response. Such major advances in our understanding of the individual pathways and components that maintain ER homeostasis after physiological and pathological challenges raises the fundamental question of precisely how these varied processes are coordinated to provide a coherent response in vivo.

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A Role for p130Cas in Mechanotransduction

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Focal adhesions are sites of contact between cells and the extracellular matrix. Sawada et al. (2006) now report that the mechanical stretching of cells forces p130Cas, an adaptor protein at focal adhesions, to undergo a conformational change. This change promotes phosphorylation of p130Cas by Src family kinases and the transduction of integrin-mediated signaling.

Physical interactions between cells and the extracellular matrix occur at focal adhesions, where integrins cluster and bind to the matix. A primary function of these cell contacts is to provide mechanical support and maintain tissue integrity. However, it has become increasingly apparent that focal adhesions also function as sensory and signaling organelles, which collect complex information concerning the chemical and physical nature of the extracellular matrix, integrate this information, and trigger appropriate cellular responses. Although it is well known that diverse matrices modulate cell morphology and fate, the molecular mechanisms responsible for these effects are still poorly understood. In this issue, Sawada et al. (2006) provide evidence that the sensitivity of focal adhesions to mechanical stimulation is mediated by stretching of the adaptor protein p130Cas, which enhances its phophorylation by Src family kinases. This, in turn, promotes the recruitment of p130Cas partners that promote cell migration by activating small GTPases, such as Rap1.

Mechanotransduction is an essential function of focal adhesions. For example, the cellular responses mediated by integrins require adhesion to a solid matrix and cannot be triggered effectively by binding to soluble matrix molecules (Discher et al., 2005). Mechanical stimulation affects the size and subcellular location of focal adhesions, as well as the activation of specific signaling events (Yoshigi et al., 2005). Moreover, the rigidity of adhesive substrates affects how cells attach, spread, polarize, and migrate (Discher et al., 2005). Mechanical signals can also be applied to the cell from the outside, such as by shear stress, direct mechanical manipulation of the cell, or stretching of the underlying substrate (Bershadsky et al., 2006).

The engagement of integrins by the extracellular matrix leads to the specific tyrosine phosphorylation of components of focal adhesions, such as focal adhesion kinase (FAK), paxilin, and the adaptor protein p130Cas. Because integrins do not possess an intrinsic enzymatic activity, these phosphorylation events are attributable to either activation of the Src/FAK pathway or to the inhibition of the corresponding phosphatases, such

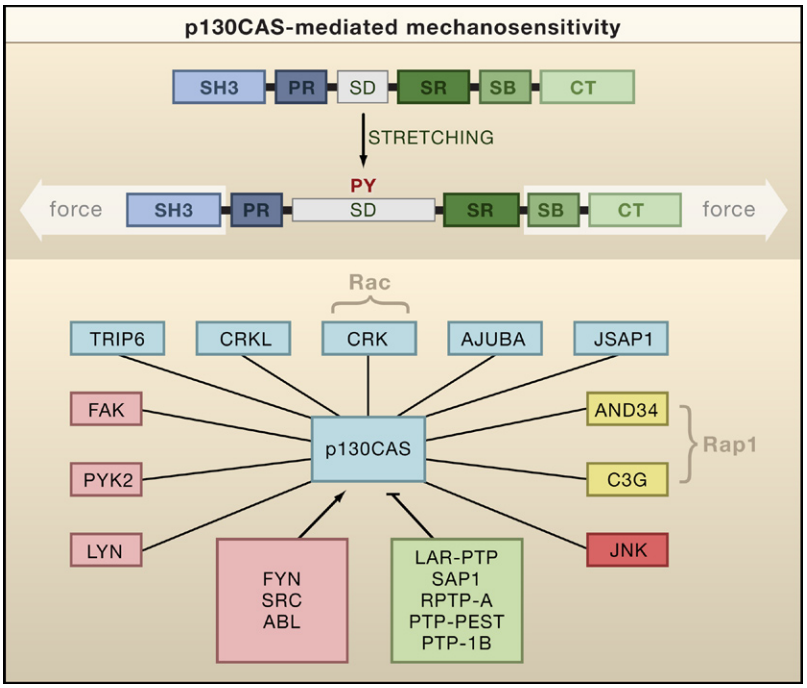

Figure 1. p130Cas and Mechanotranduction at Focal Adhesions

The domain structure of the p130CAS molecule is shown (top), before and after stretching. The domains include (from left to right): Src homology 3 (SH3) domain, the proline-rich region (PR), the substrate domain (SD), the serine-rich region (SR), the Src-binding domain (SB), and the C-terminal region. The extension of the substrate domain following stretching and subsequent tyrosine phosphorylation (PY) are indicated. p130Cas and its molecular binding partners are depicted (bottom), including adaptor ("scaffolding") molecules (blue boxes), tyrosine kinases (light red), a serine/threonine kinase (dark red), GEFs (yellow), and tyrosine phosphatases (green). Also indicated are the possible pathways involved in the activation of G proteins (Rap1 and Rac), which are believed to be involved in the stimulation of cell migration.

as RPTP-α (Giannone and Sheetz, 2006). To date roughly 150 different molecules have been shown to interact, at least transiently, with focal adhesions. Among these are transmembrane molecules, kinases and phosphatases, G protein regulators, proteases, actin modulators, and multiple adaptor proteins (Zamir and Geiger, 2001). Although this list offers a rich variety of potential adhesion-dependent signaling pathways, it has been unclear how mechanical force is converted into biochemical signals at focal adhesions.

The findings of Sawada et al. (2006) implicate the adaptor protein p130Cas in adhesion-dependent mechanotransduction. This study proposes a compelling and comprehensive mechanism for force-driven signaling, whereby p130Cas, bound to the protein scaffold at focal adhesions, is subjected to stretching. Stretching then leads to unfolding of its central "substrate domain" that enhances the accessibility of target tyrosine residues in that region, leading to elevated tyrosine phosphorylation by Src-family or FAK kinases (Figure 1).

Sawada et al. created a recombinant p130Cas substrate domain that was biotinylatated at both the amino and carboxyl terminals. This protein was then bound to avidin (which binds biotin) that had been immobilized on a latex membrane. They showed that the ability of c-Src to phosphorylate p130Cas was greatly enhanced upon stretching of the latex membrane. Using an antibody that preferentially recognizes the extended form of p130Cas, Sawada et al. showed that p130Cas is extended (and activated) at sites of high traction force in living cells (where p130Cas is presumably anchored to its natural scaffold). These sites also correlated with regions of high p130Cas phosphorylation. Together, these findings suggest that p130Cas is a direct target for the external mechanical perturbation.

This work also sheds new light on the role of p130Cas in the assembly of integrin adhesions. Since its discovery (Sakai et al., 1994), p130Cas has been implicated in many cellular functions, including adhesion signaling, cell migration, and tumor development. The extensive mapping of focal adhesion components (Zamir and Geiger, 2001) revealed multiple molecular partners that can bind to p130Cas in a phosphorylation-dependent and -independent manner. These include additional adaptor molecules, which partake in the construction of the mechanical scaffold of the adhesion site (TRIP6, CRKL, CRK, AJUBA, JSAP1), several tyrosine kinases (FAK, PYK2, LYN), a serine/threonine kinase (JNK), and two GEFs (AND34 and C3G). In addition, p130Cas has been shown to be a substrate for several tyrosine kinases (FYN, SRC, ABL) and tyrosine-specific phosphatases (Figure 1). This unique set of molecular partners suggests that the tyrosine phosphorylation of p130Cas plays a pivotal role in regulating cell adhesion and migration. Specifically, phosphorylation of the substrate domain of p130Cas can trigger the binding of the different associated molecules, some of which, such as AND34 and C3G, can activate Rap1, and thereby stimulate cell motility. Equally interesting is the binding of CRK, which can further recruit, via its SH3 domain, additional C3G, ABL, and JNK molecules, as well as Vav, Sos, and the potent Rac-guanine nucleotide exchange factors Dock1 and ELMO. The local accumulation of kinases and G protein activators correlates well with the acquisition of a migratory, invasive phenotype.

Although the work of Sawada et al. suggests that a force-induced conformational change in a kinase substrate is critical to mechanotransduction, other possible mechanisms have been considered and may yet be operative at focal adhesions. Many of these other models were envisioned to explain the somewhat counterintuitive observation that pulling on an adhesion site actually strengthens its grip

on the substrate. For instance, force-dependent activation of ion channels was initially considered a likely means of mechanotransduction at sites of adhesion. However, studies demonstrating that permeabilized cells retain the ability to recruit component of focal adhesions to the sites of adhesion suggested that it is unlikely that channels play a central role in the regulation of integrin-mediated adhesion (Tamada et al., 2004). Instead, these studies suggest that the submembrane components of focal adhesions contain all the basic elements of the mechanosensitive machinery. Other potential mechanisms include a "perturbation-reannealing process," in which mechanical force breaks protein-protein interactions, thereby stimulating their reassembly or the tension-dependent enhancement of formin-induced actin polymerization (Bershadsky et al., 2006).

It is also possible that applied force modulates the activity of potent kinases (e.g., Src-family kinases or FAK) or phosphatases by directly affecting their conformation, and consequently their enzymatic activity. Future work may establish whether other mechanosensory events occur at focal adhesions and could show how these events are coupled to the stretching of p130Cas.

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Follow Your Nose: Axon Pathfinding in Olfactory Map Formation

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Two new studies report how discrete identities of olfactory sensory neurons are converted into a spatial map of axonal connections (Imai et al., 2006; Serizawa et al., 2006). They find that levels of cAMP signals derived from olfactory receptors (ORs) can direct targeting of axons along an axis, and that ORs and neural activity regulate expression of adhesion/guidance molecules in mosaic patterns that can sort axons into discrete locations.

Neural maps are a fundamental feature of brain architecture, forming the connections that transfer information from one area of the nervous system to another. These maps can be classified into two broad categories: continuous and discrete. In a continuous topographic map, such as the visual projection from the retina to the midbrain tectum, the spatial organization of the projecting neurons is maintained in the spatial order of their connections to the target, with nearest-neighbor relationships preserved. In contrast, in a discrete map, axons from spatially dispersed neurons with the same identity converge in one location in the target field, converting discrete information into a spatial representation. The best studied example of a discrete map is in the mammalian olfactory system.

Landmark work by Buck and Axel (Buck and Axel, 1991) identified the olfactory receptors (ORs), which transduce odorant information into electrical activity. In mice, there are approximately 1000 OR genes, which are thought to be expressed in a mutually exclusive manner in olfactory sensory neurons. Although neurons expressing the same receptor are dispersed in the olfactory epithelium, their axons converge into a pair of glomeruli at characteristic positions in the olfactory bulb. This results in a discrete chemotopic map that converts OR identity into a spa-