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The molecular basis for cell adhesion

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Cell adhesion plays central roles in regulating the assembly of cells into tissues and organs and in the generation and orchestration of transmembrane signaling events which determine cell behavior and fate. Studies carried out by members of the group, as well as long-term collaborations with the groups of Lia Addadi, Avri Ben-Ze'ev, Alexander Bershadsky, Zvi Kam and Mark Safro, are briefly presented below. The molecular diversity of matrix adhesions, their mechanical properties and dynamics are characterized using advanced digital light microscopy as well as electron microscopy. We showed that matrix adhesions are highly complex at the molecular level (Fig. 1) and may differ in their molecular composition, signaling properties and dynamics. These difference is attributable to the composition and rigidity of the matrix, contractility of the actin cytoskeleton and the combined action of src and FAK tyrosine kinases (Fig. 2). Special attention is devoted to early adhesive interactions, mediated by the large and highly hydrated glycosaminoglycan, hyaluronan whose cooperation with the integrin system as well as its organization and exposure on the cell surface, are studied. The formation of novel integrin-mediated adhesions is investigated in freshly-plated spreading cells, as well is in migratory endothelial cells. It was found that different proteins join the newly formed adhesions at different time points, suggesting a specific hierarchy of focal adhesion assembly. The involvement of matrix molecular heterogeneity and rigidity is also investigated using two- and three-dimensional micro-patterning of adhesive surfaces. Studies adddress the involvement of cell adhesion in transmembrane signaling via cell-cell and cell-matrix adhesions including the effects of such interactions on growth regulation, the promotion of myogenic differentiation in competent cells and the cross talk between diferent small G-proteins and the Ras-MAPK pathways. In addition, we study the involvement of ErbB-3/ ErbB-2 receptor tyrosine kinases in cell motility

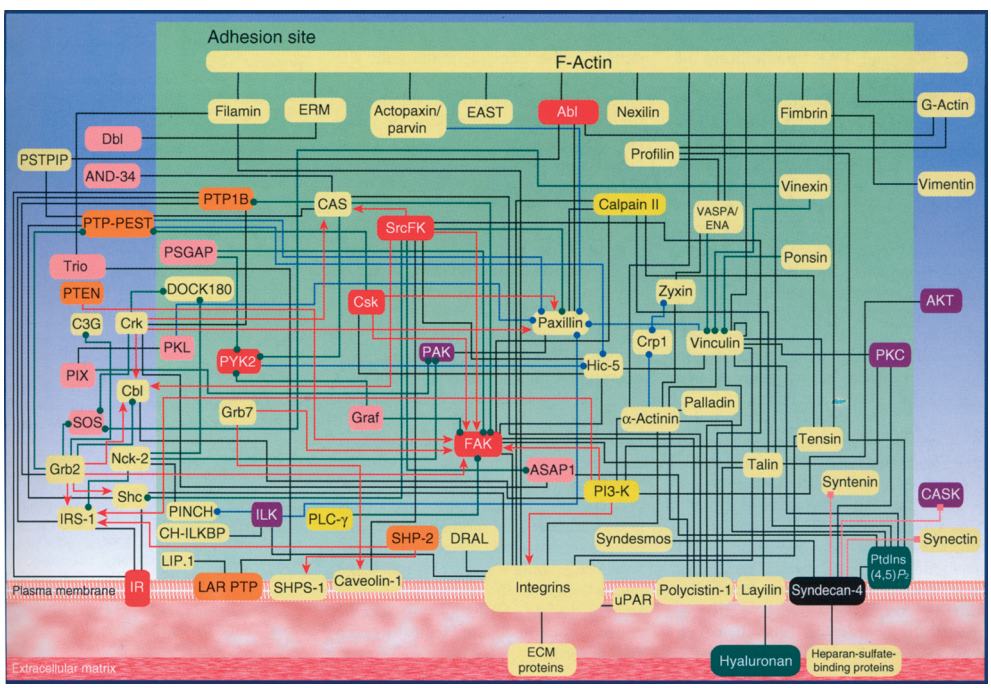

Fig.1 *A scheme summarizing known interactions between the various constituents of cell-matrix adhesions. For further details see Zamir and Geiger 2001a and 2001b.*

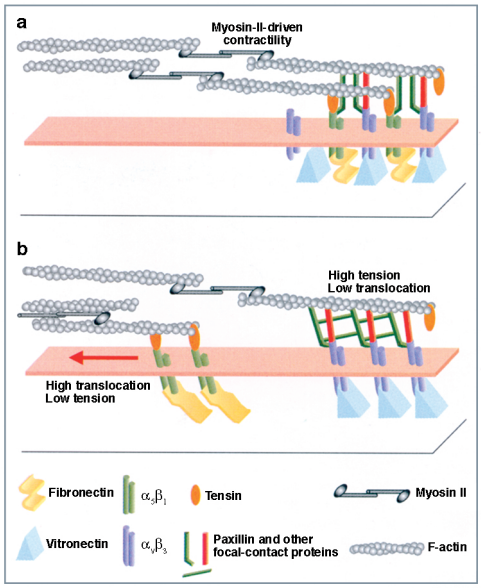

Fig.2 *A Model for the involvement of actomyosin-driven forces in the formation and segregation of fibrillar adhesions and focal contacts. For further details see Zamir et al., 2000.*

and cytoskeletal reorganization. Focusing on the regulation of focal contact assembly we are studying the roles of specific molecules such as vinculin and tyrosine kinases, including focal adhesion kinase and pp60src in focal contact formation. For these studies we use cells from which the respective proteins were genetically eliminated as well as transfections with dominant negative mutants. Expression of GFP fusion protein with the phospho-tyrosine-binding domain, SH2, enables the monitoring of tyrosine phosphorylation events in live cells. New approaches for quantitative analysis of cytoskeletal organization are developed to accuratly evaluate the influence of various stimuli and environmental conditions on the cells. These studies are carried out by computerized image processing of complex cytoskeletal patterns. Another line of studies addresses structural and signaling activities of β-catenin. We investigate the effect of phosphorylation on the distribution and signaling of this molecule and the cross-talk between it and the tumor suppressor p53. Studies with clinical orientation include the use of antibodies to adhesion-associated molecules for tumor diagnosis, application of HAV peptides for cancer therapy and the modulation of cell adhesion as novel approach for the treatment of glaucoma.

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