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In-situ forming gel devices as local depot therapeutic for rheumatoid arthritis

Statement of the Problem: More efficient anti-inflammatory therapies with reduced side effects are needed to treat Rheumatoid Arthritis (RA), a chronic and disabling autoimmune condition that affects about 1% of the population in developed countries. Even though a multitude of cell types is involved, macrophages play a central role in the pathophysiology of RA. Locally implantable, targeted, macrophage-specific RNA interference (RNAi)-based therapies could therefore revolutionize RA therapy.

Methodology: Three-layered micelles (3LM) encapsulating nucleic acids were formed from tri-block copolymers of PLLA-PEI-PLLA and PLLA-PEG-PLLA in a three-step procedure. Their structure and DNA entrapment in the core was determined by TEM. Hydrodynamic diameters and zeta potentials were measured by dynamic light scattering. DNA release in neutral and acidic pH was detected by modified SYBR gold assays. For targeting of activated macrophages, folic acid (FA) was attached to the PEG-chain of a PLLA-PEG di-block affording PLLA-PEG-FA. Subsequently, 3LM were formed with PLLA-PEG-FA in the outer polymer shell. RAW264.7 cells were activated with LPS or left resting. Primary macrophages were isolated after *in vivo* activation. One day later, the cells were transfected with targeted and non-targeted 3LM, and GFP expression was quantified by flow cytometry. Thermo-responsive hydrogels were obtained by stereocomplexing 3LM which contain PLLA-PEG-PLLA in the outer core with PDLA-PEG-PDLA.

Conclusion & Significance: The core-corona structure and efficient DNA entrapment in the core were confirmed by TEM. Sizes were found to be less than 200 nm, and the encapsulation efficiency of DNA was optimized. 3LM were stable at neutral pH but released DNA in an acidic environment. 3LM were efficiently targeted to activated macrophages by blending PLLA-PEG-FA in the outer layer, while non-targeted micelles or PEI polyplexes were not efficiently taken up. Stereo-complexes of 3LM formed hydrogels above their phase transition temperature and released 3LM in acidic environment that efficiently transfected primary macrophages.

Biography

Olivia Merkel is a Professor of Drug Delivery in Department of Pharmacy at LMU Munich. From 2011 to 2016, she was an Assistant Professor of Pharmaceutics and an Associate Faculty Member of Oncology at Wayne State University and Barbara Ann Karmanos Cancer Institute in Detroit. She became a Registered Pharmacist in 2005. In 2006, she completed her MS in Pharmaceutics at Martin-Luther-Universität Halle-Wittenberg, and PhD in Pharmaceutics at Philipps-Universität Marburg in 2009. She received several awards, including an ERC Starting Grant, Galenus Foundation Technology Award, Wayne State College of Pharmacy Young Investigator Award and European Federation for Pharmaceutical Science Young Pharmaceutical Investigator Award. Currently, her research focuses on "Targeted siRNA delivery in cancer and inflammatory diseases.

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