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Abstract

Exploring Mechanotransduction In Cerebral Cavernous Malformation †

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Abstract: Cerebral cavernous malformation (CCM, OMIM #116860) is a vascular disorder of central nervous system capillaries. Affected vessels appear tangled and enlarged due to cell junction impairment, resulting in an increased blood-brain barrier (BBB) permeability, further worsened by deficiency of pericytes. The familial form of the disease arises following germline mutations at the three loci KRIT1/CCM1 (HGNC ID: 1573; 7q11.2-21), MGC4607/CCM2 (HGNC ID: 21708; 7p13) and PDCD10/CCM3 (HGNC ID: 8761; 3q26.1). However, a small percentage of patients affected by the inherited form of the disease harbors no mutations, suggesting the existence of a fourth CCM locus. In this context, by whole exome sequencing we identified the novel missense mutation c.2973C>T (p.Phe991Leu) in the PIEZO1 gene (HGNC ID: 28993; 16q24.3) and it was shown to segregate with the CCM phenotype, within the family. PIEZO1 encodes for a mechanosensitive Ca2+ ion channel that, in endothelial cells, contributes to maintaining BBB integrity. We found that PIEZO1 impairment results in increased apoptotic rate of endothelial cells, as well as in CCM gene expression perturbation. Moreover, by immunofluorescence, we showed that PIEZO1 impairment leads to endothelial cell morphology loss and to KRIT1 nuclear translocation. We used human cerebral microvascular endothelial cells (hCMECs) as cell model, Yoda1 as PIEZO1 agonist and gadolinium as PIEZO1 antagonist. Untreated cells were consider as control condition. According to our results, we think that PIEZO1 can be considered for further investigation in CCM pathogenesis.

Keywords: Cerebral cavernous malformation; Endothelial cells; PIEZO1; Mechanotransduction.

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