Multimodal Nanoprobes to Target Cerebrovascular Amyloid in the Alzheimer's Brain

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Introduction

Cerebral amyloid angiopathy (CAA) results from the accumulation of Aβ proteins primarily within the media and adventitia of small arteries and capillaries of the cortex and leptomeninges [1]. CAA affects a majority of Alzheimer's disease (AD) patients and is associated with a rapid decline in cognitive reserve. Unfortunately, there is no pre-mortem diagnosis available for CAA. However, MRI has emerged as a tool to image and identify AD in animal models. Furthermore, treatment options are few and relatively ineffective. To combat this issue, we have designed nanovehicles (nanoparticles-IgG4.1) capable of targeting cerebrovascular amyloid (CVA) and serving as early diagnostic and therapeutic agents. This work was published in Biomaterials [2].

Experimental

The nanovehicles were loaded with Gadolinium (Gd) based (Magnevist®) magnetic resonance imaging contrast agents or single photon emission computed tomography (SPECT) agents, such as ^{125}I. In addition, the nanovehicles carry either anti-inflammatory or anti-amyloidogenic agents, such as curcumin, or immunosuppressants, such as dexamethasone, which were previously shown to reduce cerebrovascular inflammation. With the anti-amyloid antibody (IgG4.1) grafted on the surface, the nanovehicles are capable of specifically targeting CVA deposits. The nanovehicles were characterized with animal models of Alzheimer's disease. Using the 21.1-T (900 MHz) magnet at the NHMFL, the nanovehicle as MRI contrast agent was evaluated with T_1 and T_2 relaxation sequences. Using the increased sensitivity of this ultra-high field magnet, high resolution MRI was done on *ex vivo* mouse brains to evaluate the nanovehicles potential to target CVA.

Results and Discussion

The nanovehicles effectively marginate from the blood flow to the vascular wall as determined by using a quartz crystal microbalance with dissipation (QCM-D) monitoring. They demonstrate excellent distribution to the brain vasculature and target CVA, thus providing MRI and SPECT contrast specific to the CVA in the brain. In addition, they also display the potential to carry therapeutic agents to reduce cerebrovascular inflammation associated with CAA, which is believed to trigger hemorrhage in CAA patients. Thus, with the anti-amyloid antibody (IgG4.1) grafted on the surface, the nanovehicles are capable of specifically targeting CVA deposits.

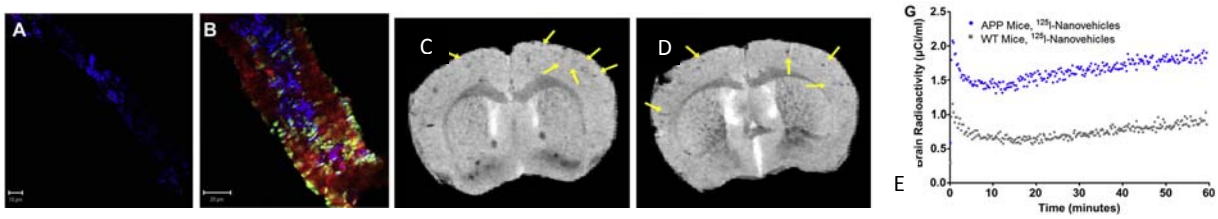

Fig 1: Uptake of AlexaFlour 647 (AF647) nanovehicles in the brain arteriole of wild type mouse (A) and brain of Alzheimer's animal model (APP Mice) (B). C-D: Ex vivo MRI of an APP mouse injected with the Gd-conjugated nanocvehicles and showing the subsequent MRI contrast. E: Brain uptake of ^{125}I-nanovehicles in APP mice vs ^{125}I-nanovehicles in wild type mice as determined by single photon emission computed tomography (SPECT).

Conclusions

This paper demonstrates our successful design of a multi-modal nanovehicle and demonstrates its ability to target CVA deposits selectively with fluorescence imaging, SPECT and MRI. In addition, they also displayed the potential to carry therapeutic agents to reduce inflammation associated with CAA, which is believed to trigger hemorrhages in CAA patient.

Acknowledgements

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References

[1] Calhoun, M.E., *et al*., Proc Natl Acad Sci USA, **96**, 14088-93 (1999).
[2] Jaruszewski, K.M., *et al.,* Biomaterials, **35(6)**, 1967-76 (2014).