Enzyme-Activated Aggregation of Peptide-Functionalized Nanoparticles for Targeted Destruction of Cancer Cells

Richard H. Huang,[1,2,3] Ye He,[2] Nazia Nayeem,[3,4] Jorge Morales,[1] Maria Contel,[4] Stephen O'Brien[1,2,3], and Rein V. Ulijn[2,3,5]

1. The City College of New York. 2. Advance Science Research Center at the City University of New York (CUNY). 3. The Graduate Center, CUNY. 4, Brooklyn College. 5. Hunter College.

Abstract

A modular peptide-functionalized gold nanoparticle (AuNP) system that displays enzyme-activated, electrostatically driven aggregation is reported in this study. Results demonstrate that the Arg-Gly-Asp (RGD) sequence within surface-immobilized peptides, originally intended to be an integrin-binding motif, serves as a minimalistic, self-complementary peptide ligand to drive electrostatic assembly of the nanoparticles. These RGD motifs become exposed on the nanoparticle surface through enzymatic cleavage by matrix metalloproteinase-9 (MMP-9). The exposure of RGD ligands at the particle surface promotes multivalent electrostatic bindings and ultimately leads to the aggregation of the AuNPs. This study also shows that a minimal change in the peptide sequence, specifically, a simple inversion of two amino acids, inactivates the enzyme-responsiveness of the system. This simple and robust nanoparticle design demonstrates the use of enzyme-activated electrostatic patterns in short peptide ligands to effectively trigger aqueous self-assembly. In vitro studies show selective killing of triple negative breast cancer cells by the MMP-9-responsive AuNPs. The MMP-9-inactivated AuNPs, in contrast, show minimal impact on the viability of the cancer cells.