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A metabolic study of HIF-2 alpha over-expressing and empty vector 7860 renal tumours using *in vivo* and *in vitro* ¹H MRS

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Aims: To study the role of HIF-2 in tumour metabolism using *in vivo* ¹H MRS and *in vitro* ¹H MRS of tumour extracts. The resultant metabolite profiles of HIF-2 alpha over-expressing 7860 renal tumour xenografts and empty vector (EV) controls were compared.

Methods: ¹H MRS *in vivo*: HIF-2 alpha over-expressing and EV 7860 renal cancer cells were implanted s.c in MF1 nude mice. Tumours were studied by localised ¹H MRS PRESS to measure metabolite levels on a Varian 4.7T spectrometer. ¹H MRS *in vitro*: After *in vivo* ¹H MRS, tumours were freeze-clamped and extracted with perchloric acid. ¹H MRS was performed on a 600 MHz Bruker spectrometer.

Results: HIF-2 alpha over-expressing tumours grew significantly faster ($p < 0.04$) and had a higher total choline level (12.73 ± 1.11 mM) *in vivo* when compared to the EV tumours (10.18 ± 0.44 mM). Significantly higher levels of free choline and phosphocholine (PC) were found in the extracts. Taurine, creatine and glucose were also significantly higher in the HIF-2 alpha over-expressors whereas, surprisingly, lactate and alanine levels (products of anaerobic metabolism) were significantly lower.

Discussion: The results suggest that the faster growth rate of HIF-2 alpha over-expressing tumours was sustained by the more effective metabolism of glucose, i.e., oxidative metabolism. Lower lactate and alanine levels were unexpected results, since (by analogy with the role of HIF-1 alpha in tumours) one would expect HIF-2 alpha over-expression to induce a state of pseudo-hypoxia in which anaerobic metabolism would be upregulated.