Tumor-Associated Macrophages as Targets for Cancer Therapy

Larry M. Wahl, Hynda K. Kleinman

Tumor-associated macrophages (TAMs) originate in the circulation and are recruited to the tumor site by specific tumor-derived attractants such as monocyte chemotactic protein-1 (1,2). By use of several mechanisms, TAMs bind to the tumor cells via glycoproteins, sugars, and phospholipids and become localized at the tumor–host tissue interface (2,3). Unlike macrophages that are involved in inflammation, TAMs proliferate at the tumor site. Although macrophages have the potential to mediate tumor cytotoxicity and to stimulate antitumor lymphocytes, the tumor cells can not only block the host’s defense program but also can benefit from the activities of the TAMs. In some cases, tumor-derived molecules actually redirect TAM activities to promote tumor survival and growth. Many tumor-derived factors—including interleukin (IL)-4, -6, and -10; transforming growth factor-β1 (TGF-β1); prostaglandin E2; and macrophage colony-stimulating factor—reduce the cytotoxic activity of the TAMs (4,5). TGF-β1 has also been shown to increase urokinase expression in TAMs (6). The strategic location of the TAMs also allows them to have a number of important additional effects on tumor cells. TAMs produce growth factors, including IL-1 and platelet-derived growth factor, which may directly promote tumor growth (1). Proteases secreted by TAMs degrade the surrounding tissue and could facilitate tumor cell expansion and invasion. Last, TAMs secrete factors that promote angiogenesis, including vascular endothelial growth factor, a protein that further supports the growth and spread of tumors. Thus, TAMs can either directly or indirectly contribute to tumor survival, growth, and metastasis and these cells could be a potential target for antitumor therapy. Possible strategies that involve TAMs include reducing the number of host macrophages and/or increasing the cells’ tumoricidal activity.

In the report by Joseph and Isaacs (7), factors that reduce the number of TAMs were tested for their effects on tumor growth. These pharmacologic agents included Linomide®, thalidomide, pentoxifylline, and genistein. Linomide caused the greatest reduction of tumor volume in the Dunning R-3327 MAT-Lu rat prostate cancer model. The findings from this study, although preliminary, suggest that Linomide may suppress tumor progression by elevating the levels of plasminogen activator inhibitor type 2 (PAI-2). No association with the levels of tumor necrosis factor-α, an angiogenesis-promoting cytokine, or granulocyte–macrophage colony-stimulating factor, a cytokine that stimulates the production of PAI-2 by macrophages, was observed. As the authors indicate, Linomide may exert its tumor-suppressing activity through several additional mechanisms. One avenue for future research will be to determine the effect of Linomide on the production by TAMs of other cytokines, such as IL-12 and IL-18. The production of IL-12 by activated macrophages serves to enhance immune function by shifting CD4+ T cells toward the Th1 subset, which secrete IL-2 and interferon γ (IFN γ). IL-12 inhibition of angiogenesis and tumor progression has, in large part, been attributed to its induction of IFN γ, which in turn stimulates the production of interferon-inducible protein 10 (IP-10) and monokine induced by IFN γ (MIG) (8–11). IP-10 and MIG are members of the CXC branch of the chemokine superfamily (12), and have been shown to have angiostatic activity (13). IL-18 (14), also identified as interferon γ-inducing factor (15), is—like IL-12—produced by activated macrophages and stimulates the release of IFN γ (16). Similar to IL-12, IL-18 inhibits angiogenesis through its stimulation of IFN γ, thus resulting in a systemic antitumor effect (17). Moreover, IL-12 and IL-18 act synergistically to induce murine tumor regression through the inhibition of angiogenesis (17). It also appears that IL-12, IFN γ, and possibly IL-18 may inhibit tumor growth by inducing tumor cells to generate antiangiogenic activity through, as yet, unknown factors (18). Thus, it is important to determine the effect of Linomide on the production of these cytokines by TAMs. If Linomide inhibits IL-12 and IL-18 due to its immunosuppressive properties, protocols in which these cytokines and Linomide are combined would be worth pursuing.

The levels of activities of two families of proteases, the matrix metalloproteinases and the urokinesins, associate positively with tumor malignancy and are also important in angiogenesis (19–22). Likewise, naturally occurring tissue inhibitors of metalloproteinases, TIMPs, have been found in various experimental systems to reduce tumor growth, metastasis, and angiogenesis (20). For example, Marimastat, a broad spectrum metalloproteinase inhibitor, is one of several inhibitors currently in clinical trials as an anticancer agent. While natural and synthetic metalloproteinase inhibitors reduce tumor growth and angiogenesis, the naturally occurring inhibitor of plasminogen activation, plasminogen activation inhibitor type 1 (PAI-1) appears to increase tumor growth by mechanisms beyond its protease-inhibition activity (23). Mice deficient in PAI-1 do not exhibit local tumor cell invasion or tumor vascularization, but when PAI-1 is given systemically, these activities are restored. In con-

Affiliations of authors: L. M. Wahl (Immunopathology Section), H. K. Kleinman (Craniofacial Developmental Biology and Regeneration Branch), National Institute of Dental Research, Bethesda, MD.

Correspondence to: Hynda K. Kleinman, Ph.D., National Institutes of Health, Bldg. 30, Rm. 433, Bethesda, MD 20892 (e-mail: kleinman@yoda.nidr.nih.gov).
contrast, the antitumor effects of the other naturally occurring plasminogen activator inhibitor, PAI-2, have been documented in a variety of cancers (24–26). There is a positive association between PAI-2 levels, reduced metastases, and increased survival. The finding by Joseph and Isaacs of increased PAI-2 after Linomide treatment may explain the antitumor effects of this drug. While the data do not show a dose response, the increased PAI-2 levels appear to be the only factor that is associated with the reduction in tumor burden. These data possibly point to a new mechanism of Linomide action and further define PAI-2 as an important modulator of tumor growth and angiogenesis. The direct effects of PAI-2 and Linomide on these processes require further documentation at this time. These future studies should also be accompanied by the examination of the effect of Linomide on macrophage production of matrix metalloproteinases as well as TIMP-2, an important protease inhibitor and suppressor of tumor growth and angiogenesis.

REFERENCES