parallel or perpendicular to MP strips, or kept under a static condition. Parallel flow caused cell elongation with enhanced stress fibers and p-FAK, and a reduction in apoptosis. In contrast, perpendicular flow caused inhibition of cell elongation, rounding of the cell, and increase in apoptosis, with the eventual peeling off of the cell. The spatial characteristics of Src activation studied by FRET also showed directionality dependence in response to shear stress. The directionality of shear stress in endothelial cell remodeling is also correlated to Rho activities. The inhibition of Rho by C3 exoenzyme abolished the effects of parallel flow. RhoV14, the constitutively active Rho, enhanced stress fibers and p-FAK, and prevented apoptosis of HUVEC on 15-μm strips under a static condition. RhoV14 also reduced cell apoptosis under both parallel and perpendicular flows. Our results indicate that cell remodeling can be modulated by changes in ECM micropatterning, anisotropic cell morphology, and mechanical forces.

S30-2 Remodeling of endothelial cells induced by tension transmitted through intercellular junctions

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Mechanical forces such as fluid shear stress and cyclic stretch play important roles in modulating the morphology and actin cytoskeletal structures of vascular endothelial cells (EC). The ability of EC to transduce mechanical signals into biochemical signals is partly governed by two types of cellular component: focal adhesions and intercellular junctions. Although many studies have examined mechanotransduction in cells involving forces delivered through focal adhesions, little is known on how forces transmitted through intercellular junctions induce remodeling of EC. In this study, we have investigated the effect on EC morphology of local tension exerted from a neighboring cell in order to understand the roles of intercellular junctions as a mechanotransduction pathway. Actin cytoskeletons in live cells were visualized by using green fluorescent protein-labeled actin. In order to apply local tension to an EC via intercellular junctions, a local stretch was applied to the neighboring EC surface using a glass micro-needle. After the application of local stimuli, morphological and cytoskeletal changes in cells were quantitatively evaluated using image processing. Localization of SHP-2, one of the tyrosine phosphatases binding to mechanosensitive intercellular adhesion molecule PECAM-1, was also examined by immunofluorescent staining. The results showed that reorientation and elongation of EC parallel to the direction of tension, associated with realignment of stress fibers, were induced by the application of local stretch generated in a neighboring EC. In addition, recruitment of SHP-2 at the force-transmitted intercellular junctions was observed after the application of local stretch. Moreover, these responses of EC to the local stretch were not affected by blocking of stretch activated ion channels, which are known to be one of the mechanotransducers. These results strongly suggest that intercellular junctions can transduce the forces into biochemical signals leading to morphological changes in EC. (Supported by Grants-in-Aid for Scientific Research (Nos. 15086203, 17200030, 17680036) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in Japan.)

S30-3 Dynamics of adhesion cluster and cell reorientation under lateral cyclic loading

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The motivation for this study was to understand experimentally observed different responses to static and dynamic loads of cells on a stretched substrate. In this work, a focal adhesion model which can consider the mechanics of stress fibers, adhesion bonds and the substrate has been developed at the molecular level by treating focal adhesion as an adhesion cluster. The stability of the cluster under dynamic loads is studied by applying cyclic external strain on the substrate. We show that there exists a threshold value of external strain amplitude beyond which the adhesion cluster disrupts quickly. In addition, our results show that the adhesion cluster is prone to losing stability under high-frequency loading; this loss of stability occurs because receptors and ligands do not have enough contact time to form bonds due to the high-speed deformation of the substrate, and also because viscoelastic stress fibers become rigid at high-frequency which involves large deformation of the bonds. Furthermore, we find that the stiffness of stress fibers plays an important role in the stability of the adhesion cluster. The essence of this work is thus to connect the dynamics of adhesion bonds at the molecular level with the reorientation behavior of cells by considering the mechanics of stress fibers: the predictions of our cluster model are broadly consistent with our experimental results. (Supported by from the National Natural Science Foundation of China through Grants No. 10502031, 10628205, 10732050 and National Basic Research Program of China Grant No. 2004CB619304, and SRF for ROCS, SEM.)

S30-4 An adaptive mathematical model of stretch-induced cytoskeletal remodeling

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Cyclic stretching of endothelial cells, such as occurs in arteries during the cardiac cycle, induces the cells and their actin stress fibers to orient themselves perpendicular to the direction of maximum stretch. The actin cytoskeleton is a dynamic structure that regulates cell shape changes and mechanical properties. It has been shown that actin stress fibers are "prestretched" under normal, non-perturbed, conditions, consistent with the ideas of cytoskeletal "prestress" that have motivated tensegrity cell models. Based on these observations, a discrete mathematical model of the actin cytoskeleton is proposed. The model incorporates the turnover of discrete elastic actin fibers to describe the evolution of fiber organization and fiber stretching, in response to diverse patterns of stretching of the matrix upon which the cells adhere. Actin fibers are assumed to disassemble following first-order kinetics, while fiber assembly is assumed to maintain total polymerized actin in the cell constant. In response to a step change in matrix stretch, the model simulations predict actin fibers are initially stretched elastically, but that average fiber stretch with the network quickly returns to the prestretch value as overly stretched fibers are replaced by new fibers assembled in the new configuration of the matrix. Further, the rate of recovery of fiber stretch depends on the fiber turnover rate. Motivated by the concept of "tensional homeostasis", the rate of fiber disassembly was assumed to increase in proportion to the deviation of fiber stretch relative to a homeostatic value. Assuming this homeostatic value is the steady-state value of fiber stretch in the absence of matrix stretch, the model simulations of cyclic strip biaxial stretch result in the gradual alignment of actin fibers perpendicular to the direction of stretch, and the subsequent decrease in average fiber stretching due to matrix stretch. The effects of varying model parameters on the rate and extent of fiber alignment will be discussed, as will the implications of the results on mechanotransduction. In summary, the model simulations predict that actin fiber turnover and tensional homeostasis play important roles in time-varying changes to the mechanical properties, cytoskeletal organization and signal transduction events in stretched adherent cells.