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A New Ally for Interferon-alpha in Cancer Therapy

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Development of Interferon in Oncology

Early research efforts on interferon (IFN) were based on the idea that the IFN was exclusively an antiviral agent. Subsequently, other biological activities were reported, including modulation of the immune system and antineoplastic activity.

Almost five decades ago, concomitant studies in animals and humans demonstrated the importance of IFN in oncology. Although the availability of recombinant IFN in the 1980s allowed the confirmation of the antitumor activity of IFN, it also generated some skepticism among clinicians and patients. This skepticism concerned the efficacy of recombinant IFN-α and its numerous side effects. For these reasons, questions about using crude IFNs or recombinant IFN-α were raised. Until now, these questions have not found complete answers. In drug discovery, the rationale behind developing pure recombinant IFN was based on the initial belief that IFN is a single molecule. In addition, the crude IFN was viewed only as non-pure IFN preparations, not as a mixture of different IFN types that may play some beneficial roles for patients.

During 1970s, scientists started using IFN as plural (IFNs) since three different IFNs were defined, depending on the cells type. IFN-α was characterized from virus-infected leukocytes, IFN-β from fibroblasts and IFN-γ produced by transformed lymphocytes and designated the immune interferon. However, we are now realizing that each type of IFN is not completely restricted to a group of cells; moreover virus-infected leukocytes mainly used as a source of IFN-α can also generate other IFNs [1-6].

The Pre-Recombinant IFN-α Era

During 1960s, different sources containing IFN-α were available [7-9]. The first *in vivo* studies in cancer models were conducted by the Gresser group and the antitumor activity of the IFN was clearly demonstrated for murine leukemia [10]. For more details, see Dr. Ion Gresser's review on the historical development of IFN antitumor discovery [11]. In order to extend the antitumor studies in the clinic, large scale IFN-α production was first developed from human blood leukocytes, collected from healthy donors [12] and later from the lymphoblastic Namalwa cell line [13,14]. The IFN purification was optimized in Cantell's laboratory [15] and the IFN preparations produced were used to treat a number of malignancies [16,17]. Encouraging results were obtained including complete responses in some patients [18].

The Recombinant IFN-α Era

Since 1960, pharmaceutical companies have been interested in the development of interferon as a drug. At the Roche Institute, IFN-α was first purified to homogeneity [19], sequenced and the first commercialized recombinant IFN, designated Roferon A tested. This was approved in 1986 by the US Food and Drug Administration (FDA). Other brands of recombinant IFN-α were also approved for the treatment of several neoplasms. Currently, the global market of recombinant IFN-α is valued at several billion dollars [20,21].

Emergence of IFN-λ in the Side of IFN-α: Key for IFN Therapy

The first clinical trial in oncology was based on crude IFN, including not only type I IFN which is mainly represented by IFN-α subtypes but presumably also the type III IFN, the new IFN-λ. From a signaling point of view, IFN-λ acts in a similar way as IFN-α but in a tissue specific manner [2]. IFN-λ is co-produced with IFN-α after viral infection [1-6] and acts through cell receptors, distinct from those of IFN-α [2,3,22,23]. We were the first to discover that IFN-λ also induces a potent antitumor activity in a melanoma model and other tumor models [3,24-26]. We speculate that the presence of both IFN-α and IFN-λ in the IFN preparation may be more potent than the present IFN therapy based on recombinant IFN-α. Therefore, the use of a new IFN therapy, based on the combination of IFN-α and IFN-λ may help the clinicians overcome the main obstacles of the IFN therapy today [2]. The natural presence of both IFN-α and IFN-λ in the IFN preparation may improve the IFN therapy and reduce the side effects.

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