Brain

The metabolic adaptation evoked by arginine enhances the effect of radiation in brain metastases

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Abstract

Selected patients with brain metastases (BM) are candidates for radiotherapy. A lactatogenic metabolism, common in BM, has been associated with radioresistance. We demonstrated that BM express nitric oxide (NO) synthase 2 and that administration of its substrate L-arginine decreases tumour lactate in BM patients. In a placebo-controlled trial, we showed that administration of L-arginine before each fraction enhanced the effect of radiation, improving the control of BM. Studies in preclinical models demonstrated that L-arginine radiosensitisation is a NO-mediated mechanism secondary to the metabolic adaptation induced in cancer cells. We showed that the decrease in tumour lactate was a consequence of reduced glycolysis that also impacted ATP and NAD+ levels. These effects were associated with NO-dependent inhibition of GAPDH and hyperactivation of PARP upon nitrosative DNA damage. These metabolic changes ultimately impaired the repair of DNA damage induced by radiation in cancer cells while greatly sparing tumour-infiltrating lymphocytes.