Aberrant vascularization is a hallmark of cancer progression and treatment resistance: newly formed tumor blood vessels deliver oxygen and nutrients to the tumor microenvironment, fueling tumor growth, progression, and metastasis. Targeting endothelial cells (ECs), which line blood vessels, has emerged as a fundamental strategy for cancer treatment. However, inefficient eradication of tumor-associated ECs remains a major barrier for current anti-vascular therapy. Here, we show that ECs undergo transformation to mesenchymal stem cell (MSC)-like cells, leading to EC chemotherapy resistance in glioblastoma multiforme (GBM).

Our analysis with human patient-derived ECs shows that GBM-associated ECs are resistant to chemotherapy treatment, such as temozolomide (TMZ). Transcriptome analysis by deep sequencing revealed that ECs undergo mesenchymal transformation and stemness-like activation in the GBM microenvironment. To validate the stemness identity of tumor-associated ECs, we tested self-renewal potential and multi-potency of the GBM patient-derived ECs. GBM-ECs were cultured in MSC medium or neurobasal medium for analysis of functional stemness identities. Demonstrated through various assays, the GBM-ECs in MSC medium formed colonies, and they were able to differentiate to smooth muscle cells, pericytes, and fibroblasts upon treatment of appropriate growth factors. Neurobasal medium culture of GBM-ECs induced sphere formation, another characteristic of stemness. These findings suggest that transformed ECs acquire stem-like cell identity.

This study provides strong functional evidence for tumor-associated EC plasticity. It implies that de-transformation of ECs may provide an efficient strategy for anti-vascular and vessel normalization therapies for GBM and possibly other malignant tumors.