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Summary

Desmoplasia in liver cancer: translating tumour microenvironment insights into clinical practice

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Cancer-associated fibroblasts and desmoplasia are active biological drivers in liver cancer, but no CAF-targeting or extracellular matrix-targeting therapies have been approved, highlighting the need for precision approaches that combine stromal modulation with immunotherapy rather than indiscriminate stromal depletion.

KEY POINTS

- Hepatic stellate cells were identified as the main source of cancer-associated fibroblasts in liver tumors, with different patterns in hepatocellular carcinoma (fibrosis mainly around tumors, 90% developing in cirrhotic liver) versus intrahepatic cholangiocarcinoma (fibrosis accumulating inside tumors).
- The speaker reported that bulk stromal ablation can accelerate disease, citing a suspended pancreatic cancer trial using pegylated hyaluronidase (peg pH 20) that caused deleterious inflammatory effects, demonstrating desmoplasia is an active biological driver requiring careful targeting strategies.
- Higher myofibroblastic signature in intrahepatic cholangiocarcinoma was associated with worse patient survival, and the same mediator can act differently in different liver tumor contexts (the speaker stated HGF restrains hepatocellular carcinoma but promotes intrahepatic cholangiocarcinoma).
- No FDA or EMA approved therapies target cancer-associated fibroblasts or extracellular matrix in liver cancer, with very few ongoing clinical trials (mainly targeting TGF-beta axis and FAP), and TGF-beta inhibition failed in prior clinical trials despite reducing hepatic stellate cell activation.

- The speaker emphasized that stromal depletion without immune context fails and recommended pairing stromal modulation with immune checkpoint and chemo-immunotherapy strategies, noting that targeting tumors rewires the entire ecosystem as demonstrated in preclinical KRAS inhibitor studies showing tumor microenvironment re-adaptation with reduced myeloid cells and increased CD8 T cells.
- In the discussion, the speaker expressed concern that no preclinical study has perturbed FAP specifically in cancer-associated fibroblasts despite ongoing FAP-targeting clinical trials, and advocated for precision medicine approaches though acknowledged the difficulty of obtaining patient samples to stratify responders.

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