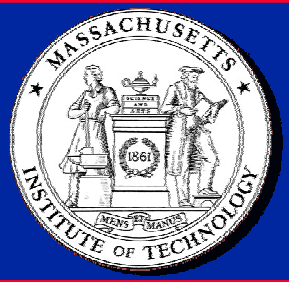
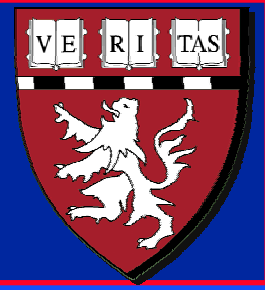


Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System



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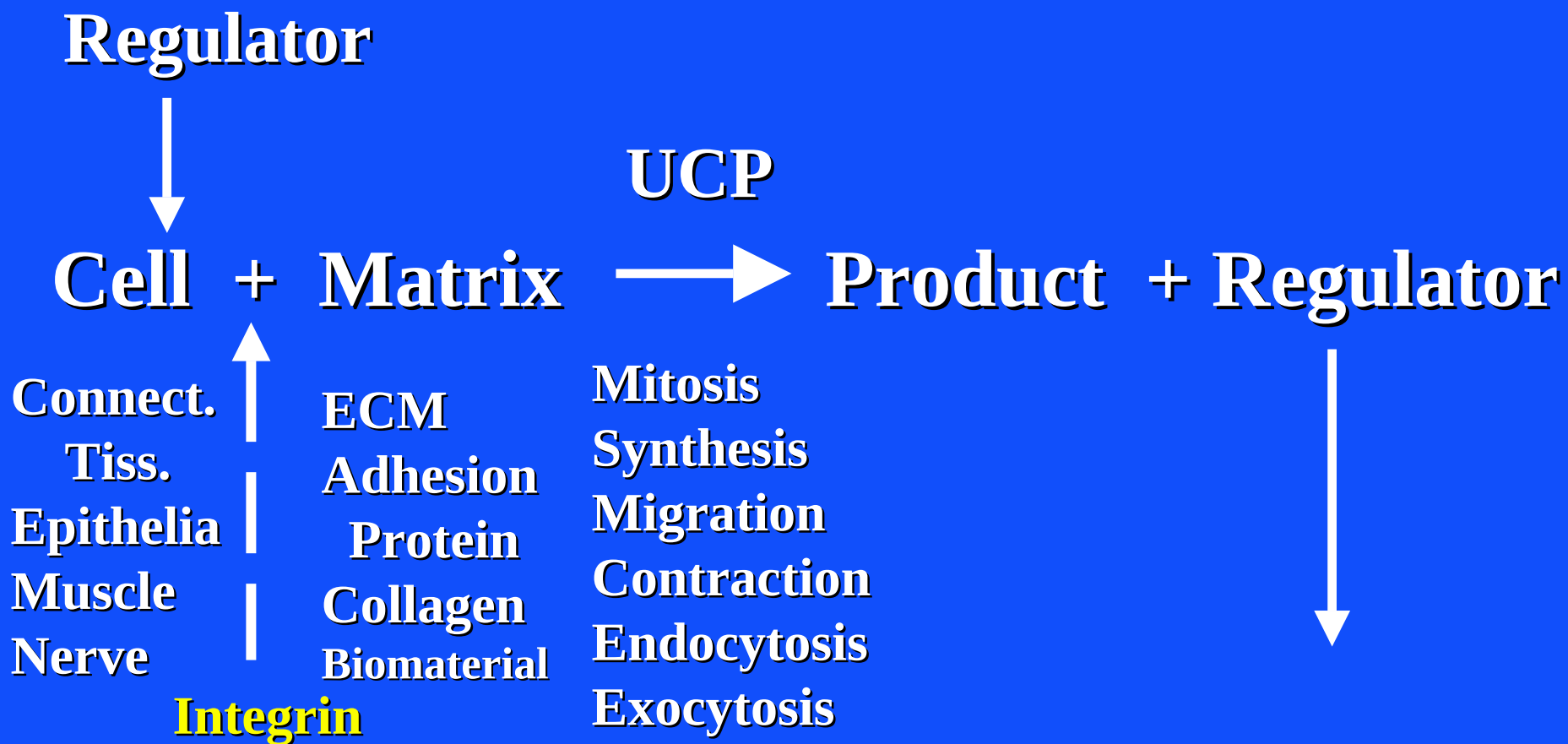
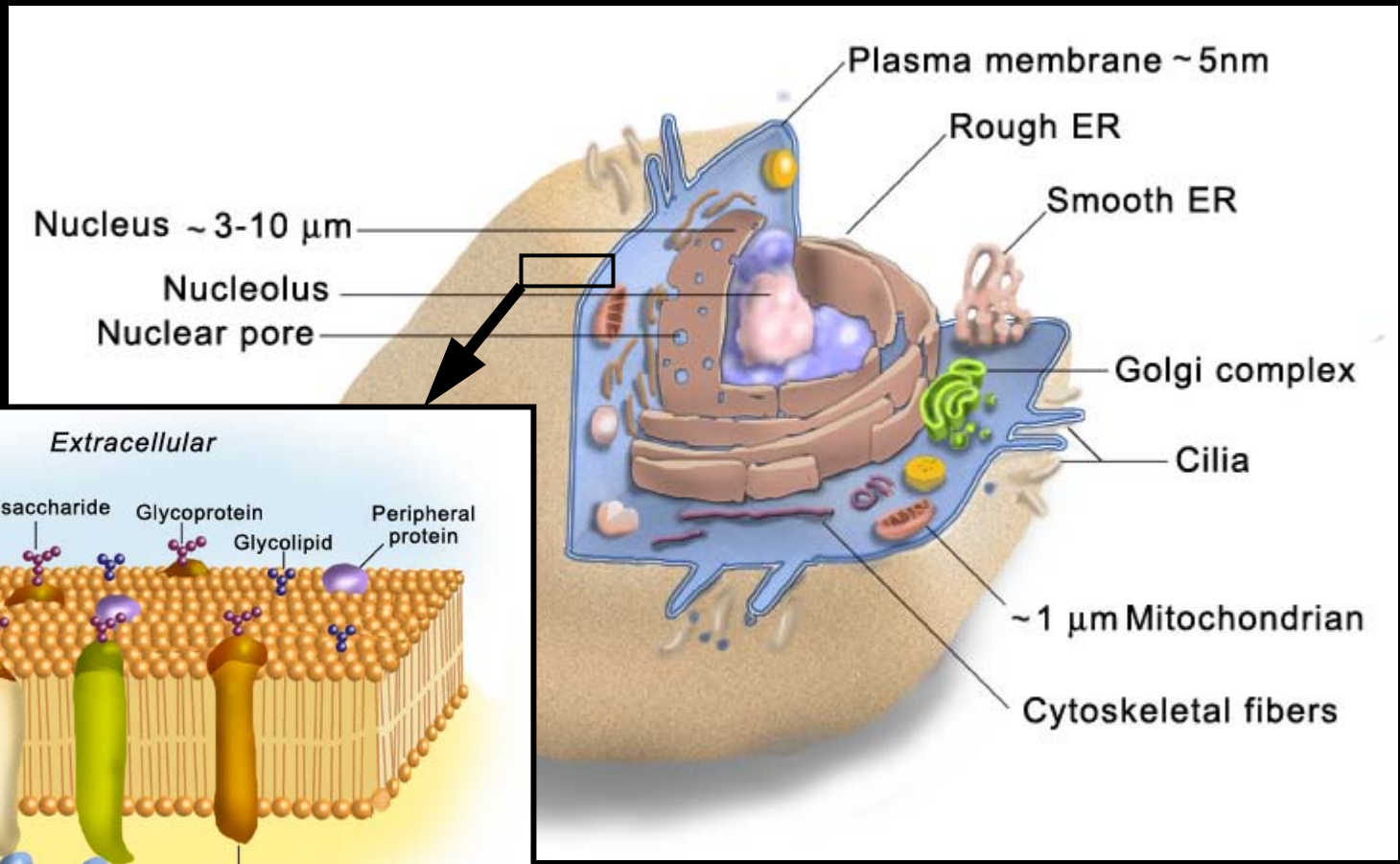
INTEGRINS

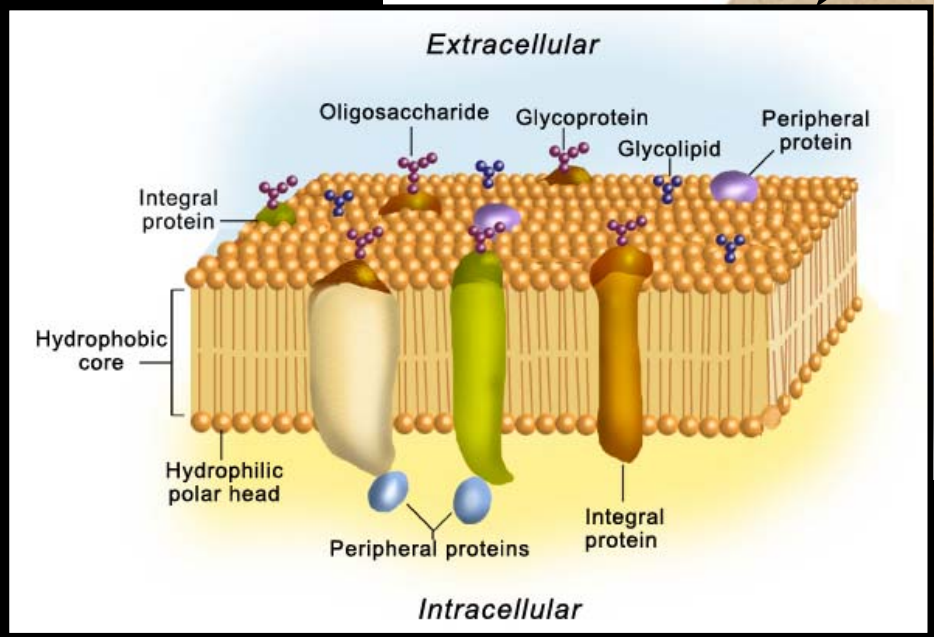
I.V. Yannas, Ph.D. and M. Spector, Ph.D.

UNIT CELL PROCESSES



The Cell and Its Membrane Molecules

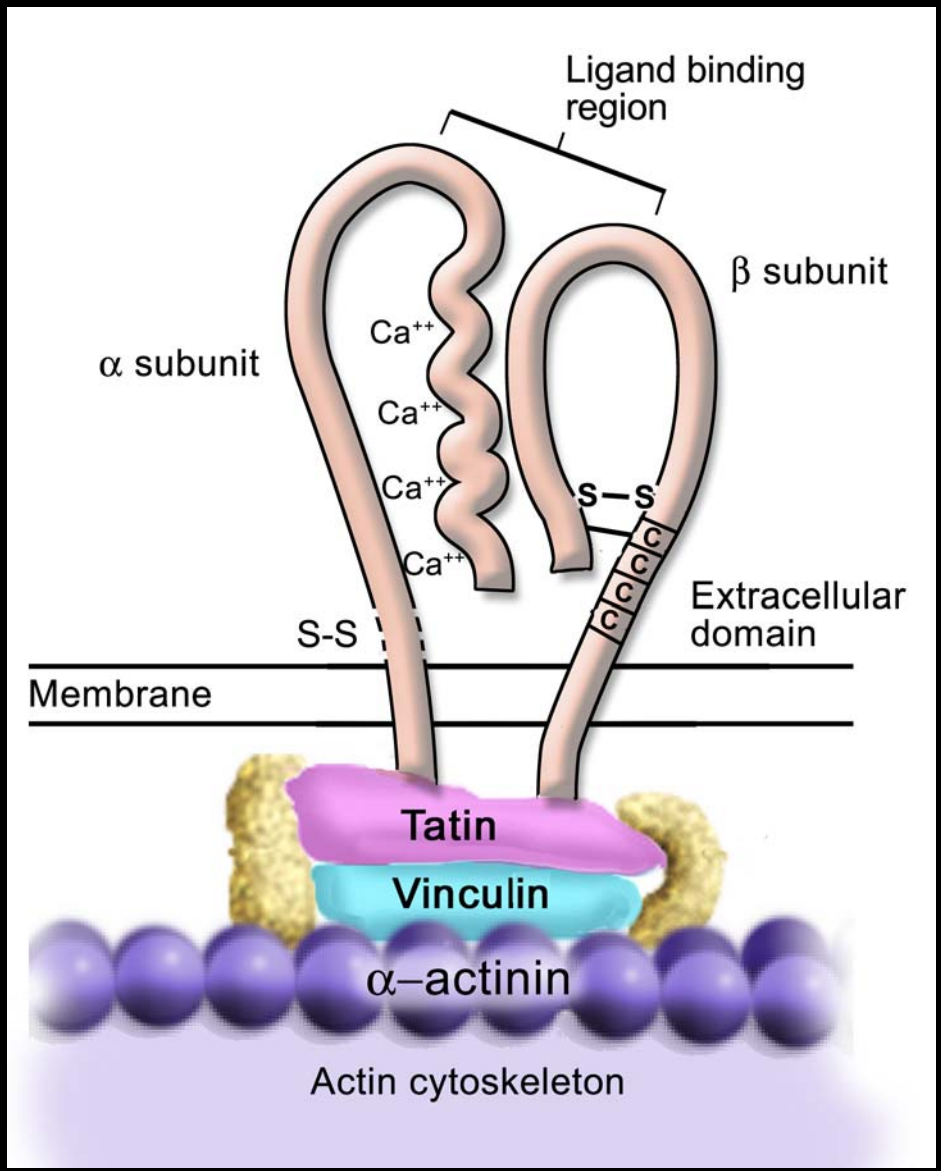




CELL ADHESION MOLECULES

Type	Cell-Matrix	Cell-Cell
Integrin *	√	√
Homophilic • N-CAM • Cadherin		√
Heterophilic		√

* Integrins bind to adhesion proteins and some to collagen



After SM Albelda, CA Buck, FASEB J., 4:2868 (1990)

Schematic of a typical integrin

The RGD* amino acid sequence on adhesion proteins (*e.g.*, fibronectin) was identified as the integrin-binding region (*i.e.*, the ligand for integrin receptors) – E Ruoslathi and MD Pierschbacher, Sci., 238:491 (1987)

* arginine-glycine-aspartic acid

Integrin Signaling, FG Giancotti, E Ruoslahti, Sci., 285:1028 (1999)

Figure 2. Matrix binding promotes integrin clustering and association with the cytoskeleton. This in turn promotes further integrin clustering and matrix organization in a positive feedback system. RGD, Arg-Gly-Asp integrin-binding motif; Tal, talin; Pax, paxillin; Vin, vinculin; CAS, p130CAS.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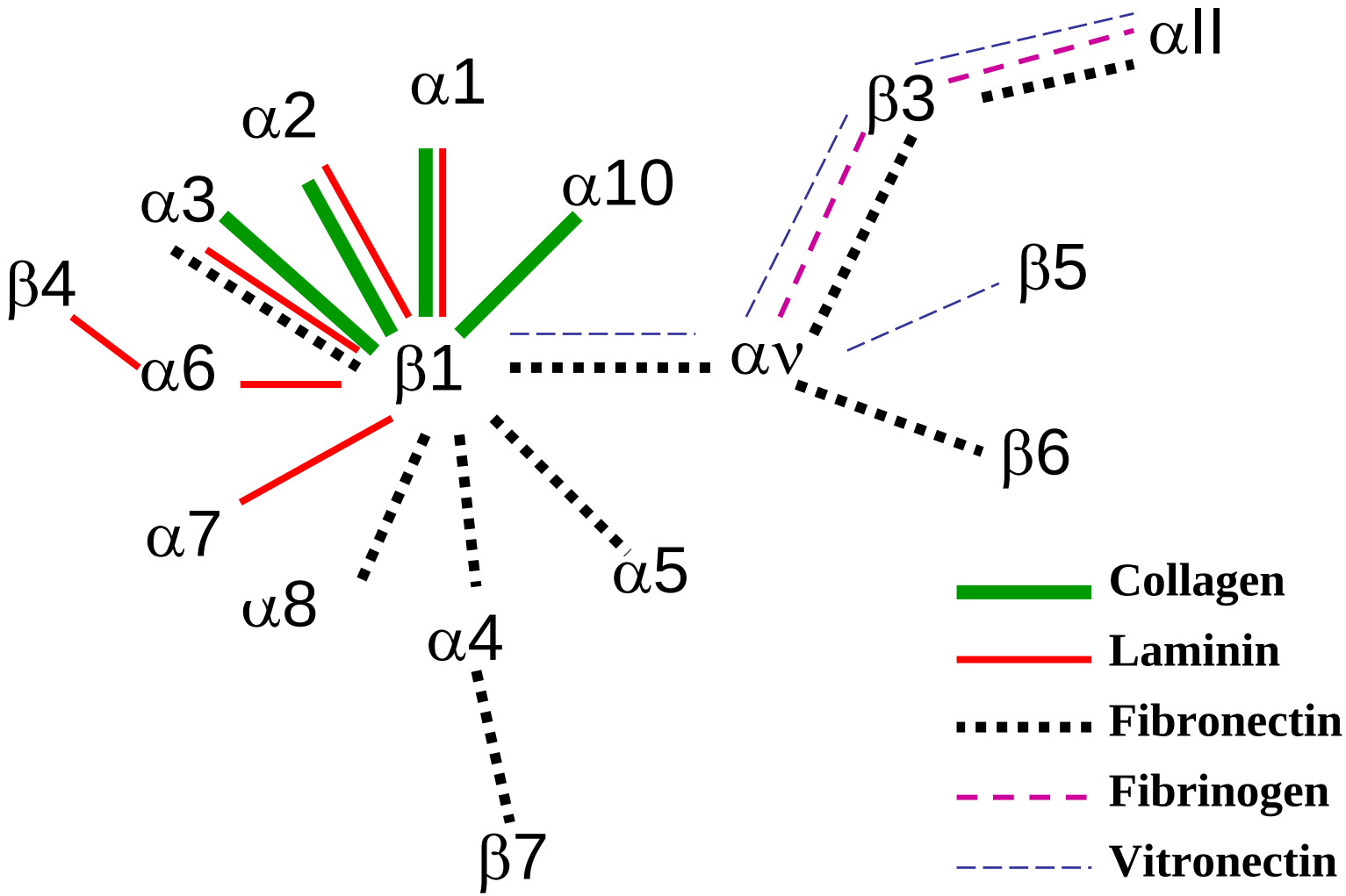
INTEGRINS AND THEIR LIGANDS



Adapted from: http://www.scripps.edu/cb/gardner/integrins.htm

INTEGRINS

(from http://life.kjist.ac.kr/htm/lab/cell/integrin/integrin.htm)

Integrins are **membrane-bound molecules (receptors)** that can bind to extracellular matrix molecules ("adhesion proteins" and collagen). They are the principal mechanism by which cells both bind to and respond to the extracellular matrix. They are part of a large family of cell adhesion molecules which are involved in cell-extracellular matrix and cell-cell interactions. Functional integrins consist of two transmembrane glycoprotein subunits that are non-covalently bound. Those subunits are called alpha and beta. The alpha subunits all have some homology to each other, as do the beta subunits. **The receptors always contain one alpha chain and one beta chain and are thus called heterodimeric**. Both of the subunits contribute to the binding of ligand. Until now 16 alpha and 8 beta subunits have been identified. From these subunits some 22 integrins are formed in nature, which implicates that not all possible combinations exist. The beta-4 subunit for instance can only form a heterodimer with the alpha-6 subunit. On the other hand the beta-1 subunit can form heterodimers with ten different alpha subunits. Because not all the beta-1 alpha heterodimers have the same ligand specificities, it is believed that the alpha chain is at least partly involved in the ligand specificity.

INTEGRINS

(from http://life.kjist.ac.kr/htm/lab/cell/integrin/integrin.htm)

Integrins differ from other cell-surface receptors in that they bind their ligands with a low affinity (106-109 liters/mole) and that they are usually present at 10-100 fold higher concentration on the cell surface. The integrins however can only bind their ligands when they exceed a certain minimal number of integrins at certain places, called focal contacts and hemidesmosomes. So when the integrins are diffusely distributed over the cell surface, no adhesion will be present, but when after a certain stimuli these integrins cluster for example in focal contacts their combined weak affinities give rise to a spot on the cell surface which has enough adhesive (sticking) capacity to adhere to the extracellular matrix. This is a very useful situation, because in this way cells can bind simultaneously but weakly to large numbers of matrix molecules and still have the opportunity to explore their environment without losing all attachment to it by building or breaking down focal contacts. If the receptors were to bind strongly to their ligands, cells would probably be irreversibly bound to the matrix, depriving them from motility. This problem does not arise when attachment depends on multiple weak adhesions.

INTEGRINS

(from http://life.kjist.ac.kr/htm/lab/cell/integrin/integrin.htm)

- Integrins can bind to an array of ligands. Common ligands are fibronectin and laminin, which are both part of the CT extracellular matrix and basal lamina. Both of these ligands mentioned above are recognized by multiple integrins. For adhesion to ligands both integrin subunits are needed, as is the presence of cations. The alpha chain has cation binding sites.
- Integrins are composed of long extracellular domains which adhere to their ligands, and short cytoplasmic domains that link the receptors to the cytoskeleton of the cell.
- The structure of alpha subunits is very similar. All contain 7 homologous repeats of 30-40 amino acids in their extracellular domain, spaced by stretches of 20-30 amino acids. The three or four repeats that are most extracellular, contain sequences with cation-binding properties. These sequences are thought to be involved in the binding of ligands, because the interaction of integrins with their ligand is cation-dependent.

Integrin Signaling, FG Giancotti, E Ruoslahti, Sci., 285:1028 (1999)

Figure 1. Cell survival and cell proliferation require interaction with the extracellular matrix. (A) Epithelial cells in some tissues, such as skin and gut, are continuously renewed from stem cells that rest on a basement membrane. Neighboring cells migrate into the space left empty by cells that have moved away to differentiate. (B) Certain epithelia, such as those of the mammary gland and prostate, are not continuously renewed. In this case, interaction with the matrix appears to promote differentiation. During involution, the basement membrane is dissolved by proteolysis, and the cells undergo apoptosis.

Integrin Signaling, FG Giancotti, E Ruoslahti, Sci., 285:1028 (1999)

Figure 4. Major signaling pathways that are known (solid arrows) or presumed (dashed arrows) to be coordinately regulated by integrins and growth factors receptors. These pathways control immediate-early gene expression, the cell cycle machinery, and cell survival.