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IL-33/ST2 axis in innate and acquired immunity to tumors

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Interleukin-33, a ligand for ST2/T1, has an important role in allergy, autoimmunity and inflammation. The role of IL-33/ST2 axis in cancer is not elucidated. Using metastatic breast cancer model we provide evidence that lack of ST2 signaling led to reduced tumor growth and metastasis and enhanced anti-tumor immunity.

Interleukin-33 (IL-33) is a member of the IL-1 family of cytokines and was identified as a natural ligand for ST2/T1, an orphan receptor in the IL-1R family. IL-33 is produced as a biologically active full-length molecule and may function as an alarmin, when released after cell damage or as nuclear IL-33 that reduces NF-kB–triggered proinflammatory genes expression in non–IL-33 receptor–mediated manner. Outside the cell, IL-33 acts as a classical cytokine by binding to its receptor, membrane bound ST2L (now designated IL-33Rα-chain) and IL-1R accessory protein (IL-1RAp), leading to NFkB and MAPK activation.[1,2] These findings highlight the complex role of this multifunctional cytokine.

IL-33 is constitutively expressed in endothelial and epithelial cells of mucous membranes, keratinocytes and fibroblasts. ST2 (IL-33 receptor) exists as a full-length membrane molecule (ST2L) and as soluble, decoy variant ST2 (sST2). ST2L is expressed by T cells (Th2, but not Th1 cells), NK and NKT cells, mast cells, monocytes, dendritic cells and granulocytes. ST2L was shown to be stably and selectively expressed by murine Th2,[3] and also human Th2 cells and NKT-like cells.[4] IL-33 polarizes naïve T cells to produce IL-4, IL-5 and IL-13 (Th2-associated cytokines), potently induces pro-inflammatory cytokines and chemokines by mast cells and eosinophils and amplifies polarization of alternatively activated M2 macrophages. Although ST2 (and IL-33) may act primarily through a Th2-pathway, IL-33/ST2 axis can also promote Th1-type responses depending on the local conditions, for example, the presence or absence of IL-12.[1]

IL-33 participates in many diseases with dual, proinflammatory or protective roles depending on the cellular and cytokine context.[1] Namely, IL-33 has a protective role during progression of atherosclerosis, obesity, TNF-α mediated bone loss and experimental fulminant hepatitis. We have demonstrated that ST2 deficiency led to more severe Con-A induced hepatitis associated with increased numbers of TNF-α, IFN-γ and IL-17 producing liver infiltrating mononuclear cells and increased systemic pro-inflammatory cytokines. Moreover, pre-treatment with IL-33 prior to Con-A injection led to attenuation of liver injury and increased liver $CD4^+Foxp3^+$ and IL-4 producing CD4+ T cells.[5]

IL-33 is believed to be mainly involved in allergen-specific Th2-type inflammation and administration of neutralizing antibodies against ST2 or IL-33 was shown to attenuate eosinophilic pulmonary inflammation in the murine model of allergic asthma.[6] We have shown that deletion of ST2 enhanced disease induction or severity in several experimental models of organ specific autoimmunity. Thus, ST2−/− mice were more sensitive to induction of multiple low dose streptozotocin diabetes,[7] experimental allergic encephalomyelitis (EAE) (unpublished data) and Con-A induced fulminant hepatitis,[5] the findings that suggest anti-inflammatory effects of IL-33/ST2 axis. Indeed, Anthony et al.[8] have elegantly shown that intravenous immunoglobulins (ivIgs) suppress inflammation through novel Th2 pathway that involves IL-33. IgG crystallizable fragments stimulate the induction of IL-33 by dendritic cells and macrophages which promote IL-4 producing basophils that increase the expression of the inhibitory Fc receptor FcγRIIB on effector macrophages.

The data on the role of IL-33/ST2 axis in cancer are lacking. We provided the evidence that deletion of ST2 signaling may enhance anti-tumor immune response in a murine model of metastatic 4T1 breast carcinoma.[9] We showed delayed appearance of palpable primary tumor, slower tumor growth and reduced number and size of metastatic colonies in lungs and livers in ST2−/− mice. ST2 deletion led to increased absolute numbers of CD4+ and CD8+ T cells in local lymph nodes and spleens after tumor challenge. ST2−/− splenocytes, NK and CD8+ T cells had enhanced cytotoxicity with higher frequency of activated, NKp46+ $CD107a^+$ cells NK cells both constitutively and after tumor inoculation. ST2−/− mice had increased numbers of IFN-γ expressing NK cells, while undetectable IL-10 producing NK cells.

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