B-cell receptor signaling and CD40 ligand-independent T cell help cooperate in Helicobacter-induced MALT lymphomagenesis

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Gastric B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) develops in the context of chronic inflammation caused by Helicobacter pylori infection. Most pathophysiological features of the early stages of MALT lymphomagenesis can be reproduced by experimental infection of BALB/c mice with Helicobacter species. We have previously shown that MALT lymphomas are infiltrated by T-helper cell type 2-polarized T cells and that human and murine tumor B cells carry polyreactive surface immunoglobulins. Using the murine model of the disease, in this study we show that explanted tumor B cells proliferate upon stimulation with the same panel of self and foreign antigens that are recognized by their surface antibodies. Tumor cell proliferation is strongly enhanced by the presence of intratumoral CD4(+) T cells in a CD40/CD40L-independent manner. A large proportion of tumor-infiltrating CD4(+) T cells are CD25(+)FoxP3(+) regulatory T cells (Tregs) with highly suppressive activity, which are recruited by the tumor cells through secretion of the Treg-attracting chemokines CCL17 and CCL22. The depletion of CD25(+) cells was as efficient as CD4(+) T cell depletion in blocking tumor growth in vitro and in vivo. In conclusion, our data suggest that B-cell receptor-derived signals cooperate with T-helper cell signals in driving the progression of MALT lymphoma, providing an explanation for the unique antigen dependence of this B-cell malignancy.
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