Development of Biodegradable Fluorescent Nanogels as a Theranostic System

Dipendra Gyawali, Shengyuan Zhou, Yi Zhang, Jian Yang*
Department of Bioengineering, The University of Texas at Arlington, Arlington, Texas 76019
Joint Biomedical Engineering Program between UT Arlington and UT Southwestern Medical Center (jianyang@uta.edu)

Statement of Purpose: A successful drug delivery system should provide safe packaging of clinically approved drugs and deliver them to the targeted site of interest. However, it is also equally important to carry a diagnosis capability in the delivery system. In the past decade, significant efforts have been placed on the development of theranostic systems that not only deliver therapeutics but also diagnosis for the management of fatal diseases such as cancers. Fluorescent labeling and imaging have fueled the significant growth of life science and medical research due to the increasing demands on analyzing biomolecules, tracking biological process, and visualizing diseases and therapeutic efficacy. We have recently developed aliphatic biodegradable photoluminescent polymers (BPLPs), which are free of photobleaching organic dyes and toxic quantum dots (QDs). The superior photoluminescent properties (high quantum yield, photobleaching resistance, and tunable emission up to near infrared area) and degradability of the polymers, compared to traditional organic dyes and QDs, make them unique.[1] In contrast to the traditional organic dye or QDs which are just imaging agents but not implant materials, BPLP are polymers that could potentially be made into theranostic medical implants, such as theranostic nanoparticles for cancer drug delivery and cancer diagnosis. Herein, we further develop photocrosslinked biodegradable photoluminescent polymer (PBPLP) and study its potential application as theranostic devices.

Methods: PBPLP prepolymer was synthesized according to previously published methods[1] with few modifications. Briefly, Citric acid, polyethylene glycol, maleic acid, and L-Cysteine were reacted at 135º C under nitrogen flow. L-Cysteine is used as a representative amino acid to make blue fluorescent polymers. Average molecular weight, chemical composition, functionality, and fluorescent properties of the prepolymers were characterized. These prepolymers were further crosslinked into PBPLP nanogels by free radical crosslinking in presence of acrylic acid (crosslinker). In vitro degradation and swelling properties were evaluated. In vitro cytotoxicity and cellular uptake of PBPLP nanogels were evaluated against colon cancer cell lines (HT-29). These nanogels were loaded with anti-cancer drugs and surface modified with monoclonal anti-carcinoembryonic antigen antibody for cancer drug delivery and targeting. Evaluation of the targeting and delivering efficiency of these antibody-tagged, drug-loaded flourescent nanogels were conducted by incubating them in a co-culture system using colon rectal cancer cells and non-cancerous cells.

Results: Low-molecular-weight PBPLP prepolymers (1 to1.5 KDa, MALDI-MS) were characterized by FTIR to confirm polyester formation. Prepolymers were further crosslinked via free radical crosslinking into stable crosslinked PBPLP (CPBPLP) nanogels with the size range of 85 nm to few micrometers. CPBPLP nanogels demonstrated superior photostability over conventional organic dyes upon 3-h continuous exposure under UV light. In vitro degradation study showed that CPBPLP nanogels were completely degradable within a week or so. Upon incubation with HT-29 cell lines, these nanogels demonstrated negligible toxicity (below 5%) and rapid internalization to the cytoplasm of cells (Fig. 1). PBPLP nanogels conjugated with monoclonal anti-carcinoembryonic antigen antibody and encapsulated with paclitaxel suggested that the CPBPLP nanogels system could potentially serve as a novel theranostic drug delivery system for cancer diagnosis and treatment.

Conclusions: In this work, we have developed a new class of photocrosslinked biodegradable photoluminescent polymer that could be fabricated into monodisperse nanogels. These nanogels demonstrated unique intrinsic fluorescence without dye/QD conjugation and completely degradable. Upon incubation of nanogels with cells, they were rapidly internalized without noticeable toxicity. This nanogel system can potentially serve as an in-vivo safe fully biodegradable theranostic nano-device for cancer management.

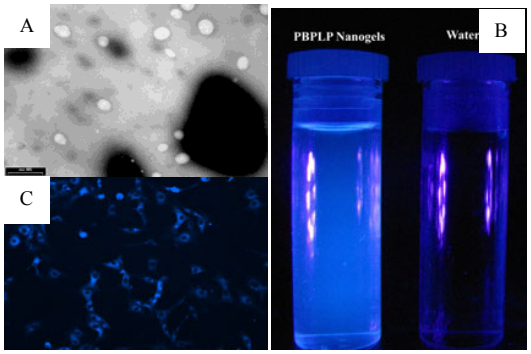

Figure 1: A) TEM image of PBPLP nanogels (scale bar 200 nm), B) PBPLP nanogels under UV light, and C) Observation of cellular uptake of PBPLP nanogels under a fluorescent microscope.

References:

1) Yang J, Zhang Y, Gautam S, Liu L, Dey J, Chen W, et al. Development of aliphatic biodegradable photoluminescent polymers. Proc Natl Acad Sci U S A 2009, 106(25):10086-10091.

Acknowledgement

This work was supported in part by a NSF CAREER award (0954109), a NIBIB R21 award (EB009795-01), and a CPRIT High Impact/High Risk Research Award (RP110412).