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CANCER STEM CELLS

# Underground movement

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Patients diagnosed with pancreatic cancer have a high mortality rate, and few (1–4%) are alive after 5 years. There are many reasons for this dismal outcome, including the difficulty of early diagnosis, resistance to chemotherapy and significant metastatic burden. Christopher Heeschen and colleagues have investigated whether cancer stem cells are important for the aggressive nature of this disease.

CD133 seems to be a marker favoured by tumour cells that have stem-cell-like qualities, and pancreatic cancer appears to be no exception. Examination of tumour samples from patients showed that only a few cells in the bulk of the tumour were positive for CD133. Interestingly, scattered $CD133^+$ cells were also evident at the invasive front of the tumour. Do $CD133^+$ cells from pancreatic tumours have cancer stem-cell-like properties? The authors showed that $CD133^+$ but not $CD133^-$ cells were capable of forming tumours in athymic mice, and that only $CD133^+$ cells reproduce a histologically identical tumour in serial transplant assays.

In order to investigate the properties of these cells further, the authors turned to human pancreatic cancer cell lines and established that these also have $CD133^+$ cells with the same cancer stem-cell-like qualities. These cells were grown *in vitro* in conditions that favour the formation of sphere-like aggregates that are associated with the growth of cancer stem-cell-like cells from other tumour types. The authors used these cells to show that the $CD133^+$ cells could differentiate in culture to produce the major cell type that makes up the bulk of pancreatic tumours (cytokeratin-positive cells). Moreover, they also showed that $CD133^+$ cells are resistant to gemcitabine treatment, a frontline drug used to treat pancreatic cancer.

But what of the $CD133^+$ cells at the invasive edge of the tumour — do these have the same properties as those in the bulk of the tumour? Peripheral $CD133^+$ cells express the chemokine receptor CXCR4, which binds the chemokine CXCL12 and is associated with tumour metastasis. Orthotopic transplantation of mice with either $CD133^+;CXCR4^-$ and $CD133^+;CXCR4^+$ cells or with only $CD133^+;CXCR4^-$ cells showed that the $CXCR4^+$ population were associated with metastatic growth. Indeed, treatment of mice with the CXCR4 inhibitor AMD3100 significantly reduced the incidence of metastases. Examination of human pancreatic tumours showed that tumours with increased numbers of $CD133^+;CXCR4^+$ cells were associated with a more advanced metastatic disease.

From these results the authors conclude that there might be two populations of pancreatic cancer stem-cell-like cells: $CD133^+$ cells that maintain the growth of the primary tumour and migratory $CD133^+;CXCR4^+$ cells that produce metastatic growth. They also suggest that targeting the CXCR4–CXCL12 receptor–ligand interaction might be therapeutically valid.

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**ORIGINAL RESEARCH PAPER** Hermann, P. C. *et al.* Distinct populations of cancer stem cells determine tumour growth and metastatic activity in human pancreatic cancer. *Cell Stem Cell* **1**, 313–323 (2007)