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Commentary

Vascularity of Nongynecological Leiomyosarcoma Depends on Colony-Stimulating Factor 1 but Not on Vascular Endothelial Growth Factor

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Tumor-associated macrophages (TAMs) orchestrate various aspects of cancer progression, including the promotion of tumor angiogenesis independent of vascular endothelial growth factor (VEGF) signaling. Thus, macrophage-targeted therapy, such as colony-stimulating factor 1 (CSF1) blockade, represents a promising anticancer strategy. However, the role of macrophages varies according to the type of cancer. Therefore, it is important to know whether and to what degree specific tumors depend on macrophage-driven angiogenesis. In this issue of *The American Journal of Pathology*, Espinosa et al[1] investigated 149 cases of leiomyosarcoma (LMS), a malignant neoplasm of smooth muscle. They report that the number of macrophages and the levels of CSF1 expression highly correlated with microvessel density and poor prognosis in nongynecological LMS cases. Notably, the microvessel density of these tumors showed either no correlation or negative correlation to VEGF-A. These data provide a rationale for CSF1 targeted therapies in nongynecological LMS, validating the use of CSF1 inhibitors, rather than VEGF blockers, for suppression of tumor angiogenesis in certain types of tumors.

Macrophages and Angiogenesis

CSF1 mediates the differentiation of monocytes into macrophages. Macrophages function in both nonspecific (innate immunity) and specific (adaptive immunity) defense mechanisms in vertebrate animals through phagocytosis of cellular debris and pathogens. Aside from its well-known role in the immune system, macrophage roles in angiogenesis have also garnered attention. Recent genetic evidence demonstrates that macrophages promote angiogenic branching[2] and anastomosis[3] in physiological settings. Macrophages stimulate vessel sprouting in aortic ring cultures by secreting a soluble factor other than VEGF-A, rather than by direct contact with endothelial cells.[4] These data suggest that macrophages promote angiogenesis independently of the VEGF signaling.

Tumor Angiogenesis and VEGF

The tumor microenvironment is prominently visible on histological examination and consists of a complex mixture of cell types. Moses Judah Folkman,[5] well-known as the father of tumor angiogenesis, first proposed the importance of tumor vascularity. He declared that if a tumor could be stopped from growing its own blood supply, it would wither and die. Since then, various studies have led to the discovery of a growing number of anti-angiogenic molecules limiting tumor angiogenesis. Among them, VEGF blockers are one of the most accepted anti-angiogenic treatments because tumor angiogenesis mostly depends on VEGF. Several VEGF blockers have already been approved for clinical use in cancer, and multiple lines of studies[6,7] have reported significant therapeutic efficacy; however, a fraction of patients are refractory or acquire resistance to VEGF inhibitors.[8] In these patients, compensation by other pro-angiogenic mechanisms may contribute to poor responsiveness to VEGF blockade. The extent of refractoriness varies from one cancer to another and differs among various types of VEGF blockers. Understanding the molecular basis of

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these cancer type–dependent resistance mechanisms against VEGF blockade offers opportunities to improve anti-angiogenic treatment.

Macrophages: Cellular Hubs Essential for Tumor Angiogenesis

During cancer progression, TAMs play diverse and complicated roles.[9] TAMs orchestrate various aspects of cancer progression, including diverting and skewing adaptive responses, cell growth, matrix deposition and remodeling, and constructing a metastatic niche. The promotion of tumor angiogenesis is one of the most important roles of TAMs. Pollard and colleagues[10] first established the role of TAMs in the angiogenic switch, which is identified as the formation of a high-density vessel network that promotes the tumors into a malignant state. Recently, myeloid cell/macrophage-driven angiogenesis associated with refractoriness or resistance to VEGF blockade.[2,11] However, this significance of macrophage-driven angiogenesis highly varies according to the type of cancer. Therefore, it is important to know how specific tumors depend on macrophage-driven angiogenesis.

LMS and Macrophages

LMS, a malignant neoplasm of smooth muscle, is a relatively rare form of cancer, composing between 5% and 10% of soft tissue sarcomas.[12] LMS is resistant to treatment, with little responsiveness to chemotherapy or radiation. The best prognosis is obtained when LMS is surgically removed, including a wide margin of normal tissues, at an early stage, while the tumor is small and still *in situ*.[13] LMS predominantly occurs in the female genital tract (gynecological LMS) or deep soft tissues (nongynecological LMS). van de Rijn and colleagues[14] have investigated the tumor microenvironment of LMS, finding that more TAMs in nongynecological LMS indicate a poorer prognosis. Moreover, they found that the expression of CSF1, a major differentiation and survival factor for macrophages, positively correlates with poor prognosis in both gynecological and nongynecological LMS.[15] However, given that the functions of TAMs are diverse and complicated, as previously described, it is unclear how TAMs and CSF1 contribute to the poor clinical outcomes of LMS.

Macrophage-Driven Angiogenesis in LMS

In their article, Espinosa et al[1] explored the link between TAMs, CSF1, and poor prognosis in LMS. They quantified microvessel density, CSF1 expression, and patient prognosis in 149 LMS cases. The data show that high microvessel density in nongynecological, but not gynecological, LMS cases significantly predicts poor patient outcome. Furthermore, most cases presenting high microvessel density were CSF1 positive; when combining high microvessel density with CSF1 expression, an even stronger prognostic correlation with patient outcome was obtained. More important, they found either a nonsignificant or a negative correlation between microvessel density and VEGF-A expression. In xenograft studies using immune-deficient mice, CSF1 expression and TAM recruitment remained consistent between primary tumors and those grown as xenografts in mice, supporting the stability of these features as intrinsic to LMS tumors.

Future Perspective

Espinosa et al[1] demonstrated that microvessel density predicts the outcome of nongynecological, but not gynecological, LMS, which is in stark contrast to what is known for soft tissue sarcomas.[16] Microvessel density correlates with important clinical features in patients with sarcomas, ranging from soft tissue to bone sarcomas. Identifying the diagnostic subtypes of sarcomas, as in nongynecological and gynecological LMS, is essential. Although these data provide a rationale for CSF1 targeted therapies in nongynecological LMS, further functional studies, such as CSF1 inhibition in the LMS tumor model, may aid in using this strategy in clinical settings. It is also important to know whether the CSF1 receptor is expressed in tumor cells of LMS and in macrophages. A recent study[17] showed that, in acute myeloid leukemia, the expression of the CSF1 receptor is increased in leukemia-initiating cells, which could be a therapeutic target for leukemia eradication. Finally, viewing these results broadly, the presented data for LMS may validate the use of CSF1 inhibitors, rather than VEGF blockers, for the suppression of tumor angiogenesis in other types of tumors.

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