MRI monitoring of endogenous stem cell therapies in animal models of stroke

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Introduction: In animal models of stroke, endogenous neural precursor cells can be activated with growth factors such as epidermal growth factor (EGF) and erythropoietin (EPO) [1], leading to increased neurogenesis, generation of new tissue at the lesion site, and behavioural recovery. To translate similar therapies into the clinic, it is critical to evaluate, non-invasively and at multiple time points, this process of tissue repair and regeneration. In this study, we used a rat model of stroke to demonstrate the feasibility of using MRI to distinguish between regenerating and pathological tissues when using endogenous stem cell therapies.

Methods: Stroke induction and treatment: Focal ischemia was induced in Wistar rats (males, 224g) using a devascularization model [2]. An opening was made in the skull over the motor and sensory cortices. A sterile saline-soaked cotton swab was used to wipe the pia and attached blood vessels from the cortical surface, creating focal ischemia. MR-compatible infusion cannulae were implanted into the contralateral lateral ventricle, and connected to an osmotic minipump that delivered vehicle (artificial cerebral spinal fluid plus 0.1% bovine serum albumin), or epidermal growth factor (EGF, 10 μg/ml) for 7 days. On Day 8, the EGF pump was exchanged with one containing erythropoietin (EPO, 1365IU/ml). This EGF+EPO cocktail has been shown to enhance differentiation and numbers of newly generated neurons [3, 4]. This treatment results in the formation of a tissue plug at the site of injury, which is not seen in untreated controls.

MRI: Rats were anesthetized (isoflurane), placed in an MR-compatible head restraint and scanned at 3T (GE Signa) using a custom-designed surface coil. Imaging was performed starting at 1 day until 56 days post-stroke. Imaging frequency was varied among cohorts to probe the effect of anesthesia in the animal model of stroke. Three 3D fSPGR sequences (flip angles: 2°, 10°, and 15°; 40×40mm FOV; 1mm slice thickness; matrix 128×128; 16 NEX) were used to calculate T1-weighted MRI and corresponding T2 map (56 days post stroke) and histology of representative animals had a tissue plug with T2 values that resembled that of normal cortical tissue, whereas untreated groups failed to grow tissue in the lesion. NeuN stain revealed neurons in the tissue plug, whereas neurons in the untreated cavity. MR imaging was able to predict the outcome of the treatment as early as two weeks post stroke (much earlier than functional recovery, Fig.4). In a limited number of animals (4 out of 33) the treatment was not successful (no tissue plug formation). In these animals the T1 and T2 relaxation of lesions were larger than in the regenerating brains.

Summary: We have demonstrated that MRI can be a powerful tool in the evaluation of stroke recovery. Tissue plug growth in the lesion site has MR characteristics (T1 and T2) similar to that of normal brain tissue, and differs distinctly from the cavity. Moreover, MRI is able to predict the outcome of the treatment as early as 2 weeks post stroke. Future experiments will investigate whether changing the dosage of drug delivered affects the recovery process.

References: