Therapeutic implication for regulation of immune cells via tumor vessels

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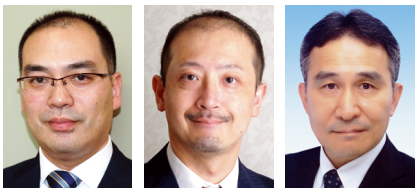


Abstract

Tumor blood vessels in the tumor microenvironment play important roles in solid tumor progression. The characteristics and functions of tumor endothelial cells (TEC) in tumor blood vessels are different from those of normal endothelial cells (NEC). Indeed, compared with NECs, TECs have different morphology, altered blood flow, enhanced permeability, and structural abnormalities. The tumor microenvironment consist of cancer cells, endothelial cells, immune cells and fibroblasts and the interaction of these cells influences cancer progression.

In the present study, we investigated the influence of TECs on tumor growth and the host immune response. We compared TECs to NECs for their effects on CD8+ T-cell functions. We performed next-generation sequencing on TECs and NECs to investigate potential treatment targets, and we identified glycoprotein nonmetastatic melanoma protein B (GPNMB) as a candidate target. Finally, we investigated the effects of targeting GPNMB in TECs.

Background & Results

In the field of cancer research, many studies have been conducted using human cancer cell lines and immunodeficient mice. On the other hand, to create a model that reproduces the cancer microenvironment including immune cells, it is impossible to perform sufficient analysis using immunodeficient mice. In this study, we used immunocompetent mice to analyze the immune function in the cancer microenvironment and created a novel mice model that is reproductive of tumor microenvironment.

Tumor formation was promoted in the group with cancer cells (BNL-T) and TEC (BNL-T+TEC) compared to the control administered with normal vascular endothelial cells (NEC) (BNL-T+NEC). The tumor volume increased approximately 1.5 times (Fig. 1A, B). In the tumor tissue, it was confirmed that CD8-positive T cells (green) remained in the CD31-positive tumor blood vessel lumen (red) in the BNL-T+TEC group (Fig. 1C). The IFN-γ production of CD8-positive T cells was significantly decreased, and CD8-positive T cells exhaustion was observed.

The next-generation sequencing of TEC and NEC identified 42 genes, and expression analysis using GSEA revealed that IFN-γ response signals were involved (Sup. Fig. 1A, B). GPNMB, which is a transmembrane protein, was one of the IFN signal-related genes, and GPNMB expression was observed in the cytoplasm of TECs. *In vivo*, GPNMB was expressed in TEC *in vitro* and *in vivo*. (Sup. Fig. 1C, D).

The knockdown of GPNMB expression in TEC significantly decreased the tumor volume, and increased the number of tumor-infiltrating CD8-positive T cells. The PD-1-positive Tim-3-positive CD8-positive T cells, which are exhausted T cell markers, were significantly decreased (Fig. 2A). Furthermore, the ability of CD8-positive T cells to produce IFN-γ was significantly restored, indicating an improvement in T cell exhaustion (Fig. 2B).

Significance of the research and Future perspective

For the comprehensive control of the tumor microenvironment, it is necessary to clarify the intercellular interactions of not only cancer cells but also constituent cells such as endothelial cells and immune cells. In recent years, there has been remarkable progression in immunotherapy using immune checkpoint inhibitors, and synergistic effects have also been shown by the combination therapy with immune checkpoint inhibitors and anti-angiogenesis inhibitors in some cancers. This indicates that targeting the constituent cells of the cancer microenvironment can be a treatment for cancer itself. The main drugs for cancer treatment have been shifted to immune checkpoint inhibitors. In the future, it is expected that research on immune cells mediated by tumor endothelial cells in the cancer microenvironment will progress in order to maximize the effects of immunotherapy.

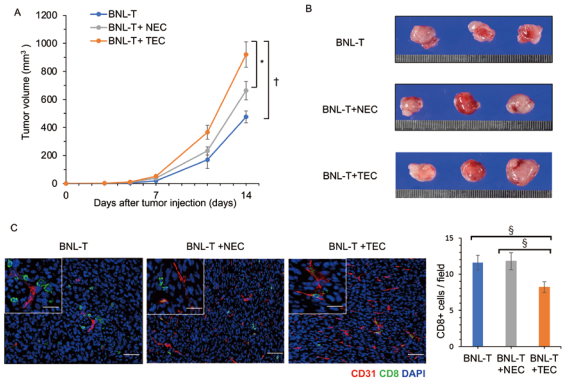


Figure 1

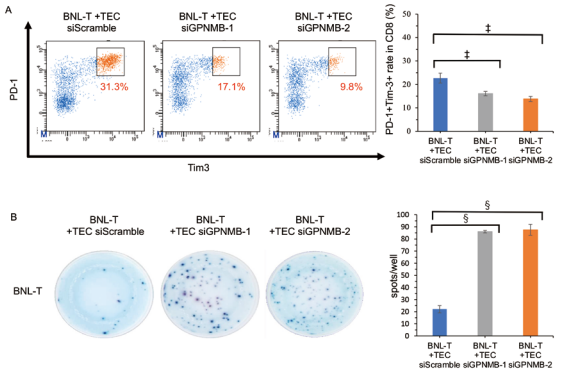
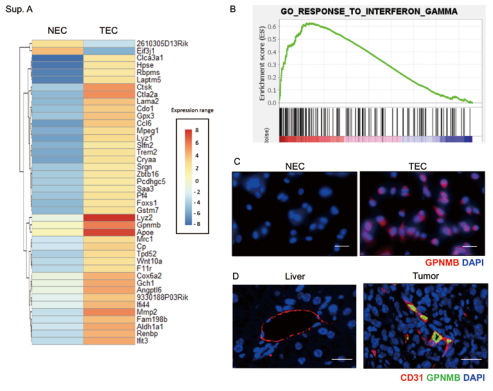


Figure 2



Supplementary Figure 1

Patent
Treatise Sakano, Yoshihiro; Noda, Takehiro; Kobayashi, Shogo et al. Tumor endothelial cell-induced CD8+ T-cell exhaustion via GPNMB in hepatocellular carcinoma. Cancer Sci. 2022, 113(5), 1625-1638. doi: 10.1111/cas.15331
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