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Hot Topic

Toll like receptors and pancreatic diseases: From a pathogenetic mechanism to a therapeutic target

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ABSTRACT

Toll-like receptors (TLRs) mediate interactions between environmental stimuli and innate immunity. TLRs play a major role in the development of numerous pancreatic diseases, making these molecules attractive as potential therapeutic targets. TLR2, TLR7 and TLR9 are involved in the initiation of type 1 diabetes mellitus (T1DM), whereas TLR2 and TLR4 play a major role in the onset of type 2 diabetes mellitus (T2DM). Furthermore, TLRs cause derangements in several tumor suppressor proteins (such as p16, p21, p27, p53 and pRb), induce STAT3 activation and promote epithelial–mesenchymal transition as well as oncogene-induced senescence. In this review we will focus on the contribution of TLRs in pancreatic disease including cancer and we describe recent progress in TLR-modulation for the treatment of these patients.

Introduction

Activation of innate immunity is achieved through the stimulation of pattern recognition receptors (PRRs). Among them, Toll-like receptors (TLRs) were the first group to be identified. They can be activated by a panel of pathogen-associated molecular patterns (PAMPs) [1,2] and alarmins [3] endogenous molecules released by activated or necrotic cells in response to stress or tissue damage into the extracellular compartment [4].

Another feature of PPRs is their capability to recognize self-molecular patterns originated from damaged cells, named Damage Associated Molecular Patterns (DAMPs).

TLRs are single-pass transmembrane proteins with an intracellular C-terminal tail known as the Toll/IL-1 receptor (TIR) and an extracellular N-terminal that contains leucine-rich repeats (LRRs). TLR ligation leads to activation of two major intracellular signaling pathways. All TLRs, except TLR3, can activate a Myeloid differentiation primary response protein 88 (MyD88)-dependent pathway (Fig. 1). This pathway involves IL-1R-associated kinases (IRAK), tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF-6) and mitogen-activated kinases and leads to the transcription of pro-inflammatory genes through the activation of nuclear factor κβ (NFκB) and/or the activation of activating protein 1 [5,6]. Furthermore, TLR3 and TLR4 can activate the TIRAP inducing interferon β (TRIF) pathway, leading to the synthesis of interferon-α/β (IFN-α/β) [5].

At present, twelve TLRs have been identified in mice (TLR1–TLR9 and TLR11–TLR13) and ten in human (TLR1–TLR10) [3]. Most TLRs are on the cell surface, except for TLR3, -7, -8, and -9, mainly present in the endosomes [2]. A further classification divides TLRs based on the type of recognized PAMPs: TLR1, TLR2, TLR4 and TLR6 detect lipids, whereas TLR5 and TLR 10 recognize proteins and TLR3, TLR7, TLR8 and TLR9 detect nucleic acids [5]. The list of PAMPs and alarmins recognized by human TLRs is shown in Table 1.

The involvement of TLRs in the pathophysiology of several diseases has become a major research field [6,7]. This review summarizes the role of TLRs in the pathogenesis of inflammatory related pancreatic disease as well of pancreatic cancer, highlighting their potential use as future therapeutic targets.

Methods

Data for this review were identified from the Pubmed database, using the subsequent MeSH (Medical Subject Heading) terms:

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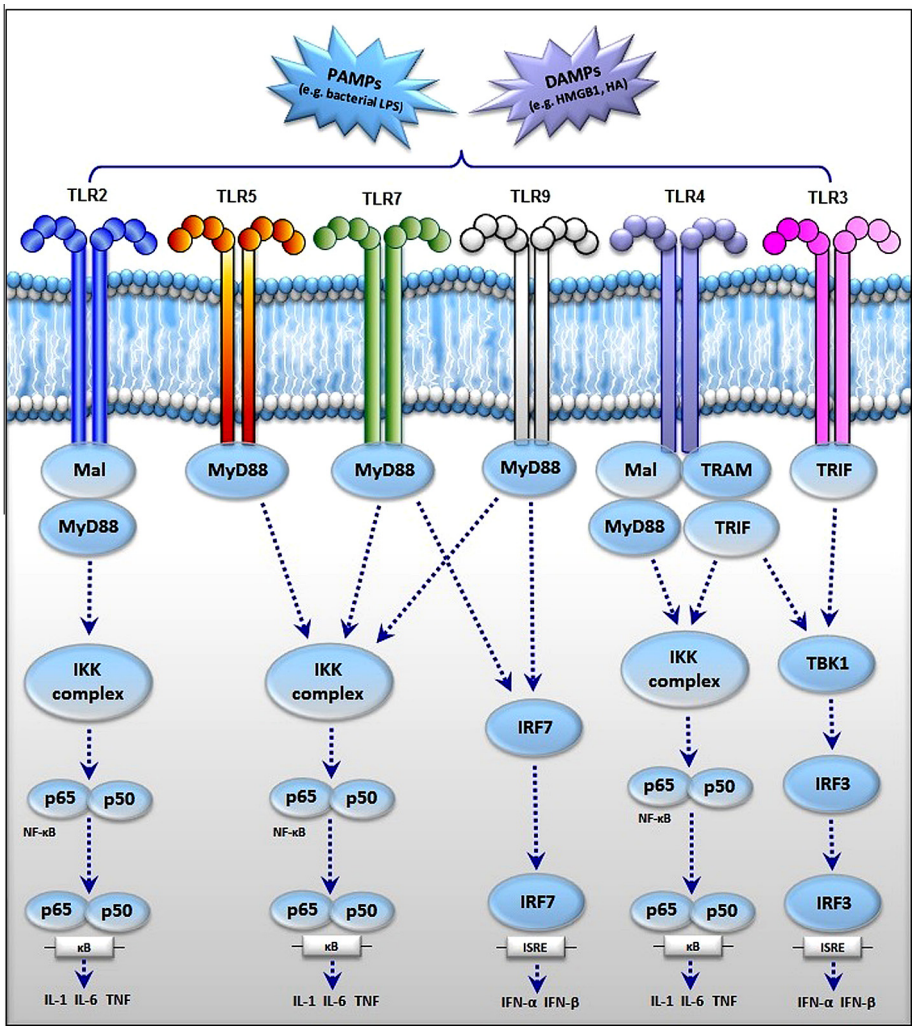

Fig. 1. TLR signaling pathways. All TLRs except TLR3 can activate a Myeloid differentiation primary response protein 88 (MyD88)-dependent pathway. TLR2 and TLR4 also recruit a MyD88-like adaptor molecule Mal, thus activating NF-κB through an IkB kinase (IKK) complex. NF-κB then translocate to the nucleus where it binds to κB promoter elements resulting in the expression of inflammatory cytokines, such as TNF-α, IL-1 and IL-6. TLR3 via the TIR-domain containing-adaptor inducing interferon-b (TRIF) leads to the activation of interferon regulatory factor (IRF) 3. IRF3 dimerises and translocates into the nucleus and binds to interferon-sensitive response element (ISRE) motifs, thus promoting the expression of interferon (IFN)-α/β. TLR4 can also utilize the TRIF-related adaptor molecule (TRAM) for the activation of NF-κB and IRF3. On the other hand, TLR7 and TLR9 can also activate IRF3 related molecules such as IRF7, leading to the expression of IFN-α/β.

Table 1
Ligand recognition by Toll-like receptors.

TLRs	Localization	PAMP	Origin of PAMP
TLR1	Plasma membrane	Triacyl lipopeptides	*N. meningitidis* triacyl lipopeptides bacteria, mycobacteria
TLR2	Plasma membrane	Glycoinositolphospholipids, glycolipids, haemagglutinin, lipoarabinomannan, lipoprotein/ LIPOPEPTIDES, lipoteichoic acid, zymosan, peptidoglycan, phenol-soluble modulin, porins	*Trypanosoma cruzi*, *Treponema maltophilum*, virus, mycobacteria, various pathogens, gram-positive bacteria, gram-positive bacteria, *S. epidermidis*, neisseria, fungi
TLR3	Endosome	Double-stranded RNA	Virus
TLR4	Plasma membrane	Envelope protein, fusion protein, heat-shock protein 60, lipopolysaccharide, taxol	Mouse-mammary tumor virus, respiratory syncytial virus, *Chlamydia pneumoniae*, gram-negative bacteria, plants,
TLR5	Plasma membrane	Flagellin	Bacteria
TLR6	Plasma membrane	Diacyl lipopeptides, zymosan, lipoteichoic acid	Mycoplasma, gram-positive bacteria, fungi
TLR7	Endosome	Single-stranded RNA	Virus
TLR8	Endosome	Single-stranded RNA	Virus
TLR9	Endosome	DNA (CpG), haemozoin	Bacteria, virus, *Plasmodium* spp., *Rhodnius* spp., *Schistosoma* spp.
TLR10	Endosome	Not determined	Not determined

"Inflammation", "Immune Response" "TLR", "Toll-like receptor", each combined with "Cancer", "Diabetes", "Pancreatitis", "Pancreatic cancer", "Pancreatic Ductal Adenocarcinoma", "Sterile Inflammation", and "Systemic Inflammatory Response Syndrome (SIRS)". A further search was done of related articles and references from relevant papers. The ongoing trials were searched out on the official website www.clincaltrials.gov, with the last search on April 2014. No language was restricted. The final reference list was