Chapter

Immunogenetic and Immunotherapy in Tuberculosis

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Abstract

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTb). TB causes mortality of millions of people every year. *Mycobacterium bovis Bacillus Calmette Güerin* (BCG) is the only officially approved vaccine that protects against miliary TB and children but fails to protect in adulthood presumably because of the lack of long lasting immunological memory. The problem is even more aggravated because of the emergence of multidrug-resistant strains. Therefore, immunogenetics and immunotherapy of antimycobacterial immunity are complex and poorly characterized. However, several studies either in the mouse model or *in vitro*, using derived dendritic or macrophages derived from PBMCs or human cell lines, have shown that Th1 type cellular immune response represented by IFN-γ, IL-12 in conjunction with IL-17, and IL-23 are key players of the immune protection to M. *tuberculosis*. It is known that under different settings type I IFNs promote bacterial virulence and disease exacerbation, since a study with active TB patients was concomitant with a dominant neutrophil-driven interferon inducible gene pattern. Furthermore, in an independent cohort of TB patients, ex vivo experiments with BMDCs (bone marrow–derived dendritic cells) and myeloid from lung showed that there is a cross action between the components of IL-1β, eicosanoid pathways (prostaglandin, lipoxins, and leukotrienes) in active TB, while excessive type I IFNs and IL10 induction, concomitant with an inhibition of iNO3 and prostaglandin, could be found. These responses could be used as a therapeutic target instead of any other treatment based on antibiotics. Furthermore, the work from us has demonstrated that interferon alpha plus BCG vaccine protects against mycobacterial infections through modulating the Th1-type cellular immune response, iNOs, and IL-1β production. These immunomodulatory properties of interferon alpha could influence the outcome of the innate and acquired host immune responses in tuberculosis.

Keywords: type I IFNs, adjuvants, *mycobacterial* infections, BCG vaccine, Th1-type cytokines, IL17, iNOS3

1. Introduction

Tuberculosis is the most serious cause of mortality after HIV/AIDS [1, 2]. Until now, BCG is the only officially approved vaccine that protects against miliary TB in children but it fails to protect in adulthood [1–3]. Therefore, the search for subunits agents that can boost primarily the central memory is still an issue of intense research worldwide [1, 2]. Several candidates have been developed and are under clinical studies [4–8]. Type I IFNs emerge, thus, as a

potential candidate adjuvant in bacterial infections. More than half century ago, interferons were first described like an antiviral "activity" [9–12]. Later on, they were recognized as innate inflammatory cytokines, and considered to be major connector of the innate and adaptive immunity. In general, type I IFNs could be considered like pleiotropic cytokines that belong to a multigenic family as outlined in **Table 1** [11, 12].

Plasmacytoid dendritic cells (pDCs) are known to be major producers of type I IFNs producing up to hundred to a thousand times more IFNs-α than other cell types [13, 14]. To be produced, a recognition between pathogen-associated molecular patterns (PAMPs) on the pathogen surface (viral and bacterial), Toll-like receptors (TLRs) (bacterial), with the pattern recognition receptor (PRRs), antigen-presenting cells (dendritic cells and macrophages) is necessary; followed by the activation of Myd88, interferon regulatory factor 3 (IRF3), IRF5 and IRF7 (IFN-α), and NFκβ [13, 15]. Except leucocytes (which produce primarily IFN sub-types), all cells are capable of detecting intracellular PAMPs and producing IFN-β following activation of IRF3 and NF-κβ [14, 16]. After viral or bacterial infections, there is an increase in the IFNs production in different types of cells. The functions *in vivo* of type I IFNs are the activation of DCs (dendritic cells), critical antigen-presenting cell for initiating immunity [13], in fact, type I IFN-treated DCs prime T cells *in vitro* promote the expression of costimulatory molecules [15], stimulate human blood monocytes differentiation into DCs [15]. Regardless of its role as an antiviral agent [11, 12], type I IFNs are also able to enhance adaptive immunity. A huge body of studies have shown type I IFNs immunomodulatory properties either to virus as well as to bacteria infections [12–15]. We think in agreement with other groups that type I IFNs have a strikingly dichotomy behavior, since their actions can be either positive or negative depending on the settings and the surrounding scenery that will strongly influence the outcome of the host immune response.

IFNs I 17 sub-types	IFNs II	IFNs III 4 sub-types
All nucleated cells	Immune cells	Epithelial cells
α /β		
α: 12 genes Ifn-β (PBMCs)		(IFN-λs)
Ifn-ε (genital tract) Ifn-κ(keratinocytes	IFN-Y	IFN-λsI IFN-λsII
Ifn-ω Ifn-ζ (mice and		IFN-λsIII
rrophoblastic) Ifn-τ (ungulates)		IFN-λsIV
Ifn-δ (pigs)		

Table 1.
The multigenic family of type I IFNs in nature.

2. The type I IFNs in nature

As outlined in **Table 1**, several human type I IFNs are already known to be selectively produced in a tissue-specific. As a multigenic family, type I IFNs, in particular, IFN-alpha, are comprised of 13, while IFN-β, IFN-ε (genital tract), IFN-κ (keratinocytes), and IFN-ω are only coded for a single gene. For the signalization to be carried out, there are basically two main steps that are common to the 17 IFNs. First is the binding to and signal through a shared heterodimeric receptor complex composed of a single chain of IFNAR1 and IFNAR2, which is present in almost on all nucleated cells [13–15]. Second, a signal is propagated within the cell via the JAK-STAT signaling pathway [13–15]. This is also common to type III IFNs. As occurred in other interaction receptor-ligand, there are low or high affinity binding, and this could impact in the stability and the variety of the complex formed and therefore in the outcome of the host response [13–15]. This point has been the focus of intense research, because many questions arise for this interaction. Thus, for example, it is intriguing: why some interferons signal through the same receptor? Is there a redundancy of the immune system or is tailoring for each type of pathogen? Is the molecular evolution that has an impact also in the transcriptional gene printing, or in the adjuvant activities?

One of the hallmarks of the IFN action in nature is its immunomodulatory behavior [7, 10, 17]. These include among others the role of type I IFNs in the connection of innate and adaptive immune responses, such as B activation for enhancement of Ab responses [7, 10, 18], promotion of Th1 responses in terms of IgG2a Ab production, and CD4 + T cells activation and induction of an *in vitro* and *in vivo* differentiation of monocytes into functionally active DC [8, 19, 20], NK and T cytolytic activity, upregulation of histocompatibility antigen class I expression, induction of proliferation, and long-term survival of memory CD8 + T cells [7, 19, 20].

3. Is there any specificity in the type I IFN induction?

At glance yes, it would seem that there is specificity in the type I IFNs induction. As highlighted above, type I IFNs induction is a consequence of the host-pathogen interaction [10, 16]. Thus, while membrane-bound PRRs are endowed with the ability to recognize viral or bacterial PAMPS (located in the cell surface, and within endosomal compartments [20]), it could be possible that the expression profile of each cell type in particular of these PRRS on the innate immune cells that could potentially give rise to specificity in IFN subtype production—an early step during infection inward ultimately fine-tuning the immune response—an issue that is challenging because to measure the different profiles of IFN-α for each cell type has enormous limitations under physiological conditions, but it is true that should be pinpointed whether the IFN responses are qualitatively different in response to distinct pathogens [9, 20]. Furthermore, IFN-β and/or the IFN-α subtypes signal through TLRs (TLRs are membrane-bound compartments) of cosmopolitan expression in different human cells, which can potentially give some specificity to the interaction. Thus, it is known from the literature that TLR3, TLR7, TLR8, and TLR9 recognize viral nucleic acids [9, 10, 16]. Another type of receptor, specialized in detecting pathogen-derived RNA in the cytoplasm, that is also involved in the production of IFN-β in nonimmune cells, is the members of the RIG-I-like receptors (RLRs), a family of cytoplasmic RNA helicases important for host viral responses and includes retinoic acid-inducible

gene I (RIG-I)-melanoma differentiation-associated protein 5 (MDA5) and the laboratory of genetics and physiology-2-(LGP3). The signalization through these receptors initiates via these intracellular PRRS set in motion a series of events that has resulted in IRF3 and NF-κβ activation, both of which are required for the production of IFN-β and the release of chemokines that recruit immune cells to the site of infection [7, 9, 16].

4. How type I IFNs become central players in the connection between innate and acquired immune response

Type I IFNs are the dominant player of the connection between the innate and adaptive immune responses through the main interaction with antigen-presenting immune cells, such as dendritic cells (DCs), in particular, with plasmacytoid dendritic cells (pDCs) [6, 18, 21], which are precisely the major producers of type I IFNs producing up to a hundred to a thousand times more IFNs-α than other cell types [13, 14]. This is supported from *in vitro* experiments that have shown that type I IFN-treated DCs prime T cells *in vitro* more effectively [11, 12, 15].

5. How to calibrate host immune response to bacterial infections?

Calibrating host immune system for bacterial infections initiated as outlined above through the surface membrane conserved molecules organized in "patterns" such as peptidoglycan (PGN), lipopolysaccharide (LPS), and nucleic acid structures or pathogen-associated molecular patterns (PAMPs). Whereas, innate cells have the counterpart, "PRRS" (pattern recognition pathogen) [8, 10, 16], that automatically unlock the unspecificity of the type I IFNs production, the recognition of the "self" versus "nonself" [9], one PRRS for a particular type of PAMPs either bacterial, fungal, or virus; followed by a more general signalization route through Myd88 and IRFs (this could be also specific for each type of IFNs), and finally, NF-κβ translocation to the nucleus and thus IFNs production [8–10]. The synthesis of type I IFNs is not the job of a specialized cell type. However, an important distinction must be made between those cells that produce just enough type I IFNs to affect the local environment, and those produced by IFN-producing cells (IPCs) which could contribute to connect innate and adaptive immune responses more effectively. How much is produced or how much should be produced depends mostly on the tissue involved and the signal received, in particular, viral, bacterial [6, 18, 21]. Therefore, it is intriguing that all IFN-α proteins interact with the same receptor complex and have a spectrum of distinct effects, that goes from the specific antiviral capacity of individual IFN-α to differences in the activation of natural killer (NK) cells [16, 17]. Trying to understand why some types of IFNs, one temptative explanation could be, different temporal or spatial regulation of their expression, which might impact in the molecular calibration of the host immune response to viral or bacterial infections since TLR signaling targets (such as NF-κβ) and IFNAR signaling targets (such as STAT) converge at their promoters [10, 16]. Thus, it seems possible to think that it is the TLR4 signaling that arises as a key player for type I IFNs production by different cell types in response to Gram-negative pathogens. Several studies have in addition highlighted this point, some has been concentrated in the LPS effect [8, 16] on the type I IFNS induction, while others have focused in the gene that encode inducible oxide nitric synthase (iNOS), which is more evident once a bacterial signal through TLR, as demonstrated with Chlamydia spp. [8, 16]. Despite this gap in our

knowledge, the gene encoding iNOs is a paradigm for antimicrobial genes requiring type I IFN synthesis and expression downstream of TLR, implying a potential important role of type I IFN synthesis during nonviral infection. More recent infection studies that have investigated the mechanism behind this type I IFN effect demonstrated its importance in generating TNF-α, Il-1β, or bacterial signals (Chlamydia spp). IL-12-independent cellular immunity to *S. typhimurium*. This was attributed to the ability of type I IFNs to stimulate STAT-4 tyrosine phosphorylation in NK cells and Th1 cells. Together with IL-18 signals, this triggers expression of the IFN-alpha gene [8, 16]. In addition, it has been described that the induction of intrinsic immunity to kill bacteria or prevent their invasion and the regulation of chemokines, proinflammatory cytokines, and phagocytic cells. The mechanism by which IFN-α/β promotes host protective responses or susceptibility in bacterial pathogens is poorly defined and the factors that determine whether a response will be protective or pathogenic are not yet fully understood. However, it is well known that type I IFNs that are released during bacterial infection by IFN-producing cells (IPDCs) can cause the activation of signal transducer and activator of transcription 4 (STAT 4) in natural killer (NK) and T helper (TH1 cells) [5, 8, 10, 16]. In conjunction with interleukin 18 (IL-18)-derived signals, STAT-4 stimulates the expression of the IFN-alpha genes, which provide antibacterial immunity, such as macrophage activation [22, 23]. In addition, type I IFNs make important contributions to the maturation and activation of dendritic ells (DCs) [24], and in this way, influence antigen presentation, T cell activation, and the development of adaptive immune responses.

6. Dichotomy in the type I IFNs' action in bacterial infections

In contrast to viral infections, IFN-α/β can be protective or can have detrimental effects for the host during bacterial infections in a bacterium-specific manner, although less is known about the role of these. By one side, IFN-α/β-mediated signaling primes the production of interleukin-10 (IL-10), proinflammatory cytokines, and antimicrobial effector mechanism. But, IL-10 mediates a negative feedback loop, suppressing the production of proinflammatory cytokine, including IL-12, tumor necrosis factor (TNF), and IL-1 α/β cytokines that are key in the host resistance to bacterial infections. Moreover, some studies have addressed to decreased bacterial load and/or improved host survival in the absence of IFN-α/β-mediated signaling. Thus, for example, IFN-α/β contributes to priming the host to clear the virus, while increasing host susceptibility to bacterial assault. Interestingly, under this scenario, IFN-α/β produced in response to infections is damaging to the host but would normally be protecting during a primary infection, i.e., *S. pneumoniae* or *E. coli* [8, 10, 16]. This would imply that the circumstances of IFN-α/β production and action are crucial to determine host protection versus pathogenesis and highlight also the dichotomy role of IFN-α/β depending on the pathogen. These different issues have been pinpointed and clearly showed that, for example, on mycobacterial infections, there is a detrimental effect of type I IFNs in active TB patient, which showed in blood a remarkable transcriptional gene expression profile in neutrophils that correlated with extensive lesion in lung [25]. In a different cohort of patients from Africa, it was also found that this same result, the broad signature of IFN-α/β, could be found anywhere [25]. These findings have revealed the dark side of these cytokines that is—the ability to suppress host immune protective response by downregulating the Th1-type cellular immune responses (IFN-gamma IL12 production), iNOS3 synthesis while inducing IL-10. In

summary, favorable or unfavorable effect can be determined by the infecting strain, the severity of infection, the stage of infection, and the interplay among the different immune effector mechanisms.

7. Signalization pathways of type I IFNs as an adjuvant

Adjuvants can stimulate innate immunity by interacting with specialized pattern recognition receptors (PRRs) including Toll-like receptors (TLRs) [26, 27] and nucleotide-binding oligomerization domain receptors [28]. These PRRs are immersed in the membrane surface of the antigen presenting such as DCs or macrophages, even in epithelial and B cells. Once this interaction is initiated, it is followed by serial reactions that lead to the production of proinflammatory cytokines and chemokines that will influence drastically the outcome of the host immune response. The shape of this response will be affected by initial stimulus, and therefore, the antigen-presenting cells (M1, M2) as well as the T cell population will adopt a state of differentiation (Th1/Th2/Th3) [29]. However, many cell types, including nonhematopoietic cells, express PRR and produce cytokines during innate immunity [30]. In conjunction, adjuvant action could be viewed as the contribution of cytokines milieu and the different cellular sources of them in order to initiate and potentiate immunity from the native polyclonal repertoire cells and molecules.

The role of IFN-I as natural immune adjuvants for commercial vaccines [18, 21, 31] was established by showing that either mucosal or intramuscular administration of influenza virus antigen-admixed IFN-I to mice enhances viral resistance and increased production of antiviral Ab [18, 21]. The adjuvant activity of IFN-I leads to potentiate the adaptive immune response by directly stimulating lymphocytes or activating DC that represents the critical antigen-presenting cells governing the fate of helper T cell responses [18, 21, 24, 25]. The immunity-promoting activity of IFN-I can result from a direct effect on T cells. In this situation, IFN-I acts as "third signal" of activation, helping to sustain survival of proliferating cells. IFN-I also supports Th1 differentiation, activation of STAT-4 signaling, and IFN-γ production [24, 25]. These activities are reminiscent of the biological effects of IL-12 and could have a role in the observed adjuvant type I IFN activities. Indeed, the variable need for IFN-I to act directly on T cells during activation and differentiation may thus arise from a similarly variable production of IL-12.

8. How type I IFNs shape the host immune system to antimycobacterial infection?

Despite the wealth of studies, shaping the host immune response to bacterial infection is complex and still remains to be characterized. Type I IFNs can shape the antimycobacterial immunity by enhancing action of dendritic cells and monocytes, by promoting CD4+ and Cd8 T cell responses, by enhancing NK cell responses and B cell responses [8, 10, 16, 18, 21]. Type I IFNs (IFN-α/β) have a direct effect on the maturation of DCs, through increasing cell surface expression of MHC molecules as well as costimulatory molecules such as CD80 and CD86, leading to an augmented activation of T cells. Another effect of type I IFNs (IFN-α/β) is to promote the migration of DCs to lymph nodes through upregulating chemokine receptor expression thus promoting T cell activation. Moreover, direct downregulation of IFN-γR expression may not be the central mechanism by which IFN-αβ exerts their effects on IFN-γ activity [7–10, 18, 21–23], instead, in both mouse and human cells,

it has been shown that IFN-αβ potently suppresses the ability of macrophages to upregulate antimycobacterial effector molecules and to restrict bacterial growth, in response to both *M. leprae* and *M tuberculosis.* The importance of this mechanism of action of IFN-αβ is further suggested by experiment using Ifngr 1-/- or Ifnar1-/- mice, which suggests that IFN-αβ contributes to host protection in the absence of the IFN-γ pathway [16, 17, 22, 23]. In another study, it was observed a natural mutation in the gene ISG15 in humans that conferred host-protective response mediated by type I IFNs (IFN-αβ) *to M. tuberculosis* infection [23]. No further studies were made. Similarly, it has been reported that IL-12p70 suppressed type I IFNs (IFN-αβ) during *M. tuberculosis* infection [27, 28, 32]. This suppression could result from the presence of IL-10, the downregulation of IFN-γR, and/or the induction of negative regulators of IFN-mediated signaling such as protein arginine methyltransferase-1(PRMT1) [9, 10, 21, 22]. Finally, IFN-αβ, possibly by influencing chemokine expression, has been shown to be involved in the generation and trafficking of *M. tuberculosis* permissive innate cells to the lungs in a mouse model thus contributing to the exacerbation of infection [8, 9, 26, 31, 32].

Several human clinical studies have obtained favorable assessment of using aerosolized IFN-α as adjuvant therapy for patients with tuberculosis [33]. However, it has been shown that there is a TB reactivation during IFN-alpha treatment for hepatitis D infection [33]. In a different study, it has been also demonstrated that in active TB patients, there is a correlation between the extent of lung lesion with the transcriptional signature of type I IFNs in blood, in particular, in neutrophils [25]. This was also found in a cohort of Africa and Indonesia. These findings implied that the type I IFNs are common broad signature and strengthened the role of these cytokines in the pathogenesis of TB [8, 9, 25, 26, 34]. Indeed, seminal work by Giacomini et al., [24] have demonstrated that IFN-β improves *M. bovis* BCG vaccine immunogenic capacity by exerting a strong influence of DCs maturation, throughout enhancing costimulatory molecules such as CD86, CD83, and therefore, increased IL-12 which will act on macrophage killing activities [18, 20, 29, 30]. Later on, further studies by Mayer-Babier et al. [34] have demonstrated that the action of type I IFNs in tuberculosis could reside in the pathways of IL-1β, arachidonic acids, prostaglandins, and iNOs. Active TB patients showed an increased production of these molecules. This constitutes the first cue for a clinical therapeutic target of TB [34]. In more recent work by us, we found that type I IFNs action, in particular, interferon alpha, could exert its action in conjunction with *M. bovis* BCG vaccine that potentially could be signaling through Toll-like receptor and/or tentative through IFN-R1, leading to a protective antimycobacterial immune response, i.e., Th1-type cytokines and so far to IL-17 and IL23 production [35–37].

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