Letter to the Editor

Clinical Cancer Research

Tumor Stromal Phenotypes Define VEGF Sensitivity—Response

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We appreciate the opportunity to add to the comments by Van den Eynden and colleagues (1) about the potential influence of the tumor stromal phenotype on response to angiogenesis inhibitors. Van den Eynden and colleagues (1) have undertaken a pathologic analysis of liver metastases originating from primary tumors of different histologic origin. Their work is complementary to our study (2) and highlights that the architecture of the stroma in tumors is worthy of investigation.

Our study examined primary tumors and suggested that two major phenotypes were apparent; the stromal vessel (SV) phenotype in which nests of tumor cells are encapsulated in dense stroma containing the vasculature, and the tumor vessel (TV) phenotype in which angiogenic vessels are embedded directly between tumor cells.

In a tumor model that displayed the SV phenotype, we observed a proportion of microvessels that had an angiogenic phenotype and were susceptible to treatment with a VEGF signaling inhibitor. However, an approximately equal or greater proportion of mature vessels were also present and remained following treatment with a VEGF signaling inhibitor, with the net consequence that tumor growth was not inhibited significantly. This phenotype was also evident in some primary tumors, in which dramatic single-agent responses to VEGF inhibitors have not been observed clinically. It appears that the SV phenotype may also be found in the "desmoplastic" and "pushing" phenotypes described by Van den Eynden and colleagues, and therefore also relevant to metastatic disease.

Van den Eynden and colleagues (1) also suggest the existence of a third stromal architecture relevant to liver metastasis. The "replacement" phenotype, involves infiltrative tumor cell invasion into the normal liver and cooption of established mature sinusoidal vasculature. The authors indicate that the vasculature under these conditions is nonangiogenic and should, therefore, be resistant to VEGF inhibitor treatment, but then also suggest that such vasculature is similar in appearance to the TV phenotype, we describe. We agree that coopted vessels may not be sensitive to VEGF inhibitors. However, we do not consider the TV phenotype to involve vascular cooption, but to instead describe settings in which the tumor cells are in direct association with, and reliant upon, highly angiogenic immature vessels. Tumor xenografts that mirror the TV phenotype were found to be sensitive to treatment with a VEGF signaling inhibitor.

The "replacement" phenotype observed in liver metastasis is an important observation and does suggest that other stromal architectures are likely to exist, not only between different tumor types but also at different stages of disease or in different organs. We would, therefore, agree that additional work is warranted to further examine tumor stromal architecture and its potential influence on the efficacy of antiangiogenic therapies. It will be important to position the role of the stroma in context with other mechanisms known to influence sensitivity to antiangiogenic therapies.

Disclosure of Potential Conflicts of Interest

N.R. Smith, X. Wang, J. Kendrew, C. Womack, and S.T. Barry are employees of AstraZeneca. D. Baker, M. Farren, A.J. Pommier, R. Swann, S. Mistry, K. McDaid, and S. Wedge are former employees of AstraZeneca. N.R. Smith, X. Wang, K. McDaid, J. Kendrew, C. Womack, S. Wedge, and S.T. Barry have ownership interests in AstraZeneca. No other potential conflicts of interest were disclosed.

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