Letter to the Editor

Correspondence re: J. P. Alexander *et al.*, T-Cells Infiltrating Renal Cell Carcinoma Display a Poor Proliferative Response Even Though They Can Produce Interleukin 2 and Express Interleukin 2 Receptors. Cancer Res., *53:* 1380–1387, 1993.[1]

In a recent paper in the March 15, 1993, issue of *Cancer Research* (1), Dr. Alexander and colleagues have addressed an old but still unresolved issue of immunocompetence of human TIL.[2] Using purified or sorted TIL from patients with renal cell carcinoma, Alexander *et al.* confirmed the results consistently and repeatedly obtained by our group with TIL isolated from various types of human solid tumors (2–5). Human TIL, when first isolated from the tumor, express both the IL2 receptor and CD3-TCR complex comparably to autologous peripheral blood T-lymphocytes and are able to express mRNA for IL2 and γ-interferon as well as produce these cytokines upon simulation *in vitro* with phytohemagglutinin or anti-CD3 antibody (1, 6, 7). However, TIL either do not proliferate or proliferate poorly in response to these signals. The functional deficit of human TIL appears to be largely restricted to proliferation, although both mobility and antitumor cytotoxicity of fresh TIL may be also decreased (8, 9). The deficit has been attributed to a variety of causes, including tumor-derived immunosuppressive factors capable of selectively inhibiting TIL proliferation (2). Alexander *et al.* (1) suggest that the selective functional deficit in TIL may be due to a loss of a signalling pathway required for T-cell proliferation.

It is worth calling attention to the fact that just 4 months earlier, Augusto Ochoa and colleagues have published in *Science* (10) their studies on signal transduction in T-lymphocytes from mice bearing established colon carcinomas (MCA-38). These T-lymphocytes expressed the CD3-TCR complex comparably to T-cells from normal mice, but their TCR-dependent Ca^{2+} flux and the expression of $p56^{lck}$ and $p59^{fyn}$ protein tyrosine kinases were depressed. Furthermore, structural changes were detected in the CD3-TCR complex on T-cells from tumor-bearing mice: the amount of CD3-γ chain was decreased, the CD3-ζ, a critical signal-transducing element of the CD3-TCR complex, was absent and substituted by the Fc-εγ chain. The abnormal TCR complex was detected on both $CD8^+$ and $CD4^+$ T-cells from tumor-bearing mice (10). These interesting and important observations seem to provide a plausible explanation for the functional deficit seen in human TIL and open a way for testing the hypothesis that this deficit is related either to structural changes in the TCR, to altered protein tyrosine kinase pathways or both.

An understanding of the mechanisms through which tumor subverts immune cells is particularly important for immunotherapy of cancer and, especially, adoptive immunotherapy with human TIL. These cells have been considered to be a preferred source of antitumor effector cells for therapy (11). However, their very proximity to the tumor suggests that the deficit in a signal-transducing pathway might be greater in TIL than peripheral blood lymphocytes. While exogenous IL2 alone or in combination with other cytokines seems to be capable of reversing the proliferative defect of TIL, it remains unclear whether the reversal is complete or whether all TIL are equally responsive to cytokines. If TIL prove to be deficient in a signal-transducing pathway, their use for therapy makes little sense, until we learn how to correct this deficit. The newly described insights into regulation of the signals mediated via the CD3-TCR complex (12) should be helpful in this respect. The possibility exists that with a better definition of the pathways involved, *in vivo* correction of the deficit might become feasible, *e.g.*, through a local delivery of appropriate signaling molecules or antagonists of tumor-derived immunosuppressive factors.

Dr. Alexander's paper coming in the wake of Ochoa's findings brings the issue of immune defects in patients with cancer into sharp focus. Although the nature of immune defects in human TIL remains unresolved, it is likely that Ochoa's elegant experiments in mice will serve as a model for studies with human TIL. Such studies are crucial for the future development of new strategies in cancer immunotherapy.

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Received 4/20/93; accepted 9/30/93.

[1] No Reply received.

[2] The abbreviations used are: TIL, tumor-infiltrating lymphocytes; TCR, T-cell receptor; IL2, interleukin 2.