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Molecular Mechanotransduction: how forces trigger cytoskeletal dynamics[1]

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Mechanical stresses elicit cellular reactions mediated by chemical signals. Defective responses to forces underlie human medical disorders, such as cardiac failure and pulmonary injury. Despite detailed knowledge of the cytoskeleton's structure, the specific molecular switches that convert mechanical stimuli into chemical signals have remained elusive. Here we identify the actin-binding protein, filamin A (FLNa) as a central mechanotransduction element of the cytoskeleton by using Fluorescence Loss After photoConversion (FLAC), a novel high-speed alternative to FRAP. We reconstituted a minimal system consisting of actin filaments, FLNa and two FLNa-binding partners: the cytoplasmic tail of ß-integrin, and FilGAP. Integrins form an essential mechanical linkage between extracellular and intracellular environments, with ß integrin tails connecting to the actin cytoskeleton by binding directly to filamin. FilGAP is a FLNa-binding GTPase-activating protein specific for Rac, which in vivo regulates cell spreading and bleb formation. We demonstrate that both externally-imposed bulk shear and myosin II driven forces differentially regulate the binding of integrin and FilGAP to FLNa. Consistent with structural predictions, strain increases ß-integrin binding to FLNa, whereas it causes FilGAP to dissociate from FLNa, providing a direct and specific molecular basis for cellular mechanotransduction. These results identify the first molecular mechanotransduction element within the actin cytoskeleton, revealing that mechanical strain of key proteins regulates the binding of signaling molecules. Moreover, GAP activity has been shown to switch cell movement from mesenchymal to amoeboid motility, suggesting that mechanical forces directly impact the invasiveness of cancer.

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