In vivo evaluation of thromboresistance on PLLA/phospholipid polymer blend

Hyung Il Kim,[1,2] Kazuhiko Ishihara,[1] Seung Bok Lee,[3] Ji-Hun Seo,[1] Hye Young Kim,[3]
Dong Whan Suh,[3] Tomohiro Konno,[1] Madoka Takai,[1] Jeong-Sun Seo[2,3]
[1]School of Engineering, University of Tokyo, Tokyo, Japan
[2]Macrogen Inc, Seoul, Republic of Korea
[3]Seoul National University College of Medicine, Seoul, Republic of Korea

Statement of Purpose:

The purpose of this research is to obtain thromboresistant and biodegradable materials for cardiovascular stent application. Stent thrombosis is life-threatening cardiovascular complications mediated by thrombosis at implantation sites of drug-eluting stents.[1] In order to reduce stent thrombosis, novel polymer blends composed of poly(L-lactic acid) (PLLA) and a water-soluble amphiphilic poly(2-methacryloyloxyethyl phosphorylcholine-co-*n*-butyl methacrylate) (PMB30W; Fig. 1) were prepared.[2] To evaluate the effect of phosphorylcholine groups of PLLA/PMB30W after animal implantation, biodegradation profiles and biocompatibility of PLLA tubing and PLLA/PMB30W tubing have been studied.

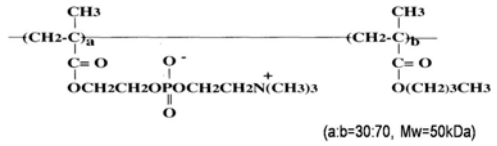

Fig. 1. Chemical structure of PMB30W

Methods:

The PLLA/PMB30W tubing were constructed by a solvent blending technique[2] and sterilized with ethylene oxide gas. After implantation into interscapular subcutaneous tissues of rats, weight change of polymer scaffolds and molecular weight change of polymers were calculated by a gravimetric method and gel permeation chromatography, subsequently. The inner surface of tubing after implantation was analyzed by X-ray photoelectron spectroscopy (XPS). After implantation into abdominal aorta of rats and internal carotid arteries of rabbits, cross-sectional areas of PLLA tubing and PLLA/PMB30W tubing have been determined. After contact with human blood cells, the inflammatory reaction of PLLA tubing and PLLA/PMB30W tubing has been studied.

Results and Discussion:

PLLA tubing and PLLA/PMB30W tubing exhibited extremely slow degradation profiles in an animal implantation. At 6 months after implantation, weight loss change has been occurred about 2 % in both PLLA and PLLA/PMB30W tubings. The molecular weight of PLLA implants has not decreased by 6 months.

Table 1. Change of molecular weight of PLLA.
(Mf=Mn after 6 months; Mi= Mn before implantation)

	PLLA	PLLA/PMB30W
Mf/Mi	1.01±0.18	0.96±0.08

The inner surface of PLLA/PMB30W tubing demonstrated high density of phosphorylcholine groups, which have been detected by XPS. After the implantation, high P/C ratios also have been observed on the inner surface of PLLA/PMB30W.

Compared to PLLA tubing, the PLLA/PMB30W tubing reduced blood clot formation and deposition of cells on the surface *in vitro* and *in vivo* (abdominal aorta of rats and internal carotid arteries of rabbits). Minimal lumen areas and mean lumen areas have been significanlty increased on the implanted PLLA/PMB30W tubing as shown in Figure 2.

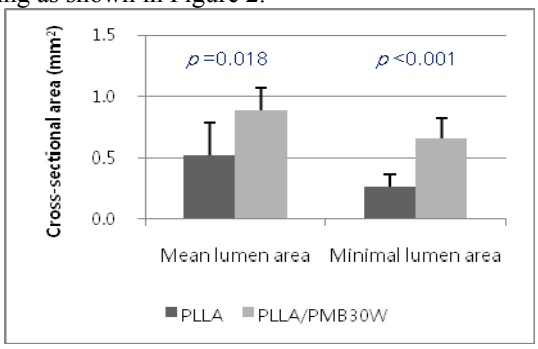

Fig. 2. Cross-sectional area of polymer tubing after 30 days implantation into left (PLLA) and right (PLLA/PMB30W) cartid arteries of rabbits.

After contact with human blood cells on PLLA/PMB30W, numerous inflammatory markers (MIF, TNF-a, IL-1b, IL-6) have been decreased, compared to PLLA. Human blood cells could recognize phosphorylcholine groups on biomaterials and reduce the inflammatory reaction.

Conclusions:

Extensive *in vitro* and *in vivo* models to evaluate biodegradation and thromboresistance of PLLA/PMB30W have been conducted for development and evaluation of cardiovascular materials. Here, we present our direct evidence that phosphorylcholine groups strongly improved the blood compatibility when high density of phosphorylcholine groups was constructed on the surface.

References:

1. Serruys PW et al. Lancet. 2009; 897-910.
2. Kim HI et al. Tissue Eng. Part C. 2009; 15: 125-133.

Acknowledgements:

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