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Topic Category: 4210-ASIP Vascular cell biology & dysfunction in disease

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Presentation Preference: Oral

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Sponsor's Society: Pathology - American Society for Investigative Pathology (ASIP) - Host Society
Keywords: 1. vascular malformation 2. angiogenesis

VEGF is required for the initiation of Cerebral Cavernous Malformations

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There is a narrow developmental window of susceptibility shortly after birth in which genetic deletion of CCM genes is sufficient to lead to spontaneous vascular malformations. Using injection of viral vectors, we show that CCM lesion formation not only requires loss of CCM genes but also active angiogenesis. Furthermore, VEGFR2 activation is increased following the depletion of KRIT1, CCM2 or CCM3 gene expression in endothelial cells (although increased VEGFa production is only seen with the loss of KRIT1). Subsequently, we show that inhibition of VEGF with the kinase inhibitor SU5416 reduces CCM lesion formation and vascular permeability in Krit1ecKO mice, with a decreased likelihood of lesion hemorrhage as shown by peri-lesion iron deposits. This mechanism is not specific to KRIT1, as inhibition of VEGF using bevacizumab also reduces lesion formation in Ccm3ecKO mice.

Support or Funding Information
This work was supported by NIH grant HL117885 to A.J.G, NIH grant NS075168 to K.J.W., and AHA pre-doctoral fellowship 14PRE2048009 to P.V.D.