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Review Article

Molecular mechanisms of mechanotransduction in integrin-mediated cell-matrix adhesion

Zhenhai Li[a,1], Hyunjung Lee[b,1], Cheng Zhu[b,c,*]

[a] Molecular Modeling and Simulation Group, National Institutes for Quantum and Radiological Science and Technology, 8-1-7 Umemidai, Kizugawa, Kyoto 619-0215, Japan
[b] Wallace H Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA
[c] George W Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA

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ABSTRACT

Cell-matrix adhesion complexes are multi-protein structures linking the extracellular matrix (ECM) to the cytoskeleton. They are essential to both cell motility and function by bidirectionally sensing and transmitting mechanical and biochemical stimulations. Several types of cell-matrix adhesions have been identified and they share many key molecular components, such as integrins and actin-integrin linkers. Mechanochemical coupling between ECM molecules and the actin cytoskeleton has been observed from the single cell to the single molecule level and from immune cells to neuronal cells. However, the mechanisms underlying force regulation of integrin-mediated mechanotransduction still need to be elucidated. In this review article, we focus on integrin-mediated adhesions and discuss force regulation of cell-matrix adhesions and key adaptor molecules, three different force-dependent behaviors, and molecular mechanisms for mechanochemical coupling in force regulation.

1. Introduction

Cell–matrix adhesions are discretely distributed on the cell surface and mediate cell interactions with the ECM. They are essential for cellular functions, such as cell rolling, migration, differentiation, tissue remodeling and homeostasis [1]. The adhesions can either be quickly disassembled or progressively matured from focal complexes to fibrillar adhesions in changing the shapes and molecular compositions of the adhesion complexes. Mechanical force plays a key role in adhesion maturation [2]. During the past two decades researchers have focused on force regulation of molecular interactions including integrins and adaptor molecules involved in cell-matrix interactions. Along with the development of sophisticated single molecule experimental techniques, molecular and structural insights into the mechanical regulation of cell-matrix adhesions have been provided [3].

Before we explore the details of force regulation and transmission at the adhesion sites, we first describe characteristics of different integrin-mediated adhesions. Four different cell-matrix adhesion structures have been defined in cultured cells: focal complexes (nascent adhesions), focal adhesions (FA), fibrillar adhesions, and three-dimensional (3D) matrix adhesions [4,5]. Nascent adhesions are force-independent and are transient adhesion structures, which are formed at the periphery of spreading or migrating cells in early stages of cell attachment. They can mature into a force-dependent FA when proper linkages are established with the actin cytoskeleton, and the typical size of nascent adhesions is less than 0.2 μm^2 [6]. Compared to nascent adhesions, FAs are relatively stable and highly regulated structures by modulating association and dissociation of focal adhesion proteins. FAs can further develop into fibrillar adhesions, which are more stable structures. Recent studies have shown that cells in a 3D matrix interact with the environment with distinguished properties and behaviors compared to that of the adhesions formed in the two-dimensional (2D) matrix. This type of cell-matrix adhesion is called 3D matrix adhesion [4,7].

In different stages of cell-matrix interactions, the composition of adhesions and adaptor molecules varies (Fig. 1). Focal complexes are multi-molecular structures that include integrin, talin, paxillin, vinculin, and actin [8–12]. Focal complexes develop into FA by recruiting zyxin [9,13,14]; and tyrosine phosphorylation is also required for the recruitment and further maturation of FAs [15,16]. FAs typically disassemble within 10–20 min, however when $\alpha_5\beta_1$-integrin adheres to a fibronectin matrix, FAs further mature into fibrillar adhesions as they elongate the shape of adhesion sites and change the molecular compositions. Stress-fibers are anchored on adhesion sites and the sites

* Corresponding author at: Wallace H Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA.
E-mail address: cheng.zhu@bme.gatech.edu (C. Zhu).
[1] Co-first authors.

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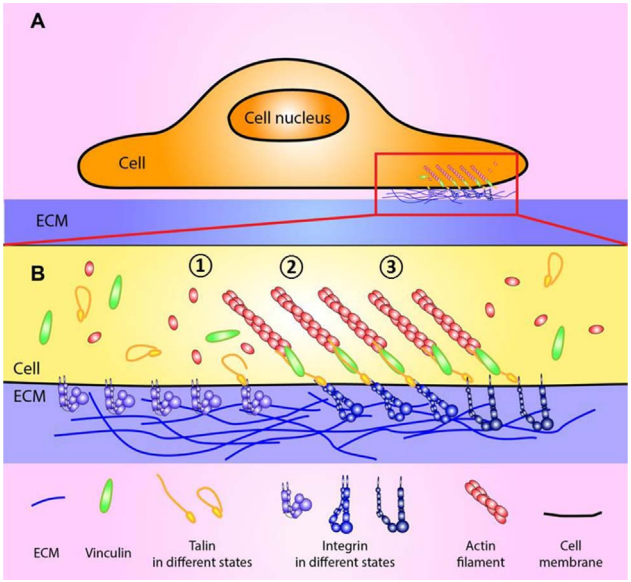

Fig. 1. Schematic of the integrated mechanotransduction at the integrin-mediated adhesion site. (A) Interaction of cell with the ECM, which is mediated by a multi-protein complex, FA. The red rectangle is enlarged in B. (B) A widely accepted model for force-mediated FA maturation with key adaptor molecules. Integrin interacts with its ECM ligands (e.g. fibronectin) and it triggers signal transduction of followings: (1) integrin in inactivated state. Talin is recruited to the FA site and starts interacting with integrin β3-tail. Vinculin and other adaptor molecules are also recruited and concentration of free G-actin is accumulated at the adhesion site. (2) Integrin engages with its ligand, and transition to intermediate state. F-actin polymerization is accelerated and force is loaded on the linkage of integrin-adaptor molecule to the actin cytoskeleton. Force-activatable molecules (e.g. vinculin and talin) in the adhesion complex sense the externally applied force and modulate their activation and affinity states for their ligands to transduce the mechanical signaling. (3) Conformational activation of integrin, an extended-open high-affinity state, is fully induced by talin-β-integrin tail binding, integrin ligand binding to integrin head piece, or force applied on integrin. The activation results in modulation of interaction kinetics for its ECM ligands to further develop FAs. FA is matured and stabilized at this stage.

move toward to the center of the cell. Fibrillar adhesions specifically contain $\alpha_5\beta_1$ integrin and tensin to form a very stable $\alpha_5\beta_1$-tensin complex, which is scarcely observed in the migrating cell [17,18]. Throughout the maturation of cell-matrix adhesions, integrins are key players. Integrins are a family of transmembrane proteins: the ecto-domain of integrin binds to its ECM ligands and the cytoplasmic tail links to the cytoskeleton via adaptor molecules including talin, α-actinin, vinculin, and tensin, thereby connecting the intracellular cytoskeletons to the ECM through the adhesion sites and transmitting bidirectional signals (Table 1).

There are other types of integrin-mediated structure: podosome and invadopodia. Briefly, these are actin-rich dynamic protrusions on the periphery of the plasma membrane [19]. They are found in many cell types, including invasive cancer cells, endothelial cells and immune cells and act as sites of ECM degradation and attachment for cell migration. These two structures share many characteristics in structure and molecular composition (e.g. biomarkers such as WASP, Tks4, Tks5 and MT MMP) [20]. Typically podosomes imply normal cell and invadopodia is cancer cells [21]. Podosomes are highly regulated by many actin regulators, so actin turnover occurs within seconds and the structure lasts only minutes. Compare to that, FAs are more stabilized structures and can last hours.

In this review article, we have focused on molecular mechanisms underlying force regulation of the integrin-mediated adhesion complex. The first part of this review is about the key molecules involved in mechanotransduction and the second part covers characteristics and mechanisms of force regulation.

2. Key adaptor molecules in the integrin-mediated adhesion

2.1. Integrin

Integrins are the most intensively studied and best characterized among cell-matrix adhesion proteins. In 1986, Hynes and colleagues had revealed structural features of a transmembrane glycoprotein and named the complex ‘integrin’ to denote the role in transmembrane association between ECM and the cytoskeleton [22]. At the same year, Ruoslahti lab also had independently discovered a family of RGD-specific adhesion receptors, a integrin family [23].

Integrins are a heterodimeric transmembrane protein of non-covalently associated α and β subunits. There are 18 α- and 8 β-subunits known, forming at least 24 distinct αβ combinations. Integrins are classified according to their ligands. Collagen-binding integrins include $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_{10}\beta_1$, and $\alpha_{11}\beta_1$ [24–27]; laminin-binding integrins include $\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_6\beta_4$ and $\alpha_7\beta_1$ [28,29]; and fibronectin-binding integrins include $\alpha_5\beta_1$, $\alpha_8\beta_1$, $\alpha_{IIb}\beta_3$ and the $\alpha_v\beta_3$ [30,31]. Integrins consist of a relatively large ectodomain, membrane-spanning helixes, and relatively short cytoplasmic tails. The molecular weight of integrins varies from 90–160 kDa, and the molecular weight of the ectodomain is between 80–150 kDa. Integrins can be classified into two main groups, according to the presence or absence of an αI-domain in the α-subunit. In αI-less integrins, the binding sites to the ligands reside at the interface between the β-propeller domain of α

Tablee 1
Adaptor molecules involved in integrin-mediated mechanotransduction at FAs. Integrins transmit mechanical outside-in and inside-out signaling via adaptor molecules, which are recruited to the adhesion sites under mechanical force loading conditions..

Protein	Functions	Force-dependent behavior	Ref.
Integrins	Transmembrane receptor linkage of the actin cytoskeleton to the ECM	Clustering at FAs conformational activation with high-affinity for its ligands	
Zyxin	LIM protein Localized at FAs and along the actin cytoskeleton	Recruiting Ena/VASP and α-actinin Enhancing actin polymerization in cooperation with Ena/VASP	[40,41]
Tensin	Linkage of integrins to the actin cytoskeleton during FA maturation	Maturing FAs into fibrillar adhesion by inducing a_5b_1 integrin translocation	
Talin	Linkage of integrins to F-actin at FAs	Involving in integrin activation by binding to the integrin β-tail Conformational activation with high-affinity for its ligands (e.g. exposing cryptic VBSs)	[39,40, 41,58]
Paxillin	Interacting with tyrosine kinases (e.g. Src and FAK) and adaptor molecules (e.g. vinculin and talin)	Stabilizing FAs as force increases Recruiting FAK	[71]
Vinculin	Linkage of integrin-talin complex to F-actin Binding alternately to talin or α-actinin	Conformational activation with regulation of affinity for the ligands (e.g. talin, α-actinin and F-actin)	
α-actinin	Linkage of integrin to the actin cytoskeleton via interaction with vinculin, zyxin and F-actin	Stabilizing FAs as tensile force increases	[41,71]
Filamin	Crosslinking two F-actins into an orthogonal structure Interacting with integrin	Conformational activation with regulation of affinity for the ligands (e.g. integrin)	[72]