1H MRS Metabolite Profiles of Medulloblastomas in Transgenic SMO Mice

K. S. Hekmatyar1, M. Wilson2, N. Jerome3, J. L. Griffin1, A. Peet1, and R. A. Kauppinen1

1Radiology, Dartmouth Medical School, Hanover, New Hampshire, United States, 2University of Birmingham, United Kingdom, 3Dartmouth Medical School, United States, 4Biochemistry, University of Cambridge, United Kingdom

INTRODUCTION

Medulloblastomas, that are believed to arise from granule-cell precursors (GCP), are the most frequently diagnosed pediatric brain tumours in children [1]. It has become obvious that genetic and molecular abnormalities underpinning human medulloblastomas are numerous [2]. One commonly observed genetic alteration concerns the sonic hedgehog –dependent signaling involving approximately 30% of human medulloblastomas [3]. The sonic hedgehog (Shh)-Patched (Ptc) signaling pathway plays a crucial role in mitogenetic regulation of GCP [4]. Recently, a genetically modified (GEM) mouse line has been generated overexpressing smoothened receptor (SMO) in GCPs with very high incidence of medulloblastomas after the age of 2 months [5]. In vivo [6, 7] and ex vivo [8] 1H MRS studies point to high taurine concentration in human medulloblastomas. A recent high resolution magic angle spinning (HR-MAS) analysis of medulloblastoma specimens revealed that creatine, glutamine, phosphocholine (PC), myo-inositol and glycine are higher in these tumours than in other pediatric brain tumour originating from neuronal cell lines [8]. In the present study we have used SMO mice to characterize metabolite profiles both in vivo and ex vivo in the SMO model of medulloblastoma with known molecular pathology.

METHODS

The SMO mice were obtained from Fred Hutchinson Cancer Research Center (FHCRC, Seattle, WA). The SMO mice of 118±42 days (range 68–180 days) and age matched wild type (WT) controls were scanned for MRI and 1H MRS. C57Bl/6 mice were used as age matched wild type (WT) controls. Animals were anaesthetized with 4% halothane, 70% nitrous oxide and 10% oxygen. The SMO mice were a gift from FHCRC, Seattle, WA. Supported by MRC (UK).

RESULTS

In a cohort of 13 SMO mice scanned three types of cerebellar appearances in T2-weighted MRI were seen (Fig. 1A) and HR-MAS analyses of cerebellar specimens showed that in addition to the in vivo MRS changes glycine, phosphocholine and scyllo-inositol are elevated, whereas GABA and myo-inositol concentrations are decreased in the medulloblastoma tissue (Fig. 2A).

CONCLUSIONS

Medulloblastomas in the SMO mice show metabolite profiles which are characterized by very low NAA, low GABA and myo-inositol and high taurine, CCM, scyllo-inositol and glycine. Interestingly, a large body of these metabolic alterations is reported from human medulloblastomas with heterogeneous molecular pathology [8]. It appears that taurine, CCM (especially PC) and scyllo-inositol are potential common MRS biomarkers for medulloblastomas, whereas myo-inositol, GABA and glycine may be more associated with tumours with aberrant SMO signaling in GCPs.

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REFERENCES