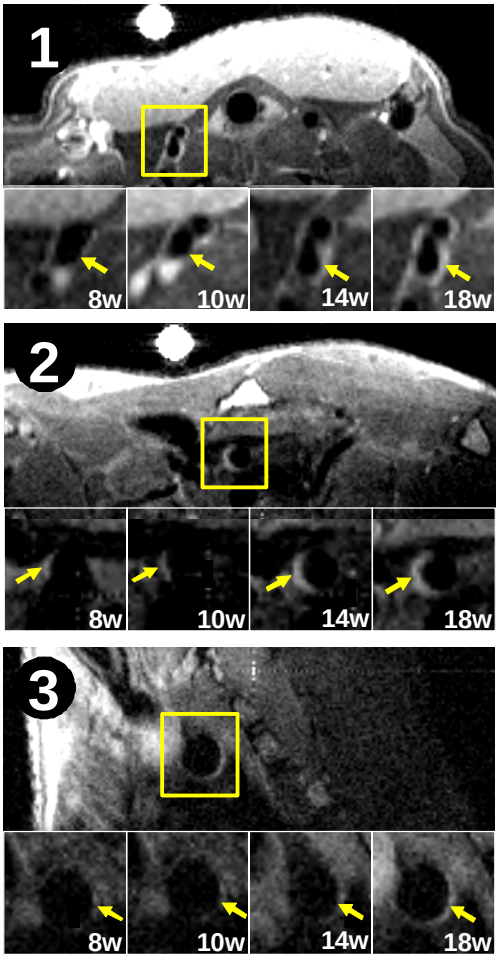
Plaque Progression in the ApoE-/- Mouse Model of Atherosclerosis Monitored in Three Vascular Beds

B. Künnecke[1], S. Grüner[2], J. Fingerle[2], and M. von Kienlin[1]

[1]Magnetic Resonance Imaging & Spectroscopy, F. Hoffmann-La Roche Ltd, Basel, Switzerland, [2]Metabolic Disease Biology Area, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background - Novel treatment strategies for atherosclerosis aim at plaque stabilisation and regression by plaque de-loading. Hence, non-invasive imaging modalities for longitudinal plaque monitoring will be essential prerequisites in forthcoming pharmacological intervention studies in order to stratify plaque load at baseline and ascertain treatment success. Mouse models of atherosclerosis, in particular the apolipoprotein-E knockout (ApoE-/-) mouse, have become accepted tools in preclinical research. The ApoE-/- mouse holds promise in that not only plaque formation is modelled in plaque-prone vascular beds, but plaques in the innominate artery have been reported to show aspects of vulnerability akin to the human situation [(1)]. Yet, preclinical drug intervention studies have been hampered by substantial individual variability of plaque formation in this disease model. In order to determine the proper intervention time point, hence non-invasive plaque monitoring with a highly reproducible modality is required. MRI of arterial walls in mice would potentially qualify and has been available since long but low spatial resolution, long scan times and a lack of quantitative appraisals have largely prevented plaque MRI to enter in preclinical intervention studies [(2)]. Here, we report on a large-scale study in which long-term plaque progression in the ApoE-/- mouse model of atherosclerosis was non-invasively monitored with MRI and subsequently corroborated with histology. Disease progression and biological heterogeneity were concomitantly assessed in the three plaque-prone vascular beds comprising carotid arteries, aortic arch, and the innominate artery with putative vulnerable plaques.

Methods - 32 male ApoE-/- mice were fed an atherogenic high-fat/high-cholesterol diet starting at 4 weeks of age. After 8, 10, 14 and 18 weeks on this Western diet, the plaque burden was repeatedly assessed with MRI. 16 hours prior to each MRI examination, the mice were injected with 0.1umol of the targeted contrast agent Gadofluorine M (Bayer Schering Pharma AG, Berlin, Germany) in order to enhance the atherosclerotic plaques [(3)]. MR measurements were conducted on a Bruker Biospec 7T / 20cm instrument equipped with a body resonator and a crescent-shaped surface coil. Black-blood plaque imaging [(4)] was carried out with a RARE2 sequence with TE_{eff}/TR=15/595ms, 15 contiguous slices with 0.4mm thickness and 98um x 98um in-plane resolution, and a total scan time of 13 minutes per vascular bed. After each MRI examination, 4 animals were sacrificed for corroborative histology.



Results and Discussion - Atherosclerotic plaque burden in ApoE-/- mice was repeatedly assessed in three plaque-prone vascular beds comprising the carotid- and innominate arteries, and the aortic arch. Figures 1-3 show MR images of the respective vascular beds (overview) and time series of plaque progression from 8 to 18 weeks of feeding with Western diet (close-ups). State-of-the-art image resolution at short measurement times allowed plaque burden in three relevant vascular beds including the innominate artery with putative vulnerable plaques to be screened in a large cohort of mice. Clear-cut progression suggestive of evolution from early plaque formation to full-fledged fibrous plaques could be observed in all three vascular beds. Volumetric analysis revealed that plaque formation usually starts at a few well-known seed points, e.g. distal from the bifurcations and the left wall of the innominate artery. Quantitative analysis of plaque volume provided evidence for a statistically significant increase of plaque burden over time which was corroborated with en-face histology. Plaque progression in the three vascular beds was found to be very heterogeneous within and across animals, thus emphasising the need for eliminating this confound in drug intervention studies.

Conclusions - The present study demonstrates that atherosclerotic plaque burden and its progression in the ApoE-/- mouse model can be rapidly and reliably assessed using contrast enhanced high-resolution MRI. Though plaque burden was found to be heterogeneous, its longitudinal and quantitative appraisal with MRI provides the imperatively required starting point for drug intervention studies that aim at plaque stabilisation or regression.

References

1. Jackson CL. Arterioscler Thromb Vasc Biol 2007; 27:973-977
2. Weinreb DB *et al.* NMR Biomed 2007; 20:256-264
3. Meding J *et al.* Contr Med Molec Imag 2007; 2:120-129
4. Briley-Saebo KC *et al.* J Magn Reson Imag 2007; 26:460-479