Shaping Cells by Force and Rigidity through Protein Stretching

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CONTROL of cell morphology involves the integration of mechanical sensing and cell motility to produce the desired shape of the organism [1]. Nanometer level analyses of cell behavior have revealed only a limited number of types of motility involving complex mechanochemical steps [2]. For example, cell spreading on matrix-coated surfaces have revealed three different types of motility, an initial blebbing, continuous spreading, and periodic contraction motility. Overall, cell traction forces are primarily dependent upon myosin II [3]. Long term matrix forces appear to be sensed by protein unfolding and we have defined two different cytoplasmic mechanisms. One example is the activation of protein phosphorylation by stretching. The scaffolding protein, p130Cas has a central substrate domain with 15 tyrosines and active c-Src phosphorylates stretched p130Cas at least 7-fold faster than native, indicating that stretch is the major factor controlling the level of phosphorylation[4]. Secondly, the stretching of proteins can unveil binding sites such as the stretching of talin causing the increased binding of vinculin[5].

In the case of periodic contraction motility that is also seen at the leading edge of migrating cells, motility proceeds by cycles of edge protrusion, adhesion and retraction and the period is dependent upon the width of the lamellipodial actin [6]. After careful examination of the process, we find that myosin II pulls the rear of the lamellipodial actin network causing upward bending, edge retraction and initiation of new adhesion sites. The network is then released from the edge and condensed over the myosin. Protrusion resumes as lamellipodial actin regenerates from the front and extends rearward until it reaches newly assembled myosin, initiating the next cycle. Upward bending, observed by evanescence microscopy and electron microscopy, is consistent with ruffling when adhesion strength is low[7]. Thus, actin polymerization periodically builds a mechanical link, the lamellipodium, connecting myosin motors with the initiation of adhesion sites, suggesting that major functions driving motility are coordinated through a biomechanical process. In another type of motility, collagen fibers are pulled in by cells in a hand-over-hand fashion in a process that requires myosin IIB [8]. Because these different motility types are robust and occur in many different cell types, we suggest that most cell mechanical functions are accomplished by various combinations of these different motility types. Thus, it is important to define each type of motility at the nanometer level with the new nanotools that are available. Such a mechanistic understanding of cell function will open new ways to target specific cell functions that are critical for disease and wound repair.

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