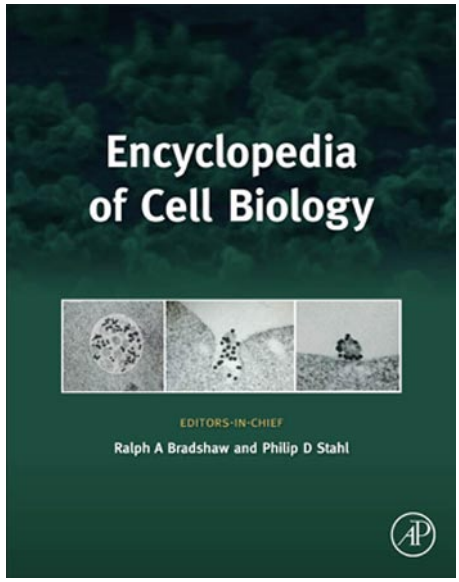

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Cell Adhesion to the Extracellular Matrix

B Geiger and A Livne, Weizmann Institute of Science, Rehovot, Israel

Glossary

Integrins A diverse family of adhesion receptors, mediating cell–matrix or cell–cell contacts. Integrins are heterodimeric transmembrane receptors consisting of α and β chains; in combination, they define the specificity of the adhesive interaction at the cell's exterior, and the local interaction with the cytoskeleton within the cells.

Invadopodia Protrusive cell adhesions associated with cancer cell invasion and metastasis. Invadopodia consist of an integrin-based adhesion domain through which they are attached to the matrix, a protrusive, actin-rich domain, and a proteolytic domain, responsible for local degradation of the matrix.

The Extracellular Matrix (ECM)

The ECM is composed of fibrillar networks that serve as scaffolds on which and within which tissue cells live (Hay, 1991; Alberts *et al.*, 2007). Interaction with the ECM affects the survival, proliferation, differentiation, and migration of individual, the so-called 'anchorage dependent' cells (Stoker *et al.*, 1968). In intact tissues it supports structural stability, sustains functional homeostasis and regulates the fate and behavior of the constituting cells (Davis and Camarillo, 1995; Menko and Boettiger, 1987). Adhesion-mediated signaling is based on the capacity of cells to sense and respond to changes in the chemical and physical properties of the ECM (Watt and Driskell, 2010) in a wide variety of processes, including embryonic development, tissue remodeling, and wound healing, as well as in disease states such as cancer invasion and metastasis (Egeblad *et al.*, 2010a,b). However, despite the strong evidence for physiological cell-ECM cross-talk *in vivo*, the molecular mechanisms underlying adhesion-dependent signaling, are poorly characterized, most likely due to the chemical and physical diversity and molecular complexity of living organisms (Hynes and Naba, 2012). Thus, many studies addressing adhesion-mediated processes are conducted *ex vivo*, enabling the design and fabrication of matrices with well-defined properties. In this chapter we will primarily address the mechanisms underlying cell adhesion to the ECM in such well-defined culture conditions.

Indeed, the ECM is highly diverse in structure, ranging from loose connective tissue to densely packed tendons, and sheets of basement membrane. Its variability can mainly be attributed to distinct molecular compositions and postdeposition remodeling. Connective tissue fascia and tendons, for example, contain high levels of collagen I, while basement membranes are enriched with collagen V, laminin, and different proteoglycans (Ricard-Blum, 2011; Yurchenco, 2011). Especially interesting is the fact that in addition to scaffolding networks, the ECM is loaded with growth factors (e.g., fibroblast-, transforming- and heparin-binding epidermal growth factors) that associate with specific components of the matrix (e.g., heparin sulfate proteoglycan) and stimulate the nearby adhering cells (Gospodarowicz *et al.*, 1980; Hay, 1991; Hynes, 2009; Munger and Sheppard, 2011; Sarrazin *et al.*, 2011). This process, whereby the ECM serves as a spatially defined signaling environment, is being applied as a powerful tool for culturing tissue cells under close-to-native conditions, *ex vivo*.

Another feature of the ECM that affects the attached cells is its dimensionality. Thus, cells can differentially respond through adhesion to one-dimensional (1D) matrices dominated by elongated fibrils (Doyle *et al.*, 2009); two-dimensional (2D) matrices such as basement membranes; and three-dimensional (3D) matrices, in which the cells are totally or partially embedded in the matrix (Cukierman *et al.*, 2001; Elsdale and Bard, 1972; Nelson and Bissell, 2006). Recent studies have demonstrated that cells can respond to the microtopography or even nano-topography of the surface to which they adhere (Baharloo *et al.*, 2005; Cukierman *et al.*, 2001; Curtis and Wilkinson, 1997; Geblinger *et al.*, 2010; Geiger *et al.*, 2001; Grossner-Schreiber *et al.*, 2006; Vogel *et al.*, 2006). Nano-patterning technologies have also been utilized to test the capacity of cells to recognize particular spacings between adhesive ligand epitopes, thus demonstrating that cells require certain threshold ligand proximities, usually within the range of a few tens of nanometers, for stimulating cell spreading and cytoskeletal reorganization (Cavalcanti-Adam *et al.*, 2007; Geiger *et al.*, 2009; Grinnell and Petroll, 2010; Massia and Hubbell, 1991; Yamada and Cukierman, 2007).

Diversity of ECM Adhesions

Clearly defined adhesions with the ECM are formed by essentially all adherent animal cells, in culture and *in vivo*; yet their molecular composition, subcellular distribution, size, and morphology can be quite heterogeneous. Particularly widespread and important are focal adhesions, usually located near the cell periphery, and associated with bundles of actin microfilaments (Geiger *et al.*, 2009; **Figure 1**). Focal adhesions share certain features in common: they are oval structures, several square microns in size, that are mediated by integrins, and interact with the actin cytoskeleton at the inner aspects of the membrane. Their development is stimulated by the small GTPase Rho, and requires actomyosin contractility. Characteristic focal adhesion plaque proteins include vinculin, paxillin, talin, and tyrosine-phosphorylated proteins. Interestingly, the molecular composition of the ECM (e.g., fibronectin vs. vitronectin or laminin) and the cellular interactions with these matrices via different integrins (e.g., $\alpha_5\beta_1$ vs. $\alpha_v\beta_3$) lead to the formation of focal adhesions of distinct morphology, size, and subcellular distribution (**Figure 2**). Focal adhesions are

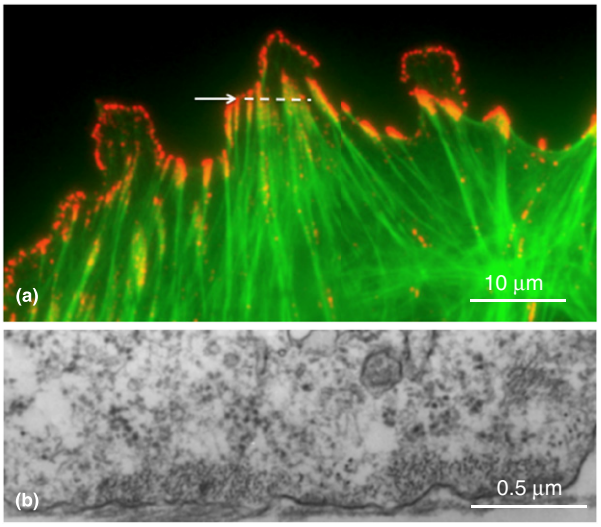

Figure 1 (a) Focal adhesions (red) are usually located at the cell periphery, anchoring contractile actin bundles (green), termed 'stress fibers,' to the ECM. (b) Electron microscope image showing a side view of the cell edge (e.g., dashed line in (a)). From bottom to top: ECM (dense patches), cell membrane (continuous line), actin fibers associated with focal adhesions (sparse patches next to cell membrane), microtubules, and cell organelles.

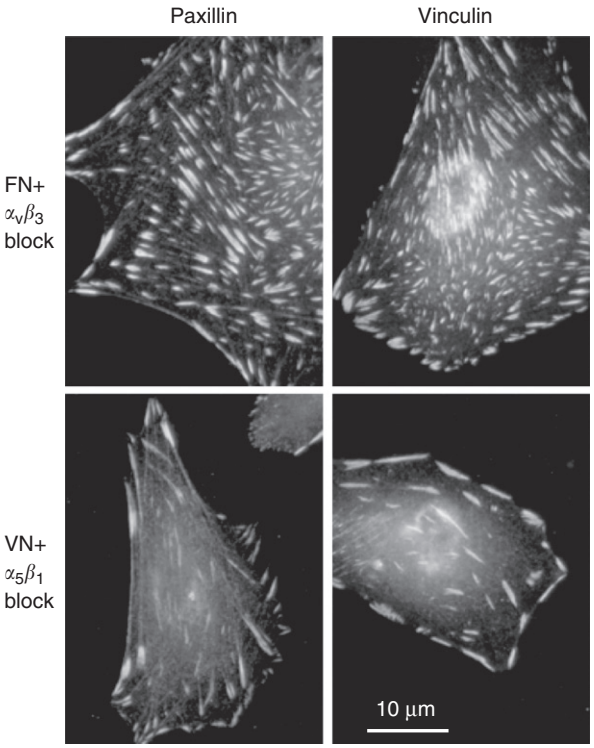

Figure 2 The molecular composition of the ECM (here, the glass surface is coated with fibronectin or vitronectin) and the cellular interaction with these matrices via different integrins ($\alpha_5\beta_1$ and $\alpha_v\beta_3$, respectively) lead to the formation of focal adhesions (stained here for vinculin and paxillin) with distinct morphology, size, and subcellular distribution. Images courtesy of B. Zimerman.

mainly prominent in cultured cells growing on solid surfaces; yet structures with similar molecular properties are also found *in vivo* (e.g., myotendinous junctions, adhesions to the basement membrane). One clear example for *in vivo* analogs of focal adhesions is the dense plaque of smooth muscle tissues, which is the anchorage site of the contractile actin machinery to the plasma membrane. This was demonstrated both by antibody labeling of smooth muscle sections, which displayed an abundance of adhesome components in these sites (North *et al.*, 1993; Winograd-Katz *et al.*, 2014), and by cryo-electron tomography (Bokstad *et al.*, 2012), which revealed, in these sites, specific focal adhesion-associated particles (Patla *et al.*, 2010).

Another form of integrin adhesion is focal complexes, small (around 100 nm in diameter), dot-like structures that are primarily located along the lamellipodium's edge (Zamir and Geiger, 2001; **Figure 3(a)**). These sites can be associated with cell migration, or serve as precursors of focal adhesions. Their formation is induced by the Rho family GTPase Rac. In the more central locations of many cell types, 'fibrillar adhesions' (known also as 'ECM contacts'), dot-like or elongated structures associated with ECM fibrils, are also found (Zamir *et al.*, 2000; **Figure 3(b)**). Fibrillar adhesions are typically associated with 'soft' extracellular fibronectin fibrils, mediated by the fibronectin receptor $\alpha_5\beta_1$ integrin, and enriched with the cytoplasmic protein tensin. Fibrillar adhesions emerge from focal adhesions in an actomyosin-dependent fashion. Another form of ECM adhesion is the invadosome, including podosomes and invadopodia, small (around 0.5 μm in diameter) cylindrical structures consisting of typical focal adhesion proteins, including vinculin and paxillin (Linder, 2009; Revach and Geiger, 2014). Podosomes are found in cells such as macrophages and osteoclasts (**Figure 4(a)**), whereas invadopodia are predominantly found in invasive or metastatic cancer cells (**Figure 4(b)**). Characteristic proteins, indispensable for invadosome formation are gelsolin and dynamin, both of which localize to the actin cores of these structures.

It is noteworthy that most of the matrix adhesions described above, interact, through their cytoplasmic aspects, with the actin cytoskeleton. Nevertheless, the adhesion of epithelial cells to the underlying basement membrane is also mediated by another class of adhesions, known as hemidesmosomes, which typically associate, within the cell, with the keratin-based intermediate filament system. The primary integrin that mediates these interactions is $\alpha_6\beta_4$, which is accompanied, in some tissues, by additional transmembrane matrix receptors as well (Litjens *et al.*, 2006). The third cytoskeletal network, microtubules, is apparently not associated directly with matrix adhesions, yet it has been shown that microtubules negatively regulate focal adhesion stability (Bershadsky *et al.*, 1996; Kaverina *et al.*, 1999). In addition, podosomes in osteoclasts and other cell types depend on the presence of intact microtubules, and dissociate upon cell treatment with microtubule-disrupting drugs (Destaing *et al.*, 2003, 2005).

The Integrin Adhesome

The molecular components of the adhesion machinery, consisting of over 200 distinct proteins that localize to focal

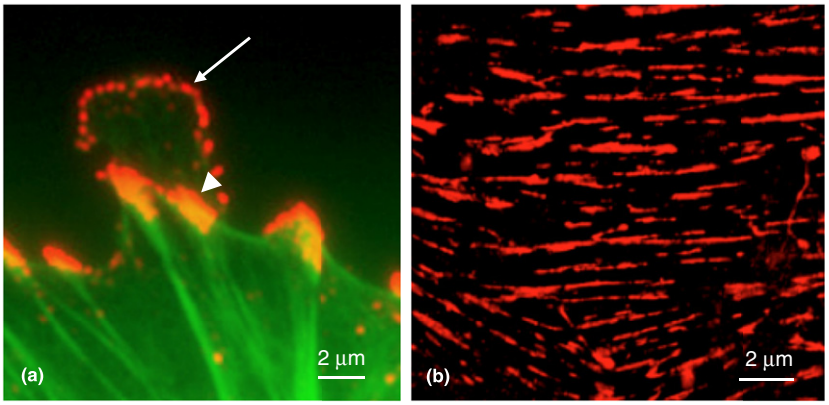

Figure 3 (a) Focal complexes (arrow) are small (~100 nm in diameter), dot-like adhesions primarily located near the lamellipodium edges. These sites can serve as precursors of focal adhesions (arrowhead), and may be involved in cell migration. (b) Fibrillar adhesions are dot-like or elongated structures, and associated with ECM fibrils located near the cell center in various cell types.

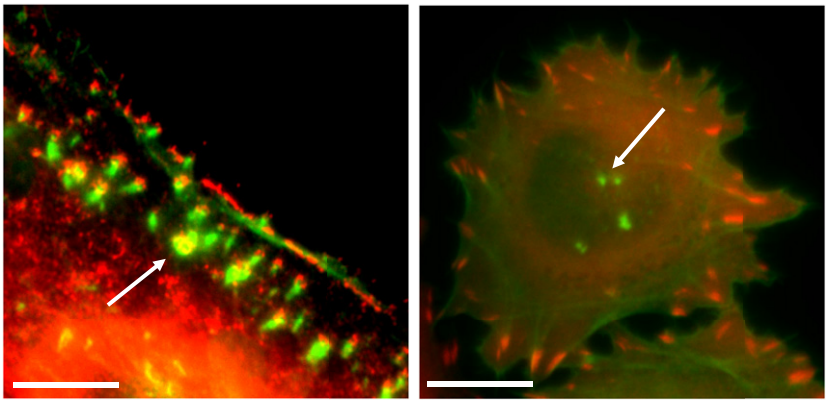

Figure 4 Invadosomes, including podosomes and invadopodia, are small (~0.5 μm in diameter) cylindrical adhesion structures consisting of focal adhesion proteins such as vinculin (red) surrounded by an actin core (green). (a) Podosomes (arrow) at the periphery of an osteoclast. (b) Invadopodia (arrow) are prominently found in the vicinity of the cell nucleus in invasive or metastatic cancer cells. Images in (a) are courtesy of S. Batsir; images in (b) courtesy of O. Revach, Weizmann Institute of Science.

adhesions either constitutively or transiently, are known, collectively, as the 'integrin adhesome' (Zaidel-Bar and Geiger, 2010; Zaidel-Bar *et al.*, 2007). An updated list of components, available in (Winograd-Katz *et al.*, 2014) can be divided into two major domains: a 'scaffolding domain,' consisting of the adhesion receptors (mostly different integrins), a multitude of adapter proteins that connect the receptors to the cytoskeleton, and various actin-binding and regulatory proteins. In addition, a 'regulatory domain' consisting of a multitude of signaling proteins (e.g., kinases, phosphatases, G-proteins and their activators or inhibitors), generates and mediates adhesion-dependent signaling cascades, thereby affecting cell behavior, as well as the development and modulation of the adhesions themselves (Figure 5).

The transmembrane components of focal adhesions contain different pairs of α- and β integrin subunits, which bind to specific matrix components via their extracellular domains (Giancotti and Ruoslahti, 1999). The matrix specificity of cells is primarily attributed to the type of integrin they possess, and to their state of activation. The most common integrins found in focal- and related ECM adhesions are the fibronectin receptor, $\alpha_5\beta_1$, and the vitronectin receptor, $\alpha_V\beta_3$. Additional membrane receptors, though less characterized at the structural and functional levels, include other integrins, as well as potentially adhesive molecules such as syndecan-4 and the hyaluronan-binding protein layilin (Lanza *et al.*, 2013).

Associated with the cytoplasmic aspect of the plasma membrane is the focal adhesion plaque, consisting of multiprotein complexes that interact with the cytoplasmic tails of the integrin chains and, eventually, link them to the actin cytoskeleton. Some of these plaque components, including α-actinin, talin, filamin, and tensin, contain binding sites for both integrins and actin, while other integrin-associated molecules do not directly bind to actin, but rather to different actin-associated proteins or additional 'adapter' proteins. Notably, these adapters, which include signaling proteins such as focal adhesion kinase (FAK), the LIM-domain protein DRAL, or adhesion mechano-regulators such as vinculin, can play regulatory roles. In fact, vinculin plays a pivotal role as a central linker interacting with many plaque proteins, including

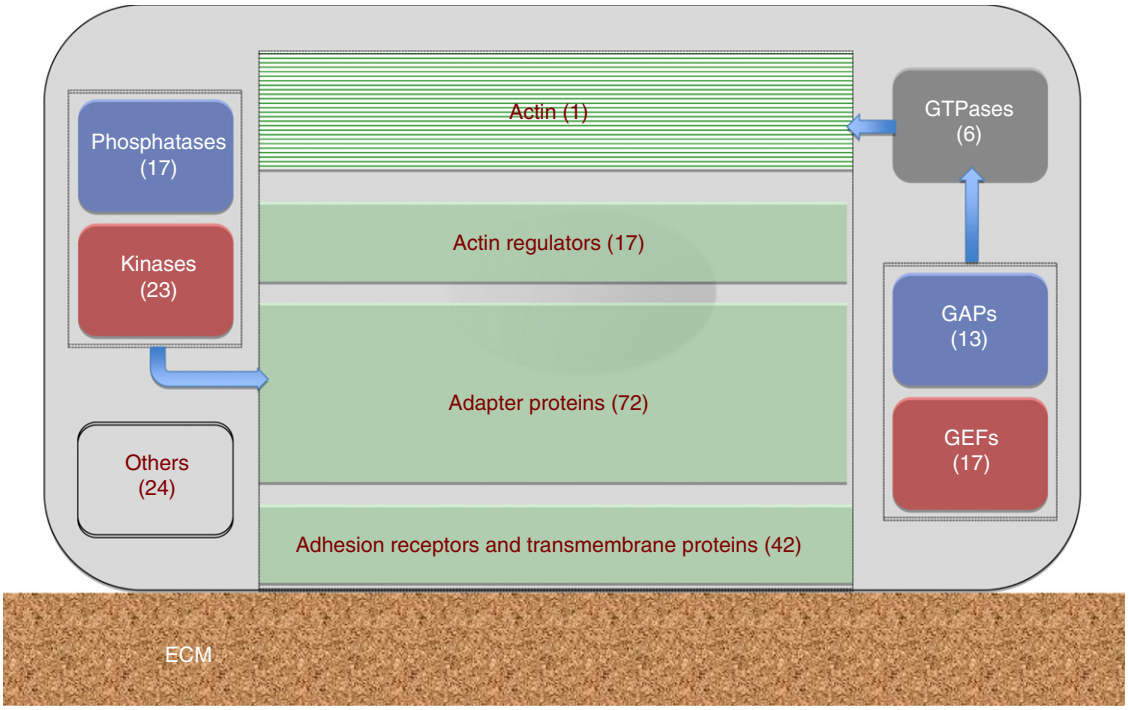

Figure 5 Diagram depicting the different functional and chemical groups comprising the integrin adhesome. Some 232 distinct proteins and other molecules are known to be contained in, or directly associated with, focal adhesions and other, similar adhesion sites. The adapter proteins, together with the actin regulators, form the scaffolding domain of the adhesion site, providing it with its unique mechanical properties. The stability and dynamics of the adhesion are controlled by its regulatory components, which include diverse elements of signaling cascades, mostly kinases and their corresponding phosphatases, as well as small Rho GTPases and their GEF and GAP regulators.

talin, α-actinin, VASP/Ena, ponsin and vinexin, as well as with acidic phospholipids and actin. Taken together, the adapter components and actin regulators of focal adhesions form the 'scaffolding domain' of the adhesion site, and generate the unique mechanical properties of these structures. Furthermore, many signaling molecules were shown to interact with these adhesions, and regulate their stability and dynamics. These 'regulatory components' include diverse components of signaling cascades, mostly kinases (tyrosine- and serine/threonine-specific) and the corresponding phosphatases, as well as small Rho GTPases and their GEF and GAP regulators. It is likely that dynamic, continuous cross-talk between the scaffolding and signaling domains is responsible for both the global 'adhesion-mediated signaling' believed to be generated in focal adhesions, as well as for the local dynamic reorganization of the adhesion sites in which they reside. Further details about the interplay between these two functional domains of adhesion sites are described in (Zaidel-Bar and Geiger, 2010).

Geometric and Mechanical Sensory (Mechanosensing) Functions of ECM Adhesions

The ECM presents cells with highly complex and diverse physical environments. Different tissue types may vary dramatically in rigidity (bone vs. cartilage), activity (beating heart vs. static brain), and geometry (2D basement membrane vs. 3D stroma), all of which influence cell organization and function. Over the past two decades, a number of physical features of the cellular microenvironment have been observed, primarily *ex vivo*, to play key biological roles:

- Spatial distribution of ECM ligand molecules: The spacing of ECM ligands in physiological conditions may vary greatly. To mimic such conditions, cultured cells were plated on 2D substrates with controlled, nanoscale-positioning of the ECM ligands (Arnold *et al.*, 2008). Cells spread and migrated on the nanopatterned surfaces when ligand spacing was below a critical value ($\sim$70 nm), while at higher spacings, cell viability was severely hampered, eventually leading to apoptosis. Moreover, cells could detect and respond to minute gradients in ligand spacing (comparable to ligand positioning inhomogeneities), indicating that the ECM cues were averaged over a number of adhesion sites, to improve cellular sensitivity. Notably, an intrinsic focal adhesion length scale was observed in the same range as that of 'optimal' ligand spacing (Patla *et al.*, 2010). Three-dimensional structural reconstruction of focal adhesions using cryo-electron tomography revealed particles located at the cell membrane, and attached to actin fibers with a mean interspacing of approximately 45 nm.
- ECM geometry: The ECM provides cells with a 3D microenvironment. However, in some cases, the effective cell–matrix contacts are geometrically confined. For example, epithelial and endothelial cells adhere to the basal lamina, a practically 2D substrate (Stamenovic *et al.*, 2009). In addition, cells adhering to single ECM filaments effectively sense a 1D geometry (Sharma *et al.*, 2012). *In vitro* studies

mimicking these different geometries have demonstrated particularly diverse cell shapes, polarities and migration speeds (e.g., Doyle *et al.*, 2009). In addition, the porosity level of the 3D ECM scaffold was shown to influence cell morphology and migration dynamics (e.g., ameboid vs. mesenchymal motion, and individual vs. collective migration) (Friedl and Gilmour, 2009).

- ECM topography: While the vast majority of cell culture studies are conducted, for imaging purposes, on flat substrates, cells *in vivo* adhere to rough surfaces as well. In such cases, the cell membrane can bend and deform to remain in contact with the ECM. In turn, the resulting curvature of the cell membrane and adhesion sites may affect cell behavior, by exposing cryptic protein binding sites or activating mechanosensitive ion channels (Hoffman *et al.*, 2011). One example of the correlation between surface roughness and cell response was observed in bone-resorbing osteoclasts, in which the resorption dynamics are highly dependent on ECM topography (Geblinger *et al.*, 2010).
- ECM rigidity: *In vivo*, ECM rigidities span over 7 orders of magnitude, with different cell types typically associated with characteristic stiffness regimes (Discher *et al.*, 2005; Swift *et al.*, 2013). Loss of the cell's ability to sense changes in ECM rigidity are associated with cell dysfunction and disease (Janmey and Miller, 2011). For example, tumor stroma is typically stiffer than normal stroma, and its progression in 3D models correlates with ECM rigidity. In 2D cultured systems, substrate rigidity has been associated with cell morphology (Geiger *et al.*, 2009; Vogel and Sheetz, 2006), migration (Lo *et al.*, 2000; Saez *et al.*, 2007), proliferation (Janmey and Miller, 2011; Orr *et al.*, 2006), gene expression and differentiation (Discher *et al.*, 2005; Guilak *et al.*, 2009). The mechanism through which cells probe the rigidity of their microenvironment involves application of actomyosin contractile forces via the cell-ECM adhesion sites, notably focal adhesions.
- External forces: The ECM mechanically couples cells anchored to it. In this manner, cells are exposed to external forces, which may be critical for tissue development, function, remodeling and healing. Remarkably, both constant (e.g., blood flow experienced by endothelial cells) and rhythmic force perturbations (e.g., originating in the respiratory or cardio-vascular systems) have been associated with cell realignment at well-defined and uniform angles (Wang and Grood, 2000).

The Cross-Talk between the Cell and the ECM

The ECM is a highly complex network of adhesive filaments with specialized chemical, mechanical and geometric properties (Geiger and Yamada, 2011). It serves as an effective tissue scaffold, providing cells with the precise environmental conditions required for proper development, survival and proliferation. Similar to the cytoplasmic aspects of focal adhesions described above, the ECM is characterized by both scaffolding and signaling properties. The scaffolding elements attached to the extracellular faces of focal adhesions consist of tightly packed arrays of ECM filaments, which are nearly colinear with the cytoplasmic actin filaments that attach to the focal adhesion at the cell interior (Singer, 1979). In addition, there is ample evidence that the ECM serves as a depot for growth factors that can stimulate the growth, differentiation and dynamics of the attached cells (Brizzi *et al.*, 2012; Gospodarowicz *et al.*, 1980; Hynes, 2009). This combination of external stimulation of adherent cells by chemical and physical

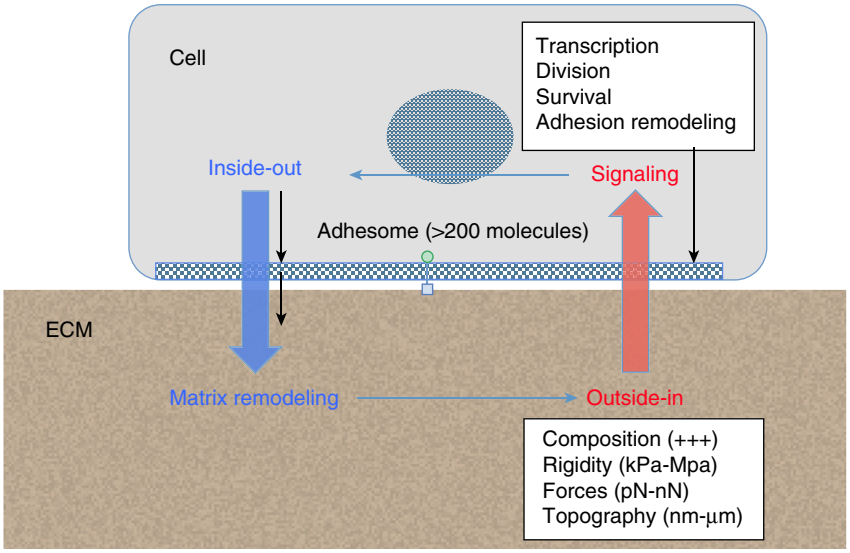

Figure 6 Diagram depicting the cross-talk between cells and the ECM. The properties of the ECM scaffold, such as composition, rigidity, and topography, and associated external forces, induce the formation of cellular adhesion structures (the 'outside-in' effect). The resulting signaling cascades that follow, through the integrin adhesome, may in turn drive an 'inside-out' process of ECM remodeling by the cell. Thus, bi-directional cross-talk between the cell, through its adhesion machinery, and the surrounding microenvironment is perpetually maintained, remodeling the ECM and, in turn, affecting cell behavior, structure, and fate.

ECM-mediated cues is, most likely, underlying the 'anchorage dependence' properties of normal cells, which are often lost upon malignant transformation (Stoker *et al.*, 1968).

ECM adhesion sites also serve as major environmental sensors, which are induced to assemble by means of chemical and physical cues generated at their points of contact with the ECM and activating, across the membrane, various signaling cascades that affect cell behavior and fate (**Figure 6**). Typical signaling events triggered by the adhesion include the activation of tyrosine phosphorylation caused by the accretion and activation of FAK and Src, the activation of Rho and Ras small GTPases, and the subsequent activation of the extracellular signal-regulated kinase (ERK) pathway (Geiger *et al.*, 2009). It is proposed that the tethering of FAK to clustered integrins leads to its autophosphorylation, followed by the recruitment of Src, which binds to phospho-FAK via its phosphotyrosine-binding domain (SH2), and followed by further phosphorylation of a series of downstream targets (Mitra and Schlaepfer, 2006). It is further believed that the local accumulation of a rich variety of kinases, phosphatases and their substrates in the sub-membrane focal adhesion plaque plays a key role in the adhesion-mediated signaling process (Geiger *et al.*, 2009). That said, definitive information concerning these signaling processes and their cellular effects remains scarce. It is interesting to note that, apart from the long-term and long-range adhesion signals that affect overall cell fate, there are also local signals, which act at, and affect focal adhesion structure and stability.

Clearly, however, the ECM scaffold and the sensory-signaling machinery of the cell conduct a complex molecular dialog that has far-reaching consequences for the cells. The focal adhesion-based sensory system is capable of sensing multiple molecular and physical cues such as ligand chemistry and spacing, surface nano-topography, geometry, rigidity and external forces. This rich information is integrated by focal adhesion-associated networks and triggers a cytoplasmic response; a process known as an 'outside-in response.' In turn, the same signaling cascades, triggered by environmental cues, can induce an 'inside-out response,' modifying the neighboring ECM (e.g., through dissolution with proteases, mechanical perturbation, or additional fiber deposition) which, in turn, can affect the original environmental signals. It is proposed that this bi-directional cross-talk between the cell, through its adhesion machinery, and the microenvironment is perpetually maintained, remodeling the ECM and, in turn, regulating cell behavior, structure and fate.

Acknowledgments

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See also: Cytoskeleton and Motors: Complex Cytoskeletal Structures: The Extracellular Matrix

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