Stealthy Magnetophages, a New Tool for Molecular Imaging

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Introduction

Phage display is a powerful tool in the context of molecular imaging. This technique allows to select, from a heterogeneous mixture of bacteriophages, displaying each a different peptide on their proteic wall, a vector that is subsequently coupled to a "contrastophore", i.e. USPIO for MRI. In our previous work [1], we have developed the concept of magnetophages, obtained by direct coupling of USPIO to phages isolated after the phage display procedures. We have shown that magnetophages can be used as in vitro molecular imaging contrast agents (MICA). However, in vivo they are taken up by the phagocytic cells of the reticulo-endothelial system (RES), particularly in the liver. This capture makes magnetophages unavailable to interact with the target. Therefore, "stealthy magnetophages" escaping the RES and showing a prolonged circulation time are suitable.

Materials and Methods

Stealthy magnetophages were obtained by covalent coupling of pegylated USPIO to the amino groups of the proteins of the phage wall. Stealthy magnetophages and non-stealthy magnetophages (i.e. nonpegylated USPIO), specific or not to the apoptotic marker phosphatidylserine (PS), were injected either to anesthetized control male mice or to mice bearing apoptotic liver. MRI images were acquired at 4.7 Tesla (Bruker Avance 200 system, Karlsruhe, Germany) using a T_2-weighted spin-echo sequence (TR/TE = 2000/20 msec, NE = 4, matrix 128x128, slice thickness = 2.5 mm, FOV = 6 cm). Intensities of regions of interest (ROI) defined in the liver were measured. Analysis of the images was based on the relative enhancement of the signal (RE) with respect to the pre-contrast image.

Results

Figure 1 shows that non-stealthy magnetophages, specific or not to PS, induce the RE decrease, probably due to their nonspecific internalization by the Kupffer cells of the apoptotic and healthy livers. On the contrary, figure 2 shows the decrease of RE only in the mice with apoptotic livers. This is conceivably correlated to the specific accumulation of stealthy magnetophages in apoptotic livers and not in healthy ones.

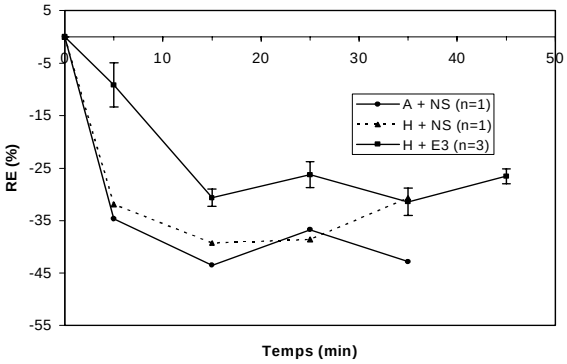

Figure 1 : Non specific magnetophages (NS) and magnetophages specific of PS (E3) injected in healthy (H) and apoptotic livers (A). Decrease of RE shows that magnetophages are accumulated in the liver.

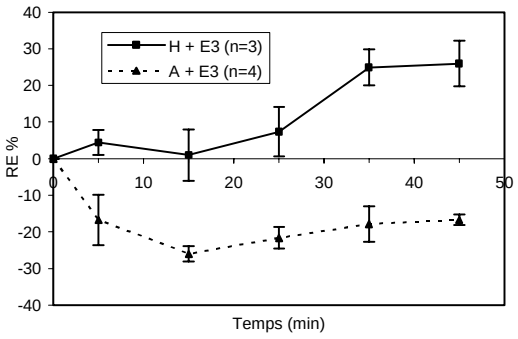

Figure 2 : Injection of stealth magnetophages specific of PS (E3) in apoptotic (A) and healthy livers (H). Decrease of RE in the first case suggests that magnetophages are accumulated in the apoptotic liver.

Conclusion

Stealthy magnetophages specific to PS can discriminate apoptotic liver from healthy one. They are invisible to the RES and can therefore be vectorized to their target. Stealth magnetophages can thus be used as in vivo molecular contrast agent.

References

[1] J. Segers et al., Proc. Intl. Soc. Mag. Reson. Med, 11, p 1710, ISMRM, Kyoto, Japon (2004)