DEVELOPMENT OF NANOTHERANOSTICS TO DIAGNOSE AND TREAT CEREBRAL AMYLOID ANGIOPATHY

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Introduction: Cerebral amyloid angiopathy (CAA) is characterized by the deposition of amyloid beta (Aβ) proteins in the cerebral microvasculature. Individuals with CAA suffer from recurrent hemorrhagic strokes and capillary endothelial dysfunction which is believed to accelerate neurodegeneration in Alzheimer’s disease (AD) patients.

Aims: The objective of this work is to develop a theranostic nanovehicle (TNV) capable of delivering diagnostic and therapeutic agents to detect and treat CAA.

Methods: A TNV consists of a polymeric nanocore made from gadopentetate dimeglumine (Gd-DPTA), a magnetic resonance imaging (MRI) contrast agent, conjugated chitosan. Cyclophosphamide (CYC), an immunosuppressant known to treat vascular inflammation resulting from CAA, was entrapped in the nanocore. A F(ab)² fragment of novel anti-amyloid antibody (IgG4.1) modified with putrescine was conjugated to the surface of the nanocore. The ability of TNVs to target cerebrovascular amyloid was determined in BBB models in vitro using laser confocal microscopy and in AD transgenic mouse brains using 21.1-Tesla MRI system. The ability of TNVs to reduce cerebrovascular inflammation caused by Aβ proteins was determined by monitoring IL-6 levels in the cerebral vasculature.

Results: Following intravenous administration, the accumulation of TNVs in the brain was 4 fold higher in AD transgenic mice than in the wild type mice. But the accumulation in the peripheral organs such as kidney, spleen and liver was similar in both animals. The TNV administration significantly reduced IL-6 levels in the cerebrovascular tissue.

Conclusions: The TNVs are capable of targeting cerebrovascular amyloid in AD transgenic animals and reduce vascular inflammation.