

# Signal-Dependent Transcriptional Control of Notch4 Signaling in Vascular Endothelium

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Notch signaling is an evolutionary conserved pathway that modulates cell fate determination. The process whereby the primitive vascular network develops into the mature vasculature, known as angiogenic vascular remodeling, is controlled by multiple signals, including the Notch signaling pathway. Of the two mammalian Notch receptors expressed in vascular endothelium, Notch1 is broadly expressed in diverse cell types, whereas Notch4 is preferentially expressed in endothelial cells. The endothelial cell-specific expression of Notch4 suggests that dynamic changes in Notch4 expression are crucial for the regulation of angiogenesis. As mechanisms that confer Notch4 expression were unknown, we investigated how *Notch4* transcription is established and regulated in endothelial cells and in transgenic mice. The *Notch4* promoter and the 5' portion of *Notch4* assembled into an endothelial cell-specific histone modification pattern. The *Notch4* promoter was sufficient to confer endothelial cell-specific transcription in transfection assays, but intron-1 or upstream sequences were required for expression in the vasculature of transgenic mouse embryos. Activator Protein-1 (AP-1) complexes occupied *Notch4* chromatin in a cell-type-specific manner and conferred endothelial cell-specific transcription. Vascular angiogenic factors synergized with hydrocortisone to activate and maintain *Notch4* transcription in endothelial cell lines. The same signals activated AP-1 and reprogrammed the endogenous *Notch4* gene from a repressed to a transcriptionally active state in nonendothelial HeLa and 10T1/2 cells, accompanied by the changes in histone modifications. These results reveal a growth factor-AP-1-Notch4 axis, which we propose to be crucial for transducing angiogenic signals during vascular development and remodeling and to be deregulated upon aberrant signal transduction in cancer.

## Reference

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