Zirconium-89 labelled probe for molecular imaging of inflammation in experimental atherosclerosis

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Swedish Research Council (22036); the Swedish HLF (20150423, 20170669); ALF (20150517, 447561, 726481); Söderberg Foundations, VINNOVA and KI

Background: Early detection of inflamed atherosclerotic lesions by molecular imaging might improve risk assessment beyond that of vascular stenosis and plaque morphology imaging, and improve the clinical management of high-risk patients.

Purpose: To target the key features of unstable atherosclerotic lesions, we studied the feasibility of our radiotracer, based on modified human serum albumin (HSA), to identify inflamed atherosclerotic lesions by in vivo molecular imaging.

Methods: We applied a maleylated HSA (Mal-HSA) probe, recognised by scavenger receptors on macrophages, in an experimental in vivo imaging study of atherosclerosis. Mal-HSA was coupled with a positron-emitting metal ion, Zirconium-89 (89Zr). The targeting potential of this probe was evaluated and compared with unspecific 89Zr-HSA and 18F-FDG in a mouse model of atherosclerosis (Apoe-/-, n=22) and compared with wild-type (WT) mice (C57BL/6, n=21) as controls. Radiotracer accumulation in the aortic arch was analysed in vivo by the fusion of positron emission tomography–magnetic resonance imaging (PET-MRI), radiotracer bio-distribution was measured ex vivo by gamma counter, and plaque uptake was evaluated by phosphor imaging (PI) autoradiography (ARG).

Results: PET-MRI, gamma counter measurements, and PI-ARG showed the accumulation of 89Zr-Mal-HSA in the atherosclerotic lesions of Apoe-/- mice. The maximum standardised uptake value (SUVmax) for 89Zr-Mal-HSA at 16 and 20 weeks were 26% and 20% higher (P<0.05) in Apoe-/- mice than control WT mice, whereas no difference in SUVmax was found for 18F-FDG in the same animals. 89Zr-Mal-HSA uptake in the aorta as evaluated by gamma counter 48 h post-injection was 32% higher (P<0.01) for Apoe-/- mice compared to WT mice, and the aorta-to-blood ratio was 10-fold higher (P<0.001) for 89Zr-Mal-HSA compared with unspecific 89Zr-HSA. HSA probes were mainly distributed to the liver, spleen, kidneys, bone and lymph nodes. The PI-ARG results corroborated the PET and gamma counter measurements, showing higher accumulation of 89Zr-Mal-HSA in the aortas of Apoe-/- mice compared to WT mice; 9.4 ± 1.4 vs 0.8 ± 0.3% (P<0.001).

Conclusions: The modified HSA-based radiotracer showed in vivo targeting of inflamed atherosclerotic lesions of mouse aorta, which could also be verified ex vivo. 89Zr-Mal-HSA seems to be a promising diagnostic tool for the identification of vascular inflammation. Further methodological studies are needed to verify its applicability for detecting rupture-prone plaques.
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