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EDITORIAL

Bone marrow vascular niche and the control of tumor growth in hematological malignancies

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Bone marrow contains hematopoietic stem cells (HSCs) and nonhematopoietic cells. HSCs are self-renewing multipotent progenitors that give rise to all types of mature blood cells, whereas the nonhematopoietic component is composed of osteoblasts/osteoclasts, endothelial cells, endothelial progenitor cells, T lymphocytes, macrophages, mast cells, fibroblasts and mesenchymal stem cells. All of these cells contribute to the formation of specialized 'niches', which are close to the marrow vasculature ('vascular niche') or to the endosteum ('osteoblast niche').[1] Depletion of either osteoblasts or endothelial cells is negatively associated with HSC survival, suggesting that both niches are important for maintaining HSC.[2,3]

The term 'vascular niche' indicates a site rich in blood vessels where endothelial cells and mural cells, such as pericytes and smooth muscle cells, create a microenvironment that affects the behavior of several stem and progenitor cells.[4] The vessel wall serves as an independent niche for the recruitment of endothelial progenitor cells, mesenchymal stem cells and HSCs. Moreover, 'vascular niche' in the adult bone marrow is defined as a place for stem cell mobilization or proliferation and differentiation.

The activation by angiogenic factors and inflammatory cytokines switch the 'vascular niche' to promote tumor growth. In other words, in certain tumors, the selective expression of angiocrine factors by endothelial cells of the 'vascular niche' might be responsible of tumor growth (Table 1).[5]

Within the bone marrow, HSCs interact with sinusoidal endothelial cells and undergo self-renewal or differentiation.[3,6] In turn, endothelial cells promote the growth of leukemic cells and gliomas.[7,8]

The side population (SP) is a cell fraction functioning as stem cell population in hematopoiesis, which is labeled at low levels with a fluorescent dye that binds DNA.[9] Wulf *et al.*[10] reported that SP cells have been identified in the bone marrow of patients with acute myeloid leukemia (AML), and that transplanted SP cells derived from AML patients could generate AML-like disease in immunodeficient mice, suggesting that the presence of SP cells in the bone marrow 'vascular niche' might explain the ability of leukemic cells to escape antileukemic drugs.

It has been shown that leukemia stem cells expressing primitive cell surface markers, such as $CD34^+$ and $CD38^-$ can repopulate nonobese diabetes/severe combined immunodeficiency mice regardless of the acute AML type.[11,12] Ninomiya *et al.*[13] have analyzed the spatial localization of transplanted human leukemic cells into immunodeficient mice and showed that these cells were initially localized on the surface of osteoblasts in the epiphysial region, and expanded to the inner vascular and diaphysial regions within 4 weeks. Moreover, after high-dose administration of cytosine-1-D-arabinofuranoside, residual leukemic cells were localized in the perivascular endothelium and in contact with the trabecular endosteum, suggesting that leukemic cells receive antiapototic signals not only from osteoblasts but also from the vascular endothelium.

Identifying the mechanisms involved in the generation of inductive signals released by endothelial cells in the 'vascular niche' that promote tumor growth or favor the development of resistance and escape to conventional chemotherapy, might provide new insights into the development of new therapeutic strategies in hematological malignancies.

Table 1 Angiogrine factors produced by the vascular niche

Angiopoietin 2 (Ang-2)
Bone morphogenetic protein-2 and -4 (BMP-2 and BMP-4, respectively)
Brain-derived nerve growth factor (BDNGF)
Endothelin-1 (ET-1)
Fibroblast growth factor-2 (FGF-2)
Granulocyte-colony stimulating factor (G-CSF)
Granulocyte macrophage-colony stimulating factor (GM-CSF)
Insulin-like growth factor (IGF)
Interleukin-6 and -8 (IL-6 and IL-8, respectively)
Laminin α4
Monocyte chemotactic protein-1 (MCP-1)
Nitric oxide (NO)
Pigmented-derived epithelial factor (PEDF)
Placental growth factor (PlGF)
Platelet-derived growth factor B (PDGFB)
Stromal cell-derived factor-1 (SDF-1)
Transforming growth factor beta (TGF-β)
Vascular endothelial growth factor A (VEGF-A)

Conflict of interest

The author declares no conflict of interest.

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