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Type I IFN Exhaustion is a Host Defence Protecting Against Secondary Bacterial Infections

Y. Furuya* & A. Müllbacher†

*Department of Emerging Pathogens and Vaccines, John Curtin School of Medical Research, Australian National University, Canberra, Australian Capital Territory, Australia; †Department of Immunology, John Curtin School of Medical Research, Australian National University, Canberra, Australian Capital Territory, Australia;

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Correspondence to: Y. Furuya, Center for Immunology and Microbial Disease, Albany Medical College, Albany, New York 12208, USA. E-mail: furuyay@mail.amc.edu

Abstract

Type I interferons (IFN-I) have been known for decades for their indispensable role in curtailing viral infections. It is, however, now also increasingly recognized that IFN-I is detrimental to the host in combating a number of bacterial infections. We have previously reported that viral infections induce partial lymphocyte activation, characterized by significant increases in the cell surface expression of CD69 and CD86, but not CD25. This systemic partial activation of lymphocytes, mediated by IFN-I, is rapid and is followed by a period of IFN-I unresponsiveness. Here we propose that IFN-I exhaustion that occurs soon after a primary viral infection may be a host response protecting it from secondary bacterial infections.

The double-edged sword of IFN-I

Since it was first shown in 1957 that IFN-I 'interferes' with viral replication within host cells [1], it has become one of the best studied cytokine. The beneficial effects of IFN-I are well appreciated in numerous viral experimental models as inducers of antiviral state. Type I interferon is one of the few successful antiviral treatments in therapeutic clinical use, as in chronic hepatitis C infections [2]. Viral infections of most somatic cells result in an early synthesis of IFN-I production. Specialized cells called plasmacytoid dendritic cells (pDCs) are the major IFN-I producers [3] and mediate systemic IFN-I responses following viral infections [4]. The primary role of IFN-I is to limit initial viral replication and to facilitate subsequent adaptive immune responses. IFN-I is a multifunctional cytokine that positively influences cells of both innate and adaptive immunity and therefore is considered as a bridge that links innate and adaptive immunity (reviewed in [5]). With a few exceptions of chronic viral infections [6, 7], most studies agree that IFN-I is protective against acute viral infections. This has been clearly demonstrated in knockout mouse studies, in which mice deficient of functional IFN-I receptors are highly susceptible to viral infections, such as influenza virus [8], encephalitic flaviviruses [9], Schmallenberg virus [10] and lymphocytic choriomeningitis virus [11].

Besides the antiviral response, a bacterial infection also leads to the induction of IFN-I synthesis. However, in contrast to the role of IFN-I in response to a viral infection, the effect on the host in the case of bacteria may be either beneficial or detrimental (Table 1). The precise mechanism/s behind this dualistic effect of IFN-I on bacteria is not fully understood, but recent studies have provided some insights into how IFN-I can suppress antibacterial immunity. For example, Teles *et al.*[12] reported that the *in vitro* induction of IFN-I by human monocytes in response to *Mycobacterium leprae* promotes the production of the anti-inflammatory cytokine IL-10. IL-10 together with IFN-I synergistically limits the production of type II IFN (IFN-γ) [12], an important effector cytokine against bacterial infections. In a mouse model of *Francisella tularensis* and *Listeria monocytogenes* infections, IFN-I was shown to suppress gamma delta T cell/IL-17 responses and a subsequent neutrophil recruitment [13]. As both IL-17 and neutrophils play an important role in antibacterial immunity (reviewed in [14]), IFN-I is highly detrimental to the host during *F. tularemia* infections. Regardless of differences in reported mechanism/s, it is clear that IFN-I can enhance the host susceptibility to certain bacterial pathogens by suppressing the host's antibacterial immunity.

Virus-induced partial lymphocyte activation and associated IFN-I exhaustion

Live viral infections in a mouse model cause IFN-I-dependent systemic partial lymphocyte activation [5, 15,

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Table 1 Benefits and adverse effects of IFN-I..

Protective against:	Reference	Detrimental against:	Reference
Streptococcus pneumoniae	[57]	*Listeria monocytogenes*	[13, 58–61]
Bacillus anthracis	[62]	*Francisella tularensis*	[13]
Salmonella typhimurium	[63–65]	*Chlamydia muridarum*	[66]
Shigella flexneri	[65]	*Yersinia pestis*	[67]
Chlamydia trachomatis	[68]	*Mycobacterium tuberculosis*	[38, 39]
Chlamydia psittaci	[69, 70]	*Staphylococcus aureus*	[46, 71]
Legionella pneumophila	[72]	*Streptococcus pneumoniae*	[34, 35, 46]
		Brucella abortus	[73]
		Mycobacterium leprae	[12]

16], characterized by increased expression of activation markers CD69 and CD86, but not CD25 (the interleukin-2 receptor α chain) [15, 16]. The vast majority of lymphocytes undergo this partial activation within 24 h of a viral infection with the cell surface marker expression returning to normal at around day 5 post-infection [16]. A recent report suggested a possible biological role for this phenomenon. It has been shown that the early activation of CD69 temporarily retains lymphocytes in secondary lymphoid organs, presumably promoting antigen-specific interactions of lymphocytes with antigen-presenting cells [17].

Concurrent respiratory infections are common among young children and the elderly, and epidemiological studies during the influenza pandemic of 2009 identified co-infection with other respiratory viruses such as coronavirus, human bocavirus, respiratory syncytial virus and human rhinoviruses [18–20]. Consistent with epidemiology studies, mouse models of viral diseases show enhanced susceptibility to secondary, unrelated viral episodes following primary viral infections [16, 21]. While the biological role of partial lymphocyte activation during a primary infection is not yet understood, its consequence, a refractory period of an IFN-I response to secondary infections, has attracted attention due to their clinical implications [5, 16]. We showed that an unrelated secondary adenovirus infection following a primary Semliki Forest virus (SFV) infection fails to trigger partial lymphocyte activation for a duration of 5–9 days post-primary infection due to IFN-I exhaustion [16]. We found that IFN-I levels are below the detection limit at day 1 after a secondary viral infection, and the hosts regain its capacity to mount IFN-I responses 9 or more days after a primary viral infection. Thus, it is likely that IFN-I exhaustion is responsible for the heightened susceptibility to secondary viral infections.

Co-infection models examining synergistic consequences between respiratory pathogens are predominantly concerned with combinations of viral and bacterial pathogens. This is largely due to information gained from the devastating Spanish influenza pandemic of 1918 when the majority of deaths were due to bacterial co-infections or subsequent bacterial infections [22, 23]. In the case of the 2009 Swine flu pandemic, 18~34% of influenza episodes admitted to intensive care units worldwide were due to complications caused by bacterial co-infections [24–29]. Of these cases, *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most commonly isolated bacterial pathogens. These pathogens colonize the upper respiratory tract and nasopharyngeal cavity [30, 31], and it has therefore been hypothesized that influenza infections allow outgrowth of colonized *S. pneumoniae* or *S. aureus* and result in mucosal co-infections [32–34]. Such secondary infections occur most frequently at 5–10 days after primary viral infections, thus suggesting that a transient immunosuppression may be responsible for the bacterial outgrowth. A mechanism proposed for a synergism between influenza and *S. pneumoniae* suggests that the antiviral IFN-I response elicited by the primary influenza virus infection enhances the susceptibility of the host to secondary bacterial challenge via suppression of antibacterial immunity [34–36].

Recent mathematical modelling of epidemiological data from the 1918 influenza pandemic has shown a positive correlation between *Mycobacterium tuberculosis* and influenza death [37]. *M. tuberculosis* is a clinically important bacterial pathogen that latently infects one-third of the world's population. Negative effects of IFN-I during *M. Tuberculosis* infection have repeatedly been shown [38–41]. However, with an exception of highly virulent strains [40], *M. tuberculosis* does not generally induce strong IFN-I responses [42] despite possessing a Toll-like receptor (TLR)-9 agonist (DNA-containing CpG motifs), which is a potent IFN-I inducer. This phenomenon has been recently explained, namely the detection of mycobacterial lipoproteins through TLR-2 inhibits the TLR-9 signalling pathway [42, 43] via depletion of a signalling molecule, IL-1R-associated kinase 1, and thereby in turn suppresses IFN-I production during *M. tuberculosis* infections. This TLR-2-dependent negative regulation of the IFN-I response during *M. tuberculosis* infections is likely to be beneficial to the host by limiting the harmful effects of IFN-I. This inhibitory mechanism may also play a positive role during other bacterial infections as TLR-2 recognizes a wide range of bacterial pathogens. What is interesting is that TLR-2 signalling impairs TLR-7-, TLR-9- but not TLR-3-induced IFN-I synthesis [42, 43]. This in turn explains why influenza virus co-infections in *M. tuberculosis*-infected mice impairs bacterial control in an IFN-I-dependent manner [44]. Influenza virus generates multiple ligands of pattern recognition receptors during the viral replication cycle, which includes dsRNA (TLR-3 agonist) and ssRNA (TLR-7 agonist). Thus, influenza virus infections can override TLR-2-dependent inhibition of IFN-I responses in *M. tuberculosis*-infected mice through TLR-3 signalling and induce IFN-I responses that ultimately result in outgrowth of *M. tuberculosis*. These findings

provide answers as to why the risk of influenza death was higher among patients with tuberculosis than non-tuberculosis patients during an influenza pandemic [37].

Hypothesis: Type I IFN exhaustion serves to increase the resistance of virally infected mice against secondary bacterial infections

Recent studies have focused on the mechanism of how primary viral infections render the host vulnerable to a sequel of bacterial infections. Severe forms of viral–bacterial co-infections are rare and only seen when the virus itself is highly virulent such as the 1918 Spanish influenza virus [23]. In fact, according to the Centre for Disease Control and Prevention, only 29% of fatal cases of patients with H1N1 influenza had bacterial co-infection [45]. When the primary viral infection is highly pathogenic, it is difficult to ascertain whether the increased susceptibility is due to suppression of antibacterial immunity or the consequence of viral pathology itself. We hypothesize that severe forms of viral–bacterial co-infection are an exception to the rule and that in most cases, that is, with less virulent viruses, primary infections do not lead to severe secondary bacterial pathology. Thus, there have to exist immune mechanisms that limit secondary co-infections.

Our current understanding of the biology of IFN-I is that it is beneficial and essential to recover from most if not all acute viral infections, but may be detrimental to the host when fighting off bacterial pathogens. We also know from our previous studies [16] and reports from others [21] that IFN-I deficiency as a consequence of exhaustion occurs after primary viral infections and the host is rendered more susceptible to secondary unrelated viral infections during this transient period of IFN-I exhaustion. Based on these observations, we hypothesize that the host evolved a negative feedback loop mechanism to limit IFN-I production, which is rapid but transient rendering the host less susceptible to opportunistic bacterial infections that are more prevalent than secondary unrelated virus infections. This transient deficiency in IFN-I benefits the host as it does not lower resistance to common secondary bacterial infections (Fig. 1). In support of this hypothesis, IFN-I exhaustion is most likely to be evolutionarily as it appears to be a consequence of all primary viral infections. We and others have shown this to be the case for adenoviruses, alphaviruses, orthomyxoviruses, murine cytomegalovirus and lymphocytic choriomeningitis virus [16, 21]. From an evolutionary perspective, there must have been a strong selective advantage to transiently exhaust IFN-I responses after primary viral infections to occur. Thus, it is reasonable to speculate the evolutionary advantage of negative feedback regulation to suppress virus-induced immune responses that are detrimental against secondary bacterial infections.

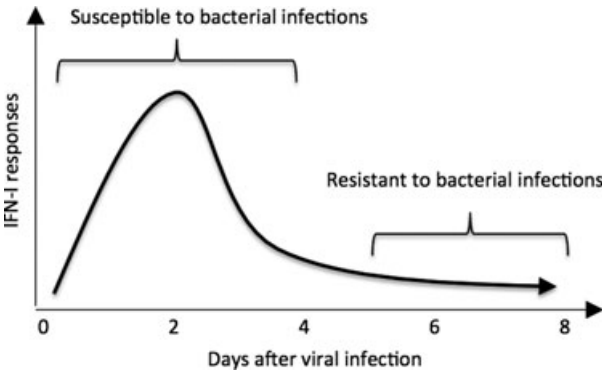

Figure 1 Proposed impact of virus-induced host IFN-I deficiency on susceptibility against secondary bacterial infections. Viral infections induce early IFN-I responses followed by a transient period of IFN-I exhaustion. The hosts are highly susceptible to secondary bacterial infections during the peak of IFN-I and then become resistant during transient suppression of IFN-I responses.

Experimental approach

It has been shown previously, exploring influenza virus/*S. pneumoniae* co-infection models, that secondary challenges, with either virus or bacteria, at the peak or during the IFN-I response, are highly lethal and the increased lethality is attributable to IFN-I [34–36]. It would be interesting to find out whether the outcome of such co-infection experiments would differ if mice undergoing a primary virus infection were challenged with bacterial pathogens at the time of IFN-I exhaustion, 5–9 days post-infection. Thus, to provide evidence for the above-outlined hypothesis, all that would be required is to establish correlates of strength of IFN-I response and exhaustion with severity of secondary bacterial challenges. A time course of bacterial infections after primary virus infection and/or poly I:C treatment would provide an answer to this question. Poly I:C, a synthetic analogue of double-stranded RNA, mimics RNA viral infections, but would eliminate potential unrelated viral-induced pathologies affecting secondary bacterial pathologies. It has been shown that poly I:C-treated mice mount IFN-I responses that render the host transiently more susceptible to bacterial infections [41, 46]. Evaluation of the severity of bacterial growth, morbidity and mortality should establish whether IFN-I exhaustion ameliorates secondary bacterial pathology. Poly I:C-treated experimental groups will eliminate potential unknown viral-induced complications.

Discussion

It is somewhat surprising that the by now widely known phenomenon, that of an IFN-I refractory period after a viral infection, has as yet not been investigated as to its consequences for the host's susceptibility to bacterial infections, given its potential clinical implications. The

known detrimental consequences of the refractory period to secondary viral infections, namely heightened susceptibility, are somewhat hard to understand in evolutionary terms unless there exists an overriding host–benefit rationale. This may well turn out to be protection from potentially lethal bacterial infection, which can be controlled in the absence of IFN-I.

What has been investigated are the causes for the impaired IFN-I responses following viral infections. As pDCs are the principal secretors of IFN-I, the prevailing hypothesis for IFN-I impairment is centred on pDCs [5, 21, 47]. pDCs that have been induced to produce large amounts of IFN-I in a primary antiviral response are either depleted, through mechanisms such as NK cell-mediated cytotoxicity [48, 49], or are induced to mature and have to be replaced by haematopoesis, or they acquire a transient state of unresponsiveness and paralysis such as that reported in experiments using *in vitro* stimulation after *in vivo* viral infections [50]. Although, in our mouse model using avirulent SFV, we did not observe quantitative reduction in pDCs [16], others have reported significant decrease in numbers of pDCs soon after acute or during persistent viral infections [21, 51]. Consistent with the above animal data, human patients infected with hepatitis B virus (HBV), hepatitis C virus (HCV) or HIV have decreased numbers of circulating pDCs [52–55]. In addition, patients with HCV infection receiving IFN-Iα therapy exhibit decreased numbers of pDCs in blood compared with untreated controls [56]. Thus, a strong negative correlation exists between the quantity of the IFN-I response and pDC numbers. Recent study by Swiecki *et al.*[51] has shown that pDC depletion during systemic viral infection occurs in an IFN-I-dependent manner through upregulation of pro-apoptotic expressions of Bid, Bim, Noxa and Bax and downregulation of anti-apoptotic Bcl-xl and Bcl-2.

Besides quantitative changes, qualitative differences in pDCs have also been documented. pDCs isolated from mice undergoing IFN-I exhaustion are unable to produce IFN-I in response to CpG, a TLR-9 agonist, after treatment *ex vivo* [21]. Interestingly, the functional defect of pDCs is limited to IFN-I production because synthesis and secretion of other cytokines such as TNF-α, IL-12 and MCP-1 are not impaired [21]. Collectively, it is likely that the inability of the host to mount an IFN-I response during the refractory period against a secondary challenge is due to both a pDC intrinsic defect in IFN-I production and an overall reduction in pDC numbers, the consequence being a vastly reduced IFN-I output, which may render the host less susceptible to secondary bacterial infections.

Research into viral/bacterial co-infections has in recent years become much more fashionable due to its potential clinical significance. Most studies have focused on understanding how viral infections cause heightened susceptibility to subsequent bacterial infections. Much less attention has been directed on understanding how the host has evolved mechanisms to enhance resistance against such secondary bacterial infections. The evidence presented above supports our hypothesis that inhibition of IFN-I production is a mechanism by the host to reduce susceptibility to bacterial infections during recovery from primary virus infections.

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