Dynamically Reversible Iron Oxide Nanoparticle Assemblies for Targeted Amplification of T1-Weighted Magnetic Resonance Imaging of Tumors

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Smart magnetic resonance (MR) contrast agents based on biocompatible extremely small-sized iron oxide nanoparticles (ESIONs) with pH-sensitive polymeric ligands, by which MR contrast can be selectively enhanced under acidic tumor microenvironment, are anticipated to significantly improve the diagnostic accuracy.1,2 However, their efficiency is often diminished due to the presence of hydrophobic ligands on their surface. After the disassociation of the assemblies in acidic microenvironment, these hydrophobic coatings on individual ESIONs can greatly suppress their water accessibility, resulting in minimally enhanced T1MR signal. Moreover, such polymer-based pH-sensitive assembly agents can convey false information in vivo as the disassembly process is initiated not only by the acidic microenvironment but also under diluted conditions where the polymer concentration is below its critical aggregation concentration (CAC).3 We herein report a pH-sensitive iron oxide nanoparticle assembly (IONA) that are cross-linked by small-molecular aldehyde derivative ligands.4 The dynamic formation and cleavage of hydrazone linkages in neutral and acidic environments, respectively, allow the reversible response of the nanoassemblies to pH variations. At neutral pH, IONAs are structurally robust due to the cross-linking by the strong hydrazone bonds. In acidic tumor microenvironment, the hydrazone bonds are cleaved so that the IONAs are quickly disassembled into a large number of hydrophilic ESIONs. As a result, significantly enhanced T1MR contrast is achieved, as confirmed by the measurement of r1 values at different pH conditions. Such acidity-targeting MR signal amplification by the pH-sensitive IONAs was further validated in vivo, demonstrating a novel T1 magnetic resonance imaging (MRI) strategy for highly sensitive imaging of acidic tumors.

References