CANCER

# Targeting IL-17 in pancreatic cancer

Like many solid cancers, pancreatic intraepithelial neoplasia (PanIN) is characterized by a strong stromal response in which increased numbers of immune and mesenchymal cells are found in the tissue surrounding the tumour, and it is accelerated by chronic inflammation (pancreatitis). However, the underlying mechanisms are not well understood. In a recent paper in *Cancer Cell*, McAllister and colleagues show that the pro-inflammatory cytokine interleukin-17 (IL-17), probably originating from infiltrating immune cells, drives the progression of PanIN, and that chronic pancreatitis could contribute to tumour formation through the increased production of IL-17.

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KRAS mutations are found in over 90% of pancreatic cancers, and mice expressing an inducible form of activated KRAS ($KRAS^{G12D}$) in pancreatic epithelial cells develop PanIN-like lesions. In this paper, the authors showed that $KRAS^{G12D}$ expression promotes the infiltration of IL-17-expressing T cells, and that this effect is augmented by chemically induced pancreatitis. Depletion of $CD4^+$ T cells from mice with both $KRAS^{G12D}$ expression and chemically induced pancreatitis (KP mice) delayed the development of PanIN without altering the overall stromal response.

To specifically address the role of IL-17, it was overexpressed in the pancreas of mice using an adenoviral vector. This substantially exacerbated stromal expansion and the formation of PanIN lesions driven by $KRAS^{G12D}$, even in the absence of chemically induced pancreatitis, further indicating that IL-17-producing T cells recruited to the pancreas are important in driving PanIN progression.

Consistent with the proposed role of IL-17, $KRAS^{G12D}$ mice in which the T cell population was first eliminated by a lethal dose of irradiation and then reconstituted using bone marrow from *Il17a*$^{-/-}$ mice had fewer pre-neoplastic and overt PanIN lesions than mice reconstituted with wild-type bone marrow. In this model, the pancreatic inflammation caused by irradiation functionally replaced chemically induced inflammation.

Expression of $KRAS^{G12D}$ also increased the levels of IL-17 receptor found on the surface of pancreatic epithelial cells in a cell-autonomous manner. The expression of IL-17-induced genes was correspondingly upregulated in PanIN cells from KP mice. Some of these genes, such as mucin 5AC (*Muc5ac*) and *Il6*, have previously been associated with pancreatic tumour progression. These data suggest that the tumorigenic activity of IL-17 could be mediated, at least in part, by the activation of IL-17 receptors on pancreatic epithelial cells.

The authors therefore investigated whether interrupting IL-17 signalling could have therapeutic value. Treatment of KP mice with a cocktail of antibodies, some of which targeted IL-17 and some of which targeted the IL-17 receptor, reduced the pancreatic surface area occupied by PanINs, particularly by advanced forms of the disease.

Overall, these data support a role for IL-17 in the formation and progression of PanIN. Antibodies targeting IL-17 or the IL-17 receptor are currently being evaluated in clinical trials for the treatment of autoimmune diseases such as psoriasis and rheumatoid arthritis, and this study suggests that such antibodies could also have the potential to prevent PanIN and possibly other cancers as well.

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**ORIGINAL RESEARCH PAPER** McAllister, F. *et al.* Oncogenic Kras activates a hematopoietic-to-epithelial IL-17 signaling axis in preinvasive pancreatic neoplasia. *Cancer Cell* **25**, 621–637 (2014)
**FURTHER READING** Miossec, P. & Kolls, J. K. Targeting IL-17 and $T_H17$ cells in chronic inflammation. *Nature Rev. Drug Discov.* **11**, 763–776 (2012)