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Distinct functions of IRF-3 and IRF-7 in IFN-alpha gene regulation and control of anti-tumor activity in primary macrophages

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ABSTRACT

Type I IFN (IFN-α/β) have important biological functions ranging from immune cell development and activation, to tumor cell killing and most importantly inhibition of virus replication. Following viral infection or activation of Toll-like receptors (TLRs) via distinct ligands, IFN-α/β are produced. Two members of the interferon regulatory factor (IRF) family – IRF-3 and IRF-7 – are the major modulators of IFN gene expression. Activation of IRF-3 and IRF-7 by TBK1/IKKε mediated phosphorylation promotes IFN gene expression and potentiates the production of IFN responsive genes important to the development of an effective antiviral immune response. IFN treatment can augment anti-tumor properties and they are potentially key players in cancer therapy. For example, adoptive transfer of IFN-γ-activated macrophages can mediate tumor cell killing via direct cell–cell contact, as well as release of soluble cytotoxic pro-inflammatory molecules. A recent study investigated whether IRF-3 and IRF-7 could mediate the acquisition of new anti-tumor effector functions in macrophages. Adenovirus mediated transduction of the active form of IRF-7 into primary macrophages resulted in the production of type I IFN, upregulation of target genes including TRAIL and increased tumoricidal activity of macrophages; in contrast, the active form of IRF-3 led to induction of cell death. These studies indicate that IRF-7 transduced macrophages may be an attractive candidate for *in vivo* adoptive therapy of cancer.

1. Introduction

The interferon (IFN) family constitutes an important class of cytokines and is composed of transcriptionally activated and secreted proteins with pleiotropic biological effects on the host. IFNs play a central role in the resistance of mammalian hosts to pathogens, and in the modulation of antiviral and immune responses [30,68]. The IFN proteins group into two classes: type I (IFN-α and -β) and type II (IFN-γ), which bind two distinct cell surface receptors, type I and type II IFN receptors, respectively (for review see [51]). It is important to point out that other antiviral, IFN-like molecules termed IFN-λ, which

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could be classified as type III IFN, have recently emerged [78]. Although, some immunomodulatory effects are shared by IFN-α/β and IFN-γ, type I IFNs exert stronger antiviral, anti-proliferative and antiangiogenic effects than IFN-γ and are widely administered as adjuvant therapy in cancer and viral related diseases.

2. Biological effects of type I interferons

IFN-α/β exerts a vast spectrum of biological functions, the best characterized of which is its role in the effective inhibition of replication of many RNA and DNA containing viruses. After IFN stimulation, hundreds of cellular genes known as interferon-stimulated genes (ISGs) are transcriptionally activated [17]. These genes encode proteins such as RNase L, dsRNA-dependent protein kinase (PKR), and 2′–5′ oligoadenylate synthetase (OAS), that mediate antiviral activities directly or indirectly.

In the establishment of an effective antiviral response, type I IFN upregulates various effector molecules that directly affect protein synthesis, cell proliferation and cell survival. IFN-α and -β are used in clinical settings for the treatment of chronic hepatitis C. In addition, it has been shown that IFN-α treatment reduces the risk for HCC in patients with chronic hepatitis C (for review see [50,71].

IFN-α/β also exerts profound effects on the immune system (Fig. 1). IFN-α/β regulates the homeostatic differentiation of hematopoietic cells such as B cells, T cells, osteoclasts, myeloid dendritic cells (DCs) and natural killer (NK) cells. In the case of immature DCs, activation and maturation of DCs can be induced by IFN-α/β, leading to the upregulation of major histocompatibility complex (MHC) molecules (especially class I MHC), chemokines, chemokine receptors and costimulatory molecules (CD40, CD80, CD86), which in turn leads to efficient homing in secondary lymphoid organs and $CD8^+$ or $CD4^+$ T cell responses [70]. In NK cells, IFN-α/β increases levels of perforin and leads to the induction of cytotoxic activity [6]. T lymphocyte responses are also modulated through IFN-α/β promotion of Th1 differentiation [9,49]. In particular, the inhibition of T cell death is promoted directly by IFN-α [43]. The development and function of B cells are also affected by type I IFNs. B cell receptor (BCR) mature B2 cell responses are enhanced by IFN-α/β [8] and as with T cells, type I IFN can inhibit B cell development and survival by increasing resistance to Fas-mediated apoptosis.

IFN-α/β also possessses potent anti-proliferative and anti-tumor functions [5,64]. In clinical settings, IFN-α/β is administered to patients suffering from various malignancies such as melanoma, hairy cell leukemia, renal cell carcinoma and Kaposi's sarcoma. The immunomodulatory role of type I IFN on DC and T lymphocyte function may explain various aspects of IFN-induced tumor immunity [5] (for review see [67]). IFN-α/β are also known to induce apoptosis; type I IFN exerts a pro-apoptotic effect associated with an increase in cyclin kinase inhibitors and several pro-apoptotic molecules (Fas/FasL, p53, Bax, Bak), as well as activation of pro-caspases 8 and 3 [11].

3. Role of IRFs in virus mediated IFN activation

IFN-β and/or IFN-α are rapidly produced following the sensing of incoming viral particles (via nucleic acid or ribonucleoprotein complexes) in the cytoplasm of cells or after engagement of Toll-like receptors (TLRs) in immune cells [31,73]. Viral entry or engagement of TLR3 or TLR4 induces the activation of latent transcription factors involved in immunomodulation, including IRF-3, NF-κB and ATF-2/c-Jun [40,61]. The production of

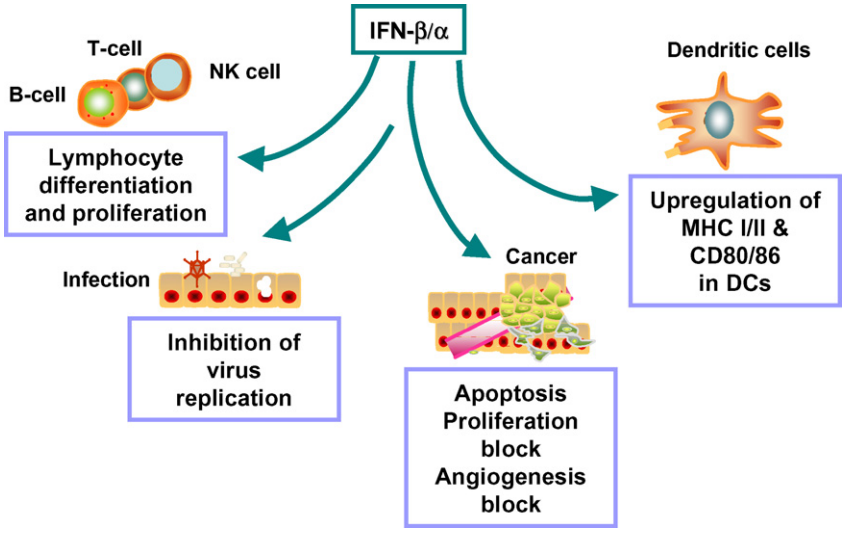

Fig. 1 – Diverse biological effects of type I interferons (IFN-α/β). IFN-α/β plays a central role in modulating host antiviral and immune responses by exerting a wide variety of biological functions. Immune cell development and differentiation are affected by type I IFN expression. These cytokines induce dendritic cell maturation by upregulating MHC class I and II and CD80/86 co-stimulatory molecules, as well as B-cell, T-cell and NK-cell differentiation and proliferation. In addition, IFN-α/β possesses pro-apoptotic, anti-proliferative and anti-angiogenic functions. Because of their potent effects on immune regulatory cell activation, IFN-α/β mounts an effective innate and adaptive immune response necessary for the inhibition of virus replication.