Cerebral cavernous malformation pathogenesis

CCMs arise due to loss of function in one of the genes that encode the CCM complex, a negative regulator of MEKK3-KLF2/4 signaling in vascular endothelial cells. Gain-of-function mutations in PIK3CA (encoding the enzymatic subunit of the PI3K (phosphoinositide 3-kinase) pathway associated with cell growth) synergize with CCM gene loss-of-function to generate rapidly growing lesions [1].

Ren et al. demonstrated that CCM growth requires increased PI3K/AKT/mTOR pathway and loss of CCM protein function. They identified PIK3CA gain of function (GOF) and CCM loss of function (LOF) somatic mutations in the same cells in a majority of human CCMs. Using mouse models, they showed that CCM growth requires both PI3K GOF and CCM LOF in endothelial cells, and that both CCM LOF and increased expression of the transcription factor KLF4, a downstream MEKK3 effector, augment mTOR signalling in endothelial cells. Consistent with these findings, the mTORC1 inhibitor Rapamycin effectively blocks CCM formation in mouse models. They established a three-hit mechanism analogous to cancer in which aggressive vascular malformations arise through the loss of vascular "suppressor genes" that constrain vessel growth and gain of a vascular "oncogene" that stimulates excess vessel growth. These findings suggest that aggressive CCMs may be treated using clinically approved mTORC1 inhibitors [2].

Genes mutated in cerebral cavernous malformation (CCM) encode proteins that modulate junction formation between vascular endothelial cells.

Most cerebral cavernous malformations are linked to loss-of-function mutations in 1 of 3 genes, namely CCM1 (originally called KRIT1), CCM2 (MGC4607), or CCM3 (PDCD10).

How disruption of the CCM complex results in disease remains controversial, with numerous signalling pathways (including Rho, SMAD and Wnt/β-catenin) and processes such as endothelial mesenchymal transition (EndMT) proposed to have causal roles. CCM2 binds to MEKK3 [3].

Although a role for these three genes in the formation of these intracranial vascular lesions has been established since the 1990s, additional works have further elucidated the molecular mechanisms by which mutations in these genes and the resultant aberrant proteins interact, leading to the formation of CCMs.

Therefore, it is reasonable to assume that a molecular pathway exists that requires all three proteins to function together correctly for proper cellular function. Moreover, research is demonstrating how each component protein is capable of interacting with numerous other signaling and cytoskeletal molecules allowing for a diverse range of functions in molecular signaling pathways via unique protein–protein interactions.

Significant research findings from 2000 to 2015 have further enhanced our understanding of the pathogenesis of CCM formation. The use of advanced sequencing technologies to characterize genomic mutations and the identification of new signaling pathways and protein–protein interactions have led to great strides in understanding the molecular genetics involved in the development of CCMs. However, many unanswered questions remain, and future studies are clearly needed to improve our understanding of CCM pathogenesis. "Gene to protein to disease" mechanisms involved

in the pathogenesis of CCMs should shed further light on potential therapeutic targets. [4].

The Phosphoinositide 3 kinase (PI3K)/Akt pathway is known to play a major role in angiogenesis. Studies have shown that the phosphatase and tensin homologue deleted on chromosome ten (PTEN), a tumor suppressor, is an antagonist regulator of the PI3K/Akt pathway and mediates angiogenesis by activating vascular endothelial growth factor (VEGF) expression.

Understanding the biology of these proteins with respect to their signaling counterpart will help to guide future research towards new therapeutic targets applicable for CCM treatment [5].

Studies identify gain of MEKK3 signalling and KLF2/4 function as causal mechanisms for CCM pathogenesis that may be targeted to develop new CCM therapeutics [6].

CCMs arise from the loss of an adaptor complex that negatively regulates MEKK3-KLF2/4 signalling in brain endothelial cells, but upstream activators of this disease pathway have yet to be identified.

Tang et al. identify endothelial Toll-like receptor 4 (TLR4) and the gut microbiome as critical stimulants of cerebral cavernous malformation formation. Activation of TLR4 by Gram negative bacteria or lipopolysaccharide accelerates CCM formation, and genetic or pharmacologic blockade of TLR4 signalling prevents CCM formation in mice. Polymorphisms that increase expression of the TLR4 gene or the gene encoding its co-receptor CD14 are associated with higher CCM lesion burden in humans. Germ-free mice are protected from CCM formation, and a single course of antibiotics permanently alters CCM susceptibility in mice. These studies identify unexpected roles for the microbiome and innate immune signalling in the pathogenesis of a cerebrovascular disease, as well as strategies for its treatment [7].

In this scenario, the lack of effective pharmacologic options remains a critical barrier that poses an unfulfilled and urgent medical need [8].

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