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Antibody against CD44s inhibits pancreatic tumor initiation and post-radiation recurrence in mice

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CD44s is a surface marker of tumor-initiating cells (TICs); high tumor levels correlate with metastasis and recurrence, as well as poor outcomes of patients. Monoclonal antibodies against CD44s might eliminate TICs with minimal toxicity. This strategy is unclear for treatment of pancreatic cancer, and little is known about how anti-CD44s affect pancreatic cancer initiation or recurrence after radiotherapy. We measured CD44s levels in tissue samples and pancreatic cancer cell lines by immunohistochemistry, real-time PCR and immunoblot; levels were correlated with patient survival times. We studied the effects of anti-CD44s in mice with human pancreatic tumor xenografts, and used flow cytometry to determine effects on TICs. Changes in CD44s signaling were examined by real-time PCR, immunoblot, reporter assay, and *in vitro* tumorsphere formation assays. The levels of CD44s were significantly higher in pancreatic cancer than adjacent non-tumor tissues. Patients whose tumors expressed high levels of CD44s had a median survival of 10 months, compared to 43 months for those with low levels. Anti-CD44s reduced growth, metastasis, and post-radiation recurrence of pancreatic xenograft tumors in mice. The antibody reduced the number of TICs in cultured pancreatic cancer cells and in xenograft tumors, as well as their tumorigenicity. In cultured pancreatic cancer cell lines, anti-CD44s downregulated the stem cell self-renewal genes *Nanog*, *Sox-2*, and *Rex-1* and inhibited STAT3-mediated cell proliferation and survival signaling. The TIC marker CD44s is upregulated in human pancreatic tumors and associated with patient survival time. CD44s is required for initiation, growth, metastasis, and post-radiation recurrence of xenograft tumors in mice. Anti-CD44s eliminated bulk tumor cells as well as TICs from the tumors. Strategies to target CD44s might be developed to block pancreatic tumor formation and post-radiotherapy recurrence in patients.

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