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Letter by Horowitz Regarding Article, “Protein Interactions at Endothelial Junctions and Signaling Mechanisms Regulating Endothelial Permeability”

To the Editor:

The recent review by Komarova et al¹ on Protein Interactions at Endothelial Junctions and Signaling Mechanisms Regulating Endothelial Permeability addresses a central topic in vascular biology that plays an important role in diabetes mellitus, cancer, and other common disorders. However, several statements in the review overlook evidence that does not support the views they promote:

1. Adherens junctions are presented as the “gatekeeper of the endothelial barrier,” practically the only junction that is acutely responsive to external stimuli by undergoing turnover. This statement promotes a common but erroneous assumption in the field. Ultrastructural studies had shown that tight junctions are pervasive not only in the brain and retina but also in the aorta and mesenteric artery (reference 40 in the review by Simionescu et al²) and in the capillaries of the myocardium^{3,4} and the lung,^{5,6} to name a few. Similarly, there is ample evidence for tight junction turnover in response to agonists, including vascular endothelial growth factor (VEGF).^{7,8}

2. The review assigns solely a junction-disassembly function to RhoA. Although this is a widely-held perception, it is simplistic—RhoA participates in both the maintenance and disassembly of cell junctions. At least in part, this depends on the RhoA effector: activation of Dia promotes junction stabilization, whereas activation of Rho-associated kinase triggers junction disassembly.⁹ This lapse applies also to the spatial control of Rho GTPase activity, where it is stated that RhoA is suppressed at endothelial adherens junctions. We had shown this is not always the case.⁴

3. Figure 2 presents the premise that nonmuscle myosin II unfolds (undergoes 10S–6S transition) on activation. This premise had been the subject of a long-lasting debate in the smooth muscle field but was shown conclusively to be incorrect.¹⁰ Nonmuscle myosin is highly homologous to smooth muscle myosin. As far as I know, the folded myosin conformation has never been detected in either nonmuscle or smooth muscle cells, although a monoclonal antibody specific to this conformation has been available.¹¹

4. The review states that angiopoietin-1 inhibits VEGFR2 by uncoupling Src from the receptor, based on an irrelevant reference (reference 179 in the review by Whittard and Akiyama¹²), while overlooking evidence showing that Src inhibition by angiopoietin-1 is mediated through the sequestration of the kinase away from VEGFR2 by Dia.¹³

Disclosures

None.

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