Cytokine Dysregulation in Invasive Cervical Carcinoma and Other Human Neoplasias: Time to Consider the TH1/TH2 Paradigm

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Tumor immunology has evolved in parallel with the immunology of infectious diseases and has attempted to reproduce the successes obtained in the prevention and cure of infections by directing the immune system to attack tumor antigens. However, this objective has not yet been reached. The lack of success has been analyzed in depth and mainly attributed to the fact that neoplastic cells may be weakly immunogenic. Failure has led to questioning the importance of tumor-specific immune responses in controlling disease progression and has raised doubts about the value of immune response-based therapy in clinical oncology. Tumor-specific immune responses are nevertheless evident in tumor-bearing patients as shown by the following observations: 1) The tumor mass is frequently infiltrated with mononuclear cells; 2) tumor-specific cytotoxic T lymphocytes (CTLs) are present in patients with cancer, as are natural killer (NK) cells; and 3) an altered pattern of expression of major histocompatibility complex (MHC) class I and class II molecules is observed on the surface of tumor cells [reviewed in (1)]. Numerous mechanisms have been postulated in an attempt to understand the failure of the immune system to control or impede tumor growth. These mechanisms include the following possibilities: 1) Some tumors could be poorly immunogenic, and/or MHC expression could be down-regulated; 2) antitumor immunity could select immune response-resistant tumor cells; 3) antigens can be shed by the tumor, bind to tumor-specific lymphocytes, and prevent the recognition of tumors by such lymphocytes; and 4) tumor cells could be tolerogenic either because they do not express costimulatory molecules or because they do not produce cytokines [reviewed in (1)].

With regard to cytokine production profiles, it has been realized that qualitative as well as quantitative alterations in cytokine production can result in complex and severe impairments of immune function. Qualitative analysis of the immune response has been facilitated by the TH1/TH2 model of immune regulation (2). Because the immune responses of patients are not limited to CD4+ T cells, the model was expanded to include a functional definition of type 1 and type 2 cytokines (3). Thus, type 1 cytokines (i.e., those involved in the T helper 1 [TH1] immune response: interleukins 2, 12, and 15 [IL-2, IL-12, and IL-15, respectively] and interferon gamma [IFN γ]) are those that mainly induce cell-mediated immunity; in contrast, type 2 cytokines (i.e., those involved in the T helper 2 [TH2] immune response: interleukins 4, 5, 6, 10, and 13 [IL-4, IL-5, IL-6, IL-10, and IL-13, respectively]) predominantly stimulate humoral immunity (3). This model has recently been used to analyze a number of infectious and inflammatory diseases in humans. In all these diseases, impairment of the immune response was shown to be secondary to alteration not only in the quantity but also mainly in the quality of cytokine produced and, thus, in the activation of inefficacious effector mechanisms (4). Alterations in type 1 and type 2 cytokine profiles have been analyzed in human neoplastic diseases and have been observed to be present in a plethora of different human diseases. Thus, production of type 2 cytokines, and in particular IL-10 production, was reported to be abnormally elevated in human neoplasia, including bronchogenic carcinomas (5,6), renal cell cancers (7,8), basal and squamous cell carcinomas (9), lymphomas (10), gliomas (11), melanomas (12,13), pancreatic and gastric adenocarcinomas (14), and human papillomavirus (HPV)-associated cervical intraepithelial neoplasia (15). A concomitant reduction in type 1 cytokines has been reported in patients with many of these same tumors. Thus, similar to what has been observed in infectious and inflammatory diseases (4), human neoplastic diseases are frequently associated with dysregulation of the equilibrium between the production of certain type 1 and type 2 cytokines.

Why could such impairment be deleterious in permitting the development and growth of tumors? Type 1 cytokines exert potent antitumor effects, as summarized by the following observations. First, IL-12 is a potent activator of cellular immunity, has antitumor and antimetastatic activities against several murine tumors, and up-regulates IFN γ production (16,17). Second, IL-2, IL-12, and IFN γ activate CTL- and NK-mediated cytolytic functions associated with effective antitumor defense mechanisms (1). Third, IL-2 induces the transformation of NK cells into lymphokine-activated killer cells (17). Fourth, IL-12

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inhibits angiogenesis induced in vivo by human tumor cell lines (18). Fifth, IFN γ enhances the presentation of antigenic peptides to TH lymphocytes (19). Sixth, IFN γ directly inhibits the growth of cervical carcinoma cell lines (20). In contrast, type 2 cytokines (IL-10 in particular) were shown to down-modulate tumor-specific immune response by 1) directly suppressing IFN γ and IL-12 production, thereby preventing the activation of CTLs and NK cells; 2) reducing MHC expression on the surface of tumor cells, thus preventing the optimal expression of binary complexes formed by tumor antigen in association with MHC molecules on the surface of such cells (21); and 3) inhibiting tumor antigen presentation by antigen-presenting cells (22).

These data all point to the possibility that tumor growth could be associated with cytokine-induced qualitative alterations in the immune response. Based on the above findings, the next logical question of whether tumor growth is favored by an imbalance in cytokine production has now been addressed by Tartour et al. (23) in this issue of the Journal. Tartour et al. analyzed the association of prognosis with intratumor expression of IFN γ messenger RNA (mRNA) in biopsy specimens of primary cervical lesions from patients with invasive cervical carcinoma. They showed that poor prognosis and tumor recurrence were associated with detection of a low number of IFN γ mRNA copies in tumor biopsy specimens. These results support the line of research pursued by these authors, who previously showed that an abnormally elevated concentration of IL-6 (a type 2 cytokine) is associated with poor prognosis in patients with renal or cervical carcinoma (24) as well as in those with metastatic melanoma (25). These results [in analogy with the observations made in the study of other intracellular infectious diseases, e.g., leprosy and acquired immunodeficiency virus (AIDS) (3)] lend further support to the idea that tumor growth may indeed be favored by cytokine imbalance, as was suggested by the following observations: 1) Type 1/type 2 imbalance (augmented IL-4; reduced IFN γ) is detected in splenic T cells of mice bearing renal cell carcinoma (26); IFN γ gradually decreases in the progression of such carcinoma (26), and a reversion to a type 1 cytokine pattern is observed in successfully treated mice (26); 2) extended and aggressive HPV infection of the portio is associated with defective type 1 cytokine and augmented type 2 cytokine production (15); and 3) TH responses to HPV antigens (a classical type 1-stimulated immune response) decrease with increasing disease severity (27); these TH responses are associated with clearance of HPV infection and regression of cervical intraepithelial carcinoma (28); and CTL lines raised against HPV epitopes can eradicate established HPV-induced tumors in mice (29).

What interpretations and generalizations can be made from these observations? First, it is noteworthy that striking similarities are observed in the basic immunologic defects that favor the development and progression of infectious, inflammatory, and neoplastic conditions that are etiologically unrelated. Qualitative impairment of the immune response, exemplified by alterations in type 1-to-type 2 cytokine production, could be the primum movens permitting pathologic disease to develop. The second consideration is that, if therapeutic efforts continue to focus exclusively on treating the consequences of immune impairment (antitumor therapy is aimed at reducing the tumor mass; the goal of anti-HIV therapy is to reduce viral load and eliminate the virus), such efforts will continue to result in limited disease control, at best (30).

References

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262 EDITORIAL

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