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Review Article

Mechanosensing in cell–matrix adhesions – Converting tension into chemical signals ☆

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ABSTRACT

Cell-matrix adhesions have since long been recognized to be critical for the survival and proliferation of cells. In fact, these adhesive structures do not only physically anchor cells, but they also induce vital intracellular signaling at cell-matrix adhesion sites. Recent progress in the cell adhesion field is now starting to provide data and ideas how this so far enigmatic signaling process is induced and regulated by intracellular acto-myosin tension, or stiffness of the extracellular matrix. Understanding how cells are using this mechanosignaling system will be key to control biological processes such as development, cancer growth, metastasis formation and tissue regeneration. In this review, we illustrate and discuss the mechanosignaling mechanisms important in the regulation of cell-matrix adhesions at the molecular level.

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Contents

1. Introduction

Chemical reactions are essential for biological functions, and molecular interactions are needed for the chemical reactions to take place. Compartmentalization or restriction to membrane surfaces increases the local concentration and thus facilitates protein–protein or protein–peptide interactions, creating protein complexes with specific cellular functions. For adherent cells, fluid shear forces and mechanical cues generated by motor proteins and tissue deformation are important elements of the signaling machinery, constantly modifying the structure and function of the proteins. In turn, mechanical strain on a protein network requires proteins to act as cross-linkers, or softeners to either reinforce or destabilize the mechanical scaffold. Cells have mechanisms to sense the strain or compliance of the extracellular scaffold, as well as to detect shear forces acting on its force-bearing structures such as cytoskeleton, cell–cell and cell–matrix adhesions. A critical aspect of such sensing mechanisms is the conversion of a mechanical force into local (chemical) signaling, that will induce cell behavior to counteract the mechanical challenge or to modulate cell-

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anchorage, creating survival signals important for the healthy state of cells.

Integrin-receptor containing cell–matrix adhesion sites are among the most complex but also highly versatile mechanosensing systems. Cell–matrix adhesions enable cells to monitor their adhesive state, as well as rapidly respond to changes in mechanical tension or shear forces by modulation of cellular adhesion and migration. All multicellular organisms require this sensing system to maintain the architecture and homeostasis of tissues and organs. Thus we may predict that any relevant signaling system involved in the regulation of cell growth, shape and migration is interfacing with the integrin-dependent mechanosignaling found in cell–matrix adhesion sites. So far, only a small fraction of its regulatory potential has been identified and for only a few of its components, the details at the molecular level are known.

Here we would like to describe emerging concepts, explaining the cellular mechanosensing in cell–matrix adhesions (aka focal adhesions) at the molecular level. Our aim is not only to describe the well-proven functions, but also to speculate about possible poorly characterized mechanisms involved.

2. Biological phenomena in mechanosensing and how mechanosignaling controls cell behavior

Mechanosensing at cell–matrix adhesion sites is at the origin of durotaxis, a mechanism describing the ability of cells to migrate towards a stiffer surface [1]. A potentially similar effect is seen when cells are plated on a nanostructured gradient of integrin peptide ligands [2], where a cellular response is directed uphill. Cells also respond to externally applied stress by changing their adhesion sites [3] and stress fiber orientation [4]. For example, endothelial cells exposed to a fluid shear stress reorient their cytoskeleton, which is associated with Rho-family GTPase-mediated intracellular signaling [5]. Cyclic stretching of fibroblasts plated on an elastic membrane induces remodeling of the actin cytoskeleton, but also stress induced expression of the non-adhesive extracellular matrix protein tenascin-C [6]. Interestingly, this stress-mediated response requires mechanical coupling of cells to fibronectin, but leads to the expression of tenascin-C that in turn reduces cell-adhesion and enhances motility of cells [7]. This demonstrates that the ECM and its specific composition is an integral part of the integrin-dependent mechanosensing of cells. The role of the ECM in the mechanosensing also includes growth factors, such as TGF-β that can be released from their latent and matrix-bound forms in response to tension transmitted via integrins [8]. This indirect mechanosignaling pathway provides further insights into signaling mechanisms that require integrin-mediated stretching and remodeling of ECM proteins. Alternatively, matrix-bound but not soluble growth factors induce robust wound healing [9], or synergies with integrin-dependent adhesion [10], suggesting that mechanosignaling is also very important for the regulation of the integrin/receptor tyrosine kinase interface.

During cancer initiation, growth and migration, extracellular matrix deposition and stiffness modifies cell fate and behavior. While a stiffer ECM induces dedifferentiation of mammary gland epithelial cells [11], cancer cells can use amoeboid like movements, potentially induced by paxillin stimulated, RhoA-mediated contractility [12], making them less dependent on the physical state of the extracellular scaffold. On the other hand, melanoma cells are also able to escape inhibitor treatment by initiating a rigidity sensing-response involving focal adhesion kinase (FAK) [13]. Recently, another mechanism of tension-mediated signaling has been proposed to be implemented by the increased expression of cell surface mucins. A highly hydrated mucin layer on the cell surface is acting like a hydrodynamic spring to push cells away from the ECM scaffold, thereby reinforcing the mechanical link and signaling output of integrin-mediated cell–matrix adhesions [14].

Tension-induced signaling within focal adhesions is best seen when staining cells with phosphotyrosine antibodies [15]. Subsequent signaling-mediated maturation of cell–matrix adhesions has long been observed in adherent cells in culture. When plated on rigid surfaces, the stronger the intracellular tension, the bigger the cell–matrix adhesions become [16]. Alternatively, maturation of focal or nascent adhesions occurs in response to extracellular as well as intracellular acto-myosin tension [3,17]. An increase in mechanical tension on cell–matrix adhesions induces the recruitment of paxillin and FAK, a process dependent on the focal adhesion scaffold, occurring even after extraction of membranes [18]. More recent proteomics studies [19] confirm this tension-mediated recruitment of LIM-domain containing proteins such as paxillin and zyxin, suggesting that LIM-domains form a molecular structure sensitive to tension induced revelation of binding sites in the actin cytoskeleton [20] or within cell–matrix adhesion sites [21]. Although paxillin and Hic-5 are differentially orchestrating intracellular signaling and cytoskeletal remodeling [12], a mechanism to their tension-mediated recruitment to cell–matrix adhesions has only recently been proposed [21] (see below).

The combination of cell surface patterning and stem cell research has opened a new dimension of mechanosensing, where an apparent match between substrate stiffness and physiological contractility of cells is searched [22]. The amount of available surface for cellular attachment has also an impact on differentiation towards osteoblasts or adipocytes [23], which is apparently linked to the activation of the YAP/TAZ transcription factors [24].

A key role in mechanosignaling is seen during directed cell migration. Cell detachment and steering at the cell rear requires myosin contraction [25]. Apparently, induction of paxillin-mediated recruitment of FAK/src kinases at cell–matrix adhesions regulates adhesion turnover and cell detachment, which allows cell migration [26,27].

In order to illustrate the molecular mechanisms involved in cellular mechanosensing, we focus on a few proteins important for this process, namely fibronectin, integrin, paxillin/FAK and talin. With these examples it is possible to get an insight into the repertoire of functions employed during mechanoregulation.

3. Talin – primary mechanosensor or just a structural scaffold?

Talin is a cytoplasmic adapter protein capable of directly connecting integrins to the actin cytoskeleton. Talin consists of an N-terminal head domain (~residues 1–430) responsible for integrin binding, which has homology to FERM proteins. Talin rod domain (~residues 430–2500) consists solely of α-helices, which are packed into bundles of 4–5 helices [28]. The rod domain contains actin binding site as well as a dimerization domain at the C-terminal end of the protein. The rod has also up to 13 binding sites for vinculin, up to 3 binding sites for RIAM and also putative binding sites for integrin, paxillin and possibly also for several other proteins [29]. One could thus consider talin a large scaffolding protein.

Talin has however unique mechanosensory characteristics: the activity and functions of talin are regulated at several levels and mechanical cues appear to play significant roles in talin interactions and function in cells. First of all, talin autoinhibition is holding the protein in a resting. inactive state until released by synergistic actions of RIAM binding [30] and lipid interactions [31,32] (Fig. 1). Subsequent talin–integrin interaction is tightly linked to integrin activation, a process essential for the formation

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