The Importance of Tumor Angiogenesis

The Evidence Continues to Grow

Noel Weidner, MD

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In this issue of the Journal, Özdemir et al present evidence that hypercholesterolemia impairs angiogenesis in patients with breast carcinoma and, therefore, lowers the risk of metastases. This conclusion is predicated on accepting the validity of 2 very important observations. First, tumor-induced angiogenesis (ie, as measured by intratumoral microvessel density [iMVD]) is a bona fide predictor of aggressive tumor growth and metastasis, and second, circulating cholesterol (especially hypercholesterolemia) has antiangiogenic and, thus, antitumor effects.

For a tumor to grow, the tumor cells not only must proliferate but also adjacent supportive host tissues, especially new blood vessels, must form around the tumor cells. Indeed, there is a plethora of evidence (now global) that tumor growth and spread is angiogenesis-dependent, that tumor cells can produce diffusible angiogenic regulatory molecules, and that angiogenesis antagonists can slow or prevent tumor growth.

To metastasize, a tumor cell must gain access to the vasculature from the primary tumor, survive the circulation, escape immune surveillance, localize in the vasculature of the target organ, escape from (or grow from within) the vasculature into the target organ, and induce tumor angiogenesis. Moreover, tumor spread is amplified when the new metastasis sheds additional tumor cells to form even more metastases by following the same sequence of events.

Angiogenesis is needed, because without it tumor cells would not shed into the circulation. Greater numbers of tumor vessels increase the opportunity for tumor cells to enter the circulation, facilitating tumor spread and, thus, correlating with aggressive tumor behavior. Subsequently, many studies have shown that iMVD correlates with tumor aggressiveness of many different tumor types. Moreover, tumor angiogenesis promotes tumor growth because the new vessels allow exchange of nutrients, oxygen, and waste products by a crowded cell population for which simple diffusion of these substances across its outer surfaces is no longer adequate. In addition to this perfusion effect, endothelial cells release important paracrine growth factors for tumor cells. The invasive chemotactic behavior of endothelial cells at the tips of growing capillaries is mediated in part by their secretion of various collagenases, urokinases, and plasminogen activator. These degradative enzymes likely facilitate the spread of tumor cells into and through the adjacent fibrin-gel matrix and connective-tissue stroma.

Much of this evidence, as well as probable tumor angiogenic mechanisms, has been summarized extensively in a variety of reviews. But, it is important that these publications have been further substantiated by a recent systemic literature review with meta-analysis by Uzzan and coworkers of MVD as a prognostic factor in women with breast cancer. These authors performed a meta-analysis of all 88 published studies (43 independent studies involving 8,936 patients) linking iMVD to relapse-free and overall survival. The authors found that high iMVD significantly predicted poor survival. Furthermore, 22 studies separately analyzed lymph node–negative patients (n = 3,580), for whom predictors of poor survival are especially needed. This latter meta-analysis included 15 studies for relapse-free survival (2,727 patients) and 22 for overall survival (1,926 patients)—again, high MVD significantly predicted poor survival. The authors believed that between-study variations could result from patient selection criteria, various techniques for staining and counting microvessels, and different cutoff selections. Standardization of MVD assessment was recommended.
The second important observation is that serum cholesterol levels affect endothelial cells and angiogenesis.22-42 This comes as no surprise, given the well-established association between hypercholesterolemia and atherosclerosis. First, Özdemir and colleagues1 point out that hypercholesterolemia is associated with endothelial cell dysfunction, which might be related partly to toxic lipoprotein degradation products.23 Second, experiments in rabbits indicate that endothelial replication, necessary for vascular growth, is markedly impaired in the presence of hypercholesterolemia24 and that both diet-induced and genetic hypercholesterolemia impair angiogenesis.24-27 Third, hypercholesterolemia is associated with impaired β-dependent endothelial cell growth manifested by impaired adaptive growth responses of large arteries and microvessels.27 Finally, some studies have reported a relation impaired adaptive growth responses of large arteries and hypercholesterolemia (mean ± SE, 54.6 ± 5.1) (P < .01). Patients with normocholesterolemia had endothelial and tumor cells. Of 51 patients with invasive ductal carcinoma, 28 had hypercholesterolemia and 23 had normocholesterolemia. Patients with normocholesterolemia had higher iMVD values (mean ± SE, 76.4 ± 8.2) than those with hypercholesterolemia (mean ± SE, 54.6 ± 5.1) (P < .01). For patients with normocholesterolemia, the risks of recurrence and distant metastasis were significantly higher than for patients with hypercholesterolemia (P < .01). For patients with hypercholesterolemia, expression of endothelial VEGF and bFGF was lower than for patients with normocholesterolemia (P < .05 and P < .01, respectively). In addition, tumoral bFGF and VEGF expression correlated negatively with the presence of hypercholesterolemia (P < .01). Özdemir and coworkers1 concluded that hypercholesterolemia possibly impairs tumor angiogenesis by suppressing endothelial and tumoral bFGF and VEGF expression and, therefore, lowers the risk of metastases in cases with invasive breast carcinoma. Their conclusions are reasonable, given current experimental observations.

References