

Specialty area: Preclinical MR of Cancer

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Highlights:

- Tumor energy metabolism provides vital handles for cancer diagnosis and therapy
- MRI and MRS offer unique windows on tumor energy metabolism
- Hyperpolarized ^{13}C -MRS is challenging the role of FDG-PET in tumor imaging

Title: Tumor Energy Metabolism

Target audience: Radiologists, oncologists and research scientists with an interest in tumor metabolism

Outcome/objectives: After attending this talk, participants should be able to describe major alterations in tumor energy metabolism and how these insights can be exploited to optimize the utility of MRI and MRS for cancer diagnosis and therapy monitoring

Abstract

Energy metabolism (EM) concerns the flow of energy through living systems. EM in most tumors strongly differs from that in non-malignant tissues and thus provides opportunities for diagnostics, treatment planning and therapy monitoring. The distinct nature of tumor EM is also actively studied for identifying distinctive therapeutic targets. This lecture will highlight the key characteristics of tumor EM and the major tools offered by MR to study these.

Otto Warburg is the pioneer of tumor EM (Warburg, 1923). He found that tumor lactate formation persists in the presence of excess O_2 , now known as the Warburg effect (or aerobic glycolysis). This effect is remarkable, among others because the ATP yield of lactic fermentation is low, *i.e.*, only 2 molecules of ATP are generated by the conversion of glucose to lactic acid. Aerobic respiration, in which glucose is oxidized to CO_2 and water, is much more energy effective. Although understanding of the Warburg effect is incomplete, there is increasing evidence that specific alterations in the mitochondrial machinery of the tumor cell play a vital role in malignant transformation. A key question is why aerobic glycolysis is advantageous (Gatenby, 2004; Vander Heiden, 2009). It has been argued that most glucose utilized by cancer cells is required for synthesis of biomass to sustain rapid cell division. Gatenby et al. (2004) have alternatively proposed that persistent aerobic glycolysis is an adaptation to intermittent hypoxia in pre-malignant lesions. Despite knowledge gaps, the glycolytic phenotype is widely exploited for diagnosis and treatment (Garber, 2010).

MRI and MRS provide many windows for studying tumor EM. The focus in the talk is on the utility of MRS, which detects the molecules vital to tumor EM and also provides non-invasive read-outs of therapeutic interventions. Traditionally, ^{31}P -MRS is used to measure levels of ATP, P_i and phosphorylated glycolytic intermediates, and tissue pH (Gillies, 2005). ^1H -MRS affords detection of enhanced lactate levels that accompany the glycolytic phenotype (Gillies, 2005). ^{13}C -MRS also can be used to gain an improved understanding of tumor energy metabolism. As the natural abundance of ^{13}C is only 1.1 %, the use of highly ^{13}C -enriched substrates enables specific studies of the fate of molecules of interest. DeBerardinis et al. (2007) were able to show that glioblastoma cells had a functional TCA cycle that was characterized by an efflux of substrates for use in biosynthetic pathways, particularly fatty acid synthesis.

A relatively new technology that may have a sizable impact on non-invasive research of tumor EM is the combination of ^{13}C -MRS and hyperpolarization (Ardenkjaer-Larsen, 2003; Brindle, 2008, 2012). Nuclear spin hyperpolarization can be used to dramatically enhance the MR sensitivity ($> 10,000$ times). Hyperpolarization of injected molecules allows spectroscopic imaging of their distribution in the body and subsequent metabolism. The resonances of the hyperpolarized substrate and the products that are formed from it through intermediary metabolism can thus be measured against a relatively low background of normally polarized material. The hyperpolarization decays with the T_1 time constant and by RF pulse excitation, implying that the measurements should be carried out quickly. In particular, the fate of

hyperpolarized [1-¹³C]-pyruvate has been extensively studied in preclinical models of cancer (Brindle, 2008). A prominent product formed from injected pyruvate is [1-¹³C]-lactate, which results from the exchange reaction catalyzed by the enzyme lactate dehydrogenase. The pyruvate-to-lactate flux, which is high in cancer, was strongly reduced in treated tumors undergoing drug-induced cell death (Day, 2007). The reduction in the measured flux after drug treatment and the induction of tumor cell death were explained by loss of the coenzyme NAD(H) and decreases in concentrations of lactate and enzyme in the tumors. It is very well conceivable that this technique could be used in the future for response monitoring in the clinical setting. The first clinical trials have recently begun.

References

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