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Type 1 Interferon Dynamics in Bacterial Infection

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Review Article

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Abstract

Several reports have demonstrated that bacteria can induce type I interferon in infected cells and that IFN-I may help control bacterial infection. Moreover, type I IFN play an essential role in the immune homeostasis of gastrointestinal tract and maintain barrier integrity in endothelial cells. Also pDC produce large amount of type I IFN due to their constitutive expression of the transcription factor IRF-7. The work presented here has unravelled the potential of type 1 IFN in the immune system including various subtypes, their production by different cell types and their host defense against bacterial pathogens. These findings would help set up future avenues of research to elucidate a key mechanism of action of these cells and provide new therapeutic insights.

Keywords: IFNAR1; IFNAR2; pDC; ISG; TLR4-TRIF pathway; TLR4-TRIF pathway; IFNAR1$^{-/-}$ mice

Introduction

Interferons (IFN) are a heterogeneous class of soluble immune mediators which were discovered 50 year ago and named for their potent ability to "interfere" with viral replication [1,2]. The IFN family is primarily classified into three main subclasses — type I, type II and type III IFNs. In humans and mice, the type I IFN family consists of 16 members including IFNβ, IFNε, IFNκ and IFNω and 12 IFNα subtypes [3]. All type I IFN bind to a ubiquitously expressed heterodimeric receptor encompassing two common chains, IFNAR1 and IFNAR2 [4-6]. Once type I IFN bind to its receptor, it activates a signalling cascade including JAK/STAT pathway [7] to induce various type I interferon inducible genes (ISG), such as 2-5 *oas*, *Isg15*,*Irgm, Pkr* [8-11]. The biological functions of these ISGs include antiviral, antibacterial, antiproliferative and immunomodulatory [12].

Production of Type 1 IFN

Type I IFNs can be produced by different cells, comprising leukocytes, fibroblasts and endothelial cells and the mechanisms by which pathogens are sensed can be different. Type I IFN is mainly produced in response to pathogen recognition receptor, such as TLR, NLR, RIG-I, AIM2, cGas and STING [13,14]. The signalling cascades that prime the induction of type I IFNs may vary according to the stimulus or the responding cell types [3]. For instance, ssRNA viruses or host cell products induce type I interferon production in pDCs, cDCs and macrophages through TLR7-MyD88 and TLR8-MyD88 pathway. dsRNA viruses induce type I interferon production in macrophages, cDCs and epithelial cells through TLR3-TRIF and RIG-1 pathway [15]. Gram negative bacteria induce type I interferon production in the macrophages and cDCs through TLR4-TRIF pathway

binding to LPS [16-19]. CpG DNA derived from bacteria or viruses induce type I interferon secretion in pDCs, cDCs and macrophages through TLR9-MyD88 pathway [20,17].

The Antibacterial Response

Type I IFNs are recognized for their induction of robust antiviral immune responses. The role of type I IFNs in response to viral infection is variable and they exhibit multiple modes of action, such as inhibition of protein synthesis, induction of apoptosis and initiation of inflammatory responses. During bacterial infections, type I interferon can be protective or detrimental to the host, though little is known about their potential in bacterial infections [21]. Type I interferon can contribute to host resistance in bacterial infections by inducing proinflammatory cytokines, triggering DCs, inducing secretion of antibodies, or inducing antimicrobial effectors [22]. Also they can impair host response by inducing apoptosis, suppressing proinflammatory cytokines, producing IL-10 and IL-1 receptor antagonist or restricting host responses to IFNγ during bacterial attack [23].

In bacterial infections, the functions of type I interferon are pleiotropic and do not always favour the immune response of the host against the infection. For instance, type I interferon impairs *Chlamydia* growth cycle resulting in chronic infection [24]. Also, IFNAR1$^{-/-}$ mice are protected against *Chlamydia muridarum* infection, exhibiting extended survival and decreased bacterial burdens compared to wild-type control [25]. In Legionnaires' disease, type I IFN plays a role in restricting *L. pneumophila* replication in macrophages [26,27]. For instance, IFNAR1$^{-/-}$ mice have been found to have higher bacterial loads compared to wild-type mice [28] while others have found that type I interferon do not influence the colonization of *L.pneumophila* in mice [29]. Type I IFN has been found to protect mice during *Salmonella typhimurium* infection [30]. However, recently, it has been shown that type1 interferon is harmful to the host during *S. typhimurium* infection [31]. Also, Type I interferon can reduce cellular invasion by gut bacteria, including *Shigellaflexneri*and *Salmonella enterica* [32,33].

The production of type I IFN during *Listeria monocytogenes* infections has been found detrimental to the host [34-38]. For instance, IFNAR1$^{-/-}$ mice are resistant to *L. monocytogenes* infection, with a greater survival rates, and lower *Listeria* titres in spleen and liver than wild-type mice and CD11b+DCs tend to be one of the major IFNβ-producing cells [39]. Similarly to infection with *L. monocytogenes*, type I interferons have been shown to be involved in the apoptosis of macrophages during *F. novicida*infection [40]. In addition, type I IFN signalling appears to be damaging to the host during infection with intracellular gram-positive bacteria *Mycobacterium tuberculosis*. *M. tuberculosis* infected IFNAR2$^{-/-}$ mice have decreased mortality compared to WT [41-43].

Type I interferon is crucial for host resistance to some bacterial infections. For example, IFNAR$^{-/-}$mice exhibit decreased longevity and enhanced bacterial titres following infection with group B *Streptococcus, Streptococcus pneumoniae*, *E. coli*, *Helicobacter pylori* and *Streptococcus pyogenes* infections [44-47], as well as in a model of caecal ligation and puncture [48]. Type I IFNs have been shown to have adverse effects in peritoneal sepsis [49], in *Staphylococcus aureus*- induced [50], during Whipple's disease (caused by *Tropheryma whipplei*) [51], in *Brucella abortus* infection [52], during infection with the plague agent *Yersinia pestis* [53], in *Francisellatularensis* induced respiratoryinfection [54]. In all these models, IFNAR$^{-/-}$mice are reportedly more resistant to infection than wild type controls.

Concluding Remarks

The large number of recent studies on type I interferon indicates that type I IFNs have an extensive array of immunomodulatory properties upon infection with bacteria. The study of how bacteria interact with the IFN system has told us much about bacterial pathogenesis and about the IFN system itself. Thus the role of type I interferons in response to bacterial pathogen might be diverse including either beneficial or detrimental which needs to be fully understood.

Disclosure

The authors declare no competing interests.

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