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Original Paper

Cell Adhesion Molecules and Cancer

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ABSTRACT

Theodor Boveri in 1914 recognized the significance of changes in the adhesion of tumor cells to the development of cancer. Cell adhesion is essential in all aspects of in vertebrate cells such as cell growth, cell migration and cell differentiation. The majority of adhesion molecules fall into one of four families: cadherins, integrins, immunoglobulin superfamily (IgSF) and selectins. The cadherins are a family of homophilic CAMs (cell adhesion moleculs), Ca2+ dependent. The most important members of cadherins are E-cadherins (epithelial), P-cadherins (placental) and N-cadherins (neural). Immunoglobulin superfamily CAMs (IgSF CAMs) are either homophilic or heterophilic and bind integrins, growth factor receptors cadherins or different IgSF CAMs. The integrins are a family of heterophilic CAMs that bind IgSF CAMs or the extracellular matrix. The selectins are a family of heterophilic CAMs that bind fucosylated carbohydrates, e.g. mucins. They are calcium-dependent. The three family members are E-selectin (endothelial (, L-selectin (leukocyte) and P-selectin (platelet). Recent experimental results indicate that, as well as mediating intercellular and cell–matrix interactions, cell-adhesion molecules also directly modulate signal transduction. Changes in the expression or function of cell-adhesion molecules can therefore contribute to tumor progression via altering the adhesion status of the cell or affecting cell signaling. The ability to colonize a specific organ has been correlated with the preferential adhesion of the cancer cells to endothelial cells derived from the target organ. This review summarizes recent findings about role of adhesion molecules in the tumor progression.

Keywords: Cell Adhesion, Cancer, Cadherins, Integrins, IgSF, Selectins

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Cadherin superfamily consists of classical and non-classical cadherins. Classical cadherins are the main mediators of calcium-dependent cell–cell adhesion. Non-classical cadherins include desmosomal cadherins and the recently discovered large subfamily of protocadherins, which are implicated in neuronal plasticity. The functional role of non-classical cadherins in tumor progression is unknown. Most human cancers originate from epithelial tissue (1, 2).

In most, if not all, cancers of epithelial origin, E-cadherin-mediated cell–cell adhesion is lost concomitantly with progression towards towards tumor malignancy. There is an inverse correlation between E-cadherin levels, tumor grade and patient mortality rates. Loss of E-cadherin function elicits active signals that support tumor-cell migration, invasion and metastatic dissemination. The loss of E-cadherin function during tumor progression

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can be caused by various genetic or epigenetic mechanisms including: mutation, E-cadherin expression is down regulated at the transcriptional level, E-cadherin gene locus hyper methylation and proteolytic degradation by MMPs (Matrix Metalloproteinases) (3). Loss of E-cadherin triggers active signals that initiate EMT (Epithelial Mesenchymal Transition). Mechanisms of E-cadherin signaling were included modulation of RTK signaling, activation of the WNT signaling pathway and signaling through RHO GTPases (4). In melanoma, prostate and breast cancer, loss of E-cadherin function is accompanied by the gain of expression of mesenchymal cadherins, for example, neuronal (N)-cadherin and cadherin-11, in a process that is known as the cadherin switch. N-cadherin has been shown to promote cell motility and migration — an opposite effect to that of E -cadherin. N-cadherin-induced tumor-cell invasion can even overcome E-cadherin-mediated cell-cell adhesion. N-cadherin facilitates binding of FGF2 to the receptor. It can serve as a surrogate ligand for FGFR. Also N-cadherin recruits PI3K to the adhesion complex, resulting in the activation of AKT (also known as protein kinase B) and increased cell survival. VE-cadherin is a non-classical cadherin that is specifically expressed in endothelial cells. It associates with vascular endothelial growth factor receptor-2 (VEGFR2) and modulates its signaling activities. VE-cadherin contributes in the development and integrity of the vascular network (5).

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Ig-CAMs

The immunoglobulin superfamily is a large group of cell surface and soluble proteins that are involved in the recognition, binding or adhesion processes of cells. In table 1 has been shown involvement of Ig-CAMs in tumour progression (1).

Table 1 | **Involvement of Ig-CAMs in tumor progression**

CAM	Tumor type	Changes in expression during tumor progression
NCAM	Pancreatic and colon cancer, astrocytoma Neuroblastoma, certain neuroendocrine tumours	Downregulated Upregulated
L1	Melanoma, breast and prostate cancer	Upregulated
DCC	Colorectal cancer, pancreatic cancer, neuroblastoma, various carcinomas	Downregulated
CEA	Various carcinomas	Upregulated
CEA-CAM1	Carcinoma of the prostate, breast, colon and endometrium	Downregulated
Mel-CAM	Melanoma, prostate cancer Breast cancer	Upregulated Downregulated
NrCAM	Glioblastoma Pancreatic cancer	Upregulated Downregulated

CAM, cell-adhesion molecule; CEA, carcinoembryonic antigen; DCC, deleted in colorectal cancer; Ig-CAM, immunoglobulin-like CAM; Mel-CAM, melanoma CAM; NCAM, neural CAM; NrCAM, neuronal CAM.

NCAM was expressed in many cell types, including epithelial cells of various organs, muscle cells and pancreatic β-cells. The biological significance of this change in NCAM expression and its role in tumor onset and/or progression are not understood. NCAM (Neural CAM) associates with FGFRs. Loss of NCAM function during tumor progression affects cell–matrix adhesion through the loss of FGFR-induced, integrin-mediated cell–matrix adhesion. Cell-adhesion molecules of the CEA (Carcinoembryonic Antigen) family have long been thought to have a role in tumorigenesis. Functional role in tumor development is not known. CEACAM1 modulates the angiogenic process via induce neovascularization in certain experimental systems and it acts as an anti-angiogenic factor in prostate cancer (1, 6). The gene encoding the DCC (Deleted in Colorectal Cancer) Ig-CAM was originally identified as a tumor suppressor, because of the high frequency of LOH (Loss of Heterozygosity) of this gene in colorectal cancer. DCC has been reported to induce apoptosis. L1 has functional similarities to NCAM. The expression of L1 is also up regulated in certain tumor types (7).

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Integrins

Integrins are structurally organized into heterodimeric transmembrane complexes variously assembled through the non-covalent association between an α and a β subunit. So far, 18 α subunits, 8 β subunits, and 24 or 25 complexes have been identified. Cytoplasmic tails of integtins modulate receptor distribution, receptor surface expression, ligand binding affinity of the extracellular domain, cell adhesion, and cell spreading. Integrins are crucial regulators of differentiation, growth, survival, migration and invasion (8). They can mediate cell-ECM interaction and cell-cell interaction. By interacting with the ECM and, inside the cell, with the cytoskeleton, integrins transfer signals from the extracellular environment to intracellular compartments and control many cellular functions, such as migration, survival, proliferation, differentiation, and gene expression. Cell adhesion to the ECM is required for cell cycle progression and proliferation in different cell types.Loss of cell anchorage to the ECM has been shown to up-regulate the expression of cyclin kinase inhibitors (CKIs) such as p27/kip1, while at the same time decreasing the levels of cyclin D1 and A. There are metastatic melanoma cells that express little or no αVβ3 integrin on their surface suggesting that no single adhesion receptor is irreplaceable in melanoma progression (9). The best characterized signaling pathways that activated by integrins are the FAK, PI3-kinase and Ras/MAP kinase. Integrin signaling pathways that control cell migration are altered in prostate cancer (10).

-Integrins are involved in the pathogenesis of bone metastasis at many levels and further study to define integrin dysregulation by cancer will yield new therapeutic targets for the prevention and treatment of bone metastasis.

Selectins

Selectins, a family of mammalian lectins engaged in adhesion reactions are expressed by leukocytes, endothelial cells, and platelets. Slectins interact with cell-surface glycoconjugates and mediate rolling and adhesion of several types of cells (11). L-selectin is constitutively expressed by leukocytes, E-selectin by activated endothelial cells and P-selectin by platelets and activated endothelial cells. P-selectin (CD62P) is expressed on the membrane of endothelial cells and platelets following cellular activation. P-selectin binds to several types of human cancer cells such as colon, lung and breast cancer, as well as to melanoma and neuroblastoma. The potential role of P-selectin in metastasis it was suggested that targeting P-selectin may offer novel therapeutic strategies to treat metastatic cancer. P-selectin bind to several human cancer cells including: neuroblastoma, colon cancer, breast cancer, malignant melanoma, gastric cancer and lung cancer. L-selectin (CD62L), is structurally and functionally similar to other selectins. L-selectin is essential for homing of lymphocytes to secondary lymphoid organs. L-selectin is constitutively expressed on most leukocytes. Tumor cells express sialomucins that can serve as L, P or E-selectin ligands. The role of selectins in tumor progression included: interaction of tumor cells with platelets and leukocytes resulting in the formation of circulating emboli, interaction of tumor cells with endothelial cells leading to extravasation of tumor cells and utilization of reciprocal pro malignancy signals delivered by the selectins or by their ligands to interacting cells that express the corresponding co-receptor. Platelets play multiple roles in tumor progression and metastasis. Together with leukocytes, they form aggregates with circulating tumor cells thereby protecting the tumor cells from immune insults and shear stress.

The aggregates also facilitate the binding of tumor cells to endothelial cells thereby promoting extravasation. L-selectin enhances metastasis by recruiting leukocytes to platelet tumor emboli in the circulation. The increased size of the emboli could facilitate their mechanical trapping in the microvasculature. L-selectin expressing leukocytes could bridge the emboli to the vascular endothelial cells expressing L-selectin ligands. They facilitate metastasis by induction of as yet unidentified L-selectin ligands on endothelial cells via fucosyltransferase-7. In colorectal cancer E-selection expression is upregulated on endothelial cells that are located in close physical contact to invading tumor cells. This is probably due to the secretion of pro inflammatory cytokines by the invading tumor cells (11-13).

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