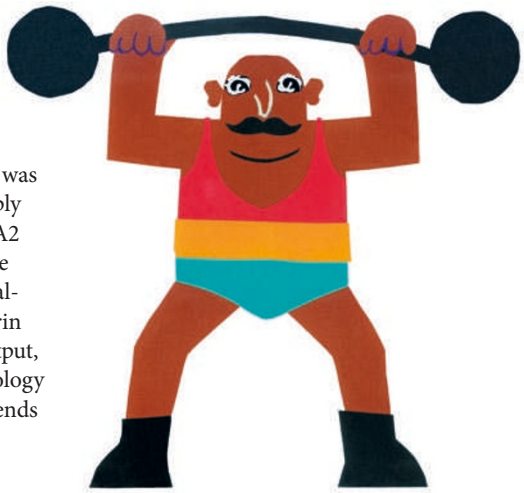
Nature Reviews Molecular Cell Biology | AOP, published online 31 March 2010; doi:10.1038/nrm2884

MECHANOTRANSDUCTION

Using the force



> the spatial organization of receptors can affect downstream cellular responses to ligands.

Mammalian cells respond to physical forces through chemical signalling networks. Salaita *et al.* set out to elucidate the mechanisms of this chemo-mechanical coupling, and reveal that the spatial organization of receptors can affect downstream cellular responses to ligands.

EPHA2 is a receptor protein Tyr kinase that is activated by ephrin A1 and exhibits functional alterations in cancer. The signalling junction between EPHA2-expressing human breast cancer cells and supported membranes containing laterally mobile ephrin A1 was reconstituted. The spatio-mechanical regulation of EPHA2 signalling was then studied using barriers to restrict the lateral movement of ephrin A1 and therefore of EPHA2.

On contact with EPHA2-expressing cells, ephrin A1 in the supported membrane formed clusters that underwent radial transport to the junction centre. This depended on ephrin A1 lateral mobility, as it did not occur when ephrin A1 was on a non-fluid membrane (a fully saturated lipid bilayer). Furthermore, EPHA2 degradation and phosphorylation (which occur after ephrin A1 binds EPHA2) were reduced when ephrin A1 was on the non-fluid membrane. On the fluid membrane, EPHA2–ephrin A1 clusters colocalized with areas of high EPHA2 phosphorylation, and their radial transport was shown to be driven by actomyosin contractile forces.

This cytoskeletal reorganization was altered when barriers, which apply apposing forces, restricted EPHA2 movement. This also reduced the recruitment of ADAM10, a metalloprotease involved in Eph–ephrin release. Therefore, signalling output, in terms of cytoskeleton morphology and ADAM10 recruitment, depends on the spatial organization of EPHA2. Interestingly, a panel of EPHA2-expressing mammary epithelial cell lines revealed that ephrin A1-induced EPHA2 reorganization correlated with invasion potential and could therefore be a marker of cancer progression.

So, the physical manipulation of EPHA2–ephrin A1 organization can alter cellular responses to ephrin A1. On EPHA2–ephrin A1 interaction, a cell applies force through actomyosin contractility to mediate EPHA2–ephrin A1 radial transport, and barriers that apply opposing forces alter this response. The spatio-mechanical properties of ephrin A1-expressing cells, therefore, could functionally alter the response of EPHA2 signalling and contribute to cancer progression.

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ORIGINAL RESEARCH PAPER Salaita, K. *et al.* Restriction of receptor movement alters cellular response: physical force sensing by EphA2. *Science* **327**, 1380–1385 (2010)
FURTHER READING Manz, B. N. & Groves J. T. Spatial organization and signal transduction at intercellular junctions. *Nature Rev. Mol. Cell Biol.* 31 Mar 2010 (doi: 10.1038/nrm2883)