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Commentary & View

The roles of cell adhesion molecules in tumor suppression and cell migration

A new paradox

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Abbreviations: ECM, extracellular matrix; CADM1, cell adhesion molecule 1; DAL1, differentially expressed in adenocarcinoma of the lung; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1

Key words: hepaCAM, cell adhesion molecules, tumor suppressor, migration, E-cadherin, CADM1, integrin α7, CEACAM1

In addition to mediating cell adhesion, many cell adhesion molecules act as tumor suppressors. These proteins are capable of restricting cell growth mainly through contact inhibition. Alterations of these cell adhesion molecules are a common event in cancer. The resulting loss of cell-cell and/or cell-extracellular matrix adhesion promotes cell growth as well as tumor dissemination. Therefore, it is conventionally accepted that cell adhesion molecules that function as tumor suppressors are also involved in limiting tumor cell migration. Paradoxically, in 2005, we identified an immunoglobulin superfamily cell adhesion molecule hepaCAM that is able to suppress cancer cell growth and yet induce migration. Almost concurrently, CEACAM1 was verified to co-function as a tumor suppressor and invasion promoter. To date, the reason and mechanism responsible for this exceptional phenomenon remain unclear. Nevertheless, the emergence of these intriguing cell adhesion molecules with conflicting roles may open a new chapter to the biological significance of cell adhesion molecules.

It is well known that many cell adhesion molecules function as tumor suppressors (reviewed in ref. 1). These molecules exert their tumor suppressive effect mainly through cell-adhesion-mediated contact inhibition. Cell adhesion molecules allow cells to communicate with one another or to the extracellular environment by mediating cell-cell or cell-extracellular matrix (ECM) interactions (reviewed in refs. 2 and 3). Broadly, these proteins can be classified into five families including immunoglobulin superfamily, integrins, cadherins, selectins and CD44. Apart from participating in the development and maintenance of tissue architecture, cell adhesion molecules serve as cell surface receptors critical for capturing, integrating and transmitting signals from the extracellular milieu to the cell interior (reviewed in refs. 2 and 3). These signaling events are vital for the regulation of a wide variety of cellular functions including embryogenesis, immune and inflammatory responses, tissue repair, cell migration, differentiation, proliferation and apoptosis. Alterations of these cell adhesion molecules are a common event in cancer (reviewed in refs. 1, 2, 4 and 5). The disrupted cell-cell or cell-ECM adhesion significantly contributes to uncontrolled cell proliferation and progressive distortion of normal tissue architecture. More importantly, changes in cell adhesion molecules play a causal role in tumor dissemination. Loss of cell adhesion contacts allows malignant cells to detach and to escape from the primary mass. Gaining a more motile and invasive phenotype, these cells break down the ECM and eventually invade and metastasize to distal organs.

Based on the above understanding, it is conventionally accepted that cell adhesion molecules with tumor suppressor activity, when expressed in cancer cells, are able to exert inhibitory effect on cell motility. The ability of cells in migration/motility is a prerequisite for cancer invasion and metastasis (reviewed in refs. 1 and 5). Indeed, a number of cell adhesion molecule-tumor suppressors have been reported to be capable of reducing cell migration. The most classical example is E-cadherin, a calcium-dependent cell adhesion molecule. E-cadherin is expressed exclusively in epithelial cells and its expression is commonly suppressed in tumors of epithelial origins. The cytoplasmic domain of E-cadherin interacts with catenins to establish an intracellular linkage with the actin cytoskeleton (reviewed in ref. 6). The assembly of E-cadherin with the cytoskeleton via catenins at the sites of adherens junctions is important for the stabilization of cell-cell adhesions. Disruption of E-cadherin-mediated cell-cell adhesion, due to loss of expression or function of E-cadherin and/or catenins, is assocated with tumor development and progression (reviewed in ref. 7). Forced expression of E-cadherin in several cancer cell lines not only slows

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down cell growth[8,9] but also significantly reduces the invasiveness of the cells.[10,11] On the other hand, inhibition of E-cadherin by function-blocking antibodies and antisense RNA restores the invasiveness in non-invasive transformed cells.[11] Furthermore, using a transgenic mouse model of pancreatic beta-cell carcinogenesis, it has been demonstrated that E-cadherin-mediated cell adhesion is important in preventing the transition from well differentiated adenoma to invasive carcinoma.[12]

Cell adhesion molecule 1 (CADM1), another example, has also been implicated in cancer progression. CADM1 is a member of the immunoglobulin superfamily and mediates cell-cell adhesion.[13] The molecule associates with the actin cytoskeleton via the differentially expressed in adenocarcinoma of the lung (DAL1) protein; and the formation of CADM1-DAL1 complex is dependent on the integrity of actin cytoskeleton.[14] Inactivation of the CADM1 and/or DAL1 gene usually through methylation has been reported in diverse human cancers.[15,16] A paper by Ito et al. showed that restoration of CADM1 expression in esophageal squamous cell carcinoma cells not only suppresses cell growth, but also retards cell motility and invasion.[16]

In contrast to E-cadherin and CADM1, integrin α7 is a cell-ECM adhesion molecule which also possesses tumor suppressor activity. Ren et al. showed that integrin α7 gene is mutated in several human malignances; and the mutations are associated with an increase in cancer recurrence.[17] Forced expression of integrin α7 in integrin α7-deficient leiomyosarcoma cells results in decreased colony formation and slower cell motility. Conversely, knockdown of integrin α7 in lung cancer cells expressing wild-type integrin α7 increases the colony number and cell motility rate. In addition, the researchers revealed that mice bearing xenograft tumors overexpressing integrin α7 have reduced tumor size with no obvious metastasis.

In 2005, we first reported the identification of a cell adhesion molecule belonging to the immunoglobulin superfamily, designated as hepaCAM.[18] To date, we have shown that the gene is frequently downregulated in a variety of human cancers.[18,19] Re-expression of hepaCAM in the hepatocellular carcinoma HepG2 cells[18] and breast cancer MCF7 cells[19] inhibits colony formation and retards cell proliferation. In addition, expression of hepaCAM in MCF7 cells results in cell cycle arrest at the G_2/M phase and cellular senescence. Concurrently, the expression of several senescence-associated proteins including p53, p21 and p27 is enhanced. Moreover, downregulation of p53 by p53-specific small interfering RNA in cells expressing hepaCAM clearly reduces p21 without changing p27 and alleviates senescence, indicating that hepaCAM induces senescence through a p53/p21-dependent pathway.[19] Together, the data suggest that hepaCAM is a tumor suppressor. Interestingly, the expression of hepaCAM in both HepG2 and MCF7 cells stimulates both cell-ECM adhesion and cell migration.[18,20,21] The function of hepaCAM as a tumor suppressor in cell migration is contradictory to other cell adhesion molecule-tumor suppressors. Noteworthily, hepaCAM-mediated cell motility is evidenced by its direct interaction with the actin cytoskeleton.[21]

Evidences are currently emerging to support the contradictory roles of cell adhesion molecules that both inhibit cell growth and promote cell motility when restored in cancer cells. In addition to hepaCAM, the immunoglobulin superfamily carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is implicated to function as a tumor suppressor and a metastasis promoter. The characteristics and functions of CEACAM1 have been demonstrated in individual reports. CEACAM1 is frequently downregulated or dysregulated in multiple human tumors,[22-25] and is capable of suppressing cell growth and inducing apoptosis.[26-28] Ebrahimnejad et al. demonstrated that exogenous expression of CEACAM1 enhances melanoma cell invasion and migration; and this enhanced motility can be reverted by anti-CEACAM antibodies.[29] The ability of CEACAM to co-stimulate tumor suppression and invasion was finally established by Liu et al. in restricting thyroid cancer growth but promoting invasiveness.[30] Introduction of CEACAM1 into CEACAM1-deficient thyroid cancer cells results in G_1/S phase cell cycle arrest accompanied by elevated p21 expression and diminished Rb phosphorylation. Overexpression of CEACAM1 also increases cell-ECM adhesion and promotes cell migration and tumor invasiveness. In xenografted mice, CEACAM1 expression results in reduced tumor growth but increased tumor invasiveness. Conversely, silencing of endogenous CEACAM1 accelerates tumor growth and suppresses invasiveness.[30]

It is an exciting issue to address why a cell adhesion molecule is able to suppress tumor growth yet promote tumor progression. Could there be a molecular switch that controls the functions of the gene between a tumor suppressor and a migration promoter in cancer or are the functions executed simultaneously? The expression level, the extracellular cues as well as the interacting partners of the cell adhesion molecules may likely play a critical role in regulating its functions. The question is under what circumstances these factors come into play. To answer all these questions, and maybe more, on the intriguing findings of these proteins, more extensive and intensive experimentation is required. Nevertheless, it is obvious that the emergence of these cell adhesion molecules that function in a contradictory manner opens a new chapter to the biological significance of cell adhesion molecules.

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