and characterization of endogenous ligands of TLRs provide a novel perspective for exploring the etiology of autoimmune diseases. After ligands bind to TLRs or their accessory protein, such as myeloid differentiation protein 2 (MD-2) for TLR4, TLRs dimerize (hetero- or homodimerize) and undergo a conformational change that in turn leads to the recruitment of downstream signaling molecules. A family of five adaptor proteins known as myeloid differentiation primary response gene 88 (MyD88), TIR domain-containing adaptor protein (TIRAP)/MyD88 adaptor-like protein (MAL), Toll/IL-1R (TIR) domain-containing adapter-inducing interferon-β (TRIF), TRIF-related adaptor molecule (TRAM) and sterile α- and armadillo motif-containing protein (SARM) are involved in the downstream signaling pathways of TLRs (O'Neill et al., 2003; O'Neill & Bowie, 2007; Roelofs et al., 2008). These downstream pathways also involve many kinases (IRAKs, TAK1, MAPK, PI3K, etc.), IRFs and NF-κB (for a recent review, see Akira & Takeda, 2004), which leads to the production of pro-inflammatory factors (IFN-α, IFN-β, IFN-γ, IL-6, etc.), perpetuating inflammation (Fig. 1).

Increasing evidence suggests that innate and adaptive immune responses that mediate autoimmune diseases are, at least in part, driven by the binding of PAMPs and DAMPs to TLRs (Mills, 2011). TLR activation induces the production of pro-inflammatory factors and type I interferons, which contributes to the development and/or progression of systemic autoimmune diseases (Marshak-Rothstein, 2006). Therefore, targeting TLRs and modulating TLR signaling have emerged as an important strategy for the treatment of ACTDs.

Table 1
Expression profile of TLRs among different immunocompetent cells.

Cell type	TLRs expressed	Ref.
Macrophage	TLR1-9	McCoy and O'Neill, 2008
B cell	TLR1, TLR2, TLR3, TLR4, TLR6, TLR7 and TLR9, but not TLRs TLR5 and TLR8	Gururajan et al., 2007
T cell	TLR1-9	Babu et al., 2006; Tabiasco et al., 2006
Dendritic cell	TLR1-9	Reis e Sousa, 2004

Note: TLR expression levels show a high degree of variation among individuals. In mice, there may be strain-specific differences in TLR expression.

2. Systemic lupus erythematosus and TLRs

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that involves almost every organ of the human body, including the skin, kidney, blood cells, blood vessels, heart, pleura, central and peripheral nervous systems, muscles and joints (Tassiulas & Boumpas, 2008). Approximately 40% of SLE patients exhibit defects in the clearance of apoptotic cells, which are removed rapidly by macrophages in healthy individuals (Kruse et al., 2010). An SLE murine model also shows a defect in the clearance of cellular debris (Herrmann et al., 1998). The inefficient clearance of cellular debris leads to an increased release of host DNA and RNA, which induces the production of autoantibodies (Kruse et al., 2010). A number of studies have provided data consistent with the idea that TLRs recognize the host DNA/RNA-containing immune complex and promote the inflammation and activation of immune cells, leading to the production of pathogenic autoantibodies and the development of clinical features of autoimmunity.

2.1. TLR3

TLR3 in SLE patients may act on mesangial cells in kidneys directly. The TLR3 ligand polyinosinic/polycytidylic acid (poly(I:C)) worsens glomerulonephritis in $MRL^{lpr/lpr}$ mice without an increased titer of anti-dsDNA antibodies (Patole et al., 2005). Nonetheless, deactivation of TLR3 does not affect the production of autoantibodies against either RNA- or DNA-containing antigens or the severity of glomerulonephritis (Christensen et al., 2005).

2.2. TLR4

The function of TLR4 is associated with the production of autoantibodies and glomerulonephritis in SLE. A repeated injection of low-dose LPS into lupus-prone mice (MRL/n, BXSB, or NZW) accelerates the development of lupus, increases the production of autoantibodies and worsens renal injury (Hang et al., 1983). Activation of TLR4 results in the production of anti-dsDNA antibodies and the development of immune complex-mediated glomerulonephritis in transgenic mice (Liu et al., 2006). Inhibition of TLR4 signaling by Chaperonin 10 has been found to suppress cutaneous lupus and lupus nephritis (Kulkarni et al., 2012). These results suggest that enhanced TLR4 signaling alone is a sufficient and a potent trigger to induce SLE. Renal injury is reduced and anti-nuclear, anti-dsDNA and anti-cardiolipin antibodies titers are decreased in TLR4-deficient $C57BL/6^{lpr/lpr}$ mice compared with TLR4-producing $C57BL/6^{lpr/lpr}$ mice