Cytokine 88 (2016) 251–258

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Review article

Abnormal regulation of the antiviral response in neurological/neurodegenerative diseases

Mannie Man Wai Lam, Jonathan P. Mapletoft, Matthew S. Miller *

Department of Biochemistry and Biomedical Sciences, Institute of Infectious Diseases Research, McMaster Immunology Research Centre, McMaster University, Ontario, Canada

ARTICLE INFO

Article history:
Received 5 August 2016
Received in revised form 1 September 2016
Accepted 2 September 2016

Keywords:
Innate immunity
Neurodegenerative diseases
Amyotrophic lateral schlerosis
Viruses
Type I interferonopathies

ABSTRACT

Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis are a few examples of debilitating neurological/neurodegenerative diseases for which there are currently no curative treatments. Recent evidence has strongly suggested a role for neuroinflammation in both the onset and progression of these diseases. However, the mechanisms that initiate neuroinflammation are presently unclear. Mounting evidence suggests that environmental factors are likely involved. One proposed mechanism linking both genetic and environmental factors is dysregulation of the antiviral response. Indeed, many mutations that have been linked to neurological conditions occur in genes related to the antiviral response. Although the products of these genes may have potent antiviral activities – they can also have deleterious effects when their expression is not appropriately regulated. For that reason, expression of antiviral genes is a tightly controlled process. Herein, we review the various antiviral genes that have been linked to neurological conditions. We focus specifically on type I interferonopathies, the symptoms of which are often evident at birth, and neurodegenerative diseases, which frequently onset later in life.

Contents

1. Introduction . . . 251
   1.1. Type I interferonopathies and neuroinflammation in neurological diseases . . . 252
   1.2. Interferon induced with helicase C domain 1 (IFIH1) . . . 252
   1.3. Sterile alpha motif and histidine-aspartate-domain-containing protein 1 (SAMHD1) . . . 252
   1.4. Ubiquitin-specific peptidase 18 (USP18) . . . 253
   1.5. TANK-binding kinase 1 (TBK1) . . . 253
   1.6. C1q . . . 254
   1.7. Acid phosphatase 5, tartrate-resistant (ACP5) . . . 254
   1.8. Senataxin (SETX) . . . 255
2. Discussion and future perspectives . . . 255
   Acknowledgements . . . 256
   References . . . 256

1. Introduction

The innate immune system serves as a first line of host defense through its ability to sense and respond to pathogens and danger signals. Almost all cell types express germ line-encoded pattern recognition receptors (PRRs), which are able to detect pathogen-associated molecular patterns (PAMPs). Detection of PAMPs by PRRs activates downstream signaling pathways resulting in the production of antimicrobial effector molecules and cytokines that recruit and co-ordinate the cellular immune response. In the context of viral infections, the type I interferon (IFN) response is the primary pathway stimulated upon sensing of viral PAMPs. These IFNs subsequently induce a plethora of IFN-stimulated genes (ISGs) that include cytokines, chemokines, and anti-viral factors [1].

* Corresponding author at: McMaster University, MDCL 2324, 1280 Main St W, Hamilton, ON L8S 4K1, Canada.
E-mail address: mmiller@mmcaster.ca (M.S. Miller).

http://dx.doi.org/10.1016/j.cyto.2016.09.002
1043-4666/

Despite the protective role of IFNs and cytokines in early immunological responses, unregulated infection-induced inflammation often results in severe immunopathology. Well known examples of this include Toxic Shock Syndrome, caused by superantigens that induce T cell expansion and excessive cytokine release [2], and influenza A virus-induced hypercytokinemia, which is positively correlated with disease severity [3,4].

Although poorly controlled inflammation can have pathological consequences in almost any tissue, the central nervous system (CNS) is especially sensitive. Due to the difficulties in regenerating lost neurons, neuroinflammation is particularly dangerous and can result in permanent damage to the CNS. As a natural defense mechanism, specific cells called microglia protect this "immune privileged" organ. Microglia are macrophage-like cells that constantly survey the microenvironment of the CNS for pathogens. When stimulated by pathogens or immunological signals, microglia become activated and respond rapidly to destroy the pathogens and minimize damage to the CNS [5]. However, overactivation of microglial cells can cause excessive neuroinflammation, which has been implicated in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [6]. Interestingly, a recent study by O'Rourke et al. specifically implicated deficient expression of C9orf72 - a well known ALS gene - in abnormal microglial function. Deficient expression of C9orf72 resulted in neuroinflammation similar to that observed in ALS patients harbouring mutations in C9orf72 [7]. However, the underlying triggers of microglial activation and how aberrant activation of microglia feeds into neurodegenerative disease etiology remains poorly understood.

The innate immune system plays a crucial role in orchestrating the immune response to pathogens. However, in some cases, the innate immune response can become chronically activated in the absence of stimulation, leading to neurotoxic effects. The most well-characterized examples of this phenomenon are the type I interferonopathies, including Aicardi-Goutières syndrome (AGS) [8]. In other cases, polymorphisms in genes involved in innate immune pathways may result in pathological consequences only after being triggered by infectious agents, like viruses. Understanding the links between the innate immune response, neuroinflammation, and neurodegenerative diseases may open up new frontiers for therapeutic interventions. Here, we will discuss the mounting evidence directly linking aberrant innate immune regulation with the onset of certain neurological and neurodegenerative diseases, and will emphasize the need for more intensive studies that may provide the basis for novel drug development and disease prevention strategies.

1.1. Type I interferonopathies and neuroinflammation in neurological diseases

Type I interferonopathies are characterized by the constitutive activation of type I IFN, or excessive IFN production during viral infections. Type I IFN signaling is tightly controlled by multiple signaling proteins and therefore, gain- or loss-of-function mutations in almost any of these proteins can have severe consequences. Type I interferonopathies usually involve inborn mutations in genes encoding proteins that activate type I IFN pathways or terminate these pathways when the infection is resolved [9].

One feature common to many type I interferonopathies is the activation of microglia resulting in chronic neuroinflammation. Interestingly, neuroinflammation is also considered to be a universal signature of many neurodegenerative diseases, including AD, PD, MS and ALS [6]. Even though inflammation may not directly cause disease, it is suspected to play an important role in disease progression. Local, acute inflammation is beneficial and important for clearance of pathogens and wound healing, but systemic and chronic inflammation is detrimental and can result in tissue damage and neurotoxic effects [10,11]. Interestingly, mutations that result in deficient type I IFN responses are equally harmful and could also contribute to neurodegenerative diseases. For example, deficiencies in neuronal IFN-β has been shown to cause Lewy body- and PD-like dementia in the absence of the genetic mutations that have been associated with these diseases [12]. In addition, IFN-β-deficient mice show a reduction in dopaminergic neurons, accumulation of senescent mitochondria, and increased level of α-synuclein-containing Lewy bodies in the brain, which were reversed by the overexpression of recombinant IFN-β [12]. These observations suggest that IFN-β also has a protective role in neurons as a critical regulator of autophagy-mediated protein degradation [12]. Taken together, neurodegenerative diseases associated with either upregulation or absence of the type I IFN response highlight the importance of maintaining tight control of type I IFN function during the immune response. Dysregulation of these responses, either through gain- or loss-of-function mutations, may result in different pathological processes, but still ultimately result in neurological diseases (Fig. 1). Understanding the pathophysiological similarities and differences of diseases caused by exacerbated type I IFN signaling versus those caused by deficiencies in type I IFN signaling will need to be carefully elucidated in order to identify and exploit novel therapeutic targets.

1.2. Interferon induced with helicase C domain 1 (IFIH1)

IFIH1, also known as melanoma differentiation-associated protein 5 (MDA-5), is a cytosolic double-stranded RNA (dsRNA) sensor that activates type I IFN signaling [13], potentially through the adaptor molecule, mitochondrial antiviral signature protein (MAVS) [14]. MAVS is a mitochondrial outer membrane protein that can potentiate a series of signaling cascades leading to the activation of transcription factors such as IFN regulatory factor (IRF)-3 and IRF-7 to induce the production of type I IFN and other antiviral effector molecules [15]. Gain-of-function mutations in *IFIH1* have been classically associated with AGS, but are also implicated in Singleton-Merten syndrome (SMS) [16]. AGS is an early-onset encephalopathy characterized by cerebral atrophy, leukodystrophy, and intracranial calcification [17]. AGS patients invariably have elevated IFN-α levels in the cerebrospinal fluid and serum and increased expression of ISGs, reminiscent of *in utero* viral infections [17]. Recessive mutations in *TREX1*, *Rnaseh2b, ADAR* and *SAMHD1* are also associated with AGS. Even though the role of these genes in the type I IFN induction pathway are less clear, patients with such mutations routinely present with elevated type I IFN levels [17]. The six disease-associated heterozygous mutations in *IFIH1* display highly variable genetic penetrance. Symptomology can vary from prenatal onset with subacute neurodegeneration beginning at one year of age to evidence of biochemical penetrance for IFN upregulation without any clinical features up to 80 years of age [8]. Mechanistic data suggests that structural alteration of MDA-5 may lower the activation threshold for sensing endogenous dsRNA species [8] or, in more severe cases, may lead to constitutive IFN activation in the absence of endogenous dsRNA [18]. As a result, the antiviral response becomes chronically activated in the absence of infection. However, a black box persists in the space linking chronic IFN signaling and the associated neurological phenotypes.

1.3. Sterile alpha motif and histidine-aspartate-domain-containing protein 1 (SAMHD1)

SAMHD1 regulates cellular deoxyribonucleotide triphosphate (dNTP) levels and has also been shown to restrict reverse