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Meckel-Gruber syndrome patient cells exhibit alterations in cell-substrate interaction, deformation response, and gene expression consistent with defects leading to liver fibrosis

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Objective

Meckel-Gruber syndrome (MKS) is a lethal ciliopathy characterised by CNS malformations, cystic kidneys, polydactyly, and liver fibrosis. Most of these can be explained by disruption of cilium-dependent signalling pathways. However, the aetiology of liver fibrosis is less well-understood. We hypothesised that alterations in cell-substrate interaction, ECM organisation, dysregulated secretion and ECM organisation are upstream of fibrosis in MKS.

Methods

We used a combination of imaging, biophysics and RNA-Seq expression analysis to study alterations in cell adhesion and matrix composition in neonatal fibroblasts isolated from patients with mutations in *MKS2* (TMEM216) or *MKS3* (TMEM67), alongside age-matched controls.

Results

We found that MKS cells exhibit striking differences in spreading morphology on ECM substrates in comparison to controls. While *MKS2* cells spread faster than controls on all substrates examined, *MKS3* cells showed a substrate-specific increase in spreading on collagen IV. We also observed differences in the morphology and distribution of focal adhesions, which appeared more mature and pervasive. Of the ~3000 genes with altered expression levels in *MKS* cells, those associated with ECM components as well as fibrosis-implicated upstream effectors of ECM organisation and cell-substrate signalling were highly over-represented. These differences were consistent with those reported in other studies of liver fibrosis. Finally, MKS cells were less resistant to deformation and fragmentation under externally applied pressure.

Conclusions

We propose that a combination of defective regulatory signalling and excess ECM deposition, together with changes to cortical integrity and/or plasma membrane tension may contribute to the fibrotic pathology observed in patients.

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