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PANCREATIC CANCER

# Pancreatic tumour formation and recurrence after radiotherapy are blocked by targeting CD44

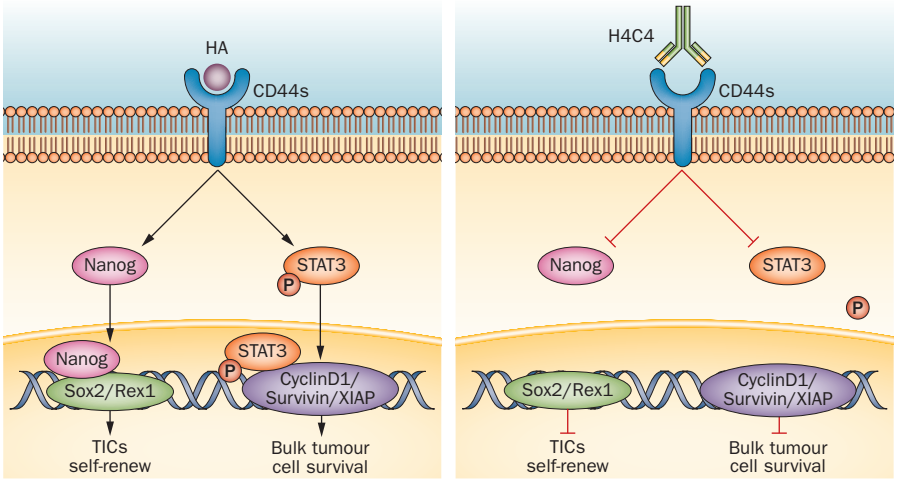
Targeting the standard isoform of cell-surface receptor CD44 (CD44s) may have potential as a strategy for blocking the formation and post-radiotherapy recurrence of pancreatic tumours.

CD44 is a receptor for hyaluronic acid (HA) and has a role in cellular processes, such as cell survival, differentiation, proliferation, adhesion, migration and chemoresistance. CD44 is upregulated in several cancers, including pancreatic cancer, and CD44s is a marker for tumour initiating cells (TICs, cancer stem cells), which are involved in resistance to radiation and post-radiotherapy tumour recurrence. Signalling downstream of CD44s is known to regulate TICs. Liang Xu and colleagues therefore examined whether targeting CD44s could inhibit the ability of TICs to promote pancreatic tumour recurrence and resistance to radiation.

The researchers first measured CD44s levels in human pancreatic cancer cell lines and in tumorous and adjacent non-tumorous tissue samples from patients with pancreatic adenocarcinoma who were undergoing surgery (36 pairs of fresh tissue samples plus 156 paired microarray specimens). CD44s expression was upregulated in pancreatic adenocarcinoma. Analysing survival data from 66 patients indicated a correlation between CD44s levels and overall survival.

For the rest of the study, the team worked with two pancreatic cancer cell lines—PANC-1 and MIA PaCa-2—and the human pancreatic primary tumour early passage xenograft J-2. They found that, compared with nIgG control, mouse anti-CD44 monoclonal antibody H4C4 decreased pancreatic cancer cell growth and invasion *in vitro* in a dose-dependent and time-dependent manner.

Mice were transplanted with the human pancreatic cancer cells and H4C4 or nIgG injected intravenously the next day and then 2–3 times per week for 2–10 weeks.




H4C4 is proposed to inhibit bulk tumour cell survival and TICs by regulating the STAT3 and Nanog signalling pathways downstream of CD44, which is a major receptor for HA and other extracellular components. Permission obtained from AGA Institue/Elsevier Ltd © doi:10.1053/j.gastro.2013.12.035.

"To study post-radiation recurrence, the human tumor xenografts were first irradiated with a full course of X-ray radiation to eradicate the bulk tumour cells, while only the TICs remained in the residual scars. Then the mice were randomized and treated with either H4C4 or nIgG," explains Xu.

H4C4 reduced the growth, metastasis and post-radiation recurrence of the pancreatic xenograft tumours and was found to reduce the number and tumorigenicity of TICs. Further work revealed targeting CD44 eliminated TICs by inhibiting Nanog signalling and that it inhibited STAT3-mediated cell proliferation and survival.

"This paper provides further evidence of the importance of CD44 cells in determining response of pancreatic cancer to therapy," confirms Bill Greenhalf of Royal Liverpool University Hospital, UK. Although he is also reassured by validation of H4C4's mode of action, via Nanog and STAT3 signalling, he cautions on several points. "The *in vitro* study cannot answer the very real concerns regarding the toxicity of CD44 targeting on normal stem cell populations. H4C4 targets human CD44 and the tumour cells it is targeting are human cells on a mouse background. In the absence of randomization to treatment in the clinical study we cannot be sure how much of the effect seen was due to treatment and we cannot be absolutely certain that some unknown bias was not responsible for the effect seen."

Greenhalf also believes the findings support clinical trials targeting CD44 in combination with other therapies. "This would probably best be carried out for pancreatic cancer in an adjuvant setting, providing tissue samples that could be analysed for CD44 and other markers of TICs. Meanwhile, CD44 staining should be analysed in resected samples from patients properly randomized in clinical trials," he concludes. Xu and colleagues are now studying the humanized anti-CD44 antibody, and are, indeed, planning future clinical trials.

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