Experimental Neurology 258 (2014) 5–16

Contents lists available at ScienceDirect

Experimental Neurology

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

Review

Pattern recognition receptors and central nervous system repair

Kristina A. Kigerl [a], Juan Pablo de Rivero Vaccari [b], W. Dalton Dietrich [b], Phillip G. Popovich [a,*], Robert W. Keane [c,**]

[a] Department of Neuroscience — Center for Brain and Spinal Cord Repair, Wexner Medical Center at The Ohio State University, USA
[b] Department of Neurological Surgery — The Miami Project to Cure Paralysis, USA
[c] Department of Physiology & Biophysics — University of Miami Miller School of Medicine, Miami, FL 33136, USA

ARTICLE INFO

Article history:
Received 20 November 2013
Revised 31 December 2013
Accepted 2 January 2014

Keywords:
Pattern recognition receptors
Spinal cord injury
Toll-like receptors
NOD-like receptors
Inflammasome
Neuroinflammation

ABSTRACT

Pattern recognition receptors (PRRs) are part of the innate immune response and were originally discovered for their role in recognizing pathogens by ligating specific pathogen associated molecular patterns (PAMPs) expressed by microbes. Now the role of PRRs in sterile inflammation is also appreciated, responding to endogenous stimuli referred to as "damage associated molecular patterns" (DAMPs) instead of PAMPs. The main families of PRRs include Toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-like receptors (RLRs), AIM2-like receptors (ALRs), and C-type lectin receptors. Broad expression of these PRRs in the CNS and the release of DAMPs in and around sites of injury suggest an important role for these receptor families in mediating post-injury inflammation. Considerable data now show that PRRs are among the first responders to CNS injury and activation of these receptors on microglia, neurons, and astrocytes triggers an innate immune response in the brain and spinal cord. Here we discuss how the various PRR families are activated and can influence injury and repair processes following CNS injury.

Contents

* Correspondence to: P. G. Popovich, Department of Neuroscience, Wexner Medical Center at The Ohio State University, 460 W. 12th Ave., Columbus, OH 43210, USA. Fax: +1 614 688 5463.
** Correspondence to: R. W. Keane, Department of Physiology and Biophysics, University of Miami Miller School of Medicine, 1600 NW 10th Ave, Miami, FL 33136-1060, USA. Fax: +1 305 243 5931.
E-mail addresses: phillip.popovich@osumc.edu (P.G. Popovich), rkeane@miami.edu (R.W. Keane).

0014-4886/$ – see front matter © 2014 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.expneurol.2014.01.001

Introduction

Pattern recognition receptors (PRRs)

The innate immune system senses potential pathogens and detects disruptions in tissue homeostasis by several receptor families. Collectively, these receptor families are referred to as pattern recognition receptors (PRRs) (Janeway, 1992). Unlike receptors involved in the adaptive immune response that are customized to recognize a specific protein or antigen, PRRs detect general "patterns" or sequences/structures commonly present on the surface of potential pathogens called pathogen associated molecular patterns (PAMPs). These receptors are highly conserved across multiple species and can be one of the first lines of defense against a possible infection. In addition to responding to PAMPs, PRRs also respond to "danger" signals or danger-associated molecular patterns (DAMPs). The "danger hypothesis" of immune system function was first proposed by Matzinger (1994, 1998) in direct opposition to the idea that the immune system evolved to recognize self vs. non-self. This theory has grown as more endogenous ligands have been identified that are recognized by PRRs (Table 1). There are several sub-families of PRRs including Toll-like receptors (TLRs), Nod-like receptors (NLRs), C-type lectin receptors (CLRs), and RIG-like receptors (RLRs); each helps to orchestrate the innate immune response (Fig. 1). Some of these receptors are expressed on the cell surface (i.e. scavenger receptors and some TLRs) and facilitate surveillance of the extracellular environment while others are expressed intracellularly (NLRs, RLRs, some TLRs) and are activated by internalized inflammatory stimuli (e.g., DNA or RNA). Activation of these PRRs leads to production of inflammatory mediators that help remove pathogens or restore tissue homeostasis (Fig. 2). However, chronic activation of these receptors can cause inflammatory disease.

Pathogen associated molecular patterns and damage associated molecular patterns

Tissue injury, cellular stress, or disease induces the release of molecules that stimulate an innate immune response. Molecules released from pathogens are known as pathogen associated molecular patterns (PAMPs) whereas molecules of endogenous origin that are released from cells or from compartments within the cell into the cytoplasm are termed danger or damage associated molecular patterns (DAMPs) (Tang et al., 2012). DAMPs are released into the cytoplasm after central nervous system (CNS) injury and are recognized by several PRRs. DAMPs are also known as alarmins (Bianchi, 2007) and include heat shock proteins (hsp), hyaluronan, uric acid, galectins, thioredoxin (TRX), adenosine triphosphate (ATP), high mobility group box 1 (HMGB1), IL-1α and IL-33. Alarmins and DAMPs have been recently reviewed (Hirsiger et al., 2012), so only those DAMPs that are known or suspected to activate PRRs following CNS injury are considered in this review.

Pattern recognition receptor families

Toll-Like receptors

Toll-like receptors (TLRs) are homologues of the Toll receptor first identified in *Drosophila* (Medzhitov et al., 1997; Rock et al., 1998; Taguchi et al., 1996). In *Drosophila*, Toll plays a role during development in dorsal–ventral patterning and is important for anti-fungal immunity (Anderson et al., 1985a, 1985b; Hashimoto et al., 1988; Lemaitre et al., 1996). The existence of human TLRs and their pivotal role in innate immune function was first discovered in the 1990s (Janeway, 1992; Medzhitov et al., 1997; Nomura et al., 1994; Poltorak et al., 1998; Taguchi et al., 1996). To date, 13 murine TLRs and 10 human TLRs have been identified. TLRs are expressed in intracellular endosomal compartments (TLR3, TLR7, TLR8 and TLR9) or as transmembrane (cell-surface) receptors (all other TLRs). The extracellular domains of TLRs contain leucine-rich repeats (LRRs) (Fig. 1), which are believed to recognize the molecular structure of PAMPs/DAMPs (Table 1). Bacterial lipopolysaccharide (LPS) was the first identified ligand for TLRs, specifically as a ligand for TLR4 (Poltorak et al., 1998).

TLRs belong to the Toll/interleukin-1 receptor (TIR) family and signal via a TIR domain located on the cytosolic end of the receptor (Fig. 1). TLR signaling is initiated by dimerization and recruitment of adapter proteins such as MyD88, which is an adapter protein used by all TLRs except TLR3. Recruitment of MyD88 occurs through specific TIR–TIR domain interactions that activate IL-1R-associated kinases

Table 1
Microbial and endogenous ligands for PRRs.

Receptor	PAMPs	DAMPs	References
TLR1	Peptidoglycan (with TLR2), triacylated lipoproteins		
TLR2	Peptidoglycan, zymosan, lipoteichoic acid	HSP60, HSP70, HMGB1, versican, necrotic cells	Asea et al. (2002); Vabulas et al. (2001), Li et al. (2001), Yu et al. (2006); Park et al. (2004), Kim et al. (2009)
TLR3	Viral dsRNA	mRNA	Kariko et al. (2004)
TLR4	LPS	HMGB1, HSP60, HSP70, hyaluronic acid, fibronectin, fibrinogen	Ohashi et al. (2000), Asea et al. (2002), Vabulas et al. (2001), Termeer et al. (2002), Okamura et al. (2001), Smiley et al. (2001), Yu et al. (2006), Park et al. (2004)
TLR5	Bacterial flagellin		
TLR6	Peptidoglycan (with TLR2), diacylated lipoproteins		
TLR7	ssRNA	miRNA, RNA	Lehmann et al. (2012)
TLR8	ssRNA		
TLR9	Unmethylated CpG DNA	mtDNA; n-formyl peptides	Zhang et al. (2010)
TLR11	Uropathogenic *E. coli*		
NLRs	Bacterial muramyl dipeptide (MDP), DAP-PGN, anthrax toxin, bacterial RNA	ATP, uric acid crystals, Ca^{++}, K^{+} efflux, acidosis, amyloid-β	Halle et al. (2008), Lee et al. (2012), Mariathasan et al. (2006), Martinon et al. (2006); Murakami et al. (2012), Petrilli et al. (2007), Rajamäki et al. (2013), Rossol et al. (2012), Minkiewicz et al. (2013)
RLRs	Viral dsRNA, polyA:C	ROS	Tal et al. (2009)
ALRs	dsDNA, polyA:T	Cytosolic DNA	Adamczak et al. (2012), Hornung et al. (2009)