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Protocols

Hydrophilic modification of intraocular lens via surface initiated reversible addition-fragmentation chain transfer polymerization for reduced posterior capsular opacification

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ABSTRACT

Phacoemulsification followed with intraocular lens (IOL) implantation is the most effective clinical surgeries in treating cataracts. However, posterior capsular opacification (PCO), a common complication of this surgery, may cause vision decrease after surgery. PCO is mainly caused by the adhesion, proliferation and trans-differentiation of the residual lens epithelial cells (LEC) after surgery. Surface modification of IOL to reduce the LEC adhesion is of great importance in PCO prevention. Herein, surface initiated reversible addition-fragmentation chain transfer (SI-RAFT) polymerization was utilized to modify the IOL materials for generating a comb-like polyethylene glycol (PEG) brush coating on the surface. The ATR-FTIR, XPS, and contact angle characterizations indicate the successful immobilization of the RAFT agent, as well as the subsequent SI-RAFT polymerization of PEG macromonomer. More interestingly, the PEG brush coating shows excellent hydrophilicity on the surface. The in vitro LEC culture and bacteria adhesion results show that the hydrophilic modification can effectively reduce the bio-adhesion. The in vivo implantation results show that the PEG brush modified IOL presents good biocompatibility, and significantly decreases the posterior capsular hyperplasia. These results demonstrate that the surface modification of IOL with excellent hydrophilic brush via SI-RAFT may provide a good alternative for IOL anti-PCO modification.

1. Introduction

Cataract, resulting from the formation and accumulation of abnormal components in place of the transparent lens, is the most common cause of vision impairment in the world today. By the year 2020, there will be 32 million cataract operations performed every year, as predicted by the World Health Organization in 2015 [1]. Surgical removal of cataractous lens followed with intraocular lens (IOL) implantation is the only effective treatment currently [2]. However, posterior capsular opacification (PCO), also known as secondary-cataract, occurring months to years after surgery, decreases visual acuity significantly [3]. The incidence of PCO in adults is within the range of 20–40% after 5-year postoperation, and it is as high as 100% in childhood cases [4]. PCO is regarded to be the result of adhesion of residual lens epithelial cells (LECs) onto the implanted IOL and posterior capsule after cataract surgery. The wound healing process promotes residual LECs to adhesion, proliferation, epithelial-mesenchymal transition (EMT), and extracellular matrix deposition via auto/paracrine cell signaling pathways between the IOL and capsule interface [5].

Neodynium:YAG (Nd:YAG) laser capsulotomy is used to treat PCO clinically [6]. Nevertheless, this strategy brings new complications, including retinal detachment, intraocular pressure increasing or IOL optic damage [7]. Many attempts have been taken to reduce the PCO incidence, such as postoperative administration of anti-proliferative or anti-inflammatory drugs, upgrading in surgical technique, improvement of IOL design, as well as novel IOL materials investigation [8–11]. Besides these attempts, surface modification of biomedical materials and implantable devices to improve their biocompatibility has gained more and more attention in recent years [12–16]. With advantages in economic and effective aspects, IOL surface modification may be a prospective way to improve the biocompatibility for PCO prevention purpose.

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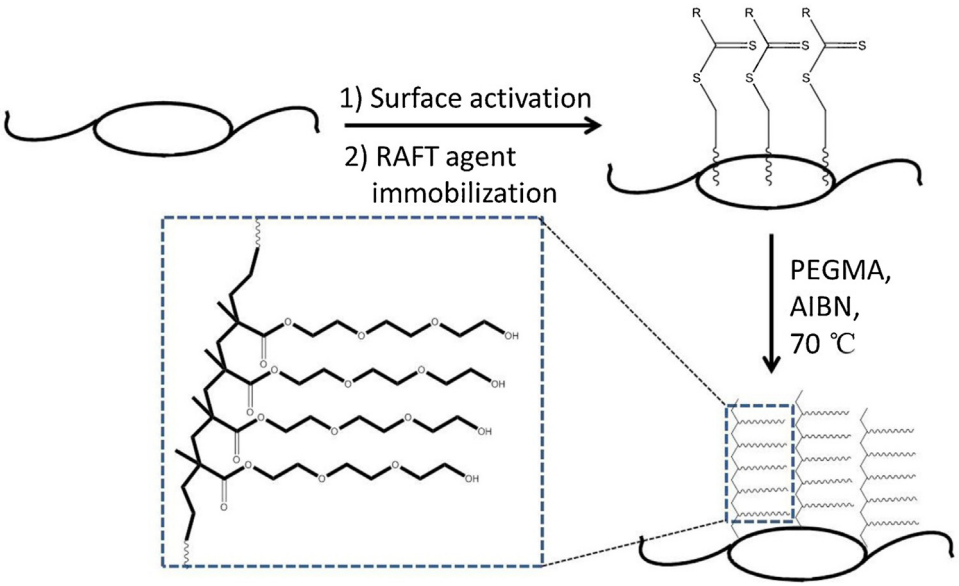

Scheme 1. IOL surface modification with PEG brushes via SI-RAFT polymerization.

Several methods have been introduced for the IOL surface modification to control the LEC adhesion and proliferation on IOL materials in the past decade, including the plasma treatment, chemical grafting, and layer-by-layer deposition [17–21]. For example, surface passivation with Fluorine decreases the LEC adhesion [22]. IOL surface tethering with hydrophilic molecules, such as heparin, polyethylene glycol (PEG) or phosphorylcholine (PC) moieties also reduces the adhesion and proliferation of the LEC onto the surface [23–25]. The hydrophilic molecules "grafting to" the IOL surface have improved the material hydrophilicity and reduced the acute bio-adhesion on the IOL materials effectively. However, the long-term biocompatibility still needs to be improved [26,27].

The well-defined polymer brush, obtained from living radical polymerization reactions, is one of the most effective methods to achieve surface modification [28]. Surface modification with polymer brushes shows two main advantages: one is that the surface property can be predictably tethered by choosing the polymer brushes component; the other one is the excellent long-term stability owing to chemical and mechanical robustness [29,30]. The polymer brushes can be obtained via either "grafting to" or "grafting from" method [31]. By utilizing active species on the surface to initiate polymerization, the "grafting from" approach usually results in a high grafting density comparatively [32]. Reversible Addition-Fragmentation chain-Transfer (RAFT) polymerization is one of the attractive living radical polymerization reactions, which is compatible with diverse monomeric structures under mild reaction conditions [33]. RAFT polymerization has gained more and more attentions in biomedical applications as RAFT technique requires no metal catalysts, resulting in less toxicity [33]. Upon immobilization of the RAFT agents on surfaces, surface initiated RAFT (SI-RAFT) polymerization can be carried out, which provides an effective control over the thickness and density of the polymer grafting [34].

Herein, SI-RAFT polymerization was carried out to generate PEG brushes on the surface of the IOL materials (Scheme 1). To our knowledge, it is the first time that SI-RAFT technology was used to improve the IOL surfaces to improve their in vivo biocompatibility. Taking advantages of effectiveness of the "grafting from" method and the well-defined PEG brushes via SI-RAFT, the aim of this work is to generate an anti-fouling coating on IOL surface, which would efficiently inhibit the LEC adhesion and proliferation, thus reducing the PCO incidence.

2. Experimental

2.1. Materials

Polyethylene glycol methacrylate (PEGMA, Mn = 360), fluorescein diacetate (FDA), 4-cyano-4-(phenyl-carbonothioylthio) pentanoic acid (CPADB), 4,4′-azobis-(4-cyanovaleric acid) (V501), (3-aminopropyl) triethoxysilane (APTES), 2-morpholino-ethanesulfonic acid (MES), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC), *N*-hydroxysulfosuccinimide sodium salt (NHSS), and inhibitor removers (Prepacked column for removing hydroquinone and monomethyl ether hydroquinone) were purchased from Sigma-Aldrich. Cell counting kit-8 (CCK-8) and bicinchoninic acid (BCA) kits were obtained from Beyotime Biotechnol. Co., Ltd. Hematoxylin-Eosin staining kit was purchased from Leagene Biotechnol. Co., Ltd. Polydimethylsiloxane (PDMS) was prepared from Sylgard® 184 from Dow Corning, according to the manufacturer's instructions, using 10:1 ratio of elastomer base to curing agent. Foldable intraocular lens for animal experiment uses was provided by Alcons (Alcon® SN60WF). Human lens epithelial cell line (HLEC, HLE B3, CRL-11421™) was originated from American Type Culture Collection (ATCC). PEGMA was passed through the inhibitor remover column before usage. The clinical postoperative administration drugs were obtained from Eye Hospital of Wenzhou Medical University. All other chemicals were of analytical grade and used without further purification.

2.2. PEG brush tethering and characterization

PDMS silicone materials or IOL were used as the substrates for PEG brush coating modification via SI-RAFT. Each experiment was initiated by oxygen plasma pre-treatment by radio-frequency capacitively plasma reactor (PJ-II, AST Products, Inc., USA) at an oxygen pressure of 0.3 Torr for 30 s, which resulted in a hydroxyl species modified substrate surface [27]. The materials were treated with 1% APTES solution overnight, which resulted in a stable amino group functionalized substrate surface [19]. Then the carboxyl group-ended RAFT agent was coupled onto the aminolyzed substrates via carbodiimide chemistry [35]. Briefly, 0.22 mg/mL