Multi-scale surface modification of Ti for orthopedic implant application

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States of purpose: Surface roughness of biomedical implants has been recognized as a critical factor of osseo-integration that determines the long-term success of the implants [1]. Sand blasting with large grits and acid etching (SLA) treatment has been a most widely used technique for creating macro-roughness on the Ti implant surface. However, there is still room for improvement of osseointegration in clinical use, where insufficient bone mass is common for aged patients or patients with diseases such as diabetes and metabolic bone diseases [2]. Recent studies have proposed the introduction of nano-scale roughness to the implant surface, which plays an important role in protein adsorption and cell adhesion that contribute to the improvement of oseeointegration [3]. Thus, in this study, we have modified the surface of Ti implants that have multi-scale roughness at both micro and nanoscales by combining SLA and selective plasma etching (SPE) treatments for improved osseointegration.

Methods: Commercially available bare and SLA-treated Ti plates were used for the experiments. For the SPE process, SLA-treated Ti substrates were placed in a vacuum chamber and cleaned by argon-based plasma in order to remove any residual surface contamination. Subsequently, the substrates were etched by Ta ions produced from sputtering of a Ta target under high negative substrate bias of 800V. Surface morphologies of all Ti specimens were observed by SEM. The *in vitro* cell tests were carried out using MC3T3 cells to evaluate cell attachment and differentiation behavior after culturing for 3 hr and 13 days, respectively. The *in vivo* animal tests were performed on four female New Zealand white rabbits using screw-shaped Ti implants with a diameter of 3.4mm (**Fig. 3A**). Tibial defects were created on each of the hind legs using a hand piece drill. Four weeks after implantation, the rabbits were sacrificed, and extracted defects were fixed, blocked using resin, and stained for histological analysis.

Results: The surface morphologies of the specimens are shown in Fig. 1. The surface of SLA Ti became irregularly roughened at micro scale with small pits (Fig. 1A). Additional SPE process for SLA-nano Ti made the rough surface of SLA Ti slightly blunted (Fig. 1B), but created regularly patterned nanopores with a diameter of ~50 nm on the SLA surface (Fig. 1C). The biological properties of the specimens were evaluated using both *in vitro* and *in vivo* tests. Compare to the non-treated and SLA Ti, the SLA-nano Ti exhibited significantly improved cell attachment density and ALP activity, implying that additional nano-scale roughness of SLA-nano Ti promotes the cellular responses. The *in vivo* bioactivity was assessed using the rabbit tibial defect model. The histological images of figure 3B indicate the area of new bone formation at the interface between the old bone and Ti implant with each surface treatment (non-treated, SLA-treated, and SLA-nano Ti). The SLA-nano Ti surface exhibits significantly improved new bone regeneration with dense and thick new bone in the defect region as compare to the non-treated and SLA-treated Ti surfaces. These *in vitro* and *in vivo* tests clearly indicate that muti-scale surface roughness of Ti improves osseointegration in defected region, implying great potential of the combined SLA-SPE surface treatment for orthopedic implants.

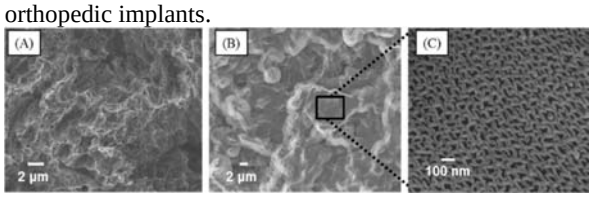

Figure 1. Surface morphology of (A) SLA Ti, (B, C) SLA-nano Ti at different magnifications

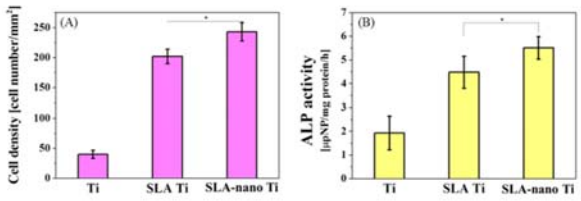

Figure 2. (A) Cell attachment density after culturing 3h, and (B) ALP activity of cells after culturing 13days on non-treated Ti, SLA Ti, and SLA-nano Ti. (* $p<0.05$)

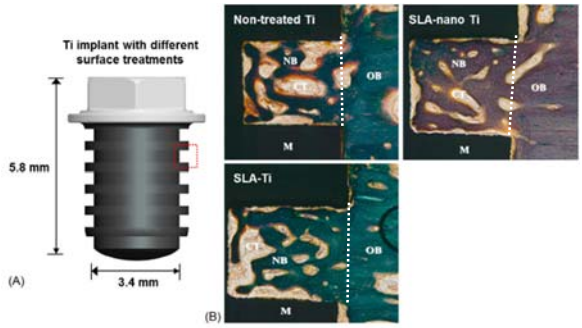

Figure 3. (A) Schematics of Ti implants used for in vivo tests and (B) histological images of new bone formation into the non-treated Ti, SLA Ti, and SLA-nano Ti. New bone (NB), old bone (OB), implant material (M), and connective tissue (CT) were marked.

Conclusions: The multi-scaled surface roughness on Ti has been successfully created via combined SLA and SPE process. The superimposed nanoscale roughness onto the micro-roughened SLA was found to significantly improve cell attachment and differentiation with *in vivo* bone regeneration. The multi-scale roughened surface by the SLA-SPE process shows great potential for surface treatment of various orthopaedic implants.

References

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[2] Gittens RA et al. Biomaterials 2011;32:3395-403.
[3] Levine BR et al. Biomaterials 2006;27:4671-81.