REVIEW

Interferon type I responses in primary and secondary infections

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The mammalian host responds to a microbial infection with a rapid innate immune reaction that is dominated by type I interferon (IFN-I) release. Most cells of vertebrates can respond to microbial attack with IFN-I production, but the cell type responsible for most of the systemic IFN-I release is thought to be plasmacytoid dendritic cells (pDCs). Besides its anti-microbial and especially anti-viral properties IFN-I also exerts a regulatory role on many facets of the sequential adaptive immune response. One of these is being the recently described partial, systemic activation of the vast majority of B and T lymphocytes in mice, irrespective of antigen reactivity. The biological significance of this partial activation of lymphocytes is at present speculative. Secondary infections occurring within a short time span of a primary infection fail to elicit a similar lymphocyte activation response due to a refractory period in systemic IFN-I production. This period of exhaustion in IFN-I responses is associated with an increased susceptibility of the host to secondary infections. The latter correlates with well-established clinical observations of heightened susceptibility of patients to secondary microbial infections after viral episodes. *Immunology and Cell Biology* (2008) **86**, 239–245; doi:10.1038/sj.icb.7100159; published online 8 January 2008

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Control of viral infections by the vertebrate host involves both the innate and the adaptive immune response. The former is mediated primarily by type I interferons (IFN-I), macrophage/monocytes and natural killer (NK) cell responses. The adaptive immune response to infection is mediated by T and B cells. Antigen-reactive T and B cells, after the primary infection has been resolved, develop the long-lasting immunological memory component. The magnitude and quality of the innate immune response are intimately involved in the subsequent adaptive primary response, which in turn determines the magnitude and quality of the memory responses. Although we have gained much insight into the mechanisms, biochemical properties and functions of the individual responses, the wider consequences of their actions are mostly still elusive. The focus of this review will be on the IFN-I responses during primary and secondary infections.

Interferon is the term given to a family of inducible glycoproteins that are produced by cells in response to biological stimuli, including viruses, bacteria, mycoplasma, protozoa, cytokines, mitogens, natural and synthetic double-stranded RNA (ds-RNA) and other substances. IFNs were discovered on the basis of their antiviral activity when influenza virus-infected chicken cells were shown to produce a secreted factor that conferred a virus-resistant state active against both homologous and heterologous viruses.¹ This observation set the stage for subsequent studies that led to the elucidation of many aspects the IFN system. According to the cell types from which they were derived, three types of IFNs were originally recognized: leucocyte (α),

fibroblast (β) and immune (γ).^{2,3} The currently accepted classification divides IFNs, based on amino-acid sequence homology, into two groups, type I (IFN-I) and type II (IFN-II). IFN-II (IFN- γ) is induced by mitogenic or antigenic stimuli of lymphocytes (NK and T cells), whereas IFN-I are induced primarily by virus infections.³ The recently identified interleukins (IL) 28 and 29, also called IFN- λ or IFN-III, display IFN-I-like anti-viral activities through a receptor complex distinct to that of IFN-I.^{4,5} Although the pattern of expression has not been elucidated yet, it is believed that different cell types, including plasmacytoid dendritic cells (pDCs), can express IFN-III during most viral infections. Their *in vivo* anti-viral activity, however, appears to be mediated against selected viruses.^{6,7}

IFN-I comprise a multi-member cytokine family that includes, IFN- α subtypes, IFN- β , IFN- ϵ , IFN- κ , IFN- ω , IFN- δ and IFN- τ .^{8,9} Of these, IFN- δ ¹⁰ and IFN- τ ¹¹ are not found in humans, IFN- ϵ is expressed in the placenta and may play a role in reproduction,¹² IFN- κ is expressed in keratinocytes,¹³ and IFN- ω is expressed in human peripheral leucocytes following viral infection.¹⁴ From an immunological perspective, therefore, IFN- α and IFN- β are the main type I subtypes of interest, and in this review we use the term IFN-I mainly to describe these two subtypes. Both are expressed in all mammalian species examined.² In addition, they are inducible by viral infections and recognize the same multicomponent cell surface receptor, the type I IFN receptor (IFN-IR).^{15–18} The IFN- α family is a multigenic group of related polypeptides encoded by more than 13

genes in humans and more than 10 genes in mice.^{19–21} IFN- β , in contrast, exists as a single gene in most species, including human and mouse. Although the reason(s) for multiple IFN- α subtypes is not fully understood, evidence suggests that they have distinct functions. Moreover, their expression, and the qualitative and quantitative profiles of genes they stimulate *in vitro*, depends on the inducing stimulus, cell type and donor.²²

In addition to their important antiviral properties IFN-I exert pleiotropic effects, including inhibition of cell growth, anti-tumour activity, involvement in homeostasis and regulatory effects on cellular and humoral immune responses.²³ In this review, we briefly address IFN-I induction and antiviral activity prior to our focus on the IFN-I response in primary and secondary infections.

IFN-I RESPONSE IN PRIMARY VIRAL INFECTION

Induction of IFN-I

Generally, the production of IFN-I (α and β) is not confined to specialized cells, and most cells of vertebrates are probably capable of producing IFN-I in response to viral infection.²³ Macrophages, NK cells, DCs and fibroblasts were reported to produce IFN-I in response to viral infection or exposure to microbial pathogens.^{24–28} However, by far the most potent producers of IFN-I are plasmacytoid DCs, which can produce up to 1000-fold more IFN-I *in vitro* than any other cell type following microbial or viral challenge.^{29,30} These cells are thought to be responsible for the systemic IFN-I responses to many viruses.^{31,32} Other DCs, non-plasmacytoid, can also act as high IFN-I producer, particularly during DC-tropic viral infections.³³

It is currently accepted that there are two receptor families involved in viral detection and induction of IFN-I.³⁴ These are the Toll-like receptors (TLRs) and the cytosolic receptors (CRs). The TLR family is composed of membrane proteins expressed by different cell types, including immune cells such as macrophages, DCs, NK cells, B and T lymphocytes.³⁵ Each TLR binds a particular type of what has been termed pathogen-associated molecular patterns, such as viral nucleic acids, lipopolysaccharides, flagellin, DNA containing cytosine phosphate guanine motifs.³⁴ The diversity of TLRs enables the immune cells expressing them to sample the host environment for pathogen presence. In addition, their ability to recognize different types of nucleic acids allows the detection of most viral infections. Pathogen recognition by TLRs results in the transcriptional induction of multiple genes, including IFN-I.^{36,37} Early IFN-I themselves provide a positive autocrine feedback loop for the production of later appearing IFN types³⁸ and a concomitant upregulation of TLRs whose ligation adds to IFN-I production, such as protein kinase R (PKR), TLR3 and TLR7.^{39,40}

In contrast, CRs are expressed within the cytoplasm of almost all nucleated cells and thus able to recognize viral nucleic acids within the infected cells.³⁴ Depletion studies have shown pDCs as not essential for IFN-I responses during DC-tropic lymphocytic choriomeningitis virus (LCMV) infection.⁴¹ This redundancy in pDC function is related to the ability of other non-pDC dendritic cells to act as IFN-I producer through their CRs, which recognize dsRNA.³³

Antiviral effects

Although the aim of this review is not a detailed discussion of the direct antiviral effect of IFN-I, it is important to note that they were discovered on the basis of their antiviral activity. Despite the differences in the ability of cells to secrete IFN-I and of pDCs to produce large quantities, it is generally accepted that all cells can synthesize some IFN-I within hours of infection by a virus, unless protein synthesis is inhibited. This IFN-I can act in an autocrine and

paracrine manner to limit replication and spread of virus.⁴² The early induction and action of IFN-I result in cellular resistance to viral infection, inhibition of viral replication and impediment of viral dissemination.^{43,44} The best-characterized direct antiviral effect by IFN-I results from the production of two ds-RNA-activated enzymes, (2'–5')-oligoadenylate synthetase⁴⁵ and ds-RNA-dependent PKR.^{46,47} Production of these enzymes is dependent on activation of the JAK–STAT pathway by the interaction of IFN- α/β with their specific cell surface receptor, IFN-IR.^{3,48} This direct effect of IFN-I results in protein synthesis inhibition in infected cells and thus limits the production of progeny viral particles.⁴⁹

Many studies have shown that the direct antiviral activity of IFN-I is important in resisting many viral infections. Mice genetically deficient in functional IFN-IR (IFN-IR^{–/–}) are extremely susceptible to viral infections such as vesicular stomatitis virus (VSV), Semliki Forest virus (SFV), vaccinia virus (VACV), LCMV,¹⁹ Sindbis virus,⁵⁰ Venezuelan equine encephalitis virus⁵¹ and Murray Valley encephalitis virus.⁵² The role of IFN-I, however, goes beyond their ability to inhibit viral replication as they were proven to be the maestro of antiviral immunity, involved in regulating the action of almost all instruments of the immune system.

Immunoregulatory role of IFN-I

To successfully control a viral infection, virus-infected cells need to be eliminated prior to formation and release of viral progeny. Such successful outcome requires a concerted action of both the innate and adaptive arms of the immune system. IFN-I may well be the most important immunoregulators that determine the type and the level of the immune response to any particular infection. IFN-I have been reported to mediate activation of NK cell proliferation and cytotoxicity *in vivo*.⁵³ However, IFN-I do not stimulate NK cell proliferation directly. They fail to elicit NK cell proliferation *in vitro* and exert anti-proliferative effects at high concentrations,⁵⁴ and their influence on NK cell responses is dependent on secondary cytokines such as IL-15.^{55,56} Moreover, it has been shown that, during viral infections, IFN-I-mediated activation of NK cell effector function is selective for cytotoxicity but does not extend to IFN- γ expression.⁵⁷ Furthermore, IFN-I may be crucial for antiviral responses mediated by macrophages, as they synergize with tumour necrosis factor to induce inducible nitric oxide synthase (iNOS) and iNOS-dependent pathways of defences mediated by macrophages.⁵⁸

The role of IFN-I in linking innate and adaptive responses is of considerable importance. Elimination of virus-infected cells requires the generation of a virus-immune cell-mediated response which, in turn, depends on the ability of infected cells to present the viral antigens in conjunction with major histocompatibility complex (MHC) molecules.⁵⁹ IFN-I induce upregulation of cell surface MHC protein expression, particularly MHC class I molecules, thereby promoting the presentation of viral antigens to CD8⁺ cytotoxic T cells.⁶⁰ However, the immunoregulatory role of IFN-I goes beyond elevating the expression of MHC molecules, and may include other effects on antigen-presenting cells (APCs) as well as T and B cells.

Effects on dendritic cells

The activation of T and B lymphocytes requires the recruitment and maturation of APCs. These APCs include B cells, monocytes/macrophages and the most potent APC, DCs. While immature pDCs have been identified to be the major IFN-I producers,^{29,30} IFN-I themselves have been shown to play an important role in DCs maturation and survival.⁶¹ *In vitro* treatment of immature DCs with IFN-I induces phenotypic and functional maturation, as evident by upregulation of

molecules involved in antigen presentation, such as MHC-I and -II, and co-stimulatory molecules, such as CD83, CD40, CD80 and CD86.^{61,62} Despite considerable redundancy in many cytokine functions, the effects of IFN-I on DC seem relatively unique, as only IL-15 can substitute for IFN-I in this respect, and only partially so.⁶³ Production of IL-15 itself is induced by IFN-I, and the activating effect of IL-15 on DC is reduced in the absence of IFN-IR.⁶³ Furthermore, *in vitro* treatment of DCs with IL-15 resulted in an initial production of IFN- β followed by IFN- α .⁶⁴

The effect of IFN-I on DC varies with the type of DC. While maturation of pDCs in response to TLR7/9 triggering is severely impaired in IFN-IR^{-/-} mice, that of conventional DC occurs normally in these mice.⁶⁵ In contrast to other types of DC, in which IFN-I exposure leads to maturation into potent APC with high expression of co-stimulatory molecules,^{61,66–68} pDCs do not upregulate co-stimulatory molecules such as CD40, or MHC-II in response to IFN-I stimulation,²⁹ unless directly infected by a virus.⁴¹ Not only do IFN-I promote pDC maturation *in vitro*, but their viability is also enhanced.^{29,69}

Given the positive effect on maturation and survival of DC, it is surprising that they exert negative influence on differentiation of immature DC from bone marrow precursors.⁷⁰ This inhibitory activity is such that viruses such as measles virus, LCMV and respiratory syncytial virus have developed means of immune evasion by subverting the IFN-I responses,^{70–72} implying that inhibition of DC precursor development provides an advantage to virus survival even at the stage when virus infection has already occurred. Thus, IFN-I mediate opposing influences on DC development, inhibiting DC precursor differentiation, but promoting the final maturation and survival of DC into initiators of the adaptive immune response.

Cytokine production by DC, in particular IL-12, has been shown to be sensitive to the abundance of IFN-I during DC activation. Low levels of IFN-I are required for IL-12p35 transcription (and consequently the production of the bioactive P70 dimer), whereas high IFN-I levels inhibit p40 transcription.⁷³ However, complete lack of IFN-I leads to deficiency in IL-12 production.

Effects on T and B lymphocytes

The profound effects of IFN-I on DC are likely to result in significant consequences for the development of adaptive immune responses. But the pleiotropic effects of IFN-I are not confined to DC physiology, as they also directly influence T and B cells. Again, the effects may be enhancing or suppressive, depending on the circumstances. IFN-I have been shown to promote the development of effector functions of T cells, such as IFN- γ production and cytolytic function, and have been termed a 'third signal' for lymphocyte activation, in addition to recognition of cognate antigen in the context of co-stimulation.⁷⁴ IFN-I also promote survival of activated lymphocytes.⁷⁵ Interestingly, while IFN-I-enhanced T-cell survival was shown to correspond to elevated expression of the anti-apoptotic Bcl-2 protein family member Bcl-xL in human T cells,⁷⁶ mouse T cells did not display elevated levels of Bcl-xL or Bcl-2,⁷⁵ suggesting that they may be mediated by different survival mechanisms. These pro-survival effects are nevertheless likely to be caused by direct action of IFN-I on T cells, rather than via *cis* effects on the APCs involved in priming the T cells, perhaps by enhancing antigen presentation, as was showcased in cross-priming studies: IFN-I led to stronger *in vivo* proliferation and prolonged expansion of IFN-IR-sufficient, but not -deficient OT-I transgenic T cells,^{77,78} thereby effectively enhancing cross-priming efficiency. Again, the molecular intracellular pathways responsible for this effect remain to be characterized. Although receptors for IL-12 and -15,

cytokines participating in the regulation of T cell survival and expansion, were upregulated, the proliferative effect of IFN-I was independent of these cytokines. Presence of IFN-I is clearly beneficial for production of IFN- γ by antiviral CD8 T cells,^{79–81} and the availability of IFN-I during an antiviral T-cell response may determine whether IFN- γ production is dependent on IL-12 or not.⁸¹

Despite this generally favourable effect of IFN-I on IFN- γ production, early in the T-cell response the effect might be inverse. T cells responding to IL-12 or anti-CD3 stimulation are negatively regulated by IFN-I, at least regarding their ability to produce IFN- γ .⁵⁷ This phenomenon was also noted in T cells isolated in the first few days after infection with LCMV⁸² and, given the prominent role of IFN- γ in activation-induced cell death (AICD) of antigen-specific T cells, this may represent a safeguard to prevent AICD of antigen-experienced T cells at a time when optimal expansion of such cells is still required and beneficial. However, the proliferative response of T cells may also be impaired by exposure *in vitro* to IFN-I, produced by CpG-stimulated APC.⁸³ To resolve this paradox, it was shown that this inhibition of proliferation only occurs when antigen-specific stimulation and co-stimulation are absent or suboptimal.^{84,85} Thus, in the absence of TCR engagement and co-stimulation, IFN-I would have a net inhibitory effect on T-cell proliferation, or may even be pro-apoptotic,⁸⁶ whereas in their presence, IFN-I would promote optimal activation. These finely adjusted effects of IFN-I on T cells may explain the reported large scale attrition of non-virus-immune CD8⁺ T cells during early LCMV infection.⁸⁷ However, it is still unclear whether T-cell attrition is a common feature to viral infection or may only be applicable to viruses that are lymphotropic.^{88,89} At least infection of C57BL/6 mice with the alphavirus, SFV, is not associated with T-cell loss.⁹⁰ When considering these sometimes contradicting effects of IFN-I it should be noted that this can probably only be asserted for IFN-I as a whole class of molecules, and that future research may well reveal that certain activities are mediated more or less exclusively by different IFN-I subtypes.⁹¹

In addition to their effects on T cells, IFN-I regulate B cell functions such as antibody secretion and isotype switching.⁹² Induction of isotype switching by IFN-I may be mediated by their effect on DCs⁹³ as well as their influence on T-cell responses.⁹⁴ Co-injection of IFN-I with a soluble protein antigen enhances *in vivo* T-cell priming.^{62,77} IFN-I enhances T helper type 1 (Th1) responses by inhibiting the secretion of typical T helper type 2 (Th2) cytokines (IL-4 and -5) but promoting production of the Th1-type cytokine IFN- γ in CD4⁺ T cells.^{94,95} Such effect of IFN-I is also linked to isotype switching as the increased production of IFN- γ subsequently promotes switching of B cells to synthesise IgG_{2a} isotype antibodies.⁹⁶ In addition, IFN-I promotes IgM, IgA, but not IgG₁ antibody production by B cells.⁹⁷

Lymphocyte activation

An intriguing observation is that the systemic IFN-I levels, as measured by serum levels, peak only 1 or 2 days after infection with a virus,^{26,86,98} with a subsequent return to baseline levels by days 3–4, suggesting that its promoting or inhibitory activities on T and B cells are part of a programming that is imprinted at that early stage. The peak of IFN-I serum levels coincides with an almost global acquisition of a partial activation phenotype in T and B cells after viral infection, as almost all lymphocytes transiently upregulate the expression of activation markers.^{86,98} Given the magnitude of this phenomenon (>80% of all T and B cells upregulate CD69 and CD86 within a day of infection), and the relative scarcity of virus antigen-specific lymphocytes at this stage of the infection, this phenomenon is obviously

independent of antigen reactivity. *In vitro* stimulation of B cells with IFN-I also leads to partial activation, characterized by CD69, CD86 and CD25 upregulation, but without proliferation or full differentiation into antibody-producing cells.⁹⁹ Moreover, injection of poly-(I:C), a synthetic ds-RNA analogue leads to proliferation of T cells in the absence of cognate antigen, albeit without upregulation of CD69 or CD25 *in vivo*.¹⁰⁰ However, we recently showed that the acquisition of a partially activated phenotype by lymphocytes is dependent on IFN-I, and also appears to be a general feature of viral infection, as it was observed after infection with alphaviruses, ortho- and paramyxoviruses, adenoviruses, orthopoxviruses and flaviviruses.⁹⁸ The state of partial activation observed in these cases is characterized by upregulation of CD86 and CD69 but, in contrast to the *in vitro* data obtained with B cells mentioned above, not CD25.

Thus, while the details vary between reports, there is agreement that IFN-I can induce a partial activation state in lymphocytes.^{98,99} *In vitro* studies have shown that treatment of B cells with recombinant IFN-I results in enhanced proliferation, receptor internalization, and signalling through the B-cell antigen receptor.⁹⁹ Therefore, we suggest that induction of partial activation serves as a mechanism to transiently lower the threshold for full, antigen-dependent, activation. It is unclear, however, how IFN-I would aid in the temporary adjustment of activation thresholds. One possible mechanism is by regulating the expression of a variety of molecules, such as CD86, CD69, and CD25. The CD86 molecule is well-described co-stimulatory molecule for T cells when expressed on APC, but few examples have been described of CD86 expression by T cells themselves. In this respect, human effector memory cells have been reported to express CD86 that was able to provide co-stimulation to naive T cells *in vitro*.¹⁰¹ In addition, expression of functional CD86 has been demonstrated on allergen-specific T cells of atopic patients,^{102,103} where in one case CD86 was able to act in a paracrine (on naive T cells) but not autocrine manner,¹⁰² as well as on a small number of CD3⁺ tumour-infiltrating lymphocytes.¹⁰⁴ However, in these instances, the T cells expressing CD86 were effector or memory T cells. It is conceivable, though, that CD86–CD28 ligation during T–T interactions, for example when sampling antigen on the same APC, or when meeting in inflamed tissues, may provide stimulatory signals to both partners. Increased CD86 (as opposed to CD80) expression by DC has been suggested to be crucial for inhibition of regulatory T cells, thus making it an important factor in the overall effectiveness of T-cell activation.^{105–107} Consequently, it is tempting to speculate that T cells expressing CD86 may inhibit regulatory T cells particularly in situations where the suppressive function is mediated via cell-to-cell contact.

CD69, on the other hand, has long been considered an early lymphocyte activation marker.¹⁰⁸ In fact, all bone marrow-derived cells, with the exception of erythrocytes, express CD69 upon activation.¹⁰⁹ Given the universal association of this molecule with early activation, it is striking that specific functions of CD69, as well as a ligand, have only recently been described. While early reports proposed mainly a stimulatory contribution to lymphocyte activation, there is increasing evidence of an immunoregulatory function.¹⁰⁹ Of particular interest is a recent finding implicating CD69 in mediating transient accumulation of lymphocytes in secondary lymphoid organs (SLO). In this report, sphingosine 1 phosphate receptor-1 (S1P1), an epithelial cell surface-expressed molecule required for lymphocyte egress from SLO, was described as a ligand for CD69.¹¹⁰ Thus, IFN-I-induced CD69 on lymphocytes led to downregulation of S1P1, and consequent inhibition of egress of lymphocytes from, and sequestration in, SLO.¹¹¹ While the main interest in these findings have been the potential of modulation of these processes for therapeutic benefit in

autoimmune disease (via temporary sequestration of autoreactive T cells in SLO, for example during relapsing-remitting disease like multiple sclerosis), we believe that the physiological role of these processes suggest that CD69-mediated concentration of such partially activated lymphocytes in SLO may promote optimal APC–T cell interaction, and hence antigen-specific activation.

Thus, IFN-I-mediated partial lymphocyte activation may affect both, reduction of the threshold for full activation via CD86-dependent processes, while at the same time maximizing the chances of antigen-specific lymphocytes meeting their cognate antigen on APC by transiently sequestering lymphocytes in SLO during the early days of an infection.

The absence, *in vivo*, of another classical lymphocyte activation marker, CD25, in this generalized partial activation is likely to be important. While IFN-I may trigger a transient 'state of alert' as suggested above, CD25 is likely to only be expressed by those T cells that have, in addition to IFN-I stimulation, received further activation signals via their antigen receptors.^{78,99,112} In this scenario, antigen recognition may be the final, and critical, switch allowing for CD25 expression, and thereby for IL-2-dependent expansion, of antigen-specific but not bystander lymphocytes.

The manipulation of activation thresholds for lymphocytes is likely to come at a cost, though, otherwise lower thresholds would be expected to be hardwired into mature, naive lymphocytes. The evident risk is that of inadvertently breaking self-tolerance.¹¹³ It is therefore not surprising that such a state of alert is not maintained indefinitely—or expressed constitutively—but rather is temporally restricted. The expression of activation markers on lymphocytes returns to background levels within 4–5 days of infection, that is soon after the disappearance of serum IFN-I.⁹⁸ We have shown that reverting lymphocytes are able to undergo renewed partial activation.⁹⁰ It will be of interest to determine whether lymphocytes once 'pre-activated' by IFN-I exposure are phenotypically different from others, such as recent thymic emigrants, or those ~20% of circulating cells that fail to undergo such activation during the primary infection stage, and if lymphocytes are able to undergo indefinite cycles of partial activation and reversion to a resting state.

Effects on memory

Given the multiple effects of IFN-I on the induction of adaptive immune responses, it is not surprising that they also contribute to formation and maintenance of immunological memory. CD8⁺ T cells have been shown to require a direct signal by IFN-I during initial antigen-specific activation in order to survive the subsequent contraction phase, and form memory T cells.^{114,115} In these studies, CD8⁺ T cells from IFN-IR^{-/-} mice showed less expansion and a diminished memory pool compared to CD8⁺ cells from wild-type mice in response to infection with LCMV, VACV, VSV and *Listeria* monocytogenes (LM). Thus, there is a divergence in the requirements for TCR-triggering and IFN-I-mediated signals in T-cell proliferation versus survival and memory formation, respectively. Furthermore, maintenance of memory T cells has been suggested to be dependent on intermittent stimulation by, among other cytokines, IFN-I. In a seminal paper that rekindled interest in IFN-I functions in adaptive immunity, Tough *et al* demonstrated that CD44^{hi} memory CD8⁺ cells briefly proliferated *in vivo* upon poly-(I:C) stimulation, before reverting to a resting phenotype.¹⁰⁰ They also observed an increase in the pool of adoptively transferred TCR transgenic memory cells 1–2 days after poly-(I:C) injection. This suggests that IFN-I are important in maintaining immunological memory by contributing to the survival of memory T cells.

In contrast, others have correlated IFN-I action with an interference with the established T-cell memory pool, in particular 'bystander' memory T cells. LCMV infection results in substantial lymphocyte apoptosis, which is mainly observed in the CD44^{hi} population of memory T cells not reactive to LCMV-derived antigens.⁸⁷ This attrition correlated with the peak of IFN-I production and was mimicked by poly-(I:C), but absent in IFN-IR^{-/-} mice. Such bystander memory cell attrition might explain the loss of T-cell memory over the course of several sequential infection with viruses unrelated to the initial infecting pathogen,^{116,117} and may be a necessity for generating 'space' for the expansion of antigen-specific T cells during an acute viral infection. Interestingly, foreign antigen-reactive memory cells are relatively deficient in their response to homeostatic signals than those CD44^{hi} T cells that preferentially repopulate lymphopenic environments, thereby becoming diluted over time and successive infections.¹¹⁸

Despite widespread lymphocyte apoptosis occurring during infection with several viruses, such as LCMV and LC, Feline leukaemia virus and Feline immunodeficiency virus,^{86,87,119} it does not seem to be an obligatory accompaniment of viral infection, as it is not observed with alphaviruses¹²⁰ or orthopoxviruses (unpublished data). Infection with LM is also characterized by significant T-cell apoptosis.^{86,121} The common theme here is that pathogens with tropism for lymphocytes produce this phenomenon, which suggests that fratricide may be responsible as suggested by Blanden *et al* 30 years ago.⁸⁸

IFN-I RESPONSES TO SECONDARY INFECTIONS

As discussed above, the importance of IFN-I responses in recovery from viral infections has been clearly established. However, our information is solely based on IFN-I responses to primary infections, and little is known in regard to the induction of IFN-I during a secondary infection during or shortly after a primary infection has been resolved. It is generally anticipated that all nucleated cells have the ability to respond with IFN-I responses to a secondary viral challenge and that interferon-producing cells are able to mount such a response analogous to that seen in a primary response.

Recently, we obtained evidence in mice that the infected host undergoes a transient period of partial immune-unresponsiveness, between 5 and 9 days after an acute primary viral episode.¹²⁰ This period is associated with exhausted IFN-I responses and an accompanied increased susceptibility to secondary unrelated viral infections. Indeed, we found that secreted IFN-I, the pre-requisite for systemic partial lymphocyte activation,⁹⁸ was not detectable 1 day after a secondary infection when mice had previously been infected for 6 days with an unrelated virus.¹²⁰ However, when secondary infections were given 9 or more days after a primary infection, IFN-I activity, as measured by lymphocyte activation status, was comparable to that seen after a primary infection. While a transient period of exhaustion in the IFN-I responses correlated with an increased susceptibility to the secondary infections, the effect of such IFN-I deficiency on regulating the immune response to the secondary infection needs to be established. Furthermore, it remains to be established why a renewed IFN-I responses is not mounted in mice at 5–9 days after a primary viral infection.

It is tempting to speculate that infected pDCs, the predominant producers of IFN-I,^{29,32} may be subject to elimination by cytolytic lymphocytes. Consistent with this idea is the temporal correlation of the peak of the cytotoxic T-cell response with the observed deficiency in IFN-I production. pDCs might also be depleted, irrespective of infection status, by NK cells,^{122,123} and may need to be replenished by

homeostatic processes. However, our observations indicate that numbers of both pDCs and conventional DCs slightly increased—rather than decreased—in spleens of aSFV-infected mice 5 days after infection.¹²⁰ This is consistent with previously reported increases in pDC numbers in the spleen of herpes simplex virus (HSV)-infected mice.¹²⁴ Alternatively, given the stimulus exerted by IFN-I to drive pDC maturation,⁶¹ a strong IFN-I signal might induce them to differentiate into a non-IFN-I-secreting phenotype. Previous studies have shown that DCs from HSV-infected mice fail to produce IFN-I when re-stimulated *in vitro*,¹²⁴ and that infection of DCs with mouse cytomegalovirus resulted in their paralysis, as defined by deficiency in production of IL-12 and IL-2.¹²⁵ Future investigations into these processes are likely to lead to clinically important understandings.

Clearly, the inability to respond to a viral infection with a potent IFN-I response carries a high risk for the host, as demonstrated by the high susceptibility of IFN-I receptor-deficient mice to viral infections.^{19,50–52} Consistent with this, the inability to release IFN-I over a period of several days after a primary infection is associated with a striking failure to control a subsequent viral infection.¹²⁰

It has been a long-standing empirical clinical observation that patients suffering from a microbial infection are often more susceptible to a secondary infection. Since IFN-I play an important antimicrobial as well as immunoregulatory role, exhaustion of the IFN-I responses may be the prime factor responsible for compromised resistance to sequential infections. Future studies aiming to address causes and consequences of IFN-I exhaustion will provide the answers and are a high priority in IFN-I research.

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