SMAD4 maintains the fluid shear stress set point to protect against arterial-venous malformations.

Banerjee K, Lin Y, Gahn J, Cordero J, Gupta P, Mohamed I, Graupera M, Dobreva G, Schwartz MA, Ola R. J

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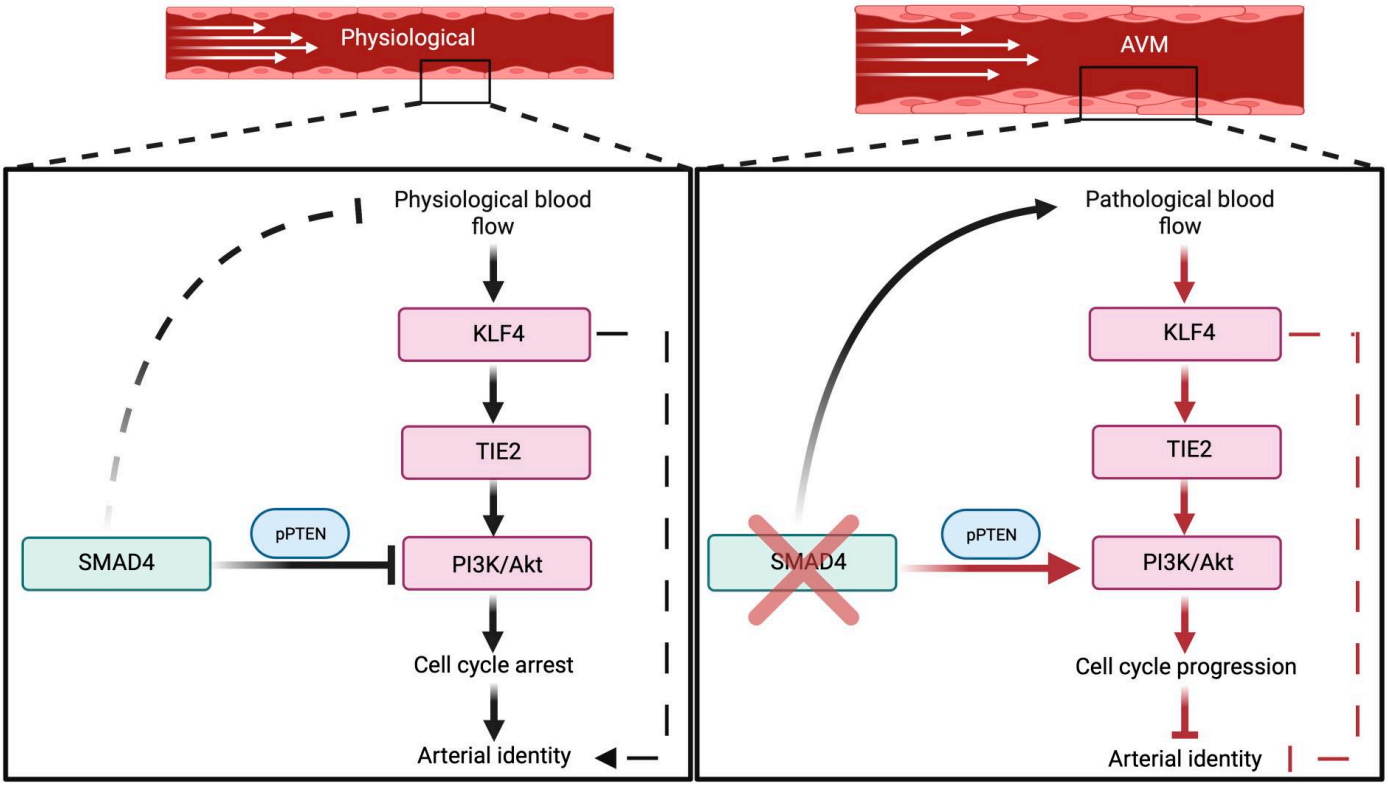

The study by Banerjee et al, aimed to elucidate the mechanism of synergy between fluid shear stress and SMAD signaling in vascular stability and its failure in Hereditary Hemorrhagic Telangiectasia (HHT).

Key findings:

- Smad4 loss, a pathological characteristic of HHT, heightened endothelial cell sensitivity to flow, leading to AVMs characterized by enhanced flow-mediated morphological responses.
- This loss led to induction of KLF4, subsequent transcriptional activation of TIE2 tyrosine kinase signaling and PI3K/Akt pathway activation
- Further, KLF4-mediated repression of cyclin dependent kinase (CDK) inhibitors, CDKN2A and CDKN2B led to cell cycle progression
- Arterial-venous malformation is driven by the loss of arterial identity due to cell cycle dysregulation.
- The KLF4-TIE2-PI3K/Akt-CDKs axis presents a potential target for developing therapeutics for vascular malformations