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Interferon-α and cancer: Mechanisms of action and new perspectives of clinical use

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Abstract

Interferons-α (IFN-α) are pleiotropic cytokines belonging to type I IFNs, extensively used in the treatment of patients with some types of cancer and viral disease. IFN-α can affect tumor cell functions by multiple mechanisms. In addition, these cytokines can promote the differentiation and activity of host immune cells. Early studies in mouse tumor models showed the importance of host immune mechanisms in the generation of a long-lasting antitumor response after treatment of the animals with IFN-α/β. Subsequently, an ensemble of studies based on the use of genetically modified tumor cells expressing specific IFN molecules provided important information on the host-mediated antitumor mechanisms induced by the local production of IFN-α. Of note, several studies have then underscored new immunomodulatory effects of IFN-α, including activities on T cells and dendritic cells, which may lead to IFN-induced antitumor immunity. In addition, recent reports on new immune correlates in cancer patients responding to IFN-α represent additional evidence on the importance of the interactions of IFN-α with the immune system for the generation of a durable antitumor response. On the whole, this knowledge suggests the advantage of using these cytokines as adjuvants of cancer vaccines and for the *in vitro* generation of highly active dendritic cells to be utilized for therapeutic vaccination of cancer patients.

Keywords: Interferon-α; Cancer; Antitumor immunity

1. Introduction

Interferons-α (IFN-α) are cytokines belonging to type I IFNs and exerting multiple effects on cell functions [1,2]. The IFN-α family is composed of at least 13 functional IFN subtypes, which share the same receptor system [3] and exert similar biological activities. In particular, 50 years of research on IFN-α have revealed that these cytokines exhibit a variety of biological effects different from those on viral replication, including antitumor activity (reviewed in [1,2]). IFN-α represent the cytokines exhibiting the longest record of use in clinical oncology. They have been used in over 40 countries for the treatment of more than 14 types of cancer, including some hematological malignancies (hairy cell leukemia, chronic myeloid leukemia, some B- and T-cell lymphomas) and certain solid tumors, such as melanoma, renal carcinoma and Kaposi's sarcoma. Even though today some new anticancer drugs have somehow replaced IFN-α in the treatment of certain hematological malignancies (i.e., hairy cell leukemia and chronic myeloid leukemia), this cytokine is still widely used in the treatment of patients with specific types of tumor, such as metastatic melanoma, and viral diseases (hepatitis C). However, in spite of many years of intense work in animal tumor models and of considerable experience in the clinical use of IFN-α, the importance of the different mechanisms of action underlying the response in patients is still matter of debate.

For a long time, it was thought that the direct inhibitory effects on tumor cell growth/functions were the major mechanisms important in the antitumor response in IFN-treated patients. In fact, IFN-α can directly inhibit the proliferation

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of normal and tumor cells *in vitro* and *in vivo*, and can exert other direct effects on tumor cells. These effects include the down-regulation of oncogene expression and induction of tumor suppressor genes, which can contribute to the antiproliferative activity of this cytokine, and the increase of MHC class I expression, which can enhance immune recognition [2]. In addition to the direct effects on tumor cells, type I IFNs exert several effects on host immune cells that can play a central role in the overall antitumor response [4]. In particular, the importance of the host-mediated antitumor effect was originally demonstrated in early studies of mice transplanted with IFN-resistant tumor cells, as clearly reviewed by Ion Gresser [5], but the possible implications for the design of novel strategies of clinical use of these cytokines remained underappreciated for many years [4]. In the first part of this review, we will summarize the main information on the mechanisms of antitumor effects of IFN stemmed from our studies on the use of genetically modified tumor cells or vectors expressing IFN-α in murine models [6]. These results, together with subsequent studies revealing previously unrecognized effects of type I IFNs on immune cells in both mouse models and humans [6–8], have led to the recognition of the importance of these cytokines in tumor immunity. Of interest, the results of clinical studies reveal new immune correlates of clinical response which might be predictive of antitumor efficacy [9–11]. In the second part of this article, we will review studies from several laboratories, including our group, showing the role of IFN-α in promoting the rapid differentiation and activity of dendritic cells (DCs), which may be important for the induction of an antitumor immune response in patients. Finally, we discuss some recent clinical data further supporting the concept that IFN-α can represent a powerful adjuvant for enhancing the efficacy of cancer vaccines and for a novel use in DC-based cancer immunotherapy.

2. Genetically modified tumor cells expressing IFN-α as tools for investigating the IFN-α-mediated antitumor mechanisms

In the studies on the antitumor effects of IFN in mice reviewed by Ion Gresser in this issue [5], a mixture of virus-induced IFNs containing both α and β subtypes was used for the treatment of animals transplanted with either IFN-sensitive or IFN-resistant syngeneic tumor cells. Thus, while these studies were instrumental for understanding the importance of the host immune system in the antitumor effects induced by type I IFNs, the specific role of IFN-α molecules remained unclear.

In the early 1990s, cytokine gene transfer into tumor cells became very popular and was regarded as a possible approach for the treatment of some human malignancies [12] as well as a more physiological strategy for the activation of an antitumor immune response as compared with systemic administration of cytokines. Most of the strategies of cytokine gene transfer were based on the insertion of cytokine genes into tumor cells in order to generate more effective cell-based cancer vaccines [13,14]. Over the following years, several clinical trials with genetically modified tumor cells producing certain cytokines (mostly interleukin (IL)-2, IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF)) have been performed in cancer patients, especially in patients with melanoma [12], showing variable results. While all this did not result in a major advance in cancer treatment, the ensemble of studies with mouse and human cells genetically modified for the production of cytokines certainly allowed us to learn a lot on the biologic role of the production of a given cytokine at the tumor site for the development of an antitumor immunity.

The first tumor cell type used by our group for IFN-α gene transfer studies was represented by Friend leukemia cells (FLC), a model extensively utilized in previous studies on the mechanisms of action of exogenous IFN-α/β in mice, as reviewed by Gresser in this issue [5]. FLC expressing IFN-α1 proved to be efficiently rejected by an IFN-induced host-mediated immune response and elicited an antitumor immunity against the subsequent challenge with metastatic parental cells [15,16]. We then extended these studies to other experimental tumors, characterized by either low immunogenicity or resistance to therapy with exogenous IFN-α/β. Using the poorly immunogenic, highly metastatic TS/A mammary adenocarcinoma, it was shown that injection of IFN-α1-secreting TS/A cells into immunocompetent mice resulted in host-dependent rejection of the genetically-modified tumor cells, mostly mediated by $CD8^+$ T cells, and in the development of protective immunity against the parental TS/A tumor [17]. When the tumorigenic behavior of TS/A clones producing comparable amounts of either IFN-α or IFN-γ was compared after s.c. injection, it was found that IFN-α-producing TS/A cells were rejected much more efficiently compared to IFN-γ-secreting TS/A cells, which exhibited only a partial delay of tumor growth [17]. Then, mice injected i.v. with TS/A-IFN-α cells exhibited fewer lung metastases and survived much longer than mice inoculated with control TS/A cells, whereas TS/A-IFN-γ cells were even more metastatic [17]. In similar studies with IFN-β and IFN-α-producing TS/A tumor cells [18], it was found that only the TS/A tumor cells secreting IFN-α were significantly inhibited in their metastatic ability when injected i.v. After s.c. injection of IFN-β-producing TS/A cells, only the high IFN-producer clones were completely rejected in the majority of mice, whereas a similar extent of tumor growth inhibition was obtained in mice injected s.c. with TS/A cells producing low amounts of IFN-α. Abrogation of tumorigenicity and induction of tumor immunity following IFN-α gene transfer was subsequently confirmed in the TS/A tumor model and extended to the MC38 murine colon adenocarcinoma by Tüting et al. [19]. In the B16 melanoma, also characterized by a low immunogenicity, IFN-α gene transfection resulted in a decreased tumorigenicity in syngeneic mice and in complete rejection of IFN-α-secreting B16 cells in allogeneic mice [20]. Using a genetically modified B16 clone secreting very high levels of IFN-α, Sarkar et al. obtained a complete abrogation of tumor growth after injection into syngeneic mice and significant induction of tumor immunity [21]. In a subsequent study [22], the highly metastatic lymphoma