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COMMENTARY

S1P-S1PR1 signaling switch: a new paradigm of tyrosine phosphorylation

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Maintenance of endothelial barrier integrity is required for preventing several cardiovascular and lung diseases including angiogenesis and ischemic stroke, rendering this area of study with broad implications [1, 2]. Importantly, the death of millions from COVID-19, a disease that often triggers vascular injury and ARDS, clearly indicates that novel therapeutic strategies are needed to reverse the course of injury [3, 4]. Vascular barrier and other forces like hydrostatic pressure controls the movement of trans-endothelial fluid across the endothelium. There is an increase in vascular permeability when extravasation increases from blood to tissues under these forces. However, there is also an increase in vascular permeability in case of large molecules which have even limited extravasation under exposure of inflammatory conditions including inflammatory cytokines and in physiological or pathophysiological conditions including ALI, ARDS and COVID-19. And the increased vascular permeability is characterized by the opening of junctions intracellularly and gap formation in endothelial cells [5].

In healthy organs, extravasation and increase in permeability of fluids and other proteins is transient and this condition declines upon the end of a stimulus, while as in case of chronic inflammation and conditions like cancer and COVID-19 this sustains further. Following tissue injury by pathogens, allergens, toxins, trauma and other stimuli, the function of endothelial barrier gets changed. Under these conditions, the regulatory mechanisms of endothelial barrier have various features in common including the alteration in organization of endothelial junctions, formation of gaps, trans-endothelial pressure gradients that direct barrier leakage [5, 6].

The vascular endothelium with which cells are continuously in contact play a critical role in maintaining lung homeostasis basally and after infection. Vascular endothelium serves to maintain tissue and fluid homeostasis throughout the body by regulating the transport of nutrients, water, and or immune cells [7]. Sphingosine-1-phosphate receptor-1 (S1PR1), a G-protein coupled receptor (GPCR), which is expressed on the EC surface, is a well-known "barrier protective" and also plays an "anti-inflammatory" role. Interestingly, the mediators of sphingolipid signaling pathway are of special interest as these are critical modulators of lung vascular homeostasis. Specifically, S1P (sphingosine 1-phosphate) and its G protein-coupled receptor S1PR1 have been shown to exert barrier-protective action in ECs. Activation of S1PR1 in ECs causes a redistribution of junctional proteins like VE-cadherin into the areas of cell–cell contact, thus tightening the endothelial barrier [8].

Like other GPCRs, phosphorylation of S1PR1 at C-terminal serine/threonine residues leads to receptor internalization by the canonical arrestin-mediated pathway, following which S1PR1 recycles to the cell-surface or undergoes ubiquitin-mediated degradation [9, 10]. Earlier Chavez et al. showed that S1P phosphorylates S1PR1 at Tyr^{143} (Y^{143}) which internalizes the receptor without inducing receptor degradation [11].

Following on the paradigm that S1P/S1PR1 signaling axis plays role in barrier disruption, Anwar et al. in a recent article [12] report the key role of S1PR1 tyrosine phosphorylation in ECs in regulating endothelial barrier breakdown under inflammatory conditions. The authors show that S1PR1 upon phosphorylation at tyrosine (Y^{143}) by S1P localizes to the ER by utilizing state-of-art technology such as TIRF microscopy and Dendra2 photoconversion technique. In this context, they discovered that S1P phosphorylated Y^{143}-S1PR1 receptor transiently localizes to ER. However, Y^{143}D-S1PR1 (which mimics phosphorylation)

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binds BiP, an ER chaperon which retains the receptor in the ER, increasing cytosolic Ca^{2+} and disrupting the barrier function.

Furthermore, the authors challenged EC with S1P and observed the effects on Ca^{2+} generation in the ER. Herein, they label the EC with Ca^{2+} sensitive dye, Fura2AM, to address whether S1PR1 phosphorylation and ER localization dictates intracellular Ca^{2+} changes in response to S1P. S1P increased intracellular Ca^{2+} in EC transfected with WT-S1PR1 but only minimally in EC expressing Y^{143}F-S1PR1 mutant. However, S1P increased intracellular Ca^{2+} in cells expressing Y^{143}D-S1PR1 to about 4–fivefold in a G-protein, Gi dependent manner. These data suggest that the phosphorylated receptor traffics to ER and leads to Ca^{2+} generation.

Importantly, Anwar et al. finds that inflammatory cytokine, TNFα, which is generated during vascular injury, such as after endotoxemia, can phosphorylate S1PR1 at tyrosine (Y^{143}) leading to internalization and transport of tyrosine $(Y)^{143}$-phosphorylated S1PR1 in the ER, leading to disruption of vascular barrier. Therefore, with these novel findings, we can now speculate that sphingolipid-derived signaling mediators operate through varied mechanisms to disrupt vascular homeostasis and barrier function. The generation of Ca^{2+} and localization of phosphorylated receptor at the ER in promoting leakage of endothelial barrier with impressive downstream signaling capacity, which disrupts lung endothelial barrier after a critical stimulation of the receptor with agonists S1P/TNFα, unravels fundamental cellular intrinsic signaling pathways. Thus, these data provide the strong basis for several new therapeutic strategies for treating lung vascular diseases including acute lung injury (ALI) and COVID-19.

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Declarations

Conflict of interest There is no conflict of interest.

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