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Cerebrovascular defects in *Foxc1* mutants correlate with aberrant WNT and VEGF-A pathways downstream of retinoic acid from the meninges

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Abstract

Growth and maturation of the cerebrovasculature is a vital event in neocortical development however mechanisms that control cerebrovascular development remain poorly understood. Mutations in or deletions that include the *FOXC1* gene are associated with congenital cerebrovascular anomalies and increased stroke risk in patients. *Foxc1* mutant mice display severe cerebrovascular hemorrhage at late gestational ages. While these data demonstrate Foxc1 is required for cerebrovascular development, its broad expression in the brain vasculature combined with *Foxc1* mutant's complex developmental defects have made it difficult to pinpoint its function(s). Using global and conditional *Foxc1* mutants, we find 1) significant cerebrovascular growth defects precede cerebral hemorrhage and 2) expression of Foxc1 in neural crest-derived meninges and brain pericytes, though not endothelial cells, is required for normal cerebrovascular development. We provide evidence that reduced levels of meninges-derived retinoic acid (RA), caused by defects in meninges formation in *Foxc1* mutants, is a major contributing

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