Review

Type I interferon response and innate immune sensing of cancer

Mercedes B. Fuertes[1], Seng-Ryong Woo[1], Byron Burnett[1], Yang-Xin Fu[1], and Thomas F. Gajewski[1,2]

[1] Department of Pathology, University of Chicago, Chicago, IL, USA
[2] Department of Medicine, University of Chicago, Chicago, IL, USA

Unexpectedly, many cancers appear to induce a spontaneous adaptive T cell response. The presence of a T cell infiltrate has been linked to favorable clinical outcome in multiple cancer types. However, the innate immune pathways that bridge to an adaptive immune response under sterile conditions are poorly understood. Recent data have indicated that tumors can induce type I interferon (IFN) production by host antigen-presenting cells (APCs), which is required for a spontaneous T cell response _in vivo_. The innate immune sensing pathways that trigger type I IFN production are being elucidated. Host type I IFNs are also required for optimal therapeutic efficacy with radiation. This recently uncovered role for host type I IFNs for antitumor immunity has important fundamental and clinical implications.

Introduction

Type I IFNs are a family of monomeric cytokines that, in mice and humans, include IFN-α (with different subtypes), IFN-β, IFN-ε, IFN-κ, and IFN-ω [1], with pleiotropic effects on many cell types. These cytokines are rapidly induced following recognition of virus- and bacterium-derived factors such as dsRNA, ssRNA, viral glycoproteins, CpG-DNA and lipopolysaccharide (LPS) by host pattern recognition receptors (PRRs) (Figure 1). Virtually every cell type expresses the type I IFN receptor (IFNAR, a heterodimer composed of the subunits IFNAR1 and IFNAR2), therefore, these cytokines are capable of exerting direct antiviral effects by inhibiting viral replication and inducing pro-apoptotic molecules that induce death of infected cells. Moreover, in noninfected adjacent cells, type I IFNs stimulate the expression of an array of genes programming an antiviral state that acts to prevent viral spread [2]. Type I IFNs are also important regulators of innate and adaptive immune responses through direct and indirect mechanisms that affect the activation, migration, differentiation, and survival of multiple subsets of immune cells including macrophages, monocytes, natural killer (NK) cells, dendritic cells (DCs), B cells, and T cells. Although it was discovered several decades ago [3], it has just been recently appreciated again that DNA or RNA derived from host cells is capable of inducing type I IFN production. Cytosolic DNA sensors such as DNA-dependent activator of IFN-regulatory factors (DAI) are capable of recognizing not only foreign but also self DNA (derived from damaged or dying cells), which also results in robust production of type I IFNs (Figure 1). This is an exciting finding that could explain sterile inflammation as in the case of autoimmune diseases and antitumor immune responses. Moreover, new findings regarding the role of type I IFNs in antitumor immunity have recently emerged, and it is interesting to speculate that DNA could be one of the tumor-derived factors capable of priming an immune response.

In this review we focus on the role of type I IFNs bridging the innate and adaptive immune response, and discuss in detail the recently revealed functions of type I IFNs in antitumor immunity.

Established role of type I IFNs in viral infection

Type I IFNs have long been established to have important antiviral activity, both _in vitro_ and _in vivo_. For example, a substantial reduction in viral clearance has been observed in IFNAR knockout mice after lymphocytic choriomeningitis virus (LCMV), vaccinia virus, vesicular stomatitis virus (VSV), Semliki Forest virus, and Theiler's virus infection. These data clearly indicate a critical role of type I IFNs against viral replication and dissemination [4,5]. Recently, Crimean–Congo hemorrhagic fever virus (CCHFV) infection in IFNAR$^{-/-}$ mice also exhibited 100% mortality in infected mice within 4 days after infection, even at a low dose (10 PFU) [6]. In another virus infection model, Hazara virus (HAZV), all challenged IFNAR$^{-/-}$ mice (10^3–10^4 PFU) died around 5 days after infection, whereas there were no clinical symptoms nor death of wild type (WT) challenged mice [7]. Type I IFNs activate signal transducer and activator of transcription (STAT)-1 and STAT-2 to induce antiviral gene expression. STAT-1$^{-/-}$ mice are unable to respond to IFNs and are highly susceptible to VSV and _Listeria monocytogenes_ infection [8]. Machupo virus (MACV) infection in STAT-1$^{-/-}$ mice induces clinical and histopathological manifestations of disease within 7–8 days [9]. In a dengue virus infection model, STAT-1/STAT-2 double-deficient mice exhibit early death after infection, whereas the single knockout mice show a lesser phenotype. This work demonstrates that both STAT-1 and STAT-2 contribute to type-I-IFN-mediated antiviral effect and positive feedback induced production of type I IFNs [10]. Another mechanism-based study has suggested an important role of STAT-6 for the antiviral effect of type I IFNs. This work demonstrates that virus-infected cells produce type I IFNs, but the activation of STAT-6 is not mediated by any cytokines secreted from

Corresponding author: Gajewski, T.F. (tgajewsk@medicine.bsd.uchicago.edu).
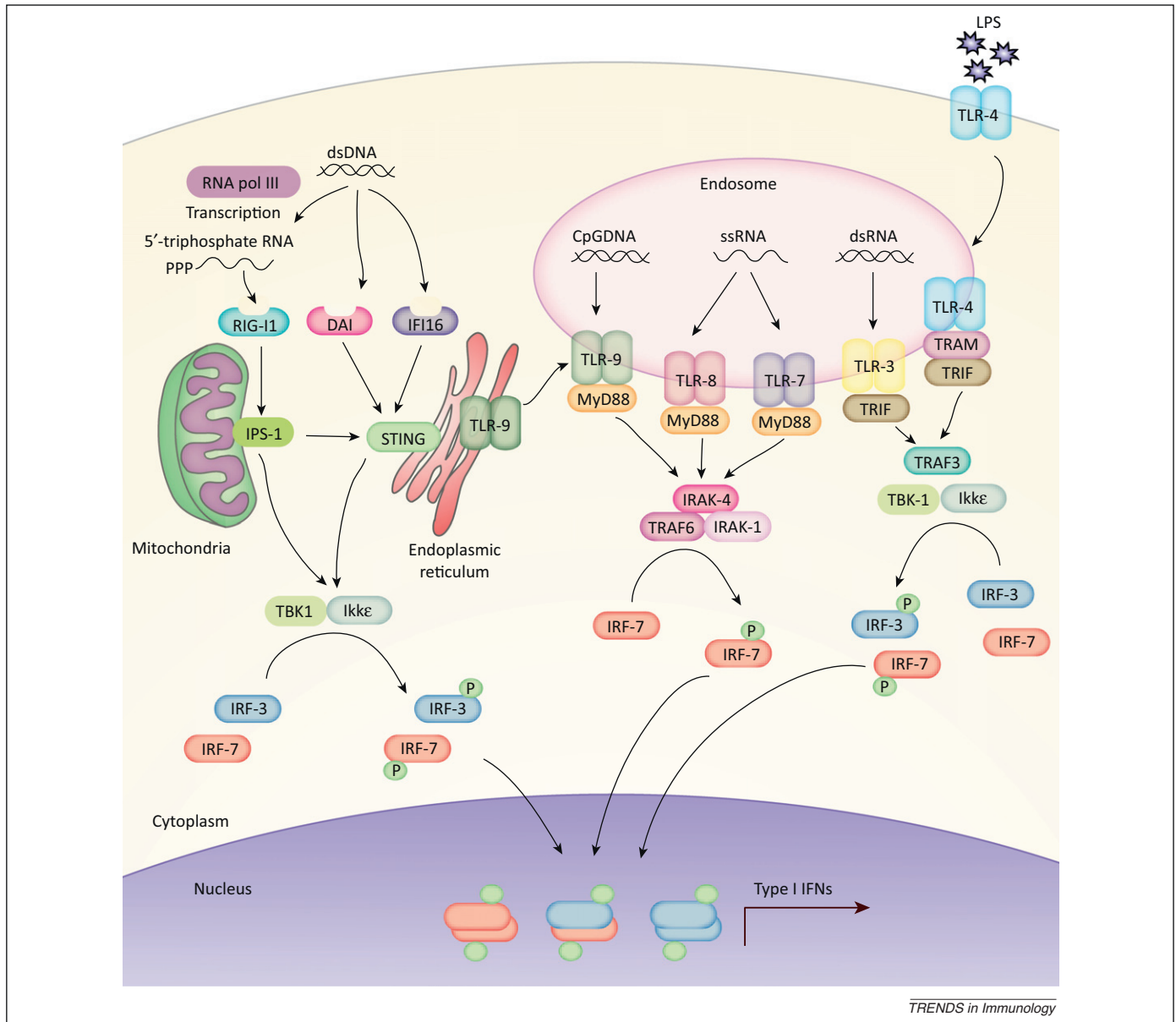
Figure 1. Major intracellular pathways leading to type I interferon (IFN) production. Cytosolic dsDNA can be directly recognized by the receptors DNA-dependent activator of IFN-regulatory factors (DAI) and IFN-γ inducible protein 16 (IFI16) (and its mouse ortholog p204), which induces a stimulator of interferon genes (STING)-dependent activation of TBK-1 and Ikkε that triggers interferon-regulatory factor (IRF)-3/7 phosphorylation, dimerization, nuclear translocation, and type I IFN gene transcription. The dsDNA can be also recognized by RNA pol III that transcribes it to RNA, activating helicase retinoic acid-inducible gene I (RIG-I) [and melanoma differentiation-associated protein 5 (MDA5)] that signals through IFN-β-promoter stimulator 1 (IPS-1) and also activates TBK-1, resulting in type I IFN production. In the endosomal compartment Toll-like receptor (TLR)-3 and TLR-4 can also activate TBK-1 and Ikkε to induce IRF-3/7 phosphorylation leading to type I IFN production, but through TIR domain-containing adapter inducing IFN-β (TRIF) and TNF receptor-associated factor 3 (TRAF3). Also in endosomes, TLR-9 and TLR-7/8 associate with myeloid differentiation primary-response protein 88 (MyD88) upon recognition of nucleotide ligands, leading to a signaling cascade that involves interleukin-1 associated kinase (IRAK-4), TRAF6, and IRAK-1 that triggers IRF-7 activation and induction of type I IFN production. Most of these pathways have been defined using infection models, and their potential role in tumor sensing is being elucidated.

infected cells. Instead, viral infection activates STAT-6 by an unknown mechanism but one which involves STING and TBK-1 [11]. STING (stimulator of IFN gene) and TBK-1 (TANK-binding kinase 1) are required for type I IFN production after viral nucleic acid sensing, thus, how viral infection regulates STAT-1 and STAT-2 activation by type I IFNs, or STAT-6 activation as an alternative pathway, will be important to elucidate.

Most cells can produce type I IFNs after direct viral infection, but it is interesting to note that the source of type I IFNs can differ in different models of viral infections [12]. Although viral nucleic acids are known to be the major stimulator of type I IFN production in infected cells via

nucleic-acid-sensing pathways including Toll-like receptors (TLRs), RIG-I (retinoic acid-inducible gene I)-like receptors (RLRs), Nod-like receptors (NLRs) and AIM2 (absent in melanoma 2)-like receptors (ALRs) [13], one recent study has shown that membrane TLR-2 can recognize mouse cytomegalovirus and vaccinia virus and induce type I IFN production from Ly6C^hi inflammatory monocytes. This study has also shown that receptor internalization is required for TLR-2-dependent type I IFN production [14]. These observations do not rule out the possibility that the TLR-2 receptor might be used for virus entry into the cell, which subsequently leads to viral nucleic acid sensing by cytoplasmic nucleic acid sensors.

Some viruses have the ability to antagonize antiviral effects mediated by type I IFNs [15]. Influenza A virus produces a nonstructural protein 1 (NS1) that interacts with the ubiquitin ligase TRIM25, which is required for activation of the RNA sensor RIG-I to produce type I IFNs. Consequently, NS1 inhibits type I IFN production through inhibition of TRIM25-mediated RIG-I CARD (caspase recruitment domain) ubiquitination [16]. In another viral evasion example, it has been shown that herpes simplex virus (HSV)-1 produces ICP-27, a multifunctional early protein required for viral protein transcription, which also inhibits STAT-1 nuclear accumulation [17]. As the role for type I IFNs in the tumor context continues to be investigated, it will be important to consider negative regulation of this pathway as well, which may point towards new targets for therapeutic modulation.

Type I IFNs as a link between innate and adaptive immune response

In addition to direct antiviral effects of type I IFNs, there also is an evident link between the production of type I IFNs and the effector arms of the host immune response. Studies in IFNAR$^{-/-}$ mice have revealed multiple mechanisms by which type I IFNs facilitate host immunity. Type I IFNs induce death of infected cells by induction of proapoptotic molecules [12]. This cell death might contribute to antigen cross-presentation by host APCs. In noninfected neighboring cells, type I IFNs induce the expression of hundreds of interferon-stimulated genes (ISGs); the function of which has been recently reviewed [18].

Although the mechanistic details are not fully understood, type I IFNs affect the activation, migration, differentiation, and survival of multiple subsets of immune cells. One of the first targets described for type I IFNs in the setting of viral infection is the NK cell population. *In vitro*, type I IFNs can enhance NK cell cytotoxic activity [19,20]. *In vivo*, TLR-induced type I IFN expression has been shown to lead to the production and transpresentation of interleukin (IL)-15 to NK cells by CD11c$^+$ DCs, which results in NK cell priming [21]. Type I IFNs also control NK cell-dependent antitumor activity in different experimental tumor models [22].

Type I IFNs have been shown to exert several effects on DCs, being able to modulate their maturation, differentiation, and migration. Type I IFNs can induce expression of the co-stimulatory molecules CD40, CD80, CD86 and the MHC class II complex [23]. In addition, DCs differentiated from human monocytes in the presence of granulocyte–macrophage colony-stimulating factor (GM-CSF) and IFN-α have shown enhanced cross-presentation ability by augmenting the duration of antigen presentation [24,25]. Several studies have pointed to the CD8α^+ DCs as the most important population for antigen cross-presentation [26,27]. Moreover, Batf3$^{-/-}$ mice, which selectively lack the CD8α^+ DC subpopulation, show an impaired capacity for antigen cross-presentation and antiviral and antitumor cytotoxic T lymphocyte (CTL) responses [28]. Interestingly, it has been recently shown that type I IFNs boost antigen cross-presentation by mouse CD8α^+ DCs, by enhancing antigen retention and promoting survival of CD8α^+ DCs, resulting in more effective induction of CD8$^+$ T cell

responses [29]. Human DCs matured in the presence of type I IFNs show upregulated expression of CCR7, the receptor for the lymph node-homing chemokines CCL19/21, which should improve migration to lymph nodes [30].

Type I IFNs have been shown to act early during an immune response to increase primary antibody responses and to promote the generation of long-lived memory cells. This effect has been shown to be either direct on B cells [31,32] or indirect, through activation of T cells [32] or DCs [33]. In a VSV model, adoptive transfer of virus-specific IFNAR$^{-/-}$ B cells into WT mice has demonstrated impairment of plasma cell formation, indicating that that type I IFNs might act directly on B cells for production of antiviral antibodies [34]. Evidence from some studies suggests a direct effect on CD8$^+$ T cells and the generation of effector and memory CD8$^+$ T cell responses during LCMV infection [35]. Type I IFNs (together with IL-12) have been shown to act as a third signal for human [36] and mouse CD8$^+$ T cells to promote effective differentiation in lytic effector cells [37]. Chimeric mice reconstituted with IFNAR$^{-/-}$ T cells show a diminished CD8$^+$ T cell response when stimulated by antigen and IFN-α, demonstrating that direct stimulation of T cells by IFN-α contributes to T cell priming induced by these cytokines [38]. Moreover, type I IFN signaling on CD4$^+$ T cells is required *in vivo* to sustain survival and induce clonal expansion of these cells during viral infection [39]. Taken together, these results from viral models suggest a multitude of effects of type I IFNs on DCs, T cells, and B cells.

The role of type I IFNs in the host response to cancer: recent evidence

The therapeutic effect of IFN-α in several human cancers has been appreciated for a number of years. However, the mechanism of action has never been thoroughly elucidated, although a component of this effect has been presumed to be through immune potentiation. Through the use of a methylcholanthrene-induced carcinogenesis model, recent data have indicated a critical role for host type I IFNs during immunosurveillance and for rejection of immunogenic transplanted tumors [40,41]. The molecular mechanism of this effect is beginning to be understood. Gene expression profiling done on human metastatic melanoma biopsies has revealed the existence of a subset of samples with an inflamed phenotype which contain activated CD8$^+$ T cells [42], including tumor-reactive cells [43]. A more detailed analysis of these samples has shown that the presence of T cell-associated transcripts correlates with the presence of a type I IFN transcriptional profile. In order to investigate a possible causal role of host type I IFNs as an innate bridge to T cell priming, mechanistic experiments have been performed using murine models. Following subcutaneous implantation of a variety of transplantable tumors in C57BL/6 mice, IFN-β was produced by CD11c$^+$ DCs in the tumor-draining lymph nodes prior to detection of a tumor antigen-specific CD8$^+$ T cell response. In STAT-1$^{-/-}$ or IFNAR$^{-/-}$ mice, spontaneous T cell priming and tumor rejection were nearly abrogated. Bone marrow chimera experiments have revealed a requirement for type I IFN signaling in the hematopoietic compartment for spontaneous rejection of immunogenic tumors *in vivo*, which has been further mapped to the APC compartment. Analysis of DC subsets

in the tumor microenvironment has revealed that endogenous type I IFNs are required for intratumoral accumulation of CD8α⁺ DCs. The use of Batf3⁻/⁻ mice, which lack the CD8α⁺ DC subset, has confirmed the requirement of this DC subpopulation for CD8⁺ T cell priming and tumor rejection. Mixed bone marrow chimera studies have mapped the major type I IFN signaling activity to the CD8α⁺ DC lineage. These results indicate that IFN-β induction is a critical component of the innate immune recognition of a growing tumor and identify a link between type I IFN activity and CD8α⁺ DCs, which could explain the requirement for this APC subset in spontaneous cross-priming of tumor antigen-specific CD8⁺ T cells *in vivo*. Together, these data argue that host APCs 'sense' some tumor-derived factor, which drives IFN-β production and cross-priming via CD8α⁺ DCs [44]. This model is shown in Figure 2. Interestingly, the work of Reis e Sousa and colleagues demonstrated a role for CLEC9A (C-type lectin 9A), a receptor highly expressed on CD8α⁺ DCs, in the cross-presentation of antigen from dying and virus-infected cells [45,46], making it logical to pursue a connection between this receptor system and the type I IFN pathway.

Using a different transplantable tumor model, Diamond *et al.* similarly have shown that endogenously produced type I IFNs are critical for the induction of an antitumor immune response resulting in the elimination of those tumors [47]. Despite the fact that type I IFNs have a broad range of cell targets during an immune response, type I IFN signaling on NK cells, granulocytes, and macrophages does not appear to be required for type-I-IFN-dependent tumor rejection. Instead, they have demonstrated that type-I-IFN-mediated signaling on CD8α⁺ DCs improve the antigen cross-presentation ability of this APC subset [47]. These results are in accordance with recent work demonstrating that type I IFNs promote cross-priming *in vivo* against cell-associated antigens derived from dying tumor cells by promoting survival of CD8α⁺ DCs and enhancing antigen persistence [29].

Potential sensing mechanisms that may promote production of type I IFNs in the cancer context

The demonstrated involvement of host type I IFN production in response to tumors *in vivo* raises the question of which innate immune sensing pathway is mediating this effect, and in response to which tumor-derived products. Presumably this process involves death of a subset of tumor cells as the tumor grows and adapts *in vivo*. Cell death can affect immune responses by releasing endogenous danger signals and activating APCs [48,49]. Several possible candidates have been described that could be involved in the induction of type I IFNs following exposure to dying tumor cells *in vivo*. TLRs have been suggested to recognize chromatin-binding protein high mobility group B1 (HMGB1) released from dying cells [50]. The LL37 antimicrobial peptide has been reported to bind self DNA and contribute to immune activation [51]. In a human psoriasis model, the antimicrobial peptide LL37 is upregulated in the skin of patients. This peptide binds to self DNA, generating a complex that is delivered to endocytic compartments in plasmacytoid DCs and results in the
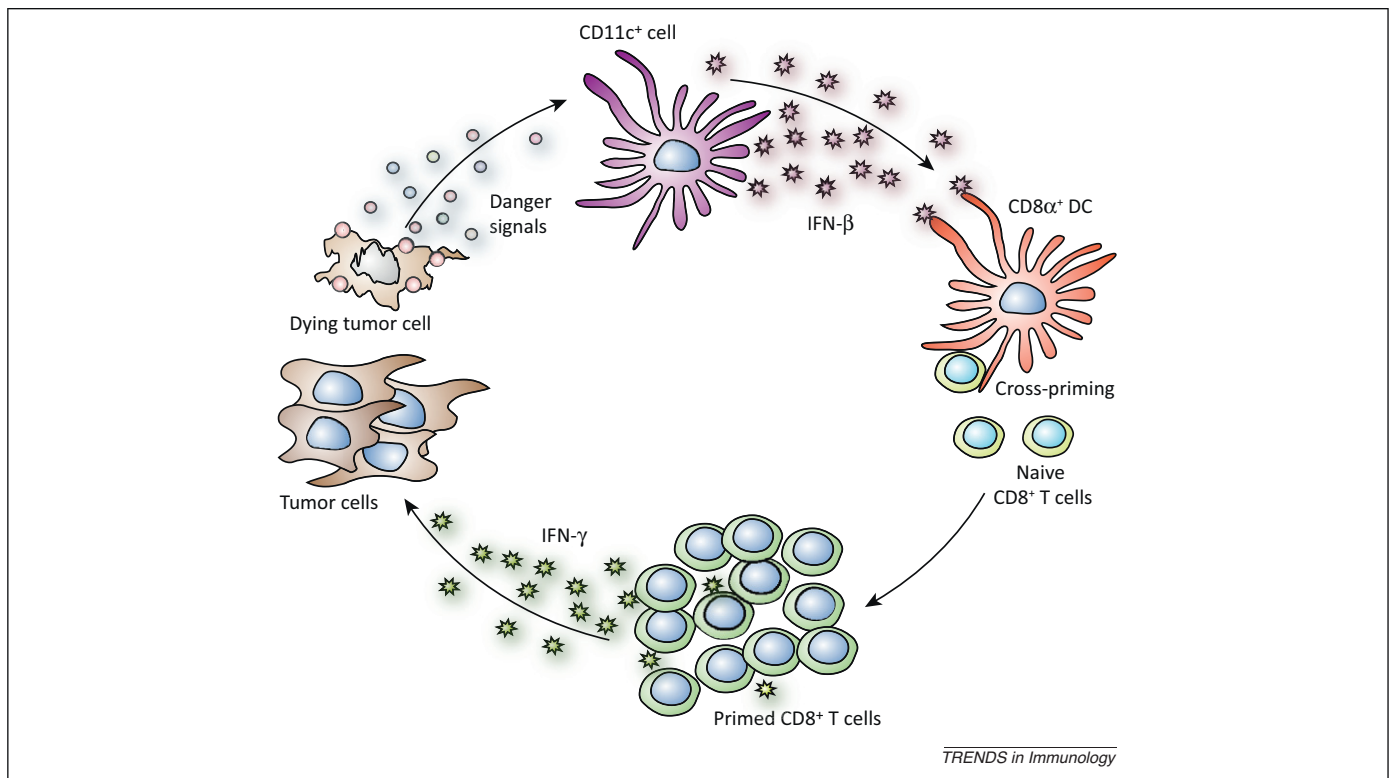
Figure 2. Working model for how host type I interferons (IFNs) contribute to a spontaneous adaptive T cell response against tumors *in vivo*. Tumor-derived factors seem to induce the early production of IFN-β by host CD11c⁺ dendritic cells (DCs). Subsequently, this IFN-β acting on the CD8α⁺ DC subset stimulates the cross-presentation of tumor-derived antigens, leading to the cross-priming of tumor antigen-specific CD8⁺ T cells. These activated T cells may, in turn, traffic to tumor sites and induce further tumor cell death.

production of type I IFNs through TLR-9 activation [51]. Although there have been no reports about the expression of LL37 in the tumor microenvironment, this mechanism is attractive to consider.

Another recent set of data have suggested that the autophagic cell death that is observed in influenza-virus-infected Bax/Bak$^{-/-}$ fibroblasts could induce type I IFN production by DCs. Type I IFNs, in turn, are required for induction of an IFN-γ-producing CD8$^+$ T cell response [52]. Although these data suggest that the viral RNA in infected fibroblasts undergoing autophagic cell death is what stimulates type I IFN production, it is possible that the process of autophagic cell death itself might be a contributor. Phagocytosis of Fas-ligand-treated apoptotic cells by DNase II-deficient macrophages results in type I IFN production that is independent of TLR signaling [53]. Thus, tumor cell death might induce type I IFN production in certain environments when DNA degradation of APCs is defective, and it is interesting to speculate that nucleic acids released from dying tumor cells could activate host DCs. The RIG-I like helicase pathways (RLHs) or the cytosolic DNA-sensing pathways could in principle recognize tumor-derived nucleic acids [54]. The CLEC9A receptor expressed on CD8α$^+$ DCs also could bind to exposed actin from dying cells and facilitate DC activation in addition to antigen delivery [55]. These possibilities will be attractive to pursue in future studies.

Participation of host type I IFNs in the therapeutic effect of radiation

In addition to a role for type I IFNs in the generation of spontaneous T cell responses against tumors, recent evidence has suggested that this pathway is amplified and required for radiation-induced tumor control *in vivo*. The dominant thinking for how local radiation therapy (RT) mediates tumor regression is that the induction of lethal DNA damage or mitosis crisis directly in tumor cells or in tumor-associated stromal cells leads to tumor shrinkage. However, radiation of tumor cells also could trigger danger signals emitted from immunogenic cell death and hence elicit danger-associated molecular patterns to stimulate antitumor immune responses [50,56]. Recent work has revealed that the therapeutic effect of ablative RT depends on CD8$^+$ T cells and that RT increases DC-mediated T cell priming [56]. However, the question remains as to which immunological components link activation of innate immunity by RT with increased cross-priming of CD8$^+$ T cells and generation of an adaptive response.

As a result of the observed role of type I IFNs in promoting cross-presentation of antigen in viral models and in spontaneous T cell responses against tumors, a possible role for type I IFNs in the therapeutic effect of RT has been pursued. In fact, host type I IFN signaling is required for tumor growth control mediated by delivery of high dose ablative RT [56]. Furthermore, local delivery of IFN-β, in the absence of RT, using an adenoviral vector is capable of promoting complete tumor rejection in a CD8$^+$ T cell-dependent fashion. It seems plausible that ablative RT induces excess DNA damage which might mimic viral infection to stimulate type I IFN production, which in turn bridges innate and adaptive immune responses.

Together, these results support a positive role for type I IFNs in the generation of tumor-specific CD8$^+$ T cell responses by local ablative RT, via the generation of DCs endowed with T cell cross-priming ability. The potential for RT and the type I IFN pathway to reverse immunosuppressive mechanisms in the tumor microenvironment also should be evaluated.

Clinical implications

The findings establishing a role for host type I IFNs in antitumor immunity have several implications for clinical translation. First, if production of low levels of host type I IFNs within the tumor microenvironment and in tumor-draining lymph nodes drives endogenous T cell priming against tumor antigens, then perhaps intratumoral administration of IFN-α or IFN-β might have greater therapeutic efficacy than systemic administration. Indeed, preliminary preclinical data from our group have supported this notion, and clinical trials of intratumoral type I IFNs are beginning in various tumor types. Second, if a major effect of endogenous type I IFNs is on promoting T cell priming in the tumor-draining lymph node, then perhaps the optimal timing for administration of IFNs for cancer therapy would be when those lymph nodes remain intact. In the setting of melanoma, IFN-α is used therapeutically in the postsurgical adjuvant setting after the regional lymph nodes have been resected, which eliminates the major site in which adaptive immune responses would be generated. Interestingly, a pilot clinical trial of neoadjuvant IFN-α given prior to a therapeutic lymph node dissection demonstrated a 50% clinical response rate [57], which is greater than the approximately 15% response rate seen in patients with distant metastatic disease. Further exploration of type I IFNs being given prior to lymph node surgery seems warranted. Third, in addition to a role for type I IFNs in the priming phase of an antitumor immune response, they also induce immune activation events that could augment the effector phase of an antitumor T cell response. This property could be critical when considering strategies to promote appropriate inflammation in noninflamed tumors that fail to recruit activated T cells and therefore appear resistant to current immunotherapies. Finally, as the detailed mechanism by which type I IFNs become induced in response to tumors *in vivo* is elucidated, then genetic variability in these pathways should be investigated as a possible contributor to heterogeneity in patient outcomes.

Concluding remarks

Type I IFNs are among the most pleiotropic cytokines, because of the ability of virtually every cell to produce them and the ubiquitous expression of their receptors. Type I IFNs have multiple effects on infected cells and also display a broad range of actions on cells of the immune system. Importantly, these cytokines have the ability to link innate and adaptive immune responses. The recently revealed functions of type I IFNs in priming spontaneous antitumor T cell responses make type I IFNs, and the innate immune sensing mechanisms that drive their production, attractive pathways for deeper investigation in preclinical and clinical contexts. An increased understanding of these innate

immune triggers may enable the development of new therapeutic interventions aimed at promoting improved adaptive immune responses against tumors *in vivo*.

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