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The role of type I interferons in CD4+ T cell differentiation

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Abstract

Type I interferons (IFNs) released upon viral infections play different and opposing roles in disease outcome. This pleiotropic effect is mainly influenced by the cellular sources, timing and target cells for these molecules. The effect of type I IFN signaling on the activation and differentiation of antiviral $CD4^+$ T cells remains ill defined, with studies reporting either a beneficial or a detrimental role, depending on the context of infection. This review will highlight several recent studies that have investigated the role of type I IFNs in the priming and polarization of $CD4^+$ T cells and discuss areas of uncertainty that require further investigation.

Keywords

Type I interferons; $CD4^+$ T cell; T follicular helper cells; Th1; Viral infection; T cell differentiation

1 Introduction

Type I interferons (IFNs) are innate molecules secreted by different cells upon infection [1]. They comprise several isoforms of IFN-α, one isoform of IFN-β, and the less characterized IFN-ε, IFN-κ, IFN-ω, IFN-δ, and IFN-τ. All type I IFNs act both in autocrine and paracrine fashions by binding to heterodimeric receptors composed of IFNAR1 and IFNAR2 subunits [2]. The name “interferon” was coined in concomitance with their discovery, and it was inspired by what is historically considered to be the main role for these molecules, i.e. interfering with pathogen replication [3,4]. Indeed, release of type I IFNs is one of the most potent mechanisms of innate immunity against viruses and other intracellular pathogens. However, growing evidence is pointing to a multifaceted role for type I IFNs, with either beneficial or detrimental effects in the fight against infection. This pleiotropic role is mainly due to the different cellular sources, timing and target cells for type I IFNs [5]. For instance, we and others have recently described how type I IFNs released upon lymphocytic choriomeningitis virus (LCMV) infection can have a negative impact on antiviral humoral responses by inducing apoptosis of virus-specific B cells activated early on [6–9]. The conflicting roles of type I IFNs in infection and cancer have been extensively reviewed

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elsewhere [5,10–12]. Here, we will discuss recent studies that investigated the role of type I IFNs in $CD4^+$ T cell activation and polarization.

2 $CD4^+$ T cell differentiation upon viral infections

$CD4^+$ T cells are key players of adaptive immunity. Naïve $CD4^+$ T cells are primed in secondary lymphoid organs (SLOs) upon binding of MHCII-peptide complexes and costimulatory molecules. Both these signals are provided by professional antigen-presenting cells (APC), mostly dendritic cells (DC), which have encountered and processed antigens either in the periphery or in SLOs [13–15]. Following the priming phase, antigen-specific naïve $CD4^+$ T cells undergo clonal expansion and effector differentiation. During these processes, $CD4^+$ T cells are exposed to a milieu enriched in cytokines produced by many cells including infected cells, DCs, and stromal cells. $CD4^+$ T cells sense these cytokines and activate differentiation programs that result in their polarization towards specialized T helper cell subsets [16,17]. Infection by viruses or intracellular bacteria mainly leads to the generation of Th1 and T follicular helper (Tfh) cells. Th1 cells express the master transcription factor T-bet and produce high levels of IFN-γ, which promotes macrophage activation and enhances $CD8^+$ T cell responses [18,19]. By contrast, Tfh cells migrate to B cell follicles where they specifically interact with cognate antigen-specific B cells and participate in germinal center (GC) reactions to ensure the generation of high-affinity, class-switched antibodies [20,21]. Both CD8-mediated cellular and B cell-mediated humoral responses are essential for proper infection control, and usually co-exist in a fine-tuned equilibrium in order to optimize anti-pathogen immunity [22–24]. The molecular and cellular determinants of $CD4^+$ T cell differentiation into Th1 or Tfh cells in vivo, and hence the relative balance between cellular and humoral immunity, are incompletely understood [25–27]. Research in the field is complicated by the plasticity of T helper cell subsets [27] and the pleiotropic nature of many cytokines. Nonetheless, type IFNs are emerging as critical factors regulating antiviral $CD4^+$ T cell fate.

3 Role of type I IFNs in antiviral $CD4^+$ T cell priming during acute infections

Several reports have shown an anti-proliferative effect of type I IFNs on $CD4^+$ T cells activated in vitro either upon anti-CD3 antibody treatment [28,29] or upon cognate antigen stimulation [29]. However, the in vivo setting is a lot more complex, since the final outcome is the net effect of type I IFNs being released by different cell types, with different kinetics and acting on different targets. For instance, it was shown that type I IFN signaling in $CD4^+$ T cells is important for clonal expansion upon acute LCMV infection [29]. When LCMV-specific $CD4^+$ T cells lacking the ability to sense type I IFN were transferred into LCMV-infected mice, $CD4^+$ T cells underwent the initial activation steps (upregulation of the activation markers CD25 and CD69 and early proliferation) but accumulated at a much lower level than their WT counterparts at the peak of the immune response. Interestingly, this was observed upon LCMV but not upon *Listeria Monocytogene*s (LM) infection [29]; whether this is due to differences in type I IFN production upon the two infections remains to be determined. Another study went further to show that LCMV-specific $CD4^+$ T cells

lacking type I IFN receptor could accumulate at levels comparable to their WT counter-parts if NK cells were depleted during LCMV infection, suggesting that type I IFN signaling can protect antiviral $CD4^+$ T cells from NK cell-mediated killing, similarly to what has been reported for $CD8^+$ T cells [30,31]. The mechanisms behind this observation seem to involve a type I IFN-mediated upregulation of selected inhibitory NK cell receptor ligands and/or downregulation of natural cytotoxicity triggering receptor 1 (NCR1) ligands on $CD4^+$ (and $CD8^+$) T cells [30,31]. Overall, the abovementioned studies strongly suggest that $CD4^+$ T cell-intrinsic type I IFN signaling is required for survival of primed antiviral $CD4^+$ T cells, especially in the context of acute LCMV infection (Fig. 1). Interestingly, however, when type I IFN signaling was inhibited on all cell types by virtue of an IFNAR-blocking antibody, LCMV-specific $CD4^+$ T cell frequencies during acute LCMV infection were not affected [32]. This unexpected result could be explained either by an incomplete IFNAR blocking by the antibody, or by the pleiotropic and sometimes opposite effects that type I IFNs play on different cellular targets during infection. For example, type I IFNs promote activation and effector function of NK cells upon viral infection [33,34], support DC maturation [35,36] and inhibit T regulatory cell-mediated suppression of antigen-specific $CD4^+$ T cells [37,38] (Fig. 1).

4 Role of type I IFNs in the antiviral $CD4^+$ T cell response during chronic infections

The above-mentioned studies pretty much converge on the idea that type I IFN signaling (whether $CD4^+$ T cell-intrinsic or -extrinsic) supports rather than interferes with antiviral $CD4^+$ T cell accumulation during acute infection. The picture is quite different, however, if we look at chronic viral infections, where viral persistence induces prolonged expression of type I IFNs [39–41]. Two studies showed that blockade of type I IFN signaling during chronic LCMV infection led to a stronger $CD4^+$ T cell response that was responsible for faster viral clearance [32,42]. Sustained type I IFN production during chronic LCMV infection induced expression of PD-L1 and IL-10 by immunoregulatory DCs, thereby contributing to an immunosuppressive environment (Fig. 1). Since in the abovementioned studies type I IFN signaling was blocked ubiquitously, however, it is impossible to definitively ascertain the target cell(s) responsible for the observed net effect. Besides DCs, there are likely additional cellular targets for type I IFN during chronic LCMV infection, potentially with opposing effects. For instance, selective deletion of type I IFN receptors in Tregs during chronic LCMV infection led to higher viral titers and increased frequency of PD-1-expressing exhausted T cells – although the effect on $CD4^+$ T cells was less pronounced than that on $CD8^+$ T cells [38]. It should be noted that in this latter setting, DCs could still sense type I IFNs, acquire a suppressive phenotype, and promote exhaustion of antiviral $CD4^+$ T cells.

5 Role of type I IFNs in $CD4^+$ T cell polarization

Since viral infections result in polarization of naïve CD4 T cells into both Th1 and Tfh subsets (although to variable degrees depending on the nature of the pathogen), a lot of effort has been devolved to the question of whether type I IFNs play a role in $CD4^+$ T cell

polarization. In vitro studies of naïve $CD4^+$ T cell polarization have shown that type I IFNs are certainly needed for the expression of the Tfh master transcription factor Bcl-6, and to a lower extent for the induction of the Th1 transcription factor T-bet [43]. Interestingly, culture of $CD4^+$ T cells with type I IFNs resulted in the expression of Tfh surface markers CXCR5 and PD-1, but not in IL-21 production. IL-21 is a cytokine produced by fully differentiated Tfh, so what can be inferred from these data is that type I IFNs initiate early Tfh differentiation but other cytokines (e.g. IL-6) are needed to complete the Tfh polarization program. Type I IFNs seem to be required for Tfh differentiation upon immunization in vivo as well; however the target cell(s) responsible for this effect seems to vary according to the experimental setting, ranging from $CD4^+$ T cell themselves to DCs and monocytes [44–46]. The differences in these settings might be explained by the complex cytokine milieu found *in viv*o, where synergies of type I IFNs with other cytokines such as IL-6 [43,45] and IL-1 [46] might have profoundly different effects on $CD4^+$ T cell polarization (Fig. 2). The notion that type I IFNs drive Tfh differentiation in vivo is not universally accepted, with some studies reporting increased Tfh cell number upon IFNAR blockade during acute LCMV infection [47]. This was also shown in a more stringent setting where Tfh were poised to express Th1-related genes due to impaired STAT3-derived signals. STAT3-deficient $CD4^+$ T cells showed higher sensitivity to type I IFNs, and treatment with IFNAR-blocking antibodies reverted the phenotype from Th1 to Tfh [47]. Interestingly, in a setting of LM infection, type I IFN signaling in $CD4^+$ T cells was shown to promote Th1 differentiation, by synergizing with IL-12-derived signals [48]. These data potentially suggest that IFNAR signaling might suppress Tfh and favor Th1 differentiation upon certain infections (Fig. 2). It is worth mentioning, however, that type I IFN signaling during LCMV infection leads to LCMV-specific B cell apoptosis [6–9]. Thus, the detrimental effect of type I IFN on Tfh development upon LCMV infection might be due to an ineffective B cell response, which is required to reach full Tfh differentiation (Fig. 2). Moreover, it was shown that type I IFN signaling results in modest but significant suppression of Tfh cells generated upon infection with a LCMV chronic strain [49]. Whereas blocking type I IFN signaling at the onset of acute or chronic LCMV infection led to increased Tfh cells [47,49], a strikingly opposite result was obtained with $CD4^+$ T cells primed during an established persistent infection [49]. Indeed, transfer of LCMV-specific $CD4^+$ T cells into mice previously infected with a chronic LCMV strain led to suppressed Th1 and heightened Tfh differentiation, and this phenotype was readily reverted when IFNAR was blocked [49]. This effect was not due to signaling of type I IFNs in $CD4^+$ T cells but to the effect of type I IFNs on other yet to be identified cells.

The role of type I IFNs on $CD4^+$ T cell responses has been investigated also in the context of malaria infection, with data suggesting that type I IFN signaling in DCs dampens $CD4^+$ T cell activation and differentiation to both Th1 and Tfh cell subsets [50–53].

Together, the available data indicate that the mechanisms underlying the different sensitivity to type I IFNs according to the type and stage of infection remain incompletely understood.

6 Concluding remarks and discussion

The studies discussed in this review show that type I IFN signaling can have disparate effects on $CD4^+$ T cell activation, depending on the cells sensing these cytokines, the nature of the pathogen and the stage of the infection. One interpretation might be that the role of type I IFNs changes based on whether the infection is acute or chronic [10], with interferons supporting $CD4^+$ T cell expansion in the acute phase, but inducing their exhaustion during the chronic phase [29,32,42]. Interestingly, one study showed that type I IFNs played distinct roles in polarization of $CD4^+$ T cells depending on whether these cells were primed at the onset or during an ongoing chronic LCMV infection [49]. Indeed, type I IFN signaling promoted Th1 differentiation early on, but inhibited *de novo* Th1 and favored instead Tfh differentiation during an ongoing infection [49]. This suggests that even within the context of the same infection, IFNAR signaling might lead to opposed effects on $CD4^+$ T cell polarization, depending on the timing of action. Moreover, the role of type I IFNs on $CD4^+$ T cell polarization seem to vary even during acute infections or immunizations [44–46]. Therefore, more than distinguishing between acute and chronic infections, one should perhaps focus on the kinetics, magnitude and targets of type I IFNs in the different immunization/infection settings. For instance, during acute malaria infection IFNAR engagement suppresses $CD4^+$ T cell responses, whereas during acute LCMV infection it supports them [29,54]. One attractive hypothesis might be that the action of type I IFNs is tightly regulated in time and space, and the cytokine milieu generated upon different infections (or at different times during the same infection) adds up to this tight regulation to confer specificity to the IFN-mediated signaling. The molecular and cellular mechanisms regulating the spatiotemporal functions of type I IFNs on $CD4^+$ T cell differentiation remain to be fully elucidated, and might be influenced by, among others, pathogen replication kinetics, tropism, cytokine milieu or cellular target(s) [5,45,47,51]. Combination of conditional knock-out models with timed delivery of blocking antibodies might shed additional light on the complex relationship between type I IFNs and $CD4^+$ T helper cell priming and differentiation.

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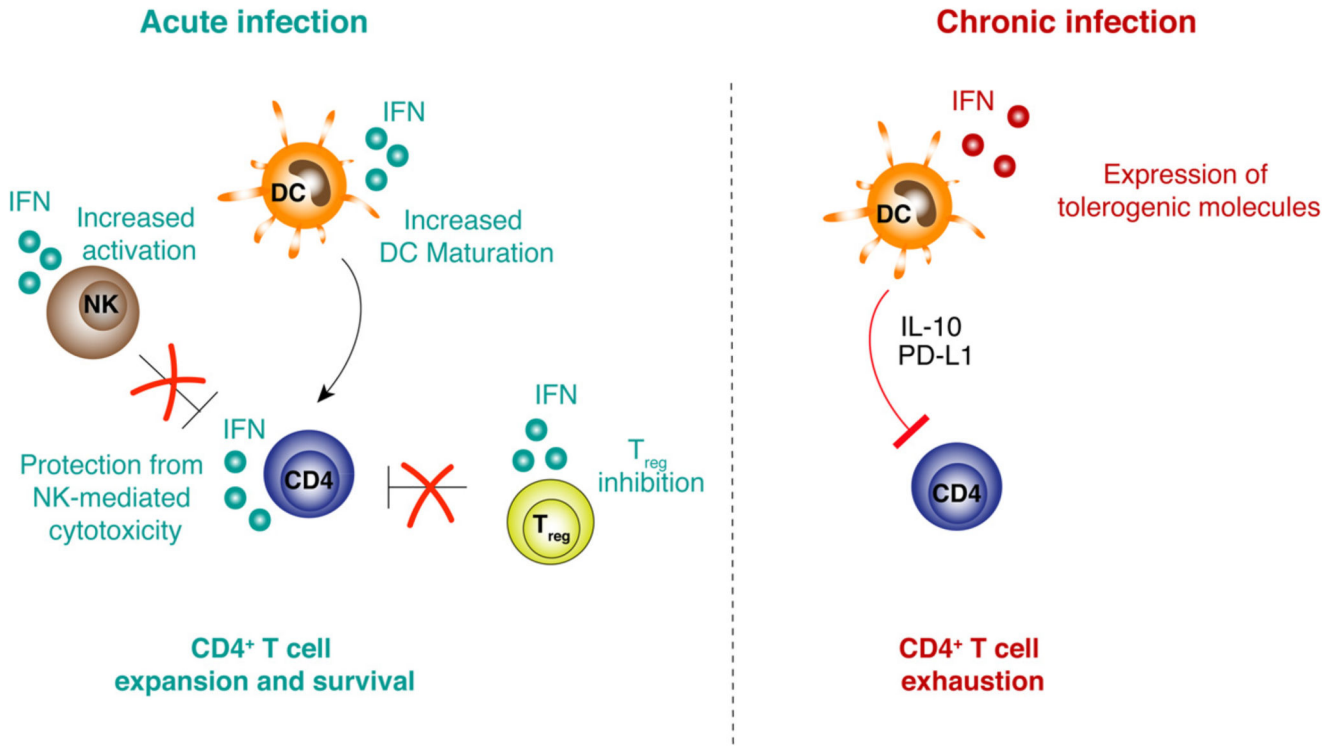

Fig. 1. Role of type I IFNs in antiviral CD4$^+$ T cell expansion.

Left panel. Type I IFNs released upon acute infections act on different cell types to support antigen-specific CD4$^+$ T cell activation. Type I IFNs sensed by DCs increase their maturation, thus providing a more efficient antigen presentation and co-stimulation to T cells. Type I IFNs act on T regulatory cells by dampening their suppressive capabilities and allowing heightened CD4$^+$ T activation. Type I IFNs enhance NK cell activation and effector functions. Finally, type I IFNs sensed by CD4$^+$ T cells protect them from NK cell-mediated killing.

Right panel. Type I IFNs released upon chronic infections create an immunosuppressive environment by increasing PD-L1 and IL-10 expression by DCs. These immunoregulatory DCs induce CD4$^+$ T exhaustion.

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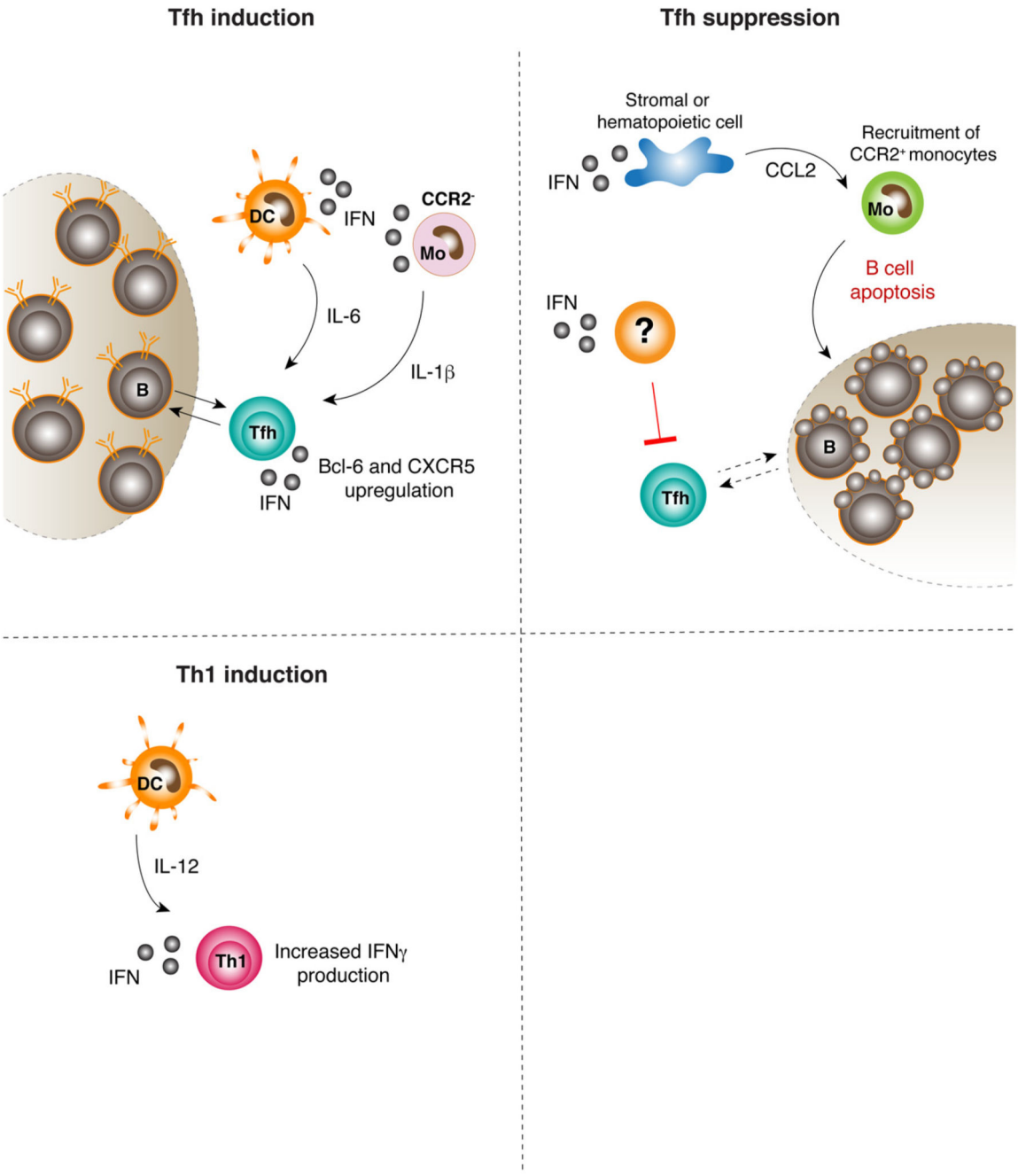

Fig. 2. Role of type I IFNs in CD4$^+$ T cell polarization.

Upper left panel. In some settings, type I IFNs can promote CD4$^+$ T cell differentiation into the Tfh subset by acting at different levels. Type I IFN signaling in DCs results in production of IL-6, a Tfh-polarizing cytokine. Type I IFNs induce CCR2$^-$ monocytes to produce IL-1β, which also results in Tfh polarization. Finally, type I IFNs sensed by CD4$^+$ T cells play a supportive role in full Tfh differentiation.

Upper right panel. Type I IFNs can also suppress CD4$^+$ T cell differentiation into the Tfh subset, in some settings. For example, upon both acute and chronic LCMV infection, type I

IFNs acting on cell types other than $CD4^+$ T cells suppress Tfh differentiation at the onset of the infection. Moreover, type I IFNs released upon LCMV infection result in the production of CCL2 by stromal and hematopoietic cells. CCL2 triggers recruitment of $CCR2^+$ monocytes, which induce LCMV-specific B cell apoptosis, thus potentially impairing full Tfh differentiation.

Lower left panel. Upon *Listeria monocytogenes* infection, type I IFN signaling in $CD4^+$ T cells can synergize with DC-derived IL-12 to increase IFN-γ production and Th1 differentiation.

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