MECHANISMS OF POST-IMMUNOTHERAPY EFFICACY ENHANCEMENT BY TUMOR LYMPHANGIOGENESIS

Colleen Foley*, Lambert Potin, Trevin Kurtanic, Melody Swartz. University of Chicago, Chicago, IL, USA

Background Vascular endothelial growth factor-C (VEGF-C) expression and subsequent lymphangiogenesis in the tumor microenvironment are associated with metastasis and poor prognosis in melanoma and other solid tumors. We previously demonstrated that while elevated VEGF-C promotes a highly immunosuppressive tumor microenvironment (TME), it paradoxically renders immunotherapy more effective in mouse models and correlates with improved survival after checkpoint blockade therapy in patients, a phenomenon we termed lymphangiogenic potentiation.1 This potentiation correlated with VEGFC-driven differences in the TME prior to immunotherapy, including increased recruitment of naïve T cells and cross-presenting CD103+ DCs in VEGFC-overexpressing tumors, setting up the TME for local T cell activation.

Other than altering the TME, tumor lymphangiogenesis may alter the systemic immune response because of increased drainage of tumor-secreted factors, which may include both immunogenic and suppressive factors, to the tumor-draining lymph node (tdLN). Here, we asked whether and how these changes may contribute to the overall immune response as well as how the anti-tumor immune response can alter the TME in melanoma.

Methods We used a B16F10 tumor model transduced to either overexpress VEGFC (B16-VEGFC) or a control vector (B16-Control) together with two different models of immunotherapy: (i) adoptive T cell transfer and (ii) peptide vaccination using transferred naïve antigen-specific pmel CD8+ T cells for in vivo tracking after activation by gp100 peptide and CpG adjuvant.

Results We found that immunotherapy resulted in an increase targeted antigen-specific T cells in the B16-VEGFC vs. B16-Control tumors, including more proliferating effector cells as well as more central memory and T progenitor exhausted cells. We also found more bystander activation and proliferation of non-targeted, endogenous CD8 T cells. This was accompanied by an increase in CXCL9 in the TME of B16-VEGFC, which recruited more activated T cells from circulation. In the B16-VEGFC tdLN, we observed increased in CD103+ DC trafficking along with higher fractions of central memory T cells in both the CD4 and CD8 compartments.

Conclusions Together, these results highlight the multitude of ways that tumor lymphangiogenesis can prime anti-tumor immunity and alter not only the tumor microenvironment, but also the systemic immune response by shaping the immune microenvironment of the tumor draining lymph node. VEGFC tumors promote more prolonged immunity after immunotherapy by supporting T cell memory development and enhancing ongoing immune activation and recruitment through increased DC trafficking to the lymph node and increased recruitment of newly activated and circulating T cells.

REFERENCE


http://dx.doi.org/10.1136/jitc-2023-SITC2023.1209