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ST2 deletion enhances innate and acquired immunity to murine mammary carcinoma

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ST2 is a member of the IL-1 receptor family and IL-33 was recently identified as its natural ligand. The IL-33/ST2 pathway regulates Th1/Th2 immune responses in autoimmune and inflammatory conditions, but the role of ST2 signaling in tumor growth and metastasis has not been investigated. We aimed to investigate whether ST2 gene deletion affects tumor appearance, growth, and metastasis, and antitumor immunity in an experimental metastatic breast cancer model. Deletion of ST2 in BALB/c mice bearing mammary carcinoma attenuated tumor growth and metastasis, which was accompanied by increased serum levels of IL-17, IFN-γ, and TNF-α and decreased IL-4. Tumor-bearing ST2$^{-/-}$ mice had significantly higher percentages of activated CD27^{high}CD11b^{high} NK cells, CD69^{+} and KLRG^{-} NK cells and higher cytotoxic activity of splenocytes, NK cells, and CD8^{+} T cells in vitro. A significantly higher number of NK cells expressing IFN-γ were found in ST2$^{-/-}$ mice compared with WT recipients. In vivo depletion of CD8^{+} or NK cells revealed a key role for NK cells in enhanced antitumor immunity in ST2$^{-/-}$ mice. We report for the first time that suppressed breast cancer progression and metastasis in mice lacking ST2 corresponds mainly with enhanced cytotoxic activity of NK cells, and increased systemic Th1/Th17 cytokines.

Key words: Cytotoxicity · 4T1 mouse breast cancer · NK cells · ST2 · Th1/Th2 cells

Introduction

The *ST2* gene, also called T1, DER-4 and Fit-1, is a member of the interleukin-1 receptor (IL-1R) family that was originally identified in oncogene- or serum-stimulated fibroblasts [1, 2]. Differential mRNA processing within the *ST2* gene generates three isoforms: a soluble form (sST2), a membrane-anchored form (ST2L), and a variant ST2 (ST2V) which is localized on the plasma membrane and predominantly expressed in the stomach, small intestine, and colon [3–5]. Soluble ST2 is found in embryonic tissues, and is secreted by macrophages, Th2 cells, and fibroblasts [1–5]. ST2L is an orphan receptor expressed on a variety of cell types including mast cells, basophils, eosinophils, dendritic cells, macrophages, Th2 cells, and NK and iNKT cells [3–15]. A member of the IL-1 family, IL-33, previously known as a nuclear factor in high endothelial venules, has been recently described as a natural ligand for ST2L [16]. IL-33 is expressed in multiple tissues and has been shown to induce the secretion of both proinflammatory and anti-inflammatory cytokines from mast cells, eosinophils, and Th2 lymphocytes [3, 17]. IL-33 is a potent activator of Th2 cells and has a dual role in disease [3, 16]. IL-33/ST2 signaling has a protective role against parasites, in

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