MIMICKING THE EXTRACELLULAR MATRIX – A BIOMATERIALS APPROACH TO INHIBIT TISSUE FIBROSIS

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Epithelial tissue is marked by the presence of a specialized, highly cross-linked, sheet-like extracellular matrix, the basement membrane. Tissue-invasive events, such as the epithelial-to-mesenchymal transition (EMT) - a key event in gastrulation, tissue fibrosis and cancer metastasis – are characterized by irreversible structural changes of the basement membrane through proteolytic processing by matrix metalloproteinases (MMPs). We have recently reported a previously unidentified laminin fragment that is released during EMT by MMP2 and that modulates key EMT-signalling pathways. Specifically, interaction of the laminin fragment with α3β1-integrin triggers the down-regulation of MMP2 expression, thereby constituting a cell-basement membrane-cell feedback mechanism. Inhibiting MMPs has been proposed as a strategy to prevent pathological cell migration and basement membrane breakdown in the course of EMT. Here, we explore this cell-matrix-cell feedback mechanism to target pathological EMT in the course of tissue fibrosis. We present an electrospun biomaterial that is functionalized with the recombinant laminin fragment and that can be directly interfaced with epithelial tissue to interfere with EMT pathways and inhibit MMP2 expression and activity in vitro and in vivo. We demonstrate how interaction of the functionalized synthetic membrane with peritoneal tissue inhibits mesothelial EMT in a mouse model of TGFβ-induced peritoneal fibrosis by decreasing active MMP2 levels, and propose a mechanism of how the laminin fragment acts downstream of α3β1-integrin in epithelial cells, after it is released from the basement membrane.