Letter to the Editor

Clinical Cancer Research

Tumor Stromal Phenotypes Define VEGF Sensitivity—Letter

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With great interest, we read the article "Tumor Stromal Architecture Can Define the Intrinsic Tumor Response to VEGF-Targeted Therapy" by Smith and colleagues (1) in which the response to VEGF-targeted therapy was linked to the vascular/stromal architecture of primary tumors.

We previously described different histologic growth patterns (GP) of the tumor–liver interface in liver metastases (LM) of patients with solid tumors, including colorectal cancer (2, 3). LMs with a "desmoplastic" GP are encapsulated by a band of desmoplastic stroma. In the "pushing" GP, the tumor cells are separated from the hepatocytes by a thin layer of reticulin fibers. Both of these patterns show histologic features consistent with angiogenesis. However, in the "replacement" GP, tumor cells invade into the liver parenchyma and coopt sinusoidal blood vessels instead of using angiogenesis (2–4).

Although Smith and colleagues (1) studied primary tumors, we note similarities between the two major vascular phenotypes they describe and the patterns of vascularization in LMs of the three GPs. Namely, the tumor-associated vasculature in the desmoplastic GP and, to a lesser extent in the pushing GP, consists of newly formed capillaries surrounded by well-developed stroma, akin to the "stromal vessel (SV)" phenotype described by Smith and colleagues On the other the vasculature of the replacement GP is comparable with the Smith "tumor vessel (TV)" phenotype. In animal models, Smith and colleagues observed that TV tumors were more sensitive to VEGF-targeted therapy than SV tumors, whereas in human metastastic colorectal cancer samples, the SV phenotype group had a poorer response to bevacizumab and FOLFIRI. In contrast with this, we reason that because the LMs of the replacement GP (which are akin to the TV phenotype) are nonangiogenic, they should be the least responsive to VEGF-targeted therapy.

In conclusion, a phenotypic variability in the stroma akin to that described by Smith and colleagues (1) for primary tumors has been described by us for colorectal cancer liver metastases. Both findings highlight the potential influence of the tumor stroma architecture on the response to anti-angiogenic therapy. In the continuing effort to personalize treatment for metastatic colorectal cancer, the questions of whether this phenotypic variability in LMs determines the outcome of VEGF-targeted therapy and the relative contributions of the primary tumor versus LMs phenotypes to this response, warrant further investigation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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