HIGH ENDOTHELIAL VENULES CONTROL THE JOURNEY OF STEM-LIKE CD8+ T CELLS FROM LYMPH NODE TO TUMOR DURING CANCER IMMUNOTHERAPY WITH COMBINED ANTI-PD-1 PLUS ANTI-CTLA-4 ANTIBODIES

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Background Recent reports revealed that CD8+ T cell antitumor responses rely on a subset of stem-like CD8+ T cells during cancer immunity and immunotherapy. However, the origin of stem-like CD8+ T cells and the mechanisms controlling their trafficking are not well established. High endothelial venules (HEVs) are specialized blood vessels mediating lymphocyte trafficking in lymph nodes (LNs),1,2 and HEV-like blood vessels defined as tumor-associated HEVs (TA-HEVs) are important regulators of lymphocyte entry into tumors.3 Here, we investigated the role of LN-HEVs and TA-HEVs in the generation and migration of stem-like CD8+ T cells during spontaneous antitumor immunity and cancer immunotherapy.

Methods In mouse syngeneic tumor models, we applied multidisciplinary approaches (immunofluorescence, flow cytometry, short-term homing assays and in vivo imaging) to identify the adhesion pathways used by LN-HEVs and TA-HEVs for CD8+ T cell trafficking. Then, using in vivo function-blocking antibodies targeting LN-HEVs and/or TA-HEVs, we defined their respective roles in the recruitment of naive CD44+PD-1+CD8+ T cells into tumor-draining lymph node and of CD44+PD-1+CD8+ T cells into tumor. Lastly, we blocked the function of LN-HEVs and/or TA-HEVs during combined anti-PD-1 plus anti-CTLA-4 cancer immunotherapy to analyze their contributions in treatment-induced CD8+ T cell responses.

Results We found that naive and stem-like CD8+ T cells use distinct adhesion pathways to interact with LN-HEVs and TA-HEVs, respectively. Blocking naive CD8+ T cell adhesion to LN-HEVs and their subsequent entry into tumor-draining lymph node abrogated the generation of stem-like CD8+ T cells and prevented their accumulation in tumor, showing that peripheral and intratumoral responses are tightly related. In peripheral blood, circulating stem-like CD8+ T cells expressed adhesion molecules and chemokine receptors enabling interaction with TA-HEVs that mediated their entry into tumor. Finally, we found that checkpoint blockade therapy increased the number and activity of stem-like CD8+ T cells in tumor-draining lymph node and peripheral blood, suggesting that peripheral responses are involved during treatment. Accordingly, HEV-mediated trafficking in tumor, but also in tumor-draining lymph node, were required for expansion and differentiation of intratumoral stem-like CD8+ T cells during checkpoint blockade therapy.

Conclusions In this study, we unveil the dual role of HEVs in tumor and periphery for CD8+ T cell responses during cancer immunity and immunotherapy, and provide mechanistic insights on the importance of peripheral responses during checkpoint blockade therapy. Our findings also strongly support the use of combined anti-PD-1 plus anti-CTLA-4 cancer immunotherapy in the neoadjuvant setting.

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