Elastic/adhesive double-layered PLA-PEG multiblock copolymer membranes for prevention of cecum and cardiac adhesions

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Statement of Purpose: Tissue adhesions cause severe and life-threatening conditions, including pain, infertility, and heart defects. The purpose of this study is to develop an anti-adhesion membrane that sticks onto the injured tissue or organ site in order to avoid the suturing for fixing the membrane which may lead to the unnecessary tissue adhesion. We previously developed poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) multiblock copolymers as soft, water absorbable, and quickly degradable biomaterials. The copolymer with the highest PEG content adsorbs body fluid in vivo and sticks to the tissues. In the present study thin film and nanofiber mat were prepared from the copolymer and evaluated in vitro and in vivo.

Methods: Oligo(L-lactic acid) (OLA) and PEG with Mn of 4,600 3,000 were copolymerized for multiblock copolymers with high molecular weight as previously described[1,2]. Briefly, they were charged into a round flask equipped with a condenser, and succinic acid for adjusting the OH /COOH ratio to 1 and stannous 2-ethylhexanoate (final 0.2 wt %) were added. Diphenylether was charged and the polymerization was performed at 2.7 kPa and 180°C for 16–24 h. The multiblock copolymers with different compositions (LE(m)-x, where x denotes PEG content of copolymers) were purified and analyzed by 1H-NMR GPC. Double layered membrane was prepared based on spin coating method and electrospinning method using HFIP as solvent. Their mechanical strength and in vitro degradation rate were evaluated.

Adhesions in Wistar rats weighing 200–300 g were induced by scrubbing the surface of the cecum using abrasive paper until the serosa membrane was peeled away and by complete cutting off the pericardium after the third rib incision. The samples were directly applied to the injured cecum or heart without suture before closure. The rats were sacrificed 1 week after surgery to observe tissue adhesion at the injured site. The injured sites were observed and the adhesion grade was estimated according to adhesion severity with a numeric score of 0–2 (0 = no adhesion, 1 = moderate adhesion, and 2 = severe adhesion). The experimental protocols were designed in accordance with the animal experimental guidelines established by the animal research committee at the National Cerebral and Cardiovascular Center Research Institute. All efforts were made to minimize the suffering and the number of animals used.

Results: The Mn of LE(m)-16, LE(m)-32, and LE(m)-53 decreased 81, 84, and 86% in 12 weeks in PBS. The PEG content of the multiblock copolymers slowly decreased with immersion time. The reduction in PEG content may be attributed to cleavage of the ester bonds connecting PLA and PEG when immersed in PBS. LE(m)-88 was not evaluated because it swelled rapidly and collapsed in PBS, which makes the polymer sticky to the tissue surface.

LE(m)-88 was a good candidate to reduce protein adsorption and cell adhesion because of its high PEG content. Its film was swollen with tissue fluid and showed a hydrogel-like nature when it was put on the injured site. Since it was easily removed from the site, it required a support membrane to fix it at the injured site. Then, the effect of support membrane was investigated using LE(m)-16, LE(m)-32, and LE(m)-53 with a lower PEG content than LE(m)-88 and less hydrophilicity. When LE(m)-32 film (not nanofiber mat) was used as support membrane no adhesion was observed in cecum adhesion. This high potency of LE(m)-32/ LE(m)-88 membranes was also confirmed in cardiac adhesion as shown in Figure 1.

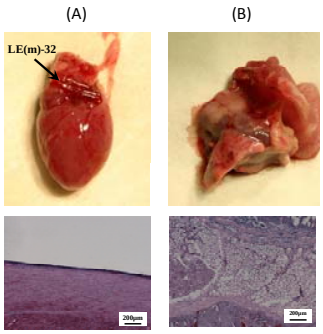

Figure 1. Prevented postoperative cardiac adhesions with double-layered PLA-PEG multiblock copolymers (A) and adhesion after control surgery (B).

Conclusions: A double-layered anti-adhesion membrane was fabricated by the combination of hydrophilic LE(m)-88 with hydrophobic LE(m)-32. The LE(m)-88 side was attached to the site of injury, and the LE(m)-32/LE(m)-88 film inhibited cecum and heart adhesion. It was very easy to use the LE(m)-32/LE(m)-88 double-layered anti-adhesion membrane during surgery. An elastic/adhesive double-layered combination of hydrophobic and hydrophilic PLA-PEG multiblock copolymer membranes could be a prospective candidate for prevention of adhesion.

References:

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