

Functionalized Nanoparticles for Molecular Imaging (FunkMoB)

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Selectively binding nanoscaled MR contrast agents open the possibility to examine biological processes in vivo on a cellular and sub cellular basis. With this technique Funk MoB will work on concrete questions concerning arteriosclerosis, oncology and neurobiological stem cell research utilizing commercial and new developed MR contrast agents.

Research Activities

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MR contrast agents for activation specific thrombocyte antibodies

in Cooperation with [von zur Mühlen C.1](#), [Neudorfer I.1](#), [Bode C.1](#), [Möller J-A.1](#), [Peter K.2](#)

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Recent progress in molecular magnetic resonance imaging (MRI) provides the opportunity to image cells and cellular receptors using microparticles of iron oxide (MPIOs). However, imaging targets on vessel walls remains challenging due to the quantity of contrast agents delivered to area of interests under shear stress conditions. We evaluate the binding properties of an activation-specific glykoprotein IIb/IIIa-receptor contrast agent targeting ligand-induced binding sites (LIBS) on activated human platelets and its properties under flow conditions in vitro, as this contrast agent would provide the opportunity to detect platelets on ruptured atherosclerotic plaques such as found in myocardial infarction or stroke

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Cellular incorporation mechanisms of super-paramagnetic iron oxides

in Cooperation with von zur Mühlen C.1, Neudorfer I.1, Bode C.1, Bassler N.2, Peter K.2 1

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Abstract Superparamagnetic Iron Oxide Nanoparticles (SPIONs) have been successfully used for Magnetic Resonance Imaging (MRI) of atherosclerotic plaques. Endocytosis into monocytes/macrophages has been proposed as the mechanism of SPION uptake, but a specific receptor had not been identified. A potential candidate is the versatile integrin Mac-1 (CD 11b/CD 18), which is involved in leukocyte adhesion, complement activation and phagocytosis. To evaluate the role of Mac-1 in SPION endocytosis, we used model cell lines recombinantly expressing Mac-1: One expressing the native Mac-1, one the mutated, and thereby high affinity Mac-1, and one control CHO cell line. Each of those was either preincubated with or without anti-CD11b antibody, and thereafter incubated with two different concentrations of vinyl alcohol/vinyl-amine copolymer coated SPIONs (0.12mg and 0.06mg Fe/ml) with a mean particle size of 9nm for the bare particles and 30nm for the polymer coated particles, respectively. After 24 hours of SPION incubation and washing of the cells, MRI was performed on a 3 Tesla whole body scanner. We used a T2* weighted 3D gradient echo sequence with a resolution of 100 mm³ and TE/TR of 9ms/700ms. Susceptibility induced signal extinction was taken as a surrogate parameter for SPION uptake.

Corresponding pictures of light microscopy (upper row) and immuno histochemistry of monocytes identified by an anti-CD14 antibody (bottom row). In panel (A), monocytes without SPION incubation can be identified with an anti-CD14 antibody, whereas in panel (B) granular iron depositions can be detected by light microscopy in monocytes incubated with amino-PVA SPIONs. Panel (C) proves intracellular iron deposition using iron staining.

Depending on affinity of the Mac-1-cells, iron oxide-induced signal void in T2* weighted MRI is more pronounced in activated Mac-1-cells than in non-activated Mac-1 cells (upper row). Preincubation of the cells with anti-CD11b antibody results in a visibly decreased signal void (middle row), suggesting significantly decreased intracellular iron uptake/binding. No visible impact of the CD11b-blockade on signal intensity can be observed in CHO cells. This signal intensity is close to the one caused by the negative control, which are cells that are not incubated with iron oxide particles (bottom row).

Conclusion We described the monocyte integrin Mac-1 and its affinity state as a mediator of SPION uptake/binding independent on particle surface coatings. Furthermore, the impact of Mac-1 receptor affinity on intracellular iron uptake can be quantified using clinically relevant magnetic field strengths. Our observations add information on the uptake mechanism of SPIONs and might serve to efficiently label cells for the imaging of atherosclerotic plaques and in particular to detect unstable plaques that are prone to rupture.

Reference "Superparamagnetic Iron Oxide Binding and Uptake as Imaged by Magnetic Resonance is Mediated by the Integrin Receptor Mac-1 (CD11b/CD18): Implications on Imaging of Atherosclerotic Plaques" von zur Muehlen C, von Elverfeldt D, Bassler N, Neudorfer I, Steitz B, Petri-Fink A, Hofmann H, Bode C, Peter K. Atherosclerosis (2007) 193:102-111

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In vivo MRI in the MMTV-PyMT model for breast cancer

in Cooperation with Schurigt U., Sevenich L., Reinheckel T., Peters C.

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Tumor cell derived proteases including cathepsins have been in the focus of recent research, since they degrade components of the extracellular matrix and basement membrane. As elevated expression of cathepsins has been observed in several human cancers, including breast, gastric and prostate cancer and cathepsins are correlated with poor prognosis, they have been shown to play important roles in tumor progression. We use the MMTV-polyoma middle T antigen (PyMT) transgenic mouse model to investigate the impact of cathepsins in breast cancer progression. For this aim we are intercrossing PyMT-transgenic mice with different cathepsin-deficient and cathepsin-transgenic mice, respectively.

The measurement of the primary tumor size normally done by palpation using a semiquantitative score from 0 to 3 is one important parameter in analysing the PyMT-model (0 point: tumor is not detectable, 1 point: tumor size \leq 0.5 cm, 2 points: tumor size 0.5-1.0 cm, 3 points: tumor size $>$ 1.0 cm). For refinement of tumor size measurement we started to study tumor bearing mice with magnetic resonance imaging (MRI) in longitudinal studies following the tumor progression from week 5 to week 14 after the birth. Recently, we demonstrated that the volumes of tumors in the PyMT model can be exactly determined by MRI. Interestingly, we found that the tumor onset can be detected by MRI earlier in comparison to the standard palpation method (figure 1).

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