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Lights, camera, actin! The cytoskeleton takes center stage in mechanotransduction. Focus on “Mapping the dynamics of shear stress-induced structural changes in endothelial cells.”

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ATHEROSCLEROSIS is characterized by chronic functional changes to the endothelial cells lining the arterial wall, including injury. Whereas significant work has been done to understand the role of atherosclerosis in cardiovascular disease, the process for initiation and development of atherosclerotic plaques remains unclear. Factors including increased plasma lipids, hypertension, high glucose, and elements in cigarette smoke, among others, show strong correlation with endothelial dysfunction and the development of atherosclerotic lesions. Interestingly, the localization of plaques to regions of arterial bifurcations, where fluid shear stress is lower on average and turbulent, predicts that the local hemodynamic effects can alter endothelial cell function and contribute to lesion formation (2).

There is now a large body of evidence demonstrating that fluid mechanical forces generated by blood flowing through the vasculature plays a significant role in regulating endothelial cell genotype and phenotype (3). Although past research efforts have deciphered many of the second messenger-signaling molecules by which endothelial cells transmit hemodynamic forces, especially its shear stress component, the exact mechanism(s) of force detection have remained elusive. Based on experimental evidence, ion channels (8), G protein coupled and growth factor receptors (1), caveolae (12), integrins (5), the glycocalyx (14), and the cell adhesion molecule PECAM-1 (11) all appear to have some capacity to function as individual mechanosensors in endothelial cells. Interestingly, these mechanosensory elements utilize similar sets of second messengers to propagate fluid mechanical signals, suggesting that signals emanating from disparate receptors integrate within the cell.

Whereas the identification of cellular elements with mechanosensory and/or transduction properties has contributed to our understanding of how endothelial cells sense fluid mechanical forces, a fundamental question remains unanswered. How are forces that are imparted on the endothelial luminal surface transmitted to more remote sites within the cell such as PECAM-1-enriched cell-cell junctions and the basal cell surface where integrin-rich focal adhesion sites are concentrated? It has long been suspected that mechanotransduction to regions at considerable distance from the flow/cell interface involve force transmission through the cytoskeletal networks; however, direct evidence to support this concept is limited.

In a recent issue of *American Journal of Physiology-Cell Physiology*, Mott and Helmke (10) present data showing real time, dynamic structural responses of the cytoskeleton, focal adhesions, and the extracellular matrix (ECM) in endothelial

cell cultures exposed to unidirectional laminar shear stress. In these studies fluorescent-tagged actin, paxillin, vimentin, and vinculin were expressed in endothelial cells. The degree of spatial displacement of structures in which these proteins were incorporated were simultaneously imaged and subsequently quantified following the acute onset of shear stress. Consistent with previous work conducted by Helmke and colleagues (4) investigating the dynamics of the intermediate filament responses to shear stress, preexisting actin stress fibers displayed a lateral shift following onset of shear stress with fibers residing on the downstream side of the cell demonstrating the largest magnitude of displacement (see Fig. 3 in Ref. 10). These events are dramatically exemplified in the movies that accompany the manuscript as supplemental material. While it is well established that shear stress can induce remodeling of the actin cytoskeleton with the formation of distinct stress fibers over a time course of hours (9) through events mediated by an array of signaling molecules including RhoA (7) and Rac GTPases (13), the current study provides the first direct observation that shear stress can indeed physically alter the actin cytoskeleton concomitant with initiation of flow.

To evaluate whether actin displacement can be transmitted to focal adhesion complexes, the authors examined terminal ends of actin fibers and observed that fiber movements correlated highly with displacement of associated focal adhesions (see Figs 4. and 5 in Ref. 10). The authors discuss the possibility that local regions of cytoskeletal strain focusing may develop as a result of force transmission and activate signaling molecules associated with focal adhesions, such as RhoA (7) and FAK (6). To show a link from the cell interior to elements outside of the cell, endothelial cells were grown on a matrix containing fluorescent-labeled fibronectin fibers. After shear onset, these fibers were rapidly displaced in a manner that correlated with shifts in actin and focal adhesions (see Figs. 8–11 and supplemental movies 4 and 5 in Ref. 10). In an important set of experiments designed to validate the observed correlations, endothelial cell were pretreated with latrunculin A to inhibit actin polymerization. These cells showed significant attenuation in the pattern and magnitude of fibronectin displacement by shear stress (see Fig. 12 in Ref. 10).

Whereas these data convincingly demonstrate that a step increase in laminar shear stress induces rapid changes in the actin network, which is transmitted to associated structures in cultured endothelial cells, some caution is urged in generalizing these findings to higher order systems. Since endothelial cells display substantial phenotypic drift once they are removed from their natural flow environment, one wonders whether endothelial cells exhibit these types of responses in vivo. Given the difficulty in applying these types of molecular approaches and imaging

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techniques in vivo, it would be worthy to determine whether similar responses are observed in endothelial cells that are acclimated to a relevant hemodynamic environment before initiating acute changes in shear stress. In addition, similar investigations could be performed under experimental conditions where shear stress patterns are designed to mimic spatially discrete areas of the vasculatures associated with atherosclerosis, such as branch points. These may elucidate mechanistic differences in mechanotransduction processes associated with endothelial cell dysfunction and vascular pathology.

Collectively, the data lend strong support to the concept that the actin cytoskeleton enables strain focusing, where applied forces can be transmitted and focused to discrete locations, in this case focal adhesion sites. Interestingly, mechanosensors such as caveolae, PECAM-1, and core proteins of the glycocalyx all have the potential to associate with the actin network through adaptor proteins. Whether forces are relayed to the cytoskeleton through these purported sensors or whether mechanotransduction events associated with these elements require force transmission through the cytoskeleton are important questions that require careful investigation.

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