Metabolic changes in luminal-like orthotopic breast cancer xenografts following estrogen supplement withdrawal

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Introduction

Endocrine therapy is one of the main treatment strategies in breast cancer. However, as much as 30-40% of estrogen-receptor positive (ER+) patients do not respond to hormonal therapy. Early evaluation or prediction of treatment response would be beneficial for these patients, as refractory patients could discontinue their current medication and be offered other treatment options. Metabolite profiling by magnetic resonance spectroscopy (MRS) is a possible tool for therapy monitoring in this patient group. Using high resolution magic angle spinning magnetic resonance spectroscopy (HR MAS MRS) with tissue metabolite quantification, the metabolic profile of a luminal-like breast cancer orthotopic xenograft model has been determined following withdrawal of supplementary 17-β-estradiol.

Methods

The luminal-like orthotopic breast cancer xenograft model (MAS 98.06) has previously been established and characterised. This model expresses both estrogen receptor (ER) and progesterone receptor (PR), and requires supplementary 17-β-estradiol (4 µg/ml in drinking water) for tumor growth. Following tumor growth to approximately 10 mm diameter, the supplementary 17-β-estradiol was discontinued for 7 days, before sacrifice and harvesting of tumor tissue (n=7). Tissue samples (25g: 3 mg) were analysed using HR-MAS MRS performed on a Bruker AVANCE DRX 600 spectrometer (Bruker BioSpin, Karlsruhe, Germany). Single-pulse spectra were obtained according to previously described procedures including ERETIC for quantification. Peak areas were calculated using peak-fitting software (PeakFit v 4.12 by SeaSolve, USA) and selected metabolites were quantified. The HR MAS results were compared to baseline data from animals which continuously received supplementary 17-β-estradiol (n=9).

Results

Following 17-β-estradiol starvation, there was a significant reduction in mean tumor volume (0.36±0.06 cm³ to 0.31±0.09 cm³, p<0.05). The HR MAS results revealed several significant differences in the metabolic profiles of the two groups of animals. The concentrations of selected metabolites are presented in Table 1, and representative spectra (region 4.3 – 2.9 ppm) in Figure 1.

Discussion

The regression in tumor size following estrogen supplement withdrawal demonstrates that the model is representative of successful endocrine therapy in luminal-like breast cancer. In this study, there was no significant change in the investigated choline metabolites, whereas the concentrations of taurine and lactate were significantly reduced. The unchanged choline metabolite concentrations are consistent with in vitro data from tamoxifen-treated MCF-7 cells. The reduced concentration of taurine most likely reflects reduced activity in the TauT-transmembrane amino acid transporter, which is known to be up-regulated by 17-β-estradiol. The reduced lactate concentration may be the result of decreased anaerobic glucose consumption, confirming in vitro data from MCF7-cells. Our data suggest that HR MAS MRS may be a tool for monitoring the effect of endocrine treatment in ER+ breast cancer. However, focus should be on glucose consumption rather than choline metabolism.

References