Deletion of IL-33R attenuates VEGF expression and enhances necrosis in mammary carcinoma

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ABSTRACT

Interleukin-33 (IL-33)/IL-33 receptor (IL-33R, ST2) signaling pathway promotes mammary cancer growth and metastasis by inhibiting anti-tumor immunity. However, the role of IL-33/IL-33R axis in neoangiogenesis and tumor necrosis is not elucidated. Therefore, the aim of this study was to investigate the role of IL-33/IL-33R axis in mammary tumor necrosis. Deletion of IL-33R (ST2) gene in BALB/c mice enhanced tumor necrosis and attenuated tumor growth in 4T1 breast cancer model, which was associated with markedly decreased expression of vascular endothelial growth factor (VEGF) and IL-33 in mammary tumor cells. We next analyzed IL-33, IL-33R and VEGF expression and microvascular density (MVD) in breast tumors from 40 female patients with absent or present tumor necrosis. We found significantly higher expression of IL-33, IL-33R and VEGF in breast cancer tissues with absent tumor necrosis. Both, IL-33 and IL-33R expression correlated with VEGF expression in tumor cells. Further, VEGF expression positively correlated with MVD in perinecrotic zone. Taking together, our data indicate that IL-33/IL-33R pathway is critically involved in mammary tumor growth by facilitating expression of pro-angiogenic VEGF in tumor cells and attenuating tumor necrosis. These data add an unidentified mechanism by which IL-33/IL-33R axis facilitates tumor growth.

INTRODUCTION

Breast cancer is the second most common cancer in the world and the most frequent cancer among women [1]. Although multidisciplinary approach improved overall survival and quality of life of breast cancer patients, identification of new prognostic markers and therapeutic modalities are needed.

Chronic ischemia followed by hypoxia can cause necrosis of tumor cells [2]. Tumor necrosis is associated with natural history of mammary carcinoma [3, 4]. Some studies have shown that tumor necrosis is a poor prognostic factor which is associated with high tumor proliferative activity [5, 6]. However, recent studies suggest that tumor necrosis could be beneficial as a favorable outcome of anti-cancer therapy and may enhance anti-tumor immune response [4, 7-12].

Necrotic cells release immunoregulatory cytokines, including interleukin-33 (IL-33) [13, 14], a member of the interleukin-1 (IL-1) family of cytokines [15]. IL-33 is dual function protein with roles as a nuclear factor and a classical cytokine [16] and functions as a prototypic „alarmin" [17]. As a cytokine, IL-33 binds a heterodimeric receptor complex comprised of IL-1 receptor-like 1 (IL1RL1; also referred to as ST2L) and its coreceptor, IL-1 receptor accessory protein (IL- 1RAcp), which regulates inflammatory gene expression through NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and MAPK (Mitogen-activated protein kinases) signaling pathways [18, 19]. IL-33 participates in many immune disorders exerting pro-, or anti-inflammatory roles [20-25].

The role of IL-33 in cancer is still unclear. We have