

Open sesame: The endothelin (B) receptor mediates the tumor endothelial barrier to T-cell homing

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Abstract

The success of immune therapy partly depends on the ability of effector cells to infiltrate tumors. The mechanisms governing homing of effector cells into tumors remain poorly understood. In particular, the role of tumor endothelium in tumor immunotherapy has not been investigated to date. Because of the clear dichotomy between presence or absence of intraepithelial TIL, we hypothesized that ovarian cancer is a suitable model to investigate the role of tumor endothelium in regulating T cell homing. Transcriptional profiling of microdissected tumor endothelial cells from human ovarian cancers revealed the molecular signature of endothelium associated with the absence of intraepithelial tumor-infiltrating lymphocytes (TIL). The endothelin B receptor (ET_BR) was associated with absence of TIL and short survival. ET_BR blockade by BQ-788 increased T cell adhesion to human endothelium, an effect countered by ICAM-1 blockade or NO donors *in vitro*. In the mouse, ETBR neutralization by BQ-788 enabled tumor response to immune therapy *in vivo*, including vaccine therapy and adoptive lymphocyte therapy. This was mediated by increased homing of effector T cells to tumors, without changes in systemic antitumor immune response, and was attenuated by ICAM-1 blockade. These findings provide a novel molecular mechanism that can be pharmacologically manipulated to enhance the efficacy of tumor immunotherapy in humans. Because ET_BR inhibitors are available for immediate clinical testing, our findings provide a new immediate therapeutic opportunity for cancer combinatorial therapy.