MRI CHARACTERIZATION OF A NOVEL MOUSE MODEL OF SPORADIC MEDULLOBLASTOMA

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Introduction: Significant progress has been made in our understanding of the pathogenesis of brain tumors partly due to the development of genetically engineered mouse models that recapitulate the human disease. MRI has been used previously in preclinical brain tumor studies to non-invasively screen for tumor presence, characterize tumor progression and to monitor treatment response [1]. However, one of the greatest translational applications of such preclinical models is the ability to investigate tumor etiology and to draw insights on the molecular pathways altered in these cancers [2,3]. Since studies performed in advanced-stage tumors may not accurately reflect the genetic alterations critical for tumorogenesis, there is a clear need for more sensitive imaging protocols that allow the analysis of the early stages of tumor development. In this study we optimized an in vivo high resolution Mn-enhanced MRI (MEMRI) protocol for the characterization of different stages of tumorigenesis in a novel mouse model of sporadic medulloblastoma (MB), the most common malignant pediatric brain tumor originating in the cerebellum (Cb).

Methods: Animal Model: One of the most relevant mouse models of Shh-induced MB is the Patched (Ptc1) mutant mouse [4]. In our study we generated a new variant of this model (referred as Ptc1-CKO) by combining Ptf1acko mice with mice homozygous for a floxed allele of the Patched gene (Ptc1Fl/Fl). Using this approach, Ptc1 was deleted in very few Ptf1a-expressing granule cell progenitors (GCPs) compared to the extensive mutation of numerous GCPs seen in other models [5]. Based on our imaging, tumors in Ptc1-CKO mice likely initiate from a single mutated granule cell progenitor and thus better reflect the likely clonal origin of sporadic human MBs. Imaging: MRI experiments were performed 24h after intraperitoneal (IP) injection of MnCl2 in isotonic saline (0.4-0.6 mM/kg) using a 7T Bruker Biospec system [4]. A 25-mm (ID) quadrature Litz coil (Doty) was used to acquire 3D T1-weighted gradient echo images. The sequence parameters were: TE/TR=3.6/50 ms, flip angle=40°, matrix=2562, time ~2h for high resolution; and TE/TR=4/15 ms, FA=18°, matrix=1282, time ~15min for high throughput imaging. Image analysis including registration, segmentation and 3D rendering were performed using AMIRA software (Visage Imaging). After imaging, mice were cardio-perfused and tumors extracted for histological (H&E) and immunohistochemical analysis using Ki67 staining. Based on our imaging, tumors in Ptc1-CKO mice showed two distinct morphological and immunohistochemical (molecular) patterns (Fig 3). In ongoing experiments, MRI images are providing spatial information for the dissection of tumor tissue for further gene expression analysis using DNA microarrays (data not shown).

Discussion: We used MEMRI to characterize a novel genetic mouse model of sporadic MB and showed that tumors display at least two distinct imaging and molecular phenotypes contrary to previous reports that all Shh-driven MBs converge to a common molecular endpoint [6]. Our in vivo MEMRI imaging protocol allowed the detection of early pre-neoplastic lesions and the analysis of advanced-stage MB tumors. Furthermore, longitudinal MEMRI studies showed that only one pre-neoplastic lesion develops into a tumor and that each pre-neoplastic lesion likely arises from a single mutant cell. This novel protocol should be useful for noninvasive volumetric analysis of individual growth rates and morphologic features in this and other mouse models. We also expect that applying our imaging approach to this unique preclinical MB model will help us better understand MB pathogenesis and will ultimately serve as a platform to test current and novel therapies.
