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Effects of hypoxia preconditioning on neuroblastoma tumour oxygenation and metabolic signature in a chick embryo model

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Abstract:

Hypoxia episodes and areas in tumours have been associated with metastatic dissemination and poor prognosis. Given the link between tumour tissue oxygen levels and cellular metabolic activity, we hypothesised that the metabolic profile between metastatic and non-metastatic tumours would reveal potential new biomarkers and signalling cues. We have used a previously established chick embryo model for neuroblastoma growth and metastasis, where the metastatic phenotype can be controlled by neuroblastoma cell hypoxic preconditioning (3 days at 1 % 02). We measured, with fibre-optic oxygen sensors, the effects of the hypoxic preconditioning on the tumour oxygenation, within tumours formed by SK-N-AS cells on the chorioallantoic membrane (CAM) of chick embryos. We found that the difference between the metastatic and non-metastatic intratumoural oxygen levels was small (0.35 % 02), with a mean below 1.5 % 02 for most tumours. The metabolic profiling, using NMR spectroscopy, of neuroblastoma cells cultured in normoxia or hypoxia for 3 days, and of the tumours formed by these cells showed that the effects of hypoxia *in vitro* did no compare with *in vivo* tumours. One notable difference was the high levels of the glycolytic end-products triggered by hypoxia *in vitro*, but not by hypoxia preconditioning in tumours, likely due to the very high basal levels of these metabolites in tumours compared with cells. In conclusion, we have identified high levels of ketones (3-hydorxybutyrate), lactate and phosphocholine in hypoxic preconditioned tumours, all known to fuel tumour growth, and we herein point to the poor relevance of *in vitro* metabolomic experiments for cancer research.

Keywords: Cell culture, chick embryo, hypoxia, NMR spectroscopy, oxygenation, tumour biology