LETTER

Normalization of the tumor vasculature through oncogenic inhibition: An emerging paradigm in tumor biology

The work by Bottos et al. (1) reported the effects of the proto-oncogene BRAF inhibition on the vasculature of solid tumors harboring the $BRAF^{V600E}$ oncogenic mutation. In particular, the work by Bottos et al. (1) showed that suppression of BRAF signaling in these tumors diminished tumor cell expression of several proangiogenic factors downstream of BRAF, which in turn stabilized vessel architecture, improved perfusion, and abrogated hypoxia. These findings are supportive of vascular normalization, a hypothesis that we first proposed in 2001 and then elaborated on in 2005 (2). Through restoration of the balance between proangiogenic and antiangiogenic factors in a tumor by whatever means, tumor blood vessels can revert from their characteristic abnormal phenotype to one more closely resembling normal tissues, improving perfusion, oxygenation, and drug delivery and efficacy.

Although vascular normalization has been most commonly described in response to direct vessel-targeted therapies (i.e., agents acting on endothelial or perivascular cell targets) (3), the concept that inhibition of oncogenic signaling invokes vascular normalization through indirect means has also been documented. We first showed this concept in 1998, showing that the initial effects of castration on androgen-dependent carcinoma are primarily vascular (preceding tumor cell death) because of an indirect mechanism where hormone depletion suppresses tumor cell production of angiogenic factors (4). We subsequently showed that, through inhibition of human epidermal growth factor receptor-2 signaling in breast cancer cells, the monoclonal antibody trastuzumab (Herceptin) normalizes breast tumor vessels by modulating the expression of at least four pro- and antiangiogenic molecules (5). Moreover, several other reports have shown similar effects from inhibiting the tumor cell oncogenes Ras, PI3K, protein kinase B (AKT), and epidermal growth factor receptor (summarized in table 4 in ref. 3). Often, the vessel normalization observed in such situations can be more durable (3), unlike the short-lived effects often seen during the normalization window after conventional antiangiogenic treatments.

It is clear that the work by Bottos et al. (1) added to a growing body of literature highlighting the potential for agents conceived initially to inhibit tumor cell survival or proliferation to also modulate the tumor vasculature favorably. Such agents have the potential, therefore, to improve tumor oxygenation through two mechanisms: first, normalization of vessels, and second, reduction of a tumor's oxygen consumption through killing of cancer cells. Indeed, the work by Bottos et al. (1) showed an interesting discordance between the two different tumor cell lines that they studied. BRAF inhibition showed differential effects on angiogenesis—promotion in one case and inhibition in the other—but both led to the same outcome, namely improved tissue oxygenation. As new tumor cell-targeted therapies are developed, both preclinical investigators and clinicians should be aware of these effects and their wide-ranging implications for the tumor microenvironment and hence, tumor progression and response to therapy.

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