Paper of the Month August 2023

‘Endothelial VEGFR2-PLCγ signaling regulates vascular permeability and antitumor immunity through eNOS/Src.’

Sjöberg E, Melssen M, Richards M, Ding Y, Chanoca C, Chen D, Nwadozi E, Pal S, Love DT, Ninchoji T, Shibuya M, Simons M, Dimberg A, Claesson-Welsh L.

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In the September 2023 paper of the month, Sjöberg *et al*. delve into the role of endothelial phospholipase Cγ (PLCγ) beyond its known importance in vascular development. They uncover that PLCγ is not only upregulated in human cancers, particularly renal cell carcinoma (RCC), but also that its higher levels are associated with increased angiogenesis and a worse prognosis. In contrast, lower PLCγ expression seems to favor immune cell engagement. The research highlights that PLCγ is a downstream effector of the VEGFR2 pY1173 site. Mouse models with reduced VEGFR2 signaling or without endothelial PLCγ showed stabilized endothelial barrier and less leakage, which also correlated with lower levels of immunosuppressive cytokines and fewer regulatory immune cells, enhancing the effectiveness of cancer therapies. The study traces a regulatory cascade from VEGFR2 pY1173 activation to eNOS and Src, culminating in the disruption of endothelial junctions. Interestingly, the VEGFR2 Y1173/PLCγ/eNOS/Src signaling pathway is active in both normal and tumor vasculature, with its activity having significant implications for the immune status within tumors and the overall disease outcome, as depicted in their graphical abstract.