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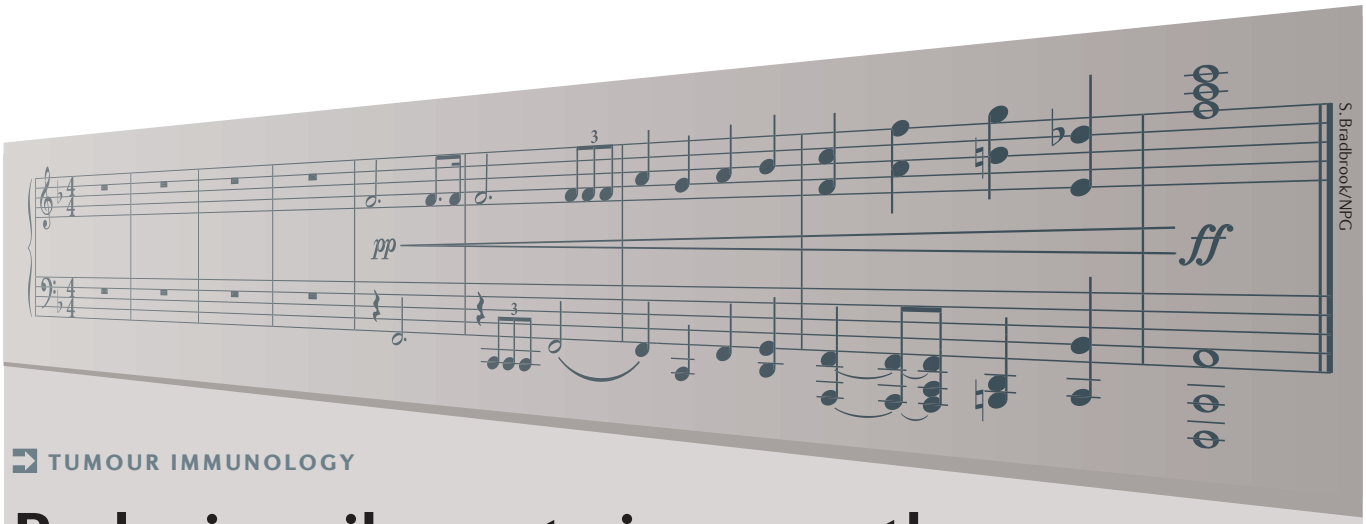

TUMOUR IMMUNOLOGY

Reducing silence to improve therapy

Tumours with a high number of inflammatory T cells are more responsive to immunotherapy with inhibitors of programmed cell death protein 1 (PD1) and its ligand PDL1, compared with tumours that have a low number of inflammatory T cells. Reporting in *Nature*, Peng *at al.* show how epigenetic gene-silencing mechanisms repress T helper 1 (T_H1)-type chemokine production in ovarian tumours; treatment with inhibitors of epigenetic modifiers reduced tumour volume, increased infiltration of effector T cells and improved the efficacy of PDL1 blockade therapy and T cell transfusion therapy in mice.

The authors hypothesized that immune-protective genes could be epigenetically silenced in cancer, which would affect cancer progression and response to immunotherapy. To test this, they used different inhibitors of epigenetic modifiers in mouse models bearing human primary ovarian cancer cells or mouse ovarian cancer cells. Treatment with a single agent had no effect, but treatment with an inhibitor of enhancer of zeste homologue 2 (EZH2) together with an inhibitor of DNA methyltransferase 1 (DNMT1) led to decreased tumour size, increased numbers of tumour-infiltrating T cells and augmented expression of the T_H1-type chemokines CXC-chemokine ligand 9 (CXCL9) and CXCL10. When this treatment was combined with anti-PDL1 and T cell transfusion, the effect was enhanced. Thus, epigenetic reprogramming increased tumour immunity, blocked cancer progression and improved the efficacy of PDL1 checkpoint blockade therapy and T cell therapy.

> “patients with low levels of the epigenetic modifiers had more tumour-associated $CD8^+$ T cells”

In a series of experiments, the authors showed that trimethylation of histone H3 at lysine 23 by EZH2 and DNA methylation by DNMT1 independently mediated the repression of T_H1-type chemokine production by ovarian tumour cells.

Finally, the authors investigated the clinical implications of their results. The nuclear levels of EZH2 and DNMT1 were determined by immunohistochemistry staining in human ovarian tissues and compared to patient survival data. The median intensity of staining for EZH2 and DNMT1 was used to divide patients into ‘low levels’ or ‘high levels’ of these epigenetic modifiers. Interestingly, the overall survival rates were lower and disease-free intervals were shorter in patients with high levels of EZH2 or DNMT1 compared with patients that have low levels of these molecules, and this effect was even more pronounced when the level of both enzymes was high. Furthermore, patients with low levels of the epigenetic modifiers had more tumour-associated $CD8^+$ T cells, which were associated with longer overall survival and disease-free intervals. Thus, epigenetic pathways in tumours seem to silence T_H1-type chemokine expression, repress T cell homing to tumours and determine why some tumours are T cell ‘inflamed’ and others are not.

To conclude, this study suggests that reprogramming of epigenetic pathways that are altered in tumours could be an efficient way to increase responsiveness to immunotherapy.

Elisabeth Kugelberg

ORIGINAL RESEARCH PAPER Peng, D. *et al.* Epigenetic silencing of T_H1-type chemokines shapes tumour immunity and immunotherapy. *Nature* http://dx.doi.org/10.1038/nature15520 (2015)

FURTHER READING Nguyen, L. T. & Ohashi, P. S. Clinical blockade of PD1 and LAG3 — potential mechanisms of action. *Nat. Rev. Immunol.* **15**, 45–56 (2015)

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