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Interleukin-33/ST2 axis promotes breast cancer growth and metastases by facilitating intratumoral accumulation of immunosuppressive and innate lymphoid cells

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The role of IL-33/ST2 pathway in antitumor immunity is unclear. Using 4T1 breast cancer model we demonstrate time-dependent increase of endogenous IL-33 at both the mRNA and protein levels in primary tumors and metastatic lungs during cancer progression. Administration of IL-33 accelerated tumor growth and development of lung and liver metastases, which was associated with increased intratumoral accumulation of $CD11b^+Gr\text{-}1^+$ TGF-$\beta1^+$ myeloid-derived suppressor cells (MDSCs) that expressed IL-13α1R, IL-13-producing $Lin^-Sca\text{-}1^+ST2^+$ innate lymphoid cells (ILCs) and $CD4^+Foxp3^+ST2^+IL\text{-}10^+$ Tregs compared to untreated mice. Higher incidence of monocytic *vs*. granulocytic MDSCs and plasmocytoid *vs*. conventional dendritic cells (DCs) was present in mammary tumors of IL-33-treated mice. Intratumoral $NKp46^+NKG2D^+$ and $NKp46^+FasL^+$ cells were markedly reduced after IL-33 treatment, while phosphate-buffered saline-treated ST2-deficient mice had increased frequencies of these tumoricidal natural killer (NK) cells compared to untreated wild-type mice. IL-33 promoted intratumoral cell proliferation and neovascularization, which was attenuated in the absence of ST2. Tumor-bearing mice given IL-33 had increased percentages of splenic MDSCs, $Lin^-Sca\text{-}1^+$ ILCs, IL-10-expressing $CD11c^+$ DCs and alternatively activated M2 macrophages and higher circulating levels of IL-10 and IL-13. A significantly reduced NK cell, but not $CD8^+$ T-cell cytotoxicity in IL-33-treated mice was observed and the mammary tumor progression was not affected when $CD8^+$ T cells were *in vivo* depleted. We show a previously unrecognized role for IL-33 in promoting breast cancer progression through increased intratumoral accumulation of immunosuppressive cells and by diminishing innate antitumor immunity. Therefore, IL-33 may be considered as an important mediator in the regulation of breast cancer progression.

Interleukin-33 (IL-33), a member of the IL-1 family, is a multifunctional cytokine released upon necrotic cell death, which secretion can also be induced in live cells under biomechanical stress conditions.[1] IL-33 is primarily expressed in nonhematopoietic cells including fibroblasts, epithelial cells and endothelial cells, but is also present in cells of hematopoietic origin, particularly in macrophages and dendritic cells (DCs).[2,3] IL-33 regulates innate and acquired immunity[3–6] through binding to membrane-bound ST2 molecule (ST2L) of the IL-33R complex expressed on murine and human Th2 cells, mast cells, natural killer (NK) cells, myeloid cells and DCs.[3,7] IL-33 promotes Th2 immune response[2,3] and polarization of alternatively activated M2 macrophages.[8] Newly identified Type 2 innate lymphoid cells (ILC2) produce large amounts of IL-5 and IL-13 in response to IL-33 in the intestine,[9] adipose tissue[10] and lungs.[11] However, IL-33 could activate Th1, NK, NKT and $CD8^+$ T cells under certain pathophysiological conditions. IL-33 has a dual role in inflammatory disorders; it has protective effects in obesity, atherosclerosis and experimental fulminant hepatitis[12–14] and proinflammatory role in asthma and antigen-induced arthritis.[15,16] In addition, IL-33 promoted expansion of suppressive myeloid cells and $CD4^+Foxp3^+$ $ST2L^+$ regulatory T cells (Tregs) in cardiac allograft model.[17]

The role of IL-33 in cancer is unclear. We have reported that deletion of the ST2 gene favors innate and acquired antitumor immunity in 4T1 mammary carcinoma model.[18] However, the most recent study demonstrates antitumor effects of IL-33 showing attenuated tumor metastasis in the B16 melanoma and Lewis lung carcinoma metastatic models in mice with transgenic expression of IL-33.[19] Increased circulating IL-33 levels observed in gastric cancer patients may

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