Cytokine & Growth Factor Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

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

Mini review

Brain heterogeneity leads to differential innate immune responses and modulates pathogenesis of viral infections

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ARTICLE INFO

Article history:
Received 29 January 2016
Received in revised form 9 March 2016
Accepted 10 March 2016
Available online xxx

Keywords:
Type I interferon
Central nervous system
Brain heterogeneity
Innate immunity

ABSTRACT

The central nervous system (CNS) is a highly complex organ with highly specialized cell subtypes. Viral infections often target specific structures of the brain and replicate in certain regions. Studies in mice deficient in type I Interferon (IFN) receptor or IFN-β have highlighted the importance of the type I IFN system against viral infections and non-viral autoimmune disorders in the CNS. Direct antiviral effects of type I IFNs appear to be crucial in limiting early spread of a number of viruses in CNS tissues. Increased efforts have been made to characterize IFN expression and responses in the brain. In this context, it is important to identify cells that produce IFN, decipher pathways leading to type I IFN expression and to characterize responding cells. In this review we give an overview about region specific aspects that influence local innate immune responses. The route of entry is critical, but also the susceptibility of different cell types, heterogeneity in subpopulations and micro-environmental cues play an important role in antiviral responses.

Recent work has outlined the tremendous importance of type I IFNs, particularly in the limitation of viral spread within the CNS. This review will address recent advances in understanding the mechanisms of local type I IFN production and response, in the particular context of the CNS.

1. Introduction

A functional central nervous system (CNS) is essential to ensure survival of the individual. Infection reduces this functionality by induction of apoptotic or inflammatory processes that lead to a loss of cognitive and motoric skills [1,2]. Therefore it is crucial that the CNS is protected from most viral infections by effective immune responses and multilayer barriers like the blood brain barrier (BBB) [3,4]. Upon pathogen entry, type I interferons (IFNs) are readily upregulated as a first line of defense [5,6]. Type I IFNs can be produced to a different extent by all CNS resident cells, namely astrocytes, oligodendrocytes, microglia and neurons [5,7–9]. However, the main IFN producing cell type may vary, dependent on the respective pathogen, the affected region and the infected cell type [5,7,8]. IFNs are produced locally at the site of infection, but the signal can induce antiviral responses through the whole brain [5,10,11]. Even though, IFN-α's and IFN-β use the same receptor or signaling, they may have differential roles during infection [12]. Considering these aspects, it is becoming clear that antiviral responses by IFNs through the brain are highly complex and differentially regulated. In this review we will shed some light on the heterogeneity of the brain and infection related aspects of the local innate immune responses.

2. Pathogen entry and the role of type I interferons in the brain

Pathogen entry sites and resulting immune responses may define not only severity but also the outcome of infection. This is supported by observations that the way of viral administration often determines the susceptibility of the host in viral infections [13,14]. Thus, the route of entry is of specific interest. Many different ways are used by pathogens to enter the CNS: (i) viremia and shedding into the CNS (ii) bypassing of BBB and the blood cerebrospinal fluid barrier (BCSFB) endothelium (iii) 'Trojan horse' mechanism by infection of immune cells (iv) axonal retrograde transport along peripheral nerves like *e.g.* seen upon infection of olfactory sensory neurons [1,2,4] (Fig. 1). Still, the way of entry does not always define the main replication site. Pathogens that use the

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http://dx.doi.org/10.1016/j.cytogfr.2016.03.006
1359-6101/

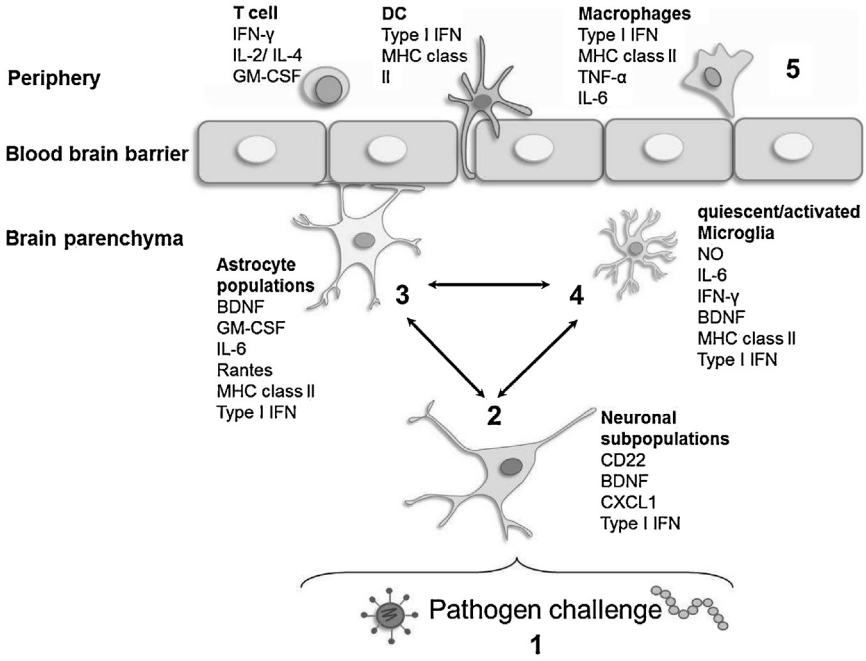

Fig. 1. Structural diversity in the CNS. Pathogens like viruses or bacteria enter the CNS via different routes, *e.g.* (1) infection of neurons or (5) trojan horse mechanism. Brain resident cells: neurons (2), astrocytes (3) and microglia (4) recognize pathogens and are able to mount Type I IFN responses as a first line of defense. Glia cells become activated, may change their morphology and secrete pro- or anti-inflammatory cytokines. Different cell types and subpopulations show different expression profiles of antiviral factors. Enhanced cytokine gradients lead to immune cell attraction to the site of infection (5). These cells also contribute to the inflammatory response in a region specific manner.

same mechanism to enter the CNS, may spread to different brain regions [15–17]. Herpes simplex virus type 1 (HSV-1) and mouse hepatitis virus (MHV), both infect the olfactory receptor neurons, replicate in the main olfactory bulb (MOB), but spread along different neuronal pathways through the brain. HSV-1 infects pyramidal (CA3) and dentate gyrus neurons of the hippocampus that remains untouched by MHV, whereas MHV infects central and posterior areas of the hypothalamus, which were unaffected by HSV-1 [16]. Viruses may also be able to use more than a single mechanism to reach the brain [18–20]. Canine distemper virus (CDV) can invade the CNS by the hematogenous route, through cerebral blood vessels and also via the olfactory bulb [21]. Poliovirus can enter the CNS through retrograde axonal transport by peripheral nerves infection and from bloodstream through the BBB [15,22].

The type I IFN system plays an important role in limiting initial replication and entry of pathogens into the brain [5,6,11,23]. Vesicular stomatitis virus (VSV) infection of peripheral nerves was restricted by subcapsular macrophages secreting type I IFNs and recruiting type plasmacytoid dendritic cells (DC) [24]. The IFN barrier also contributed to a diminished movement of polio virus into the brain via retrograde axonal transport [15]. We demonstrated that increased viremia in the periphery of IFN-α/β receptor (IFNAR) or IFN-β promoter stimulator-1 (IPS-1) knock out animals led to a higher viral replication in the CNS of langat virus (LGTV) infected animals [11,23].

Upon pathogen entry local IFN response inhibits viral replication and spread through the CNS. Type I IFN responses at the glomerular layer of olfactory bulb controls the spread of VSV from olfactory bulb into the CNS [6].

Interestingly, many other factors of the type I IFN system are involved in this antiviral response. The use of mice deficient for IFN regulatory factor-1 (IRF-1), IFNAR or IPS-1 highlighted the importance of type I IFN in the control of virus replication, since infection with neurotropic viruses revealed a higher susceptibility to CNS infection [6,11,25].

3. Innate recognition

3.1. Differential recognition by TLRs and RLRs

Upon infection DNA and RNA viruses are recognized by pattern recognitions receptors (PRRs) [23,26]. Cytosolic or endosomal sensors like retinoic acid-inducible (RIG)-I-like receptors (RLRs), Toll-like receptors (TLRs) and cyclic GMP-AMP synthase (cGAS) are probably the best characterized among them [2,23]. Many viruses were detected by a different combination of PRRs and specific RNA detection pathways can be involved in recognition of DNA viruses. Encephalitic herpesvirus HSV-1 (dsDNA genome) is detected by TLR2, cGAS/STING complexes and the dsRNA receptor TLR3, whereas west nile virus (WNV; positive ssRNA genome) is recognized by RIG-I and MDA-5 and TLR-7 pathways [27–30]. Further, the expression profile of host sensor proteins can differ between cell types and brain region. Whereas DCs mainly induce high IFN production by TLR-7/Myd88 activation, astrocytes display a very heterogeneous combination of PRRs [26,31,32]. It was hypothesized that findings about different expression patterns of TLRs on astrocytes was due to the different origin of these cells [26,33]. Brain resident microglia on the other hand express almost all types of TLRs, but their activation varies according to the activating pathogen or stimulus [34].

These regional differences were not only seen in PRR patterning but also in differential induction of downstream targets upon innate recognition. We found that IFN-β upregulation in the olfactory bulb upon LGTV infection was especially dependent on RIG-I signaling adaptor molecule IPS-1 in contrast to other brain regions [11].

3.2. Induction of type I IFNs and expression of ISGs

Type I IFN can be produced by brain resident cells including neurons, astrocytes, oligodendrocytes and microglia but can also

Please cite this article in press as: L. Zegenhagen, et al., Brain heterogeneity leads to differential innate immune responses and modulates pathogenesis of viral infections, Cytokine Growth Factor Rev (2016), http://dx.doi.org/10.1016/j.cytogfr.2016.03.006