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EGF/STAT1-maintained ECM1 expression in hepatic homeostasis is disrupted by IFNγ/NRF2 in chronic liver diseases

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In healthy liver, L-TGF-β is stored in the extracellular matrix and stabilized in an inactive form by ECM1. Upon damage, ECM1 production is downregulated, especially in hepatocytes, leading to spontaneous L-TGF-β activation and fibrogenesis. I used *in silico* promoter analyses, performed *in vitro* studies in mouse/human hepatocytes and *in vivo* experiments with different mouse models, to mechanistically delineate maintenance versus downregulation of ECM1 expression under physiological and pathological conditions. I could identify the crosstalk of signaling pathways that maintain or inhibit ECM1 expression.
In my thesis, I found that:
(1) In healthy liver, EGF and HGF are mediators of ECM1 expression maintenance. Thereby, EGF signals via EGFR/p-STAT1 S727 to the *Ecm1* promoter. The HGF signal as well integrates at STAT1 signaling.
(2) Upon liver damage and injuries:
I. Inflammation-accumulated hepatic IFNγ interferes with EGF signaling through downregulating EGFR.
II. In addition, IFNγ induces STAT1 phosphorylation at Y701, which interferes with binding of p-STAT1 S727 to the *Ecm1* gene promoter.
I and II together result in a decreased ECM1 expression.
III. Further, IFNγ promotes NRF2 nuclear translocation, which binds to the *Ecm1* gene promoter and negatively regulates its transcription, leading to inhibition of ECM1 expression.
Taken together, the EGF/EGFR/p-STAT1 S727 pathway that maintains ECM1 expression homeostasis in healthy hepatocytes is disrupted and inhibited by inflammation-accumulated IFNγ and its effects in stressed hepatocytes with the consequence of L-TGF-β activation and hepatic fibrosis.
In conclusion, my findings delineate the regulation of ECM1 expression in hepatocytes, which has potential for therapeutic manipulation of its expression with impact on TGF-β availability to treat chronic liver diseases.