Role of Cell Adhesion Molecules in Tumor Development and Progression

During the last two decades our knowledge of the molecular biology of cancer has tremendously increased. Oncogenes and tumor suppressor genes have been identified and shown to perform pivotal functions in the control of cell cycle progression, apoptosis or genome stability. It has also been recognized that cell adhesion molecules play essential roles in cancer development and metastasis. Changes in adhesion to the extracellular matrix or to neighbouring cells are prominent features of cancer cells and accompany the loss of tissue differentiation that is a hallmark of malignant transformation. Importantly, alterations in cell adhesion receptors have been linked to the onset of invasion and metastasis. In order to metastasize cancer cells lose contacts between each other and to neighbouring normal cells, penetrate through basement membranes into the underlying mesenchyme and make new contacts with endothelial cells of lymph and blood vessels and also with cells of the target organs. Different adhesion receptor families have been implicated in the various steps of the metastatic cascade. Among these are integrins which mediate contact to the extracellular matrix and cadherins which are intercellular adhesion molecules.

The E-cadherin/catenin complex has gained special interest because its function is frequently disturbed in metastatic carcinoma cells. E-cadherin is a transmembrane protein which is linked to the cytoskeleton through association with the cytoplasmic catenins. In dedifferentiated carcinomas E-cadherin or catenins are frequently down-regulated which correlates with more aggressive behaviour of the tumors and a worse prognosis. In experimental systems the expression of E-cadherin was shown to reduce progression of tumors, invasiveness and metastasis formation. From these results it was hypothesized that E-cadherin and catenins act as invasion/metastasis suppressors and that perturbation of their function is a rather late event in tumor progression.

Recent evidence, however, argues for a more complex role of these components in cancer development. In breast and gastric carcinomas mutations of the E-cadherin gene have been described that occur already in the in situ portions of the tumors, i.e. at early stages of tumor development. Moreover, certain families with high incidence of gastric carcinomas carry E-cadherin mutations in their germ line which apparently predisposes these patients for tumor formation. Thus, E-cadherin

can be classified as a true tumor suppressor which prevents early steps of tumor development.

Intriguingly, the E-cadherin/catenin system is not only involved in cell adhesion but also has a role in signal transduction. The cytoplasmic binding partner of cadherins, β -catenin, can also interact with transcription factors termed LEF-1/TCF. In normal embryonal development this interaction is tightly controlled by the wnt pathway. However, in tumors, constitutive complexes of LEF-1/TCFs with β -catenin are observed; these presumably activate transcription of oncogenic target genes. The increase in nuclear β -catenin is due to mutations of either the tumor suppressor gene product APC (which is altered in about 80% of colorectal carcinomas) or β -catenin itself. Both types of mutations lead to stabilisation of cytosolic pools of β -catenin which subsequently associates with LEF-1/TCFs in the cell nucleus. It is reasonable to speculate that the loss of E-cadherin observed in tumors might lead to the release of β -catenin from the membrane, accumulation in the cytosol and signaling to the nucleus. Conversely, E-cadherin might exert its tumor suppressor activity by depleting cytosolic pools of β -catenin.

What is the clinical importance of these new findings? First, analysis of the cadherin/catenin components could be helpful in the diagnosis of specific tumors. Loss of E-cadherin from the cell membrane and/or increase of β -catenin in the nucleus might turn out to be valuable markers for staging tumors. Obviously, more clinical work is needed to substantiate this idea. Second, there are also options for therapeutic intervention. If E-cadherin expression or function could be restored in tumors, e.g. by (re-)activation of transcription or gene-therapy approaches the cancer cells might be driven into differentiation and growth arrest. Moreover, since the association of β -catenin with transcription factors appears to be crucial for development of various tumor types, a major goal is identification of drugs that would interfere with this interaction. Strategies could also be envisioned to induce degradation of β -catenin in tumor cells that lack functional APC, e.g. by activating the β -catenin degradation machinery. In fact, patents have been issued on these matters and it is likely that pharmaceutical companies are already pursuing these approaches.

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