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Tumor immunity and type I interferon

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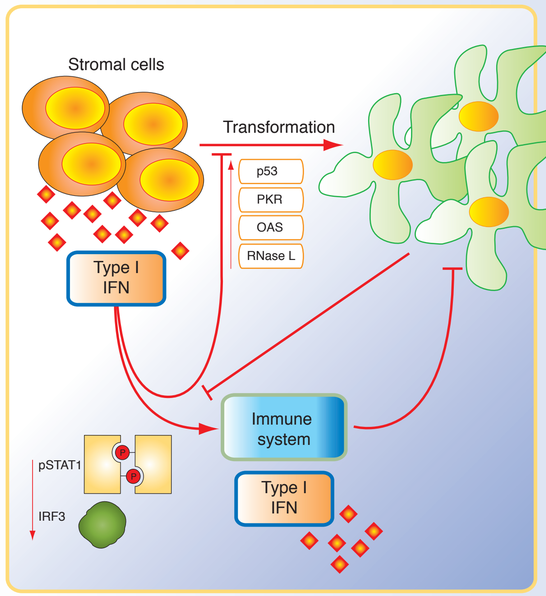
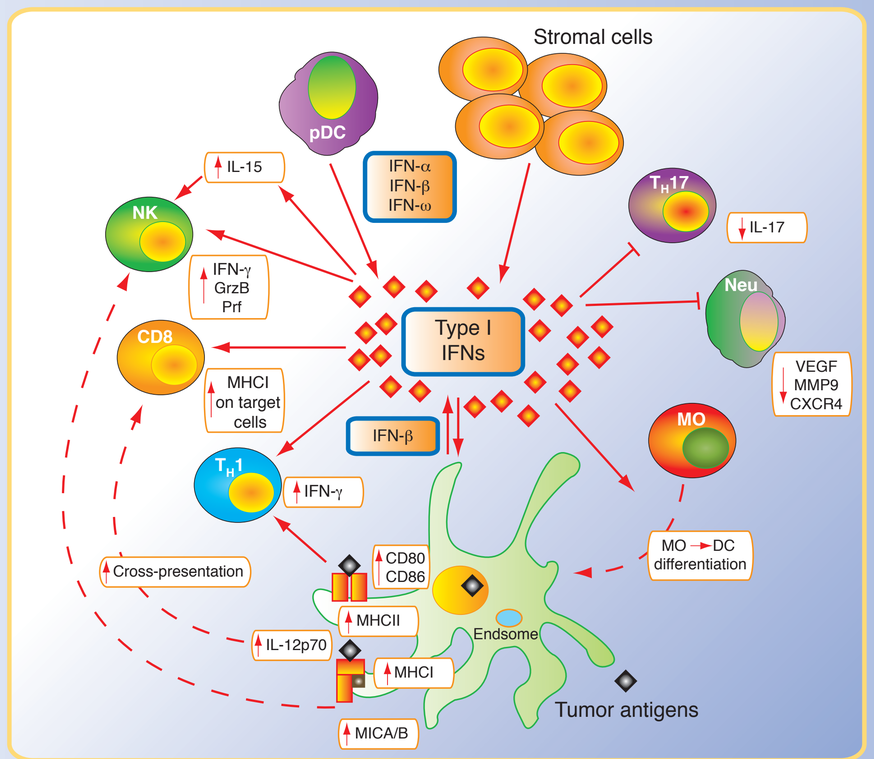
Interferons—type I (IFN-α, IFN-β and IFN-ω) and type II (IFN-γ)—have emerged as central coordinators of the interactions between tumors and the immune system, and they have nonredundant roles in the process of cancer immunoediting. Low constitutive secretion of type I interferons is important in immune surveillance and in the inhibition of cellular transformation. In addition, type I interferons regulate dendritic cell (DC) differentiation and activation and orchestrate the interaction of DCs with other cells of the immune systems, such as natural killer (NK) cells and memory CD8$^+$ T cells. The antiproliferative and antiangiogenic activities of type I interferons have paved the way for the use of these cytokines, in particular IFN-α, in clinical oncology. In some clinical settings, however, IFN-α has been superseded by newer anticancer drugs because of its severe side effects, which include autoimmunity, inflammation and tissue toxicity. IFN-λ1, a member of the type III interferon family, shows promise as an alternative antiviral and antiproliferative agents, as the relatively limited expression of its receptor may preclude the hematological toxicity associated with type I interferon. Meanwhile, the recently described effects of type I interferons on DCs and other cells of the immune response support the rationale for using type I interferon molecules as adjuvants for the generation of more effective cancer vaccines.



1. Type I interferons limits cancer growth both by preventing malignant transformation and by modulating antitumoral immune responses acting on cells of the immune response.

Endogenous type I interferons, released in low concentrations by all cells, are important in preventing cellular transformation. The molecular mechanisms of this effect are at least partially known: basal production of type I interferons sustain expression of the tumor-suppressor gene p53, and many of the products of interferon-inducible genes—such as double-stranded (ds) RNA–dependent protein kinase (PKR), RNase L and 2′,5′-oligoadenylate synthase (OAS)—also have tumor-suppressor activity. The immune system protects the host from tumor development by a process known as cancer immunosurveillance. Over time, the pressure exerted by the immune system sculpts the tumor antigenic profile, resulting in the selective growth of less immunogenic variants that eventually escape immune recognition (or cancer immunoediting). Using models of transplanted tumors and primary tumor formation, researchers have demonstrated a nonoverlapping role for endogenous type I and type II interferons in cancer immunoediting. Tumors that arise in mice lacking type I interferons are highly immunogenic and unedited and, unlike what has been observed for IFN-γ, this effect is dependent on the expression of the type I interferon receptor on immune cells and not on the tumor itself. This suggests that after the initial transformation, the effect of type I interferons on tumor growth depends on their capacity to modulate the immune response and not on their direct antineoplastic effects. The importance of type I interferons in contributing to host immunosurveillance is underscored by the observation that immune cells from people with breast cancer, melanoma and gastrointestinal cancers, as well as some tumor cell lines, have impaired type I interferon signaling.



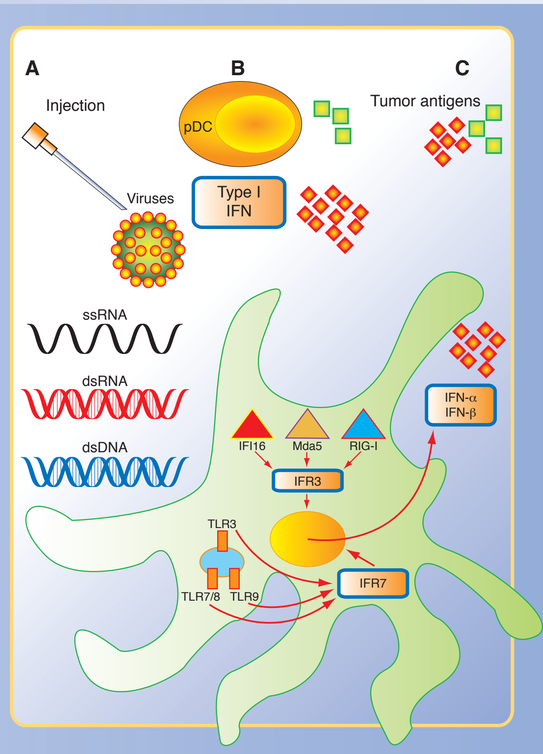
2. Immunoregulatory functions of type I interferons.

In addition to their direct antineoplastic effect, type I interferon molecules (IFN-a, IFN-b, IFN-) act on host hematopoietic cells to elicit protective antitumor immune responses. The main producers of type I interferons are plasmacytoid DCs and, to a lesser extent, conventional DCs. However, small amounts of type I interferons are released by all cells and, in tumors, by stromal cells in particular.

DCs differentiated from monocytes in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and type I interferons have a more activated phenotype, with enhanced expression of costimulatory molecules, classical major histocompatibility complex (MHC) molecules (class I and class II) and nonclassical MHC class I molecules such as MICA and MICB (which are recognized by NK cells via the stimulatory NK cell receptor NKG2D). Furthermore, during DC maturation, an autologous (autocrine?) stimulatory loop involving type I interferons is crucial in ensuring full activation of DCs. The presence of type I interferons also increases cross-presentation of tumor antigens by DCs and secretion of IL-12p70, thereby favoring priming of T helper type 1 (T_H17, T_H1) cells and differentiation of cytotoxic T lymphocytes (CTLs). Finally, type I interferons and IFN-γ together inhibit interleukin 17–producing T helper cell (T_H17) differentiation via mechanisms dependent on the transcription factors STAT-1 and T-bet, respectively.

Type I interferons induce release of interleukin 15, which has a critical role in regulating the proliferation and survival of NK cells and memory CD8$^+$ T cells. Type I interferons also directly enhance cytolytic activity of NK and CD8$^+$ cells, via increasing the expression of perforin and granzyme molecules. Lastly, type I interferons directly affect the differentiation of effector CTLs.

In the tumor context, endogenous IFN-β released by stromal cells has been shown to have an important role in contributing to innate immune surveillance, repressing secretion of proangiogenic factors by infiltrating neutrophils, By limiting the expression of the transcription factors STAT3 and c-Myc, IFN-β has been shown to downmodulate the chemokine receptor, limiting neutrophil recruitment to the tumor site, and to reduce secretion of the metalloproteinase MMP9 and of vascular endothelial growth factor (VEGF), dampening neutrophils' proangiogenic effect and recruitment of other myeloid cells to the tumor site.



3. Protocols to induce type I interferon.

A) Injection of type I interferon inducers: Through the use of recombinant or oncolytic viruses, Toll-like receptor (TLR) agonists such as single-stranded (ss) RNA, dsRNA and CpG molecules are injected into cells. In the majority of cell types, DNA and RNA molecules are recognized by cytoplasmic sensors, such as IFI16 (DNA) or RIG-I and Mda5 (RNA), which will trigger release of IFN-β in a manner dependent on the transcription factor IRF3. Dendritic cells and macrophages also release type I interferons in response to TLR3 and TLR4 triggering by dsRNA and lipopolysaccharide, respectively. Finally, natural interferon-producing cells (pDCs) exist that produce abundant type I interferons in response to triggering of the endosomal receptors TLR7 and TLR9, which are sensors for ssRNA and DNA, respectively. Constitutive high expression of IRF7 endows pDCs with this rapid type I interferon secretion capacity.

B) Injection of type I interferon producers: Activated pDCs are injected after maturation with TLR7 and TLR9 ligands or CD40L and IL3; pDCs can be pre-pulsed with tumor antigens to elicit tumor-specific immune responses.

C) Direct injection of type I interferon: Pegylated IFN-α, for example, is injected alone or in combination with tumor antigens, to harness its adjuvant activity.

Table 1 Past and present uses of type I interferon in cancer patients

Solid tumors	Melanoma
	Renal carcinoma
	Kaposi s sarcoma
Hematological malignancies	Hairy cell leukemia (second line of treatment)
	Chronic myeloid leukemia (second line of treatment)
	B and T cell lymphomas

IFN-α has been use over the past 30 years for the treatment of many cancers, as detailed in the table above. However, autoimmunity, inflammation and tissue toxicity have emerged as severe side effects of type I interferon therapy. Newer anticancer drugs have replaced IFN-α in the treatment of hematological malignancies, such as hairy cell leukemia and chronic myeloid leukemia. One promising alternative is the type III interferon IFN-λ1. Although IFN-λ1 shares with type I interferon antiviral and antiproliferative activities, it signals through a different receptor composed of two subunits, IFN-λR1 (IL28Rα) and IL10R2, whose expression is observed mainly on epithelial cells. The limited expression of this receptor may limit the hematological toxicity observed after injection of IFN-α.

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Abbreviations:

IFN, IDC, dendritic cell; **GrzB,** granzyme B; **IFI16,** interferon γ–inducible protein 16; **IL,** interleukin; **IRF,** interferon-regulatory factor; **Mda5,** interferon induced with helicase C domain 1; **MHCI,** major histocompatability complex class I; **MHCII,** major histocompatibility complex class II; **MMP9,** matrix metallopeptidase 9; **MO,** monocyte; **NEU,** neutrophil; **OAS,** 2′,5′-oligoadenylate synthetase; **PKR,** protein kinase R; **Prf,** perforin; **RIG-I,** retinoic acid–inducible gene I; **pSTAT1,** phosphorylated signal transducer and activator of transcription 1; **pDC,** plasmacytoid dendritic cell; **TH,** T helper; **TLR,** Toll-like receptor; **VEGF,** vascular endothelial growth factor.

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