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# The role of tumor-associated macrophages in breast cancer

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## ABSTRACT

Interaction of Tumor-Associated Macrophages (TAMs) with tumor cells gives insights into tumor progression and into a novel therapeutic strategy. In papillary thyroid cancer, patients with tumors containing TAMs had a better prognosis than patients without TAMs. In prostatic cancer, the reduced of total TAMs can be used as a novel prognostic marker. In melanoma maligna, high number of TAMs was statistically significant associated with poor response to treatment. In breast cancer progression, the role of TAMs is still unclear.

**Key words:** tumor-associated macrophages - breast cancer – angiogenesis - tumor progression - prognosis

## INTRODUCTION

Tumor-associated macrophages (TAMs) are heterogenous population of cells that belong to the mononuclear phagocyte systems and are derived from blood-borne monocytes that migrate into tissues where they undergo final differentiation.<sup>1</sup> In tumors development, TAMs have pleiotropic functions which can influence both in term of progression as well as in tumor regression. These differential effects of TAMs are believed to be regulated by modulation of the host immune system.<sup>2</sup> Tumor growth promotion by TAMs can be mediated by various cytokines and prostanoid that have the capacity to stimulate tumor cell growth directly and or may promote tumorigenesis indirectly through the induction of tumor vasculatures. Macrophages also have been shown to suppress many T cell and NK cell anti-tumor responses. Tumor growth reduction by TAMs can be mediated by non specific anti tumor cytotoxic mechanism or induction of specific cell lytic effects.<sup>3,4</sup>

Interaction of TAMs with tumor cells gives insights into tumor progression and into a novel

therapeutic strategy. In papillary thyroid cancer, patients with tumors containing TAMs had a better prognosis than patients without TAMs.<sup>5</sup> In prostatic cancer there were inverse relationships between number of TAM and clinical stage. The reduced of total TAMs can be a novel prognostic marker for prostatic cancer.<sup>6</sup> In melanoma maligna, high numbers of TAMs in tumor biopsies were significantly associated with poor response to treatment.<sup>7</sup>

Resembles other malignant tumors, breast cancer progression is also associated with and dependent upon neovascularization. As the tumor continues to progress, so does the degree of neovascularization. Not surprisingly, poor breast cancer prognosis has been shown to correlate with either increasing micro vascular density or production of various factors that stimulate new vessel growth.<sup>8</sup> As mentioned above, TAMs constitute a major component of the leukocytic infiltrate that have a close correlation with neovascularization, and the role of TAMs in breast cancer progression will be described.

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## DISCUSSION

### A. TAMs in generals

The monocyte develops from a pluripotent stem cell in the bone marrow under the influence of soluble hematopoietic growth factors and by physical interactions with stromal cells as well as extracellular matrix. The monoblast, which is the earliest cell committed to the monocytic lineage, differentiates via a promonocyte into a mature monocyte, which after a short period (< 24 hours), leaves the bone marrow and enters the blood stream as a quiescent (G0/G1) cell. Such monocytes may then differentiate further into resident tissue macrophages and, depending on the local microenvironment, acquire specialized phenotypic characteristics and diverse functions.<sup>9</sup>

Macrophages have a pleiotropic biological role. In the setting of tumors, TAMs have a range of functions with the capacity to affect diverse aspects of neoplastic tissues including angiogenesis and vascularisation, stroma formation and dissolution, and modulation of tumor cell growth (enhancement and inhibition). When activated, they can induce neoplastic cell death (cytotoxicity, apoptosis) and/or elicit tumor destructive reactions through alteration of the number of microvasculature.<sup>10</sup>

The number of macrophages is varies greatly (10-65%) among different tumors studied. However, the percentage of TAMs is usually maintained at a relatively stable level for a particular tumor type during transplantation into and growth in syngeneic hosts.<sup>10</sup> The infiltration of mononuclear cells is generally restricted to the stromal areas with few cells infiltrating into tumor nests and between the tumor cells themselves. This migration is mediated by chemotactic factors that induce inflammatory cells to leave the vascular compartment and egress into the surrounding areas. Some tumors, however, produce inhibitors of chemotaxis. The mechanisms modulating these processes are poorly defined.<sup>3,11</sup>

### B. TAMs and breast cancers

Breast cancers are known to contain a high proportion of infiltrating leukocytes, including TAMs. Tumor cells attract monocytes by producing chemotactic agents, including MCP-1, M-CSF, TFG- $\beta$  and undefined mediators. Tumor-derived

signals can induce both pro- and anti-tumor effector in TAMs. Depending on the signal activations and susceptibility of tumor target cells, TAM can either enhance or inhibit tumor growth. As anti-tumor effector, TAMs can mediate direct anti-tumor cytotoxicity, produce cytotoxic molecules ( $H_2O_2$ , IL-1, TNF- $\alpha$ , NO, ROI) and stimulate lymphocyte responsiveness through presentation of TAAs as well as production of immunostimulatory cytokines (eg. IL-2). On the other hand, as pro-tumor effector, TAMs produce growth factors that promote cancer cell proliferation, dissemination, enhance angiogenesis, and suppress lymphocyte responsiveness via production both of immunosuppressive cytokines (e.g. IL-10) and prostanoids.<sup>3</sup>

In breast cancer, the increase of macrophages infiltration, and macrophage-mediated angiogenesis induce the high expression of MCP-1 (monocyte chemoattractant protein-1) and VEGF (vascular endothelial growth factor). Monocyte chemoattractant protein-1 expressions in tumor cells was significantly correlated with the extent of TAM infiltration and both MCP-1 and VEGF expression have been positively correlated with TAM infiltration, angiogenesis and poor survival.<sup>12</sup> Vascular endothelial growth factor promotes the proliferation, survival and migration of endothelial cells by binding to its receptors.<sup>13</sup> The other factor responsible for increased macrophage infiltration in breast cancer is the macrophage colony-stimulating factor (CSF)-1, which is important not only for macrophage recruitment but also for tumor vascularization and progression.<sup>14</sup>

Tumor-associated macrophages also secrete proteases that degrade the extracellular matrix, for example a metalloproteinase (MMP)-9 that has emerged as an important modulator of angiogenesis and tumor development. Other proteases such as urokinase-type plasminogen activator and heparanase, release proangiogenic growth factors (e.g. FGF- $\beta$ ) that are sequestered by heparan sulphates proteoglycans in the extracellular matrix. But, MMP-9 may also have an antiangiogenic effect (at later stage) by processing the  $\alpha 3$  chain of type IV collagen to the angiogenesis inhibitor. Tumor-associated macrophages also release thrombospondin-1, interferon- $\alpha$  and interferon- $\gamma$  which are antiangiogenic. Many cytokines

(e.g. TGF- $\beta$ , IL-1b, IL-6, TNF- $\alpha$ ) are known to have pleiotropic effects, stimulating angiogenesis under certain conditions and inhibiting it under others.<sup>11</sup> It has not yet been known how the net proportion of the various proangiogenic or antiangiogenic activities of TAMs is regulated. However, the balance between angiogenesis promoting, inhibiting and modulating determine regulation the overall course of blood vessels formation.

In ductal invasive carcinoma of the breast, high levels of TAMs are associated with increased tumor angiogenesis and reduced survival.<sup>15</sup> Recent studies have indicated that in breast cancers the protumor role of TAMs is dominant and a research in a mouse model of breast cancer found that TAMs that were recruited to the tumor just before malignant conversions are essential for the angiogenic switch.<sup>16</sup> These findings establish a causal linkage to explain clinical correlation between macrophages, microvessel density and poor prognosis in breast cancers.

A research related with targeting TAMs as a novel strategy against breast cancer in murine models found that legumin-based DNA vaccine can induced a robust CD8 T cell. This condition reduced the TAMs density in tumor tissue and resulted in a marked decrease of pro-angiogenic factors released by TAMs such as FGF- $\beta$ , TNF- $\alpha$ , MMP-9 and VEGF. This in turn, led to a suppression both of tumor angiogenesis, tumor growth and metastasis.<sup>17</sup>

## CONCLUSION

The role of TAMs in breast cancer progression can either enhance or inhibit tumor growth, depending on the signal activations and susceptibility of tumor target cells. The balance between pro-angiogenic and antiangiogenic activities of TAMs determines the tumor growth and prognosis.

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