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ENDOTHELIAL CELL CLONAL EXPANSION IN THE DEVELOPMENT OF CEREBRAL CAVERNOUS MALFORMATIONS

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Cerebral cavernous malformation (CCM) is a neurovascular familial disease characterised by capillary-venous cavernomas, and is due to loss-of-function mutations to anyone of three CCM genes (CCM1,CCM2,CCM3). Familial CCM follows a two-hit mechanism similar to that of tumour suppressor genes but only a small fraction of endothelial cells form the malformations. We report that in mouse models and in human patients, endothelial cells lining the lesions have different features from the surrounding endothelium, as they express mesenchymal/stem-cell markers (End/MT). In the present work we found that cavernomas originate from clonal expansion of few Ccm3-null endothelial cells that express End/MT and stem cell markers. These cells attract surrounding wild-type endothelial cells inducing them to express End/MT markers and to contribute to cavernoma growth. These results open novel pathways to treat CCM by pharmacological tools.

Il ruolo della espansione clonale delle cellule endoteliali nella formazione delle malformazioni vascolari cavernose

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Le malformazioni vascolari cavernose del cervello (CCM) costituiscono una malattia neurovascolare rara di origine familiare che causa molteplici problemi neurologici agli individui affetti. La patologia è caratterizzata da mutazioni inattivanti uno dei tre geni che codificano le proteine del complesso CCM (CCM1, CCM2 or CCM3). Durante la nostra ricerca abbiamo osservato che, inattivando anche uno solo dei tre geni CCM nei topi, si riproduceva in maniera fedele la malattia. Abbiamo anche documentato che le cellule endoteliali che formano I cavernomi sono diverse dalle cellule dei vasi normali. Infatti, acquisiscono caratteristiche simili ai fibroblasti e crescono in maniera clonale incontrollata. Durante la loro proliferazione attraggono cellule endoteliali normali che proliferando contribuiscono all'evolversi della patologia. Questi risultati sperimentali aprono nuove prospettive per la cura farmacologica dei CCM.

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