IFN-alpha in the Generation of Dendritic Cells for Cancer Immunotherapy

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Abstract Dendritic cells (DCs) play a crucial role in linking innate and adaptive immunity, by virtue of their unique ability to take up and process antigens in the peripheral blood and tissues and, upon migration to draining lymph nodes, to present antigen to resting lymphocytes. Notably, these DC functions are modulated by cytokines and chemokines controlling the activation and maturation of these cells, thus shaping the response towards either immunity or tolerance.

An ensemble of recent studies have emphasized an important role of type I IFNs in the DC differentiation/activation, suggesting the existence of a natural alliance between these cytokines and DCs in linking innate and adaptive immunity. Herein, we will review how type I IFNs can promote the \textit{ex vivo} differentiation of human DCs and orient DC functions towards the priming and expansion of protective antitumor
immune responses. We will also discuss how the knowledge on type I IFN-DC interactions could be exploited for the design of more selective and effective strategies of cancer immunotherapy.

1 Introduction

Immunotherapy of cancer is aimed at eliciting immune responses against tumor cell associated antigens, in order to recognize and eradicate neoplastic cells or to control tumor growth. Such therapeutic approach would have the potential to eradicate neoplastic cells, especially in patients with minimal residual disease after tumor bulk resection, eventually resulting in prolongation of patients’ survival and in a substantial improvement of patients’ quality of life. Recently, an increasing interest has been focused on immunotherapeutic approaches utilizing dendritic cells (DCs), as cellular adjuvants, to effectively sensitize lymphocytes towards tumor antigens. DCs represent the key cells linking innate and adaptive immune responses, acting at the interface between the environment and the immune system by virtue of their role of professional antigen presenting cells.

A series of recent papers has revealed that type I IFNs, namely IFN-α and IFN-β, are capable of promoting the conversion of blood monocytes into highly active DCs. IFN-α and IFN-β are currently the most used cytokines in clinics, especially in the treatment of cancer and certain infectious diseases. Early studies had reported multiple effects of IFN-α/β on the immune system, including the enhancement of macrophage functions and of natural killer (NK) cell activity (Belardelli 1995; Belardelli and Gresser 1996; Belardelli and Ferrantini 2002). Besides its well known role in innate immunity (Belardelli 1995), type I IFNs are considered to play a role in the shaping of adaptive immunity, as previously demonstrated in mouse tumor models (Belardelli and Gresser 1996), and more recently by a series of papers highlighting the role of type I IFNs, and in particular of IFN-α, in the modulation of T cell functions, including the polarization of T-helper cells toward the TH-1 type of immune response. and the generation/activation of cytotoxic T lymphocytes (CTL) (Belardelli and Ferrantini 2002; Ferrantini et al. 2007). Over the last years, it has become apparent that many of the effects of type I IFNs on adaptive immunity are mediated by effects of these cytokines on macrophages and DCs. In particular, type I IFNs have been shown as potent inducers of DC differentiation from monocytes (IFN-DCs).

In this review article, we provide an overview of the existing knowledge on the ability of type I IFNs to induce the differentiation of human DCs \textit{ex vivo} and to modulate DC functions towards the generation of an antitumor adaptive immunity. We will also summarize and discuss the main results obtained in clinical trials based on the treatment of cancer patients with therapeutic vaccines comprising autologous type I IFN-induced-DCs as cellular adjuvants.