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Modulating CD27 signaling to treat cancer

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CD27 signaling can either improve T-cell function or lead to T-cell dysfunction, depending on the duration and conditions of receptor ligation. Recent studies have shown that modulating the CD70-CD27 interaction is an attractive strategy to treat solid tumors and also to directly target leukemia stem cells.

CD27 belongs to the tumor necrosis factor receptor (TNFR) superfamily and acts as a co-stimulatory molecule, enhancing T- and B-cell responses. Upon ligation by CD70, CD27 activates NFκB, promotes cell survival, enhances T- and B-cell receptor-mediated proliferative signals, and increases effector functions.[1] As a consequence, CD27 signaling increases the protective cytotoxic T lymphocyte (CTL) response and supports memory formation upon immunization with the influenza virus. However, CD27 signaling has also been reported to lead to T-cell dysfunction in some situations, most likely depending on the duration and timing of CD70 expression.[2] This view was supported by the observation that persistent signaling via CD27 in *Cd70* transgenic mice leads to exhaustion of the T-cell pool, immunodeficiency and death due to opportunistic infections. Therefore, under physiological conditions, the expression of CD70 is tightly regulated as it is only transiently expressed on activated T and B cells, on subsets of professional antigen-presenting dendritic cells (DCs) and natural killer (NK) cells.[1] In contrast, constitutive expression of CD70 has been documented during chronic viral diseases.[3] In chronic lymphocytic choriomeningitis virus (LCMV) infection in mice, continuous CD27 signaling increases the production of pro-inflammatory cytokines, mainly by $CD4^+$ T cells, resulting in the destruction of secondary lymphoid organ architecture. This leads to the suppression of antiviral immunity and to the establishment of persistent infection. In addition, persistent CD27 signaling induces CTL dysfunction directly. In line with these observations, blocking the CD70-CD27 interaction has been shown to eradicate chronic infection with LCMV.[3]

Comparable to chronic viral infections, constitutive expression of CD70 has been documented in cancer.[4] Experimental evidence in tumor models supports the view that the CD70-CD27 interaction improves antitumor immunity. *Cd70* transgenic mice mount more efficient T-cell responses against injected tumor cells than control animals, and are able to control a challenge with a lethal dose of EL4 lymphoma cells.[5] Accordingly, the administration of an agonistic anti-CD27 antibody has been shown to protect against intravenous (i.v.) injection of two different lymphoma cell lines and to delay the growth of B16 melanoma injected subcutaneously (s.c.) or i.v. seven days earlier.[6,7] In line with these earlier findings, we recently documented that CD27 signaling increases effector $CD4^+$ and $CD8^+$ T-cell function after s.c. injection of a fibrosarcoma cell line.[8] However, the injection of a lymphoma or cancer cell line s.c. or i.v. allows for a rapid spread of tumor cells to secondary lymphoid organs and, therefore, the induction of tumor-specific CTLs (**Fig. 1A**). In contrast, during oncogenesis, cancer cells normally develop outside lymphoid organs and reach them only at a late stage of tumor progression.[9] This allows solid tumors to grow before tumor-specific T-cell responses are induced either directly by tumor cells in lymphoid organs or by cross-priming as mediated by professional antigen-presenting cells. Therefore, the pathophysiological role of CD27 signaling in the microenvironment of a solid tumor can be most adequately analyzed after transplantation of solid tumor fragments. This setting more realistically mimics a situation with spontaneous tumor growth that is characterized by the persistence of tumor antigens outside secondary lymphoid organs and a tumor microenvironment maintaining a chronic, smoldering inflammation that inhibits adaptive T-cell responses. The immunosuppressive microenvironment is sustained by regulatory cytokines such as transforming growth factor β (TGFβ) or interleukin (IL)-10 as well as by tumor-infiltrating M2 macrophages and regulatory T cells (Tregs). Surprisingly, after transplantation of solid tumor fragments, the CD70-CD27 interaction appears to promote tumor growth.[8] We could demonstrate that in tumor-bearing mice, CD70 is only expressed on tumor-infiltrating lymphocytes (TILs) and that CD27 signaling increases the frequency of intratumoral Tregs (**Fig. 1B**). As documented earlier for effector $CD4^+$ and $CD8^+$ T cells, CD27 signaling directly reduced

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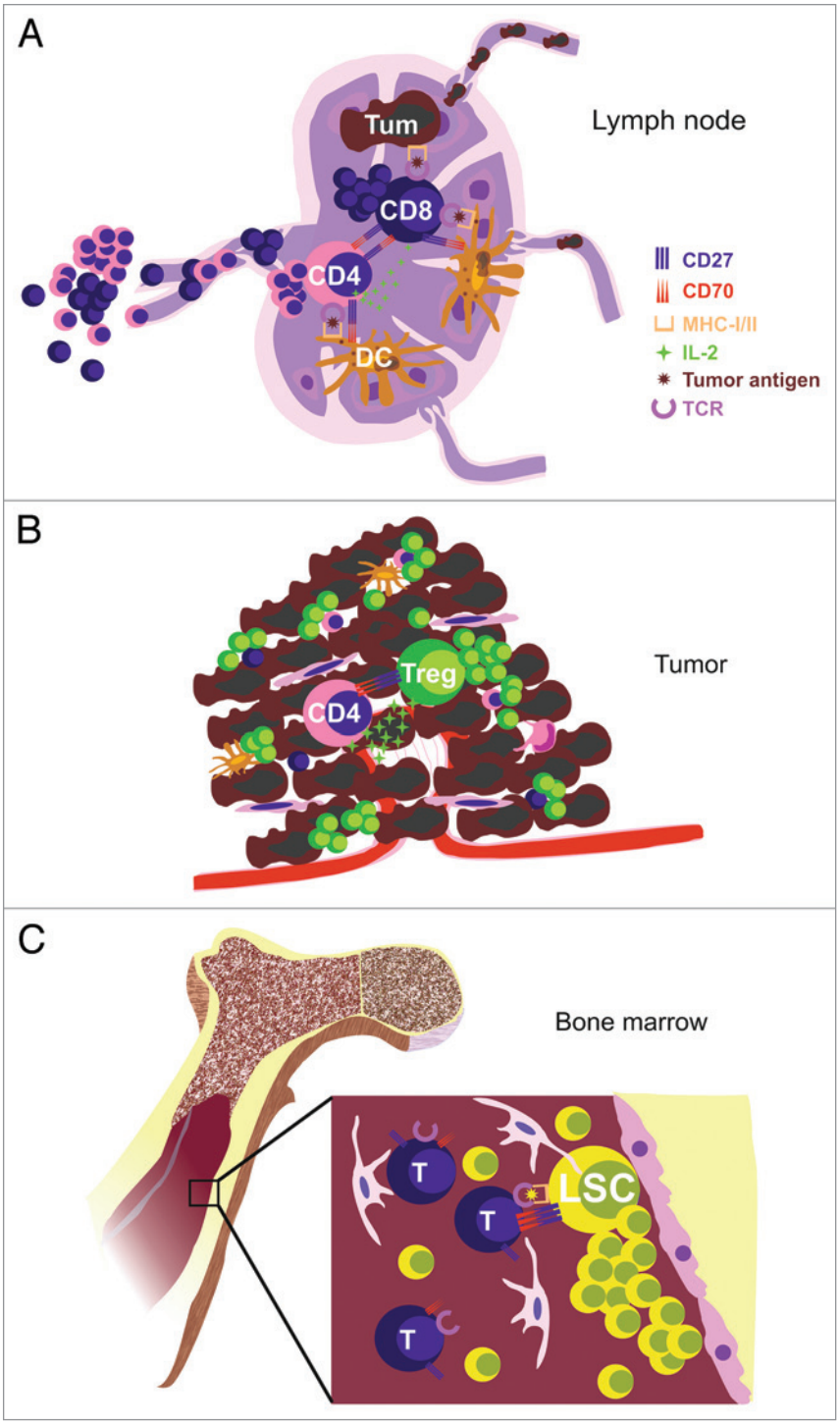

Figure 1. Distinct effects of CD27 signaling in cancer. (**A**) In the pro-inflammatory environment of secondary lymphoid organs, CD27 signaling supports the generation of tumor-specific effector T cells (Teffs). (**B**) In contrast, in the chronically inflamed tumor microenvironment, CD70-expressing $CD4^+$ tumor-infiltrating lymphocytes (TILs) secrete IL-2 and trigger CD27 on regulatory T cells (Tregs), leading to enhanced Treg survival and Treg accumulation. (**C**) In chronic myeloid leukemia, bone marrow-infiltrating T cells express CD70 that interacts with CD27 on leukemia stem cells (LSCs), resulting in LSC proliferation and leukemia progression. DC, dendritic cell; MHC, major histocompatibility complex; TCR, T cell receptor; Tum, tumor cell.

apoptosis of Tregs in vivo. However, CD27 signaling on effector T cells (Teffs) also increased the production of IL-2, a factor that is crucial for the survival of Tregs. As a consequence, the therapeutic blockade of CD27 signaling reduced the frequency of Tregs and delayed tumor progression.[8] As CD27 ligation enhances the survival of T cells, it increases the number of Teffs in a pro-inflammatory environment (e.g., in lymph nodes) but similarly increases the number of intratumoral Tregs. The effect on tumor control depends on the relative contribution of Teffs vs. Tregs. After injection of tumor cells as a single suspension, CD27 triggering mainly increases the number of Teffs. Vice versa, in an established solid tumor, CD70 ligation is provided preferentially in the tumor microenvironment and predominantly increases the number of Tregs.

In our tumor models, CD70 was only expressed by TILs but not by tumor cells themselves. However, certain human tumors such as brain cancers, renal cell carcinomas and some lymphomas have been shown to express CD70. Expression of CD70 on tumor cells seems to be a negative prognostic factor and, in agreement with our hypothesis, has been correlated with an increased accumulation of Tregs.[4]

CD27 is also expressed on malignant cells in some types of non-Hodgkin lymphoma. In addition, we recently showed that leukemia stem and progenitor cells, but not differentiated leukemia-originating granulocytes, express CD27.[10] CD27 signaling on chronic myeloid leukemia stem cells (LSCs) increased LSC proliferation and differentiation, resulting in leukemia progression (**Fig. 1C**). The therapeutic blockade of the CD70-CD27 interaction inhibited LSC proliferation and delayed the disease. Importantly, CD27 signal transduction in LSCs did not proceed via the NFκB signaling pathway as documented in T cells, but along the Wnt pathway via TRAF-2 and TNIK/β-catenin.

In summary, due to the tightly regulated expression of CD70, blocking the CD70-CD27 interaction is an attractive approach to improve antitumor immunity and may even be used to directly target cancer stem cells in some situations. However, a tailored stimulation or blocking regimen is necessary to achieve an optimal tumor control in each situation.

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