Possible Role of Suppressor Cells in the Low Effectiveness of Adoptive Immunotherapy for Humans Cancers

Strategies to augment the immune response in man via infusions of lymphokines and/or adoptive immunotherapy have extensively been performed (1, 2). The results showed that injection of lymphokine-activated killer (LAK) or tumor-infiltrating lymphocytes (TIL) resulted in tumor regression in a limited number of patients. Namely, clinically significant responses have been obtained in only 10% to 30% of the patients. One reason for limited efficacy of LAK or TIL cells may be that only a very small number of intravenously administered LAK cells reach distant tumor sites (3). To improve the therapeutic efficacy, hepatic artery infusion of cytotoxic T lymphocytes (CTL) in patients with liver cancer was reported (4). However, among 15 treated patients, 2 complete responses and 3 partial responses were only observed. These rather low response rates have raised a variety of questions about the function of the immune system in general and of T lymphocytes in particular in cancer patients.

Apparent inability to develop cell-mediated antitumor immunity to the primary tumor was not due to a total lack of immune response, but rather to a dynamic process involving the activation of suppressor T cells resulting in the inhibition of antitumor immunity in the animals (5, 6). Hence, immunological resistance against tumor was directly dependent on the balance of the activation of CTL bearing a major role for tumor rejection and suppressor T cells capable of suppressing the activity of CTL against the homologous tumor (7–10). Further, Yamauchi et al. (10) reported that cytotoxic and suppressor T cells were generated under different conditions. Namely, CTL required live tumor cells for antigenic stimulation while soluble tumor antigen could activate suppressor cells. Similar findings had been reported by Taniguchi and his colleagues (11–13). They described that soluble forms of tumor antigen (80Kd molecule) preferentially suppressed both induction and effector phases of antitumor CTL responses. The concepts described in the reports are certainly based on experiments in animal systems and are not directly ready for clinical application. However, the basic observations about the suppressor-cell network in animal models have been found in human systems (14–18), and a clinically useful application of the basic observations appears inevitable.

We previously demonstrated the generation of T-cell growth factor (TCGF)-dependent suppressor T cells from patients with systemic metastasis of gastric carcinoma (14). The cells dominantly expressing CD8 antigen were shown to inhibit the patient’s own lymphoproliferative responses to alloantigen or phytohemagglutinin. Furthermore, it has been shown that TCGF-activated peripheral blood lymphocytes (PBL) from patients with advanced gastric carcinoma inhibited the effector process of tumor cell lysis by LAK cells which had been activated in vitro by rIL 2 (15, 17). This suppression of cytotoxicity is exerted by blocking directly the activity of LAK cells. The effector cells responsible for suppression of LAK activity showed surface phenotype of CD8+ CD11b− in FACS sorting techniques (17). It has also been shown that freshly obtained PBL, especially nylon-wool adherent cells from patients with advanced gastric carcinoma directly inhibit the activity of CTL and LAK cells against tumor (18). Negative and positive selection studies by the method of immunomagnetic beads showed that CD8+ T and CD8− CD11b+ cells might be effector cells for the suppression. Possible roles of macrophages were ruled out, since the percentages of HLA-DR+ Leu M3+ cells recovered from nylon-wool adherent populations were less than 5%. These findings mean that therapeutic effect by the infusion of CTL or LAK cells for adoptive immunotherapy will be directly inhibited by circulating CD8+ T and CD8− CD11b+ suppressor cells in patients with carcinoma. The generation of the suppressor cells seems to be a result of large tumor burden (14, 15, 17). In the presence of suppressor cells, immunotherapy based on the CTL or LAK cells will be ineffective; therefore, immunotherapy needs to be conducted after such suppressor cells have been eliminated or after their activity has been suppressed. Tumor burden represents a critical limitation for immunotherapy.

There are some approaches to reduce suppressor cell function. It is possible that low doses of radiation and chemotherapy may be benefit to cancer patients by their indirect effect on the immunoregulation of defence against tumors. Indeed, data of number of different studies suggest that conventional chemotherapeutic agents, such as cyclophosphamide and bleomycin can actually boost immune responses under non-therapeutic doses since the chemotherapeutic agents can deplete or impair the suppressor cell function without immunosuppression. On the other hand, surgical removal of growing tumor burden surely improves immunoregulatory balance in favor of host by eliminating excess of suppressor cells, although surgery can not always be carried out. This method certainly removes soluble antigen which serves as stimulus for suppressor cells. A reduction of suppressor cell activity by the surgical operation facilitated the successful use of immunotherapy (19). Reduction of suppressor cell activity by irradiation, chemotherapy or surgical operation is one approach for reversing immunological unresponsiveness, but more selective and reli-
able procedures without difficulty should be discovered to attain a greater success of immunotherapy in humans.

Recently, Loeffler et al. (20) reported that the decreased cytotoxic function of splenic CD8+ LAK cells generated by murine CD3 and human recombinant IL 2 from late tumor-bearing mice was not due to the presence of CD8+ suppressor cells, but due to the impaired expression of granzyme B mRNA of the cells. Namely, they concluded that the decreased cytotoxicity of the cells was not because of cell-mediated suppression, and CD8+ cells itself played a major role in the low effectiveness of adoptively transferred LAK cells from late tumor-bearing mice. However, they have not examined whether or not infusion of LAK cells with highly cytolytic activity from early tumor-bearing mice regresses the tumor mass in late tumor-bearing mice. In such situation, immunotherapeutic tumor regression would not be observed. In addition, they did not examine whether or not splenic lymphoid cells from late tumor-bearing mice directly suppressed LAK cell activity. Their experiments appear not to be proved completely for the cause of low response of adoptive immunotherapy in mice.

Cohen et al. (21) reported that the expression of HLA-DR on melanoma cells was essential for successful adoptive immunotherapy. Indeed, recent our works (22) showed that the expression of HLA-DR tended to decrease in the order of normal gastric mucosa, primary gastric carcinoma and metastatic carcinoma from malignant ascites. Thus, the low response of adoptive immunotherapy for cancer patients at the advanced stage may be partly due to the reduced expression of HLA-DR.

In summary, it is reasonable to note that with the abrogation of suppressor mechanisms and the availability of large quantities of effective immune cells, clinically significant tumor burdens would be made to regress. Therefore, the realization that suppressor cells apparently develop in response to growing malignant tumor will lead to an important new area of research in tumor immunology.

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References