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Dual role of immunomodulation by anticancer chemotherapy

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Abstract

The anticancer efficacy of conventional chemotherapies seems to be due, in part, to augmentation of the host immune reactivity. However, a new study reveals that two common chemotherapeutic agents, gemcitabine and 5-fluorouracil, can also activate immune regulatory cells, which stimulates the emergence of protumorigenic cytokines via inflammasome pathways, limiting the antitumor efficacy of the drugs (pages 57–64).

Conventional chemotherapy as a major treatment modality for advanced cancer, although not often curative, can achieve high response rates. Recent evidence suggests that this therapeutic efficacy relies in part on the capacity of chemotherapeutic agents to interact with the immune system[1]. Chemotherapy is thought to induce various tumor cell death modalities, which can lead to the release of tumor-derived antigens that can be engulfed and processed by immune cells, resulting in their activation and induction of antitumor immunity. For instance, treatment with Taxol (paclitaxel), an antimicrotubule agent, in advanced ovarian cancer was shown to upregulate the cytotoxic T cell function that has been attributed to Taxol-induced tumor apoptosis and the accessibility of tumor antigens[2].

Chemotherapeutic agents may also interfere with the molecular and cellular mechanisms responsible for tumor-induced immune tolerance. Human colon carcinoma cells treated with 5-fluorouracil, an antimetabolite agent, became more sensitive to lysis by tumor-specific cytotoxic T cells[3]. Cytotoxic drugs such as cisplatin, doxorubicin, mitomycin C and camptothecin also primed tumor cells to elimination by immune cells, including natural killer or cytotoxic T lymphocytes[4]. Many chemotherapeutic agents can directly stimulate functional activity of antigen-presenting cells such as dendritic cells[1].

Beneficial immunomodulatory effects of chemotherapy might also be associated with lymphodepletion, that is, elimination of immunosuppressive regulatory T cells and poorly functional antitumor T lymphocytes. For example, a DNA-alkylating agent such as cyclophosphamide might act via the depletion of regulatory T cells[5]. Gemcitabine, an antime-tabolite agent, attenuates the immunosuppressive properties of the tumor

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microenvironment by eliminating myeloid-derived suppressor cells (MDSCs)[6], which are considered a key immunosuppressive regulatory cell subset in many types of cancer.

In this issue of *Nature Medicine*, Bruchard *et al.*[7] show that the effect of gemcitabine on MDSCs is more complex than simple induction of MDSC cell death. Gemcitabine and 5-fluorouracil seem to activate the proapoptotic protein Bax (Bcl2-associated X protein) in MDSCs, which leads to lysosome destabilization and the subsequent release of cathepsin B, an enzymatic lysosomal protease (Fig. 1). Cathepsin B activates the NLRP3 (NACHT, LRR and PYD domains-containing protein 3, also known as cryopyrin) inflammasome, resulting in the production and release of immunomodulatory cytokines through caspase-1 activation. This process, which is dissociated from chemotherapy-induced MDSC cell death and occurs before it, reduces anti-cancer immunity and promotes tumor growth.

Caspase-1, formerly called interleukin-1β (IL-1β)-converting enzyme, is involved in mediating programmed cell death by promoting the cleavage of crucial intracellular proteins upon apoptopic activation; however, it seems to be also uniquely involved in the inflammatory response by cleaving the precursors of IL-1β, IL-18 and IL-33. The discovery of caspase-1 and its importance in IL-1β secretion was recognized 20 years ago when it was shown that caspase-1 inhibitors reduced secretion of active IL-1β from monocytes[8]. Since that time, studies on caspase-1–deficient mice have confirmed its role in controlling inflammation. Bruchard *et al.*[7] found that MDSCs from tumor-bearing mice treated with gemcitabine or 5-fluorouracil secreted IL-1β in a caspase-1– dependent manner (Fig. 1). *In vivo*, IL-1β was found in the serum of tumor-bearing mice after 5-fluorouracil administration. MDSC depletion before 5-fluorouracil treatment prevented IL-1β elevation, suggesting that its production was mainly due to MDSCs.

Although IL-1β is known to be involved in the regulation of inflammation, immunity and hemopoiesis, its role in carcinogenesis is also established. IL-1β recruits different myeloid regulatory cells, including MDSCs, that promote tumor-mediated immunosuppression, supports malignant cell invasiveness and metastasis and may also confer a proliferative advantage to cancerous cells through autocrine mechanisms. The authors showed that chemotherapy-induced IL-1β expression by MDSCs markedly decreased the antitumor effect of chemotherapy in lymphoma, melanoma, mammary cancer and lung cancer animal models[7]. Administration of the soluble IL-1 receptor antagonist anakinra enhanced the antitumor efficacy of 5-fluorouracil, leading to tumor regression in about 50% of treated animals.

How does IL-1β affect the antitumor immunity? The protumorigenic effect of MDSC-derived IL-1β seemed to be mediated by T cell polarization toward a T helper type 17 (T_H17) phenotype, as $CD4^+$ T cell depletion enhanced the antitumor effect of 5-fluorouracil in an IL-1–dependent manner[7]. *Ex vivo* studies confirmed that gemcitabine- and 5-fluorouracil–induced MDSC-mediated T cell differentiation into IL-17–producing $CD4^+$ T cells was dependent on cathepsin B, Nlrp3, caspase-1 and IL-1. Notably, the antitumor effect of 5-fluorouracil was significantly stronger in IL-17–deficient mice, confirming that IL-1β–dependent T_H17 cell polarization of CD4 T cells limits the therapeutic efficacy of 5-fluorouracil.

Interestingly, optimal anticancer responses during chemotherapy with the anthracycline doxorubicin have been shown to require the IL-17–producing γδ T cell population, whose activation depended on IL-1β produced by dendritic cells in response to dying tumor cells[9]. Conventional helper $CD4^+$ αβ T cells failed to produce IL-17 after doxorubicin chemotherapy. Thus, it seems that different chemotherapeutic agents may use similar molecular pathways affecting the immune responses, but, by targeting different cell subsets, these agents may cause even opposite effects on the anti-tumor immunity. As Bruchard *et al.*[7] did not observe differential effects of 5-fluorouracil on monocytic and granulocytic MDSC subsets and reported no effects on dendritic cells and macrophages, it will be interesting to determine how the combination of 5-fluorouracil and doxorubicin targets IL-1β–producing myeloid cells and IL-17–expressing T cell subsets and what the resulting antitumor immune response would be.

T_H17 cells are a unique subset of T cells that have important roles in the pathogenesis of inflammatory and autoimmune diseases. Although many studies have demonstrated potent antitumor functions for IL-17 and T_H17 cells[10], T_H17 cells have also been shown to play an active part in tumor pathogenesis[11]. For instance, IL-17R deficiency increased $CD8^+$ T cell numbers and reduced MDSC tumor infiltration, whereas systemic administration of IL-17 in lymphoma- or melanoma-bearing mice promoted tumor growth, enhanced the number of MDSCs and reduced $CD8^+$ T cell tumor infiltration[12]. It is established that IL-17 is a proangiogenic factor that acts on endothelial, stromal and cancerous cells and elicits vessel formation to induce tumor vascularization and promote tumor growth[13]. Therefore, IL-17 is a pleiotropic cytokine with both pro- and antitumorigenic effects, depending on the tumor environment context, degree of inflammation and stability of heterogeneous IL-17–producing cells. More studies are required to understand how chemotherapy affects different sources of IL-17 and how these effects alter the development of pro- and antitumor responses.

The results of Bruchard *et al.*[7] studies have revealed that gemcitabine and 5-fluorouracil, in addition to depleting immunosuppressive MDSCs, also induce the release of cathepsin B from lysosomes and the activation of the NLRP3 inflammasome and caspase-1, which causes IL-1β secretion from MDSCs, resulting in IL-17 production by T cells and promotion of tumor growth. The most important strength of the Bruchard *et al.*[7] study is in providing, probably for the first time, a mechanism-based, rather than empirical, rationale for combination of specific chemotherapeutic agents with specific immunotherapeutic approaches for cancer treatment—IL-1 receptor antagonist was shown to enhance the antitumor effect of 5-fluorouracil. This finding has clear clinical implications because it suggests that only certain chemotherapeutic and immunomodulatory agents should be combined for increasing the efficacy of anticancer therapy.

Understanding the immunological events occurring in both animal models and patients undergoing chemotherapy should guide decisions about the development of appropriate combinations and scheduling for the integration of chemotherapy with immunotherapy. The study by Bruchard *et al.*[7] represents an excellent example of how comprehensive exploration of the interplay between chemotherapeutic drugs, tumor cell death and immune cells can improve diagnostic, prognostic and therapeutic management of cancer.

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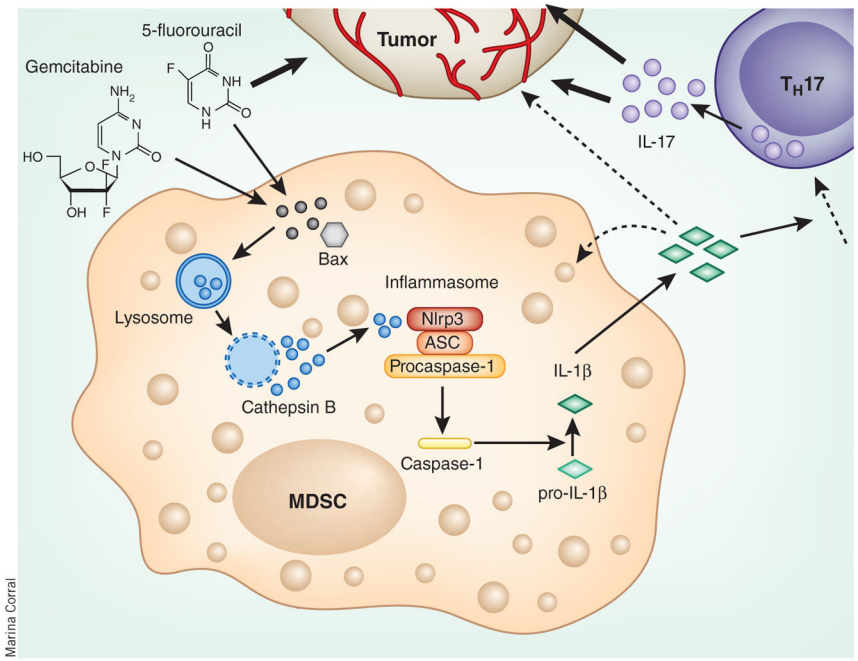

Figure 1.

Molecular and cellular pathways of chemotherapy-induced, immune cell–mediated inhibition of antitumor efficacy. The common chemotherapeutic agents gemcitabine and 5-fluorouracil activate a signaling cascade in MDSCs that leads to secretion of IL-1β. Upon cell entry, the drugs are metabolized by kinase-mediated phosphorylation, and the metabolites bind their molecular targets, including the proapoptotic protein Bax, leading to destabilization and disruption of lysosomes and release of cathepsin B. Cathepsin B directly interacts with the leucine-rich-repeat (LRR) domain of NLRP3 inflammasome (which comprises the NLR protein Nlrp3, the adaptor ASC and pro-caspase-1) causing its activation. After its assembly, the inflammasome converts pro-caspase-1 into an active enzyme, which then cleaves pro-IL-1β, a precursor of IL-1β, resulting in the formation of a biologically active cytokine that is released from MDSCs. IL-1β is an important regulator of $CD4^+$ T helper cell polarization and drives the emergence of T_H17 subsets, which produce IL-17. Soluble IL-1β may also stimulate MDSC expansion and attraction. Pleiotropic cytokine IL-17 plays an active part in tumor pathogenesis and progression by enhancing the emergence of immunosuppressor MDSCs to the tumor site, reducing tumor infiltration by cytotoxic T cells and inducing intratumor neoangiogenesis. ASC, apoptosis-associated speck-like protein containing a CARD domain.