From cirrhosis to cancer: α-SMA+ CAF and CD68+ macrophage rewiring in the cirrhosis–HCC transition

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Abstract

Introduction and aims: Hepatocellular carcinoma (HCC), the third leading cause of cancer-related mortality worldwide, often arises in the context of cirrhosis. This study investigates the spatial dynamics and functional contributions of hepatic stellate cells (HSCs/CAFs), macrophages (Mph/TAMs), and hepatocytes across distinct regions—distant cirrhosis (C), cirrhosis at the tumor margin (CT), and intratumoral tissue (T)—to elucidate mechanisms driving hepatocarcinogenesis.

Method: Using GeoMx Digital Spatial Profiling (DSP) on FFPE tissues from 8 patients with cirrhosis-based HCC, 350 regions of interest were profiled with a multiplexed antibody panel (α-SMA, CD68, CK8/18) and oligo-conjugated probes.

Results: Spatial transcriptomics revealed consistent upregulation of extracellular matrix (ECM)-related genes including COL1A1, COL1A2, FN1, and TIMP1 in HSCs/CAFs within tumor regions, suggesting a role in tumor progression. Deconvolution analysis identified a phenotypic shift from cytokine-producing to myofibroblastic HSCs (cyHSC → myHSC) from CT to T, correlating with tumorigenic transformation. Ligand-receptor analysis indicated that HSC-derived COL1A1 and FN1 interact with upregulated integrins (ITGA2, ITGA5, ITGAV) on hepatocytes, a finding validated by immunofluorescence. In vitro, FN1 and COL1 enhanced HepaRG hepatocyte adhesion, proliferation, and migration. RNA-seq of FN1-exposed HepaRG cells showed elevated TGFβ1 and MMPs (MMP1, MMP10), indicating a pro-tumorigenic transcriptional program. Co-culture with LX-2 cell supernatant induced proliferation (PCNA, Ki67) and epithelial-mesenchymal transition (EMT) markers (vimentin, N-cadherin, decreased E-cadherin) alongside integrin receptor upregulation. For Mph/TAM populations, immunoglobulin genes (IGHG1-4, IGKC) were downregulated in tumor regions, with ongoing analyses focused on subtype deconvolution and intercellular signaling. Future directions include the stimulation of HSCs/CAFs with TGFβ or GAS6, followed by ECM decellularization to assess hepatocyte

transformation on reconstituted matrices. Additionally, ECM hydrogels derived from porcine liver will be engineered with tunable COL1/FN1 ratios for 3D hepatocyte culture to dissect ECM-driven tumorigenic mechanisms.

Conclusion: These findings highlight the pivotal role of ECM remodeling, HSC and macrophage reprogramming, and integrin-mediated signaling in HCC development, offering new insights into the cirrhosis-to-cancer transition.