Development of Spontaneously Disassembling Dendrimers as a Platform Technology for PARACEST MRI Contrast Agents

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Abstract

PARACEST MRI contrast agents have been incorporated into nanocarriers to improve PARACEST sensitivity. Spontaneously disassembling dendrimers are nanocarriers can carry high payloads of chemotherapies to pathological tissues, and then rapidly release the chemotherapies during enzyme-triggered spontaneous disassembly of the dendrimers. To investigate whether a spontaneously disassembling systems can generate a PARACEST effect, a non-dendritic model system was shown to generate a PARACEST effect after enzyme-triggered spontaneous disassembly. To investigate the translation of this approach to a dendritic system, the G0 core of a spontaneously disassembling dendrimer was designed and synthesized. Additional studies are underway to refine this platform technology for PARACEST MRI, and the utility of this platform technology as a 'theranostic' for simultaneously monitoring enzyme biomarkers and the release of chemotherapeutics from spontaneously disassembling dendrimers.

Introduction:

PARACEST MRI contrast agents have been developed that can detect enzyme activity (1), although the inherent insensitivity of PARACEST limits their utility for in vivo studies. Nanocarriers with high payloads of PARACEST MRI contrast agents have been developed to improve PARACEST detection sensitivity, but the slow pharmacokinetic elimination of these nanocarriers raises concerns regarding toxicity (2). Therefore, a new nanotechnology platform must be developed that can carry high payloads of PARACEST agents, and then rapidly release the agents to accelerate pharmacokinetic elimination of the PARACEST agents. Spontaneously disassembling dendrimers are a new nanotechnology platform that can be triggered to rapidly self-cleave their polymeric branches into monomer units, which can be used to rapidly release payloads such as chemotherapies (3). This report investigates the development of this nanotechnology platform for PARACEST MRI, and whether the triggering of spontaneous disassembly can be exploited to detect enzyme activity with PARACEST MRI.

Methods:

To investigate whether spontaneous disassembly can be exploited to detect enzyme activity with PARACEST MRI, a non-dendritic model system was synthesized by conjugating a spontaneously disassembling "TriMethyl Lock" moiety and an ortho-AminoAnilide-YbDO3A PARACEST MRI contrast agent (YbDO3A-oAA-TML) (4,5). The PARACEST effects of 25 mM of YbDO3A-oAA-TML were measured before and after adding 3 units of pig liver esterase. The PARACEST effect of YbDO3A-oAA was also measured and compared to the PARACEST effect of the enzyme reaction product. To investigate whether a spontaneously disassembling dendrimer can be exploited to generate similar results, a G0 core of a spontaneously disassembling dendrimer (figure) was synthesized and characterized using NMR spectroscopy and mass spectrometry (6).

Results and Discussion:

The chemical syntheses of YbDO3A-oAA and Yb-DO3A-oAA-TML were verified using standard NMR spectroscopy and mass spectrometry. The addition of esterase enzyme to the solution of YbDO3A-oAA-TML produced a 13% PARACEST effect. This result confirmed that a spontaneously disassembling system that is triggered by an enzyme can generate a PARACEST effect, which can be used to detect enzyme activity. The chemical shift of the PARACEST effect of the enzyme reaction product was identical to the chemical shift of the PARACEST effect of YbDO3A-oAA, which confirmed that the enzyme triggered the spontaneous disassembly of YbDO3A-oAA-TML to release YbDO3A-oAA. The chemical synthesis of G0 core of a spontaneously disassembling dendrimer was verified using standard NMR spectroscopy and mass spectrometry methods. The similarity of the chemical design of the spontaneously disassembling cores of YbDO3A-oAA-TML and the dendrimer indicate that spontaneously disassembling dendrimers are a feasible platform technology for PARACEST MRI contrast agents.

Conclusions:

The triggering of a spontaneous disassembling system can release a PARACEST MRI contrast agent from the system. This release of the MRI contrast agent can change the PARACEST effect of the agent, which can be used to report on the enzyme activity. The development of the core of a spontaneously disassembling dendrimer that is similar to the core of the spontaneously disassembling system demonstrates that spontaneously disassembling dendrimers can also be developed to trigger the release PARACEST MRI contrast agents from the nanocarrier and report on enzyme activity. Additional studies are underway to investigate the kinetics of the triggering and spontaneous disassembly of higher generation dendrimers that release PARACEST MRI contrast agents, and the utility of this platform technology as a 'theranostic' for simultaneously monitoring enzyme biomarkers and the release of chemotherapeutics from spontaneously disassembling dendrimers.

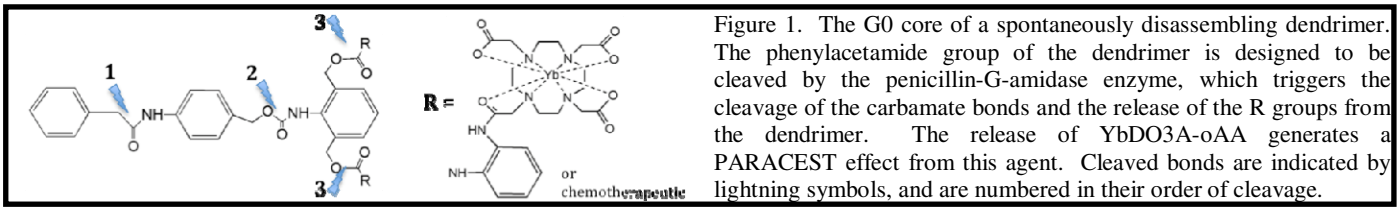

Figure 1. The G0 core of a spontaneously disassembling dendrimer. The phenylacetamide group of the dendrimer is designed to be cleaved by the penicillin-G-amidase enzyme, which triggers the cleavage of the carbamate bonds and the release of the R groups from the dendrimer. The release of YbDO3A-oAA generates a PARACEST effect from this agent. Cleaved bonds are indicated by lightning symbols, and are numbered in their order of cleavage.

References:

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