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Journal club

FORCES AS REGULATORS OF CELL ADHESIONS

As with all science, the field of mechanotransduction has no true beginning or end and has been shaped by advances that build on each other towards an ever-clearer understanding. Nevertheless, several pioneering studies of the biology of cell adhesions during the 1990s provided the basis for much of what we know about the mechanosensitivity and mechanoregulation of cells today.

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Unlike most other cell surface signalling receptors known at the time, adhesion receptors such as integrins were found to be unresponsive to soluble ligands but to be activated when the ligands were adsorbed onto solid surfaces. Ning Wang, James Butler and Don Ingber used magnetic beads coated with such adsorbed ligands and a home-made magnetic actuator to demonstrate that external forces applied across integrins trigger clustering and assembly not only of integrin receptors but also of scaffolding proteins that anchor these receptors to the actin cytoskeleton. Magdalena Chrzanowska-Wodnicka and Keith Burridge subsequently demonstrated that intracellular forces generated by non-muscle myosin II and controlled by RHOA were required to induce the assembly and maturation of integrin-mediated adhesions. The following year, Robert Pelham and Yu-li Wang tuned the stiffness of hydrogel substrates for cell culture to show that adhesions could sense and respond to substrate stiffness.

Until this period, much of the work that probed the role of mechanical forces in biology was focused on characterizing the mechanical properties of biological materials, theoretical descriptions of the mechanics of morphogenetic processes or investigating general biological effects of forces on cells and tissues. While these efforts were fruitful, only the new generation of studies exemplified by the Wang, Chrzanowska-Wodnicka and Pelham papers achieved something remarkable — these studies crossed the disciplinary boundaries of physics, mechanics, materials science and receptor biology to try and understand the molecular basis of how cells transduce forces. These cross-disciplinary endeavours led to scientific breakthroughs at several levels: they provided the first molecular insights into the interplay between mechanics of the environment, cell-generated contractility and the signalling required to coordinate adhesions; they spurred incorporation of new technologies and novel experimental approaches into modern biology; and, perhaps most importantly, they created a community in which physicists, engineers and biologists can interact to solve common, complex problems. What ensued was a plethora of studies showing how forces regulate cell adhesion, signalling and cell function through a variety of mechanisms that involve protein unfolding, clustering and coordination of classical signal transduction cascades with various mechanical inputs.

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ORIGINAL ARTICLES Wang, N., Butler, J. P. & Ingber, D. E. Mechanotransduction across the cell surface and through the cytoskeleton. *Science* **260**, 1124–1127 (1993) | Chrzanowska-Wodnicka, M. & Burridge, K. Rho-stimulated contractility drives the formation of stress fibers and focal adhesions. *J. Cell Biol.* **133**, 1403–1415 (1996) | Pelham, R. J. & Wang, Y. Cell locomotion and focal adhesions are regulated by substrate flexibility. *Proc. Natl Acad. Sci. USA* **94**, 13661–13665 (1997)