Exploring the quantitative relationship between metabolism and enzymatic phenotype by physiological modeling of glucose metabolism and lactate oxidation in solid tumors.

Abstract:
Molecular imaging using PET or hyperpolarized MRI can characterize tumor phenotypes by assessing the related metabolism of certain substrates. However, the interpretation of the substrate turnover in terms of a pathophysiological understanding is not straightforward and only semiquantitative. The metabolism of imaging probes is influenced by a number of factors, such as the microvascular structure or the expression of key enzymes. This study aims to use computational simulation to investigate the relationship between the metabolism behind molecular imaging and the underlying tumor phenotype. The study focused on the pathways of glucose metabolism and lactate oxidation in order to establish the quantitative relationship between the expression of several transporters (GLUT, MCT1 and MCT4), expression of the enzyme hexokinase (HK), microvasculature and the metabolism of glucose or lactate and the extracellular pH distribution. A computational model for a 2D tumor tissue phantom was constructed and the spatio-temporal evolution of related species (e.g. oxygen, glucose, lactate, protons, bicarbonate ions) was estimated by solving reaction-diffusion equations. The proposed model was tested by the verification of the simulation results using in vivo and in vitro literature data. The influences of different expression levels of GLUT,
MCT1, MCT4, HK and microvessel distribution on substrate concentrations were analyzed. The major results are consistent with experimental data (e.g. GLUT is more influential to glycolytic flux than HK; extracellular pH is not correlated with MCT expressions) and provide theoretical interpretation of the co-influence of multiple factors of the tumor microenvironment. This computational simulation may assist the generation of hypotheses to bridge the discrepancy between tumor metabolism and the functions of transporters and enzymes. It has the potential to accelerate the development of multi-modal imaging strategies for assessment of tumor phenotypes.