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Type I interferon response in the central nervous system

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Abstract

This review is dedicated to the influence of type I IFNs (also called IFN-α/β) in the central nervous system (CNS). Studies in mice with type I IFN receptor or IFN-β gene deficiency have highlighted the importance of the type I IFN system against CNS viral infections and non-viral autoimmune disorders. Direct antiviral effects of type I IFNs appear to be crucial in limiting early spread of a number of viruses in CNS tissues. Type I IFNs have also proved to be beneficial in autoimmune disorders like multiple sclerosis or experimental autoimmune encephalitis, probably through immunomodulatory effects.

Increasing efforts are done to characterize IFN expression and response in the CNS: to identify type I IFN producing cells, to decipher pathways leading to type I IFN expression in those cells, and to identify responding cells.

However, reversible and irreversible damages consecutive to chronic exposure of the CNS to type I IFNs underline the importance of a tightly regulated type I IFN homeostasis in this organ.

Keywords: Neurons; Viruses; IFNAR; Immune privilege; Interferon stimulated genes

1. Introduction: the central nervous system, an immunoprivileged site?

The central nervous system (CNS) is a unique site for immune responses to pathogens since neurons, one of the major CNS constituents, form an essential and largely non-renewable cell population. Viral infections resulting in neuronal loss, either by viral direct lysis or by cytolytic immune responses, would likely lead to catastrophic neurological sequelae. In comparison to the periphery, viral infections of the CNS are often associated with reduced tissue destruction, despite sometimes continued viral replication [1–3].

The restricted or highly regulated nature of immune responses in the CNS is referred to as ''immune privilege''. This concept has been introduced after the observation that grafted skin tissue was rejected much slower when occurring in some anatomical parts, such as the brain [4]. The notion of immune privilege notably fitted with the early works of Paul Ehrlich (1854–1915) who reported the existence of a blood–brain barrier after the observation that a systemically injected dye failed to penetrate the brain although it could readily spread to other organs. The blood–brain barrier, together with limited lymphatic drainage and with the paucity of antigen presenting cells have been considered to be responsible for the privileged environment of the CNS.

However, the concept of immune privilege has considerably evolved during the last decade. It is now clear that the CNS is not as isolated from the peripheral immune system as it was considered to be. Nowadays, immune privilege rather refers to an active control of immune responses in the brain. In this respect, an important regional variation should be considered. In ventricles, subarachnoid space and perivascular regions, blood borne dendritic cells (DCs) and macrophages appear to drive nearly periphery-like, yet restricted, immune responses [5,6]. In the brain parenchymal context, antigen presenting cells (microglial cells) as well as other glial cells and neurons themselves,

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modulate T cell responses toward a neuroprotective and less destructive function [7,8]. For example, it was recently shown that production of TGF-β by neurons could turn T cells into T regulatory cells, in the course of experimental autoimmune encephalitis (EAE) [9]. Moreover, neurons are thought to possess their own strategies to limit the replication and the spread of otherwise cytopathic viruses [10]. These strategies either favour non-cytolytic clearance of the virus or promote the establishment of a non-cytolytic persistent infection. Interferon-gamma (type II IFN) seems to be an important contributor to the non-cytolytic mode of clearance, although it remains to determine how it acts [11,12] (for review, see Ref. [13]).

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 type I IFN production and response, in the particular context of the CNS.

2. Importance of the type I IFN response in the CNS

The use of mice deficient for the type I IFN receptor (IFNAR) has highlighted the importance of the type I IFN response in the control of virus replication [14]. Experiments conducted with a number of neurotropic viruses have revealed that these mice were systematically much more susceptible to CNS infection than their wild-type counterparts, therefore stressing the highly protective role of type I IFNs (Table 1). In the case of Sindbis virus infection, for instance, a difference of at least 10^6-fold was reported between LD_{50} values for wild-type and IFNAR-deficient mice. This increased susceptibility to viral infection correlated with higher viral load in the CNS [15].

Type I IFN was also suggested to play an important role by limiting the progress of infection from peripheral sites to the CNS [16]. On the other hand, IFN was reported to target the tropism of poliovirus to the CNS, possibly as a result of a lower basal endogenous IFN response in the CNS than in other organs [17]. In the case of Borna disease virus which almost exclusively infects neurons, IFNAR deficiency did not lead to increased viral RNA load in the CNS of infected mice, but resulted in a surprising switch of polymerase activity, from genome transcription (mRNA synthesis) to genome replication [18].

It should also be noted that most animal viruses, if not all, express proteins that antagonize, to a certain level, IFN expression or response to IFN (for review, see Ref. [19] and Weber and Haller, accompanying article).

Importance of the IFN response has also been studied in the case of non-viral infections. Strikingly, though type I IFNs usually appear to be protective against bacterial infections, IFNAR deficiency turned out to decrease susceptibility to *Listeria monocytogenes* infections of the CNS, probably as a result of the activation of a specific macrophage population or of reduced apoptosis [20–23].

Type I IFNs also proved to be beneficial in some autoimmune conditions. IFN-β has been used for more than 10 years in the treatment of multiple sclerosis (MS). This molecule was found to decrease the relapse rate, disease activity, and accumulating disease burden in relapsing remitting MS, and possibly in secondary progressive MS [24–27]. Influence of IFN-β in autoimmune pathologies was further studied in murine experimental autoimmune encephalitis (EAE), a model for MS. EAE aggravated in IFN-β-deficient mice, suggesting that endogenously produced IFN-β is important for the control of EAE severity and chronicity [28]. Administration of IFN-β also improved the condition of diseased animals. However, the mode of action of IFN-β in EAE and MS has not been firmly established. Beneficial activity of IFN-β is thought to occur by several mechanisms including (i) the modulation of the expression of several molecules involved in the inflammatory response such as adhesion molecules, metalloproteases, and cytokines, (ii) a decrease of the Th1/Th2 ratio, (iii) a decrease of blood–brain barrier permeability, and (iv) a down-regulation of T cell activity [24,26,27,29–32].

3. Type I IFN production in the CNS

3.1. Type I IFN producing cells

In vivo, in both humans and mice, the major type I IFN producing cells were identified as being the plasmacytoid

Table 1
Influence of IFNAR deficiency on viral infections of the mouse CNS

Virus	Family	Observation	References
Hantaan virus	Bunyaviridae	Increased neurovirulence	[85]
Influenza A virus	Orthomyxoviridae	Increased viral load in CNS	[86]
Herpes simplex virus 1	Herpesviridae	Increased viral load	[87]
Measles virus	Paramyxoviridae	Increased neurovirulence	[88]
West Nile virus	Flaviviridae	Increased viral load and neurovirulence, modified tropism	[89]
Sindbis virus	Togaviridae	Increased viral load and neurovirulence, modified tropism	[15]
Poliomyelitis virus	Picornaviridae	Increased neurovirulence, modified tropism	[17]
Theiler's virus	Picornaviridae	Increased viral load and neurovirulence	[90]
Vesicular stomatitis virus	Rhabdoviridae	Increased viral load and neurovirulence	[14]
Borna disease virus	Bornaviridae	Switch from transcription to replication	[18]
Venezuelan equine encephalitis virus	Togaviridae	Increased neurovirulence	[91]
Dugbe virus	Bunyaviridae	Increased neurovirulence	[92]
Dengue virus	Flaviviridae	No clear effect of type I IFN	[93]
Murray Valley encephalitis	Flaviviridae	Increased viral load and neurovirulence	[94]