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Shaping Waves of Bone Morphogenetic Protein Inhibition during Vascular Growth

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Rationale: The bone morphogenetic proteins (BMPs) are essential morphogens in angiogenesis and vascular development. Disruption of BMP signaling can trigger cardiovascular disease such as arteriovenous malformations.

Objective: A computational model predicted that BMP4 and BMP9 and their inhibitors matrix Gla protein (MGP) and Crossveinless-2 (CV2) would form a regulatory system consisting of negative feedback loops with time delays, and that BMP9 would trigger oscillatory expression of the two inhibitors. The goal was to investigate this regulatory system in endothelial differentiation and vascular growth.

Methods and Results: Oscillations in the expression of MGP and CV2 were detected in endothelial cells (ECs) in vitro, using qPCR and immunoblotting. These organized temporally downstream BMP-related activities including expression of stalk cell markers and cell proliferation, consistent with an integral role of BMP9 in vessel maturation. In vivo, the inhibitors were located in distinct zones in relation to the front of the expanding retinal network, as determined by immunofluorescence. Time-dependent changes of the CV2 location in the retina, and the existence of an endothelial population with signs of oscillatory MGP expression in developing vasculature supported the in vitro findings. Loss of MGP or its BMP4-binding capacity disrupted the retinal vasculature, resulting in poorly formed networks, especially in the venous drainage areas, and arteriovenous malformations as determined by increased cell coverage and functional testing.

Conclusions: Our results suggest a previously unknown mechanism of temporal orchestration of BMP4 and BMP9 activities that utilizes the tandem actions of the extracellular antagonists MGP and CV2. Disruption of this mechanism may contribute to vascular malformations and disease.

- 1) Please identify members by underlining their name.
- 2) Please use box above, Abstract (with spaces) = 500 Word limit
- 3) Talk duration 15 min, questions 10 min (total time 25 min)



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