Tumor Invasion and Metastasis: An Imbalance of Positive and Negative Regulation

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Abstract
A group of coordinated cellular processes, not just one gene product, is responsible for invasion and metastasis, the most life-threatening aspect of cancer. It is now recognized that negative factors may be just as important as positive elements. Genetic changes causing an imbalance of growth regulation lead to uncontrolled proliferation necessary for both primary tumor and metastasis expansion. However, unrestrained growth does not, by itself, cause invasion and metastasis. This phenotype may require additional genetic changes. Thus, tumorigenicity and metastatic potential have both overlapping and separate features. Invasion and metastasis can be facilitated by proteins which stimulate tumor cell attachment to host cellular or extracellular matrix determinants, tumor cell proteolysis of host barriers, such as the basement membrane, tumor cell locomotion, and tumor cell colony formation in the target organ for metastasis. Facultative proteins may act at many levels both intracellularly or extracellularly but are counterbalanced by factors which can block their production, regulation, or action. A common theme has emerged. In addition to loss of growth control, an imbalanced regulation of motility and proteolysis appears to be required for invasion and metastasis.

Metastatic Cells Can Dominate the Primary Tumor Population

Metastasis is a cascade of linked sequential steps involving multiple host-tumor interactions (1–3). To successfully create a metastatic colony, a cell or group of tumor cells must be able to leave the primary tumor, invade the local host tissue, enter the circulation, arrest at the distant vascular bed, extravasate into the target organ interstitium and parenchyma, and proliferate as a secondary colony. Angiogenesis is required for the expansion of the primary tumor mass, and new blood vessels penetrating the tumor are frequent sites for tumor cell entry into the circulation (4, 5). Angiogenesis is also required for expansion of the metastatic colony. At any stage, tumor cells must overcome host immune cell killing (2). A very small percentage (<0.01%) of circulating tumor cells ultimately initiate successful metastatic colonies. Consequently, metastasis has been viewed originally by Fidler and Hart (1) as a highly selective competition favoring the survival of a subpopulation of metastatic tumor cells that preexist within the heterogeneous primary tumor.

Fidler’s metastatic subpopulation concept is well accepted, but the relative size of this subpopulation in the primary tumor may vary with time and between tumors. Estimating the size of the metastatic subpopulation is of clinical significance since a prognostic assay based on a sample of the primary tumor can be correlated with tumor cell production, regulation, or action. It appears that the metastatic subpopulation is of clinical significance since a subpopulation of metastatic tumor cells may exist within the heterogeneous primary tumor.

Interactions of the tumor cell with the basement membrane

The basement membrane is the target organ for tumor cell entry and a delicate balance acts to allow or prevent tumor cell entry at any stage. Cell adhesion to the basement membrane surface-mediated receptor-ligand interactions are essential for tumor cell invasion. Invasive tumor cells utilize a variety of integrins that recognize laminin, type IV collagen, and fibronectin in the basement membrane.

Tumor Cell Interaction with the Extracellular Matrix

During the development of invasive tumors, tumor cells disobey the social order of organ boundaries and cross into tissues where they do not belong. The mammalian organism is divided into a series of tissue compartments separated by the extracellular matrix unit consisting of the basement membrane and its underlying interstitial stroma (3, 11). The basal cells of the epithelium or organ parenchymal side of this unit are attached to the basement membrane. On the opposite side, the interstitial stroma contains stromal cells, fibroblasts, and myofibroblasts. The nervous system, muscle cells, and blood vessels are also surrounded by a continuous basement membrane.

The continuous basement membrane is a dense meshwork of collagen, glycoproteins, and proteoglycans which normally does not contain any pores large enough for passive tumor cell transversal. Consequently, invasion of the basement membrane must be an active process. Once the tumor cells enter the stroma, they gain access to lymphatics and blood vessels for further dissemination. Tumor cells must cross basement membranes to invade nerves and muscle. During intravasation or extravasation, the tumor cells of any histological origin must penetrate the subendothelial basement membrane. As a general feature of all types of carcinomas (12), defects in the basement membrane are associated with invasion. In contrast, benign proliferative disorders are all characterized by a continuous basement membrane separating the epithelium from the stroma. The general observation of defective basement membranes associated with cancer invasion and progression indicates that aggressive tumor cells may interact with basement membranes in a manner fundamentally different from that of normal cells. This general feature of malignant tumors provides the foundation for investigation of molecular mechanisms.

Interactions of the tumor cell with the basement membrane can be separated into three steps: attachment; matrix dissolution; and migration. The first step is binding of the tumor cell to the basement membrane surface-mediated cell surface receptors of the integrin (13, 14) and non-integrin (15, 16) variety. Matrix receptors recognize glycoproteins such as laminin, type IV collagen, and fibronectin in the basement membrane.

to 8 h after attachment, a localized zone of lysis is produced in the basement membrane at the point of tumor cell contact. Tumor cells directly secrete degradative enzymes (17) or induce the host to elaborate proteinases to degrade the matrix and its component adhesion molecules. Matrix lysis takes place in a highly localized region close to the tumor cell surface (18), where the amount of active enzyme outbalances the natural proteinase inhibitors present in the serum, those in the matrix, or that secreted by normal cells in the vicinity.

Locomotion is the third step of invasion which propels the tumor cell across the basement membrane and stroma through the zone of matrix proteolysis. An early step in locomotion is pseudopodial protrusion at the leading edge of the migrating cell (19, 20). The induction of pseudopodia is directional, is regulated by cell surface ligand binding, and involves a coordinated mobilization of cytoskeletal elements which interact with the inner membrane surface. The cellular machinery of tumor cell locomotion is a fertile topic for future study and will undoubtedly benefit from insights learned from studies of immune cells (2) and nonmammalian organisms (20). It is now recognized that random tumor cell motility can be regulated by tumor cell cytokines ("autocrine motility factors" and "scatter factors") (19, 21, 22). Autocrine motility factors act through a receptor-activated G protein susceptible to inhibition by pertussis toxin. Augmented random motility by tumor cells causes dispersion at the primary site. In addition, the direction and site of the tumor cell locomotion may be influenced by host organ-derived chemotactic agents. Such chemotactic signals could play a role in the organ-selective homing of metastasis. This could complement other mechanisms of organ homing which include preferential adhesion to organ-specific endothelium and preferential growth in selected organs due to local growth factors (23).

Proteinases: from Correlation to Causality

A general aspect of malignant neoplasms may be an imbalance of proteolysis which favors invasion. However, proteolysis of tissue barriers is not a property unique to tumor cells. It is utilized, for example, during trophoblast implantation, embryo morphogenesis, tissue remodeling, parasitic and bacterial invasion, and angiogenesis. Furthermore, the defect in the tumor cell cannot be simply unbridled production of degradative enzymes. This is because cell migration during invasion requires attachment and detachment of the cell as it moves forward. Lysis of all matrix components around the tumor cell would simply remove the substratum necessary for proper cell traction. Thus, it is probable that the invading tumor cell uses proteolysis in a highly organized manner both spatially and temporally which does not differ functionally from the operating mode of normal cells which migrate through tissue barriers. The difference is that tumor cells couple proteolysis with motility to achieve invasion at times and places which would be inappropriate for normal cells.

The metastasis field has progressed from establishing a correlation between proteolysis and malignant progression to the finding that the actual blockade of certain proteinases will prevent invasion and metastasis. A positive association with tumor aggressiveness has been noted for a variety of classes of degradative enzymes including heparanases (24, 25), serine (26), thiol (27, 28), and metal-dependent enzymes (29–32). Indeed, a cascade including all these enzymes is probably involved in the invasive process, and more than one enzyme is necessary but not sufficient. This conclusion is justified by the finding in multiple laboratories that inhibitors for metalloproteinases or inhibitors of serine proteinases can each block tumor cell invasion of native or reconstituted connective tissue barriers in vitro (33–36). Thus, the enzymes involved in tumor invasion and metastasis may well resemble the proteolytic cascades involved in blood coagulation.

Plasminogen activator, specifically uPA,2 has been closely linked to the metastatic phenotype (37, 38). Anti-uPA antibodies block human HEP-3 cell invasion in the chick chorioallantoic membrane assay and murine B16F10 melanoma cell metastasis following tail vein injection (39, 49). Overexpression of uPA in Hta-ras-transformed 3T3 cells enhanced lung invasion and experimental metastasis formation (41). Serine proteinase inhibitors also block tumor cell invasion through human amniotic membranes (35).

Among the list of enzymes involved in cancer, a large body of information has been accumulated concerning the matrix metalloproteinase gene family (Fig. 1). These enzymes have been subgrouped into three broad categories based on substrate preference: interstitial collagenases; type IV collagenases (gelatinases), and stromelysins (42). The interstitial collagenase is the best characterized and specifically degrades type I collagen (32). Neutrophil collagenase, which has recently been cloned, appears very similar in substrate specificity (43). The stromelysins are three related gene products, stromelysin, stromelysin 2, and PUMP-1, which degrade a variety of matrix components including proteoglycans and noncollagenous glycoproteins such as laminin and fibronectin, as well as the noncollagenous domains of type IV collagen. The role of stromelysin in squamous progression has recently been recognized (44). The type IV collagenases are named for their selective ability to cleave type IV collagen in a pepsin-resistant triple-helical domain thus generating characteristic one-fourth amino-terminal and three-fourths carboxyl-terminal fragments (45). Both a 72-kDa and 92-kDa type IV collagenase exist and complementary DNA cloning has demonstrated that each is a unique gene product (46, 47).

All classes of matrix metalloproteinases are secreted as inactive zymogens and enzyme activation is an important control step in proteolysis. A new model for matrix metalloproteinase proenzyme activation has been proposed (48–51). The essential feature of this model is that the latent form of the matrix metalloproteinase enzymes all have a metal atom sulfhydryl side chain interaction that results in a catalytically inert active center. The sulfhydryl group in this interaction is donated by coproteins such as laminin and fibronectin, as well as the noncollagenous domains of type IV collagen. The role of stromelysin in squamous progression has recently been recognized (44). The type IV collagenases are named for their selective ability to cleave type IV collagen in a pepsin-resistant triple-helical domain thus generating characteristic one-fourth amino-terminal and three-fourths carboxyl-terminal fragments (45). Both a 72-kDa and 92-kDa type IV collagenase exist and complementary DNA cloning has demonstrated that each is a unique gene product (46, 47).

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Among the matrix metalloproteinase family members, an accumulating body of evidence supports a positive correlation

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2 The abbreviations used are: uPA, urokinase-type plasminogen activator; TIMP, tissue inhibitor of metalloproteinases; NDP, nucleoside diphosphate.
the 72-kDa type IV collagenase enzyme is a normal cell component that is dramatically overexpressed in many invasive and metastatic human cancers.

**Natural Proteinase Inhibitors Suppress Invasion**

The secretion and activation of metalloproteinases are not enough to ensure that they will degrade the target matrix substrate (17, 65). This is because natural inhibitor proteins, produced either by the host or by the tumor cell itself, can block the latent or the active metalloproteinases (17). Natural proteinase inhibitor proteins, such as TIMPs (66) plasminogen activator inhibitors may therefore function as metastasis suppressor proteins which act to inhibit tumor cell invasion of the extracellular matrix. TIMP-1, the original member of the TIMP family (67), is a glycoprotein with an apparent molecular size of 28.5 kDa which forms a complex of 1:1 stoichiometry with activated interstitial collagenase, activated stromelysin, and the 92-kDa type IV collagenase. It has been reported that transfection of antisense RNA which blocks TIMP-1 expression enhances the malignant phenotype (68). One explanation for this result is that the antisense RNA blocked the production of TIMP-1 which normally prevented the malignant phenotype. In animal models, administration of recombinant TIMP-1 blocks metastasis (69, 70).

Recently, Stetler-Stevenson et al. (49, 71) have isolated, purified, determined the complete primary structure, and cloned the first new member of the TIMP family, TIMP-2. An identical inhibitor was isolated from endothelial cells by DeClerk et al. (72, 73). TIMP-1 and TIMP-2 are regulated independently and oppositely by 12-O-tetradecanoylphorbol-13-acetate, transforming growth factor β, and other cytokines. TIMP-2 is a 21-kDa protein which selectively forms a complex with the latent proenzyme form of the 72-kDa type IV collagenase. The secreted protein has 194 amino acid residues and is not glycosylated. TIMP-2 shows 37% identity and overall 65.6% homology to TIMP-1 at the deduced amino acid sequence level. The positions of the 12 cysteine residues in TIMP-2 are conserved with respect to those present in TIMP-1, as are 3 of the 4 tryptophan residues; yet the 2 proteins are immunologically distinct. TIMP-2 inhibits at a 1:1 ratio the type IV collagenolytic activity and the gelatinolytic activity associated with the 72-kDa enzyme. Unlike TIMP-1, TIMP-2 is capable of binding to both the latent and activated forms of the 72-kDa type IV collagenase and will abolish the hydrolytic activity of all members of the metalloproteinase family (49, 74). The 92-kDa type IV procollagenase can be found as a complex with TIMP-1 (46). Activation of either the latent 72-kDa or 92-kDa type IV collagenase-TIMP complex can be reversed by binding of a second role of TIMP-1 or TIMP-2. This suggests that on these enzymes there are two separate TIMP-binding sites and that binding of TIMP-1 or TIMP-2 to the latent proenzymes serves a different function than the inactivation that occurs following binding to the active species. The areas of the two proteins which differ in homology may contain the regions responsible for the functional differences (71). The net 72-kDa type IV collagenase activity consequently depends upon the balance between the levels of activated enzyme and TIMP-2. TIMP-2 is a potent inhibitor of cancer cell invasion through reconstituted extracellular matrix (75). TIMP-2 produced by the same tumor cells which make collagenase, therefore, exists as a natural suppressor of invasion.

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**Fig. 1. Matrix metalloproteinase family.** Type IV procollagenase (72 kDa and 92 kDa forms), interstitial procollagenase, neutrophil procollagenase, prostromelysin, prostromelysin-2, and PUMP-1, are represented diagrammatically and aligned to show regions of protein sequence homology. MBD, active site metal binding domain which shows homology to fibronectin but is absent from the other matrix metalloproteinases. Upon treatment with organomercurial compounds in vitro, all seven enzymes are activated with the concomitant removal of an amino-terminal segment of the latent enzyme. The removed segment contains an unpaired cysteine residue within the conserved amino acid sequence PRCGVPDV located immediately adjacent to the proenzyme cleavage site. Site-directed mutagenesis studies have shown that alterations in this sequence result in spontaneous activation of transin, the rat homologue of stromelysin. In the latent proenzyme, this sequence interacts with the metal ion through the unpaired cysteiny1 residue to block activity. Perturbation of this interaction affects activation.

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Metastasis and Tumorigenicity Can Be under Separate Genetic Control

Five years ago investigators in the metastasis field were sure that the new developments in oncogenes were relevant only to tumorigenicity and that separate genes would be found which evoke the metastatic process. At the time, biological assays of oncogenes were restricted to scoring tumorigenicity. Little attention had been paid to metastasis formation. Nevertheless, when the proper studies were done, it was found that transfection of certain oncogenes in the correct recipient cell could induce the complete phenotype of invasion and metastasis. Although the search for specific metastasis-inducing genes goes on, oncogene transfection has provided a model to switch on the effector processes which are required for the cell to carry out invasion and metastasis. These models have revealed that some of the metastasis effector genes can be regulated independently from those which confer tumorigenicity.

The incidence of aberrant gene expression and genetic alterations of the ras and myc gene families have been shown to be important in progression of human cancers and may be useful as prognostic indicators (76). Thorgerisson et al. (77) were the first to report that the activated (mutated) ras oncogene sequences, when transfected into mouse embryo-derived fibroblasts (NIH-3T3 cells), produced numerous metastases. The resultant highly metastatic cells were not more resistant to host immune cell lysis (macrophage or natural killer cells) compared to control cells, indicating that the ras oncogene had augmented the intrinsic aggressiveness of the NIH-3T3 cells. Transfection of H-ras-family oncogenes has been shown to induce metastasis in fibroblasts and epithelial cells of rodent and human origin (56, 57, 59, 78–81). However, H-ras is not the only oncogene which can induce metastatic potential. At lower efficiency, the serine-threonine kinases v-mos, v-raf, and A-raf (79, 82); tyrosine kinases v-src, v-fes, and v-fms (79); and the mutated phosphoprotein p53 (83) have been demonstrated to induce the metastatic phenotype in the appropriate recipient cell.

Experimental evidence indicates that invasion and metastasis require activation of a set of effector genes over and above those which are required for unstranded growth alone. The downstream pathways used in ras induction of tumorigenicity and metastasis have dissimilar features: (a) the adenovirus 2 Eia gene has been demonstrated to suppress ras induction of metastatic potential with no inhibition of soft agar colony formation or tumorigenicity (84); and (b) cells are capable of being transformed by ras but do not metastasize (56, 85). The failure of ras to induce metastasis in certain experimental systems probably reflects a deficiency in, or a suppression of, some of these effector proteins. Several candidate effector proteins have been associated with metastasis in ras transfection models, such as proteinases including type IV collagenase (46, 57, 59, 77), cathepsin L (86), and motility-associated cytokines (21). Thus, in these ras transfection models certain effector genes are activated, or suppressed, possibly in coordinated manner, to induce metastasis formation. Studies have revealed that several oncogenes such as v-src and ras, tumor-promoting phorbol esters and growth factors such as epidermal growth factor and platelet-derived growth factor will induce transin (rat homologue of human stromelysin) mRNA transcript levels. The observation that these agents all induce a rapid stimulation of c-fos that precedes the induction of transin mRNA and the knowledge that protein synthesis is required for this induction suggests that c-fos may act as a “third messenger” and may directly modulate transin gene transcription (44, 87). Some of these oncogene-associated effector genes may regulate cell motility and proteolysis, and this forms a common thread with separate work on proteinases, motility, and angiogenesis.

Several metastasis suppressor genes have been reported in transfection experiments. The Adenovirus 2 E1a gene, previously discussed, suppressed c-Ha-ras induction of metastatic behavior of rat embryo fibroblasts, as assayed by tail vein injections (84). In the same model system Gattoni-Celli reported that ras and E1a cotransfected rat embryo fibroblasts expressed higher levels of major histocompatibility complex class I genes (88). When the H-2Kb major histocompatibility complex gene was transfected into rat embryo fibroblasts, previously transfected with ras, reduced rates of tumorigenesis and metastasis were observed upon injection into triple-deficient mice (89). The data suggest the involvement of H-2Kb in arms of the immune response, such as macrophage-mediated cytotoxicity, or in the suppression of nonimmunological aspects of the tumor metastatic process.

TIMP-1 was demonstrated to suppress the metastatic potential of Swiss 3T3 cell using antisense transfection. The antisense TIMP-1 construct reduced TIMP activity by 47–68% in the transfected cells and increased invasiveness in an in vitro assay, as well as tumorigenicity and metastatic potential in vivo (68).

The nm23 gene was identified on the basis of its reduced steady state RNA levels in five highly metastatic K-1735 melanoma cell lines, as compared to two related, low metastatic potential k-1735 melanoma cell lines (90). In human breast cancer reduced nm23 RNA levels have been associated with the presence of lymph node metastases at surgery (91) as well as decreased patient disease-free and overall survival (92). In other cancer cell types, such as colorectal carcinoma, no significant association of nm23 RNA levels with metastatic progression was observed (93). Transfection of the murine nm23-1 complementary DNA into highly metastatic murine K-1735 TK melanoma cells resulted in a reduced incidence of primary tumor formation, significant reductions in tumor metastatic potential, and altered tumor cell responsiveness to the cytokine transforming growth factor β in vitro (94).

An important clue to nm23 function(s) came from its virtual identity with the Drosophila awd gene product (95–96). Mutations which result in reduced awd expression or the production of a mutated protein do not significantly alter embryonic development but do alter the development of multiple tissues postmetamorphosis, when presumptive adult tissue in the imaginal discs begins to divide and differentiate. These abnormalities include altered morphology of the wing discs, larval brain and proventriculus; aberrant differentiation of the wing, leg, and eye-antennae imaginal discs and ovaries; and cell necrosis, predominantly in the wing discs. nm23/awd may contribute to the normal development of tissues, which may include signal transduction of cell to cell communication. Loss of nm23/awd expression may lead to a disordered state, favoring aberrant development or tumor progression to the metastatic state.

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