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RGD targeting of human ferritin iron oxide nanoparticles can enhance in vivo carotid MRI of experimental atherosclerosis

Toshiro Kitagawa[1*], Hisanori Kosuge[1], Masaki Uchida[2], Trevor Douglas[2], Michael V McConnell[1]

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Background

Human ferritin (HFn) is a promising nanoscale protein cage platform for molecular/cellular imaging, and we have developed engineered HFn nanoparticles as MRI agents. Inflammation and angiogenesis contribute to atherosclerosis, and RGD is a well-studied ligand of the $\alpha_v\beta_3$ integrin expressed by activated macrophages and angiogenic endothelial cells.

Purpose

To evaluate RGD-conjugated HFn-iron oxide nanoparticles for enhanced *in vivo* MRI detection of murine carotid atherosclerosis.

Methods

1) Mice

Fourteen FVB mice underwent left carotid ligation after 4 weeks of high-fat diet and diabetes induction by streptozotocin.

2) RGD-conjugated HFn-iron oxide nanoparticles

Using the recombinant human heavy-chain ferritin protein cage, HFn was genetically engineered to display 24 copies of an RGD-4C peptide (CDCRGDCFC) on the exterior surface of the protein cage. Magnetite (Fe_3O_4) was encapsulated in interior cavities of RGD-conjugated HFn (RGD^+ HFn) and non-targeted HFn (RGD^- HFn) at loading factors of 5000Fe per cage, giving R2 values of 93 $mM^{-1}s^{-1}$ (magnetite diameter: 5-7nm, exterior diameter: 12nm). The injected dose was adjusted to 25mgFe/kg.

3) MRI

Two weeks post ligation, mice were imaged on a whole-body 3T MRI scanner (Signa HDx, GE Healthcare) with a phased array mouse coil (RAPID MR International), using a gradient echo sequence (TR/TE=100ms/10ms, slice thickness=1.0mm, FOV=3cm, matrix=256x256, FA=60, NEX=10). Mice were then injected with either RGD^+ (n=7) or RGD^- (n=7) HFn nanoparticles, followed by MRI at 24 and 48 hours post injection. The nanoparticle accumulation was assessed by measuring the extent of T2*-induced reduction in carotid lumen size (% reduction of carotid lumen area).

4) Histology

Perl's iron staining was performed to identify accumulation of the nanoparticles in the carotid lesions.

Results

Both RGD^+ and RGD^- HFn nanoparticles caused a reduction in lumen size of the ligated left carotid arteries at 48 hrs due to T2* signal loss ($p<0.001$ vs. pre-injection, Figures 1, 2), but the effect was significantly greater with RGD^+ HFn ($p=0.01$ vs. RGD^- HFn). There was no significant lumen reduction in the non-ligated (control) right carotid arteries. Perl's iron staining confirmed greater accumulation of RGD^+ HFn in the lesion compared to RGD^- HFn, primarily in neointimal macrophages (Figure 3).

Conclusions

Human ferritin protein cage is a versatile nanoparticle imaging platform for *in vivo* cellular/molecular MRI, with enhanced atherosclerosis imaging through multivalent RGD targeting.

[1]Stanford University School of Medicine, Stanford, CA, USA
Full list of author information is available at the end of the article

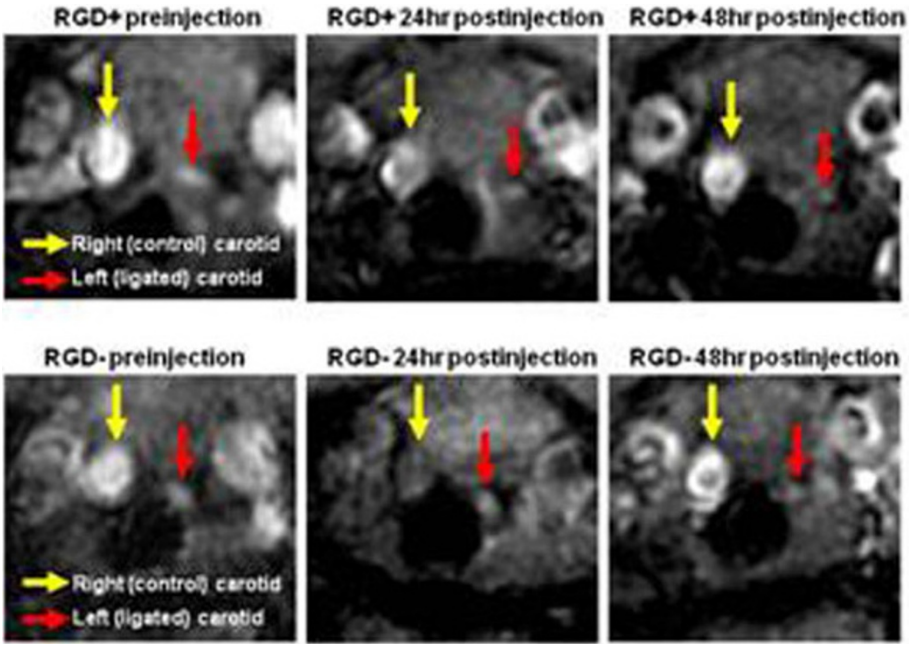

Figure 1

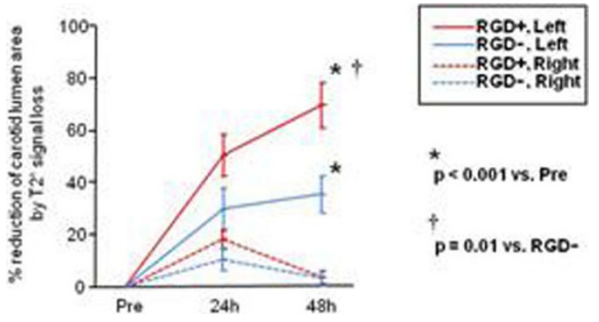

Figure 2

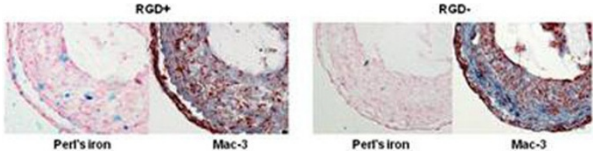

Figure 3

Author details
[1]Stanford University School of Medicine, Stanford, CA, USA. [2]Montana State University, Bozeman, MT, USA.

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