HIGH ENDOTHELIAL VENULES (HEV): MAJOR GATEWAYS FOR ANTI-TUMOR CYTOTOXIC T CELLS AND NEW PARTNERS OF CANCER IMMUNOTHERAPY

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Blood vessels and tumor angiogenesis are generally associated with tumor growth and poor clinical outcome of cancer patients. However, we found that some blood vessels present within the tumor microenvironment can be associated with favorable prognosis by contributing to tumor suppression rather than tumor growth. These specialized blood vessels, designated high endothelial venules (HEVs), are normally found in lymph nodes where they mediate lymphocyte entry from the blood (Moussion and Girard, Nature 2011; Girard et al., Nature Rev Immunol 2012). A high density of tumor HEVs in human breast carcinomas was associated with high levels of cytotoxic lymphocyte infiltration, indicating that HEVs may participate in the eradication of tumors by facilitating access of ‘killer’ lymphocytes into tumor tissues. It is therefore important to better define the molecular mechanisms and cells involved in the regulation of HEVs as well as their potential role in the response to cancer immunotherapy.

To further characterize the role of tumor-associated HEVs (TA-HEVs), we used two distinct murine tumor models: one tumor is immunoedited, escapes the immune system and progress while the other tumor, is non-immunoedited and rapidly rejected. At d8 post-inoculation, the immunoedited tumor presents a HEV-low phenotype (3-5%) as compared to the non-immunoedited tumor, which develops up to 20% of TA-HEVs (HEV-hi). These TA-HEVs correlate with a better control of tumor growth and recruitment of T cells. Effector CD4⁺ T cells from HEV-low tumor, mostly Th1 cells, exhibit an “exhausted” phenotype with higher expression of PD-1 and Eomes, and few Ki67⁺ cells. Immunotherapy using α-CTLA-4 and α-PD-1 target these “exhausted” cells to render them more effective. Interestingly this increase of infiltrating activated T cells could be responsible for the significant increase in the percentage of TA-HEVs among total blood vessels that we observed. In the context of Immunotherapy, we visualized for the first time, by real time intravital microscopy, that T cells rolled and stucked almost exclusively within TA-HEVs.

Based on these findings, we conclude that TA-HEVs are major gateways for lymphocyte entry into tumors and that their induction could be critical for the efficacy of cancer immunotherapy.