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The toll-like receptor 3 pathway in homeostasis, responses to injury and wound repair

Divya Ramnath[a,b,c], Elizabeth E. Powell[d,e], Glen M. Scholz[f,g], Matthew J. Sweet[a,b,c,*]

[a] Institute for Molecular Bioscience (IMB), The University of Queensland, Brisbane, Qld 4072, Australia
[b] IMB Centre for Inflammation and Disease Research, The University of Queensland, Brisbane, Qld 4072, Australia
[c] Australian Infectious Disease Research Centre, The University of Queensland, Brisbane, Qld 4072, Australia
[d] Centre for Liver Disease Research, School of Medicine, The University of Queensland, Translational Research Institute, Brisbane, Qld 4102, Australia
[e] Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, Qld 4102, Australia
[f] Melbourne Dental School and Oral Health Cooperative Research Centre, The University of Melbourne, Parkville 3010, Australia
[g] Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville 3010, Australia

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ABSTRACT

In addition to their established roles in host defence, Toll-like Receptors (TLRs) have emerging roles in control of homeostasis, injury and wound repair. The dsRNA-sensing receptor, TLR3, has been particularly implicated in such processes in several different tissues including the skin, intestine and liver, as well as in the control of reparative mechanisms in the brain, heart and kidneys, following ischemia reperfusion injury. In this review, we provide an overview of TLR3 signalling and functions in inflammation, tissue damage and repair processes, as well as therapeutic opportunities that may arise in the future from knowledge of such pathways.

Contents

Abbreviations: BBB, blood brain barrier; Bcl2, B-cell CLL/lymphoma 2; CNS, Central nervous system; CXCL, C-X-C motif ligand; EBI3, Epstein-Barr virus induced gene 3; FADD, Fas-associated death domain; HBV, Hepatitis B virus; HSC, Hepatic stellate cell; HSV, Herpes simplex virus; I/R, Ischemia reperfusion; IAV, Influenza A virus; IEC, Intestinal epithelial cell; IFN, Interferon; IL, Interleukin; IRF, Interferon regulatory factor; MAL, MyD88 adaptor-like; MAPK, Mitogen-activated protein kinase; MyD88, Myeloid differentiation primary response gene 88; NF-κB, Nuclear factor kappa B; PAMP, Pathogen-associated molecular pattern; Poly(IC), Polyinosinic-polycytidylic acid; PRR, Pattern recognition receptor; RHIM, Receptor-interacting protein homotypic interaction motif; RIPK, Receptor-interacting protein kinase; TBK–1, TANK binding kinase 1; TGM1, Transglutaminase-1; TICAM, TIR-containing adaptor molecule; TIR, Toll interleukin 1 receptor; TIRAP, TIR domain-containing adaptor protein; TLR, Toll-like Receptor; TNF-α, Tumor Necrosis factor alpha; TRAF6, Tumor Necrosis factor receptor-associated factor-6; TRAM, TRIF-related adaptor molecule; TRIF, TIR domain-containing adaptor-inducing IFN; UV, Ultraviolet; WNV, West Nile virus.

* Corresponding author at: Institute for Molecular Bioscience, University of Queensland, St Lucia, Brisbane 4072, Australia.
E-mail address: m.sweet@imb.uq.edu.au (M.J. Sweet).

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1. Introduction

Pattern recognition receptors (PRRs) are widely studied in innate immune cells for their roles in host defence. In this context, they are tasked with detecting and responding to conserved pathogen-associated molecular patterns (PAMPs), which are essential for microbial survival and/or pathogenicity [1]. It is now clear that PRRs function more broadly as danger-sensing systems, detecting both pathogen- and host-derived factors that accumulate when homeostasis is perturbed. Indeed, PRRs have emerged as critical regulators of homeostasis and developmental processes. Such roles may relate to PRR functions in non-immune cells such as epithelial cells, where they are also expressed [2].

Of the PRR families, the Toll-like receptors (TLRs) have been most widely studied. These transmembrane receptors, which localize to both the plasma membrane and to endolysosomal compartments, play key roles in development, homeostasis and injury repair. For example, TLR2, which detects bacterial lipopeptides, maintains homeostasis at mucosal surfaces by promoting barrier integrity in intestinal epithelial cells (IECs) [2]. Along with TLR4, which recognizes Gram-negative bacterial lipopolysaccharide, TLR2 has also been implicated as a regulator of cardiovascular functions, thermoregulation and energy metabolism in the autonomic nervous system [3]. Such studies provide examples of roles for innate immune danger-sensors in regulating normal physiological processes to maintain homeostasis. Indeed, the capacity of TLRs to regulate the expression of genes involved in inflammation and repair processes, often in a tissue-specific manner, appears to be critical for maintenance of normal physiological processes [2].

TLR3 is a dsRNA-sensing TLR, first characterized as a regulator of anti-viral responses. However, subsequent studies demonstrated that TLR3 can also detect host-derived RNA, thus enabling it to regulate injury repair processes. In this review, we provide an overview of TLR3 biology in the context of host defence and inflammation. We particularly focus on TLR3 functions in wound healing and in homeostatic control in the skin, gastrointestinal tract and liver, as well as during ischemia reperfusion (I/R) injury in the brain, heart and kidney (Fig. 1). Given that TLR3 agonists and antagonists already exist, manipulation of this pathway to accelerate tissue repair processes may be feasible in some pathophysiological settings.

2. TLR3 signal transduction and its role in host defence

2.1. Overview of TLR signalling

A total of thirteen TLRs have been identified in humans and mice; ten in humans (TLR1-10) and twelve in mice (TLR1-9, 11–13) [4]. Each TLR recognizes cognate PAMPs, resulting in activation of distinct but overlapping signalling pathways through the initial recruitment of specific combinations of Toll/Interleukin (IL)-1 Receptor (TIR) domain-containing adaptor proteins. Briefly, upon activation, all TLRs, except for TLR3, recruit the adaptor protein myeloid differentiation primary response gene 88 (MyD88), which contains a C-terminal TIR domain and an N-terminal death domain [5]. In the case of TLR4 and TLR2, MyD88-adaptor-like (MAL; also known as TIR domain-containing adaptor protein, TIRAP) acts as a bridging adaptor between MyD88 and these TLRs. Recently, TLR5 in IECs [6], and TLR7 and TLR9 in macrophages [7], have also been shown to associate with MAL, thus implicating this adaptor in tissue-specific responses to multiple TLRs. MyD88 then relays downstream signalling via the serine/threonine kinase IL-1R-associated kinases, the E3-ubiquitin ligase and scaffolding protein tumour necrosis factor (TNF) receptor-associated factor-6 (TRAF6) and the mitogen-activated protein kinases (MAPKs) [5]. This ultimately enables activation of pro-inflammatory transcription factors such as nuclear factor kappaB (NF-κB) and activator protein-1 to drive inducible expression of pro-inflammatory target genes such as IL-1β, IL-6 and TNF-α (for reviews see [5,8,9]).

TLR3 and TLR4 are both capable of signalling independently of MyD88, via the TIR domain-containing adaptor-inducing interferon (TRIF; also known as TIR-containing adaptor molecule 1, TICAM1) pathway [5]. TLR4 engages both MyD88 and TRIF, whereas TLR3 uses TRIF exclusively. TLR4 initiates the MyD88-dependent pathway at the plasma membrane, whilst signalling switches to TRIF-mediated responses once TLR4 is endocytosed [10]. Endosomal TLR4 signalling via TRIF requires the bridging adaptor TRIF-related adaptor molecule (TRAM; also known as TIR-containing adaptor molecule 2, TICAM2) [10]. TRIF signalling activates the serine/threonine kinase TANK binding kinase-1 (TBK-1), which phosphorylates the transcription factor interferon (IFN) regulating factor 3 (IRF3) [5]. IRF3 phosphorylation enables it to translocate to the nucleus and activate specific pro-inflammatory target genes, for example *IFN-β*, which encodes a type-1 IFN [5].

2.2. TLR3 signalling

Although TLR3 signalling has been extensively characterized, some new players and regulatory mechanisms have recently emerged (Fig. 2). TLR3 is assembled in the endoplasmic reticulum, from where it is recruited to endosomes by the transmembrane protein UNC93B1 [11]. It is the only TLR that directly recruits TRIF to its TIR domain to initiate signalling. This may relate to the fact that the conserved proline residue present in the BB-loop of most TLR TIR domains is an alanine in TLR3. Indeed, mutation of Ala795 in TLR3 to a proline resulted in MyD88-biased signalling [12]. As with TLR4 signalling, TRIF recruitment to TLR3 leads to the activation of the serine/threonine kinase TBK-1, which in turn phosphorylates IRF3 [13,14]. Phosphorylation occurs at multiple residues (e.g. Ser385, Ser386) in the C-terminal region of IRF3, enabling dimerization, nuclear translocation and transcription of *IFN-β* [15,16]. IFN-β signals in an autocrine fashion to activate the transcription factors signal transducer and activator of transcription (STAT) 1 and 2, resulting in the activation of type-1 IFN target genes and subsequent anti-viral responses [17]. Although IRF3 is the primary transcription factor driving IFN-β transcription during TLR3 signalling, other IRFs also function downstream of TLR3 to impart cell-specific signalling responses. For example, IRF6 is an epithelial cell-specific transcription factor that lies downstream of TLR3 signalling in keratinocytes. Specifically, it inhibits poly(IC)-inducible *IFN-β* expression, while promoting poly(IC)-inducible *IL-23p19* expression in primary human keratinocytes [18].

In addition to activating IRF3, TLR3 signalling via TRIF also activates NF-κB [19,20]. The C-terminal region of TRIF contains a receptor-interacting protein homotypic interaction motif (RHIM),

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