Review

Innate antiviral signalling in the central nervous system

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The innate immune system mediates protection against neurotropic viruses capable of infecting the central nervous system (CNS). Neurotropic viruses include herpes simplex virus (HSV), West Nile virus (WNV), rabies virus, La Crosse virus, and poliovirus. Viral infection triggers activation of pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), retinoic acid-inducible gene 1 (RIG-I) like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and cytosolic DNA sensors. Although originally characterised in peripheral immune cells, emerging evidence points to important roles for these PRRs in cells of the CNS. Here, we review recent advances in our understanding of the mechanisms by which these PRRs provide protection against neurotropic viruses, and discuss instances in which these responses become detrimental and cause immunopathology in the CNS.

PRRs control antiviral immunity

The CNS occupies a pivotal role in living organisms associated with cognition and higher-order functions and is key to their successful survival and propagation. Similar to many other organs, the CNS is susceptible to infection by invading microorganisms including viruses. Therefore, it is not surprising that mechanisms exist in the CNS to defend against such infections. The innate immune system consists of a network of PRRs that detect conserved pathogen-associated molecular patterns (PAMPs) of microbes [1]. These PRRs activate the transcription factors nuclear factor (NF)-κB and interferon (IFN) regulatory factor (IRF) family members such as IRF3. This results in the activation of mechanisms of direct intrinsic immunity, which include inhibition of protein synthesis, and also in the secretion of effector cytokines, chemokines and type 1 IFNs (IFNα and IFNβ) (Figure 1). In the context of antiviral immunity, specific PRRs are activated by nucleic acids, the dominant PAMPs of viral infection. This initial host response to infection also triggers and shapes the ensuing adaptive immune response [2]. Although best characterised in the periphery, there is a growing understanding of the innate mechanisms of antiviral immunity that function in the CNS.

Type I IFNs in particular are powerful antiviral mediators and establish an 'antiviral state' in infected and adjacent cells. Mechanistically, this occurs by the binding of IFNα and IFNβ to the IFN-α/β receptor (IFNAR), leading to the expression of IFN response genes (ISGs). These ISGs, numbering more than 300 [3], have a wide range of antiviral activity and include ISG49, ISG54, and ISG56, which are expressed in the CNS after viral infection [79].

Four main classes of PRRs have been reported: TLRs, RLRs, NLRs, and cytosolic DNA sensors [5]. Many of these receptors and their associated intracellular signalling molecules are expressed in cells of the CNS [6], and so might be expected to respond to the wide range of viruses capable of infecting the CNS, including HSV, WNV, rabies virus, and poliovirus. Here, we review recent findings that provide new insights into how the innate immune system of the CNS, and PRRs in particular, provide immunity to such viruses. We also discuss how viral activation of innate immunity in the CNS can, in some instances, lead to the overproduction of inflammatory mediators resulting in virally induced neuropathology.

Viral sensing by TLRs in the CNS

TLRs are the best studied PRRs, of which, ten are functional in humans and 12 in mice [7]. TLRs can be broadly grouped into those that are expressed on the cell surface and detect PAMPs of mainly bacterial origin, and those that are expressed intracellularly in endosomes and detect viral nucleic acids [8]. The latter include a receptor that detects double-stranded RNA (dsRNA) (TLR3), two that sense single-stranded RNA (ssRNA) (TLR7 and TLR8), and one that responds to undermethylated (CpG) double-stranded DNA (dsDNA) (TLR9). Signalling downstream of TLRs relies on the recruitment of the Toll-interleukin receptor (TIR) adaptor proteins myeloid differentiation primary response 88 (MyD88), MyD88 adaptor like/toll-interleukin 1 receptor (TIR) domain-containing adaptor protein (Mal/TIRAP), Toll/IL-1 receptor domain-containing adaptor inducing IFN-β (TRIF) and TRIF-related adaptor molecule (TRAM) [9]. MyD88, the prototypical member of the TIR group, is utilised by all TLRs with the exception of TLR3, which uses TRIF. Engagement of TLRs triggers TIR adaptor recruitment to activate IκB kinases (IKK)s such as TANK binding kinase 1 (TBK1) and IKKβ culminating in the activation of NF-κB and IRF

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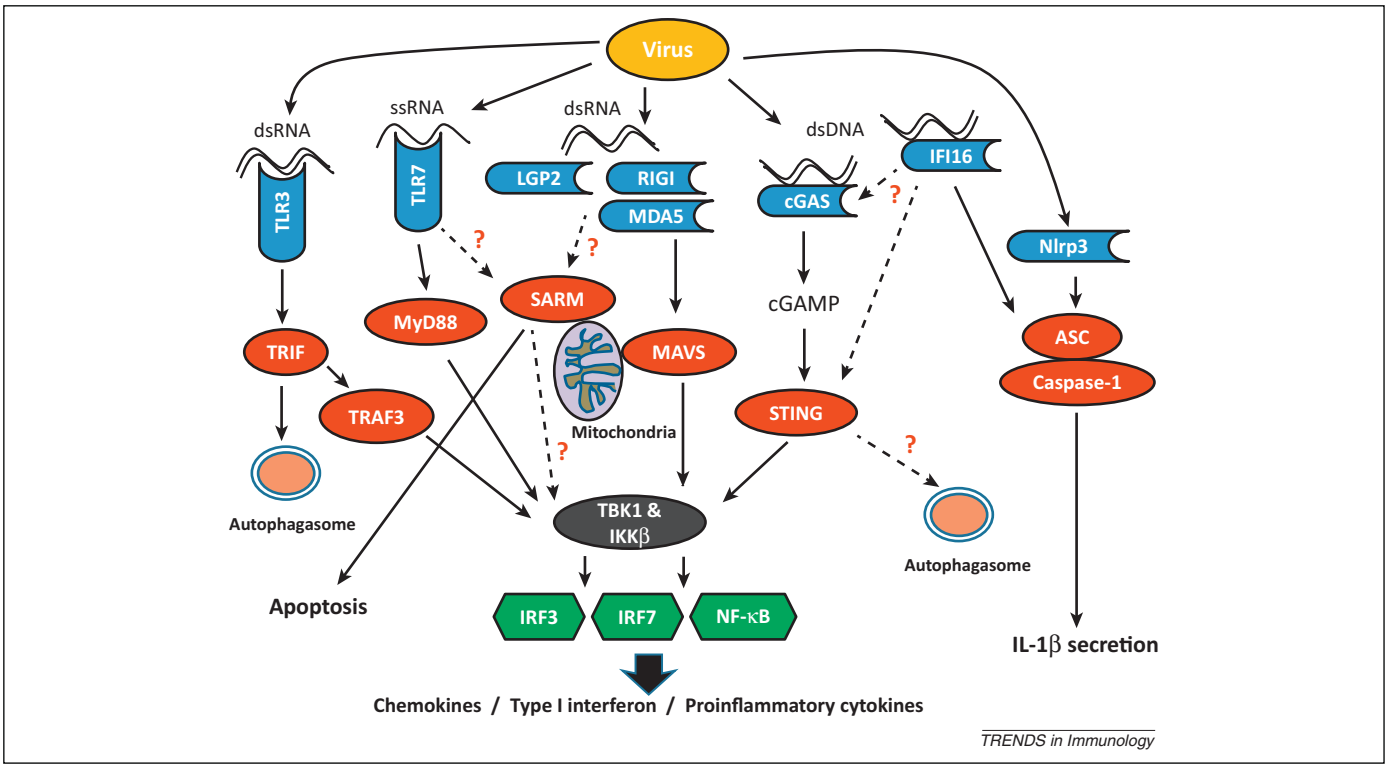

Figure 1. Antiviral signalling pathways in the central nervous system. Viruses can be detected by one of four classes of pattern recognition receptors (PRRs) in the central nervous system (CNS): Toll-like receptors (TLRs), retinoic acid-inducible gene (RIG)-like receptors (RLRs), the NLR family, pyrin domain-containing protein 3 (Nlrp3) inflammasome, or DNA sensors. Engagement of TLRs results in activation of myeloid differentiation primary response 88 (MyD88)- and Toll/IL-1 receptor domain-containing adaptor inducing IFN-β (TRIF)-dependent signalling pathways to activate proinflammatory cytokines and type I interferons (IFNs). TLR activation of TRIF signalling can also trigger autophagy. RLR activation by viruses triggers mitochondrial antiviral-signaling protein (MAVS)-dependent signalling to activate the transcription factors interferon (IFN) regulatory factor (IRF)3, IRF7, and nuclear factor (NF)-κB to trigger inflammatory gene induction. Sterile alpha and TIR motif-containing protein (SARM), which is also located at the mitochondria and activated by viruses, can induce cytokines and chemokines by currently unknown mechanisms. SARM can also trigger apoptosis in response to specific viruses. Cytosolic DNA from viruses binds and activates the enzyme cyclic GMP-AMP synthase (cGAS) leading to the production of cyclic guanosine monophosphate-adenosine monophosphate (cGAMP). This second messenger activates stimulator of interferon genes (STING) and associated signalling pathways that lead to the induction of genes that are also downstream of TLR and RLR signalling. Interferon gamma-inducible protein 16 (IFI16) also senses DNA viruses and stimulates both STING-dependent IFN induction and caspase 1 activation. Whether IFI16 acts via cGAS for IFN induction is currently unclear. At present, the pathway activated by cytosolic DNA to trigger autophagy is also unknown. Finally viral infection can activate the Nlrp3 inflammasome, the cytosolic caspase-1 containing platform to trigger interleukin (IL)-1β secretion.

family members (Figure 1) [9]. This results in the expression of genes that lead to pathogen elimination.

TLRs are widely expressed in the CNS in both the mouse and human systems [10] and have been shown to respond to neurotropic viruses. Table 1 provides a generic overview of the principal steps of viral pathogenesis in the CNS and describes the role of the PRRs in the innate immune response to the virus at each step. Given the propensity of inflammatory responses to cause tissue damage, some TLR-stimulated responses to viruses in the CNS are detrimental (Table 2). Our understanding of TLR responses to both RNA and DNA viruses in the CNS has increased in recent years, as discussed below.

TLRs provide protective immunity against CNS viruses

Poliovirus, an ssRNA virus of the Picornaviridae family, causes paralysis upon CNS entry. TLR3 confers protective immunity to infection by poliovirus; the TLR3–TRIF signalling pathway was demonstrated to limit viral replication in many organs including the brain and spinal cord [11]. The recently characterised endosomal TLR, TLR13, is expressed in mice but not humans and requires MyD88 for signalling. This TLR was shown to sense vesicular stomatitis virus (VSV) [12]. VSV is a neurotropic ssRNA virus and a member of the Rhabdoviridae family. It is a zoonotic virus that causes a disease similar to foot and mouth disease in animals and influenza-like illness in humans. The importance of TLR signalling in the response to VSV is further highlighted by the finding that mice lacking MyD88 exhibit reduced survival with increased viral load in the CNS [13]. WNV, a mosquito born flavivirus, can cause encephalitis and meningitis in infected individuals. Studies on the role of TLRs in response to WNV have mainly focused on TLR3 and TLR7, and have presented contradictory results. In the case of TLR3, one study reported a positive role for TLR3 in mediating antiviral immunity [14], whereas another showed that TLR3 contributes to WNV pathogenesis [15]. A similar situation exists for TLR7, where one study demonstrated a protective role for TLR7 [16], whereas another showed that TLR7 may actually contribute to viral dissemination [17]. Nevertheless, it is likely that TLR responses are important for protective immunity against WNV, because mice lacking MyD88 show reduced survival in response to this virus [16,18]. In addition, recent work has shown that the TLR7–MyD88 axis is necessary for induction of an adaptive immune response to an attenuated form of the virus [19]. Thus, although the discrepancies in previous reports remain to be reconciled, TLRs overall likely play a protective role against WNV infection.