CEREBROVASCULAR MALFORMATIONS

Understanding CCMs

Two new studies have eludicated pathways involved in malformation of blood vessels in mice and zebrafish. These findings are hoped to shine some light on the mysterious mechanisms involved in development of cerebral vascular malformations in humans, and could lead to potential treatments.

Cerebral cavernous malformations (CCMs) are a common type of vascular abnormality wherein blood vessels are thin and prone to leaking, which can lead to seizures, stroke, or even death. Although three genes associated with CCM have been discovered (*CCM1*, *CCM2* and *CCM3*), the relationship between mutations in these genes and the disorder are poorly understood. Now, preclinical studies by Whitehead *et al.* and Kleaveland *et al.* have identified roles for *CCM2* mutations in angiogenetic pathways.

Kevin Whitehead and colleagues investigated two mutations of the *Ccm2* gene in mice. The team observed that *Ccm2* was not required for the initial stages of vasculogenesis, but was essential for angiogenesis. In an analysis of tissue-specific mutants, *Ccm2* was confirmed to be required in the endothelium for angiogenesis, but absence of the gene in neural or smooth muscle cells had no effect on their development. In light of these results, Whitehead's team evaluated the function of *CCM2* in human endothelial cells. Human microvascular endothelial cells deficient in *CCM2* showed activation of RhoA GTPase, which could be responsible for increased actin stress fiber formation and decreased endothelial barrier formation. Simvastatin, an inhibitor of RhoA signaling, was administered to mice with mutations in one or both *Ccm2* alleles. "Statins, as known blockers of Rho GTPases, are a logical therapy for this vascular barrier defect, and were able to reverse the permeability defect," Whitehead explains. "This is the first clue towards a possible medical therapy for CCM, a disease where treatment currently is limited to removal of lesions and surrounding brain by surgery or radiation," he adds.

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Benjamin Kleaveland and colleagues carried out studies in mice and zebrafish to investigate the signaling pathway mediated by the CCM2 adaptor and the HEG1 (heart of glass) receptor. Previous studies in zebrafish have shown that mutations in *heg*, *ccm1* (also termed *krit1*), or *ccm2* result in a dilated heart during embryonic development.

Kleaveland's group found the HEG1 receptor to be selectively expressed in endothelial cells. Mice deficient in *Heg1* had defects in heart tissue, blood vessels and lymphatic vessels. Similar vascular defects were observed in zebrafish embryos deficient in *Heg1*. The worst cardiovascular defects were observed in zebrafish embryos and mouse embryos deficient in both *Heg1* and *Ccm2*. This phenotype was reproduced in CCM2-deficient human endothelial cells *in vitro*. The cardiovascular defects observed by Kleaveland *et al.* were associated with abnormal formation of endothelial cell junctions as a result of disruption of the HEG1–CCM protein pathway. The authors suggest that, in humans, CCMs could be stabilized or prevented by treatment with agents that positively regulate endothelial junction formation.

The two reports identify different mechanisms by which *CCM2* mutations might contribute to CCM, but they both indicate roles for this gene in endothelial cell development and angiogenesis. These results offer a step towards improved understanding of the disease, and identification of pharmacological treatments.

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Original articles Whitehead, K. J. *et al.* The cerebral cavernous malformation signaling pathway promotes vascular intefrity via Rho GTPases. *Nat. Med.* **15**, 177–184 (2009).
Kleaveland, B. *et al.* Regulation of cardiovascular development and integrity by the heart of glass–cerebral cavernous malformation protein pathway. *Nat. Med.* **15**, 169–176 (2009).