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Molecular mechanisms of cancer cell-cell interactions

Cell-cell adhesion-dependent signaling of the tumor microenvironment

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This issue of *Cell Adhesion & Migration* focuses on the molecular mechanisms by which cell-cell interactions in the tumor microenvironment lead to phenotypic changes that result in cancer progression including alterations in cell lineage, migration, invasion and metastasis. Tumors are heterotypic collections of many cell types including cancer stem cells, progeny tumor cells, stromal cells, and inflammatory cells all of which can communicate with one another via adhesive cell-cell contacts within the tumor microenvironment. Cancer stem cells interact with other cells in the tumor microenvironment to generate signals via cell adhesion molecules (CAMs) that control both cell survival and lineage. For example, cancer stem cells generate progeny tumor cells with different repertoires of cell-cell adhesion molecules allowing for distinct cell-cell interactions. In some cases this results in the generation of progeny tumor cells that are highly migratory, partly due to the specific array of cell-cell CAMs that they express. In addition, epithelial to mesenchymal transition (EMT), which occurs as some cells become tumorigenic, takes place in response to changes in adhesion molecule expression and stability. EMT is proposed to promote a migratory switch in previously adherent epithelial cells to generate motile and invasive mesenchymal-like tumor cells. Finally, changes in cell-cell CAM function also lead to a mesenchymal to epithelial (MET) lineage conversion in which a migratory cell switches to an adherent cell capable of colonizing metastases via cell-cell interactions. Together, cell-cell CAMs regulate the ability of a multiplicity of cell types to establish the unique niche called the tumor microenvironment to promote cancer progression.

The cancer stem cell is at the center of the current "origin of cancer" debate as it is hypothesized to be the primary progenitor of both the bulk tumor population and the metastatic cells. Cancer stem cells exist in vascular niches that are rich in heterotypic cellular interactions, primarily mediated by cell-cell CAMs. Dr Lathia and colleagues review the role of cell-cell CAMs in cancer stem cell function and interaction with other cells within the tumor microenvironment.[1]

Contacts between the heterotypic cell types can be mediated by both homophilic cell-cell CAMs, which bind the same proteins on two cell surfaces, or heterophillic CAMs, which bind different adhesion molecules. Classical cadherins and members of the immunoglobulin (Ig) superfamily of CAMs, including some members of the receptor protein tyrosine phosphatase (RPTP) family, are examples of homophilic CAMs important in mediating cell-cell adhesion. Cancer is often associated with aberrant tyrosine phosphorylation due to alterations in tyrosine

About Dr Susann M. Brady-Kalnay

Dr Brady-Kalnay received her PhD in Anatomy and Cell Biology from the University of Cincinnati School of Medicine in 1991. Under the supervision of Dr Robert Brackenbury, she studied the control of cell migration and invasion by N-CAM-dependent adhesion. After receiving her PhD, Dr Brady-Kalnay joined the Cold Spring Harbor Laboratories as a postdoctoral fellow in the laboratory of Dr Nicholas Tonks. At this time, receptor protein tyrosine phosphatases (RPTPs) were just being cloned. Dr Brady-Kalnay began working on PTPmu and demonstrated that it functioned both as a tyrosine phosphatase and as a homophilic cell-cell adhesion molecule. This led to the intriguing hypothesis that RPTPs function to transduce signals in response to cell-cell adhesion. In 1995 Dr Brady-Kalnay joined the faculty of Case Western Reserve University, where she is now a full Professor. She has recently demonstrated that proteolytic cleavage of PTPmu in glioblastoma brain tumors results in shedding of an adhesive extracellular fragment of PTPmu, a finding that was exploited to design a novel molecular recognition strategy for migrating and invasive tumor cells. These findings have great clinical significance for molecular imaging of tumors and for the generation of novel theranostics.

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kinases and phosphatases. The review by Dr Bouyain and colleagues summarizes recent structural studies that demonstrate how changes in adhesivity of RPTPs, achieved by somatic mutations and/or alteration in expression, is associated with cancer progression.[2]

Classical cadherins are also homophilic CAMs that promote adhesion by interacting with catenin signaling proteins and actin in cellular structures known as adherens junctions. The review by Dr Andl and colleagues discusses novel mechanisms of regulation of E-cadherin at the cell surface, including transcriptional regulation and regulation of E-cadherin endocytosis.[3] In addition, Dr Andl and colleagues discuss the role of N-cadherin expression and extracellular matrix adhesion in regulating EMT and collective tumor cell migration.

L1CAM regulates cell adhesion by both homophilic and heterophilic binding. While L1CAM homophilic binding promotes stable cell-cell adhesion, proteolysis and shedding of the L1CAM extracellular domain (ECD) by metalloproteases in the tumor microenvironment destabilizes adhesion. The shed ECD of L1CAM can mediate novel functions when no longer membrane bound. For example, cleaved L1CAM-ECD promotes migration by binding integrins on cancer cells. In addition, L1CAM can interact heterophilically with integrin receptors to activate signaling pathways to promote EMT, migration and metastasis. Dr Altevogt and colleagues review the function of L1CAM cleavage and L1CAM-integrin binding in migration and cancer progression.[4]

The reviews in this special focus highlight how many cell-cell CAMs can be (dis)regulated to promote cancer cell migration and metastatic dissemination. The complexity of the tumor microenvironment and all its cell-cell interactions makes treatment of cancer very difficult. The insights gathered in this issue emphasize that targeting both the extracellular and cytoplasmic domains of cell-cell CAMs may be important clinically as diagnostic tools and as novel therapeutic targets to combat cancer progression and metastasis.

References

1. Hale JS, Li M, Lathia JD. The malignant social network: Cell-cell adhesion and communication in cancer stem cells. Cell Adhes Migr 2012; 6:346-55; PMID:22796941; http://dx.doi.org/10.4161/cam.21294.
2. Nikolaienko RM, Agyekum B, Bouyain S. Receptor protein tyrosine phosphatastases and cancer: New insights from structural biology. Cell Adhes Migr 2012; 6:356-64; PMID:22796942; http://dx.doi.org/10.4161/cam.21242.
3. Le Bras GF, Taubenslag KJ, Andl CD. The regulation of cell-cell adhesion during epithelial-mesenchymal transition, motility and tumor progression. Cell Adhes Migr 2012; 6:365-73; PMID:22796940; http://dx.doi.org/10.4161/cam.21326.
4. Kiefel H, Bondong S, Hazin J, Ridinger J, Schirmer U, Riedle S, et al. L1CAM: A major driver for tumor cell invasion and motility. Cell Adhes Migr 2012; 6:374-86; PMID:22796939; http://dx.doi.org/10.4161/cam.20832.