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CRITICAL OVERVIEW CONCERNING NEW AGENTS THAT BLOCK INVASION/METASTASIS

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Metastasis is a multistep process beginning with the escape of the cell from the primary tumor, into carriers like lymph and blood vessels and penetration into and growth in a peripheral organ. Escape requires loss of cohesion among primary tumor cells while settlement in the periphery requires adhesion to endothelium and parenchyme. Thus the outcome of general interference with adhesive processes is unpredictable and only highly specific modifications of receptor adhesion molecule interactions may prove successful. Peptides or analoga (integrin/fibronectin) were not yet transferred into the clinics probably also since the concentration necessary for biological activity *in vivo* would be unrealistic. Inhibitors of membrane metalloprotease necessary for invasiveness and angiogenesis, however, are in clinical phase II and III (e.g.Marimastat). Other extracellular matrix degrading enzymes like glycosaminoglycanases should be considered for a transfer into the clinics as well. Strategies against survival of metastasizing cells in the blood stream included antithrombotics since thrombocytes had a protective effect for tumor cells in animal models. Clinical proof of principle, however, was generally not overwhelming. Adhesion to peripheral endothelial cells may be mediated like in leukocytes via the surface glycan sialyl-Lewis^x and efforts are underway to confirm this concept.

Since metastatic cells have to grow in their new peripheral environment, growth factors and receptors are not only of general importance, but required growth signals in the periphery may be specific and different compared to the primary tumor site. A flurry of activities can be observed in this field. Many growth factors trigger an intracellular signaling cascade of enzymes via their specific transmembrane receptor which will become phos-phorylated on a tyrosine in its cytoplasmic tail. Several companies have by now tyr-kinase inhibitors which inhibit not all tyr-kinases but only receptors for EGF, PDGF or the angiogenesis specific receptors $VEGFR_{1,2,3}$. The challenge now is to design yet more specific receptor-adaptor inhibitors for metastatic paracrine growth responses by the peripheral organ together with improved inhibitors against invasive degrading enzymes.

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TUMOR-ASSOCIATED ANGIOGENESIS: PATHOGENESIS AND CLINICAL IMPLICATIONS

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Compelling data implicate tumor-associated angiogenesis as being central to the pathogenesis of tumor growth, invasion, and metastasis. These processes involve multiple steps and pathways dependent upon the balance between positive and negative regulatory factors, as well as interactions among the tumor, its vasculature, and the extracellular tissue matrix. A tumor remains dormant, the cellular proliferation rate balanced by the apoptotic rate, and unable to grow in size beyond a few millimeters in the absence of the acquired angiogenic phenotype. The mechanism by which tumors switch to the angiogenic phenotype is not known. Therapeutic agents and strategies are being devised either to interrupt or inhibit one or more of the pathogenic steps or mechanisms involved in the process of tumor neovascularization or to target and destroy the tumor vasculature directly. Therapies affecting targets or pathways that cannot be circumvented by alternate mechanisms may enhance efficacy and broaden applicability. These therapeutic approaches may result in small, avascular tumors that are maintained in a dormant state or, perhaps in combination with cytotoxic therapies, they may potentiate shrinkage of tumors to and maintain them in a dormant state. As more efficacious antiangiogenic agents are developed, perhaps even these residual dormant microscopic foci may be eradicated. Antiangiogenic approaches differ from the usual cancer therapies; therefore investigators must devise new paradigms for the clinical development of agents that may only have a static effect on tumors and require long-term, chronic administration. Methods to assess the biologic activity of these compounds in patients are needed. Ultimately, antiangiogenic therapy may prove a powerful weapon in the war on cancer.

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MOLECULAR FUNCTIONS OF THE TUMOR PROGESSION PROTEIN CD44

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The terminus CD44 designates a large and complex family of surface glycoproteins which are generated by alternative splicing. The CD44 proteins play pivotal roles in a variety of biological functions, including cell-cell and cell-matrix interactions, lymphocyte migration and activation, and tumor progression. Expression of the variant exon 6 (v6) was shown to correlate with the metastatic potential of rat and human tumors and a rat v6-specific antibody interfered with metastasis formation in vivo. In human breast and colon carcinoma and in non-Hodgkin lymphoma CD44 variant expression correlates with poor prognosis.

Much of the data concerning the function of CD44 variant molecules is derived from the study of normal cells which need to create new interactions. Examples include hemopoiesis where daughter cells of omnipotent stem cells are comitted to specific lineages by interaction with new micro-environments, dendritic Langerhans cells in the skin which upon antigen contact migrate to the lymph node to present antigen, and embryonic situations where cells dissociate from one site of cellular contacts, and subsequently migrate to and expand at new locations. In these examples CD44 splice variants are utilized to attach cells to matrix components, to receive and transmit signals and to stimulate cells. Tumor cells most likely make use of these properties of CD44 proteins.

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THE CHEMOKINES IP-10 AND MIG IDENTIFIED AS MEDIATORS OF TUMOR NECROSIS IN VIVO

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Human Burkitt's lymphoma cell lines give rise to progressively growing subcutaneous tumors in athymic mice. These tumors are induced to regress by inoculation of Epstein-Barr virus-immortalized normal human lymphocytes. In the present study, analysis of profiles of murine cytokine/chemokine genes expression in Burkitt's tumor tissues excised from the nude mice showed that expression of the murine α-chemokines IP-10 and Mig was higher in the regressing than in the progressive Burkitt's tumors. Previously, IP-10 and Mig were shown to act as inhibitors of angiogenesis in vivo. Therefore, we tested the effects of IP-10 or Mig on Burkitt's tumors growth in nude mice. Inoculation of established Burkitt's tumors with purified human IP-10 or Mig caused visible tumor necrosis in a proportion of the animals, although no complete tumor regressions were observed. Constitutive expression of murine IP-10 in Burkitt's cells reduced their ability to grow as subcutaneous tumors, and caused visible tumor necrosis in a proportion of the animals. Histologically, IP-10 or Mig-treated and IP-10-expressing Burkitt's tumors had widespread evidence of tumor tissue necrosis and of capillary damage, including intimal thickening and vascular thrombosis. Thus, IP-10 and Mig are an antitumor agents that inhibit angiogenesis, promote damage in established tumor vasculature, and cause tissue necrosis in human Burkitt's lymphomas established subcutaneously in athymic mice.