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Hedgehog signalling in human brain arteriovenous malformations

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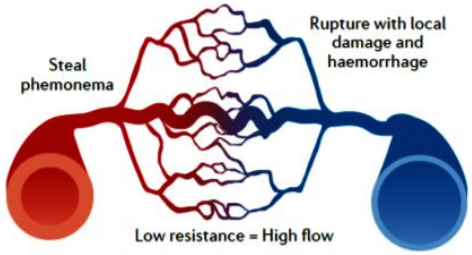
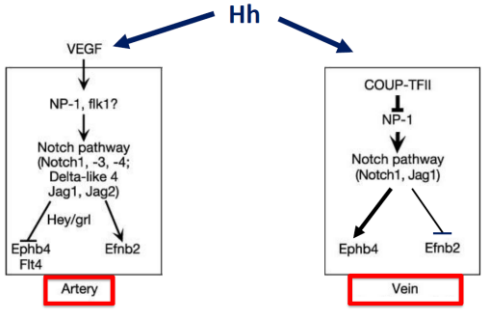
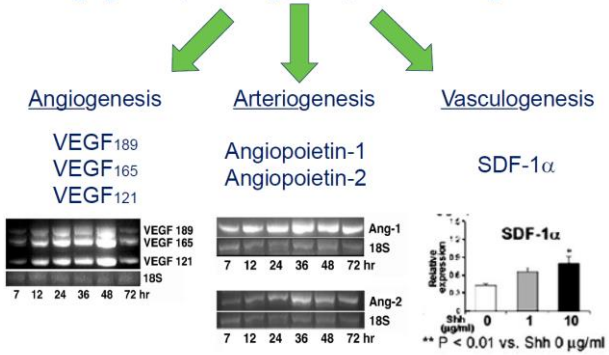


Arteriovenous malformations (AVM)

Hedgehog (Hh): an important regulator of arterial/venous identity of endothelial cells



Hh: an important regulator of angiogenesis, arteriogenesis, and vasculogenesis



- The cause of AVM remains elusive
- It probably involves ***abnormalities in the differentiation of arterial versus venous endothelial cells***
- Evidence from genetic syndromes and genome-wide association studies implicate genetic factors in disease development and progression. Mutations in the TGF-β (ALK1, ENG, SMAD4), G protein-coupled receptor (GNAQ) and Ras (RASA1) signalling pathways, as well as in factors involved in ***angiogenesis***
- Recent findings from novel animal models and genetic studies suggest that arteriovenous malformations may arise from ***aberrant vasculogenesis*** and/or ***angiogenesis*** after injury.

Hyperactivation / Dysregulation of the Hedgehog pathway

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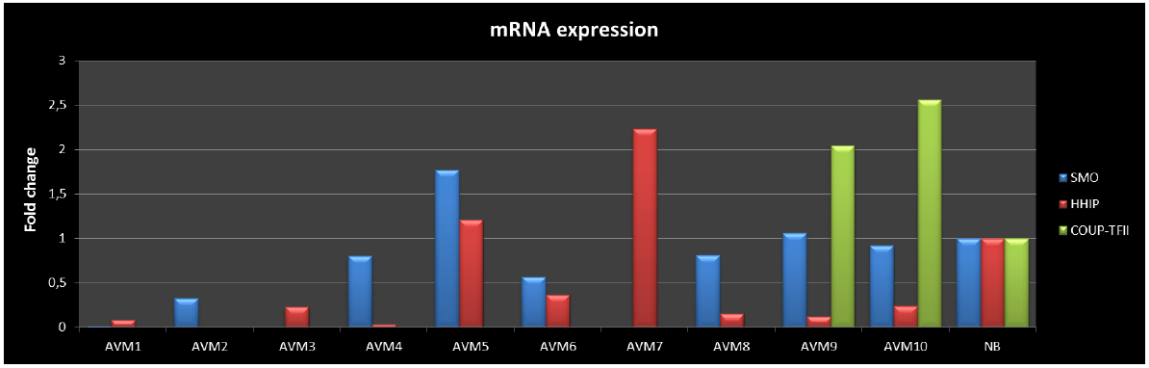
Abnormalities in arterial/venous identity
Aberrant angiogenesis

↓

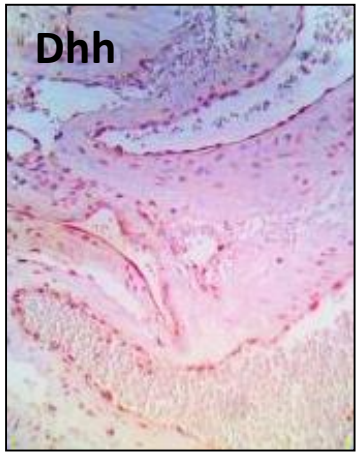
Arteriovenous malformations (AVM)

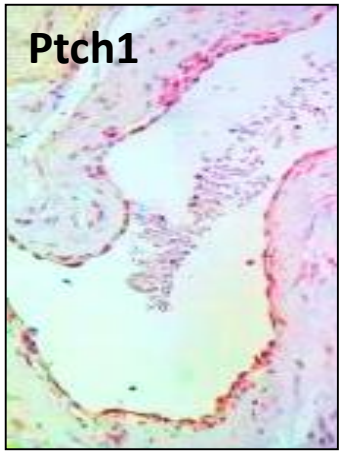
Analysis of Hh signalling in specimens of human brain AVMs



Downregulation of HHIP

HHIP in AVM vs controls, p = 0,01





Expression of Shh, Dhh and Ptch1 in AVM endothelial layer

The activation of the Hh pathway induces an in vivo angiogenesis, which is characterized by several arteriovenous shunts without an interposed capillary bed, which reminds of AVMs

murine model of corneal angiogenesis