In this issue of Clinical Cancer Research, Chien and colleagues report that expression of CD151 protein is reduced in human colon cancers compared with the surrounding normal tissues (1).

Clinical studies over the last quarter century have shown that intratumoral hypoxia is commonly observed in carcinomas and that pO2 values below 10 mm Hg are associated with increased risk of invasion, metastasis, and patient mortality (2). Laboratory investigations have shown that these clinical associations reflect a causal relationship: cancer cells transiently exposed to hypoxia ex vivo have increased metastatic properties in vivo (3). In cells subjected to reduced pO2, hypoxia-inducible factor 1 (HIF-1) is activated and plays important roles in promoting cancer pathogenesis (4). HIF-1 is a heterodimer consisting of HIF-1α and HIF-1β subunits (5). The HIF-1α subunit is regulated by O2-dependent hydroxylation, leading to binding of the von Hippel-Lindau tumor suppressor protein and subsequent ubiquitin-mediated proteasomal degradation, processes that are inhibited under hypoxic conditions (6). In animal models, HIF-1 has been shown to play critical roles in the metastasis of breast cancer cells to bone and lung (7, 8).

The defining feature of a carcinoma is the loss of cell-to-cell and cell-to-matrix associations that normally maintain an epithelium, in which an ordered layer of cells is bordered on one side by a basement membrane and on the other side by a lumen. Epithelial cell-to-cell adhesion is mediated by intercellular junctional complexes, which consist of tight junctions, adherens junctions, and desmosomes. The expression of E-cadherin, which is the principal component of adherens junctions and desmosomes, is extinguished in most carcinomas through a wide variety of molecular mechanisms (9). In clear cell renal carcinoma, in which the signature genetic lesion is the loss of von Hippel-Lindau activity, dysregulated expression of HIF-1α (and HIF-2α, which is also subjected to O2-dependent regulation and dimerizes with HIF-1β), leads to increased expression of genes that encode repressors of E-cadherin gene transcription, thereby dramatically reducing cell-to-cell adhesion (10).

In this issue of Clinical Cancer Research, Chien and coworkers (1) report that expression of CD151 protein, which is a cell surface transmembrane protein that promotes cell-to-cell and cell-to-matrix interactions, is reduced in human colon cancers compared with surrounding normal tissue, in which it is strongly expressed on the basal and lateral surfaces of epithelial cells. Although the role of CD151 in colonic epithelium has not been reported, in keratinocytes, CD151 associates with the laminin-binding integrin α6β4 and is thereby recruited into hemidesmosomes, which are specialized junctional complexes through which epithelial cells interact with the basement membrane (11). Although it has not been as well studied as E-cadherin, CD151 seems to function with E-cadherin in maintaining epithelial integrity (Fig. 1).

Chien and colleagues show that CD151 expression is inhibited when human colon cancer cells are cultured under hypoxic conditions or transfected with a HIF-1α expression vector under nonhypoxic conditions (1). In contrast to the indirect repression of E-cadherin transcription in renal carcinoma cells (10), the authors provide evidence that HIF-1 binds directly to the CD151 gene promoter and represses its activity in colon cancer cells (1). Further delineation of the molecular mechanisms by which HIF-1 binding mediates transcriptional repression of the CD151 gene is an interesting challenge for future study.

The investigators also report that the binding of colon cancer cells to laminin was inhibited by prior exposure of the cells to hypoxia or by treating the cells with small interfering RNA or neutralizing antibodies against CD151 mRNA and protein, respectively (1). A major limitation of the current study, however, is that no in vivo assays were done and thus the extent to which HIF-1–dependent CD151 loss-of-function contributes to colon cancer metastasis will require further analysis. In addition, it remains to be determined whether CD151 loss of function is associated with increased...
risk of invasion/metastasis in patients with colon cancer. Nevertheless, this study suggests a novel and potentially important molecular mechanism underlying the increased metastatic potential of hypoxic cancer cells. Loss of CD151 expression may contribute to the increased risk of local, venous, and lymphatic invasion and liver metastasis, which is observed in patients with colon cancers that overexpress HIF-1α (12).

The results presented by Chien and colleagues (1) raise many interesting questions. Is loss of both CD151 and E-cadherin (Fig. 1) required for colon cancer metastasis? Would the addition of a HIF-1 inhibitor (4) to the treatment regimen of colon cancer patients who are found to have a high-HIF-1α/low-CD151 tumor phenotype by immunohistochemistry result in the reactivation of CD151 gene expression and reduced risk of metastasis? Does loss of CD151 expression contribute to the increased risk of invasion/metastasis that is associated with HIF-1α overexpression in other human cancers (4) such as breast, esophageal, gastric, gastrointestinal stromal cell, liver, or pancreatic cancer? Is CD151 expression extinguished in some cancers by other (O₂- and HIF-1–independent) mechanisms, such as CD151 gene mutation or hypermethylation? Chien and colleagues (1) have written an intriguing first chapter of what may turn out to be a very important story.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**Fig. 1.** Invasion and metastasis involve loss of cell-to-cell and cell-to-matrix interactions. Epithelial cells maintain cell-to-cell adhesion via homotypic interactions between E-cadherin molecules (purple) expressed on the surface of adjacent cells. In addition, expression of CD151 (red) on the basal surface of epithelial cells mediates cell-to-matrix interactions. Genetic alterations and hypoxia result in increased HIF-1α expression (blue) in the nucleus of cancer cells, which may result in the repression of E-cadherin and CD151 expression, leading to decreased cell-to-cell and cell-to-matrix interactions, thereby facilitating invasion across the basement membrane and subsequent metastasis.

**References**

Does Loss of CD151 Expression Promote the Metastasis of Hypoxic Colon Cancer Cells?

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