Invasion and angiogenesis are two of the major hallmarks of glioblastoma growth. While tumor cells in angiogenic areas undergo hypoxic stress, invasive tumor cells are often found in less hypoxic areas and in close vicinity to brain vessels. This difference in microenvironment most likely influences the metabolic profile of these two different types of tumor cells. However, there is a lack of suitable in vivo models for malignant glioma to experimentally separate invasive and angiogenic tumor cells in order to analyze their metabolism. In the present study we used a human GBM xenograft model with EGFR amplification that grows invasive and independent of angiogenesis. This tumor undergoes an angiogenic switch upon overexpression of a dominant-negative EGFR mutant. Here, we show that the transcription factors Smad3, BHLHE40, CEBP and STAT3 are central transcriptional regulators of the angiogenic switch in this model. By using the REMBRANDT database to assess the clinical relevance of our model, we found that genes upregulated in the angiogenic xenografts are also upregulated in patient GBMs compared to low grades, while the genes upregulated in the invasive tumors are upregulated in low-grade gliomas compared to GBMs. Within the xenograft model, we analyzed the metabolic differences between invasive and angiogenic tumor phenotypes. In vivo MRI spectroscopy showed an upregulation of lactate and glutamine in the angiogenic compared to invasive xenografts. The upregulation of glycolysis in angiogenic xenografts was confirmed by enzyme histochemistry of key enzymes, which in addition showed a substantial upregulation of pentose-phosphate pathway activity. Analysis of mitochondrial respiratory chain revealed reduction of complex I in angiogenic xenografts compared to invasive xenografts. Thus, the use of glycolysis for energy production within human GBMs is highly dependent on the specific microenvironment. The metabolic flexibility of GBM cells highlights the difficulty of targeting one specific metabolic pathway for therapy.