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Review

Mast cells in breast cancer angiogenesis

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ABSTRACT

Mast cells, accumulate in the stroma surrounding certain tumors and take part to the inflammatory reaction occurring at the periphery of the tumor. Mast cell-secreted angiogenic cytokines facilitate tumor vascularization not only by a direct effect but also by stimulating other inflammatory cells of the tumor microenvironment to release other angiogenic mediators. An increased number of mast cells have been demonstrated in angiogenesis associated with solid tumors, including breast cancer. Mast cells might act as a new target for the adjuvant treatment of breast cancer through the selective inhibition of angiogenesis, tissue remodeling and tumor promoting molecules, allowing the secretion of cytotoxic cytokines and preventing mast cell mediated immune-suppression.

1. Mast cells and tumor growth

Since the early studies of Paul Ehrlich, who first made the observation that they often are localized around tumor masses (Ehrlich, 2013), mast cells have been associated either with resistance or susceptibility to tumors. Mast cells, indeed, accumulate in the stroma surrounding certain tumors and take part to the inflammatory reaction occurring at the periphery of the tumor. Mast cells can participate to tumor rejection by producing molecules like interleukin-1, -4, -6 (IL-1, IL-4, IL-6) and tumor necrosis factor alpha (TNF-α) that kill tumor cells. By contrast, mast cells can benefit the tumor growth by promoting expansion of its vascular supply, proteinase-mediated degradation of the tumor extracellular matrix and immunosuppression (Ribatti and Crivellato, 2011).

Moreover, mast cells synthesize and release potent angiogenic cytokines, including vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), the serine proteases tryptase and chymase, IL-8, transforming growth factor beta (TGF-β), TNF-α and nerve growth factor (NGF) (Ribatti and Crivellato, 2011). Mast cell-secreted molecules facilitate tumor vascularization not only by a direct angiogenic effect but also by stimulating other inflammatory cells of the tumor microenvironment to release angiogenic mediators and cytokines as well as extracellular matrix-degrading proteases. In fact, within the developing tumor environment, mast cells do not act alone. They are recruited early in tumor development and play a critical role in both angiogenesis and tissue remodeling. As tumor growth progresses, mast cells recruit eosinophils and neutrophils and activate T and B cell immune responses (Kinet, 2007). In addition, mast cell-derived metalloproteinases (MMPs) degrade the interstitial tumor stroma and hence release extracellular matrix-bound angiogenic factors.

The tyrosine kinase receptor Kit (CD117) is upregulated in tumor cells and mutations in c-kit are associated to the development of gastrointestinal stromal tumor (GIST), in mastocytosis and mast cell

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Table 1
Human tumors in which mast cell infiltration correlates with angiogenesis.

Haemangioma
Haemangioblastoma
Lymphomas
Multiple myeloma
Myelodysplastic syndrome
B-cell chronic lymphocytic leukemia
Breast cancer
Colon-rectal cancer
Uterine cervix cancer
Melanoma
Pulmonary adenocarcinoma

Fig. 1. Tryptase ia angiogenic in vivo in the chick embryo chorioallantoic membrane (CAM) assay. Macroscopic pictures of CAM at day 12 of incubation, treated with tryptase. Note the presence of numerous blood vessels converging toward the implant. Modified from (Ribatti et al., 2011).

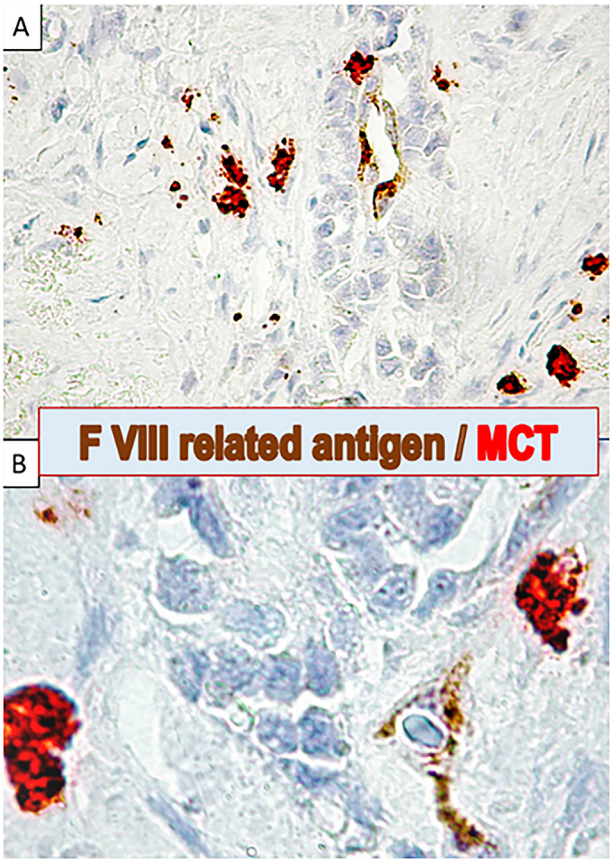

Fig. 2. Mast cells involvement in angiogenesis in breast cancer. Degranulated and non-degranulated mast cells around a tumor area including three Factor VIII (FVIII)-related antigen positive endothelial cells (A). A small blood vessel close to two tryptase-positive mast cells (MCT) (B). Original magnification. A, ×160; B, ×400.

leukemia (Pittoni et al., 2011a). Mast cells express high levels of c-kit and stem cell factor (SCF), the ligand for kit, is involved in mast cell development, survival, migration, and function (Ribatti and Crivellato, 2014). SCF enhances tumor growth through increased production of VEGF, IL-6, IL-10, and TNF-α (Huang et al., 2008a),

An increased number of mast cells have been demonstrated in angiogenesis associated with vascular, haematological and solid tumors (Table 1) in which mast cell accumulation correlate with increased neovascularization, mast cell VEGF and FGF-2 expression, tumor aggressiveness and poor prognosis.

2. Mast cells and angiogenesis in breast cancer

Breast cancer remains one of the most controversial malignancy. Despite of the fact that conventional histopathology was completed with an accurate molecular stratification, no significant improvement in prognosis and patient survival has been reported. These evidences suggested that additional factors influencing malignant progression would exist.

Increased vascularity has been shown in mammary ductal carcinoma in situ (Fig. 1) (Lee et al., 1997; Guidi et al., 1994), and highly vascular tumors have an increased risk of metastasis and a poorer prognosis (Weidner et al., 1992; Horak et al., 1992). Moreover, tumor microvascular density, p53 expression, tumor size, and peritumoral lymphatic vessel invasion are prognostic markers in node-negative breast carcinoma (Gasparini et al., 1994).

Lee et al. (Lee et al., 1998) have demonstrated that VEGF mRNA and protein were expressed significantly more in invasive ductal than in invasive lobular carcinoma. Moreover, VEGF predicts local relapse and survival in radiotherapy-treated node-negative breast cancer (Linderholm et al., 1999), and increased VEGF expression has been linked to a poorer response to systemic treatments and radiotherapy (Foekens et al., 2001). The elevated expression of VEGF in breast cancer has been associated to inactivation of tumor suppressor p53 (Linderholm et al., 2009), and the identification of VEGF receptors (VEGFRs) on tumor cells themselves revealed the presence of pro-tumorigenic effects of VEGF through the autocrine signaling pathway on proliferation, tumor cell survival by protection from apoptosis, cell adhesion and migration, and invasion (Perrot-Applanat and Di Benedetto, 2012; Barr et al., 2008). Finally, tumor that exhibit overexpression of HER2 also overexpress VEGF and unfavorable prognosis of untreated HER2-positive patients has been linked to an increased angiogenesis (Konecny, 2004).

Adrenomedullin plays a critical role in the cross-talk between tumor cells and mast cells, and is an important regulator of mast cell function related to tumor promotion (Zudaire et al., 2006). Adrenomedullin-producing human mast cell line HMC-1 induces in vivo angiogenesis, neutralizing anti-adrenomedullin monoclonal antibody blocks this ability, and immunohistochemical analysis has identified adrenomedullin-producing mast cells in tumor infiltrate of human breast cancer patients (Zudaire et al., 2006).

Tryptase angiogenic activity has been documented in vivo in the CAM assay (Fig. 1) (Ribatti et al., 2011). We have previously demonstrated in a series of 88 primary female breast cancer that the number of tryptase-positive mast cells, the area occupied by tryptase-positive mast cells, microvascular density and endothelial area, correlate to each other (Fig. 2) (Ranieri et al., 2009). We have also shown that microvessel counts increase in parallel with the number of tryptase-positive mast cells and their values were