TUMOUR MICROENVIRONMENT

Means of resistance

Resistance to cancer therapies that target vascular endothelial growth factor (VEGF) signalling is an important clinical problem, the mechanisms of which are poorly understood. A role for the tumour microenvironment in mediating resistance is increasingly being appreciated, so Chung, Ferrara and colleagues investigated how the tumour stroma might affect resistance to VEGF-targeted therapy.

Analysis of proteins secreted by lymphoma cell lines that were previously shown to be resistant (EL4 cells) or sensitive (TIB-6 cells) to antibodies that inhibit VEGF revealed a potential role for interleukin-17 (IL-17), which is produced *in vivo* by T helper 17 (T_H17) cells. This cytokine was abundantly expressed both *in vitro* by EL4 cells compared with TIB-6 cells, and in mice bearing EL4 tumours. The authors initially examined the role of IL-17 in resistance to VEGF antibodies in three different mouse models. In a syngeneic model, immunocompetent mice bearing EL4 tumours were treated with a monoclonal antibody against IL-17 and/or VEGF antibodies; combination therapy reduced tumour volume significantly more than treatment with either antibody alone. Second, genetic loss of the IL-17 receptor in the host (*Il17rc*$^{-/-}$ mice, which are defective in T_H17 effector function) improved the response of EL4 tumours to VEGF antibodies compared with wild-type mice. Third, enforced expression of IL-17 in TIB-6 cells reduced the sensitivity of these cells to VEGF antibodies when they were implanted into immunodeficient mice. These data suggest that IL-17 is both necessary and sufficient to induce resistance to anti-VEGF therapy.

What does IL-17 do in the tumour microenvironment? Serum levels of granulocyte-colony-stimulating factor (G-CSF) (an IL-17-inducible factor) were increased in wild-type EL4 tumour-bearing mice, but not in tumour-bearing *Il17rc*$^{-/-}$ mice. G-CSF regulates mobilization of several types of immune cells, and tumour-bearing wild-type mice had increased numbers of circulating and tumour-infiltrating $CD11b^+GR1^+$ immature myeloid cells compared with *Il17rc*$^{-/-}$ mice. Furthermore, EL4 tumours in mice lacking the G-CSF receptor had fewer infiltrating $CD11b^+GR1^+$ cells and an improved response to VEGF antibodies, indicating the importance of IL-17–G-CSF signalling and $CD11b^+GR1^+$ cells in mediating resistance to anti-VEGF therapy. IL-17 signalling also promoted both the effector functions of $CD11b^+GR1^+$ cells (including secretion of BV8 (also known as PROK2), a G-CSF-inducible angiogenic factor) and angiogenesis in a VEGF-independent manner.

The infiltration of T_H17 cells is associated with poor prognosis in human lung and colorectal cancers, so the authors examined mouse models of these tumour types. VEGF antibodies more effectively reduced tumour burden, recruitment of $CD11b^+GR1^+$ cells, and levels of G-CSF and BV8 in *Il17rc*$^{-/-}$ mice implanted with Lewis lung carcinoma (LLC) cells than in wild-type mice. In wild-type mice, combined treatment with IL-17 and VEGF antibodies significantly reduced LLC or CT-26 colorectal tumour burden compared with anti-VEGF alone.

In advanced human colorectal adenocarcinomas, the presence of IL-17-expresing T_H17 cells and BV8-expressing cells were significantly correlated, suggesting a role for this pathway in human tumours. It remains to be determined how generalizable these results are to other tumour types and whether this signalling axis can be exploited to improve anti-VEGF therapy.

Sarah Seton-Rogers

> “combined treatment with IL-17 and VEGF antibodies significantly reduced … tumour burden”

ORIGINAL RESEARCH PAPER Chung, A. S. *et al.* An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. *Nature Med.* http://dx.doi.org/10.1038/nm.3291 (2013)