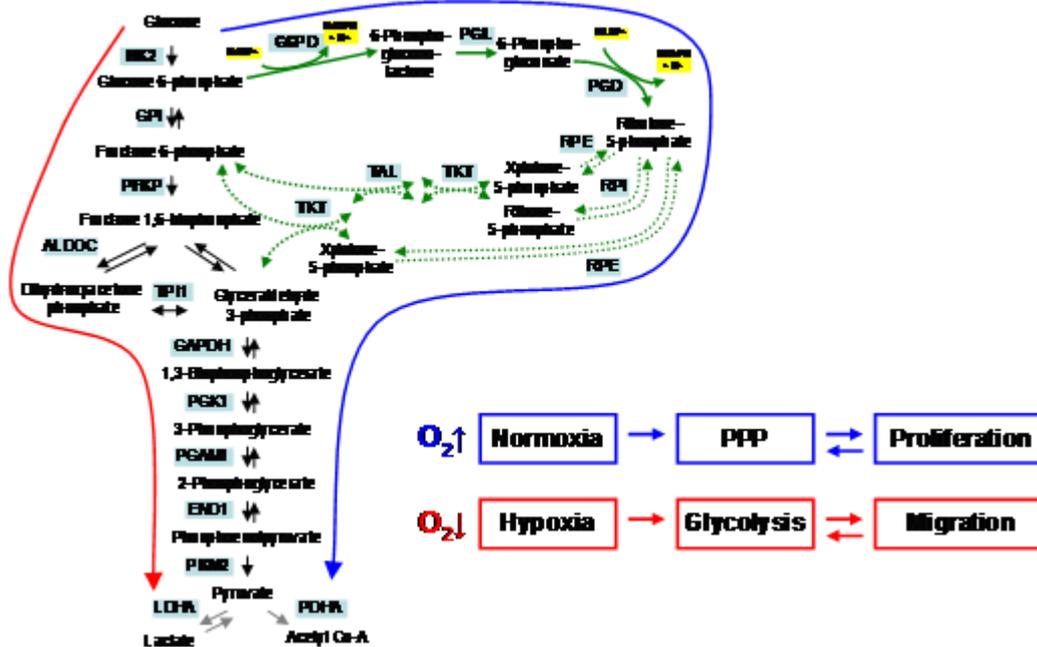


Project title: Relevance of tumor metabolism for the interaction between tumor cells and brain

Principal investigator: Prof. Dr. med. Katrin Lamszus, Laboratory for Brain Tumor Biology, Dept. of Neurosurgery, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

Tumor-specific metabolic processes play an important role in the interaction of tumor cells with the host tissue, specifically in the invasive destruction of the tissue by migrating and invading tumor cells. It is a specific property of tumor cells to generate energy predominantly through glycolysis, even when oxygen is abundant (normoxia) and metabolize glucose to lactate. This phenomenon (Warburg effect) was originally discovered by Otto Warburg and is of high scientific interest since it offers therapeutic targeting opportunities.

In previous work on glioblastoma cells we discovered an oxygen concentration-dependent metabolic switch between the pentose phosphate pathway (PPP) and glycolysis (Kathagen et al., *Acta Neuropathologica* 2013). The PPP is an alternative pathway to the preparatory phase of glycolysis. It is an anabolic pathway, whose function is the production of ribose-5-phosphate for DNA/RNA synthesis and NADPH for fatty acid synthesis and reduction of glutathione. Our previous work showed that enzymes of the PPP are highly expressed under normoxic conditions, whereas hypoxia entails downregulation of the PPP in conjunction with increased expression of glycolysis enzymes and increased glucose flux through direct glycolysis. This metabolic switch is associated with increased cell migration under hypoxia as opposed to increased cell proliferation under normoxia. In tumor tissue from glioblastoma patients we found a particularly high expression of glycolysis enzymes in severely hypoxic regions and in highly migratory (infiltrating) tumor cells, whereas these enzymes were downregulated in highly proliferative areas, which in turn displayed upregulation of PPP enzymes.



Most likely, increased tumor cell migration represents a mechanism by which tumor cells can escape a focally severe tumor hypoxia, whereas proliferation requires an increased production of new cellular "building bricks" generated through the PPP.

In the first part of our project we address the question whether the association between cell migration with glycolysis versus the association between proliferation with the PPP, is dependent or independent of hypoxia versus oxygenation, respectively. In the second part of the project we analyze whether a causal relationship between increased glycolysis or increased PPP with increased migration or proliferation, respectively, exists. In the third part of the project we investigate whether the metabolic switch between PPP and glycolysis also exists in other cell types, such as normal brain cells but also other types of cancer cells.

In summary, our studies will elucidate the functional role of the metabolic switch between the PPP and glycolysis in glioblastoma cells and other cell types and will show to what extent metabolic tumor targeting has to take into account the synchronous co-existence of different metabolic compartments, i.e. regions with different predominance of preferentially activated metabolic pathways, within glioblastomas.