Patterns of USPIO Deposition in Murine Atherosclerosis

To the Editor:

With great interest and curiosity we awaited the publication of the article by Morris et al., ever since the presentation of their preliminary data at the ISMRM conference last year. Their article answers the question whether or not MRI of plaque macrophages in a widely used murine animal model of atherosclerosis is possible with Ferumoxtran-10. This is especially important because this agent is potentially clinically applicable, and no mechanical irritation of the vessel wall intima was performed. The article also underlines the need for further research on this topic, because macrophage content and USPIO uptake in atherosclerotic lesions are apparently not linearly correlated under certain circumstances. The reduction of USPIO uptake rather than macrophage content by p38 MAPK inhibition poses many questions regarding the imaging of therapeutic effects on macrophage content and activity using USPIOs.

Because our working group conducted similar experiments on Ferumoxtran-10 in ApoE knockout mice we would appreciate a discussion of our findings with Joanne Morris and her coworkers. After the injection of 1000 μmol iron per kilogram (kg) body weight, we could observe 2 different patterns of USPIO uptake specifically into atherosclerotic lesions (Figure). In the light of the recent publication by Briley-Saebo et al., it would be interesting to discuss whether Morris et al made similar observations. Different patterns of USPIO uptake have not been described yet and might reflect the different pathways in which USPIOs accumulate in atherosclerotic lesions.

Passive diffusion into the atherosclerotic lesion via the luminal endothelium might be reflected by a homogeneous USPIO uptake into the intimal and subintimal layers (Figure, arrowheads). Colocalization with macrophages may occur through uptake of USPIOs by resident macrophages rather than through immigration of USPIO-labeled monocytes. In this case, increased USPIO content in plaques activated by angiotensin II might also represent increased endothelial permeability.

Circumscribed iron-positive areas in the media (Figure, circles) might be indicative of USPIO delivery via neovascularization or thrombosis. We do not expect residual iron oxides in the vasculature to be a cause of our results, because the half life time of Ferumoxtran-10 at the used dose is believed to be around 1 to 2 hours. We observed the peak in circumscribed iron oxide uptake after 48 hours and a plateau for up to 14 days.

In summary we think that the study of Morris et al contributed substantially to the ongoing research on MRI of macrophage content and activity in murine atherosclerosis. Further studies, however, on the uptake mechanisms of USPIOs into murine atherosclerosis are needed to clarify recent results.

Disclosures

None.

Figure. Two different patterns of iron deposition in murine atherosclerotic lesions after the administration of 1000 μmol iron per kg body weight of the USPIO Ferumoxtran-10 (100× magnification, Prussian-blue staining). Relatively homogeneous distribution of iron in the subintimal layers (arrowheads) and circumscribed iron staining in the media (circles), which are often localized around the neovascularization (stars in lumen).

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