of LADC. Finally, we performed therapeutic trials in genetically engineered and patient-derived mouse models of LADC with the FDA-approved SGLT2 inhibitor canagliflozin. RESULTS/ANTICIPATED RESULTS: We observed a switch in the modality of glucose transport during lung carcinogenesis: SGLT2 was highly expressed in pre-malignant lesions and well-differentiated LADC, whereas GLUT1 was upregulated in advanced, poorly differentiated lesions. This pattern was observed both in human samples and in murine models. This observation led us to hypothesize that early-stage LADCs are often negative on FDG PET because this imaging modality does not detect the activity of SGLT2, which is expressed in early lesions. Therefore, we performed PET imaging with the tracer Me4FDG, that measures SGLT2 activity, in our mouse model, and observed that Me4FDG accumulated in small nodules that were negative with FDG. We confirmed the functionality of SGLT2 in human LADC by Me4FDG PET in patient-derived xenografts. To investigate the role of SGLT2-mediated glucose uptake in the early stages of LADC development, we treated both genetically engineered mice and patient-derived xenografts with FDA-approved SGLT2 inhibitors, showing that SGLT2 inhibition effectively reduced LADC growth and prolonged survival in mouse models. In addition, Me4FDG uptake predicted response to SGLT2 inhibition. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results show that sodium-dependent glucose transport is a critical metabolic supply strategy in the early stages of lung adenocarcinoma development, and that Me4FDG is a novel biomarker of early LADC and of SGLT-dependent tumor growth. The discovery of SGLT2 in LADC highlighted the need for a re-interpretation of FDG-negative lung nodules, which might rely on SGLT2 for glucose uptake, and therefore may be detected by the new tracer Me4FDG. We anticipate our findings will lead to clinical studies evaluating Me4FDG as a diagnostic tracer for solitary lung nodules and early LADC, and as a biomarker for the selection of patients eligible for treatment with SGLT2 inhibitors.

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Solid-state MRI as a nonradiative alternative to computed tomography for craniofacial imaging

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OBJECTIVES/SPECIFIC AIMS: Computed tomography (CT) enables 3-dimensional (3D) visualization of cortical bone structures with high spatial resolution, and thus has been the gold-standard method for evaluation and diagnosis of craniofacial skeletal pathologies. However, ionizing radiation and, in particular, repeated scanning for presurgery and postsurgery assessments, is of concern when applied to infants and young children. Recent advances in solid-state MRI allow the capture of the short-T2 signals in cortical bone while suppressing the signal from soft-tissue protons having T2 relaxation time 1–2 orders of magnitude longer (50–100 ms). One approach, a dual-radiofrequency (RF) pulse and ultrashort echo time (UTE) imaging based method, exploits different sensitivities of bone and soft tissue to different RF pulse widths and TEs. This study aims to demonstrate the feasibility of producing 3D renderings of the human skull and visualization of cranial sutures using the bone-selective MRI technique in comparison to CT. METHODS/STUDY POPULATION: Imaging technique: Two RF pulses differing in duration and amplitude are alternately applied in successive repetition time (TR) along the pulse train. Within each TR, 2 echoes are acquired. Acquisition of the first echo starts at the ramp-up of the encoding gradient (TE1), allowing for capture of signals with very short lifetimes (bone), while that of the second starts after a longer delay (TE2). In total, 4 echoes are obtained: ECHO11 (RF1TE1), ECHO12 (RF1TE2), ECHO21 (RF2TE1), and ECHO22 (RF2TE2). During reconstruction, ECHO11 is combined with ECHO21 and ECHO12 is combined with ECHO22, resulting in 2 images. The subtraction of these 2 images yields an enhanced bone contrast. Data acquisition/processing: The pulse sequence described above was applied for MR imaging of a human cadaveric skull and 2 adult human subjects in vivo, at 3T field strength (Siemens Prisma, Erlangen, Germany). Imaging parameters: TR/TE1/TE2 = 7/0.06/2.46 ms, RF1/RF2 durations = 40/520 µs, flip angle = 12°, matrix size = 2563, field of view = 2803 mm^3, voxel size = 1.1 mm isotropic, number of radial spokes = 25,000, and scan time = 6 minutes. Segmentation of bone voxels was performed using ITK-SNAP in a semi-automatic fashion, leading to 3D renderings of the skull. For comparison, a CT scan was also performed in the human cadaveric skull with 1 mm isotropic resolution. Validation: The biometric accuracy was assessed by measuring eight anatomic distances: (1) Maximum craniocaudal aperture of the right orbit. (2) Maximum craniocaudal aperture of the left orbit. (3) Maximum height of the mandible from chin point in the midline. (4) Maximum cranial length (5) Maximum cranial width. (6) Maximum height of piriform aperture. (7) Distance between lateral most aspect of mandibular condyles. (8) Distance between lateral most aspect of posterior hard palate in both CT- and MRI-based 3D renderings of the human cadaveric skull using Mimics software (Materialise®, Ghent, Belgium). These distances were compared with those directly measured on the cadaveric skull. RESULTS/ANTICIPATED RESULTS: Compares CT with the proposed MRI method on cadaveric human skull images, along with corresponding 3D renderings. Compared with CT, the 3D rendered images maintain most features over the entire head (e.g., zygomatic arch), except for appearance of some artifacts in the mandibular region. In vivo head images in 2 adult subjects: axial magnitude images and 3D rendering. In the axial images, bone voxels as well as the inner table of the cranium are clearly visualized, and cranial and spinal bone structures are well depicted in the 3D renderings. Some voxels were erroneously included or excluded in the renderings. The mean difference in measurements of the 8 anatomic distances was 6, 4, and 2 mm when comparing MRI Versus CT, MRI Versus in situ, and CT Versus in situ, respectively. DISCUSSION/SIGNIFICANCE OF IMPACT: Bone proton magnetization exhibits a substantial level of signal decay during the relatively long duration of RF2 due to its very short T2 relaxation time. In contrast, soft-tissue retains nearly the same level of signal intensities over all echoes. Thus, subtraction of ECHO22 from ECHO11, when compared with the difference between ECHO11 and ECHO12, enhances bone contrast from soft tissue. The proposed, dual-RF dual-echo 3D UTE imaging technique produces isotropic high-resolution bone-specified images in the whole head within a clinically feasible imaging time (6 min), leading to clear visualization of craniofacial skeletal structures. These are key components necessary for translation to the clinical setting. Optimization of postprocessing for more realistic 3D renderings and thus accurate anatomic measurements is currently being implemented. The proposed method's potential as a nonradiative alternative to CT will then be thoroughly evaluated in pediatric patients.

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Surface display of chimeric proteins for exosome imaging and capturing in mammalians

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OBJECTIVES/SPECIFIC AIMS: Exosomes are living nanoscale vesicles that can shuttle large amounts of bioactive cargo for intercellular communication. The potential of these nanovesicles to serve as both biomarkers for disease diagnosis and vehicles for delivery of therapeutics has only begun to be explored. To realize these potentials, molecular tools for effective exosome tracking and capturing must be invented in order to advance basic research and clinical translation. METHODS/STUDY POPULATION: We utilize a surface display strategy that enables exosome modification in living mammalian systems. By reconfiguring the surface protein CD63 or viral envelope glycoprotein VSV-G, we generate 3 topologically distinctive protein chimeras for exosome imaging and capture in mammalian systems. RESULTS/ANTICIPATED RESULTS: We have shown that these genetically encoded protein chimeras have the ability to correctly target and integrate into exosomes in cultured human cells. Furthermore, we have demonstrated that the secreted exosomes could be successfully captured by an affinity peptide intentionally displayed on the outer surface of exosomes. DISCUSSION/SIGNIFICANCE OF IMPACT: Our study highlights the potential of these fusion proteins for exosome tracking and provides novel genetic tools for exosome research and translation, one of which is loading protein therapeutics for targeted delivery.

2018

Synaptic vesicle 2 receptors as a novel targets for neuroendocrine cancer therapy

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OBJECTIVES/SPECIFIC AIMS: (1) To delineate the function of the heavy-chain receptor binding domain (HCR), a portion of botulinum neurotoxin type A (BoNT/A) and synaptic vesicle 2 (SV2) signaling pathway, which provide a novel multipurpose biologic with potential clinical applications in tumor detection/ imaging, inhibition of tumor progression, and reduction of bioactive hormone

https://doi.org/10.1017/cts.2018.124 Published online by Cambridge University Press