Tumor-Associated High Endothelial Venules: Inroads Enabling Immune Control of Cancer Progression

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Infiltration of lymphocytes into solid tumors represents a significant bottleneck to successful control of tumor growth. The nature of tumor blood vessels is an important factor governing both quantitative and qualitative features of the immune infiltrate. In this issue, Sawada and colleagues identify a genetic signature for blood vessels, most notably high endothelial venules, which are associated with tertiary lymphoid structures and improved clinical outcome.

See related article by Sawada et al., p. 468 (4).

High-endothelial venules (HEV) are specialized blood vessels that are normally found only in secondary lymph organs. They serve to recruit L-selectin–expressing lymphocytes into the lymph node (LN) parenchyma where they encounter cognate antigen. Antigen stimulation drives expansion of HEV networks through proliferation of endothelial cells and the cooperative activities of vascular, stromal, and immune cells. These changes facilitate increased blood flow and lymphocyte trafficking to support development of adaptive immunity.

HEVs are present in human cancers where they are often associated with organized tertiary lymphoid structures (TLS) and/or a greater degree of lymphocytic infiltration. Many studies show that TLS are associated with longer survival and/or are predictive of favorable responses to immunotherapy (1). In mouse models, intratumoral HEVs can be induced in several ways including depletion of regulatory T cells, adoptive T-cell transfer, and delivery of anti–PD-L1 and anti-VEGFR2 (1, 2). Overall, these studies indicate that tumors successfully treated with immunotherapy contain HEVs (1, 2).

Key questions emerging from the above relate to the molecular identity and function of intratumoral HEVs. In this issue, Sawada and colleagues compare the transcriptomes of HEVs and non-HEVs in human breast cancer samples. HEVs and non-HEVs are distinguished using a monoclonal antibody, MECA-79, which binds to the sulfated, fucosylated glycoprotein, peripheral node addressin (PNAd); the principal marker of HEV. Laser-capture microdissection is used to isolate $PNAd^+$ and $PNAd^-$ endothelial cells from TLS-rich and TLS-free (no $PNAd^+$ cells) areas for gene expression analyses, which reveals a molecular signature identifying tumor HEVs. The authors focus on two upregulated genes, *TSPAN7* and *MEOX2*, which they find are expressed on almost all tumor HEVs and are associated with high T-cell and B-cell infiltration and improved survival. *TSPAN7*, which encodes tetraspanin 7, is compatible with the tumor HEVs having a role in extravasation of lymphocytes. *MEOX2* encodes for a negative regulator of angiogenic activity. Previous work in mice indicates that vascular normalization using anti-VEGFR2 promotes HEV formation, thus suggesting that HEV development is dependent on repression of angiogenesis. Several other potentially interesting genes that could hold clues to understanding tumor HEV function as well as how they are formed and maintained are also uncovered in the study.

Early studies drew on the LN paradigm of HEV function to explain the role of tumor-associated HEVs. However, it is becoming increasingly clear that whilst tumor and LN HEVs share many features, there are disparities, which have been revealed by differential PNAd staining as well as gene-expression profiling of tumor and LN HEVs. This is not surprising given a recent study that highlighted significant HEV heterogeneity even within LN (3), specifically indicating that HEVs exist in different functional states depending on the activation status of the LN. An interesting finding of the study by Sawada and colleagues is that there is an overlap between $PNAd^+$ and $PNAd^-$ vessels isolated from TLS-rich areas of the tumor, characterized by $TSPAN^{hi}PNAd^-$ vessels. It is possible that these vessels also contribute to the pool of tumor-infiltrating lymphocytes and a successful immune response.

Overall, this study provides a molecular signature of tumor vessels that may be useful for interrogating cancer data sets and for generating new hypotheses aimed at identifying the critical features of HEVs or HEV-like vessels that can facilitate robust antitumor immune responses. Such information will help identify routes for inducing useful vessels to enhance the efficacy of current and novel immunotherapies.

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