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REVIEW ARTICLE

Role of Recombinant Interferons in Cancer Treatment

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ABSTRACT
Under natural conditions following an appropriate stimulus, living cells produce and secrete a group of proteins and glycoproteins known as interferons. The interferon molecules have multiple and potent biological activities, among which antiviral, antiproliferative, immuno-modulatory and cell surface modifying effects may be of potential therapeutic benefit. IFNs were the first new therapeutic products resulting from recombinant DNA technology. IFNs were also the first human proteins effective in cancer treatment. There is however much to be discovered which will lead to new clinical applications. The efficacy of interferon for the treatment of select malignancies has been established, and IFN-α and IFN-β have been approved by the Food and Drug Administration for multiple clinical indications. In other tumors where studies indicated that IFN lacked direct therapeutic activity, clinical trials suggested that it increased the antitumor activity of cytotoxic chemotherapeutic agents when used in combination therapy. IFN has substantial activity in chronic myelogenous leukemia, increasing survival in patients in early chronic phase when compared with conventional chemotherapy, and has some activity in nonHodgkin's lymphoma in combination with cytotoxic agents. Recent molecular and pharmacologic studies defining cellular receptor activation , signal transduction pathways, and biochemical modulating activities of interferon have yet to be fully incorporated into clinical development. This review will emphasize upon the role of IFNs for cancer treatment and its future applications.
Keywords: Recombinant Interferons, IFN-α, IFN-β, myelogenous leukemia

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INTRODUCTION

The Interferons (IFNs) are chemical signalling molecules which belong to the class of proteins called "cytokinins". When a cell becomes infected it responds by releasing proteins called Interferons. Now these IFNs will travel to neighbouring healthy cells, bind to special receptors on those cells and intiate a response that will prepare them for viral infection. For instance, the cells begin producing anti-viral proteins that function to block viral replication. This way, when the infected cell lyses and releases more viruses, the nearby cells have already mounted a defense. Though they were discovered nearly 40 years ago but were first approved 10 years ago for commercial use in United States. Till now the use of interferons in the treatment of cancer was limited but in recent years their use in cancer chemotherapy has been an active area of research and development. The mechanism of the apparent activity of interferon against tumors currently is unknown at either the molecular, cellular or systemic level of biological organization. Basic laboratory studies provided initial rationale for clinical trials with interferon in

Human cancer by showing that interferon directly inhibits the division of a variety of cells in vitro and in vivo [1]. Julius S. Horoszewicz and Gerald P. Murphy (1989) has discussed that the progress in clinical evaluation of Interferons intially proceeded slowly because only small amounts of low purity natural preparation produced by human cells in the laboratory were available at high cost. This situation was improved in 1981 when Deoxyribonucleic acid (DNA) recombinant IFNs synthesized bybacteria were made available by pharmaceutical companies for large scale clinical trials in neoplastic disease. These trials progressed and in 1986 the United States government approved genetically enginnered human recombinant IFN α for marketing and treatment of hairy cell leukemia. This review will provide an update on the role of these recombinant IFNs in cancer treatment to delineate future direction for interferons research in the laboratory and clinical studies.

CLASSIFICATION AND FUNCTION

The classification and nomenclature of interferons are based partly on antigenicity, chemical structure and cellular origin. The current classification of the IFNs is based mainly on sequence, chromosomal location, and receptor specificity. Type I IFNs include at least 18 IFN-α genes and pseudogenes, one IFN-β gene, and six IFN-ω genes and pseudogenes [2].

The type I IFN genes all lack introns and are clustered on the short arm of human chromosome 9. The type I IFNs have secretory signal peptide signal sequences, which are removed prior to their secretion, and the mature forms of type I IFNs are 165 to 172 amino acids long. Type II IFN consists of a single IFN-γ gene, which has three introns and is located on chromosome 12. The mature IFN-γ is 166 amino acids long. Both type I and type II recombinant IFNs have been studied clinically; these include IFN-α2a, IFN-α2b, IFN-β1a, IFN-β1b, and IFN-γ. Other IFNs, including hybrid species made by molecular recombination, have been studied experimentally. Although the type I IFNs have a high level of species specificity, one human hybrid, IFN-αA/D, was found to be active on both human and mouse cells. It was of interest that neither of the parental IFNs from which IFN-αA/D was derived had this property. Different species of IFN-α and their recombinant hybrids have been found to exhibit subtle differences in biologic activities, for example, having relatively greater or less antiviral or antiproliferative activity. The IFNs exhibit substantial overlap in their cellular and biologic activities, with differences in their immunomodulatory actions being the most notable feature distinguishing type I from type II IFNs [3]. The type I IFNs also has a different cellular receptor than does type II IFN [4]. Experiments demonstrating competition among the human type I IFNs for binding to cell surface proteins led to the suggestion that the type I IFNs have a common receptor [4-5]. However, other studies clearly demonstrated differences between both different IFN-α subtypes and between IFN-α and IFN-β in their interactions with the IFN receptor, subsequent signal transduction pathways, and cellular actions [6-7]. In particular, the subunit components of the type I IFN receptor differ on IFN-β binding compared with IFN-α binding. Comparison of IFN-α- and IFN-β-induced protein tyrosine phosphorylation indicated that there are IFN- β-specific signals, and a gene that was induced by IFN-β but not by IFN-α has been identified [8-12].

INTERFERON TREATMENT IN CUTANEOUS T-CELL LYMPHOMAS

The cutaneous T-cell lymphomas (CTCL), comprising primarily mycosis fungoides and the SCzary syndrome, are indolent T-cell non-Hodgkin's lymphomas [13]. Phenotypic and functional studies have shown that the malignant cells in these disorders are the helper T-cells [14]. These lymphomas are characterized by initial symptoms in the skin and subsequent spread to peripheral blood, lymph nodes, and other organs. The prognosis is highly dependent on the stage, as determined by the type of skin lesions and the presence or absence of peripheral blood, lymph node, and visceral involvement. Overall, the cutaneous T-cell lymphomas are indolent in nature with median survivals of approximately 8 to 10 years, similar to the B-cell indolent non-Hodgkin's lymphomas. Systemic spread is nearly universal and can be documented by light microscopic examination in up to one half of the patients at the time of diagnosis [15]. Initial therapies developed for these disorders were directed at the skin. These included the use of topical nitrogen mustard applied daily to the skin [16], the 3-times-weekly use of psoralen plus ultraviolet A light irradiation (PUVA) [17], and the total body application of electron beam irradiation [18]. The median duration of response for these therapies is 1 to 2 years, and 10% to 20% of patients remain disease-free at 3 years. This long disease-free interval occurs exclusively in patients with early plaque lesions. Relapses after 3 years were reported with topical nitrogen mustard but were not observed with total skin electron irradiation. This observation suggests that some of these patients may in fact be cured of this malignant neoplasm. Long-term data are not available for PUVA therapy but late relapses appear to be common. Patients with more advanced disease stages have been treated with chemotherapy, either with single drugs or in multiagent combinations [19]. These treatments produced objective remissions in the majority of patients, but complete remissions in only 20% to 25% of the patients. Furthermore, relapse is universal; there has been no suggestion of cures reported to date. Because of the propensity for early systemic spread and the lack of cure with known treatments, new systemic approaches are clearly needed. For these reasons, the maximally tolerated doses of interferon alfa-2a were studied in these neoplasms.

SECOND GENERATION IFNS FOR CANCER

All interferons are to signifi- cant degrees related by common primary amino acid sequence, although IFN-γ only distantly [20]. Each family is distant antigenically in both homologous and heterologous vertebrate species. IFNs-α, IFN-β and IFN-ω all bind to a common heterodimeric receptor [21]. Despite binding to a common receptor, differing cellular and clinical effects result, most clearly shown by the

differing patterns of gene expression induced in a single cell type. The biological and clinical effects of IFN-ω remain largely unexplored. IFN-τ identified only in ruminants, is critical for trophoblastic implantation into the endometrium [22]. Each IFN resides at a specific genetic locus. The three major classes of IFNs (α, β, γ) were initially defined on the basis of chemical, antigenic, and biologic differences. These have now been confirmed to result from significant differences in primary amino acid sequence. Human IFNs-α, IFN-β and IFN-ω are structurally similar and located on chromosome 9. Both IFN-α and IFN-β are 166 amino acids in length with an additional 20-amino acid secretory peptide present on the amino-terminal end. Comparison of the sequences of IFN-α and IFN-β has defined approximately 45% homology of nucleotides and 29% homology of amino acids. Each of the nonallelic human IFN-α genes differ by approximately 10% in nucleotide sequence, and 15–25% in amino acid sequence. IFN-γ , 143 amino acids in length, is located on chromosome 12 and also contains a 20-amino acid secretory peptide. IFN-γ has only minimal sequence homology with IFN-α or IFN-β. Although IFN-β and IFN-γ , produced by eukaryotic cells, are glycosylated, biologic differences from the unglycosylated IFN-α2 produced in E. coli have not yet been identified. Only one of the individual IFN-α types, IFN-α2, has yet been broadly assessed clinically. Limited phase I trials of IFN-α1 have been conducted in the United States. Significantly fewer side effects resulted [23]. Yet IFN-α1 was as effective in inducing 2 5A synthetase and NK cell cytotoxicity as was IFN-α2 [24][25]. IFN-α1 has been more widely assessed in China. Reported side effects were fewer and less severe than expected with IFN-α2. IFN-α1 has been used in China mostly for chronic hepatitis B and hepatitis C infections with good effectiveness [26]. Despite having had only a limited trial in malignancies, it appears to have clinical activity in chronic myelogeneous leukemia and hairycell leukemia.

MULTIPLE MYELOMA

Multple myeloma develops in 5–10 per 100 000 population in the USA and Europe each year. Although often regarded as a disease of later life, almost 50% of patients are under the age of 70 at the time of diagnosis. Cytotoxic drug treatment given at standard doses produces regression of the myeloma in >70% of patients, but complete remissions are unusual and the median survival in most reported series is 24–36 months [27][29]. Oral melphalan and prednisolone remain the most widely used treatment and a recent meta-analysis of 18 published trials has shown no survival advantage for other combination chemotherapies [30][32]. With a desire to improve outcomes, different biologic approaches have been investigated. In patients with myeloma, IFN-α has been demonstrated to have potent anti-proliferative action and the capacity to modulate oncogene expression [33]. Also, it prolongs all phases of the cell cycle as well as overall cell generation time and markedly reduces the selfrenewal capacity of myeloma-forming cells [34]. Interest in the use of IFN in multiple myeloma was evoked after Mellsted et al demonstrated efficacy as a single agent in previously untreated myeloma [35]. Several studies have since been undertaken using this cytokine in combination with chemotherapy to exploit its synergistic anti-tumor effect and others have used it as part of maintenance therapy [36]-[39].

The first study in which IFN-α was utilized as a single agent for induction therapy of previously untreated MM patients was published in 1979 [35]. In this study, three mega-units of human leukocyte IFN- α were administered via daily intramuscular injection to four patients. All patients achieved a durable response lasting from 3 to 19 months. This result and the increasing availability of IFN-α prompted several investigators to utilize this biologic response modifier in the treatment of MM. The results obtained in the early clinical studies showed a wide response rate ranging from 20% to 100% with an overall response rate of about 30%. Recently, the Myeloma Group of Central Sweden (MGCS) has reported the results of a randomized trial comparing the administration of human leukocyte IFN-α with oral melphalan and prednisone (MP). Forty-four per cent of patients treated with MP achieved responses, whereas only 14% of the patients treated with IFN-α responded. However, in the IgA and Bence Jones myeloma subgroups, the response rate was similar in both treatment groups. Moreover, because the response rate to a second-line treatment was better in the previously IFN-treated group than in the MP group, the overall survival duration was similar in both groups [29].

FUTURE DIRECTION

In patients with gastrointestinal malignancies, a variety of approaches are currently being explored. Several studies are examining the utility of IFN in combination with other biologic agents, such as radiolabeled monoclonal antibodies, specifically to determine the feasibility of such an approach and to determine whether IFN augments the targeting of the monoclonals. Based on extensive data that IFN augments the clinical activity of 5-FU, several studies are investigating the modulatory role of IFN in combination with 5-FU and other agents against refractory gastrointestinal tumors. The role of IFN in

hematologic malignancies has also continued to expand. Based on the activity demonstrated for IFN in combination with standard alkylating agent-based therapies, combinations of IFN and the purine nucleoside analogs are being investigated. Furthermore, because of potential antiviral as well as antiproliferative activity, IFN in combination with other biologic agents is being studied in patients with virally mediated lymphomas, such as human T cell leukemia/lymphoma virus-1 and HIV. Future advances in IFN therapy are likely to be based on emerging information about the cellular actions of IFN and the IFN-related signal transduction pathways. As the components of these pathways become more clearly understood, potential targets for IFN-mediated effects will likely be identified. One gene therapy strategy to enhance IRF-1 levels in order to sensitize cells to the effects of IFN has been proposed as a model [40].

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