China Gastric Cancer Research Highlight

Fatal attraction: tumor recruitment of myeloid-derived suppressor cells is mediated by IL-17-producing CD8$^+$ T cells

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Abstract: The interaction between tumor tissue and the host immune system is critical to tumor development. These interactions are regulated through a variety of immune cells and cytokines. IL-17 is a proinflammatory cytokine produced by Th17 and Tc17 cells that affects the development of cancer. However, the role of IL-17 in influencing tumor growth or in enhancing anti-tumor immunity is somewhat controversial. Zhuang *et al.* (Gastroenterology 2012, 143:951) elucidated that the IL-17 produced by Tc17 cells plays an important role in the pathogenesis of gastric cancer. Based on the findings of Zhuang *et al.* and other studies in the literature, we propose a model involving complex interactions between Tc17 cells, regulatory T cells, monocytes, tumor cells, myeloid-derived suppressor cells, and cytotoxic T lymphocytes within the tumor microenvironment.

Key Words: IL-17; myeloid-derived suppressor cells; regulatory T cells; Tc17

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The tumor microenvironment comprises immune cells, tumor cells, stromal cells, and the extracellular matrix. This microenvironment is the key location for neoplastic progression, nurturing the proliferation, survival, and migration of tumor cells. Although a relationship between inflammation and cancer has been appreciated for several decades, researchers have not elucidated a complete picture for the complex networks in the tumor microenvironment. Recently, in an article in the journal *Gastroenterology* (1), Zhuang *et al.* provided compelling evidence that IL-17-producing CD8$^+$ T cells play an important role in the pathogenesis of gastric cancer. They proposed a model of cross-talk between the host immune system and tumor cells leading to IL-17-producing CD8$^+$ T cell development and myeloid-derived suppressor cell-mediated immunosuppression.

IL-17-producing CD8$^+$ T cells were first characterized by Liu *et al.* (2) as a distinct subset of CD8$^+$ T cells that are fundamentally different from canonical cytotoxic T lymphocytes (Tc). Because of their low levels of cytotoxicity, the IL-17-producing CD8$^+$ T cell subset was initially designated as T noncytotoxic 17 (Tnc17) (2). Several independent research groups have also reported that IL-17-producing CD8$^+$ T cells have negative or low cytolytic activity and markers (3-5). To maintain a comparative convention with cytotoxic T lymphocytes, Tc1 or Tc2, these IL-17-producing CD8$^+$ T cells are now termed Tc17 cells. Tc1 cells are well known to primarily secrete IFN-γ and kill their tumor targets by either perforin- or Fas-mediated mechanisms, whereas Tc2 cells secrete IL-4, IL-5, IL-6, and IL-10 and kill their tumor targets predominantly through the perforin pathway (6). In contrast, Tc17 cells secrete IL-17 and have fewer cytotoxic effector functions due to diminished levels of the T-box transcription factor Eomesodermin, IFN-γ, and the cytolytic molecule granzyme B (4).

Tc17 cells have been detected in a variety of tumors (1,4,7-13), autoimmune diseases (14-16), and infections (3,17). Such cells are believed to be involved in enhancing protection against viral infection (3,17) and antitumor immunity (10,11). Direct evidence from a study using

adoptive transfer to identify the role of Tc17 cells in a B16 melanoma model demonstrated that Tc17 cells exhibit antitumor immunity and reduce tumor growth (11,12). However, an increasing body of work also indicates that Tc17 cells accumulate with disease progression (7-10) or promote tumor progression due to the low expression of perforin, granzyme B, and IFN-γ (4,7).

Cytokines in the tumor microenvironment play a crucial role in tumor growth and survival. TGF-β, IL-6, and prostaglandin E2 levels have been shown to be elevated in the malignant effusions of cancer patients (18). TGF-β and IL-6 appear to be essential for the induction of IL-17-producing T cells (2,19). In addition, prostaglandin E2 has been shown to induce IL-23 production (20,21), and IL-23 is important for IL-17-producing T cell survival and expansion (19). A tumor microenvironment with these cytokines will favor the differentiation of IL-17-producing T cells. Notably, Zhuang *et al*. demonstrated that a set of key cytokines (IL-6, IL-1β, and IL-23) derived from tumor-associated monocytes plays an essential role in the induction of Tc17 cells (1). Consistent with the findings of Kuang *et al*. (8), tumor-activated monocytes also have been shown to secrete IL-6, IL-1β, and IL-23 to trigger the expansion of Tc17 cells in hepatocellular carcinoma (HCC). Altogether, these results suggest that cytokines present in the microenvironments of a variety of tumors encourage the development of IL-17-producing T cells.

Zhuang *et al*. found IL-17-producing $CD8^+$ T cells to be enriched at tumor sites in gastric cancer patients (1). A comprehensive analysis indicated that the percentage of IL-17-producing $CD8^+$ T cells increased significantly as the gastric cancer progressed, and this percentage was associated with overall survival time. In addition, these intratumoral IL-17-producing $CD8^+$ T cells expressed less IFN-γ, IL-4, IL-10, and IL-9. These results suggest that the IL-17-producing $CD8^+$ T subset in gastric cancer is neither the Tc1 nor the Tc2 subset and can be categorized as the Tc17 subset. Further characterization of Tc17 cells revealed that they express minimal amounts of perforin, granzyme B, FoxP3, or programmed death 1 receptor. These characteristics imply that the main role of Tc17 cells is likely to be the secretion of IL-17 rather than the direct execution of effector functions such as cytotoxicity or immunosuppression.

If Tc17 cells do not have a direct effector function, what is the role of the IL-17 secreted by Tc17 cells? The most important finding in the Zhuang *et al*. (1) study is the identification of a downstream mechanism for IL-17. In particular, IL-17 stimulates tumor cells to secrete CXCL12, which may recruit myeloid-derived suppressor cells to the tumor microenvironment and promote tumor progression in gastric cancer. In fact, the role of IL-17 in cancer development is still paradoxical (22). However, the study by Zhuang *et al*. strongly supports the view that the interaction of monocytes and tumor cells creates a favorable environment for Tc17 development (1); the IL-17 secreted by Tc17 then attracts myeloid-derived suppressor cells to foster immune privilege in gastric cancer. When the cytotoxic $CD8^+$ T cell is no longer a killer cell but a traitor, the consequence is tumor growth.

Regulatory T cells play a significant role in suppressing anti-tumor immunity, and their interaction with Tc17 cannot be ignored. Tsai *et al*. demonstrated that the presence of regulatory T cells and the consumption of IL-2 maintains or promotes Tc17 cell differentiation (13). These results suggest a beneficial effect of regulatory T cells for Tc17. What is the possibility that Tc17 are 'inflammatory' regulatory cells? Kryczek *et al*. identified a population of IL-17+ regulatory T cells that express both IL-17 and FoxP3 in ulcerative colitis and colon cancer carcinoma (23). They suggested that this cell population plays a role in chronic inflammatory environments. Zhuang *et al*. (1) also examined whether such intratumoral Tc17 cells expressed the conventional markers of regulatory T cells and observed these Tc17 cells to lack markers including perforin, granzyme B, programmed death 1 receptor, and FoxP3. These results indicate that the main role of these cells is likely to be the production of IL-17 rather than a direct effector function.

Taking these results together and synthesizing the recent findings from several research groups, we propose a model of a cancer immunoediting mechanism involving Tc17 cells, regulatory T cells, tumor cells, monocytes, myeloid-derived suppressor cells, cytotoxic T lymphocytes and their associated cytokines, and other mediators (*Figure 1*). Dead or dying tumor cells activate monocytes and create a unique microenvironment containing TGF-β, IL-6, and IL-1β, which induces naive $CD8^+$ T cells to differentiate into Tc17 cells. Prostaglandin E2 and IL-23 thereby contribute to the survival and expansion of such Tc17 cells. Regulatory T cells, which consume IL-2, maintain the presence of the Tc17 cells. The IL-17 secreted by these Tc17 cells (Th17 may also contribute to the production of IL-17) stimulates tumor cells to release CXCL12. Consequently, CXCR4-bearing myeloid-derived suppressor cells migrate to the tumors. The recruited myeloid-derived suppressor

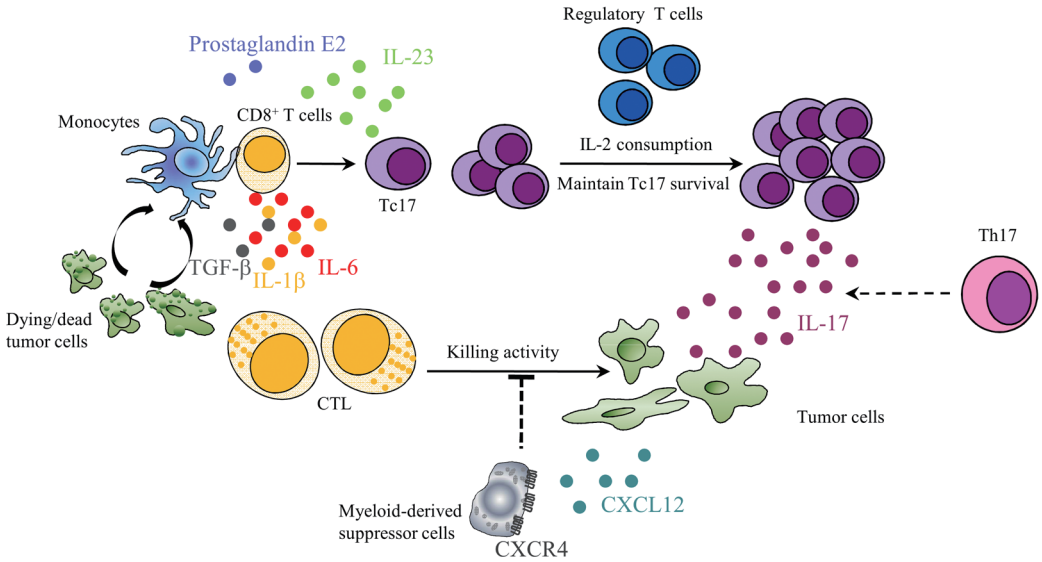

Figure 1 A proposed cancer immunoediting mechanism mediated via Tc17. Dead or dying tumor cells activate monocytes and create a unique microenvironment containing TGF-β, IL-6, and IL-1β, which induces naive $CD8^+$ T cells to differentiate into Tc17 cells. Prostaglandin E2 and IL-23 thereby contribute to the survival and expansion of such Tc17 cells. Regulatory T cells, which consume IL-2, maintain the presence of the Tc17 cells. IL-17, which is secreted by these Tc17 cells (Th17 may also contribute to the production of IL-17), stimulates tumor cells to release CXCL12. Consequently, CXCR4-bearing myeloid-derived suppressor cells migrate to the tumors. The recruited myeloid-derived suppressor cells exert their immunosuppressive function and inhibit cytotoxic T lymphocyte killing activity

cells exert their immunosuppressive function and inhibit cytotoxic T lymphocyte killing activity. As a consequence, tumor growth progresses unimpeded.

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