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Editorial

Mechanosensing: From proteins to tissues

Running your fingers across the surface of a rock or listening to a bird sing – you are mechanosensing. Our senses of touch and hearing are unique in that the translation of physical forces (including air vibrations) into biochemical signals reaches our conscious awareness. And yet, with every inhalation expanding our lungs, with every heart beat pumping blood through our vasculature, and every muscular movement of our skeleton, the cells and tissues in our body are subjected to mechanical forces (stretch, shear, compression), which they can sense and respond to.

Early studies of mechanotransduction focused on the specialized cells that mediate our perceptual mechanosensing: mechanosensory neurons and hair cells of the inner ear. Later on, attention was paid to cells that experience significant forces in their "line of duty", such as endothelial cells lining blood vessels, chondrocytes embedded in cartilage, and cardiomyocytes. More recently, it has become clear that every cell in our body has mechanosensing capabilities. Although the ability of fibroblasts to respond to mechanical perturbations was appreciated already in the early 1990s, it was the discovery in 2006 that matrix rigidity can direct stem cell lineage specification that gave a strong push to the field of mechanobiology. Research in the past decade has significantly contributed to our knowledge of the molecular and cellular basis of mechanosensing and the important roles it plays in development, homeostasis, and disease. This special issue of Seminars in Cell and Developmental Biology provides a glimpse into our current understanding of mechanosensing at various scales, from single proteins to entire tissues, and in a variety of cell types and physiological processes.

Despite great diversity in the manifestations of mechanosensing, the underlying molecular and cellular mechanisms appear to be conserved between different cell types and across phyla. Virtually every protein exists in a conformation that minimizes its free energy. An external mechanical force applied to a protein will change its energy balance and therefore may result in a conformational change, which could alter its activity. Hence, any protein positioned in a cellular structure that is subjected to force can potentially act as a mechanosensor. However, to date, only a handful of protein families have been shown unequivocally to respond directly to force; these include ion channels, adhesion receptors, and cytoskeletal adaptors.

Prominent among mechanosensitive proteins are stretch activated ion channels, localized at the plasma membrane. Increasingly, it is becoming clear that stretch activated ion-channels do not act alone, but rather in association with the actin and microtubule cytoskeletons. Nourse and Pathak review the latest studies on the widely expressed and mechanically-activated ion-channel Piezo1 and its close ties with the cytoskeleton. Mechanosensitive ion-channels feature strongly in the nervous system. Prager-Khoutorsky reviews what is known about mechanosensing in hypothalamic osmosensory neurons, which sense changes in blood osmolarity. Karkali and Martin-Blanco discuss what we have learned about mechanosensing in the nervous system from studies in *Drosophila melanogaster*.

The plasma membrane can experience changes in tension, not only from external forces, such as shear flow, but also from internal forces, such as actin polymerization and osmotic pressure. In their review, Pontes et. al summarize the challenges in measuring membrane tension and the variety of pathways through which it can affect cellular behaviour.

Primary cilia are distinct cellular structures protruding from the plasma membrane of most cells, and their mechanical deflection initiates signalling at the cell and tissue level. Spasic and Jacobs review the current molecular understanding of ciliary mechanotransduction and highlight its importance for human health.

Cells connect with their environment at discreet sites of cell–cell and/or cell-matrix adhesion. These junctions, through which forces are often transmitted, are well appreciated platforms for mechanosensing and mechanotransduction. Shumin and Kanchanawong review our current understanding of the nanoscale architecture of cadherin-mediated cell–cell junctions and integrin-mediated cell-matrix adhesions and explore how their structure is intertwined with their mechanosensory function. Thomas and Robinson provide an in-depth account of the mechanosensory function of a single actin cytoskeleton crosslinker, which resides in adhesion sites and along stress fibers: alpha-actinin-4. They make a connection between alpha-actinin-4 and cancer metastasis and suggest that mechanosensing by tumor cells can be a target for therapy. Jansen and Ballestrem address the dynamics of proteins at the interface between integrin adhesions and the cytoskeleton, in relation with their mechanosensory role; they pay particular attention to the complex mechanical properties of the extracellular matrix that can be sensed by cells.

Mechanosensing of the matrix by stem cells is the subject of a review by Smith et. al., who describe how various embryonic and adult stem cells probe their mechanical environment (by applying to it actomyosin-based forces) and direct their differentiation or early maturation based on the mechanical properties they sense. Smith et al. also discuss how matrix porosity and stiffness affects

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stem cell migration in three dimensions, influencing niche retention and fate choices.

When cells pull on the extracellular matrix they generate mechanical perturbation that can be sensed by neighbouring cells, even at a distance. Sapir and Tzlil explore this newly appreciated mode of communication between cells, and highlight how mechanical communication can complement biochemical signalling to coordinate cell behaviour.

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Progress in the field of mechanobiology in recent years has been enabled, in part, by technological innovations, such as super resolution microscopy and traction force microscopy. Two reviews in this issue discuss the promise of new technologies to further our understanding of mechanosensing. Graya and Stroka describe recent advances in microfluidic and "on-chip" biomimetic techniques that facilitate the study of endothelial mechanosensing in a controlled environment that mimics vasculature mechanics. Wasik and Schiller provide a primer for emerging methods of mass spectrometry, such as phosphoproteomics, cross linking mass spectrometry and protein correlation profiling, and they offer their view for how these methods will allow the field to move towards a comprehensive list of molecular alterations in cellular mechanosensing.

The special issue closes with four reviews highlighting the role of mechanosensing in embryonic development, adult homeostasis, and regeneration. Ramanujam et al. review recent findings in murine preimplantation embryogenesis, highlighting the roles of mechanical forces in the coupling of cell-fate determination and cell positioning. Upadhyaya provides an overview of immune cell mechanosensing, focusing on T cells and providing some insight into B cells, and how their signalling is modulated by physical forces and mechanical cues. Kriti et al. discuss mechanotransduction pathways in tubular tissues that can lead from sensation of cell stretch to activation of actomyosin contractility, providing rapid feedback for homeostasis of tube diameter. Finally, Song et al. propose that mechanosensing plays multiple roles in liver tissue regeneration.

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