COMPARISON OF THREE MRI MOLECULAR IMAGING MODALITIES: APPLICATION TO ANGIOGENESIS IMAGING IN A BRAIN TUMOR MOUSE MODEL

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Introduction

The recent development of targeted contrast agents (CA) has opened the way for MRI molecular imaging. Here we evaluated three modalities, highlighting significant differences in sensitivity, specificity and spatial resolution. As shown by their application on a mouse model of brain tumor using CA grafted with RGD peptides to specifically target αvβ3 integrins over-expressed in angiogenic vessels.

Materials and Methods

Animal model. Brain tumors (Ø≈2 to 6mm) were induced in nude mice by IC injection of U87MG cells. Animals were sorted to remove experiments with low SNR and animals with untypical behavior.

CA. For each modality, 2 CA were used (RGD and Ctrl): 2 Gd-based emulsions (r₁=2.4±1.0×10⁻⁶mM⁻¹s⁻¹), 2 lipoCEST exhibiting maximum MTR asym (asymmetric Magnetization Transfer Ratio) contrasts for B₁=7T and δ₁=8ppm, and 2 ¹⁹F emulsions (PFOB, 40% w/w).

MRI. Acquisitions were carried out with a 7T Bruker rodent scanner, before and within the 2h following IV injection of each CA.

Gd: A T₂ mapping IR-FGE sequence [2] (R=150x150x660µm³, Tₑ=12.5min) was acquired on 10 mice (5 RGD and 5 Ctrl). Concentration maps were derived using the CA relaxivity r₁.

CEST: A Multi-Slice Multi-Echo (MSME) sequence (R=150x150x660µm³, Tₑ=14min) preceded by a saturation was acquired on 24 mice (12 RGD and 12 Ctrl).

¹⁹F: A MSME sequence optimized for the CF₁ peak of PFOB [3] (R=500x500x6000µm³, Tₑ=18min) was acquired on 12 mice (6 RGD and 6 Ctrl).

Results and Discussion

As illustrated by Figure 1, CA are detected with a sub-nanomolar sensitivity by the three modalities. Moreover a higher contrast is systematically observed for RGD contrast agents inside the tumor. This difference can be ascribed to a specific association of RGD peptides to αvβ₃ integrins expressed at the neo-vessels surface. As summarized in Table 1, time courses (RGD vs Ctrl) are significantly different (p<0.05) from the first time point for Gd-based and ¹⁹F emulsions but only after 1h with the lipoCEST. For each RGD-CA a plateau is rapidly reached at concentrations specified in Table 1. A contrast decrease is only observed for the Ctrl lipoCEST, probably due to a shorter half life of flowing liposomes (~1h30) compared to emulsions (~4h).

Table 1. Main characteristics of Gd, CEST and ¹⁹F modalities

<table>
<thead>
<tr>
<th></th>
<th>Gd</th>
<th>lipoCEST</th>
<th>¹⁹F</th>
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<tbody>
<tr>
<td>Spatial resolution</td>
<td>150x150x660µm³</td>
<td>150x150x660µm³</td>
<td>500x500x6000µm³</td>
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<tr>
<td>¹⁹F significant time point</td>
<td>12.5min</td>
<td>60min</td>
<td>18min</td>
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<tr>
<td>Concentration at the plateau</td>
<td>0.4mM</td>
<td>1.6mM</td>
<td>80µM</td>
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<td>Advantages</td>
<td>Spatial resolution Specificity Quantification Space resolution</td>
<td>Spatial resolution Quite insensitive to movements Quantification Endogenous MT B₀ and B₁ inhomogeneities Spatial resolution</td>
<td></td>
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<tr>
<td>Limitations</td>
<td>Access to in vivo r₁</td>
<td>Endogenous MT</td>
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Figure 1. Example of images acquired after IV injection of RGD CA for Gd, CEST and ¹⁹F modalities (a, c, e respectively). Time course obtained after IV injection of RGD and Ctrl CA (red and blue curve respectively) for Gd, CEST and ¹⁹F modalities (b, d, f respectively). Signal is averaged in the tumor region and through the animal cohort (n=5/5 for Gd, n=12/12 for CEST and n=6/6 for ¹⁹F).

Conclusion

To our knowledge, this study is the first comparison of functionalized CA used in similar experimental conditions. As shown by their application on a brain tumor mouse model, each modality provides additional information, promising for multimodal investigation of brain diseases.