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CEREBROVASCULAR MALFORMATIONS

Microbiota promotes cerebral cavernous malformations

The microbiota plays an important part in the development of cerebral cavernous malformations (CCMs), according to new research. Bacterial signalling via the lipopolysaccharide (LPS)-activated immune receptor TLR4 could present a novel target for CCM treatments.

CCMs are vascular abnormalities comprising enlarged capillaries that are prone to haemorrhage, resulting in stroke and seizures. CCMs result from loss-of-function mutations in *KRIT1*, *CCM2* and *PDCD10*, which encode the components of a protein complex that suppresses MEKK3–KLF2/4 signalling. No therapies are available that directly target MEKK3–KLF2/4 signalling, and a team led by Mark Kahn at the University of Pennsylvania investigated whether upstream activators of MEKK3–KLF2/4 might instead be targeted.

The team developed transgenic mice in which *Krit1* or *Ccm2* could be inducibly deleted in the vascular endothelium (*Krit1*^{ECKO} and *Ccm2*^{ECKO} mice). Usually, these animals form abundant CCM lesions, but an unexpected effect was observed when the animals were moved into new housing. "We began to notice the emergence of animals resistant to developing the CCM phenotype," explains lead author Alan Tang. "Animals that had previously exhibited highly penetrant phenotypes were now essentially disease free."

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Gram-negative bacterial abscesses were observed in some of the CCM-resistant animals, suggesting that infection was influencing CCM pathogenesis. The researchers found that injection of *Bacteriodes fragillis* or the Gram-negative bacterial product LPS into CCM-resistant *Ccm2*^{ECKO} mice promoted CCM lesion formation. Conversely, mice fostered by germ-free mothers were protected from lesion formation.

Knockout of *Tlr4* in the vascular endothelium almost completely abolished CCM lesion formation, suggesting that TLR4 signalling is vital in CCM pathogenesis. Importantly, polymorphisms linked to increased TLR4 expression were associated with CCM lesions in humans.

Tang and colleagues explored the therapeutic potential of altering the microbiota or TLR4 signalling. Treatment of *Krit1*^{ECKO} mice with the TLR4 antagonists resatorvid or hypoacetylated LPS yielded 80% and >90% reductions in CCM lesion volume, respectively. In addition, treatment of *Krit1*^{ECKO} mice with broad-spectrum antibiotics reduced CCM lesion formation by >95%. These findings suggest that TLR4 inhibitors or manipulation of the microbiota present potential therapies for CCM.

"The identification of a role for the microbiota, LPS and TLR4 signalling in CCM is an important advance in our understanding of the molecular mechanisms in this disease," comments Tang. The team are now looking to translate these findings into humans, and aim to gather faecal samples from patients with CCM. "We need to know if different human gut microbiomes are associated with variable CCM disease severity," Tang concludes.

Charlotte Ridler

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