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Type I IFN response and innate immune sensing of cancer

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Abstract

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 IFN production by host antigen-presenting cells 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 anti-tumor immunity has important fundamental and clinical implications.

1. Introduction

Type I interferons (IFNs) are a family of monomeric cytokines that, in mouse 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 viral and bacterial derived factors such as dsRNA, ssRNA, viral glycoproteins, CpG-DNA and LPS by host pattern recognition receptors (PRR) (Figure 1). Because virtually every cell type expresses the type I IFN receptor (IFNAR, a heterodimer composed of the subunits IFNAR1 and IFNAR2) these cytokines are capable of exerting direct anti-viral effects by inhibiting viral replication and inducing pro-apoptotic molecules that induce death of infected cells. Moreover, in non-infected 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, NK cells, dendritic cells, B cells and T cells. Although it was discovered decades ago [3] it has been just recently re-appreciated that DNA or RNA derived from host cells are capable to induce type I IFN production. Cytosolic DNA sensors such as DAI are capable of recognizing not only foreign but also self DNA (derived from damaged or dying cells), which also results in a robust production of type I IFNs (Figure 1). This is an exciting finding that could explain sterile inflammation as in the case of

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autoimmune diseases and anti-tumor immune responses. Moreover, new findings regarding the role of type I IFNs in anti-tumor 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 anti-tumor immunity.

2. Established role of type I interferons 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 knock-out mice after *Lymphocytic Choriomeningitis Virus*, *Vaccinia virus*, *Vesicular Stomatitis Virus*, *Semliki Forest Virus* and *Theiler's Virus* infection. These data clearly indicated 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% of death in infected mice within 4 days after infection even at a low dose (10 P.F.U.) [6]. In another virus infection model, Hazara virus (HAZV), all of challenged IFNAR^{-/-} mice (10³–10⁴ P.F.U) died around 5 days after infection while, there were no clinical symptoms nor death of WT challenged mice [7]. Type I IFNs activate STAT-1 and STAT-2 to induce antiviral gene expression. STAT-1^{-/-} mice are unable to respond to IFNs and are highly susceptible to vesicular stomatitis virus (VSV) and *Listeria monocytogenes* infection [8]. Machupo virus (MACV) infection in STAT-1^{-/-} mice induced clinical and histopathological manifestations of disease within 7–8 days [9]. In a Dengue Virus infection model, STAT-1/STAT-2 double-deficient mice exhibited early death after infection, while the single knockout mice showed a lesser phenotype. This work demonstrated that both STAT-1 and STAT-2 contributed 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 demonstrated that virus-infected cells produced type I IFNs, but the activation of STAT-6 was not mediated by any cytokines secreted from infected cells. Instead, viral infection activated STAT-6 by an unknown mechanism but one which involved STING and TBK-1 [11]. Because STING and TBK-1 are required for type I IFN production after viral nucleic acid sensing, 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-like receptors (RLRs), Nod-like receptors (NLRs) and AIM2-like receptors (ALRs) [13], one recent report showed that membrane TLR-2 can recognize mouse cytomegalovirus and vaccinia virus and induce type I IFN production from Ly6C^{hi} inflammatory monocytes. This report also showed that receptor internalization was 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 effect 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 ubiquitination [16]. In another viral evasion example, it has been shown that herpes simplex virus I (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.

3. Type I interferons 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 pro-apoptotic molecules [12]. This cell death might contribute to antigen cross-presentation by host APCs. In non-infected 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 cells cytotoxic activity [19–20]. In vivo, TLR-induced type I IFN expression has been shown to lead to the production and trans-presentation of IL-15 to NK cells by D11c⁺ dendritic cells (DCs), which results in NK cell priming [21]. Type I IFNs also control NK cell-dependent anti-tumor activity in different experimental tumor models [22].

Type I IFNs have been shown to exert a number of effects on DCs, being able to modulate their maturation, differentiation and migration. Type I IFNs can induce expression of the costimulatory molecules CD40, CD80, CD86 and the MHC class II complex [23]. In addition, DCs differentiated from human monocytes in the presence of GM-CSF and IFN- α showed enhanced cross-presentation ability by augmenting the duration of antigen presentation [24–25]. Several studies have pointed to the CD8 α ⁺ DCs as the most important population for antigen cross-presentation [26–27]. Moreover, Batf3^{-/-} mice, that selectively lack the CD8 α ⁺ DC subpopulation, showed an impaired capacity for antigen cross-presentation and anti-viral and anti-tumor CTL responses [28]. Interestingly, it has been recently shown that type I IFNs boost antigen cross-presentation by mouse CD8 α ⁺ DCs, by enhancing antigen retention and promoting survival of CD8 α ⁺ DCs, resulting in more effective induction of CD8⁺ T cell responses [29]. Human DCs matured in the presence of type I IFNs showed up-regulated 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 also 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 demonstrated an 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 showed 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 this cytokines [38]. Moreover, type I IFN signaling on CD4⁺ T cells was required in vivo to sustain survival and induce clonal expansion of these cells during a 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.

4. The role of type I interferons 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 has 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 revealed the existence of a subset of samples with an inflamed phenotype which contained activated CD8⁺ T cells [42], that include tumor-reactive cells [43]. A more detailed analysis of these samples showed that the presence of T-cell-associated transcripts correlated 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 were 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 revealed a requirement for type I IFN signaling in the hematopoietic compartment for spontaneous rejection of immunogenic tumors in vivo, which was further mapped to the APC compartment. Analysis of DC subsets in the tumor microenvironment revealed that endogenous type I IFNs were required for intratumoral accumulation of CD8 α ⁺ DCs. The use of Batf3^{-/-} mice, which lack the CD8 α ⁺ DC subset, confirmed the requirement of this DC subpopulation for CD8⁺ T cell priming and tumor rejection. Mixed bone marrow chimera studies mapped the major type I IFN signaling activity to the CD8 α ⁺ 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 CD8 α ⁺ 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 CD8 α ⁺ DCs [44]. This model is diagrammed in Figure 2. Interestingly, work of Reis e Sousa and colleagues demonstrated a role for CLEC9A, a receptor highly expressed on CD8 α ⁺ 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 showed that endogenously produced type I IFNs are critical for the induction of an anti-tumor immune response resulting in the elimination of those tumors. 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 did not appear to be required for type I IFN-dependent tumor rejection. Instead, they demonstrated that type I IFN-mediated signaling on CD8 α ⁺ DCs improved 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 CD8 α^+ DCs and enhancing antigen persistence [29].

5. Potential sensing mechanisms that may promote production of type I interferons 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 antigen-presenting cells [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. Toll-like receptors (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 was upregulated in the skin of patients. This peptide binds to self DNA generating a complex that is delivered to endocytic compartments in pDCs and result in the 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 dendritic cells. Type I IFNs, in turn, were required for induction of an IFN- γ -producing CD8 $^+$ T cell response [52]. Although these data suggested 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 deoxyribonuclease II (DNase II)-deficient macrophages resulted in type I IFN production that was independent of TLR signaling [53]. Thus, tumor cell death might induce type I IFN production in certain environments when DNA degradation of antigen presenting cells 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 CD8 α^+ 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.

6. 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 anti-tumor 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.

Because 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 was 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 was 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.

7. Clinical implications

The findings establishing a role for host type I IFNs in anti-tumor 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 post-surgical adjuvant setting after the regional lymph nodes have been resected surgically, 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 anti-tumor immune response, they also induce immune activation events that could augment the effector phase of an anti-tumor T cell response. This property could be critical when considering strategies to promote appropriate inflammation in “non-inflamed” 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* become elucidated, then genetic variability in these pathways should be investigated as a possible contributor to heterogeneity in patient outcomes.

8. 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 its receptor. 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 anti tumor 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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Figure 1. Major intracellular pathways leading to type I IFN production

Cytosolic dsDNA can be directly recognized by the receptors DAI and IFI16 (and its mouse ortholog p204) which induces a STING-dependent activation of TBK-1 and Ikke that triggers 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 RIG-1 (and MDA5) that signals through IPS-1 and also activates TBK-1, resulting in type I IFN production. In the endosomal compartment TLR-3 and TLR-4 can also activate TBK-1 and Ikke to induce IRF-3/7 phosphorylation leading to type I IFN production, but through TRIF and TRAF3. Also in endosomes, TLR-9 and TLR-7/8 associate with MyD88 upon recognition of nucleotide ligands, leading to a signaling cascade

that involves 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.

Figure 2. Working model for how host type I 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⁺ 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.