To produce clinically relevant metastasis, tumor cells must complete a series of sequential and selective steps that include growth, neovascularization (angiogenesis), detachment (motility), invasion, survival in the circulation, adhesion to vessel walls (cells), extravasation into the organ parenchyma, and growth coupled with neovascularization.

In 1889, Paget asked, "What is it that decides what organs shall suffer in a case of disseminated cancer?" Paget’s study was motivated by the discrepancy between consideration of blood flow and the frequency of metastases in different organs. After examining the autopsy records of 735 women who died of breast cancer and many other patients with different neoplasms, he concluded that metastases occurred only when certain favored tumor cells (the "seed") had a special affinity for the growth milieu provided by certain specific organs (the "soil"). The formation of metastasis required the interaction of the right cells with the compatible organ environment.

A current definition of the "seed and soil" hypothesis consists of three principles. First, neoplasms are biologically heterogeneous and contain subpopulations of cells with different angiogenic, invasive, and metastatic properties. Second, although some of the steps in this process contain stochastic elements, metastasis as a whole favors the survival and growth of a few subpopulations of cells that pre-exist within the parent neoplasm. Thus, metastases can have a clonal origin, and different metastases can originate from the proliferation of different single cells. Third, the outcome of metastasis depends on multiple interactions ("cross talk") of metastatic cells with homeostatic mechanisms, which the tumor cells can usurp.

The survival and growth of cells (normal and tumor) in the body are dependent on an adequate blood supply. Tumors smaller than 1 to 2 mm in diameter can receive nutrients by diffusion, but further growth of the lesions (like any other tissue) must be preceded by the formation of new blood vessels, i.e., angiogenesis. The prevascular stage of a tumor is associated with local, noninvasive, benign tumors, whereas the vascular stage is associated with aggressive, invasive, and metastatic tumors. Indeed, the extent of neovascularization in different malignancies, such as melanoma and breast and prostate cancers, is associated with their potential for invasion and metastasis. Angiogenesis is a multistep process emanating from microvascular endothelial cells. To generate capillary sprouts, endothelial cells must proliferate, migrate, and invade host stroma, the direction of migration generally pointing toward the source of angiogenic molecules. The capillary sprout subsequently expands and undergoes morphogenesis to yield a capillary.

The induction of angiogenesis is mediated by multiple molecules that are released by some tumor cells and host cells. Among these molecules are members of the fibroblast growth factor (FGF) family: vascular endothelial cell growth factor/vascular permeability factor (VEGF/VPF) and interleukin 8 (IL-8). The extent of angiogenesis is determined by the balance between factors that stimulate and those that inhibit the process. In quiescent normal tissues, the inhibitory factors predominate. Both stimulating and inhibiting molecules of angiogenesis can also be produced by leukocytes, and the organ microenvironment can directly contribute to the induction and maintenance of the angiogenic factors basic FGF, VEGF, and IL-8.

Several factors that down-regulate or inhibit angiogenesis have already been incorporated into clinical trials, the most widely studied being interferon alfa (IFN-α). We tested the ability of IFNs to down-regulate bFGF mRNA expression and protein production in human carcinoma cell lines. We found that IFN-α or IFN-β (but not IFN-γ) down-regulated the steady-state mRNA expression and protein production of bFGF and collagenase type IV in human renal, bladder, colon, and prostate cancer cells by mechanisms independent of their antiproliferative effects. The inhibition of bFGF mRNA and protein production required long-term exposure (more than four days) of cells to IFNs. Moreover, once IFN was withdrawn, cells resumed production of bFGF. These observations were consistent with the clinical experience that IFN-α must be given for many months to bring about involution of hemangiomas. We next analyzed the expression of angiogenic molecules in surgical specimens of human hemangiomas resected during the proliferative, involuting, and involuted phases. Proliferation was associated with production of bFGF and VEGF and absence of IFN-γ, whereas involuted lesions and normal skin expressed high levels of IFN-γ and low levels of bFGF and VEGF. Further immunohistochimcal analysis revealed that IFN-γ is produced by differentiated epithelial cells of the skin, aerodigestive tract, gastrointestinal tract, and genitourinary tract and not by normal dividing cells or by carcinomas. These data suggest that cell division associated with production of positive angiogenic molecules is inversely correlated with production of IFN-γ, a negative regulator of angiogenesis.

The mouse and human IFN-γ genes have been cloned. Transduction with viral vectors containing the IFN-γ cDNA produced down-regulation of collagenase type IV and bFGF in tumor cells and activation of inducible nitric oxide in infiltrating macrophages. The inhibition of angiogenesis coupled with activation of tumoricidal properties in macrophages produced regression of human colon, prostate, ovarian, and bladder carcinomas implanted into orthotopic sites in nude mice. Collectively, these data indicate that cytokines produced by leukocytes and different organ environments can regulate the process of angiogenesis that is an integral part of the metastatic cascade.

These data suggest that therapy against metastasis can be targeted not only against the tumor cells, but also against the homeostatic factors that are favorable to tumor metastasis, growth, and survival.

General References