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Mini Review

Limited but Important Role of Innate Immunity against Prion Infection

Ishibashi D* and Nishida N
Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, Japan

***Corresponding author:** Daisuke Ishibashi, Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan

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Abstract

Whilst our understanding of prion pathogenesis has increased markedly over the last 30 years, the role host defense mechanisms play is yet to be fully shown. We investigated whether innate immunity involving key molecules such as toll-like receptors and related signaling molecules afforded protection during prion infection. Interestingly, we discovered over expression of Interferon Regulatory Factor-3 (IRF-3) was inhibitory to PrP^{Sc} replication in both pre- and post-infected cells. However, IRF-3-gene expression was reduced by chronic prion infection and the suppression of octamer-binding transcription factor-1 (Oct-1) expression. Oct-1 is known to positively regulate IRF-3 promoter activity. These results suggest that the innate immune signaling pathway through IRF-3 may play a crucial role in host defense against prion infection. Although the mechanism(s) underlying IRF-3-mediated anti-prion activity are yet to be clarified, it is conceivable that interferons and interferon-stimulated genes located downstream of IRF-3 might be involved in such prion-specific host defense mechanisms. Prions, unlike viruses, have the unique property of being composed entirely of host-encoded protein, which would assist the pathogen in evading host cell-immune responses directed at their destruction and expulsion from the host.

Keywords: Prion; Innate immunity; Interferon regulatory factor 3 (IRF-3); Type I interferon (IFN-I); Octamer-binding transcription factor-1 (Oct-1)

Abbreviations

TSEs: Transmissible Spongiform Encephalopathies; BSE: Bovine Spongiform Encephalopathy; CJD: Creutzfeldt-Jacob Disease; TLR: Toll-Like Receptor; RIG-I: Acid Inducible Gene-I; MDA5: Melanoma Differentiation-Associated Gene-5; PAMPs: Pathogen-Associated Molecular Patterns

Introduction

The characteristics of prion disease

Transmissible Spongiform Encephalopathies (TSEs), also known as prion diseases, are zoonotic diseases which include Bovine Spongiform Encephalopathy (BSE) and Creutzfeldt-Jacob Disease (CJD). Prion diseases are progressive neurodegenerative disorders which are ultimately fatal. The infectious agent, identified as a prion, is thought to be composed uniquely of abnormal Prion Proteins (PrP^{Sc}), generated from the conformational conversion of host-encoded PrP^{C} [1]. Although PrP^{Sc} accumulates in the brain and exhibits amyloid-like properties, an association between PrP-amyloid and pathological changes, including spongiform degeneration, neuronal loss and gliosis (astrocyte and microglia activation) remains unclear. To date, the latency of infection and host defense mechanisms against prion disease remain poorly understood.

Immune responses are predominantly classified as innate or adaptive. Adaptive immune responses are further categorized as humoral (characterized by antibody production through B cell activation) or cellular (recruitment of cytotoxic T cells). When exogenous pathogens invade mammalian hosts, the innate immune system immediately responds with lymphocytes (macrophages, natural killer cells and neutrophils), which attack and expunge pathogens from the host. Pathogens that evade the initial host defense response encounter the adaptive immune response [2]. It has long been thought that prion infection fails to elicit host adaptive immune responses [3] because of self-tolerance brought about by the identical sequence shared between PrP^{Sc} and host PrP^{C}. Indeed, PrP-specific antibody production [4] and lymphocytic ability [5] remained unaltered in prion-infected animals, whereas subtle changes in the immune response (e.g., follicular dendritic cells) were observed in mice spleens following prion inoculation [6]. However, a protective role for Toll-Like Receptor (TLR) 4 signaling against prion infection has been proposed under certain experimental conditions [7,8]. It is therefore important to establish whether prions can trigger TLRs in a manner similar to other viral or bacterial pathogens.

Innate immune responses and strain interference observed for multi-prion infections

Prion strain interference has been observed in mouse-adapted prions. Pre-infection of mice with an attenuated strain with a long-incubation period suppressed the effect of subsequent infection with a strong strain possessing a short incubation period [9]. Strain interference was reproduced *in vitro* in a pure cell culture system in the absence of immunocompetent cells [10]. Interference is often observed in multi-virus infections, and whilst type I Interferon (IFN-I) has been detected in some studies, it is notably absent from others. For example, IFNs were not detected in tissues of prion-infected mice or the brains of CJD patients [11-13], whilst experimental hamster- and mouse-adapted prions evoked the upregulation of

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IFN-Stimulated Genes (ISGs) Mx and 2'-5'-OAS, in animal models [14-16]. Moreover, genes of the Interferon Regulatory Factor (IRF) family were highly expressed in the microglia of CJD-infected brains [13]. Taken together, these results could suggest that IFN production is induced by the initial activation of the innate immune system following prion infection, rendering cells resistant to infection.

Protective role of the Pattern-Recognition Receptor (PRR)-mediated innate immune response in prion infection

As previously mentioned, invading pathogens are initially recognized by several lymphoid cells of the innate immune system, resulting in the production of cytokines and IFNs to protect the host from further attack. Innate immune responses are initiated through PRRs such as TLRs and intracellular sensor molecules representing Retinoic Acid Inducible Gene-I (RIG-I) and Melanoma Differentiation-Associated Gene-5 (MDA5) [17,18]. PRRs recognize characteristic molecules, or Pathogen-Associated Molecular Patterns (PAMPs), such as bacterial cell wall components and viral envelope glycoproteins, in a number of foreign pathogens [19]. Type I IFN (-α and -β), pro-inflammatory cytokines (e.g., TNF-α), and anti-inflammatory cytokines (e.g., interleukin-10) [20] mediated by transcription factors IRF-3 and/or IRF-7, are induced upon activation of downstream signaling processes following PRR stimulation. The secreted IFNs then act in an autocrine or paracrine manner to upregulate the expression of ISGs [18]. It is unknown whether prions themselves serve as PAMPs. The pretreatment of mice with innate immune activators, such as complete Freund's adjuvant (TLR2 agonist) [21] and unmethylated CpG DNA (TLR9 agonist) [22] was shown to delay the onset of prion disease. In contrast, post-treatment with LPS (TLR4 agonist) and Poly [I:C] (TLR3, RIG-I and MDA5 agonist) had no observable effect on pathogenesis in prion-inoculated mice [11,12, 23]. Hence, prion pathogenesis is altered by innate immune responses based on stimulator-dependent experimental conditions. To date, the underlying molecular mechanisms remain to be determined.

Mice deficient for the MYD88 gene, which encodes a downstream adaptor protein recruited by all TLRs except TLR3, failed to exhibit significant changes in incubation time following inoculation with prion strain RML [24]. However, the expression of inactive TLR4 or defective CD40L in mice resulted in the accelerated onset of disease [7,25]. One could speculate that PRR-stimulated TRIF-IRF-3-mediated signal transduction may play a crucial role in the host defense system against prion infection, because downstream signaling of TLR4 has distinct signal transducing pathways via MYD88 and TRIF. Thus, we focused our attention on IRF-3, a key transcription factor in the MYD88-independent pathway and in the induction of IFN-I. Our research showed IRF-3-deficient mice readily succumbed to prion disease and exhibited pathological features consistent with severe disease following intra-peritoneal inoculation with three distinct prion strains [8]. In addition, our *in vitro* studies demonstrated the IRF-3 regulated production of PrP^{Sc}, and its inverse relationship with resistance to prion infection [8]. These results suggest MYD88-independent signaling pathway IRF-3 is a key molecule in the host defense mechanism against prion pathogenesis. Recently several reports, including our own, have suggested the host defense system plays at least a partially protective role against prion infection.

How is prion pathogenesis established in the host?

Viral infection triggers phosphorylation of the IRF-3 carboxy-terminal region [19], the translocation of phosphorylated IRF-3 to the nucleus, and the transcriptional activation of IFN-I genes. Interestingly, it has also been reported that some virus infections enhance IRF-3 degradation and/or inhibit its phosphorylation, resulting in reduced IFN-I production and persistent viral infection [26-31]. Thus, we investigated whether prions regulated IRF-3 expression *in vitro*. Our studies showed IRF-3 mRNA levels and promoter activity was significantly reduced in cells persistently infected with prions. Furthermore, we are the first to report that octamer-binding transcription factor-1 (Oct-1) plays a key role in IRF-3 promoter activity, and that Oct-1 expression was significantly reduced in prion-infected cells and animals [32]. Based on these results, we cannot exclude the possibility that prion protein accumulation directly impairs Oct-1 function, whilst it is also plausible that prion infection may alter Oct-1 expression resulting from a disruption to host cell protein synthesis. We propose that prion infection may accelerate the onset of pathogenesis by disrupting the innate immune system including IRF-3.

Conclusion

We have discussed the role of IRF-3-mediated innate immune response to prion infection. We propose that PRRs such as TLR4 may recognize prion/PrP^{Sc} by an as yet undetermined mechanism, and that activated IRF-3 may induce host cellular factors including IFN-I. In other words, it has evidenced that host cells respond to prion invasion and are trying to inhibit their replication. However, prion might be able to suppress the IRF-3 expression mediating Oct-1 reduction in order to infect the cells. This host-pathogen interaction could explain the latency of prion diseases. Although further investigation is required to identify IRF-3-induced host molecules which afford protection from prion invasion [33], our findings propose a novel approach in the development of prophylactic/therapeutics against prion disease.

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