TUMOUR IMMUNOLOGY

TGFβ betrays immunity for tumorigenesis

The role of transforming growth factor-β (TGFβ) in interactions between the immune system and tumour cells is controversial, with various studies indicating that this cytokine can function as either a tumour suppressor or a tumour promoter depending on the context. Here, Yang *et al.* propose that the recruitment of immature myeloid cells to the tumour can determine the switch between an antitumorigenic and a pro-tumorigenic TGFβ-containing microenvironment.

Using a mouse model of breast carcinoma — in which mammary epithelial cells express the polyoma virus middle T antigen (PyVMT) under the control of the mouse mammary tumour virus promoter — Yang and colleagues confirmed earlier results that showed that deletion of the gene encoding the type II TGFβ receptor (*Tgfr2*) to abrogate TGFβ signalling resulted in increased pulmonary metastasis. In this case, TGFβ is, therefore, acting as a tumour suppressor.

The tumours of PyVMT-expressing *Tgfr2*-knockout mice contained a significantly higher number of Gr1⁺CD11b⁺ immature myeloid cells (also known as myeloid suppressor cells) than tumours from PyVMT-expressing control mice, and these Gr1⁺CD11b⁺ cells were found mainly at the invasive front of the tumours. To investigate the role of these Gr1⁺CD11b⁺ cells in tumorigenesis, Yang *et al.* co-injected Gr1⁺CD11b⁺ cells from tumour-bearing mice with

mouse mammary tumour cells into the mammary fat pad of BALB/c mice, and a significant increase was observed in lung metastasis compared with the injection of mouse mammary tumour cells alone or with Gr1⁺CD11b⁺ cells from normal spleens. In both *in vitro* and *in vivo* invasion assays, the addition of Gr1⁺CD11b⁺ cells from tumour-bearing mice increased the invasion of surrounding tissues by tumour cells, and this promotion of tumour metastasis was shown to be through the production of matrix metalloproteinases (MMPs).

The increased recruitment of Gr1⁺CD11b⁺ cells to tumours with *Tgfr2* deletion was shown to result from an increased production of CXC-chemokine ligand 5 (CXCL5) by the tumour cells. Blocking the interaction between CXCL5 and CXC-chemokine receptor 2 (CXCR2) on Gr1⁺CD11b⁺ cells inhibited their recruitment both *in vitro* and *in vivo*. Also, tumour-infiltrating Gr1⁺CD11b⁺ cells expressed higher levels of CXCR4 than splenic Gr1⁺CD11b⁺ cells from tumour-bearing mice, and Gr1⁺CD11b⁺ cells isolated from tumour tissues migrated in response to the CXCR4 ligand CXCL12 *in vitro*.

Surprisingly, the mammary carcinomas with *Tgfr2* deletion contained significantly higher levels of TGFβ1 than control PyVMT tumours, which the authors suggest is the result of the increased infiltration of Gr1⁺CD11b⁺ cells. Gr1⁺CD11b⁺ cells from the spleens of tumour-

bearing mice were shown to produce more TGFβ1 than Gr1⁺CD11b⁺ cells from the spleens of normal mice.

The authors therefore propose a model in which autologous TGFβ signalling by mammary epithelial cells is tumour suppressive. Defective TGFβ signalling in tumour cells allows the recruitment of Gr1⁺CD11b⁺ cells to the tumour through the increased production of CXCL5 by transformed epithelial cells and the increased expression of CXCR4 by Gr1⁺CD11b⁺ cells. The recruited Gr1⁺CD11b⁺ cells then produce TGFβ1 and MMPs, thereby promoting tumour invasion and metastasis.

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ORIGINAL RESEARCH PAPER Yang, L. *et al.* Abrogation of TGFβ signalling in mammary carcinomas recruits Gr1⁺CD11b⁺ myeloid cells that promote metastasis. *Cancer Cell* **13**, 23–35 (2008)