

MOLECULAR DIVERSITY OF ACTIN-INTEGRIN ADHESION COMPLEXES

[B.Geiger](#)¹, E.Zimmerman², E.Zamir¹, Z.Kam¹, A.Bershadsky¹ L.Addadi²

Departments of Molecular Cell Biology¹ and Structural Biology², [Weizmann Institute of Science](#), Rehovot 76100, ISRAEL

INTRODUCTION: Cell adhesion is a multistep process, initiated by surface recognition and attachment, and continuing with cell spreading, formation of focal adhesions (FA) and the activation of adhesion-mediated signalling. A conceptual temporal and spatial gap exists between the first encounter of a cell with an adhesive substrate and the advanced stages of FA formation. While ample information is available on focal adhesions structure and function, the mechanism of the first interaction events and the nature of the molecules mediating them are largely unknown. We have identified cell surface-associated hyaluronan as a major mediator and modulator of the first steps of adhesion of A6 and other cells to conventional tissue culture substrates, as well as to the surfaces of calcium-(R,R)-tartrate tetrahydrate crystals. Treatment of A6 cells with hyaluronidase suppresses their rapid interactions with these adhesive substrates, and incubation of either the hyaluronidase-treated cells or the substrate with hyaluronan restores cell adhesion. In contrast, excess hyaluronan on both the cells and the substrate strongly inhibits adhesion. We thus propose that cell surface-associated hyaluronan regulates cell-matrix adhesion at the very first encounter with the substrate. It may promote it through the establishment of exquisitely stereospecific chemical interactions, or inhibit it by virtue of steric exclusion and/or electrostatic repulsion.

Following incubation on appropriate extracellular matrix (ECM) these initial adhesion are replaced by integrin-mediated adhesions, in the form of focal complexes and FA. The latter adhesion sites were extensively characterized at the molecular level and shown to contain numerous anchor and cytoskeletal proteins (over 50 by now). Studies of these proteins, both biochemically and in situ has provided valuable information on the complexity of these adhesion sites and the molecular interactions which take place in them. These studies also raised intriguing questions concerning the structural and functional differences which may exist between the various forms of actin-integrin adhesion complexes (including FA, focal complexes, fibronexus, ECM adhesions, fibrillar adhesions and podosomes). Our studies indicate

that these sites are highly heterogeneous at the molecular level. They are also highly dynamic, continuously exchanging components with the cytoplasmic soluble pool, and translocating along the ventral cell membrane. This translocation plays an important role in the assembly and reorganization of the ECM, and is regulated by the actomyosin contractile machinery of the cells, by the Src/FAK signalling system, as well as by the physical properties (e.g. stiffness or pliability) of the extracellular matrix