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Engineering biointerfaces to reveal collagen IV disease mechanisms

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Basement Membranes (BMs) are specialized extracellular matrix (ECM) structures underlying all endothelial and epithelial cells and provide structural support to tissues as well as influence cell behavior and signaling. Mutations in the BMs major component collagen IV can cause eye and kidney defects and cerebrovascular disease including intracerebral hemorrhages (ICH). Hemorrhagic stroke accounts for 15% adult stroke and 50% pediatric stroke, carries the worst prognosis and there are no therapeutic strategies. Mutations in the genes COL4A1/COL4A2 cause BM defects due to mutant protein incorporation or its absence by ER retention and ER-stress due to intracellular retention of collagen IV. While ER-retention of collagen IV and ER-stress are associated with hemorrhagic stroke caused by a COL4A2 mutation, the mechanism(s) of collagen IV mutations disease remain poorly characterized. To provide novel insights into collagen diseases mechanisms, this study aimed to investigate the effect of defined engineered biointerfaces on cell behavior/signaling and collagen folding, secretion and degradation in COL4A2 mutant and wild-type cells. To achieve this, a high-resolution microscopy AFM was employed, biochemical analysis of COL4A2$^{+/G702D}$ cells cultured on synthetic polymers coated with ECM proteins, namely laminin, fibronectin and collagen IV. This has enabled to address the hypothesis that biomaterials can alter collagen mutant cells behavior by overcoming some of the defects caused and rescuing downstream effect of ER stress. Results show that mutant cells' behavior is influenced by the polymer biomaterials, allowing cells to secrete more ECMs. Thus, this provides an unmet opportunity to use biomaterials to influence cells behavior. Collectively, these data provide a beginning to our understanding of how these mutations affect cell function/behavior and also increase our knowledge of the disease mechanisms. The data can in the long term be used to the development of new therapeutic approaches for ICH and pathologies due to collagen IV mutations.

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