Interferons—type I (IFN-α, IFN-β and IFN-ω) and type II (IFN-γ)—have emerged as central coordinators of the interactions between the tumors and the immune system, and they have nonredundant roles in the process of cancer immunodulation. 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 orchestrate the interaction of DCs with other cells of the immune system, 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 In some clinical settings, however, IFN-α has been superseded by newer anticancer drugs, because of its severe side effects, which include autoimmunity, inflammation and tissue toxicity.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-α-1a, a member of the type III IFN family, shows promise as an alternative anti-viral and antiangiogenic agent, as the relatively limited expression of its receptor may preclude the hematotoxicity associated with type I interferon. Meanwhile, the recently described effects of type I interferons on DCs and the other immune 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 in part due to the local production of type I interferons by tumor cells. This effect may be enhanced by the expression of interferon regulatory factor-1 (IRF-1) in tumor cells, which is a key transcription factor for the expression of type I interferons in response to different stimuli. IRF-1 may also be induced by type I interferons, leading to a positive feedback loop that enhances the secretion of type I interferons. This mechanism contributes to the antitumoral activity of type I interferons, as it allows for the accumulation of type I interferons in the tumor microenvironment, which can then act as an antitumoral agent.

2. **Immune regulatory functions of type I interferons.** In addition to their direct antiproliferative effect, type I interferons (IFN-α, IFN-β, IFN-ω) act on host hematopoietic cells to elicit protective antitumoral immune responses. The main products of type I interferons are plasmacytoid DCs (pDCs) and, to a lesser extent, conventional DCs (cDCs). However, small amounts of type I interferons are released by all cells and, in tumors, by stromal cells in particular. DCs differentiate from monocytes in the presence of interferon-α (IFN-α) or interferon-ω (IFN-ω) and type I interferons have a more activated phenotype, with enhanced expression of activating markers such as CD80, CD86, and CD40. Furthermore, DCs and macrophages act as professional antigen-presenting cells, which can prime antitumoral T cells.

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

<table>
<thead>
<tr>
<th>Solid tumors</th>
<th>Hematological malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
</tbody>
</table>

IFN-α has been used for over the past 30 years for the treatment of many cancers, as detailed in the table above. However, autoimmunity, inflammation and tissue toxicity of type I interferons therapy, severe side effects have replaced IFN-α in the treatment of hematological malignancies, such as hairy cell leukemia and chronic lymphocytic leukemia. The promising alternative is the type III IFN interferon-λ. Although IFN-λ-1 shows a type I interferon anti-viral and antiproliferative activity, it is different from a different receptor. This provides a new potential for treatment of cancer.

### Table of Abbreviations

- IFN: Interferon
- MDA: Macrophage
- MIP: Monocyte
- NK: Natural killer
- PD-1: Programmed death-1
- PKR: Perforin
- RIG-I: Retinoic acid–inducible gene I
- TLR: Toll-like receptor
- Th1: T helper type 1
- Th2: T helper type 2
- IFN-α, IFN-β, IFN-ω: Interferon-α, IFN-β, IFN-ω
- IFN-γ: Interferon-γ
- IL-12: Interleukin-12
- IL-15: Interleukin-15
- MHC: Major histocompatibility complex
- MMP9: Metalloproteinase 9
- PI3K: Phosphatidylinositol 3-kinase
- PKC: Protein kinase C
- STAT: Signal transducer and activator of transcription
- TLR: Toll-like receptor
- VEGF: Vascular endothelial growth factor

### References


### Figures

- **Figure 1**: Diagram showing the role of type I interferons in cancer immunity. The figure illustrates the interaction between type I interferons and various cell types, including tumor cells, stromal cells, immune cells, and other cells of the immune system. The figure highlights the role of type I interferons in suppressing tumor growth and promoting immune cell activation.

- **Figure 2**: Diagram showing the mechanisms of type I interferon-induced apoptosis in malignant cells. The figure illustrates the role of type I interferons in triggering apoptosis in cancer cells through the activation of the tumor suppressor gene p53.

- **Figure 3**: Diagram showing the role of type I interferons in regulating dendritic cell (DC) differentiation and function. The figure illustrates the role of type I interferons in inducing the differentiation of DCs into mature, antigen-presenting cells that can prime antitumoral T cells.

- **Figure 4**: Diagram showing the role of type I interferons in regulating the activation and function of natural killer (NK) cells. The figure illustrates the role of type I interferons in activating NK cells and promoting their antitumoral activity.

- **Figure 5**: Diagram showing the role of type I interferons in regulating the activation and function of cytotoxic T lymphocytes (CTLs). The figure illustrates the role of type I interferons in activating CTLs and promoting their antitumoral activity.

### Further Reading


**PBL InterferonSource**, a division of PBL Biomedical Laboratories based in Piscataway, N.J., USA, is the world’s premier supplier of interferon products to the life science research. Founded in 1990 by Dr. Sidney Pestka, PBL is the company that serves as a reference for interferon-related needs: products, services, information and know-how.