

Abstract

Modelling COL4A1/2 SVD Associated Mutations—Towards New Treatment [†]

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Cerebral small vessel disease (SVD) is a leading cause of stroke and vascular dementia, yet its underlying mechanisms remain incompletely understood [1–3].

In particular, how mutations in collagen IV genes (COL4A1/A2) disrupt vascular structure and function is still being elucidated [4–7].

To address this, we developed a human in vitro model using induced pluripotent stem cells (iPSCs) derived from patients with COL4A1/A2 mutations [8]. These were differentiated into mural cells and endothelial cells, and co-cultured in a transwell setting to recreate a neurovascular environment.

We found that patient-derived mural cells exhibit significant abnormalities in extracellular matrix (ECM) organisation, increased apoptosis, and migration defects, along with transcriptomic changes [8,9]. When co-cultured with endothelial cells, these defective mural cells exacerbate endothelial dysfunction, leading to increased blood–brain barrier (BBB) permeability, a hallmark of SVD observed in patients [8]. This paracrine effect illustrates how mural cell pathology can directly compromise vascular integrity.

Importantly, we observed elevated matrix metalloproteinase (MMP) activity in the diseased state [8,10]. Treatment with MMP inhibitors led to partial restoration of the ECM structure, mural cell health, and significantly improved BBB integrity [11].

These findings not only recapitulate key features of the human disease but also provide a compelling case for MMPs as a therapeutic target in SVD, paving the way for future treatment strategies.

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