FDG (2'-fluoro-2'-deoxyglucose) tumor metabolism detected by ^{19}F-MRS *in vivo*, correlates with therapeutic response

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Introduction

High aerobic glycolysis is a common phenotype of tumors, associated with raised rates of glucose transport and phosphorylation and decreased glucose-6-phosphate dephosphorylation [1]. This phenomenon allows non-invasive detection of solid tumors in the clinic using ^{18}FDG PET-images. Since FDG uptake is proportional to the number of viable cells, prediction of response following chemo/radiotherapy is also possible. However, this has not always been successful, due to infiltration of the tumor by macrophages which are also glycolytic [2], and perhaps inaccurate modeling of the glycolytic rate since the PET-method does not distinguish FDG from FDG-6-phosphate. ^{19}F-MRS is also unable to resolve FDG-6P signals from FDG *in vivo*, but studies of rodent brain, heart and ascites have shown that FDG-6P can epimerise to FDmannose-6P which is resolved from the FDG-group *in vivo* [3-5]. The FDM-6P undergoes further metabolism to a species that persists *in vivo* [5]. The aim of this study was to determine if substantial FDM-6P could be detected in solid tumours *in vivo* and if FDG-uptake (total ^{19}F-signal) or formation of FDM-metabolites correlated with tumor response.

Methods

RIF-1 tumours (0.4-1 g) were induced sc in C3H mice. Anesthetized animals were placed in the bore of a 4.7T SISCO 200/300 spectrometer at 37^{0}C. Tumours hung into a 2-turn ^{1}H/^{19}F surface coil (12 mm dia.) with a reference bulb containing 2 µmoles of 5FU (10 µl) fixed under the coil. A 0.2 ml bolus of FDG in 0.9% saline (1.4 mmole/kg) was injected ip, and ^{19}F-spectra were acquired immediately in 10 min blocks (1500 transients of 0.4 sec, sw of 20 kHz, 45^0 pulse at coil center), for 120 min. Mice then received a single dose of 5FU (1 mmole/kg ip), which causes tumour shrinkage within 48 hr, followed by a return to the pre-treatment size after ca. 10 days [6]. 24-48 hr later the ^{19}F-MRS experiment was repeated and response was assessed by measuring tumors every 2-3 days for 7-10 days. Tumor volume was calculated by measuring length, width and depth using calipers and the formula: l*w*d*(π/6). Some tumors were freeze-clamped 2 hr after FDG treatment for ^{19}F-MRS analysis *in vitro*. FITSPEC was used to calculate the δ_F and peak integrals after 40 Hz line broadening. Under the conditions used *in vivo*, the FDG and metabolites were 32% saturated and the 5FU standard 74% saturated, allowing estimation of drug concentrations in the tumour.

Results

^{19}F-analysis *in vitro* of a 30 mM solution of FDG showed ca. 0.1% contamination with a signal likely to be FDM. The T_1's of α and β-FDG were 1.74 and 1.85 sec respectively, with a resolution of 0.25 ppm when using 10 Hz line-broadening. In tumors, the FDG-signal (i.e. a group composed of FDG and FDG-6P) had a T_1 of 1.4±0.2 sec. The FDG signal (0 ppm) appeared at -31 ppm upfield from the 5FU reference within 2 min of administration. In some tumours, the maximum signal intensity of this group (Cmax) was at 10 min, in others at 30-60 min as shown in Figure 1. In all tumors studied, the major FDM group (α-FDM±P) was detectable after 10 min at -5.3 ppm from the FDG-group, and sometimes the minor FDM group (β-FDM±P) was detectable after 60 min further upfield at -23.8 ppm. Unlike brain tissue, other pentose phosphate pathway metabolites were not detectable *in vivo*. Extract analysis *in vitro* confirmed this but revealed the presence of numerous other metabolites of FDG, which have already been described in mouse ascites.[3] After 2 hr the FDM-groups were 10-20% of the total ^{19}F-signal detectable.

In animals in which the FU response was assessed, the pre-treatment mean Cmax of the FDG-group was 2.0±0.2 mM 30-90 min post injection, while the FDM-group increased linearly during this period at a rate of 2.7±0.4 nmoles/min/g (mean±sem, n=7). Following 5FU treatment, the change in total FDM formed at 90 min and the change in rate of FDM formation correlated significantly with % change in tumor size at 7 days (r =0.99 and 0.94 respectively). However, the total ^{19}F-signal correlated weakly with response (r =0.43).

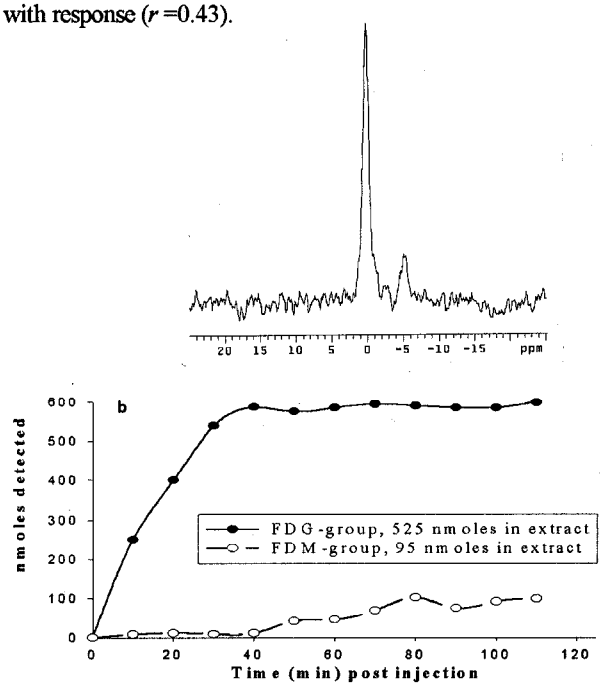

Figure 1a and b. Detection *in vivo* of uptake and metabolism of FDG by a 0.33 g RIF-1 tumor. (a) ^{19}F-MRS signals at 100-120 min post injection (b) time course from 0-120 min.

Discussion

These results confirm studies by others that FDG is extensively metabolised beyond FDG-6P *in vivo*, and shows for the first time that this is detectable in solid subcutaneous tumors using non-invasive ^{19}F-MRS. More importantly, these observations suggest detection of the FDM-group metabolites, may predict tumor response to therapy; an observation of potential clinical significance.

References

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