PhD12 BIOQIC

Sensors for quantification of tumor-induced tissue structure alterations by enzyme-activated Xe-MRI contrast

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Application Area: Cancer **Modality:** MRI **Related:** PhD 4-8,10,11,15

Background

Matrix metalloproteinases (MMP) play a pivotal role in tumor development, including proteolytic degradation of the extracellular matrix (ECM), and alteration of cell-cell and cell-ECM interactions[1]. Developing an MMP-related imaging protocol enables quantitative insights that go beyond the diagnostic value of conventional MRI: MMP-activity triggers an amplification process since each protease unit digests multiple sensor substrates that are then detected at much larger quantity. Xenon NMR has the potential to detect such sensor conversion at nanomolar concentrations[2,3].

Hypothesis

An enzyme-triggered local sensor enrichment will be promoted by an activatable cell penetrating peptide (ACCP). Hence, enzymatic cleavage turns the respective sensor into a smart contrast agent for discerning between an “off” and an “on” state. This project will investigate activity of MMP2/9 related to basal membrane digestion and migration of metastatic cells in animal models of pancreatic cancer. Two different sensor designs will be compared for optimum signal amplification.

Methods

The project is focused on MRI with hyperpolarized ^{129}Xe, in particular the saturation transfer method Hyper-CEST for establishing the link between image contrast and enzyme activity. Saturation transfer methods with hyperpolarized nuclei demonstrated quantitative insights for concentrations of CEST-active sensors[4]. Quantification of the ECM structural changes will be correlated to elastography, atomic force microscopy and optical stretcher experiments.

Work Packages

WP1: Peptidic APPC compound

WP2: Liposomal APPC compound

WP3: qHyper-CEST in cell culture

WP4: ECM characterization

← year 1 → ← year 2 → ← year 3 →

WP1: Investigation of the Hyper-CEST performance of the in-house synthesized sensor, including qHyper-CEST evaluation, and identification of optimized saturation transfer conditions.

WP2: Characterization of cage-loaded liposomal carriers with ACPPs as alternative design and comparative studies of both sensor designs with respect to cell uptake, biocompatibility, and NMR sensitivity.

WP3: Studies for establishing the link between amount of sensor cleavage at various enzyme concentrations and incubation times as well as identification of the onset of image contrast for live cell experiments or tissue samples.

WP4: Correlating the achieved image contrast with observations from alternative methods such as elastography, atomic force microscopy and optical stretcher experiments.

Clinical Translation

This proof-of-principle study will give important insights for a quantitative link between Xe MRI contrast and MMP2/9 activity. In the follow-up of this PhD project, preclinical studies are intended to establish enzymatic imaging markers.

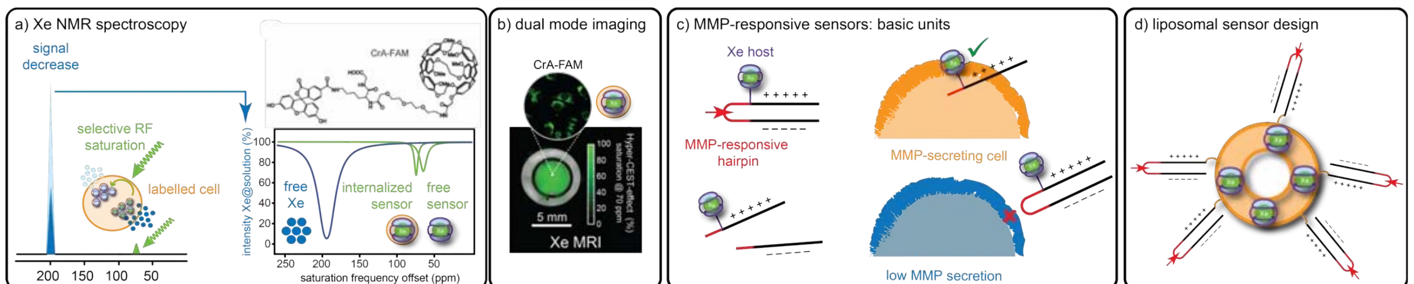

Figure: MMP-activated Xe NMR and MRI. a) Caged Xe yields low NMR signal in direct detection but allows for signal enhancement due to chemical exchange saturation transfer of reversibly bound, hyperpolarized nuclei (Hyper-CEST). Cellular uptake of dye-labelled Xe hosts can be followed by Hyper-CEST spectroscopy. b) Hyper-CEST also enables ultra-sensitive MRI with nanomolar target concentration in labelled cells. Such sensors have been used for unspecific cell tracking. c) The MMP-responsive sensor will contain the Xe host grafted onto an activatable cell penetrating peptide (ACPP). Cleavage of the MMP-specific target sequence in the hairpin triggers the cellular uptake. d) Liposomal carriers containing the ACPP on the outside and many Xe hosts inside the membrane will be tested for potential higher sensitivity due to their locally increased payload of CEST-active sites.

Literature

1.Lebel, R. & Lepage, M. Contrast Media Mol. Imaging 9, 187–210 (2014).
2.Rose, H. M. et al. Proc. Natl. Acad. Sci. 111, 11697–11702 (2014).
3.Witte, C. et al. Angew. Chem. Int. Ed. 54, 2806–2810 (2015).
4.Kunth, M., Witte, C. & Schröder, L. J. Chem. Phys. 141, 194202 (2014)