

resistance of cancer cells to otherapy. A bi-directional activation between cancer cells and fibroblasts causes the formation of the malignant phenotype of cancer. Cancer cells induce the production of MMPs by fibroblasts, which results in degradation of the ECM and enhances the invasiveness of cancer cells. In return, fibroblasts secrete GFs such as; MGF, keratinocyte GF, and IGF- $\frac{1}{2}$, which stimulate the proliferation of cancer cells. Cancer cells produce PDGF, which induces fibroblast proliferation and the expression of IGF- $\frac{1}{2}$. IGFs secreted by fibroblasts in turn induce cancer cell proliferation and the synthesis of PDGF. these signalling pathways cat in positive feedback loops. One approach to anti-cancer therapy is the inhibition of the feedback loop between fibroblasts and cancer cells, through inhibitor if fibroblast directly and disruption of CAF associated paracrine GF signals. Cancer cells may alter the adjacent stroma ro create a microenvironment that permits and supports tumor growth. Morphological evidence describes it as an desmoplastic reaction involving many cell types including CAFs. CAFs are not susceptible to apoptosis CAFs are elongated mesenchymal cells positive for alpha smooth muscle actin (alpha-SMA), fibroblast activation protein (FAP), Thy-1 desmin and the S104 positive fibroblasts that surround ducts, glandular structures and aggregates of neoplastic cholangiocytes. Patients who have a desmoplastic reaction rich in CAFs have a significantly lower overall survival and a worse disease free survival than patients with ICC with lower levels of alpha=SMA positivity.

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