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MICROENVIRONMENT

Suppressing the rejection of pancreatic tumours

The immune system is often co-opted by developing tumours to promote an immunosuppressive microenvironment that prevents rejection. This is particularly evident for pancreatic ductal adenocarcinoma (PDA), which initially develops as pancreatic intraepithelial neoplasia (PanIN; a premalignant lesion) and is associated with the infiltration of immunosuppressive leukocytes. Two papers in *Cancer Cell* now characterize a mechanism of immunosuppression in pancreatic tumorigenesis.

To investigate immunomodulation in PDA development, Bayne and colleagues used KPC genetically engineered mice, which have pancreas-specific *Kras*^{G12D} and *Trp53*^{R172H} mutations. Pylayeva-Gupta and colleagues used an allograft model in which green fluorescent protein (GFP)$^+$ pancreatic ductal epithelial cells (PDECs) expressing KRAS-G12D were injected into the pancreata of syngeneic mice. Both mouse models developed PanINs and PDAs with features of the human disease, particularly the infiltration of myeloid-derived suppressor cells (MDSCs). MDSCs (which are GR1$^+$CD11b$^+$) seem to be immature myeloid cells with similarities to macrophages, dendritic cells and granulocytes and are thought to suppress T cell-mediated antitumour immune responses. Bayne and colleagues found that MDSCs derived from KPC mice suppressed T cell proliferation and the production of interferon-γ *in vitro*. These authors noted that KPC mice developed splenomegaly as MDSCs and their KIT$^+$ precursors accumulated in the spleen, indicating that a tumour-derived factor might promote the development of MDSCs. Indeed, they found that culturing KIT$^+$ splenocytes isolated from tumour-bearing KPC mice with conditioned media from PDA cells promoted their proliferation and the expression of GR1 and CD11b; these cells suppressed T cell proliferation *in vitro*.

Based on the splenomegaly and the recruitment of MDSCs to PanINs and PDAs, both groups looked for a tumour cell-derived secreted factor that could be responsible. Analyses of supernatants from allograft tumour tissue and from the culture of a panel of pancreatic tumour cell lines showed that granulocyte–macrophage colony-stimulating factor (GM-CSF) was consistently highly expressed. Tumour cells in human PanIN and PDA samples also expressed GM-CSF, but Pylayeva-Gupta and colleagues found that other types of pancreatic lesion that are not associated with oncogenic KRAS did not. Transcripts of *Csf2* (which encodes GM-CSF) were also increased in GFP$^+$ KRAS-G12D PDECs, indicating that KRAS-G12D causes the upregulation of GM-CSF expression. This cytokine induced the proliferation and differentiation into MDSCs of bone marrow-derived haematopoietic precursor cells isolated from the allograft mouse model, and of KIT$^+$ splenocytes from KPC mice.

Does GM-CSF secretion by pancreatic tumour cells promote an immunosuppressive microenvironment *in vivo*? Bayne and colleagues implanted GM-CSF-suppressed PDA1 cells into wild-type mice and found that the cells failed to grow and that the implant sites appeared necrotic. Moreover, the number of infiltrating CD45$^+$GR1$^+$CD11b$^+$ cells at these sites was substantially decreased compared with sites of control PDA1 cell implantation; depletion of GR1$^+$CD11b$^+$ cells also inhibited the growth of PDA1 cells *in vivo*. Pylayeva-Gupta and colleagues knocked down GM-CSF expression in GFP$^+$ KRAS-G12D PDECs, which reduced their engraftment and specifically decreased the infiltration of GR1$^+$CD11b$^+$ cells. These GFP$^+$ cells were absent from the graft sites 2 weeks after implantation (although the grafts were similar to controls 1 week after implantation). Moreover, the graft sites had infiltrates of CD8$^+$ T cells 2 weeks after implantation, but not after 1 week, indicating that GM-CSF-mediated recruitment of MDSCs probably occurs when T cells begin to infiltrate graft sites. Both groups then showed that implanting GM-CSF-suppressed PDA1 cells or GFP$^+$ KRAS-G12D PDECs into mice lacking CD8$^+$ T cells restored engraftment but did not rescue the infiltration of GR1$^+$CD11b$^+$ cells.

Together, these papers show that GR1$^+$CD11b$^+$ MDSCs are recruited by KRAS-G12D-transformed pancreatic tumour cells in the early stages of tumour development to suppress CD8$^+$ T cell-mediated antitumour immune responses and thereby allow tumour growth.

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ORIGINAL RESEARCH PAPERS Bayne, L. J. *et al.* Tumor-derived granulocyte-macrophage colony-stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. *Cancer Cell* **21**, 822–835 (2012) | Pylayeva-Gupta, Y. *et al.* Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia. *Cancer Cell* **21**, 836–847 (2012)

> “MDSCs are recruited by KRAS-G12D-transformed pancreatic tumour cells … to suppress CD8$^+$ T cell-mediated antitumour immune responses”