Cells cannot survive if they lack adequate oxygen and nutrient supply or cannot dispose of toxic molecules. Oxygen can diffuse from capillaries for only 150–200 µm. When distances of cells from a blood supply exceed this, cell death follows (1,2). Thus, the growth and survival of tumor masses beyond 0.5 mm in diameter require neovascularization, i.e., angiogenesis (3).

In this issue of the Journal, Achilles et al. (4) injected human liposarcoma cells (tumor fragments or cells) into the subcutis of severe combined immunodeficient mice. The different tumor fragments and liposarcoma cells gave rise to fast-growing, slow-growing, or small dormant tumors. The growth rate of the tumors correlated directly with microvessel density and correlated inversely with tumor cell apoptosis. The authors concluded that human liposarcomas are heterogeneous for induction of angiogenesis and suggest that the failure to induce angiogenesis can be responsible for the failure to xenotransplant human neoplasms into immunodeficient mice (1). Achilles et al. (4) have provided one more illustration of the “seed and soil” hypothesis.

In 1889, Paget (5) proposed that the growth and spread of cancers occurred when certain favored tumor cells (seed) had a special affinity for the growth milieu provided by specific tissues or organs (soil). A current definition of the seed and soil hypothesis consists of two principles. First, neoplasms are heterogeneous and consist of cells with different biologic properties; second, the outcome of cancer growth and spread depends on multiple interactions of tumor cells with host homeostatic factors (6).

By the time of diagnosis, malignant neoplasms are biologically heterogeneous and contain multiple subpopulations of cells with different properties, including differences in morphology, growth rates, karyotypes, metabolic characteristics, antigenic or immunogenic potential, production of extracellular matrix proteins, cell surface receptors, adhesion molecules, hormone receptors, drug and radiation sensitivities, angiogenic potential, invasiveness, and the ability to metastasize (6).

Angiogenic heterogeneity within a single tumor (zonal or intralobular) between different metastases even in a single organ (interlesional) and different neoplasms of the same histologic type is also documented (7,8). For example, the implantation of murine or human cancer cells into orthotopic sites of nude mice produces progressively growing local tumors. The expression of proangiogenic molecules (and, therefore, vessel density) in the lesions is zonal, i.e., intralobular heterogeneity. Small tumors (3–4 mm in diameter) express more basic fibroblast growth factor (bFGF) and interleukin 8 (IL-8) than large tumors (>10 mm in diameter), whereas more vascular endothelial growth factor (VEGF) is expressed in large tumors. Immunostaining showed a heterogeneous distribution of angiogenic factors within the tumor; expression of bFGF and IL-8 was highest on the periphery of a large tumor, where cell division is maximum. VEGF expression was higher in the center of the tumor (7). Similarly, heterogeneous dependence on angiogenesis was reported recently for cell subpopulations isolated from human melanoma xenografts and cells from teratomas with differential expression of hypoxia-inducing factor-1α (8).

Heterogeneity of blood vessel distribution in surgical specimens of human cancers is well documented (9,10). Benign neoplasms are sparsely vascularized and tend to grow slowly, whereas malignant neoplasms are highly vascularized and fast growing (9). The distribution of vessels in a tumor, however, is not uniform, and Weidner et al. (10) cautioned that, to predict the aggressive nature of human neoplasms, one must determine the mean vessel density (MVD) in the “areas of most intense neovascularization,” i.e., tumors exhibit intralobular or zonal heterogeneity for MVD. Similarly, the expression of proangiogenic molecules in surgical specimens of human colon carcinoma was determined by in situ hybridization technique. Matrix metalloproteinase-9 and bFGF were overexpressed at the periphery of the tumor (leading edge), where cells were rapidly dividing, whereas VEGF expression was higher in the center of the lesions (11).

The extent of angiogenic heterogeneity in malignant neoplasms is regulated by the organ microenvironment. For example, human renal carcinoma cells implanted into the kidney of nude mice produce a high incidence of lung metastasis, whereas those implanted subcutaneously are not metastatic (12). Histopathologic examination of the tissues revealed that the tumors growing in the subcutis of nude mice had few blood vessels, whereas the tumors in the kidney had many (12). The subcutaneous (or intramuscular) tumors had a statistically significant lower level of messenger RNA transcripts for bFGF than the tumors in the kidney, whereas the expression of interferon beta (which diminishes transcription of bFGF) was high in epithelial cells and fibroblasts surrounding the subcutaneous tumors and not detected in or around tumors growing in the kidney (13). The production of IL-8 by melanoma cells is regulated by complex interactions with keratinocytes in the skin (14). IL-8 expression can be increased by coculturing melanoma cells with keratinocytes (skin) and inhibited by coculturing melanoma cells with hepatocytes (liver) (15). The organ microenvironment also influences the expression of VEGF/vascular permeability factor. Human gastric cancer cells were implanted into orthotopic (stomach) and ectopic (subcutaneous) organs of nude mice. Tumors in the stomach were highly vascularized, expressed high

**Correspondence to:** Isaiah J. Fidler, D.V.M., Ph.D., Department of Cancer Biology-173, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030 (ifidler@mdanderson.org). See “Note” following “References.”

© Oxford University Press
levels of VEGF, and grew more rapidly than the subcutaneous tumors. In addition, metastasis occurred only from the tumors implanted in the stomach (16).

The successful transplantation of cells from surgical specimens of human neoplasms requires that the cells initially proliferate in the recipient organs and then induce angiogenesis to support additional growth (17). To proliferate, many tumor cells can usurp physiologic growth factors that are produced by the microenvironment when homeostasis is disturbed. For example, after resection of more than half of the liver, the liver undergoes rapid cell division termed “regeneration” without cell division occurring in the kidneys. Similarly, subsequent to nephrectomy, the contralateral kidney compensates by hypertrophy and hyperplasia but the liver does not (17). Autocrine or paracrine growth factors that control the repair of tissues are known to be tissue specific. During liver regeneration, it is common to find high levels of transforming growth factor-α (TGF-α) and hepatocyte growth factor (HGF) in the circulation (18). The finding that human colon cancer cells capable of growing in the liver parenchyma (Dukes’ stage D) express a higher number of functional receptors for TGF-α (epidermal growth factor receptor) and HGF (c-met) than do cells with low metastatic potential (Dukes’ stage B) supports the hypothesis that the production of liver-specific metastasis results from the proliferation of tumor cells expressing growth factor receptors for tissue-specific paracrine factors involved in homeostasis (19). Indeed, liver regeneration in nude mice stimulates growth of colon cancer cells only, whereas hypertrophy–hyperplasia of the kidney stimulates the growth of renal cancer cells only (17).

In conclusion, the progressive growth of neoplasms and the production of metastasis are dependent on the development of vasculature, i.e., angiogenesis. The extent of angiogenesis is determined by the balance between positive- and negative-regulating molecules, which are released by tumor and host cells in the microenvironment. More than a century ago, Paget articulated the principle that metastasis occurs only when the right cell (seed) grows in the correct environment (soil). All current data support this concept and recommend that orthotopic implantation of tumor cells in recipient animals is mandatory for studies of tumor progression, angiogenesis, invasion, and metastasis (20,21).

REFERENCES


NOTE

Supported in part by Public Health Service grants CA16672, R35CA42107, CA90270, and CA83639 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.