Diagnostic Value of R2* in identifying ALK mutations in transgenic murine models of neuroblastoma

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Introduction

Neuroblastoma (NB) is the most common extra-cranial solid tumour of childhood and accounts for 15% of mortality in paediatric cancer. Approximately 50% of patients with poor prognosis disease exhibit amplification of the proto-oncogene MYCN associated with frequent relapse, aggressive tumour biology and enhanced tumour angiogenesis (1, 2). The TH-MYCN genetically-engineered-mouse model (GEMM) spontaneously develops tumours that closely recapitulate most major features of high-risk human NB; including the anatomical distribution, radiology and biological features (3). Recently, mutations in the anaplastic lymphoma kinase (ALK) gene were described in virtually all cases of hereditary NB and in approximately 15% of somatic NB tumour tissues, making ALK mutations the second most common genomic alteration in NB (4, 5). We used a similar GEM modelling approach to construct a new model of NB, which contains an ALK mutation (ALK-F1174L), concomitantly with the TH-MYCN transgene, since the ALK-F1174L mutation alone is not sufficient to drive tumour formation. Here, we present a multi-parametric imaging study, which compares the tumours from the TH-ALK-F1174L/TH-MYCN mice to TH-MYCN mice.

Materials and Methods

Tumour-bearing mice were identified by palpation. 1H MRI was performed on a 7T Bruker horizontal bore microimaging system using a 3cm birdcage coil. Anatomical T1w RARE coronal images were acquired through the abdomen of the mice (FOV=4cm, matrix=128x128, 20 slices, 1mm thick, 4 averages, TE=36ms, TR=5000ms, turbo factor=8). Baseline R2* was measured using a multi gradient-echo (MGE) sequence (TE=6-28ms, TR=200ms, 8 echoes, 8 averages, FOV=3cm, matrix=128x128, 3 axial slices, 1mm thick, NEX=8) Native T1 and T2 were quantified using an inversion recovery (IR) TrueFISP sequence (baseline scan, TI=25-1450ms, 50 inversion times, TE=1.2ms, TR=2.5ms, scan TR=10s, 8 segments, NEX=8). Data Analysis: MGE, IR-trueFISP data were fitted on a pixel-by-pixel basis using in-house software (ImageView), providing parametric maps of R2*, T1, T2.

Results and Discussion

Tumours from TH-ALK-F1174L/TH-MYCN mice demonstrated a significantly slower R2* than TH-MYCN mice (Table 1, Figure 1.A). This difference was already evident on T2*-weighted images. Signal intensity from tumours in the TH-ALK-F1174L/TH-MYCN decays slower than the signal arising from the tumour in the TH-MYCN mice, evident at TE=21.9ms (Figure 1.B). R2* is sensitive to the concentration of deoxygenated haemoglobin, thus suggesting a difference in the vascular phenotype between the two models. At excision, the very dark-red colours of tumours in TH-MYCN mice contrast with the pale appearance of tumours in the TH-ALK-F1174L/TH-MYCN mice (Figure 1.D). Tumours from TH-MYCN mice present a large amount of “blood lakes” (Figure 1.C), which could result in vascular stasis. These structures are absent from the tumours in the TH-ALK-F1174L/TH-MYCN mice. Overall this study suggests that tumours from the TH-ALK-F1174L/TH-MYCN mice have a lower blood volume than TH-MYCN and/or may present more functional vessels. Investigation with DCE-MRI and USPIO imaging are on-going to assess potential differences vascular perfusion/permeability, and the architecture between the two models.

Conclusions

We have demonstrated that the TH-ALK-F1174L/TH-MYCN model has a phenotypically different vasculature from the TH-MYCN model, identifying a role for the ALK gene in the regulation of tumour angiogenesis. If the TH-ALK-F1174L/TH-MYCN mice prove to recapitulate the clinical presentation of ALK-mutated childhood NB, T2*-weighted imaging could be incorporated in diagnostic scanning, providing a method for identifying patients with mutations in ALK, and therefore helping with patient stratification and treatment decisions.

References