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Targeting cancer cells resistant to hypoxia and nutrient starvation to improve anti-angiogeneic therapy

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Angiogenesis, formation of new blood vessels, is essential for tumor progression, invasion, and metastasis.[1] Vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) are primary regulators of angiogenesis, coordinating with other angiogenic factors such as fibroblast growth factors (FGFs), hepatic growth factor (HGF), angiopoietins, and Notch-Dll4. Anti-VEGF antibodies (e.g., bevacizumab) and small molecular inhibitors of VEGFRs (e.g., sunitinib and sorafenib) were validated as the first cancer therapeutic agents targeting the tumor microenvironment.[1] These anti-angiogenic therapies effectively suppress the growth of solid tumors and are widely used for the treatment of malignant colorectal cancer, some non-small cell lung cancers, hepatocellular carcinoma, kidney cancer, and neuroendocrine tumors. Angiogenesis inhibitors suppress the formation of new tumor vasculature and may normalize existing vasculature, resulting in increased efficacy of combination chemotherapy.[2] However, the effectiveness of anti-angiogenic treatments is limited to certain types of cancer. In addition, they may not completely eradicate tumor growth and may elicit malignant progression by, for example, inducing resistance to chemotherapy.[3] Thus, the molecular mechanism underlying the elimination of such resistant and refractory cancer cells needs to be elucidated.

Following the inhibition of angiogenesis, cancer cells can be exposed to both hypoxia and nutrient starvation, which may stimulate tumor aggressiveness.[4] We developed a simple model system to maintain cancer cells under conditions of both hypoxia and nutrient starvation, and demonstrated that long-term hypoxia and nutrient starvation induces tumor aggressiveness.[4] Therefore, the tumor microenvironment associated with hypoxia and nutrient starvation may be important in the regulation of tumor progression. However, with the exception of known hypoxia-induced factors, the factors that regulate angiogenesis under conditions of hypoxia and nutrient starvation are unclear. Epigenetic regulation of angiogenesis may play a role, but this has not yet been fully elucidated. Previously, we reported that the histone demethylase JHDM1D is highly expressed in various cancer cells under conditions of nutrient starvation and that subsequent suppression of solid tumor growth was associated with the downregulation of several pro-angiogenic factors such as VEGF-B and angiopoietins.[5] Conversely, another histone demethylase JMJD1A stimulated tumor angiogenesis under conditions of hypoxia and nutrient starvation by upregulating the expression of several pro-angiogenic factors, such as angiopoietins, FGFs, and HGF, resulting in increased infiltration of tumor-associated macrophages.[4] Importantly, JMJD1A inhibition suppressed tumor growth when used in combination with anti-VEGF (bevacizumab) and anti-VEGFR treatment (sunitinib), possibly by sensitizing the refractory cells of the tumor to anti-angiogenic treatment. This suggests that modification of epigenetic regulators can improve anti-angiogenic therapy.[4]

The adaptation of cancer cells to tumor microenvironments such as conditions of hypoxia, nutrient deficiency, acidosis, and reactive oxygen species can be achieved via alteration of cancer metabolism and enrichment of cancer stem cells. This is required for tumor progression and metastasis.[6,7] The response to oxygen or nutrient deficiency and acidosis can be attained by metabolic alterations to glycolysis (Warburg effect), glutamine metabolism, and other metabolic pathways. Recently, global metabolomic analysis revealed important metabolic pathways in several cancer types. As a result of glucose and glutamine depletion, metabolic pathways other than glycolysis and glutamine metabolism can be utilized under hypoxia and nutrient starvation conditions. Indeed, our preliminary results suggest that histone demethylase JHDM1D may regulate tumor growth and metabolism under conditions of nutrient starvation and may play an important role in tumor aggressiveness.[5] Cancer cells, including cancer stem cells, have considerable histological and functional heterogeneity.[8] As described above, hypoxia and nutrient starvation induced tumor aggressiveness, at least in part, via epigenetic regulation. Therefore, a hypoxia and nutrient-starved tumor microenvironment may enrich cancer stem cells, thus contributing to tumor aggressiveness and recurrence. In conclusion, strategies to sensitize cells to anti-angiogenic therapies in hypoxic and nutrient-starved tumor microenvironments will potentially prevent tumor recurrence and aggressiveness. (**Fig. 1**)

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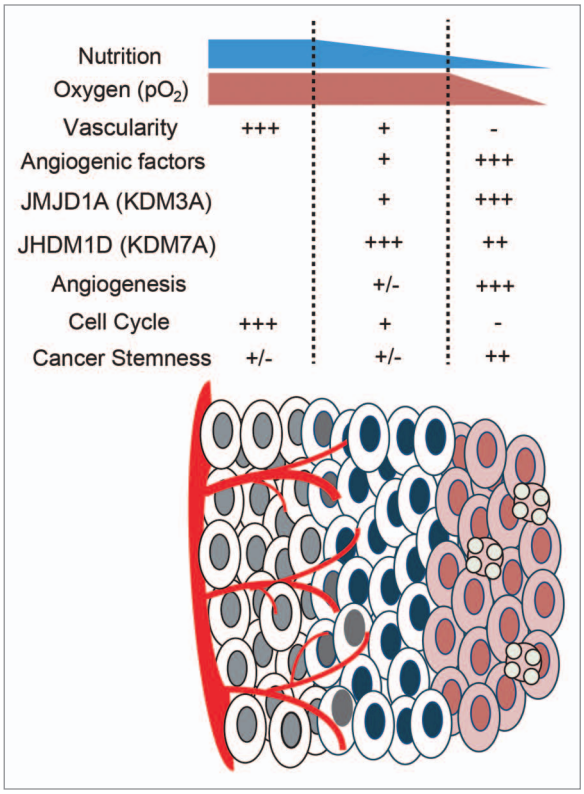

Figure 1. Schematic regulation of angiogenesis under conditions of hypoxia and nutrient starvation. Tumor tissue induces both hypoxic and nutrient-starved regions. The perivascular region (vascular rich) is rich in both oxygen and nutrients. The surrounding region has fewer nutrients, which induces JHDM1D expression (+++) and suppresses angiogenesis (+/–). Regions distal to the vascular-rich area become hypoxic and starved of nutrients, which stimulates induction of angiogenic factors (+++) resulting in an increase in expression of JMJD1A and angiogenesis (+++). Hypoxia and nutrient starvation suppresses cell cycle progression, but enriches non-proliferating cancer stem cells, contributing to tumor aggressiveness.