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Commentary

Adoptive Immunotherapy of Cancer with Macrophages: Current Approaches and Further Prospects

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THE CLASSIC treatments of neoplasias by surgery, radiotherapy and/or chemotherapy can result in amelioration or even the cure of some types of cancer. Other forms of neoplasia are either unresponsive or may acquire resistance to therapy, thus attesting that there is no single, generally applicable cure of cancer. Numerous variables are responsible for this situation. Among these, the inherent genetic instability, leading to heterogeneous tumor cell populations, and the appearance and selection of adaptive tumor cell phenotypes, are particularly noteworthy [1]. The selection and privileged outgrowth of highly malignant tumor cell phenotypes may also be promoted by host factors such as the limited efficiency of host effector mechanisms. As a consequence of the multiple variables pertaining to host and to tumor, each tumor/host interrelation has its individual characteristics which may undergo continuous modifications as tumor growth progresses. It is these preconditions which encumber each type of tumor therapy.

To solve the cancer problem, alternative treatments are imperative. Over the past decades, immunotherapeutic approaches to the treatment of cancer have increasingly been attempted [2, 3]. These approaches are based on the hypothesis that the immune system might be capable of eliminating tumor cells in a similar way as it protects the host from viral, bacterial or fungal infection. The bulk of work performed in defined animal systems attests that in a given situation, immune mechanisms are able to cope with neoplasia [1–5]. This applies not only to immunogenic tumors, e.g. virus-induced tumors, but as well to autochthonous tumors without detectable immunogenicity. Experimental studies have indicated that depending on the individual reactivities of tumor and host, e.g. the tumor cell type and the conditions prevailing in local host tissues, a variety of cellular and humoral mechanisms may become operative and may affect the outcome of the interaction of tumor and host. In the past decades, numerous protocols to augment native immunologic defenses against neoplasias have been studied. These include inoculation of immunostimulants (e.g. BCG and other microbial agents, LPS, MDP), monoclonal antibodies, immunotoxins, cytokines (e.g. interferons, interleukins, tumor necrosis factor), growth and differentiation factors, or the adoptive transfer of *in vitro*-activated host effector cells [1–8]. In recent years, adoptive cellular immunotherapy has been increasingly used in experimental and clinical studies. Among the multiple possible approaches, the *in vitro* expansion and enhancement of the tumoricidal potential of autologous host effector cells and their subsequent reinfusion into the host, combined with administration of cytokines, are currently being utilized in local/regional and/or systemic adoptive immunotherapy [5]. It should be realized, however, that immunotherapy of neoplasia is still at a very early stage. It will take many years to transfer the experimental approaches to the clinic and to develop these treatments in an individualistic fashion.

Among the many cell types which may contribute

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to the host's tumor defense, *mononuclear phagocytes* (Mø) hold a major role [2, 8]. The viability and proliferation of the large majority of tumor cell lines are either not affected or even enhanced by resting Mø. On interaction with macrophage-activating agents, such as microorganisms and/or their products, or lymphokines, Mø evolve tumoricidal activity which is operative against a wide array of tumor cell types. Tumor cell killing by activated Mø (AMø) appears to require intimate cell-to-cell contact but to lack immunologic specificity; it may be enhanced by antibody (antibody-dependent cellular cytotoxicity, ADCC). Experimental and clinical attempts to take advantage of the extensive tumoricidal potential of AMø have followed various pathways. Efforts to activate Mø *in situ* and to enhance host defense against tumors by local or systemic administration of cytokines or microbial agents led to different results. Inoculation of lymphokines (e.g. IFN-gamma) or other soluble immunopotentiators (e.g. muramylpeptides and derivatives), mostly did not elicit tumoricidal activity in Mø, most likely because of their rapid clearance [1]. To prolong their local availability, liposomes were used as carriers of these soluble agents to Mø [1]. Inactivated, noninfective microorganisms (e.g. BCG, *C. parvum*, *Listeria*) generally proved to be more efficient promoters of host tumor defense than lymphokines; intralesional inoculation appeared to be particularly effective. However, immunotherapy with microbial agents, although usually safe, has been considered essentially futile for clinical use.

Another approach to immunotherapy with Mø is the administration of autologous, *ex vivo*-activated cells, analogous to that with lymphokine-activated killer cells. The conditions for such attempts, in particular the availability of cells in sufficient number and purity, have been considerably improved by various recent developments. Utilizing a combination of cytapheresis and counter current centrifugal elutriation, it is now possible to purify up to 10^9 monocytes per day and cancer patient [8]. These monocytes have a purity of 90% or greater. Selective propagation and differentiation is achieved during *in vitro* culturing in suspension in a serum-free medium supplemented with appropriate growth factors, such as macrophage colony-stimulating factor (M-CSF). For the induction of tumoricidal activity, these cells are incubated with macrophage-activating agent, in particular recombinant IFN-gamma, and can then be utilized directly in local, regional or systemic cancer immunotherapy protocols. Adoptive immunotherapy with IFN-gamma-activated blood monocytes was recently employed in local/regional and systemic treatment protocols of human cancer [8]. In semifluid tumors such as peritoneal carcinomatosis, repeated infusion of activated monocytes over a prolonged period of time appeared to be effective; in contrast, no regressions were noted in patients with metastatic disease on systemic administration of activated monocytes. Utilizing the methods outlined before for isolation, *ex vivo* differentiation and activation, Dumont *et al.* [9] tested tumoricidal activity of human monocytes *in vitro* and *in vivo*. *In vitro*, such activated cells were found to be cytostatic (monocytes) or cytolytic (Mø) against human ovary cancer cells and the U937 monocyte tumor cell line. The putative *in vivo* effects of activated Mø were tested in a human ovary carcinoma growing subcutaneously as a solid tumor in nude mice. When a tumor of 20 mm^2 had developed, 10^6 activated Mø per animal were inoculated twice a week into the peritumoral area. After a total of five injections, the size and mass of these tumors showed some regression; within the same period of time, tumors of controls, injected with saline, increased three-fold in size. In this model, the *in vivo* tumoricidal activity of activated monocytes was clearly lower than that of long-term cultured activated Mø, suggesting that the ability to evolve tumoricidal activity is dependent on the degree of cell differentiation. It appears from these very preliminary observations that adoptive immunotherapy of tumors with *ex vivo*-activated autologous Mø is feasible and is accompanied by only minor toxic side-effects.

Apart from Mø, a variety of other cell types dispose of inherent antitumor potential. In adoptive cellular immunotherapy, most progress to date has been made with lymphokine-activated killer (LAK) cells [5, 10, 11]. In this protocol, the *in vitro* generation of large numbers of LAK cells from lymphoid precursors is induced by incubation of mononuclear blood cells with interleukin-2 (IL-2). These LAK cells, which express marked tumoricidal activity, are then reinjected into the patient; to promote and to prolong their bioactivity *in vivo*, systemic administration of IL-2 is essential. The efficacy of LAK cell adoptive immunotherapy, which is complicated by acute toxicity, is presently not yet sufficiently clear. When the current attempts to increase its efficiency by refinement of the methodology and to reduce its toxicity succeed, it may become a useful means in the treatment of some forms of human neoplasia. Approaches to adoptive immunotherapy with NK cells and antigen-specific cytotoxic T cells still suffer from the difficulty of obtaining purified killer cells in sufficient number for clinical trials. It is obvious that adoptive cellular cancer immunotherapy with autologous, *ex vivo*-differentiated and activated effector cells, is in an early stage. The major hurdles which have to be surmounted are (a) to dispose of large numbers of readily accessible autologous cells which can be selectively induced to differentiate, to proliferate,

and to evolve tumoricidal activity *in vitro*; (b) the availability in sufficient amounts of highly active, nonimmunogenic and nontoxic cytokines for induction and maintenance of tumoricidal effector cell activity; (c) to bring the effector cells to the tumor site; and (d) to prolong the maintenance of the tumoricidal activity of effector cells at the tumor site. Consequently, a great deal of further work, including *in vitro* testing and *in vivo* research in experimental models and in cancer patients is required before the potential of such therapy can be reliably assessed.

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