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Alleviation of capsular formations on silicone implants in rats using biomembrane-mimicking coatings

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ABSTRACT

Despite their popular use in breast augmentation and reconstruction surgeries, the limited biocompatibility of silicone implants can induce severe side effects, including capsular contracture – an excessive foreign body reaction that forms a tight and hard fibrous capsule around the implant. This study examines the effects of using biomembrane-mimicking surface coatings to prevent capsular formations on silicone implants. The covalently attached biomembrane-mimicking polymer, poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC), prevented nonspecific protein adsorption and fibroblast adhesion on the silicone surface. More importantly, in vivo capsule formations around PMPC-grafted silicone implants in rats were significantly thinner and exhibited lower collagen densities and more regular collagen alignments than bare silicone implants. The observed decrease in α-smooth muscle actin also supported the alleviation of capsular formations by the biomembrane-mimicking coating. Decreases in inflammation-related cells, myeloperoxidase and transforming growth factor-β resulted in reduced inflammation in the capsular tissue. The biomembrane-mimicking coatings used on these silicone implants demonstrate great potential for preventing capsular contracture and developing biocompatible materials for various biomedical applications.

1. Introduction

Breast augmentation constitutes approximately 20% of all plastic surgery procedures in the world, and the number of cases continues to increase with society's growing interest in beauty [1]. In addition, demands for breast reconstruction surgery are increasing as a result of patients who have had mastectomies to remove cancerous tissues. Implants based on silicone elastomer bags that are filled with silicone gel, saline or other fillers are the most widely used implants for both breast augmentation and reconstructive surgical procedures [2]. Recipients are generally well satisfied with the breast-like mechanical properties and low cost of the silicone-based breast implants, but limited biocompatibility still provokes serious problems. Gabriel et al. [3] previously reported that, among 749 women who had breast implantation, 208 (27.8%) had received revision surgery due to single or multiple complications. Among them, capsular contracture – serious fibrous capsule formation around implants – was the most frequent complication, causing 131 women (17.5%) to undergo further surgical intervention. It has been reported that capsular contracture occurs over a timescale ranging from several months to years after breast implantation [4–7].

It has been hypothesized that capsular contracture might result from excessive foreign body reactions on the silicone surface, gel

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bleed, dust, glove powder, etc., or by subclinical infection by normal skin flora (usually by *Staphylococcus epidermidis*) [8–12]. The foreign body reaction include, in particular, the inflammatory process and exaggerated scar response to a foreign prosthetic material [13,14]. Here, a fibrous capsule develops around the implant by the natural healing response to the presence of a foreign body, but results in excessive fibrotic scarring. Although the mechanism has not yet been elucidated in detail, the foreign body reaction is likely initiated by non-specific adsorption of proteins on the silicone surface within several minutes of implantation [15]. Macrophages are then recruited to the implantation site and form giant cells within 2 days due to their inability to successfully phagocytose the too-large foreign body. Collagenous encapsulation and excessive formation of fibrous tissue around the implant occur within 3 weeks.

Surface modifications of silicone implants have been studied as a means of reducing excessive foreign body reactions. Silicone implants coated with polyurethane [16] or fabricated with textured surfaces [17] have demonstrated limited success in clinical studies. However, the prevalence of capsular contracture after implantation remains significantly high [18], so the search for more biocompatible surfaces continues.

Among the various methods used to prepare biocompatible surfaces, coating with biomembrane-mimicking materials is very attractive [19]. Poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) mimics the head group of phosphatidylcholine in the cell membrane and exhibits exceptional anti-protein-adsorption activity, anti-thrombotic activity and hemocompatibility when used in coating materials for coronary stents [20], artificial joints [21], drug delivery carriers [22] and biomicrofluidics [23]. Increased hydrophilicity due to zwitterionic groups and biomembrane-mimicking phosphocholine moieties of PMPC are important contributors to the outstanding biocompatibility exhibited by PMPC-coated materials [24].

The present study examines the effects of PMPC coating on capsular formation around silicone implants inserted into rats (Fig. 1). Although implants coated with other polymers, including hyaluronic acid (HA), polyethyleneglycol (PEG) and polyacrylamide (PAAm) [25], failed to alleviate capsular formation, we suspected that, given its biomembrane-mimicking properties, PMPC-coated silicone implants have the potential to modulate the initiation process and to reduce excessive capsular formation. It has been previously reported that the surface of polydimethylsiloxane (PDMS), a silicone elastomer, was successfully coated by PMPC, resulting in significantly reduced protein adsorption and cell adhesion [26,27]. In this study, successful PMPC coating of the silicone implants was confirmed via dynamic water contact angles and X-ray photoelectron spectroscopy (XPS). Subsequently, nonspecific protein adsorption and the adhesion of fibroblast cells, which were the primary collagen-producing cells, were measured. More importantly, PMPC-coated silicone implants were inserted subcutaneously into the backs of rats, and the resulting capsular formations were carefully compared to those observed on bare silicone implants. Various quantitative studies comparing capsular thickness, inflammatory cells, vascularity and amounts of transforming growth factor-β (TGF-β), α-smooth muscle actin, myeloperoxidase and CD34 were performed to examine the effects of PMPC coating on capsular formation.

In vivo analysis of PMPC-coated silicone implants is very important for finding ways to reduce the side effects of implantation, including capsular contracture, through a greater understanding of the mechanisms of foreign body reactions, and is crucial for establishing strategic footholds regarding the use of biocompatible materials in various biomedical applications.

2. Materials and methods

2.1. Materials

PDMS elastomer base and curing agent (Sylgard 184) were purchased from Dow Corning (USA). Benzophenone, bovine serum albumin (BSA) and bovine plasma fibrinogen (BPF) were purchased from Sigma-Aldrich (USA). 2-Methacryloyloxyethyl phosphorylcholine (MPC) monomer was purchased from KCI (Korea). Dulbecco's modified Eagle's medium (DMEM), Dulbecco's phosphate-buffered saline (DPBS) and fetal bovine serum (FBS) were purchased from WelGENE (USA).

2.2. Preparation of silicone implants

The silicone implants were prepared from the silicone elastomer (PDMS) base (Sylgard 184) according to the manufacturer's protocol. A mixture of the base and the curing agent (10:1, w/w) was poured on a glass plate, degassed in a vacuum chamber and cured in an oven at 100 °C for 1 h. The cured silicone plate was cut into a disk (15 mm diameter, 0.5 mm thickness for in vitro and 2 mm thickness for in vivo) and preserved in acetone.

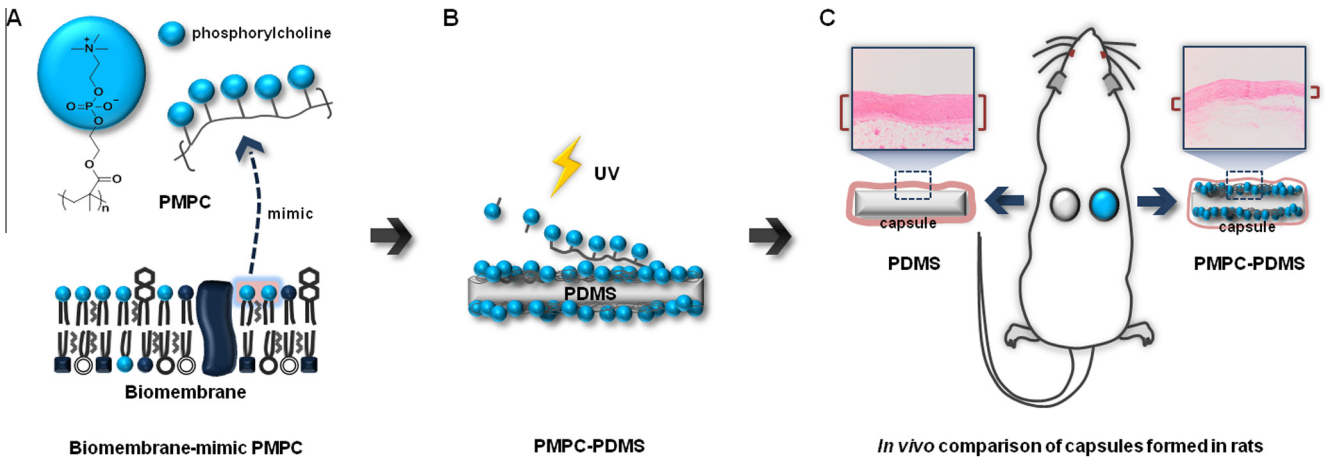

Fig. 1. Schematic illustration of silicone-implant coating and implantation. (A) Biomembrane-mimicking PMPC, a hydrophilic and biocompatible polymer containing the head group of the most abundant phospholipid in cell membranes. (B) Preparation of PMPC–PDMS via UV-induced surface polymerization of MPC on PDMS. (C) In vivo comparison, for the purpose of examining biocompatibility, of capsules formed on PDMS and PMPC–PDMS in rats.