Click chemistry played a Janus-faced role in biodegradable polymer design

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Introduction: Most biodegradable elastomeric polymers such as poly(glycerol sebacate) (PGS), poly(ε-caprolactone) (PCL), and citrate-based biodegradable elastomers (CABEs) such as poly (1, 8-octanediol citrate) (POC) [1] and biodegradable photoluminescent polymers (BPLPs) [2], are weak in mechanical strength, especially when molded into porous scaffolds and/or used in vivo at wet state, thus significantly limiting their applications in tissue engineering areas. The introduction of urethane or amine groups into polyesters has been proved as an effective way for improving mechanical strength of polyester elastomers. It was reported that the triazole rings resulted from click chemistry could imitate amide bonds thus can also serve as mechanical strength improving moieties. On the other hand, biofunctionalization, especially site- or ligand-specific biofunctionalization to regulate cell/tissue-biomaterial interactions, has been a challenge. As one of the most effective, site-specific reactions, click chemistry, especially copper-free click chemistry, has been a promising way for functionalizing bio-related systems. Herein, click chemistry was introduced into CABEs as a Janus-faced role and a novel mechanical chemistry design strategy to simultaneously improve the bulk material mechanical strength and enable easy surface site-specific biofunctionalization, we believe that this strategy may be broadly applied to other functional biodegradable polymer designs too.

Methods: Azide (pre-POC-N$_3$) and alkyne (pre-POC-Al) functionalized POC pre-polymers were synthesized separately by polycondensation of citric acid (CA), 1, 8-octanediol (OD), and azide or alkyne functional diols (DAzD or AID in Scheme 1A) via an one-pot polycondensation process. Then, pre-POC-N$_3$ and pre-POC-Al were mixed and crosslinked via a thermal synchronous binary (TSB) crosslinking mechanism, both thermal click reaction between azide and alkyne groups and esterification between –COOH and –OH groups took place simultaneously to form TSB crosslinked POC-click elastomers (Scheme 1B). The uniquely introduced extra azide groups on POC-click polymers enabled an easy biomolecule conjugation via another copper-free click reaction, strain-promoted alkyne-azide cycloaddition (SPAAC) in aqueous environment. As an example, collagen mimetic peptide p15, which can effectively promote the adhesion and proliferation of endothelial cells (ECs), was clicked on to POC-click films and scaffold (Scheme 1B and S1) through SPAAC, and the viability/proliferation of human umbilical vein endothelial cells (HUVEC) on modified films were investigated. Chemical and thermal properties of polymers were characterized by NMR, FTIR, DSC and TGA, and the in vitro and in vivo cytocompatibility and degradation profile of POC-click polymers were also investigated. The mechanical properties of them were also studied.

Results: The tensile stresses of POC-click polymers are 10-40 MPa higher than that of POC (5 MPa), the Young’s modulus of POC-click-3 even reaches as high as around 300 MPa, which is nearly 60 times higher than that of POC. POC-click polymers also exhibited favorable “first slow then fast” degradation profile without obviously prolonging the degradation time.

Scheme 1. (A) Synthesis of pre-POC-N$_3$ and pre-POC-Al; (B) Thermal synchronous binary cross-linked POC-click film and porous tubular biphasic scaffold Preparation and p15 conjugation on them by strain-promoted alkyne-azide cycloaddition (SPAAC).

The residual azide groups on POC-click polymers (Scheme 1B) paved the way for convenient bioactive molecule conjugation on the surface of POC-click films or scaffolds via SPAAC. The p15 clicked POC-click polymer film or scaffold exhibited promoted human umbilical vein endothelial cells (HUVEC) cell adhesion and proliferation ability.

Conclusions: The present work successfully combined two kinds of copper-free click reactions, thermal click reaction and SPAAC, which serve as a novel crosslinking method and efficient surface conjugation route respectively. The application of click chemistry as a Janus-faced role could be extended to the other CABEs such as BPLPs and possibly many other biodegradable polymers such as PGS and PCL. The using of click chemistry as a Janus-faced role would attract broad interests in the field of biomaterials as it is applicable to modify a number of different types of polymers for improved mechanical properties and biofunctionality.

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References:

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