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JUVENILE DEVELOPMENT AND AGEING MEDIATED CHANGES IN CORTICAL STRUCTURE AND VOLUME IN THE RAT BRAIN

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Introduction. Animal models can provide mechanistic insight into disease pathology and evolution, as well as a platform to test potential therapies. However, most pre-clinical research employs juvenile, 3month old (300g) animals, which is not necessarily representative of the natural disease state. We are conducting a lifespan study on rats, imaging the juvenile development as well as ageing processes of the brain with non-invasive techniques including functional and anatomical MRI and different PET-tracers, respectively. An explorative study like this benefits from an automated evaluation technique that is based on individual structural changes rather than manual ROI analysis. To overcome this limitation, we used elastic coregistration and individual deformation fields to address changes in the frontal cortex from MR images

Material and Methods. From postnatal day 21 two groups of four male Wistar rats were housed pairwise. Food restriction (80% of ad libitum consumption) started at months 3 in order to minimize obesity, a risk factor for age-related diseases (1). Animals were employed in MR experiments on a bimonthly basis. Group 1 was followed from the age of 3weeks up to 14months, Group 2 from 10 until 20months. MR experiments were conducted on an 11.7T Bruker BioSpec horizontal bore scanner. Animals were anaesthetized using 2% Isoflurane in 70:30 N2O:O2 and vital functions were monitored continuously. T2 maps were chosen for their anatomical detail and quantitative reproducibility. Maps were calculated from an MSME (multi slice multi echo) sequence (10echoes) with TE=10ms, TR=5000ms, FOV=28x28mm and a resolution of 0.146x0.146mm in plane and 0.5mm slice thickness (without gaps). For every individual all T2 maps from the different ages were coregistered non-rigidly using a Bspline transform (2), and the corresponding deformation fields calculated. Deformation maps indicated volumetric changes of brain regions. At specific time points (3weeks and 3months) a subset of rats was sacrificed for histological evaluation (cresyl violet).

Results. The deformation maps revealed a decrease in cortical thickness during juvenile development (3weeks to 3months). In parallel, quantitative evaluation of the frontal cortex showed a reduction of T2 relaxation time. A further T2 reduction was observed after the age of 6months, however, without significant changes in volume. Preliminary histological evaluation revealed a higher cortical cell density at 3months when compared to 3weeks of age.

Conclusion. Elastic coregistration is a useful tool for lifespan studies, providing unbiased information on volume changes on an individual basis. The deformation fields allow the creation of physiologically meaningful ROIs for quantitative analysis of imaging parameters. A combination of reduced T2 and decreased cortical volume is implying an increasing tissue density (myelination and cell number) during development, lowering the relative amount of free water, and thus reducing the cortical volume. This was confirmed by histological evaluation.

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A UNIQUE NEW HUMANIZED MOUSE MODEL FOR MULTIPLE MYELOMA: OPPORTUNITIES FOR STUDYING MM IN ITS NATURAL ENVIRONMENT AND PRECLINICAL TESTING

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Introduction Multiple myeloma (MM), one of the most common hematological malignancies in adults, is a neoplasm of terminally differentiated B cells, i.e. plasma cells. The transition of a plasma cell to a fully transformed, aggressive myeloma is a multistep process, which requires the acquisition of mutations in multiple genes. Most of this evolution takes place in the bone marrow (BM). Studying the pathogenesis of MM is seriously hampered by the lack of appropriate conditions for the engraftment of patient-derived MM cells (pMM) which, unlike MM cell lines, strongly depend on a human microenvironment to engraft, survive and expand, indicating that the interaction of MM cells with the cellular and extracellular components of the human BM microenvironment plays a crucial role in the growth behavior of MM cells.

Methods Here we report the development of a unique mouse model to study the pathobiology of MM by implementing a technology for creating a natural human bone environment in the immune deficient RAG2$^{-/-}\gamma_c^{-/-}$ mouse. To this end we combined a procedure to culture-expand human BM-derived mesenchymal stromal cells (MSC) that were seeded on biphasic calcium phosphate (BCP) particles and subsequently implanted subcutaneously in RAG2$^{-/-}\gamma_c^{-/-}$ mice. Within 6 weeks this leads to the formation of so-called ossicles that contain substantial amounts of human bone, while the remaining open spaces are filled with mouse hematopoietic cells and blood vessels, creating an environment that strongly resembles the human bone marrow.

Results A striking finding was that this humanized environment in the mouse as a 3-D natural 'niche' for pMM cells. Intrascaffold injection of pMM cells resulted in engraftment and outgrowth of tumor cells in close contact with the human bone layer in the ossicles. In addition, intracardial injection, revealed that these primary tumor cells were also capable of homing to the implanted artificial BM-niches, while no tumor cells were detected in the mouse BM. The outgrowth of pMM in this model is accompanied by an increase in osteoclast number on the bone surface, indicating the presence of bone resorption, one of the most important clinical sequelae of MM. Interestingly, by gene-marking pMM cells with luciferase and using bioluminescent imaging, we were able to follow myeloma outgrowth in time, and visualize the effect of treatment.

Conclusion Hence, this novel humanized mouse model provides the first opportunity to investigate patient-derived MM plasma cells in a more natural environment, which may lead to better insights in the pathogenesis of this disease. Furthermore, it could serve as a model for preclinical testing of new therapeutic approaches for the treatment of MM patients.