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Response to 310613, Letter to the Editor (Horowitz)

Yulia Komarova, **Kevin J Kruse**, **Dolly Mehta**, and **Asrar B. Malik**

Keywords

Endothelial permeability; Tight junctions; Adherens junctions

Dear Editor

We thank A. Horowitz for the interesting points concerning our review on protein interactions at endothelial junctions and their role in regulating endothelial permeability (1). Unfortunately, in a review as broad as this, it is not possible to cite all important works in this field.

We agree with A. Horowitz that tight junctions (TJs) are ubiquitous adhesion complexes in endothelial cells (Ref, in the review ref), and have therefore been extensively discussed in our review, particularly in reference to the blood brain barrier (pg. 180–181 and 193; Ref 18, 40–63, 67–78; 347–348). We also agree that endothelial adherens junctions (AJs) are studied in much greater detail. This should come as no surprise since multiple lines of evidence indicate that VE-cadherin adhesion, the main adhesion complex of AJs, is not only required but also sufficient to restrict permeability of the endothelial barrier (Ref 84–87, 166, 187; except of course in the blood brain barrier). Hence, AJs are in fact the “gatekeepers” of the endothelium in various vascular beds. This is evident from multiple findings. For example, it is known that loss of VE-cadherin adhesion, whether through genetic manipulation *in vivo* (Ref 85–87, 2–3), functional blocking antibodies (84), or pro-inflammatory mediators (Ref 188–190) invariably increases endothelial permeability. In contrast, stabilization of VE-cadherin adhesion *via* knock-in or overexpression of VE-cadherin chimeras (4; Ref 166) or artificial bridging of VE-cadherin molecules in *trans*-orientation (Ref 187) has the opposite effect in restricting permeability. Deletion of claudin-5, an adhesion protein of TJs expressed in endothelial cells (5), causes no loss of endothelial barrier function except for increased permeability seen in the blood brain barrier to small molecules (<800 D; Ref 59). Deletion of occludin gene, another protein of TJs, has no apparent increase in endothelial permeability (Ref 67).

Despite the known role of AJs in the maintenance of tissue fluid homeostasis, we agree that the vascular biology field will benefit from further work on the dynamics of TJ proteins at inter-endothelial junctions and their role in regulating permeability of different types of endothelial cells. We also think that the function of both tight and adherens junctions should

Disclosures.

None

be studied in concert. It will require direct side-by-side real-time assessment of both junctions to define how they can act together to control tissue-fluid homeostasis in health and disease. These types of studies will be critical for understanding the important role of cross-communication between TJs and AJs in reinforcing assembly or disassembly of the junctional barrier and how they together influence the acto-myosin-regulated tension in endothelial cells.

Studies by Horowitz (6) and others (as discussed in the review, pg.193, Ref 73, 346–347) suggest an emerging role of RhoA at TJs in the cross-interaction with AJs. RhoA signaling at TJs (Ref 347) is not only required for maintaining the integrity of TJs but also facilitating assembly of the VE-cadherin mechanosensory complex at AJs. We mentioned in our review that “high activity of RhoA at endothelial TJs might be required for generation of intracellular forces that are transmitted to VE-cadherin adhesion allowing formation of stable AJs (1; Ref 73).” This compartmentalized regulation of RhoGTPase signaling at junctions may be important for achieving “the proper balance, magnitude, and directionality of mechanical forces across VE-cadherin adhesion” (1). The organization as well as regulation of RhoGTPase signaling is likely different at epithelial and endothelial AJs (Ref 154–159). Perhaps this is the result of the unique architecture of inter-endothelial junctions in some vascular beds in which TJs are intermingled with AJs. Therefore, any generalizations about commonality of signaling events at epithelial and endothelial cell-cell junctions should be treated with a great deal of caution.

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