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The added value of type I interferons to cytotoxic treatments of cancer

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ABSTRACT

Type I interferons (IFNs) exert anti-proliferative, antiviral and immunomodulatory activities. They are also involved in cell differentiation and anti-tumor defense processes. A growing body of literature indicates that the success of conventional chemotherapeutics, epigenetic drugs, targeted anticancer agents and radiotherapy (RT) relies, at least in part, on the induction of type I IFN signaling in malignant cells, tumor-infiltrating antigen presenting cells or other immune cells within lymphoid organs or blood. The mechanisms underlying type I IFN induction and the clinical consequences of these observations are only beginning to be elucidated. In the present manuscript, we reviewed the recent advances in the field and provided our personal view on the role of type I IFNs induced in the context of cytotoxic anticancer treatments and on its possible exploitation as a complement in cancer therapy.

1. Introduction

Although the role of type I interferons (IFNs) in the protection against viral infections has been known for decades, their role in cancer development and treatment is still under deep investigation. Type I IFNs are a cytokine family (comprising IFN-α, IFN-β and IFN-ω) endowed with pleiotropic effects, including dendritic cell (DC) development/activation [1,2], T helper (Th)1 cell differentiation, T cell memory turn over [3] and natural killer (NK) cell activation [4]. IFN-α, which includes several subtypes, and IFN-β are already in use in the clinic for the treatment of neoplastic and autoimmune diseases, respectively [5]. Other members of the type I IFN family have been also identified [6], but they are less investigated in the context of anticancer treatments and will not be discussed in this review. The interaction of type I IFNs with their high-affinity cell surface receptor leads to the activation of the Janus kinase (JAK) – signal transducer and activator of transcription (STAT) pathway resulting in the transcriptional regulation of more than 2000 IFN-stimulated genes (ISGs) [7].

Besides their antiviral and antiproliferative properties, IFN-α/β play a pivotal role in the dynamic relationship between the host immune system and cancer [8–10]. Pioneering studies from Gresser and colleagues in the 80s and 90s revealed the importance of the host immune system in the antitumor effect of type I IFNs [11,12]. The main actors in the antitumor response varied depending on the site of tumor growth and included macrophages,

Abbreviations: Ab, antibody; ATLL, adult T-cell leukemia/lymphoma; ATM, ataxia-telangiectasia mutated; Aza, 5-azacytidine; BAFF, B-cell activating factor; BM, bone marrow; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; CIC, cancer initiating cell; CRC, colorectal cancer; CSC, cancer stem cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; CTX, cyclophosphamide; CXCL10, C-X-C motif chemokine ligand 10; Dac, 5-aza-2-deoxycytidine; DAMPs, damage-associated molecular patterns; DAI, Z-DNA binding protein or ZBP-1; DC, dendritic cell; DDR, DNA damage response; DNMTi, DNA methyltransferase inhibitor; HER2, epidermal growth factor receptor 2; HMGB1, high mobility group box 1; HSPC, hematopoietic stem/progenitor cell; ICD, immunogenic cell death; IFI16, IFN-γ-inducible 16; IFITM, interferon induced transmembrane protein; IFNs, interferons; IFNAR1, IFN-α/β receptor 1; IL, interleukin; IRDS, IFN-related DNA damage resistance signature; ISG, IFN stimulated gene; ISGF3, IFN-stimulated gene factor 3; JAK, Janus kinase; MAVS, mitochondrial antiviral signalling adaptor; MCA, 3′-methylcholanthrene; MDA5, melanoma differentiation-associated protein 5; miRNA, microRNA; MRE11, meiotic recombination 11; MyD88, myeloid differentiation primary response gene 88; Mx1, MX dynamin-like GTPase1; NF-κB, nuclear factor–κB; NK, natural killer; NLR, NOD-like receptors; NOTCH, neurogenic locus notch homolog protein; OAS, 2' oligoadenylate synthetase; OVA, ovalbumin; PBMC, peripheral blood mononuclear cell; PD-1, programmed-death-1; PD-L1, programmed death-ligand 1; PRR, pattern recognition receptor; RIG-I, retinoic acid-inducible gene-I; ROS, reactive oxygen species; RT, radiotherapy; SOCS, suppressors of cytokine signalling; STAT1, signal transducer and activator of transcription 1; STING, stimulator of IFN genes; TBK1, TANK-binding kinase 1; Th1, T helper 1; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRIF, TIR-domain containing adaptor protein-inducing IFN-β; USP18, ubiquitin-specific peptidase 18; U-STAT1, unphosphorilated STAT1.

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NK cells, and T cells [13]. In the early 1990s, Maria Ferrantini and coworkers from our laboratory performed studies with *ifna1* gene-transduced tumor cells (Friend erythroleukemia, B16 melanoma, TS/A mammary carcinoma) in animal models and observed that in the poorly immunogenic, highly metastatic, TS/A mammary adenocarcinoma mouse model, injection of IFN-α1-secreting TS/A cells into immunocompetent mice resulted in host-dependent rejection of tumor cells. Most importantly, tumor rejection was mediated by $CD8^+$ T cells and surviving mice developed a protective immunity against the parental TS/A tumor (rev in [14]). Along these lines, Narumi et al. showed that intratumoral *ifna1* gene transfer resulted in enhanced antitumor responses, through the stimulation of the antigen-presenting capabilities of tumor-infiltrating DCs. Interestingly, the antitumor responses were evident also in distant, non-transduced tumor lesions [15]. In another report, forced *ifna1* gene expression in tumor-infiltrating macrophages blunted their innate pro-tumoral activity and reprogrammed the tumor microenvironment toward more effective DC activation and immune effector cell cytotoxicity against the primary tumor and experimental metastases [16].

Besides the demonstration of an immune-mediated anticancer activity stimulated by forced *ifna1* gene expression, a role for endogenously produced IFN-α/β in tumor development had also been demonstrated in the early 80s with the *in vivo* administration of neutralizing antibodies (Abs) to IFN-α/β [17] or by knocking out the IFN-α receptor gene (*ifnar1*) in mice [18]. In subsequent years, studies from Schreiber and colleagues confirmed and extended these observations identifying IFN-α/β as a critical component of the cancer immunoediting process. Indeed, type I IFNs were critically required, in immunocompetent mice, to restrain the outgrowth of 3′-methylcholanthrene (MCA)-induced sarcomas. However, tumors arising in *ifnar1*$^{-/-}$ mice were shown to be more immunogenic than tumors developed in wild type hosts because of lack of selection of escaping variants by an IFN-induced potent immune response [19]. DCs represent important cell targets in type I IFN-mediated antitumor responses. In fact, mice lacking *ifnar1* in $CD8\alpha^+$ DCs fail to reject highly immunogenic malignant cells due to a defect in antigen cross-presentation [20]. In humans, infiltration of spontaneously regressing melanoma lesions with cytotoxic immune cells correlates with spontaneous type I IFN activation, thus highlighting the existence of important interconnections between type I IFN system and spontaneous antitumor immune response in cancer patients [21].

Endogenous type I IFN levels have also been correlated with metastatic dissemination in mouse models, whereby reduced or impaired type I IFN production enables metastatic spreading to the bone in spontaneous mammary tumor models [22].

Altogether, these data highlighted the role of type I IFNs in regulating host-tumor interactions and further paved the way for the studies addressing the role of this cytokine family in therapy-induced immune responses.

2. Type I IFNs: sensing of danger following radiotherapy

Among cytotoxic treatments of cancer, radiotherapy (RT) was the first for whom the therapeutic efficacy was shown to depend

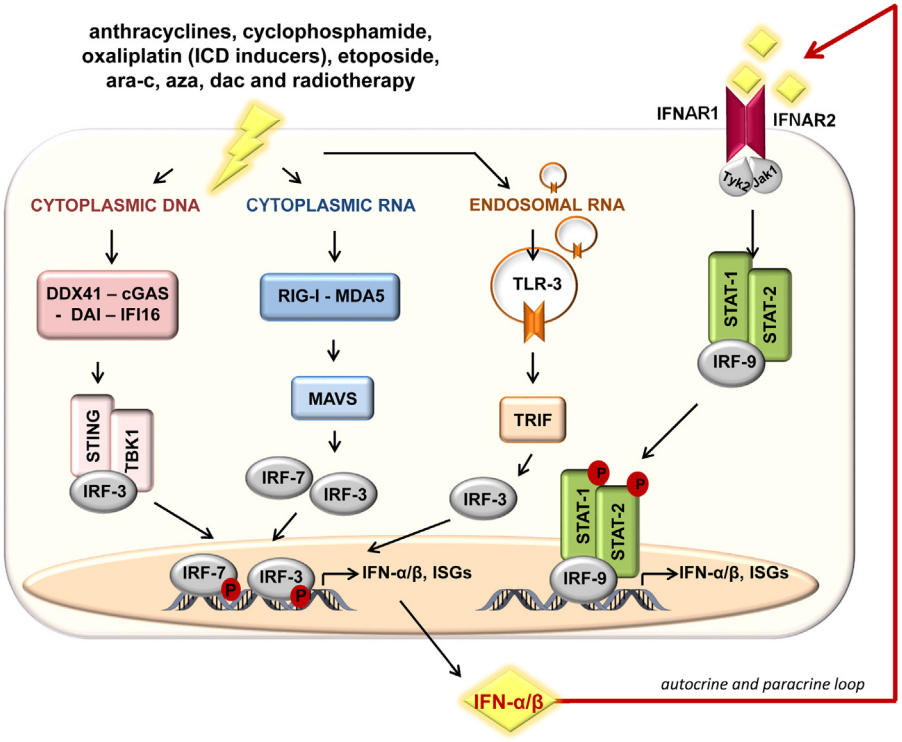

Fig. 1. Molecular pathways leading to type I interferon (IFN) response following cytotoxic treatments. ICD-inducers, (*i.e.* anthracyclines, cyclophosphamide, oxaliplatin), etoposide, cytosine β-D-arabinofuranoside hydrochloride (Ara-C), epigenetic drugs [*i.e.* 5-azacytidine (Aza), 5-aza-2-deoxycytidine (Dac)], or radiotherapy induce the release of DNA and/or RNA fragments that are perceived by specific cytosolic or endosomal receptors. DDX41, cGAS, DAI or IFI16 may bind DNA in the cytosol and activate the type I IFN response, through the STING-TBK1-IRF-3 axis in the cytosol. RIG-I and MDA5 detect cytoplasmic RNAs and, through the mitochondrial signaling protein MAVS activates TBK1 ultimately leading to IFN-α/β and ISG gene transcription. RNA molecules in the endosomes bind to TLR-3, which recruits TRIF and activates IFN-α/β transcription through phosphorylated-IRF-3. Following their extracellular release, IFN-α/β bind to a common receptor (IFNAR), thus stimulating the JAK1-STAT pathway and, through the recruitment of IRF-9, regulating the expression of several ISGs. Among these is IRF-7, which initiates the transcription of a second wave of type I IFNs via an autocrine/paracrine positive feedback loop.
DAI: DNA-dependent activator of IFN-regulatory factors; DDX41: DEAD-Box Helicase 41; IFI16: IFN-γ-inducible protein- 16; IRF: interferon regulatory factor; cGAS: DNA-dependent activators of interferon-regulatory factors cGMP–AMP synthase; MDA5: melanoma differentiation-associated protein 5; RIG-I: RNA helicase retinoic acid-inducible gene-I; STING: stimulator of IFN genes; TBK1: TANK-binding kinase 1