CellPress

Special Issue: Quantitative Cell Biology

Review

Towards a Dynamic Understanding of Cadherin-Based Mechanobiology

Brenton D. Hoffman[1,*] and Alpha S. Yap[2]

Cadherin-based cell–cell adhesions are a primary determinant of tissue structure. For several decades, it had been thought that the primary function of these ubiquitous structures was to resist external mechanical loads. Here we review recent evidence that cadherins also couple together the force-generating actomyosin cytoskeletons of neighbouring cells, serve as potent regulators of the actomyosin cytoskeleton, and activate diverse signalling pathways in response to applied load. In considering the force sensitivity of the molecular-scale processes that mediate these events, we propose a dynamic picture of the force-sensitive processes in cell–cell contacts. This quantitative and physical understanding of the mechanobiology of cadherin cell–cell junctions will aid endeavours to study the fundamental processes mediating the development and maintenance of tissue structure.

Trends

Cadherin complexes bear mechanical forces that arise from cellular contractility in adherent cells. Coupling to actomyosin via association with myosin-bound F-actin leads to contractile forces being applied to cadherins and their associated proteins.

Bond properties within the cadherin–catenin complex influence mechanosensitivity of cadherin junctions. Catch bonds have been identified to mediate adhesive binding between cadherin ectodomains and the association of the cadherin–catenin complex with F-actin.

Functional responses to mechanical stimulation of cadherin adhesions are diverse and operate over substantially different time scales. These include changes in actin dynamics (operating over minutes) and entry into the cell cycle (operating over hours).

Forces and Cadherin Junctions

A primary mechanical function of cell–cell adhesion is to resist detachment forces. This is exemplified by the classical cadherins, which have traditionally been thought to passively resist large-scale forces arising external to the junctions, such as those associated with morphogenetic tissue movements (e.g., epiboly in the early embryo) or tissue stresses from external loading due to gravity, muscle activity, or mechanical trauma [1–3]. This basic conceptual framework has guided research in the field for many years. Recently, though, it has come to be appreciated that the relationship between force and adhesion is more complex. A key insight is that many of the forces that cadherins experience are generated by their host and neighbouring cells [4–8], which can contribute to the tension that tissues display under physiological circumstances [9]. Cadherin adhesion thus serves to couple the contractile actomyosin cortices of cells together [10]. Furthermore, cell signalling at cell–cell junctions can promote actin assembly and myosin activation, leading to the active generation of contractility [11]. It is also increasingly apparent that cells sense, interpret, and respond to those applied forces through a poorly understood process termed mechanotransduction [12,13].

The application of force to junctions affects many aspects of their biological and mechanical function. For instance, on the molecular scale, force is a key determinant of the strength of cadherin–cadherin interactions as well as the composition of cell–cell adhesions [14–16]. On larger length scales, this leads to the emergence of tissue level tensions that are at least partially driven by actomyosin contractility within the constituent cells [8,9]. Such tension contributes to morphogenetic events such as cellular rearrangements and cell extrusion. Thus, the active generation, transmission, and sensing of mechanical forces play integral roles in cadherin

[1]Department of Biomedical Engineering, Duke University, Durham, NC 27708-0281, USA
[2]Division of Cell Biology and Molecular Medicine, Institute for Molecular Bioscience, The University of Queensland, Brisbane QLD 4072 Australia

*Correspondence:
brenton.hoffman@duke.edu
(B.D. Hoffman).

biology. Arguably, this is one of the major recent developments in our understanding of the cell biology of these ubiquitous adhesion systems.

The realisation that cadherin junctions are mechanically sensitive structures implies that physical principles guide and constrain the behaviour of these biological systems. In short, cadherin junctions and the tissues that they support must obey quantitative physical laws and a consideration of these laws can guide our understanding of their cell biology. In this article we review recent developments important in our understanding of the mechanobiology of cadherin adhesion systems. We first focus on molecular developments that reveal the important roles that bond properties play in the biochemistry of cadherin complexes and discuss a range of mechanosensitive biological processes that involve cadherin interactions. But this poses an important challenge: molecular mechanisms and biological outcomes operate on vastly different time scales that do not readily map to one another. Instead, there must be regimes that operate on intermediate time scales to mediate between these two levels. How those intermediate time scales arise is an important challenge for future research and we discuss some ways in which this problem might be addressed through the application of quantitative and physical principles.

Force Sensitivity in the Cadherin Molecular Complex

Composition of the Cadherin Molecular Complexes

Classical cadherins function as membrane-spanning macromolecular complexes. The cadherin ectodomains mediate adhesive binding between cadherins presented on neighbouring cells, while the cytoplasmic tails interact with many cytoplasmic proteins. The best-understood cadherin-interacting proteins are the catenins (β-, ∝-, and p120), which form a stoichiometric complex with classical cadherins (Figure 1A). However, it is clear that this minimal cadherin/catenin complex can interact with many other cytoplasmic proteins. Recent efforts to identify the interactome of cadherins, using proximity biotinylation techniques [17], identified hundreds of potential proteins and interactions [18,19]. While many of these interactions have yet to be validated, these observations suggest that the biology of cadherins arises from the precise network of interactions that are engaged in any particular context.

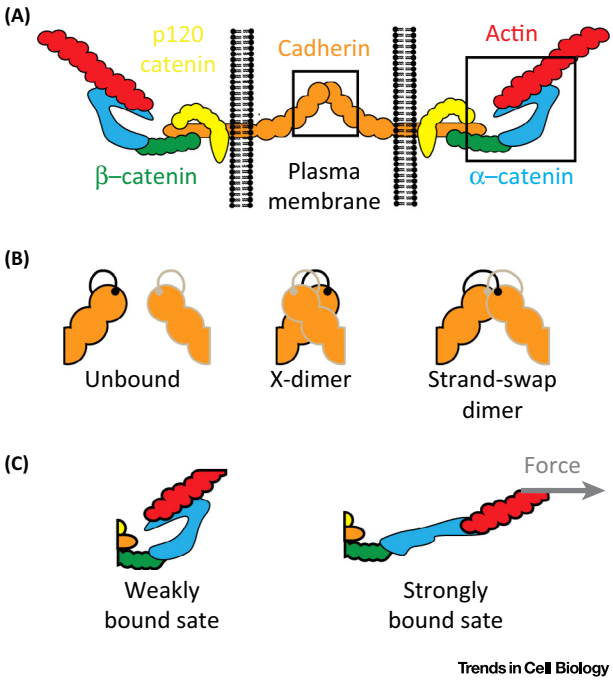

Figure 1. The Mechanobiology of the Cadherin–Catenin Complex. (A) The minimal cadherin–catenin complex that mediates the mechanical coupling of the actomyosin networks between neighbouring cells. Localisation of cadherins to the plasma membrane is regulated by p120–catenin. Mechanical linkages between cadherin and actin are mediated by β- and ∝-catenin. (B) Zoom-in of left box shown in A. Diagram of the various conformations that mediate cadherin–cadherin interactions. The X-dimer conformation is thought to be transient, but resists unbinding resulting from applied loads in certain regimes. The strand-swap conformation is more prevalent in mature adhesions, but is weakened in response to applied mechanical loads. This conformation is mediated by the exchange of strands containing conserved tryptophan residues between the binding cadherins. (C) Zoom-in of right box shown in A. The binding interactions between the cadherin–catenin and actin can be stabilised by applied mechanical loads. This is likely related to the ability of ∝-catenin to undergo force-induced conformation changes.