Immunotherapy I: Cytokine gene transfer strategies

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Abstract

The cytokine approach to gene therapy of cancer stems from early studies of direct, repeated injection of recombinant cytokines at the tumor site, and extension of the bystander effect that enables a few cytokine gene transduced cells in a tumor to bring about its total destruction. This effect can be extended through the immune system, since cytokine-activated regression of a small mass of tumor cells can afford systemic protection. Transduced cells used as a vaccine provide a local concentration of both cytokine and tumor antigens. Cytokines sustain antigen uptake and presentation by increasing the immunogenic potential of the environment through the recruitment of antigen presenting cells and leukocytes, and activation of a cascade of events which amplify and tone up the efficacy of a vaccine. The promises and difficulties of this approach are discussed by considering what is still missing from experimental studies and what can best be done as soon as possible in animals and humans to reach compelling conclusions.

I. What is the approach?

Engineering of tumor cells with the gene of a particular cytokine is an efficient way of ensuring that this cytokine will uninterruptedly be present at the tumor site. Its repeated local injection, of course, would seem to serve the same purpose. Bolus administration, however, does not provide a constant supply of cytokine. Its effects are much less evident than those achieved by the injection of engineered tumor cells [1], whose proliferation results in both the provision of antigen and a continuous local build-up of the cytokine until a physiological or a pharmacological threshold is reached, and its biological activity begins.

The initial release of cytokines usually elicits an early inflammatory reaction. An interesting feature is the way the feedback from this reaction governs the release of the cytokine. The cytokine released increase in quantity as the engineered tumor ex- pands, then when the inflammatory reaction becomes effective its release decreases in function the efficacy of the reaction provoked. The debulking efficacy of this action is determined by the type of cytokine, its quantity and activity, the histotype of the tumor and the molecules it releases, and its extracellular matrix [2].

II. Cytokines at the tumor site: why?

It is not perfectly clear why so much interest was first aroused by the idea of bringing cytokines to a tumor site and what this was expected to achieve. The influence exerted by Rosenberg et al.'s results with systemic administration of high doses of IL-2 and LAK cells [3] was such that the first aim of local cytokine administration was to eradicate growing tumors through activated LAK cells or other cyto- lytic effectors [4]. Direct tumor therapy was also the
objective that lay behind the initial studies of insertion of a cytokine gene into somatic cells. Bubenik et al. pioneered the use of cytokine gene engineered normal cells to inhibit tumor growth [5]. In this and subsequent studies, transfer of normal or transformed cells engineered to produce IL-2, IL-4 or IL-12 to the vicinity of proliferating tumors led to their eradication [6–11]. The impressive reactions induced by transplantation of many mouse and human tumors engineered to release IL-4 [6], IL-2 [12], IFN-γ [13], and many other cytokines (review in 14) resulted in their inhibition.

On the other hand, experiments in non-tumoral systems had shown that IL-2 offsets defective antigen recognition [15] and overcomes tolerance [16], and thus suggested the use of cytokines to impair tolerance and activate effective and specific immune recognition of tumor associated antigens (TAA), which are poorly immunogenic by nature. Repeated injections of a tumor mass with very low doses of recombinant cytokines, indeed, often induce a local antitumor response followed by a specific, systemic and persistent immunity against non-immunogenic tumors [9].

Three facts have emerged from studies on local cytokines:

a) the oncogenic potential of tumors can be significantly hampered through the immune reaction elicited by cytokines injected at the tumor site, or locally released by engineered tumor cells.

b) the reaction elicited by engineered normal or neoplastic cells is sometimes strong enough to eradicate a tumor antigenically unrelated to the cytokine-releasing cells. This extended bystander effect displays a certain degree of selectivity since surrounding normal tissue remains undamaged.

c) prompt debulking of tumors engineered to release cytokines is often followed by establishment of a systemic, tumor-specific immune memory. If poorly immunogenic or apparently nonimmunogenic tumors can be rendered immunogenic enough to raise such a memory by the local presence of cytokines, a new form of vaccination against tumors themselves, would seem intrinsically feasible.

It must be remembered, however that these are three distinct findings that must not be lumped together, nor used to validate each other. Engineered tumor cells rejected by a nonspecific immune reaction are not ipso factor capable of eliciting a systemic memory response, nor does a greater ability to elicit some of the mechanisms of this response necessarily mean that these will cure an established tumor. Both events follow from the ability to elicit an immune response. The mechanisms and their outcomes, however, are not the same, nor inevitably consequential.

Evaluation of the potential of cytokine gene transfer strategies and of what they have achieved so far must thus depend on definition of the goals being sought, the mechanisms activated, and the prospects arising from the actual results of experimental and clinical studies. ‘Gene therapy’ is a seductive concept that coupled with the difficulty in the establishment of appropriate controls has often led to untenable and overoptimistic conclusions.

III. The lesson provided by animal studies

The effects elicited by a local cytokine will be determined by the mechanisms brought into play. However, since most cytokines are multifunctional one must expect that distinct immune mechanisms will be kinetically activated, and that their overall effect will depend on their interlinking and overlapping. The complexity of the action of cytokines and immune mechanisms, and the features of individual tumors hampers our ability to predict and analyse what actually takes place at a tumor site. Generalization of the findings observed and assessment of the extent to which they may be valid in other situations are equally hazardous undertakings.

III. A. Local tumor debulking

The first nonspecific reaction elicited by the cytokine secreted by engineered tumor cells often leads to their rejection and seem to favour induction of the immune recognition of TAA [2]. Transition from nonspecific debulking reaction to a systemic memory is more common with certain cytokines