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Intercellular adhesion: mechanisms for growth and metastasis of epithelial cancers

Eric M. Balzer^{1,2,3} and Konstantinos Konstantopoulos^{1,2,3,*}

¹The Institute for NanoBioTechnology, Johns Hopkins University, Baltimore, MD, USA

²Johns Hopkins Engineering in Oncology Center, Physical Sciences in Oncology Center of the National Cancer Institute, Johns Hopkins University, Baltimore, MD, USA

³Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA

Abstract

Cell–cell adhesion molecules (CAMs) comprise a broad class of linker proteins that are crucial for the development of multicellular organisms, and for the continued maintenance of organ and tissue structure. Because of its pivotal function in tissue homeostasis, the deregulation of intercellular adhesion is linked to the onset of most solid tumors. The breakdown of homeostatic cell adhesions in highly ordered epithelial sheets is directly implicated in carcinogenesis, while continued changes in the adhesion profile of the primary tumor mass facilitate growth and expansion into adjacent tissue. Intercellular adhesion molecules are also involved in each subsequent phase of metastasis, including transendothelial migration, transit through the bloodstream or lymphatics, and renewed proliferation in secondary sites. This review addresses various roles of cadherin- and selectin-mediated intercellular adhesion in tumor initiation and malignant transformation, and discusses the mechanisms for the arrest and adhesion of circulating tumor cells to the vessel endothelium. Considering the contributions of these CAMs to cancer progression in the context of a systematic biological framework may prove valuable in identifying new ways to diagnose and treat cancer.

INTRODUCTION

The metastatic journey of a cancer cell is defined as a stepwise progression through various host environments to reach new and unfamiliar sites and establish secondary tumors. Whereas, neoplasia concerns the deregulation of mitosis, the central theme in metastasis is the acquisition—or activation—of cell motility. However, we now know that both of these processes involve the modification of adhesive interactions between the tumor cell and its occupied niche. The importance of cell–cell and cell–matrix adhesion is evident and well documented during active phases of cell movement, such as directed locomotion through host parenchymal and stromal tissue. In addition, the importance of cell adhesion in more ‘passive’ phases of dissemination has also been emphasized in recent years, as blood-borne

tumor cells must adhere to components of the vasculature to survive the circulation and successfully extravasate into distant tissues. The binding interactions between tumor cells and cellular components of the microenvironment are many and varied during the course of tumor progression, which requires tumor cells to exercise phenotypic plasticity in order to interact with tissues at each stage of the metastatic process.

In general use, the term ‘cell adhesion’ collectively refers to the broad fields of cell–cell and cell–substrate adhesion. These distinct forms of adhesion are actually mediated by separate classes of cell adhesion molecules (CAMs), which are divided into four major groups: the cadherins, the integrins, the selectins, and the immunoglobulin superfamily. As a complete discussion of each of these classes is beyond the scope of any single review, we will restrict our focus to CAMs that mediate intercellular adhesion, since cell–cell adhesion is involved in every phase of the metastatic process. Specifically, we will discuss cadherin-mediated mechanisms of intercellular adhesion implicated in the onset of primary tumorigenesis and enhanced cellular mobility, and selectin-mediated mechanisms for the dissemination of individual tumor cells through vascular compartments. Emerging theories regarding the role of cell–cell adhesion in promoting the survival and extravasation of circulating tumor cells (CTCs) will also be discussed in the context of both acute disease and latent recurrence. Finally, we will discuss methodologies for systematic analysis of the complex interconnected roles of cell–cell adhesion on the tissue scale to aid the design of novel chemotherapies.

THE LOSS OF CELLULAR COHESION DISRUPTS EPITHELIAL STRUCTURE AND IS AN EARLY EVENT IN PRIMARY CARCINOGENESIS

At its most fundamental level, cancer is a disease of disorder. When an epithelial cell loses the ability to regulate its division and execute controlled growth patterns, it reverts to a unicellular mode of operation and therefore abandons the altruistic social scheme required in complex multicellular organisms. Deregulated cell growth patterns manifest as structural changes in the cancerous tissue that become more exaggerated as the disease progresses. Beginning with the onset of hyperplasia, dividing cells must alter their adhesive properties to each other and to the surrounding elements of their physiological niche, to accommodate the growing mass of the cell population. Accordingly, there were reports as early as the 1940s that cancerous cells display weaker cell–cell adhesiveness, and that tumor tissue is often easier to mechanically separate than normal tissue.^{1,2} As such, histological irregularities are inevitable hallmarks of neoplasia. In fact, the common usage of the word ‘cancer’ derives from the Greek words ‘carcinos’ and ‘carcinoma’, meaning crab or crablike, which the ancient Greek physician Hippocrates used in the fourth century BC to describe the radial finger-like extensions of invading cells from the center of a malignant tumor mass. Today, we know that intercellular adhesion critically regulates of the structural changes that drive the acquisition of invasive potential.

As the vast majority of solid tumors develop from epithelial tissues,³ there has historically been a strong focus on dissecting epithelial biology as a means to understand the mechanisms that drive tumor formation and metastasis. Healthy epithelia are polarized sheets of tightly associated cells that line surfaces throughout the body and perform a vital

barrier function. Epithelial cells are unique among polarized cell types in that maintenance of their apical–basal polarity requires proper structural assembly, which in turn depends on intercellular junctions that provide structural integrity and conduits for nutrient and fluid exchange. Among these are gap junctions formed by intercellular linkage between connexins proteins, and tight junctions formed by heterotypic association of occludins and claudins,⁴ the latter of which is responsible for determining the ‘leakiness’ of a barrier with respect to the transepithelial diffusion of dissolved solutes and proteins.^{5,6} Perhaps, the most widely studied of these junctional complexes are the cadherin-mediated adherens junctions, which are directly implicated in the onset and malignant transformation of carcinomas.

The cadherins and cadherin-like proteins comprise a superfamily of calcium-dependent intercellular adhesion glycoproteins that serve critical roles in development and tissue homeostasis.^{7,8} In the context of cancer, the best studied of these are the classical cadherins, which are named for the tissues from which they derive.⁹ E-cadherin, an integral membrane protein expressed in differentiated epithelial tissues, contains an extracellular domain that homo-typically binds to other E-cadherin molecules on the surface of neighboring cells. Clusters of intercellular E-cadherin homodimers at cell junctions link to the actin cytoskeleton through cytoplasmic adaptor proteins. Known as adherens junctions, these protein complexes establish and maintain the structure of epithelial sheets.¹⁰ In 1994, it was demonstrated that E-cadherin null mouse embryos at the blastocyst stage fail to form the trophectodermal epithelium and die shortly after implantation,¹¹ emphasizing the pivotal role that E-cadherin plays in epithelial morphogenesis. Around the same time, it was also discovered that selective E-cadherin expression can suppress invasion of tumor cells by enhancing cell–cell adhesion,^{12,13} corroborating observations that tumor cells display a reduced proclivity to self-adhere.^{1,2} Studies such as these have helped to establish the notion that malignancy involves dedifferentiation of epithelial cells through the loss of key epithelial markers. Accordingly, E-cadherin is among the most critical determinants of the epithelial phenotype and has been directly implicated in the transition from localized to invasive disease.

THE CADHERIN SWITCH AND THE EPITHELIAL-MESENCHYMAL TRANSITION IN TUMOR PROGRESSION

A strong research emphasis has been placed on the stage of solid tumor development in which poorly differentiated epithelial cells acquire a mobile phenotype and release from a primary growth to infiltrate the surrounding extracellular matrix (ECM). Cells within the primary tumor mass undergo a transition from an epithelial morphology to that of a nonpolarized, migratory mesenchymal phenotype, in a process known as the epithelial-to-mesenchymal transition (EMT). The ability of cells to exhibit this morphological plasticity in switching between epithelial and mesenchymal states was first described for the developing chick embryo by Frank Lillie in 1908,¹⁴ but it was not until 1982 that Greenberg and Hay introduced the term ‘epithelial–mesenchymal transformation’ to identify EMT as a distinct developmental program.¹⁵ Cell cohesion is among the defining hallmarks of the epithelial phenotype, while progression toward mesenchymal status requires tumors cells to dissolve homotypic cell–cell bonds in favor of cell–matrix and heterotypic inter-cellular

interactions. In fact, the suppression of homotypic cell–cell adhesion is a known regulator of EMT, as function-blocking antibodies against E-cadherin induce EMT in kidney epithelial cells.¹⁶ Similarly, transcriptional silencing of E-cadherin has been shown to induce an EMT in breast and colon carcinoma cell lines.¹⁷ Conversely, exogenous expression of E-cadherin in poorly differentiated epithelial tissues lacking E-cadherin can induce the reverse phenomenon, a mesenchymal–epithelial transition, and is sufficient to restore the expression of epithelial markers, such as cytokeratins and occludin. Restoration of E-cadherin also is sufficient to induce the reformation of adherens junctions,¹⁸ and suppress metastasis.^{13,19}

In vivo, E-cadherin can be silenced through multiple means. Inactivating loss-of-function or deletion mutations are possible, although tumor cells more commonly suppress E-cadherin epigenetically *via* promoter hypermethylation at the *CDH1* locus.^{20,21} Because phenotypic reversibility is an inherent feature of organogenesis that is required for adult tissue homeostasis, EMT should not be thought of as a permanent and inflexible process, but rather as a form of dynamic adaptation that enables cells to efficiently respond to migratory stimuli.²² Tumor cells enact this adaptation by modifying their adhesive properties to facilitate release from the tissue of origin and dispersal through new environments (Figure 1). The loss of E-cadherin expression is usually accompanied by the upregulation of N-cadherin, a separate member of the cadherin family which is causally linked to the increase in motility and invasiveness of dedifferentiated tumor cells.²³ A naturally occurring component of embryogenesis, this ‘cadherin switch’ spatiotemporally correlates with cell scattering and the mesenchymal phenotype, and is a prominent pathological marker for EMT and pathological cancer staging.^{24–26} It is believed that upregulation of N-cadherin promotes the invasion of tumor cells by facilitating heterotypic adhesion to N-cadherin-expressing fibroblasts of the adjacent stromal tissues^{23,25} (Figure 1). Heterotypic cell–cell adhesion also appears to facilitate the interaction of tumor cells with N-cadherin-expressing endothelium.²⁷ N-cadherin has also been shown to dissolve vascular endothelial-cadherin-mediated endothelial cell junctions on contact with N-cadherin-expressing melanoma cells, which promotes tumor cell diapedesis.²⁸ Findings such as these provide mechanistic insight into the manner in which N-cadherin promotes tumor dispersal, and have challenged the notion that the loss of E-cadherin necessarily precedes the gain of N-cadherin during tumor progression. Specifically, the proinvasive effects of N-cadherin can exert dominant effects over the anti-invasive effects of E-cadherin when ectopically expressed.^{23,29} Thus the upregulation of N-cadherin is capable of initiating early phases of dissemination from the primary site independently of E-cadherin. However, the presence of independent regulatory mechanisms suggests that temporal overlap of E- and N-cadherin expression is likely to occur to some extent throughout the course of the cadherin switch and EMT.

Signaling Mechanisms of Cadherin-Mediated Adhesion

The reduced levels of functional E-cadherin are causally linked to the initiation of EMT, a relationship which is attributed to the intracellular signaling functions of the E-cadherin complex. Although the intercellular association of E-cadherin ectodomains provides a direct physical connection between adjacent epithelial cells, the cytoplasmic tail region performs signaling functions that are also crucial for the maintenance of cell–cell adhesions. The cytoplasmic cadherin complex is a collection of cadherin-associated adaptor proteins. The

foremost of these associated signaling components is β -catenin, which binds directly to the cytoplasmic tail of E-cadherin. Normally sequestered at the plasma membrane, free cytoplasmic β -catenin is phosphorylated by glycogen synthase kinase-3 beta (GSK-3 β), which targets it for degradation by the proteasome.³⁰ However, suppression of GSK-3 β through activation of the Wnt signaling pathway allows β -catenin to translocate to the nucleus where it binds and inhibits the transcriptional repressors TCF/LEF, resulting in transcription of genes associated with cell proliferation, such as c-myc and cyclin D1. Nuclear translocation of β -catenin helps explain the pathological linkage between hyperplasia and the gradual breakdown of epithelial morphology observed during early tumor development, as the release of β -catenin from the plasma membrane impedes efficient cadherin function and cell cohesion, while simultaneously promoting the expression of gene targets that favor cell growth.

Several mechanisms have been described for the activation of β -catenin during tumor progression. Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), can cleave both E- and N-cadherin,^{31,32} causing β -catenin to be shed from the plasma membrane. Because ADAM10 is upregulated in response to nuclear translocation of β -catenin, this action induces a feedback loop that perpetuates the degradation of cadherin-mediated cell junctions and release of β -catenin into the cytoplasm, allowing nuclear translocation, and the upregulation of pro-growth signals. Signaling through β -catenin can also be achieved through activation of the Wnt pathway, and can directly modulate the expression of the ECM proteins fibronectin and laminin-5 γ 2, and membrane type 1-matrix metalloproteinase,^{33,34} which collectively promote a mesenchymal phenotype and reduce epithelial cohesion. Furthermore, the strength of cadherin-mediated cell–cell adhesion can be enhanced or weakened by selective phosphorylation of specific carboxy-terminal cadherin residues, which influence the binding of β -catenin.³⁵ In addition, gain-of-function mutations in β -catenin or loss-of-function mutations in either GSK-3 β or the adenomatous polyposis coli tumor suppressor can induce transcription of the pro-EMT transcription factors including Twist, Snail, ZEB, and Slug,^{17,36–39} each of which favors the suppression of E-cadherin and the upregulation of N-cadherin. Tumor cells can therefore utilize both random mutagenesis and epigenetic silencing to suppress cadherin-mediated cell–cell cohesion, thereby deregulating β -catenin and other Wnt pathway effectors⁴⁰ to promote the invasive phenotype.

ADHESIVE INTERACTIONS OF INVADING AND CIRCULATING TUMOR CELLS

Invading tumor cells must breach multiple tissue barriers to disseminate to secondary locations. For carcinomas, the first barrier encountered is the epithelial basement membrane (BM)—a dense 50–100 μ m thick sheet of ECM containing type IV collagen, laminin, and various proteoglycans.⁴¹ Healthy epithelial sheets adhere to the BM through basal compartmentalization of substrate adhesion molecules, but neoplastic transformation and the gradual onset of epithelial dysplasia progressively disrupt this structural scheme by abolishing cellular polarity⁴² and promoting release from the BM. Cells undergoing EMT also secrete proteolytic enzymes, which degrade the BM and enable expansion into healthy

tissues at the periphery of the tumor mass.^{43,44} Although a loss of BM adhesion in this context is necessary for tumor cells to escape the primary site, invading cells continue to depend on adhesion to the ECM and cellular components of the stromal tissues to move through the dense interstitial matrix and ultimately intravasate into the vasculature.

The circulatory system of the human body is the main conduit for tumor spread, as cells that successfully intravasate into the blood or lymph can be rapidly transported to distant tissues. Tumor cells may enter the bloodstream by actively invading through the vessel endothelium in response to a chemotactic stimulus, or by attracting new vessels *via* secretion of vascular endothelial growth factor (VEGF) or other angiogenic stimuli.⁴⁵ Alternatively, tumor cells may enter into circulation by more passive or circumstantial means, as when shed directly into the blood from highly vascularized primary tumors, or sloughed off into systemic circulation as a result of surgical manipulation of the primary lesion.^{46,47} However, they enter the vasculature, CTCs correlate with elevated risk for metastatic colonization, a realization which has spurred efforts to develop effective screening methods for CTCs in patient blood. The majority of the current CTC literature deals with the technical challenges of tumor cell detection; however, it is important to understand the biological mechanisms, which disseminated tumor cells (DTCs) utilize to survive and eventually escape the circulation. The adhesive interactions of nonadherent tumor cells with components of the endothelium and other blood-borne cells are of particular interest in this regard. Two models of vascular CTC retention are supported by the collective body of research: a passive mechanism whereby tumor cells and tumor emboli are mechanically trapped by size restriction in the microvasculature, and an active mechanism wherein tumor cells engage host structures to resist shear forces of blood circulation (Figure 2). The evidence for both of these mechanisms will be discussed.

CTCs interact extensively with constituents of the blood, including platelets, leukocyte subpopulations, and other immune cells. Tumor cells may also maintain or re-establish homotypic adhesion during deposition into the bloodstream, and circulate as clusters that are detectable by optical screening methods.⁴⁸ The propensity for tumor cells to aggregate in suspension is a documented phenomenon⁴⁹ that has been shown to promote survival through resistance to anoikis,⁵⁰ and the development of stem-like properties.^{51,52} Although E-cadherin-negative cells can be detached from a stationary tumor mass by fluid shear flow rates found in lymphatic vessels or venules (~ 3.5 dyn/cm²), primary tumor cells expressing E-cadherin resist disaggregation in excess of 100 dyn/cm². In this example, the loss of E-cadherin would enable lymphatic circulation to detach small groups of cells from vesiculated tumors, and deposit them in lymph nodes without the prerequisite for EMT or localized invasion.⁵³ Conversely, aggregates of E-cadherin-positive cells deposited into the bloodstream may also benefit from strong cohesion, as tumor cell clusters better resist hematogenous stresses, including mechanical deformation and death of individual arrested cells,^{54–56} immunocytotoxic recognition by circulating natural killer (NK) cells,^{57–59} and anoikis^{50,60,61} (Figure 2).

Tumor cells undergo heterotypic clustering with blood platelets in a manner that correlates with metastatic potential.⁶² The recruitment of platelets to the tumor cell surface prevents the recognition of surface antigens by cytolytic NK cells, and has been shown to promote

metastasis in mice.⁶³ Platelet adhesion is mediated primarily by the selectins, a family of transmembrane C-type lectin CAMs that bind glycosylated surface ligands.⁶⁴ Upregulation of tumor-associated tissue factor by tumor cells leads to the production of thrombin, which activates platelets and mobilizes stores of P-selectin from cytoplasmic α granules to the cell surface, facilitating platelet adhesion to sialofucosylated glycoproteins, such as CD44 variant isoforms,^{65,66} carcinoembryonic antigen,⁶⁷ and podocalyxin⁶⁸ on the surfaces of neuroblastoma, small cell lung cancer, and colon carcinoma cells.^{69,70} Selectin-mediated tethering occurs rapidly, but is relatively weak,⁷¹ and is subsequently augmented by firm bonds between platelet integrins ($\alpha_{IIb}\beta_3$) and tumor cell glycoproteins which may utilize fibrinogen and Von Willebrand factor as bridging molecules.^{72,73} Leukocytes may also aggregate with CTC-platelet emboli *via* an L-selectin-dependent pathway⁶⁴ (Figure 2). Activated endothelial cells, expressing P- and E-selectin, may directly capture free-flowing tumor cells.^{74,75} Moreover, activated platelets attached to the surface of an endothelium bound tumor cell can bind free-flowing tumor cells in a P-selectin-dependent manner,⁷⁵ and augment the extent of tumor cell adhesion to the endothelial cell-coated vessel wall. Successful tethering of activated platelets to endothelium adherent tumor cells can lead to vascular hyperpermeabilization through secretion of VEGF,⁷⁶ which may promote the extravasation of associated tumor cells into secondary sites.

In animal models of metastasis, 98% of melanoma cells injected into the venous circulation arrested in the pulmonary capillary bed and were retained there for at least 1 h,⁷⁷ indicating that CTCs arrest efficiently within the microvasculature. In an effort to understand the mechanisms underlying this vascular arrest of CTCs, new and compelling findings have documented that free-floating epithelial cells protrude their plasma membrane with thin bundles of cytoskeletal filaments, following liberation from the substratum. Termed microtentacles, these protrusions are comprised primarily of microtubule bundles and vimentin intermediate filaments, and utilize a kinesin-dependent motion to probe the immediate extracellular environment to engage nearby cells.^{78–81} Microtentacles have been implicated as contributors to metastatic potential,^{79,82} and have been directly linked to the onset of *twist*-induced EMT,⁸³ and lung retention of CTCs.^{82,84} The prevailing hypothesis is that microtentacles not only reinforce the cohesion of epithelial cells as part of a normal wounding response, but also provide an unintended advantage for the reattachment of CTCs—particularly in the absence of anoikis—by stimulating the adhesion of epithelial cells to both endothelial monolayers and exposed regions of ECM.^{79,85} Microtentacles may also facilitate aggregation of CTCs at sites of primary endothelial attachment, whereby a single cell arrests on the endothelium and subsequently tethers additional cells as others flow past (Figure 2). This mechanism was directly observed for colon and breast tumor cells *in vivo*, and was found to depend on the interaction of tumor-associated T³ glycoantigen and galectin receptors.⁸⁶ Although no evidence to date has indicated that microtentacles contain specific plasma membrane domains specialized for adhesion, it may be that these structures perform their pro-adhesive function by bringing receptors/ligands into the proximity of their cognate ligands/receptors on nearby targets.

Adhesion of CTCs to components of the circulatory system, together with resistance to anoikis, appear to facilitate a phenomenon known as tumor dormancy, in which occult DTCs

persist quiescently for extended periods of time and establish latent metastases long after the primary therapy has ended. Such DTCs represent a major clinical challenge, as they resist antiproliferative chemotherapies and can resume proliferating given appropriate environmental stimulus, such as reimplantation into the primary site.⁸⁷ According to the ‘seed and soil’ hypothesis, CTCs (the ‘seeds’) indiscriminately populate organs throughout the body, but proliferate only in permissive environments (the ‘soils’). Indeed, organ-specific patterns of metastasis have been reported for many cancers,⁸⁸ which may result from selective activation of tumor cells in spite of widespread organ seeding through ubiquitous adhesive interactions. In contrast, an exceedingly low frequency of reactivation events are reported to occur *in vivo* relative to the number of tumor cells that successfully seed secondary organs.⁷⁷ Given the relative inefficiency of DTC proliferation in secondary sites, in spite of high rates of tumor cell retention, novel therapeutic tools to reduce the efficiency of CTC readhesion may be effective tools to reduce the overall survival of micrometastatic progenitor cells. The mechanisms of CTC adhesion discussed here, including selectin-ligand pairing, cell–cell aggregation, and the possible underlying role of microtentacles in each of these processes, should be further explored to design therapies that challenge the retention and establishment of dormant DTC populations in distant organs.

CONCLUSION

Summary Statement and Clinical Perspectives for Systems Analysis

Cellular adhesion is a fundamentally important component of adult homeostasis, and virtually every phase of multicellular development. On the tissue scale, organs and their supporting stroma depend on appropriate cell–cell and cell–substrate interactions to execute their functions and maintain proper structure. On the microscale, individual cells utilize their contact with external substrates to relay and incorporate stimuli that direct their behavior and influence a host of processes, including gene expression, motility, and differentiation. Neoplastic transformation necessitates changes in the adhesion profiles that break down the primary tissue structure to accommodate the expanding tumor mass. Cancer cells respond to these disturbances in ‘normal’ cell adhesion *via* a host of intracellular signaling events that can alter their migratory and invasive properties and provide both the impetus and the means to abandon the social scheme of the primary organ. This dedifferentiation of specialized cell types is at the heart of the malignant transformation for most solid primary tumors, such that epithelial cells revert to mesenchymal phenotype, initiate novel adhesions with cells in the stromal components, and begin secreting proteolytic enzymes to expand into healthy tissues. Arrival within the blood or lymphatics provides tumor cells the opportunity to aggregate homotypically with other tumor cells. Alternatively, tumor cells may heterotypically associate with hematocytes and leukocytes, shielding them from immunological and mechanical stresses encountered in circulation, and also promoting adhesion to the endothelium and regions of exposed BM. Given the relative success of clinical management for most solid primary cancers, and the inability of current therapies to effectively suppress the spread and reactivation of DTCs, there is a pressing need to develop novel strategies to selectively target these cells. Because of the systemic presence of CTCs and DTCs, accomplishing this difficult task this will likely require that novel therapeutic strategies

holistically consider the effects of novel anti-CTC/-DTC therapies on all components of the biological system (i.e., endothelium, and host blood cells) and not just the tumor cells.

Because the adhesive profile of cancerous tissue changes as tumors progress, chemotherapeutic strategies which target cell adhesion should also account for the inherent complexity in biological systems, and the inevitable side effects of interfering with endogenous adhesion receptors. Recent advances in proteomics have made it possible to dynamically observe such molecular adaptations over the course of tumor progression, and require only small samples obtainable from tissue biopsies.⁸⁹ These analyses are sensitive to changes in both the tumor and its surrounding microenvironment, the latter of which is highly influential in determining patient prognosis.⁹⁰ Together, the tumor and its associated stroma comprise a complex biological system that is collectively more predictive of clinical outcome than either of its individual parts. With this in mind, rapid clinical proteomic analyses may foster the development of personalized medicine by assigning diagnostic and/or prognostic value to adhesion biomarkers, thereby helping to improve detection, diagnosis, and therapeutic management of cancer on a patient-to-patient basis. In addition, the development of computational modeling techniques can provide quantitative analyses of how individual intercellular adhesion events collectively drive tissue assembly on the population scale.^{91,92} The strength of this approach is that it can determine the influence of individual parameters (such as expression of function of adhesion receptors) on the collective behavior of an integrated biological system (i.e. a tumor and its surrounding environment); a scenario that is unattainable in *in vitro* experimentation. Such computational approaches may help basic researchers to integrate important cell and molecular biology discoveries into a larger framework which can quantitatively predict how modification of an adhesion protein (e.g., *via* deletion or inhibition) could influence the structure, growth patterns, and drug susceptibility of a tumor. Systems analysis is a powerful tool which can be used to predict the clinical effectiveness of novel anti-adhesive compounds at very early stages in the drug discovery process, helping to streamline and optimize the development of novel chemotherapies.

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FIGURE 1.

Neoplastic transformation and malignant conversion are driven by the loss of epithelial adhesions. (a) Epithelial cells are depicted schematically as polarized cells that adhere basolaterally to one another atop a basement membrane (BM), forming a barrier that separates the lumen and stromal compartments of parenchymal tissues. (b) Progressive loss of tight junctions and adherens junctions accompanies proliferation *in situ*. As the primary tumor expands, cells respond to the loss of E-cadherin and release of β -catenin by undergoing an epithelial-to-mesenchymal transition that enables the redistribution of integrin profiles to release from the BM, secretion of proteases to degrade the stroma, and upregulation of N-cadherin to facilitate interactions with mesenchymal cells during subsequent invasion.

FIGURE 2.

Mechanisms of circulating tumor cell (CTC) adhesion. (a) Schematic illustration showing active and passive mechanisms of CTC arrest. Tumor cells may be passively introduced to the circulation at sites of tumoral vascularization, or they may actively seek out nearby blood vessels ('migration', 'invasion', and 'intravasation'). In the passive model (blue-dotted line), cells may be deposited as homotypic clusters that lodge in narrow capillaries due to size restriction (I). In the active model (green-dotted line), invasive tumor cells extend dynamic microtentacle projections and heterotypically associate with platelets and leukocytes to maximize contact with the vessel wall. Tumor cell platelet-leukocytes emboli adhere to endothelial L-selectin ligands (II), while tumor cells can also directly tether to arrested platelets and fibrin that concentrate at sites of tissue injury (III). (b) Fluorescence micrograph of microtentacles on the surface of an invasive MDA-MB-436 breast tumor cell. The pictured cell is in the process of adhering to an endothelial monolayer on its ventral surface (not pictured) (scale bar = 10 μm).