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IMMUNOTHERAPY

HEV: THE GATEWAY TO TUMOUR CONTROL?

New research has uncovered that regulatory T cells (T_{REG}), which suppress the responses of other immunological cells, might help cancers grow unchecked by blocking the formation of the blood vessels that traffic immune cells to the tumour site. These vessels, called high endothelial venules (HEV), are specialized for lymphocyte recruitment in secondary lymphoid tissue and might be the critical link in explaining why some tumours fail to respond to immunotherapy despite lymphocyte activation after T_{REG} cell depletion.

The researchers used transgenic DTR-Foxp3$^+$ mice (in which T_{REG} cells can be depleted) to study the immune response to cancer. Led by Awen Gallimore, they discovered that the extent of T-cell infiltration into the tumour—and not the level of T-cell proliferation—was crucial for tumour destruction. The tumours of mice that were replete with T_{REG} cells grew, whereas the growth of the tumours of T_{REG}-depleted mice was controlled. Immunohistochemical analysis of the tumours samples revealed the presence of HEV in tumours from T_{REG}-depleted mice, but not T_{REG}-replete mice, which strongly implicates these cells in the neogenesis of HEV. Furthermore, HEV-positive tumours showed significantly reduced growth rates than their HEV-negative counterparts ($P=0.0082$). The difference in growth can be attributed to the greater number of infiltrating CD8$^+$ T cells in HEV-positive tumours than HEV-negative tumours ($P=0.0034$).

"These findings reinforce the fundamental importance of giving T cells access to tumour tissue," explained Gallimore. Indeed, the role of HEV in promoting immune-mediated tumour control might be exploited clinically. For example, one can envisage implementing therapies that target and enhance HEV neogenesis given in conjunction with T_{REG}-depleting agents. To achieve these goals, however, the mechanisms of HEV neogenesis must first be elucidated. "Our focus now is on deciphering the signals that drive HEV development after T_{REG} depletion and to exploit this activity for the purpose of delivering large numbers of high-affinity, central memory T cells to the tumour mass," concluded Gallimore.

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Original article Hindley, J. P. *et al.* T cell trafficking facilitated by high endothelial venules is required for tumor control after regulatory T cell depletion. *Cancer Res.* doi:10.1158/0008-5472.CAN-12-1912