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EDITORIAL

Is angiogenesis essential for the progression of hematological malignancies or is it an epiphenomenon?

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It is well established that solid tumor growth consists of an avascular and a subsequent vascular phase.[1] Assuming that the latter process is dependent on angiogenesis and on the release of angiogenic factors, acquisition of an angiogenic capability can be seen as an expression of neoplastic transformation to tumor growth and metastasis. Practically, all solid tumors progress through these two phases.

As the bone marrow and lymphatic organs are predominant sites of tumor accumulation in hematological malignancies, it was initially believed that angiogenesis would not be as relevant in these disorders, classically defined as 'liquid tumors', as in solid tumors. In fact, as leukemia and other hematological tumors do not develop as compact tumor mass, the necessity for angiogenesis was not readily apparent as for solid tumors.

However, increased microvessel density in bone marrow and lymph nodes may be important in providing oxygen and nutrients to the malignant cells. Moreover, the increased endothelial cell mass is important for producing cytokines and growth factors that act on the malignant cells in paracrine fashion, promoting their proliferation or survival. Stromal cells in bone marrow may also be involved in such paracrine interactions. As the malignant cells produce angiogenic factors and express receptors for these factors, functional autocrine loops may also be important in hematological malignancies.

In 1993, Judah Folkman [2]in an address before the 35th Annual Meeting of American Society of Hematology hypothesized that leukemias were angiogenic, and that they could eventually prove to be angiogenesis-dependent. This idea was based on findings that the angiogenic molecule basic fibroblast growth factor was abnormally elevated in the urine of newly diagnosed leukemic patients,[3] and that bone marrow stroma cells and peripheral blood cells express basic fibroblast growth factor.[4]

In 1994, Vacca and coworkers [5] showed that increased angiogenesis in multiple myeloma is highly correlated with plasma cell proliferation. These investigators compared the microvascular density of bone marrow in patients with active multiple myeloma, nonactive multiple myeloma and benign monoclonal gammopathies of undetermined significance, and showed that there was a significant difference in microvascular density between these three conditions.[5] Assuming that microvascular density depends on angiogenesis, these results are consistent with the notion that angiogenesis favors expansion of the multiple myeloma mass by promoting plasma cell proliferation.

Later, increased vascularity was observed in the lymph nodes of B-cell non-Hodgkin's lymphoma[6] and B-cell chronic lymphocytic leukemia,[7] as well as in bone marrow specimens form patients with childhood acute lymphoid leukemia,[8] acute myeloid leukemia,[9] chronic myelocytic leukemia,[10] myelodysplastic syndromes[11] and idiopathic myelofibrosis.[12]

Tumor cells are often the progeny of malignant precursors, which may be both adherent and localized to areas of the hematopoietic microenvironment that require neovascularization for expansion. The first cells involved in the pathology of these diseases may be the cells adherent to stromal areas that require microvascularization for successful colonization. Maintenance of disease may require the continued survival of tissue-adherent cells, either to provide progenitors or growth factors needed to perpetuate the disease.

Numerous clinical studies have shown that the degree of angiogenesis or the levels of angiogenic factors are correlated with the extent of stage of disease, prognosis or response to therapy. Taken together, these data strongly suggest that angiogenesis induction in hematological tumors has a pathophysiological relevance for disease progression.

Antiangiogenic agents have been shown to be effective in the treatment of hematological malignancies, even if a single antiangiogenic agent is unlikely to act as a magic bullet for their treatment. Strategies that target both the stromal and tumor compartments, such as combining traditional cytotoxic chemotherapy with antiangiogenic agents, may markedly improve the therapeutic response. For example, enhancement of antitumor efficacy can also be achieved by combining drugs that block vascular endothelial growth factor signaling with chemotherapeutics or irradiation, thereby 'normalizing' and sensitizing tumor vasculature and improving oxygenation and delivery of chemotherapeutic agents to tumor cells and endothelial cells.

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