Links between innate and adaptive immunity via type I interferon

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Type I interferon (IFN-α/β) is expressed rapidly following exposure to a wide variety of infectious agents and plays a key role in innate control of virus replication. Recent studies have demonstrated that dendritic cells both produce IFN-α/β and undergo maturation in response to IFN-α/β. Moreover, IFN-α/β has been shown to potently enhance immune responses *in vivo* through the stimulation of dendritic cells. These findings indicate that IFN-α/β serves as a signal linking innate and adaptive immunity.

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Abbreviations

APC	antigen-presenting cell
DC	dendritic cell
dsRNA	double-stranded RNA
IFN-α/β	type I interferon
IFN-α/βR	IFN-α/β receptor
NIPC	natural interferon-producing cell
PRR	pattern-recognition receptor
TLR	Toll-like receptor

Introduction

The immune response to infection can be divided into innate and adaptive components that synergise in the clearance of pathogens. The innate response, which includes both constitutive and rapidly inducible mediators, is crucial in limiting the early replication and spread of infectious agents. By contrast, the generation of an adaptive immune response involves considerable lag time but culminates in the production of specialised effector mechanisms that are highly efficient in eliminating the pathogen. In addition to these complementary activities, it is evident that there is a fundamental connection between innate and adaptive immunity. Namely, the magnitude and quality of the adaptive immune response is dependent on signals derived from the innate response to infection [1].

The key cell type involved in translating information from the innate response into a language understood by the cells of the adaptive immune system is the dendritic cell (DC). DCs possess an innate ability to recognise signs of infection and also serve as the main antigen-presenting cells (APCs) for the activation of naïve T cells. Importantly, these two phenomena are tightly linked: resting (immature) DCs are very poor at stimulating T cells but acquire the ability to do so following the receipt of infection-associated stimuli [2]. DCs can sense the presence of infection directly, utilising pattern-recognition receptors (PRRs) such as lectin receptors [3], scavenger receptors [4] and Toll-like receptors (TLRs) [5] to recognise a diverse array of conserved structural features of infectious agents. Additionally, DCs are able to detect indirect indicators of infection, such as the expression of cytokines by infected cells [2]. Amongst infection-induced cytokines, type I interferon (IFN-α/β) is notable in being rapidly and widely expressed and participates in the innate response both as a signal for the presence of infection and as an effector molecule inhibiting the spread of infection. Here, we review recent evidence that IFN-α/β also serves as an important link between the innate and adaptive immune responses.

Triggering of IFN-α/β expression

The term 'IFN-α/β' encompasses a large group of closely related cytokines that exert their activity through a common receptor, the IFN-α/β receptor (IFN-α/βR). These cytokines include IFN-α (multiple subtypes), -β, -δ, -τ, -ω and -κ, and a factor known as limitin [6–8]. In response to viral infection, transcription of IFN-α/β genes is induced rapidly through a mechanism involving the transcription factors IRF-3 and IRF-7 [9•].

Cellular production of IFN-α/β following virus infection is triggered by double-stranded RNA (dsRNA), which is produced by most viruses at some point during their replication cycle [10], and also by certain viral glycoproteins [11–14]. In addition, expression of IFN-α/β is induced by bacterial infection, and by components of bacteria such as lipopolysaccharide (LPS) and bacterial DNA [15]; responses to the latter are triggered by unmethylated CpG motifs common to bacterial but not mammalian DNA. Recognition of these molecules involves a variety of PRRs, including TLR3 (triggered by dsRNA) [16], the mannose receptor (viral glycoproteins) [17], TLR4 (LPS) [18] and TLR9 (CpG DNA) [19]. Interestingly, expression of several TLRs, including TLR3, is upregulated following treatment of cells with IFN-α/β, suggesting that a positive feedback loop involving IFN-α/β can sensitise cells for a stronger innate response to infection [20•].

Natural IFN-α/β-producing cells

Although virtually any cell type can express IFN-α/β following virus infection, it has been evident for many years that some cells are capable of secreting very large amounts of IFN-α/β — up to a thousand times more than typically produced by most cells following exposure to viruses. These 'natural interferon-producing cells' (NIPCs) were identified as rare cells in human blood that exhibit a plasmacytoid morphology and lack haematopoietic-lineage markers [21]. In addition to producing IFN-α/β in response to viruses, NIPCs also do so when treated with

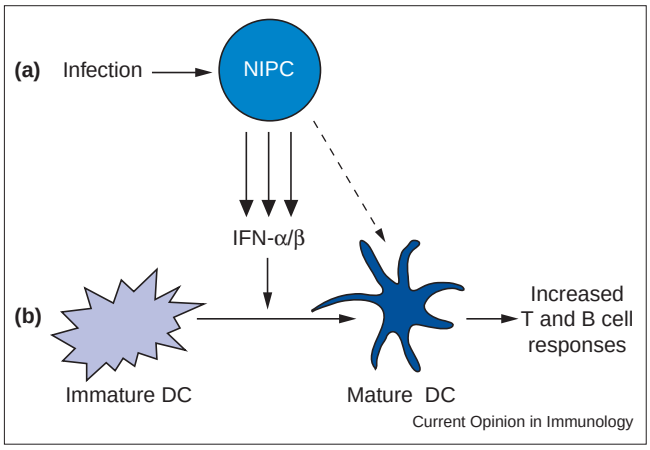
CpG DNA [22]. Hence, these cells appear to play a key role in the innate response to infection; the large amount of IFN-α/β produced by these cells may act systemically to induce an antiviral state and/or prime other cells for IFN-α/β expression [23]. Since the triggering of IFN-α/β-production by NIPCs does not require active infection of these cells (i.e. contact with inactivated viruses or bacterial DNA is sufficient), NIPCs are likely to be very efficient in their role as sentinels, monitoring for the presence of infection.

Interest in these cells from an immunological point of view arose when it was demonstrated that human NIPCs were also capable of differentiating into cells with the characteristics of DCs. Thus, following treatment with various stimuli, including viruses, CpG DNA or IL-3+CD40L, these cells took on the typical morphology of mature DCs, upregulated costimulatory molecules and acquired the ability to stimulate proliferation of allogeneic naïve T cells [24–27]. More recently, an equivalent population of plasmacytoid cells capable of both high IFN-α/β-secretion and differentiation into DCs was identified in the mouse [28••,29••]. In both mice and humans, these cells are found predominantly in the T cell areas of secondary lymphoid organs, implying a role in the immune response.

The exact role of NIPC-derived DCs as APCs is unclear, since the capacity of these cells to internalise, process and present antigens remains to be investigated fully. However, the ability of DCs generated from human NIPCs to stimulate allogeneic T cells appears similar to that of monocyte-derived DCs, implying that these cells may indeed be bona fide APCs. Human NIPCs were initially thought to be pre-DC2 — precursors for type 2 DCs, which would promote the differentiation of responding T cells towards a Th2 phenotype [24,30]. This suggestion was based on the finding that $CD4^+$ T cells produced Th2-type cytokines (IL-4, IL-5 and IL-10) following stimulation by allogeneic NIPCs that had been matured in the presence of IL-3+CD40L. However, it was subsequently shown that the nature of the T cell response was dependent on the DC maturation stimulus. Thus, when maturation of NIPCs is induced by viruses, the resultant DCs promote a more Th1-like response [27,31].

By contrast to human DCs, mouse NIPC-derived DCs appear to be relatively weak APCs when compared with DCs isolated from the spleen for their ability to stimulate T cell proliferation *in vitro* [28••,29••]. However, this could be a reflection of either the poor survival of NIPCs *in vitro* or a failure to induce full maturation of these cells with the stimuli employed. Hence, a true assessment of their APC function awaits examination of the ability of NIPCs to initiate immune responses *in vivo*. If mouse NIPCs do differentiate into APCs *in vivo*, it will be of interest to determine whether the mature stage of these cells corresponds to any of the DC subpopulations that have been previously defined.

Figure 1



IFN-α/β links innate and adaptive immunity. (a) Virus infection results in the secretion of large quantities of IFN-α/β by NIPCs, and probably also results in the maturation of these cells into DCs. IFN-α/β acts both as an innate effector in the control of virus replication and as an activator of DCs. (b) Immature DCs exposed to IFN-α/β become potent APCs capable of initiating T and B cell responses.

The dual role of NIPCs as both high IFN-α/β-secretors and DC precursors is particularly intriguing in view of the fact that the same stimulus — exposure to infectious agents — triggers both responses. The implication is that the innate and adaptive immune responses are activated not only simultaneously, but also through the same initiating cell type. However, it is evident that the link between these two aspects of the response goes considerably further. Thus, in addition to being produced by DCs, IFN-α/β also has functional effects on these cells (see below and Figure 1).

The effect of IFN-α/β on DCs

There is evidence that IFN-α/β affects various subtypes of DCs. For NIPCs, IFN-α/β acts as an autocrine survival factor, although it does not stimulate the differentiation of NIPCs into DCs [27,29••,32]. Conversely, IFN-α/β has been shown to promote the differentiation of human peripheral blood monocytes into DCs [33,34•]. In these studies, culture of monocytes in IFN-α/β+GM-CSF, rather than the typical combination of IL-4+GM-CSF, resulted in the accelerated generation of DCs with enhanced T cell stimulatory capacity. Notably, IFN-α/β+GM-CSF-matured DCs were shown to induce a potent primary antibody response when pulsed with antigen and injected into scid mice reconstituted with autologous peripheral blood lymphocytes [34•].

Furthermore, IFN-α/β-treatment of immature DCs, derived *in vitro* from either human monocytes or mouse bone marrow precursors, induces phenotypic and functional maturation of these cells [35,36]. Thus, IFN-α/β-treated DCs express higher levels of CD83, MHC class I and II, CD40, CD80 and CD86, and have an increased ability to stimulate T cell proliferation. Importantly, IFN-α/β also

has similar effects on DCs generated *in vivo*. This has been demonstrated for $CD11c^+$ immature DCs isolated directly from human blood [32] as well as DCs isolated from mouse spleen; the latter undergo maturation in response to IFN-α/β *in vivo* or *in vitro* [37].

These observations suggest that IFN-α/β production by NIPCs within the T cell zones of secondary lymphoid organs will lead to maturation of DCs in these sites. In addition, secretion of large amounts of IFN-α/β by NIPCs in the blood could lead to sensitisation of DCs in diverse peripheral tissues. In this respect, it is notable that IFN-α/β+GM-CSF-matured DCs upregulate expression of the chemokine receptor CCR7 [38•], which is required for DC entry into lymph nodes [39,40]. This implies that DCs exposed to IFN-α/β in peripheral tissues will acquire the ability to migrate to lymphoid organs, a requisite for the initiation of T cell responses.

It should also be borne in mind that most cell-types are capable of expressing IFN-α/β, albeit at lower levels than NIPCs. Therefore, maturation of DCs in non-lymphoid tissues may also be triggered following infection of neighbouring stromal cells. Furthermore, DCs other than NIPCs can express IFN-α/β [41], and IFN-α/β produced by human monocyte-derived or mouse bone-marrow-derived DCs or by mouse splenic DCs has been shown to exert autocrine stimulatory effects on the respective DC populations [35,37].

The adjuvant activity of IFN-α/β

The finding that IFN-α/β induces maturation of DCs implies that IFN-α/β may have inherent adjuvant activity. Considerable work has been done to address this possibility, dating back to the early 1970s (reviewed in [42]). In these studies, the effect of IFN-α/β on diverse outcomes — including the antibody response to sheep red blood cells, delayed-type hypersensitivity (DTH) reactions and tumour rejection — was examined. Although the results gave an overall indication that IFN-α/β has immunostimulatory activity, a clear consensus that this was the case was not established.

More recently, two studies have provided firm evidence that IFN-α/β does in fact possess adjuvant activity. Firstly, Gallucci *et al.* demonstrated that co-injection of IFN-α/β with a soluble protein antigen improved the priming for a DTH reaction to the protein [36]. This result implied that *in vivo* T cell priming had been enhanced by IFN-α/β. Secondly, we showed IFN-α/β potently enhanced the antibody response against a soluble protein [43••]. Here, IFN-α/β-treatment increased the production of all subclasses of IgG and induced long-term antibody production and immunological memory. In addition, administration of IFN-α/β enhanced the priming of IFN-γ-secreting $CD4^+$ T cells. Strikingly, IFN-α/β was able to augment the antibody response (including induction of isotype switching) when only DCs were able to respond to IFN-α/β, providing direct evidence for a link between IFN-α/β and the initiation of immune responses by DCs.

Given these results, it can be hypothesised that the natural adjuvanticity associated with infectious agents is mediated in part through induction of IFN-α/β. In support of this idea, recent studies have demonstrated that the immunostimulatory activity of several adjuvant compounds is reduced in IFN-α/βR-deficient mice. This was shown to be the case for three such compounds: firstly, for poly IC [43••], a synthetic dsRNA; secondly, for complete Freund's adjuvant [43••], which contains heat-killed *Mycobacterium tuberculosis* as a key active component; and thirdly, for CpG DNA [44•,45•]. Each of these had a diminished ability to enhance either T cell or B cell responses in the knockout mice. Interestingly, T cell secretion of IFN-γ and B cell production of IgG_{2a} antibodies were consistently lower in IFN-α/βR-deficient mice compared with controls, implying that IFN-α/β plays a role in the polarisation of immune responses by these Th1-biasing adjuvants.

Conclusions

IFN-α/β is a rapidly inducible component of the innate response to infection and provides a signal for initiation of the adaptive immune response. IFN-α/β contributes to the immunostimulatory activity of microbial adjuvants and can itself act as an adjuvant. The participation of IFN-α/β in immune responses is allied to its production by a population of DC precursors and its stimulatory effects on DCs. A full understanding of the role of IFN-α/β in linking the innate and adaptive response will be aided by future studies investigating the function of NIPCs as APCs and the mechanisms by which IFN-α/β-exposed DCs direct immune responses.

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