

Endothelin: Ominous Player in Breast Cancer

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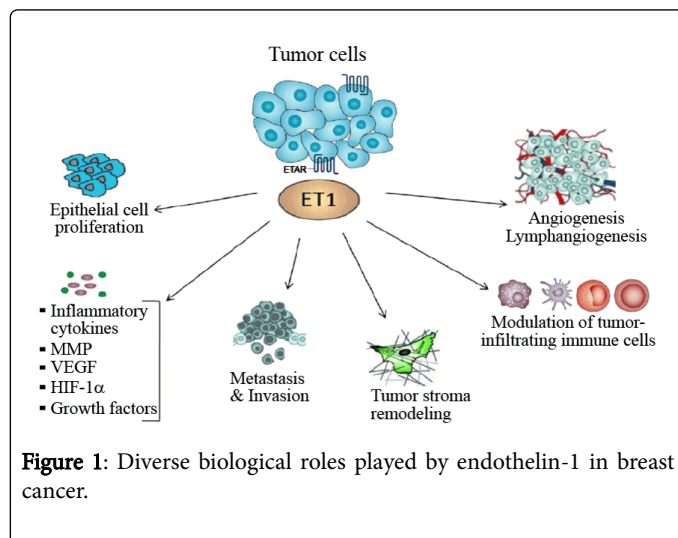
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Editorial

The function of endothelin (ET) in breast cancer is now under focus and there is a growing interest in the role of ET axis (endothelin and its receptors) in cancer. Several studies have reported a much higher expression of ET-1 among all other isoforms (ET-1, ET-2 and ET-3) in breast carcinomas than in normal breast tissue [1-3], indicating that the ET-1 system is primarily associated with breast cancer. ET-1 exerts its physiological effects via two receptors, ETA and ETB, which are G-protein-coupled transmembrane receptors found in both vascular and nonvascular tissues. Currently there are several evidences that ET-1 may modulate mitogenesis, apoptosis, angiogenesis, tumor invasion and development of metastases by exerting its autocrine or paracrine action [4,5]. The diverse biological roles played by ET-1 in breast cancer have been represented in Figure 1.



The studies of Wulfig et al, and several others have demonstrated that the level of ET production and its expression in breast tumor correlates with higher vascularity and angiogenesis [6,7]. The ET axis is associated with tumor angiogenesis by directly modulating endothelial cell proliferation, migration, invasion, protease production, and tube formation or by indirectly inducing hypoxia-inducible factor-1 α -mediated VEGF production in cancer cells [4,8-11]. ET-1 contributes to the process of angiogenesis, stimulating endothelial cell growth predominantly through ETB and inducing vascular smooth muscle cell and pericyte mitogenesis mediated through ETA [8].

The mechanism by which endothelins induce an invasive phenotype is complex and not fully understood today. It is thought to be promoted via several different mechanisms including the modulation of matrix metalloproteinase (MMP) activity, induction of pro-invasive

cytokines (TGF- β) and inhibition of anti-invasive cytokines (IL-10) by macrophages [12]. In addition to inducing invasion, ET-1 and ET-2 are also chemotactic factors for breast tumor cells and this is modulated via both endothelin receptors and a MAPK-mediated pathway [13]. ET-1 might modulate tumor stroma remodeling by acting on both ETA and ETB expressed on cancer-associated fibroblasts [14]. In turn, the tumor receives cues from the stroma, including epithelial-to-mesenchymal transition (EMT)-inducing factors and hypoxic stimuli, in response to which the tumor cells acquire invasive or stem cell-like properties. There is also evidence for involvement of the ET axis in blood perfusion of breast tumors in rodent model [15]. Blood flow to the tumor tissue was significantly increased in response to ET-1 and it was mediated through ETB [15].

A local ET-1 axis has been shown to augment the response of immune cells in the tumor microenvironment. In particular, it modulates dendritic cell function, such as increase in cell survival, cytokine production and T cell activation [14]. Moreover, ET-1 acting through receptors expressed on tumor-associated macrophages activates pro-inflammatory transcription factors and stimulates the production of inflammatory cytokines, which is a necessary step for intravasation, extravasation and metastatic colonization. Thus, ET-1 binding to its receptors elicits pleiotropic effects on tumor cells and on the host microenvironment

During the past two decades, the paradigm for cancer treatment has evolved from relatively non-specific cytotoxic agents to targeted agents due to an improved understanding of cancer pathogenesis [16]. The analysis of ET axis and in particular of ETA may improve the prediction of relapse and death and may identify patients who may profit from ETA targeted adjuvant therapy. The focus of cancer therapy targeting ET-1 to date has been to antagonize the autocrine-paracrine effects of ET-1 on tumor cells, mediated mainly by ETA. Many receptor antagonists have been developed and undergone preclinical and clinical testing [17,18]. Further research into the ET axis in breast cancer and pre-clinical trials of the receptor antagonists will provide an answer as to whether the ET receptors are a suitable therapeutic target for breast cancer.

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