Tumors contain a vastly complicated cellular network that relies on local communication to execute malignant programs. The molecular cues that are involved in cell-cell adhesion orchestrate large-scale tumor behaviors such as proliferation and invasion. We have recently begun to appreciate that many tumors contain a high degree of cellular heterogeneity and are organized in a cellular hierarchy, with a cancer stem cell (CSC) population identified at the apex in multiple cancer types. CSCs reside in unique microenvironments or niches that are responsible for directing their behavior through cellular interactions between CSCs and stromal cells, generating a malignant social network. Identifying cell-cell adhesion mechanisms in this network has implications for the basic understanding of tumorigenesis and the development of more effective therapies. In this review, we will discuss our current understanding of cell-cell adhesion mechanisms used by CSCs and how these local interactions have global consequences for tumor biology.

Introduction: Building the Network Infrastructure

Current treatment regimens for many solid tumors are still palliative in nature, usually involving a combination of surgical resection, aggressive radiation and chemotherapy. These treatments, despite significant initial regression of the tumor bulk, are often followed by tumor recurrence, decreased quality of life and eventually death. Malignant tumors of numerous origins are now recognized as a heterogeneous population of cells constituting a cellular hierarchy with therapeutically resistant stem-like cells, termed cancer stem cells (CSCs), at the summit. It should be noted that multiple models for tumor formation exist noneclusively. Tumorigenesis may be explained by clonal evolution, microenvironmental factors and stem cell initiation. As such, one or a combination of these processes may be involved in individual tumor formation.

CSCs (also referred to as stem-like tumor cells, tumor initiating cells or tumor propagating cells) possess several features of normal stem cells, namely the ability to self-renew and recapitulate cell types of the specific organ, in this instance the diverse tumor mass. The defining feature of a CSC is its ability to form a tumor upon secondary transplantation. Using this functional assay, CSCs have been isolated from primary human cancers, including brain, breast, skin, colon, colon, skin and prostate. Mechanistic studies have been aimed at understanding the signaling pathways of CSCs, as this is critical for understanding their biology and will aid in the development of more potent therapeutic strategies. Complementary studies have been conducted with in vivo models and utilized microenvironments of different molecular backgrounds, highlighting the importance of direct and dynamic interaction of CSCs with the surrounding stromal microenvironment or “niche.” The complex niche interactions by CSCs regulate malignant programs. However, limited information is available as to how these aberrant cell populations home to and communicate with the microenvironment. Targeting the stem cell niche may permit control of CSC genesis and maintenance through cell-cell, cell-extracellular matrix and cell-soluble factor interactions.

The focus of this review will be to highlight adhesion and communication mechanisms involved in niche interactions. The contribution of many of these interactions are yet to be defined across CSC systems, but evidence demonstrates that they can impact the CSC phenotype in certain contexts. Cell-cell communication is likely to be involved in larger scale tumorigenic programs such as self-renewal, proliferation, survival and invasion and in some cases, epithelial to mesenchymal transition (EMT). The major interactions to be covered include tight junctions, gap junctions, integrins, cadherins and immunoglobulin superfamily cell adhesion molecules (CAMs) including junctional adhesion molecules (JAMs), receptor tyrosine phosphatase PTP, intercellular CAM (ICAM), L1CAM (CD171) and neural CAM (NCAM). The role of these communication and adhesion mechanisms are discussed in detail below and summarized in Figure 1. Importantly, little is known about how these structures modulate important cell fate decisions in CSCs. Determination of cell-cell interaction effects on symmetric and asymmetric division programs and EMT is likely to be informative considering the processes are vital to CSC compartment maintenance, outgrowth, and tumorigenic progression.

Extracellular Matrix

The extracellular matrix (ECM) is a key component of many tumor microenvironments, allowing communication that can...
modify both the tumor cell and microenvironment, thereby promoting malignant phenotypes. Importantly, many tumor microenvironments, such as those in the brain, have a specialized ECM that is unique from normal ECM which mediates invasion. In addition to binding numerous receptors, integrins act as receptors for many ECM ligands (including laminins, fibronectin, collagens and vitronectin) and serve as signal transduction machinery, linking extracellular adhesion to intracellular programs. Integrins are known to interact with multiple receptors including EGFR, insulin-like growth factor receptor (IGFR-1), platelet derived growth factor (PDGF), vascular endothelial growth factor receptor 2 (VEGF2) and the endothelial cell receptor Tie2. As such, they influence diverse signaling cascades such as PI3K and MEK-ERK and numerous cell types including endothelial cells and immune cells.

**Cell Adhesion Molecules**

CAMs are comprised by multiple groups including calcium-dependent integrins and cadherins and calcium-independent immunoglobulin superfamily cell adhesion molecules, which include JAM, PTPμ, NCAM, ICAM and L1CAM. These adhesion molecules have diverse functions in normal setting and have been shown to influence numerous immune cell types (monocytes, T cells, platelets and DC cells) as well as other stromal cells including fibroblasts and endothelial cells.

Cadherins comprise a multi-member glycoprotein family of transmembrane calcium-dependent adhesion molecules that maintain tissue structure in normal and pathologic settings. This is accomplished through regulation of cell-cell interaction, migration and signaling. The cadherin super-family is defined by extracellular cadherin repeats, a central transmembrane region and variable intracellular binding domains conserved among each of the four subgroups, classical, desmosomal, atypical and protocadherin. The cadherins possess intrinsic signaling capabilities, modulating additional pathways depending on binding partners. These binding partners consist of varied extracellular receptors: these include fibroblast growth factor receptor 1 (FGFR1), epidermal growth factor receptor (EGFR) and Frizzled receptors. As such, cadherin family members have been shown...
to regulate diverse signaling pathways known to influence cell fate decisions including the MEK-ERK, canonical Wnt, FGF, AKT and PI3K signaling cascades. Additional partners include ADAM metalloproteases, integrins and cis and trans self-interaction, which directly regulate cell-cell interaction and migration. As such, cadherins are involved in the regulation of microenvironmental members including fibroblasts, endothelial cells and immune cells including T cells and macrophages.

JAMs are transmembrane adhesive glycoproteins that functionally participate in the organization of endothelial tight junctions (TJ) and mediate a variety of biological processes including leukocyte transendothelial migration. The JAM family consists of JAM-A, JAM-B and JAM-C, which are structurally composed of two immunoglobulin (Ig) extracellular loop domains and intracellular PDZ binding domains. Two JAM-A proteins can not only form dimers on the same cell but also between adjacent cells. This dimerization consequently activates the PDZ binding motif for interaction with other PDZ domain-containing proteins such as afadin and ZO-1. Additionally, it has been reported that the formation of afadin and PDZ-GEF2 complex in epithelial cells activates downstream Rap1A, which further stabilizes the protein level of integrin β1, a key CSC integrin.

Protein tyrosine phosphorylation is a key process in cellular signaling with finite control accomplished through antagonistic actions of kinases and phosphatases which exist as soluble cytosolic and transmembrane proteins. Receptor tyrosine phosphatase PTPμ is a member of the meprin/A5/PTP containing subclass of protein tyrosine phosphatases which regulates adhesion dependent signaling. PTPμ is comprised of an extracellular, juxtamembrane and two intracellular phosphate domains. PTPμ stabilizes cell-cell contacts through homophilic interaction via its extracellular immunoglobulin domain as well as by interaction with E, N, and R and VE cadherin, and γ catenin and gap junction protein Cx43.

Neural cell adhesion molecule (NCAM) alternatively known as CD56 exists as three isoform classes based on molecular weight; 120, 140 and 180 kDa. The 140 and 180 kDa isoforms are observed mainly in embryonic development with NCAM 120 present in adult tissues including neurons, glia, natural killer cells, T cells, skeletal muscle and the epithelia of multiple organs. NCAM possess conserved intracellular domains, a short transmembrane domain, and a large extracellular region consisting of repeated immunoglobulin and fibronectin III domains. Effects on cell-cell adhesion are mediated through homophilic binding, both cis and trans, via its immunoglobulin domain. Additional interaction with fibroblast growth factor receptor, N cadherin and β catenin has been observed indicating signaling potential. Additional studies have shown NCAM interaction with FGFRs influences β integrin expression, suggesting a role in the regulation of cell-matrix interactions.

ICAM-1 is a member of the intercellular cell adhesion molecule family consisting of five members, 1–5, which possess an extracellular domain with immunoglobulin repeats, a transmembrane domain, and cytoplasmic domain. Cell bound and soluble forms have been characterized: sICAM-1 is a product of proteolytic cleavage of the extracellular domain of cell membrane integrated ICAM-1. ICAM-1 expression has been observed on the macrophages, vascular endothelium, and lymphocytes and is associated with immune recognition of exposed endothelium as well as cellular extravasation. ICAM-1 is known to bind β integrins, Muc1 and fibrinogen, thereby modulating cell-cell and cell matrix interactions.

L1CAM (CD171) is expressed by leukocytes, epithelia of the intestine, neurons and Schwann cells, among other cell types, and is involved in embryogenesis, neuronal growth and extension and axonal outgrowth. L1CAM binds in a trans and cis homophilic manner as well as heterotypically with ECM proteins: these include chondroitin sulfate proteoglycan and integrin family members, thereby implicating this protein in cell-cell and cell-matrix interactions. Interestingly, L1CAM has also been shown to interact with NUMB, a protein known to regulate asymmetric cell division.

Tight junctions mediate cell-cell interactions in areas where the membranes of two closely associated cells join. In these areas of contact, networks are formed by rows of transmembrane proteins including main constituent claudin, occludins, E cadherin, JAMs, catenins and actin. Through these junctions, cytoskeletons of neighboring cells are fused together allowing efficient cell-cell interaction and communication. Tight junctions serve the two main functions of barrier formation and cell polarity control. The barriers formed by tight junctions may be of two types, functional or protective, and may be tight or leaky depending on the number of contacts. These differences permit tight junction fine tuning to mediate selective transport of ions and osmosis or complete blockade as observed in the protective barrier of the skin. Another important function of tight junctions is to dictate cell polarity through the prevention of lateral diffusion of integral membrane proteins. Tight junctions are therefore critically involved in epithelial to mesenchymal transition, a key aspect of the regulation of cell-cell contact and migration.

With regards to cancer, CAMs impart varying effects on tumor growth, metastasis and outcome with effects showing tumor type specific differences. If generalizing, CAMs appear to function by and large as tumor suppressors. Current knowledge regarding CAMs in CSCs is still relatively immature and conflicting, with a more detailed description of what has been characterized below.

**Integrin Regulation in the CSC Microenvironment:** Enabling Identification and ECM Communication

In the context of CSCs, integrins are also a critical component as they are active in specialized CSC niches. The role of integrins in a variety of CSC systems is summarized in Table 1. Integrin expression itself has been used to enrich for CSCs directly from human patient specimens or xenografted breast, glioblastoma multiforme (GBM), prostate and squamous cell carcinoma tumors. Additionally, integrins have been used to identify cells with CSC properties in animal models of breast and prostate cancer. Aside from functional enrichment, high levels of integrins were linked to a CSC signature and informed poor patient prognosis in glioma and breast tumors. While it is clear CSC
have developed unique integrin signatures to interact with their niches, there are also certain integrins that are reduced or lost, driving the ability of CSCs to proliferate, self-renew, and metastasize. For example, vitronectin via integrin αvβ3 promotes the differentiation of colon and breast CSCs. Metastasis can be blocked by integrin α2β1 in a breast cancer animal model and integrin αv is a potent inhibitor of metastasis in prostate cancer models both in vitro and in vivo. These results highlight loss of specific integrin expression is associated with CSCs and a metastatic phenotype. It suggests that integrins serve in many cases to act as anchors, possibly maintaining CSCs as fixed, quiescent entities within their microenvironment preventing replication, differentiation and tumor progression. Importantly, the expression of ECM will be critical to determine as this has been informative in normal neural stem cell niches and is likely to clarify integrin function in neoplastic niches. Aside from characterizing the signature and function of integrins on CSCs from different tumor types, future studies interrogating the tumor microenvironment are likely to provide a comprehensive landscape of pro- and anti-CSC ECM/integrin relationships that will be informative for prospective CSC enrichment and targeting. Additional integrins are expressed with other cell types within the tumor microenvironment and may overlap, further emphasizing the need to determine the integrin profile in the tumor microenvironment.

### Cadherins in CSCs: Promoting EMT and Invasion

Cadherins, vital to embryogenesis, have also been implicated in tumorigenesis in numerous and diverse cancer types. Upon dysregulation of cadherin function in the tumor mass, cells undergo EMT, breaking contacts with interacting tumor and stromal elements. The lack of normal cell-cell interactions frees tumor cells to migrate, proliferate and differentiate abnormally. These cell behaviors result in tumor invasion, metastasis and progression. With regards to CSCs, sphere formation and tumorigenic potential assays have shown P cadherin and E cadherin regulate the CSC state in prostate and breast cancer, namely self-renewal and tumorigenicity. In these contexts, cadherin interaction with integrins or cadherins on neighboring cells of the CSC niche maintain a quiescent state with stemness increased upon loss of these interactions, correlating with accelerated tumorigenic potential and decreased patient prognosis. Taken together these data suggest that similarly to integrins, cadherins function as anchors with loss of CSC interaction with microenvironmental partners allowing for reentry into the cell cycle with subsequent tumor progression. Cadherins are also expressed on other cell types in the niche and characterization studies identifying conserved and unique cell-type specific cadherins will be beneficial to future targeting efforts.

### JAMs in CSCs: Facilitating Cell-Cell Communication and Metastasis

The role of JAM-A in stabilizing integrin β1 suggests the possibility that JAM-A directly mediates the interaction of cells in the tumor microenvironment. As metastasis is involved in the transmigration of malignant tumor cells via lymphatic and/or blood vessels, JAM may also be involved in this process. However, there is conflicting evidence about the precise roles of JAM family members in transmigration and limited information as to how CSCs may be involved. Expression of JAM-A correlates with poor prognosis in breast cancer patients. Recent studies have shown that knockdown of JAM-A in MCF7 breast cancer cells reduces their adhesion and migration through the activation of Rap1 GTPase and β1-integrin. However, another study observed that overexpression of JAM-A in MDA-MB-231 cells inhibited both migration and invasion through collagen gels. Furthermore, JAM-A KD enhances the invasiveness of MDA-MB-231 cells as well as T47D cells. These findings suggest that JAM-A regulates the transmigration of tumor cells and is involved in mediating ECM-dependent migration. JAM-A is expressed on hematopoietic stem cells (HSCs) where it plays a role in homing and self-renewal. Future studies will be required to determine the role of JAMs in CSCs, which is likely to involve both cell-cell and cell-ECM communication with contributions to multiple pro-tumorigenic phenotypes. While JAMs are expressed on endothelial cells and likely other tumor cell types, further interrogation of JAM expression and function will also provide key CSC cross-talk information.

### Receptor Tyrosine Phosphatase PTPμ: Specifying an Invasion Signal

PTPμ is abundantly expressed in the vascular endothelium and brain tissue, but downregulation has been observed in GBM and prostate cancers. In GBM, PTPμ function is decreased by proteolytic cleavage resulting in the release of an extracellular
fragment and upon which the inhibitory effect of PTPμ on cell migration is lost. Overexpression of PTPμ results in blockade of cell replication and migration. Along these lines, CD133+ glioma cells, putative glioma CSCs, have been shown to display high levels of cleaved PTPμ compared with their CD133- non stem cell tumor counterparts. Further, released PTPμ fragments have been shown to influence glioma cell migration and survival in vitro and are thought to promote tumor progression in vivo. Despite these insights, the function of PTPμ in CSC biology remains poorly understood, however observed interactions with cadherin, β-catenin and connexin family members is suggestive of a regulatory role. Taken together, it appears that released PTPμ fragments may serve to promote tumorigenesis while intact PTPμ functions in similar fashion to integrins and cadherins and may maintain the CSC population in a quiescent state while PTPμ expressed on endothelial cells and may have a role in angiogenesis and a differential response to cleavage products.

**NCAM**

The role of NCAM in tumor progression remains unclear as contradictory results have been obtained. Why NCAM 120 expression profiles switch to NCAM 140 and 180 during tumorigenesis is also unclear but may reflect a change in function. In colon carcinoma and astrocytoma, where it acts as a tumor suppressor, NCAM expression is downregulated. Alternatively, increased expression has been observed in neuroblastoma and GBM with expression correlating with poorer patient prognosis. NCAM expression has been detected on numerous normal stem cell populations. With regards to CSCs conflicting reports abound. Downregulation of NCAM in CSC populations is observed in peripheral neural sheath tumors in contrast to reports in GBM where NCAM expression correlates with Olig 2 expression, a well-known GBM stem cell marker. Additional studies are required to further address these issues, better define the role of NCAM in microenvironmental regulation and clarify the expression of NCAM in CSCs and other tumor microenvironment cells.

**ICAM**

ICAM-1, in similar fashion to NCAM, has a checkered history with conflicting reports. In breast cancer, ICAM-1 has been associated with improved prognosis. Alternatively, breast cancers have also shown elevated levels of ICAM-1 as compared with surrounding healthy tissue with knockdown correlating with decreased invasive potential. Similarly, poorer patient prognosis in melanoma and colorectal cancer is associated with increased ICAM-1 expression levels. It may be that differential levels of soluble ICAM-1 or immune activation in the host may account for these differences. ICAM-1 is considered a marker for mesenchymal stem cells, but little data are available for CSCs. Elevated levels of ICAM-1 have been observed in lung cancer CSCs. Additional work is required to evaluate the role of ICAM-1 in the tumor microenvironment and specific expression on all cellular components of the niche.

**L1CAM**

In multiple cancer types, L1CAM appears to promote tumorigenicity and has been shown in colorectal cancer to be protective against apoptosis induced by chemotherapy. In colorectal cancer, elevated levels of L1CAM have been observed. Additionally, in renal cell carcinoma and melanoma, expression of L1CAM correlates with metastatic progression. In GBM, L1CAM regulates cell motility and CSC display elevated levels of L1CAM vs. normal progenitors and silencing of L1CAM resulted in decreased viability, sphere formation and tumorigenic potential. Further, L1CAM’s role has been extended to radiation resistance through the control of DNA checkpoint activation. Thus, it appears that in contrast to many other adhesion molecules that maintain a quiescent stem population, L1CAM may be integral in the conversion to a malignant phenotype, essential in therapeutic resistance, and may be restricted to CSCs, depending on the tumor type. L1CAM plays a major role in cell migration and this is extensively reviewed by Kiefer et al. in this issue.

**Tight Junctions: Joining Together Cells for CSC Maintenance**

With regards to CSCs, EMT is associated with the acquisition of stem cell traits leading to cell outgrowth, and tumor progression. It is unclear what role of tight junction disruption plays in the acquisition of stem cell traits and CSC function. However, a claudin low phenotype has been observed in breast CSCs, suggestive of decreased tight junction formation. It therefore appears that, like integrins and cadherins, tight junctions serve to maintain the CSC compartment in a quiescent state, with disruption of these contacts resulting in cell migration, replication, and thereby driving tumor progression. Tight junctions are also expressed on other niche cells, although the roles may be different than that in CSCs and may be a reflection of cell-type specific functions.

**Gap Junctions: Mediating Cell-Cell Communication in CSCs**

Cell-cell communication is another mechanism by which cells are capable of rapidly transferring nutrients and ions between adjacent cells. This may be a driving force in translating single cell events to tumor phenotypes or response to therapies. From the perspective of a tumor which contains cellular heterogeneity, how gap junctions regulate CSC communication with one another and other normal and neoplastic cell types remains poorly understood. Gap junctions are composed of two hemichannels consisting of six individual connexin (Cx) subunits and among stem cells, Cx43 is one of the most well characterized. Cx43 is highly expressed on neural stem cells, regulating proliferation and self-renewal as well as migration. Cx43 has recently been shown to regulate hematopoietic stem cell interaction with the osteogenic niche. However, gap junctions may have different roles depending on the tumor type and specific
connexins. For example, Cx43 expression is reduced with increased brain tumor malignancy, and overexpression in glioma CSCs increases tumor latency. Similar results were also observed with elevated Cx43 expression in a model of fibrosarcoma. There is evidence for increased connexin expression in CSCs. For example, in a hepatoma model of CSCs, accumulation of Cx32 increased self-renewal. These studies provide evidence that connexins may regulate aspects of the CSC phenotype. Further studies in human derived patient CSCs and mouse models will better define their role in driving CSC maintenance. Additionally, it may be possible for different cell types (both normal and neoplastic) to communicate via unique connexins. While the specific connexin(s) were not indicated, gap junction mediated communication between leukemia cells and the stroma in an in vitro model inhibited proliferation and increased therapeutic resistance. While there is limited evidence for gap junction specific function only on CSCs, other niche cells express various Cx subunits and defining the cell-type specific Cx units within the tumor microenvironment and their function is a top priority. Furthermore, functional studies on CSCs and correlating single cell communication to tumor phenotypes will likely transform our view of cancer and drive the development of more effective therapies.

Future Perspectives: Expanding the Network

CSCs are key components of the tumor, driving progression and therapeutic resistance. As they are contained within distinct niches, communication mechanisms within the microenvironment are likely to contribute to many aspects of their phenotype as well as regulate the niche itself. The expression pattern of CSCs themselves may contribute to the composition of the niche and influence the behavior of other niche cells. While data are still accumulating for cell adhesion molecules and direct communication mechanisms, specific growth factors have been shown to originate from CSCs and influence niche cells as well as niche cells influencing CSC maintenance by specific mitogens. It is likely that ECM ligands and cell-cell interactions will show the same reciprocal relationships and models are likely to emerge in which the CSC have receptors for ligands that are produced by the tumor microenvironment. Furthermore, these microenvironmental components are also likely to influence mode of cell division, ultimately influencing CSC numbers and the overall tumor phenotype.

From what is known, integrins and cadherins regulate stem cell behaviors, namely niche homing, maintenance of the stem cell in the niche, as well as recruitment of stromal cells such as endothelial cells, fibroblasts, and immune cells. A similar function in the CSC niche is likely whereby integrins and cadherins act as tracks for homing to the niche in addition to acting as factors which maintain CSCs. PTPμ may play a role in the conformation of a quiescent phenotype on CSCs once they have entered the stem cell niche along integrin and cadherin tracts. JAM has previously been described in transendothelial cell migration of leukocytes. Additionally, JAM signaling has been shown to increase integrin expression in epithelial cells. It is unclear what role JAM plays in CSC biology as conflicting reports exist. Taken together, JAM may therefore serve to fertilize the microenvironmental soil allowing for CSC entry and retention. NCAM, ICAM and L1CAM function in stromal cell recruitment. NCAM and ICAM display contradictory results with regards to CSC function. L1CAM on the other hand appears to promote CSC mediated tumorigenesis and metastasis. Differences in receptor expression and function may be context or tumor type dependent relying on a milieu of cell receptors and ligands to mediate a cumulative effect on cell recruitment and retention.

Changes extending from the niche to the entire organ during tumor development may also provide cues to CSCs. Integrating this information with respect to how cells at the individual level communicate with one another as well as the microenvironment will be an important step in developing more effective therapeutic strategies. Specifically, defining the cellular and extra-cellular components of the niche, specific receptors on CSCs, and cell adhesion mechanisms present will aid in this overall goal. Future studies will therefore need to better define how tumor cells communicate within their malignant social network.

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