EPITHEORESE KLINIKES FARMAKOLOFIAS
KAI FARMAKOKINETIKES, INTERNATIONAL
EDITION 13: 92 (1999)

The Cell Adhesion Molecules Integrins and Cadherins as Molecular Targets for Anticancer Therapeutics Development

I.S. Vizirianakis[1,2], A.S. Tsiftsoglou[2] and R.H. Kramer[1]

1. Tumor Biology Laboratory, Department of Stomatology, UCSF, HSW 604, Box 0512, San Francisco, CA 94143-0512, and 2: Laboratory of Pharmacology, Department of Pharmaceutical Sciences, Aristotle University, Thessaloniki 540 06, Greece

Neoplastic cells are characterized by unrestrained growth, independent of substratum attachment, and ability to invade surrounding tissues and metastasize in organs distant from the boundaries of primary tumor. Metastasis is the major cause of death in patients with malignancies. Cell-cell and cell-matrix adhesion molecules are critical in the early events of metastasis as well as in anchorage-dependent cell growth, differentiation and apoptosis. Therefore, the concept of anti-adhesion cancer therapy is a strong rationale for developing drugs that can target these basic biochemical events in neoplasia. Integrins are largely responsible for cell-extracellular matrix adhesion and the cadherins for cell-cell adhesion.

Binding of integrins with their ECM ligands and formation of integrin-cytoskeletal complexes in focal adhesions are regulated by complex signal transduction mechanisms involving a large number of proteins associated with integrins. Altered integrin gene expression is implicated in progression and in invasive/metastatic behavior of tumor cells. Such integrins are for example the laminin-binding integrins α1β1, α2β1, α3β1, α6β1, α6β4, and α7β1. Further, the α5β1 integrin, the classic receptor for fibronectin, plays an important role in cell survival of CHO and colon carcinoma cells, whereas similar observations have been made for the α2β1 integrin in breast carcinomas. Integrin-related signal transduction through the event of integrin clustering is mediated either directly by activation of FAK, or by modulation of signaling pathways that activate the RAS-MAP-kinase cascade mechanisms. In addition, integrin-mediated cell anchorage is implicated in an apoptotic pathway, known as anoikis, by two possible mechanisms. One involves the integrins, FAK, PI3-K and Act and the other involves the integrins, Bcl-2, caspaces and MEKK-1. Based on the role of integrins as critical players in vital cellular processes, it is not surprising that two synthetic peptides (AcDRGDS and AcDRLDS) that interfere into the interaction of integrins with fibronectin inhibit the metastatic potential of different tumor cell lines both *in vitro* and *in vivo*. By thorough examination of integrin functions at the molecular level, it is expected to develop novel stategies to block cancer cell growth, invasion and metastasis.

E-cadherin, a transmembrane protein that mediates Ca^{++}-dependent cell-cell adhesion in epithelial cells, participates in signal transduction pathways through binding with α-, β- and γ-catenins. The catenins are crucial molecules for cadherin function in cell adhesion and growth, as well as in tumor invasion and metastasis. β-Catenin is also a pivotal member of a signal-trans-

duction pathway in vertebrates that involves the wnt-1 proto-oncogene, the adenomatous polyposis coli (APC) tumor suppressor protein, the glycogen synthase kinase-3B (GSK) and the Lef/Tcf transcription factors. The binding of β-catenin with APC facilitated through the phosphorylation of these molecules by GSK, seems to be the rate-limiting step for β-catenin degradation in the cytoplasm by the ubiquitin-proteasome complex. Deregulation of this system by activation of the Wnt-1 signaling pathway, inactivates GSK and leads to β-catenin accumulation into cytoplasm. When β-catenin accumulates into cytoplasm it binds to Lef/Tcf family members, then the complex translocates into nucleus and activates gene transcription, e.g. c-myc. At the same time, c-myc and Rb, two critical molecules in cell growth and differentiation, can activate transcription of E-cadherin gene in epithelial cells through interaction with transcription factor AP-2. Recent data also support the notion that E-cadherin is involved in anchorage-related cell growth. Therefore, the importance of E-cadherin/β-catenin complex in tumor growth and invasion makes it a putative target for specific anti-invasive cancer therapy by designing molecules that can affect its function at different levels.