Endothelial progenitor cells in non-Hodgkin's lymphoma

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Tissue growth needs to be accompanied by a formation of new blood vessels, or angiogenesis. This is a complex process that requires multiple growth factors,[1] such as acidic and basic fibroblast growth factors, interleukin-8, transforming growth factors-α and –β, hepatocyte growth factor, tumor necrosis factor-α, epidermal growth factor, angiogenin, angiopoietin-1, platelet-derived growth factor and vascular endothelial growth factor. In cancer, angiogenic factors can be produced by the tumor cells themselves but also by surrounding hematopoietic cells in the tumor microenvironment, including monocytes, lymphocytes, dendritic cells, neutrophils and mast cells.[2] Both quiescent, differentiated, vascular endothelial cells and bone marrow-derived endothelial progenitor cells (EPC) contribute to angiogenesis to variable degrees.[3]

Identification of EPC

The existence of circulating EPC was first described by Asahara *et al*. in 1997 as a population of postnatal blood cells that formed an adherent layer of cells of endothelial morphology after 7 days of culture in endothelial growth medium.[4] These cells expressed several markers in common with endothelial cells such as CD34, CD31, VEGFR2 (KDR), and Tie2.[4] Further studies in mice revealed that bone marrow-derived cells naturally participate in the formation of new blood vessels in ischemic limb.[5]

EPC were later found to express other cell markers such as VE-cadherin and CD14, CD133, CD146, and CD105 (CD11b-) .[6-8] Functional evidence for the bone marrow component of circulating EPC was originally based on mice models of hematopoietic stem cell transplantation, in which EPC of the recipient were shown to originate from donor stem cells by clonal analysis.[9] In humans, it has been shown that transplanted hematopoietic stem cells can differentiate into vascular endothelial wall.[10] While CD34 positive cells comprise only about 0.1% of the total circulating white blood cell population, hematopoietic or angiogenic growth factors induce significant release of these cells from the bone marrow into the peripheral blood circulation.[4] Interestingly, the gene expression profile of EPC more closely resembled that of freshly isolated endothelial cells from tumors rather than that of cultured endothelial cells.[11]

EPC as a therapeutic tool in tissue regeneration and cancer

Circulating EPC are involved in repairing damaged vasculature and in tumor angiogenesis, thus promoting wide interest in their therapeutic potential in ischemic diseases and cancer.[6,12-14] Cancer growth is inevitably dependent of angiogenesis, and it has been shown that the number of EPC in the peripheral bloodstream is frequently elevated in patients with cancer, which at least in part can be affected by angiogenic growth factors. Interestingly, circulating EPC can be either of non-malignant cell origin or may originate from the same neoplastic clone. For example, recent reports demonstrated that a population of circulating EPC may carry identical genetic abnormalities as the primary tumor cells in patients with multiple myeloma[15] or myeloproliferative disorders,[16] suggesting that both EPC and the tumor cells may have originated from the same multipotent hemangioblast precursor cell.[15,16] The precise mechanism underlying recruitment of EPC to tumor sites remains poorly understood, but recent reports suggested the involvement of c-Kit ligand expression by endothelial cells.[17]

In this issue of the Journal,[18] Igreja *et al*. report on their studies of circulating EPC in 70 patients with non-Hodgkin's lymphoma. They showed that EPC were frequently detected in patients' blood, bone marrow, and tumor samples. The levels of circulating EPC decreased in patients achieving complete responses, but were sustained or increased in non-responding patients. Although this is one the largest studies performed on patients' samples, blood, marrow, and lymph node samples were not examined from the same patients.

So, what does this study mean? First, one should remember that the presence of circulating EPC is not always associated with malignant conditions. Healthy individuals, including pregnant women, have been reported to have detectable EPC in their blood. However, in the study reported by Igreja and colleagues, there were higher levels of EPC in patients with active lymphoma. Whether these patients are more suitable candidates for anti-angiogenesis therapy is currently unknown. Second, the presence of circulating EPC does not always correlate with a high level of incorporation of these cells into the tumor neovasculature. For example, although many patients with lung carcinoma had detectable levels of circulating EPC, only a few showed clear evidence of incorporation of these cells into the tumor blood vessels.[19] Third, although several markers have been used to describe EPC, these markers are not agreed on by all investigators, making it difficult to compare results from different studies.

Finally, in addition to the potential implication of EPC in cancer therapy, the presence of circulating EPC has been reported to confer a poor prognosis in multiple myeloma[20] and non-small cell lung cancer[19] as the level of

these cells may predict response to chemotherapy.[21] While this observation is intriguing, simpler and more reproducible predictive markers have been used. However, this observation may be further explored in selecting patients for anti-angiogenesis clinical trials.

Future issues concerning EPC

While it has been years since anti-angiogenic therapy has been introduced for the treatment of cancer, such therapy remains only marginally effective and is associated with significant potential toxicity. Characterization of tumor-associated EPC may provide clues for more specific anti-angiogenesis therapy that may selectively target tumor vasculature, thus minimizing toxicity to normal vessels. The study by Igreja and colleagues is another step in the right direction.

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Intravascular large B-cell lymphoma: the heterogeneous clinical manifestations of its classical and hemophagocytosis-related forms

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In this issue, Ferreri and the International Extranodal Lymphoma Study Group document that the clinical features of patients with intravascular lymphoma (IVL) vary based on the presence or absence of hemophagocytosis (HPC), rather than geographical region, differentiating IVL into classical and HPC-related forms. IVL is defined morphologically by the distribution of tumor cells exclusively in the lumina of blood vessels. IVL has unique clinical characteristics due to massive involvement of extranodal sites, without lymphadenopathy or leukemic manifestations, and is currently regarded as a rare entity listed in the category of diffuse large B-cell lymphomas of the World Health Organization (WHO) classification.[1] However, since