CCL17 suppresses macrophage anti-tumor activity to promote tumor growth

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Tumor-associated macrophages (TAMs) suppress anti-tumor immunity and promote tumor progression by producing cytokines, chemokines, growth factors and metabolites. Repolarization of TAMs into macrophages with anti-tumor activity is a promising strategy to overcome immunosuppression in the tumor microenvironment and resistance to immunotherapy being a major problem for example in colorectal cancer. The chemokine CCL17 is constitutively expressed in dendritic cells and is induced by cytokines in M2-polarized macrophages. CCL17 induces chemotaxis of CCR4-expressing regulatory and effector T cells, but its function in the tumor microenvironment has not been studied.
Using the CCL17-eGFP-knock-in mouse line we investigated the role of this chemokine in murine models of colon cancer and its paracrine function in macrophages.
CCL17 deficient mice developed fewer tumors in a colitis-induced colon tumor model and showed reduced tumor growth in the subcutaneous syngeneic MC38 colon cancer model. The observed effects in both models were conserved in Rag1 deficient mice, indicating T- and B-cell independent mechanisms. Intriguingly, the frequencies and phenotypes of TAM subsets were significantly altered in the absence of CCL17: CD206+ TAMs were less abundant correlating with reduced Arginase-1 and increased TNF-α expression in the tumors. CCL17 deficient bone marrow derived macrophages (BMDM) showed a similar phenotype and significantly inhibited MC38 tumor growth in vivo. These results highlight the central role of TAMs for the control of tumor growth in CCL17 deficient mice. Stimulated CCL17 deficient BMDMs showed increased NFkB signalling and were more potent in inhibiting tumor cell growth in vitro compared to CCL17-competent BMDMs.
Thus, beyond its role as a classical chemokine and TAM marker, CCL17 also regulates TAM function and is a potential target for TAM repolarization.

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