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Editorial

Endothelial Progenitor Cells in Breast Cancer

Abstract

Recent evidences demonstrated the importance of bone marrow derived Endothelial Progenitor Cells (EPC), in the contribution to postnatal physiological and pathological neovascularization, and in tumor growth and angiogenesis. These cells are recruited undifferentiated, in response to systemic or chemoattractive signals, such as Vascular Endothelial Growth Factor (VEGF), they lodge in the growing or lesioned tissue and differentiate into endothelial cells in response to local stimuli and cell-cell interactions. The extent and the significance of the EPCs contribution for the growing of most tumors, including those of the breast, are still not fully defined. We analyzed the peripheral blood of breast cancer patients and found that they have circulating EPCs. We also found an association between expression of AC133+Kdr+ and VEGF plasma levels in these patients. Strategies to impair the mobilization and incorporation of EPCs into breast tumors may contribute to halt the growth of these tumors.

Introduction

Malignant transformation requires the generation of a fertile macro environment in which tumor cell proliferate, and under certain circumstances form a highly invasive and metastatic tissue [1,2].

The formation of new vessels within a tumor, angiogenesis, is dependent on proliferation and migration of endothelial cells [3]. Two possible sources of endothelial cells are (1) migration and co-option of pre-existing vascular walls endothelial cells or (2) recruitment of EPCs from the bone marrow [4].

Initial studies showed that EPCs could be identified by their expression pattern of specific cell-surface markers, which included Kinase Insert Domain Receptor (KDR) [4] and AC133 [5]. EPCs are tracked by the cell-surface molecule AC133, a five transmembrane-spanning 120 kD glycoprotein [6,7]. It has been demonstrated previously that acute elevation of VEGF levels in vascular trauma patients is the primary factor inducing mobilization of EPCs [4] and it has been widely described that VEGF is up-regulated in most tumour types including those of the breast [8]. Gill and collaborators [4], have shown previously that late-outgrowth endothelial cells differentiating from the non-adherent population of plated Peripheral Blood Mononuclear Cells (PBMNCs) represent a population of BM-derived anchorage-independent BM-derived EPCs characterized by high proliferative potential. These late-outgrowth colonies have been shown to be a characteristic of AC133+KDR+ cells [4]. There is a growing body of evidence showing that EPCs, AC133+KDR+ cells, might be implicated in the development of some tumors [9-11]. We analyzed the expression of EPC's markers in PBMNCs from breast cancer patients by RT-PCR. Our results suggest that a population of cells expressing AC133 and KDR are mobilized to the peripheral circulation in breast cancer patients. We found that 16.7 % of breast cancer patients have circulating EPCs confirmed by the expression of AC133 and KDR markers [12]. These results are in agreement with several other authors who found that EPCs are recruited during

breast cancer development [11-14]. Since VEGF plasma levels are elevated in vascular trauma patients in comparison to VEGF levels in plasma of healthy donors, we sought to evaluate the VEGF plasma levels in breast cancer patients. We and others found that VEGF plasma levels in these patients correlates with the presence of AC133+KDR+ [11,12]. Given that our observations show an increase of circulating progenitor cells in the peripheral blood of breast cancer patients, we sought to evaluate the expression of AC133 and KDR in breast tumors. For this purpose RT-PCR of frozen breast tumors and matching normal tissue was performed. We found that 88.9% of breast tumors express AC133 and KDR. In contrast, only 25.0% of the normal adjacent tissue expressed these markers [12]. To our knowledge there is no report in the literature at present addressing AC133 and KDR expression in breast tissue. The tumor specimens that did not express the EPC's markers were highly correlated with the size of the tumor (115.0 ± 4.1 ; $p=0.0004$), the tumor weight (516.0 ± 34.1 ; $p=0.0088$) and the age of the patient (69 ± 2.2 ; $p=0.0159$) [12]. These data suggest that breast tumors recruit EPCs in a very targeted and focal fashion and indicate that the tumor recruits EPCs during cancer progression and they are no longer needed when the tumor reaches a plateau of growth.

Taken together, these results show that breast cancer patients have elevated levels of VEGF and that these levels correlate with circulating AC133+KDR+ cells in these patients. Furthermore, the expression of these EPC's markers in a panel of breast tumors but not in the respective adjacent normal tissue highlights the importance of these cells as targets for breast cancer therapy. It is expected that these cells could be used as biomarkers of early diagnosis and treatment of breast cancer.

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