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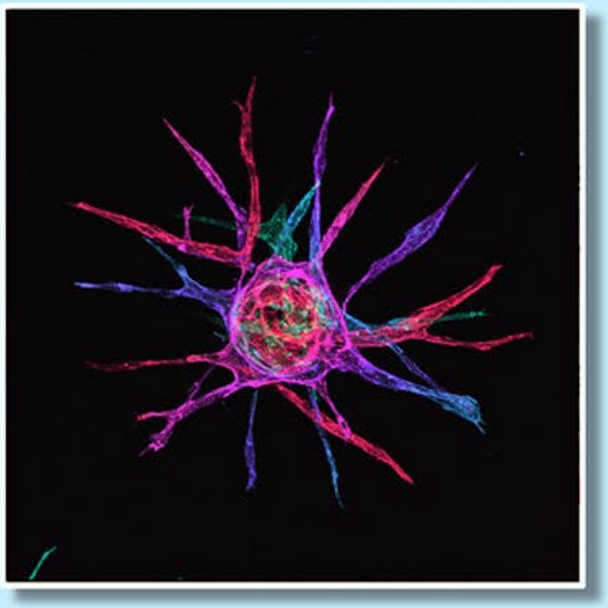

Human Umbilical Vein Endothelial Cells Sprout from a Bead in a 3D Fibrin Matrix

The Inhibitory Protein PMEPA1, but not SMAD7, Inhibits BMP Signaling in Endothelial Cells

Angiogenesis is the development of blood vessels from existing vasculature via sprouting of endothelial cells. It is regulated by growth factor signals including Bone Morphogenetic Protein (BMP), a member of the TGFb superfamily of signaling pathways. The BMP ligand leads to intracellular signaling and response via engagement with the heterotetrameric BMP receptor on the surface of an endothelial cell. The receptor complex phosphorylates intracellular SMAD1/5/8 proteins. These proteins then bind to SMAD4 protein to facilitate nuclear translocation and transcriptional regulation.[1] Another signal, Notch, downregulates endothelial cell responsiveness to BMP signaling by mechanisms that are not fully understood.[2] A screen to investigate Notch-regulated BMP/TGFb pathway members identified two proteins, PMEPA1 and SMAD7, that are upregulated by Notch and negatively regulate BMP signaling.[1,3] Knockdown of PMEPA1 expression significantly increased signaling in response to BMP ligand, indicating that PMEPA1 inhibits BMP signaling in endothelial cells. However, SMAD7 knockdown did not affect BMP responsiveness. Preliminary results from experiments designed to test the effect of reduced levels of PMEPA1 or SMAD7 in a 3D blood vessel formation sprouting assay do not indicate that PMEPA1 nor SMAD7 have a strong effect on 3D angiogenesis. We hypothesize that PMEPA1 modulates the responsiveness of endothelial cells to BMP by virtue of their Notch status. Understanding the function of these Notch-regulated BMP/TGFb pathway inhibitors is critical, as they hold therapeutic potential for diseases of aberrant BMP signaling.[4]

1. Itoh, S., Itoh, F. 2011. Growth Factors. 5:163-173.
2. Kevin P Mouillesseaux, David S Wiley et al. 2016. Nat Comm. 7:13247.
3. Watanabe, Y. et al. Mol. Cell. 37, 1: 123-134.
4. Welti, J. et al. J Clin Invest. 123, 8: 3190-3200.