Targeting radiation-induced neuroinflammation using ICAM-MPIO

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Target audience

Basic scientists and oncologists interested in preclinical research on detecting early signs of radiation-induced inflammation.

Purpose

Current magnetic resonance imaging methods lack sensitivity and specificity for imaging early post-irradiation inflammatory changes in the brain. Intercellular adhesion molecule (ICAM1) plays a key role in the early inflammatory cascade following brain irradiation. ICAM1 proteins mostly express on the luminal surface of the endothelium of brain venules and capillaries and promote the recruitment and migration of leukocytes. This expression of ICAM1 is upregulated in a time-dependent manner with a peak at 48h post-irradiation[1].

Micron-sized particles of iron oxide (MPIO) consist of an iron oxide core surrounded by an inert polymer coat. Recently MPIO have been shown to be useful for molecular imaging of adhesion molecules using T2* MRI[2].

In this work we used 2.8 µm sized MPIO labeled with anti-ICAM1 antibodies to selectively image in vivo endothelial ICAM1 expression in an animal model of early radiation injury.

Methods

MPIOs (M-280 tosylactivated Dynabeads, Invitrogen, UK) were conjugated with monoclonal antibodies against rat-specific ICAM1 (Abcam, UK) according to Sibson et al[3].

In vitro binding of ICAM-MPIO was assessed by incubating TNF-α stimulated rat endothelial cell lines (GP8 and RBE4) with both free MPIO and ICAM-MPIO.

The right hemisphere of four young male Wistar rats (mean 93g) was irradiated with 20Gy using the Small Animal Radiation and Research Platform (SARRP, X-Strahl, UK). 48 hours later, the animals were continuously scanned before and up to 2h after injection of either ICAM-MPIO (n=2) or free MPIO (n=2) with a 3D FLASH sequence (TR=50ms, TE=10ms, isotropic resolution 120µm, NA=2,TA=31') on a PharmaScan 70/16 MR system (Bruker, Germany). Ex vivo imaging was performed on formalin-fixated brains of the rats using the imaging sequence described (NA=12).

Results

In vitro tests showed binding of the ICAM-MPIO to the stimulated endothelial cell lines whereas free MPIO showed a random distribution in the cell cultures without binding to the cell walls (data not shown).

After administration of free MPIO no significant differences were observed between the pre and both the in vivo and ex vivo post-injection scans (Fig 1D-F). After ICAM-MPIO administration clear signal dropouts were observed on the T2* images, with the highest signal differences of the labeled MPIO during the scan of 1 to 1h30 post-injection. The ICAM-MPIO could be clearly localized in the hippocampus, the white matter of the corpus callosum and to a lesser extent the cortex of the irradiated right hemisphere (arrows Fig 1B and C).

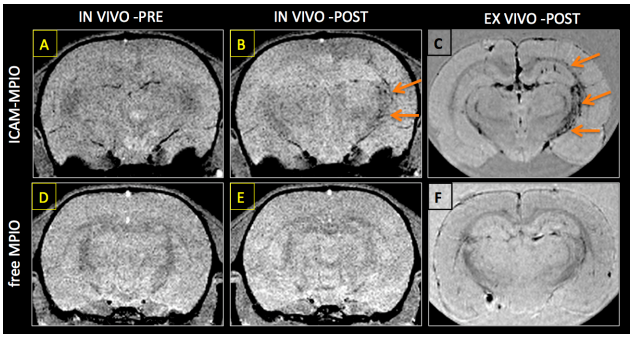

Fig. 1. Accumulation of ICAM-MPIO in the ipsilateral hippocampus and corpus callosum following 20Gy irradiation of the right hemisphere

Discussion and conclusion

Using ICAM1 labeled MPIO we were able to visualize acute inflammation following irradiation of a rat brain hemisphere with 20Gy. Free MPIO showed no binding to the activated endothelium both in vitro and in vivo.

Imaging ICAM1 in acute inflammation after irradiation will allow for in vivo preclinical assessment of the impact of radiation dose and volume on the inflammatory response as well as in vivo assessment of e.g. prophylactic treatment with anti-inflammatory drugs.

References

1. Yuan H et al. Radiat Res, 2005; 2. McAteer MA et al. Nature Medicine, 2007; 3. Sibson N et al., Methods Mol Biol, 2011