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Keeping the Flow Going: FGFR1 Protects Vascular Patency by Inhibiting Occlusive Neointimal Hyperplasia

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Old is gold and new is diamond! This is certainly not true for neointimal hyperplasia (NIH), in which blood vessels develop new components in the intimal layer (thus the term, neointimal), compromising the vascular lumen. NIH is characterized by proliferating vascular smooth muscle cells and excess subendothelial matrix and is seen in several conditions including chronic transplant rejection, post-vascular interventional stenosis, and atherosclerosis. NIH constitutes a major source of cardiovascular morbidity and mortality. Endothelial to mesenchymal transformation (EnMT), mediated through transforming growth factor (TGF)–β/smad2 signaling, has been implicated in its pathogenesis. However, the upstream molecular regulators of this critical process remained elusive. Leveraging an array of cellular approaches, animal models, and human data, Chen *et al.* demonstrate an interplay of TGFβ and fibroblast growth factor receptors (FGFRs) pathways regulating NIH, and in doing so, they define one more axis in the signaling network regulating EnMT and NIH. FGFRs belong to a family of ubiquitously expressed tyrosine kinase receptors, which regulate cellular functions including endothelial cell phenotype and vascular permeability.

Using real-time polymerase chain reaction the authors first demonstrated FGFR1 as the predominant member of FGFR expressed in endothelial cells. They then silenced various FGFR members (FGFR1 to FGFR4) to show that FGFR1 transmitted a signal in response to FGF ligand in endothelial cells, as depicted by changes in the morphology of cells and phosphorylation of extracellular signal–regulated kinase 1 (ERK1)and FRS2-α major downstream targets of FGFR pathway. Silencing *FGFR1* resulted in changes typical of EnMT, such as an increase in smooth muscle cells markers and up-regulation of transcription factors typically associated with EnMT and increase in phosphorylated Smad2, indicating an enhanced TGFβ activity.

To determine the human relevance of the above findings, rejected heart transplant allografts were examined. The coronary endothelial cells in the NIH area exhibited a profound reduction in FGFR1 and concurrent up-regulation of Smad2. Chen *et al.* then employed several animal models to examine the relevance of FGFR1-TGFβ axis in NIH in transplant rejection. A cross-species animal model of allograft rejection was created by implanting a normal human coronary artery in the infrarenal aortae of immunodeficient SCID mice. Infusing human PBMCs accelerated the rejection. Close to 90% reduction in endothelial cells' FGFR1 expression was found in the regions of NIH of transplanted aorta compared with controls, further supporting that loss of FGFR1 is associated with neointimal hyperplasia. However, the inducible endothelial cell-specific knock out (ECKO) established

the causal relationship of FGFR1-TGFβ axis with NIH. Both the aortic and venous transplantation from FGFR1 ECKO animals into controls resulted in NIH and loss of endothelial markers and appearance of smooth muscle cell markers (collagen 1) only upon induction of Cre, which deleted the FGFR1 gene, which strongly supports causal relationship of loss of FGFR1 with EnMT and NIH. Intriguingly, the FGFR1-TGFβ-EnMT relationship was found specifically in inflammatory-associated NIH (such as with transplant rejection), not other hypoxia-associated NIH, as examined in the hind-limb ischemia model.

Overall, it appears that in endothelial cells, FGFR1 signaling is critical to suppress TGFβ signaling and maintain endothelial phenotype and protect from EnMT. Loss or inhibition of FGFR1 strips off this protective mechanism, activating TGFβ pathway to initiate EnMT and NIH formation. Although the mechanism (or mechanisms) suppressing FGFR1 in these disease processes remains an enigma, the above work provides a missing link in the conundrum of EnMT and delineates a previously unidentified therapeutic target that can be leveraged to block this sinister occlusive vascular pathology of neointimal hyperplasia.

P.-Y. Chen *et al.,* Fibroblast growth factor receptor 1 is a key inhibitor of TGFβ signaling in the endothelium. *Sci. Signal.* ***7***, ra90 (2014). **[Full Text]**