Early detection of brain metastasis using novel MRI contrast agent targeting VCAM-1

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Background: Contrast-enhanced magnetic resonance imaging (MRI) is currently the most sensitive method for brain metastasis detection, but relies on blood-brain barrier (BBB) compromise and, consequently, is sensitive to late-stage metastases only. We have developed an MRI-detectable contrast agent targeted specifically at the endothelial adhesion molecule VCAM-1 (VCAM-MPIO) and have shown that this agent enables detection of endothelial activation early in brain pathology [1]. Based on our recent findings that brain metastases develop in close association with existing brain vessels [2], we hypothesised that VCAM-1 is upregulated during metastasis development and that our VCAM-MPIO may enable early detection of brain metastases.

Methods: Female balb/c mice (8-10 weeks) were injected intracardially with 1x10⁶ 4T1 cells, a metastasising murine mammary carcinoma line. Purified monoclonal rat antibodies specific to mouse VCAM-1 (clone M/K2, Cambridge Bioscience) or control IgG-1 (clone Lo-DNP-1, Serotec) were conjugated to myone tosylactivated MPIO (1-µm diameter; iron content 26%; Invitrogen) as described previously [1]. Either 5 or 10 days after 4T1 cell injection animals were anaesthetised and injected intravenously with either VCAM-MPIO or control IgG-MPIO (4 x 10⁸; 4.5mg iron / kg body weight; n = 3-4 per group). After 1h animals underwent MRI at 7T and a T2*-weighted 3D gradient-echo dataset was acquired (acquisition ~1h; isotropic resolution 88mm). Post-gadolinium T1-weighted images were acquired to assess BBB integrity. For each image, the brain was manually masked to exclude extracerebral structures.

Results: Immunohistochemically, upregulation of VCAM-1 was co-localised to brain metastases. In vivo MRI revealed focal areas of signal hypointensity throughout the brain, indicating VCAM-MPIO accumulation. Immunohistochemical analysis demonstrated co-localisation of the MRI hypointensities with metastases. Quantitatively, the volume of hypointensities in the VCAM-MPIO injected animals was greater than in IgG-MPIO-injected animals (i.e. background). None of the animals showed BBB breakdown.

Conclusion: Upregulation of VCAM-1 during metastasis development enables earlier detection of metastases in the brain, using our novel VCAM-1-targeted contrast agent, than is currently possible clinically. Early detection of brain metastases may significantly alter patient prognosis.