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Background

Nanotube technology has been around for a while and well-studied by multiple labs around the world. Khosravi et al. has done an animal study looking at the vascularization around implants[1]. Utilizing a literal glass window, they monitored vascular on-growth and vessel maturation that led to new bone formation around the implant. The test materials were machine finished titanium (TiMA) and micron roughened anodized titanium nanotube surface (TiNT). The authors found that the nanotube surface TiNT significantly outperformed the machine finished surface TiMA in speed of vascularization, bone volume around implant and bone to implant contact.

The foundation of creating new bone is the vasculature that will feed the new bone, provide oxygen and remove waste[2,3]. Without the resources needed to make bone, the body will make fibrous tissue that can't stabilize orthopedic implants. With insufficient resources, the body will heal more slowly.

Titanium dioxide nanotubes have demonstrated the ability to interact with the body to encourage a healing response that further recruits vasculature[1,2]. Nanotube surfaces with specific size and range of size features on titanium implants enable these effects through increased protein binding and spacing of cell attachments[4,5].

Methods

Implants composed of Grade 4 commercially pure titanium were machined into a cross-shaped structure, 4 mm in diameter and 500 µm thick, with a central hole 2 mm in diameter. Four flutes, each with an internal radius of 0.5mm, were machined into the cross-shaped structure to limit bone contact during implantation and encourage vascular growth and leave a void space that can be used to visualize vascular ingrowth. The titanium surfaces were machine-finished to create a control surface (TiMA). Half of the implants were further modified by grit blasting, acid etching, and anodization to create titanium dioxide nanotubes (TiNT).

Titanium cranial implants were implanted into the skull bone of mice. The schematic of the implantation is shown in Figure 1. A glass window was glued over the implant to prevent infections and allow for visualization of the vascular growth and maturation process. To visualize the vascular system, fluorescent dye was injected into the tail vein of mice prior to visualization of vascular structures with confocal microscopy. The glass window allowed for sequential visualization of the same implant/mouse and the tracking of vascular growth onto the implants. After 42 days, the animals were sacrificed, and the implants were scanned using micro-CT imaging to quantify bone growth onto the implants.

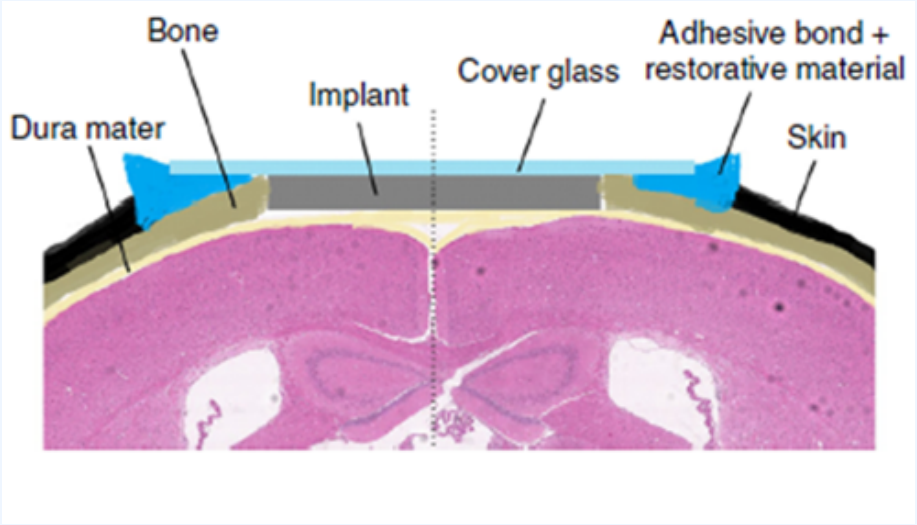

Figure 1: Placement of the titanium implants into the skull of the mouse allows bone contact. Covering the wound with a glass cover allows for visualization of the vascular bed with fluorescent microscopy and tracking of vascular on-growth and maturation. This image is modified from the work of Khosravi et al[1].

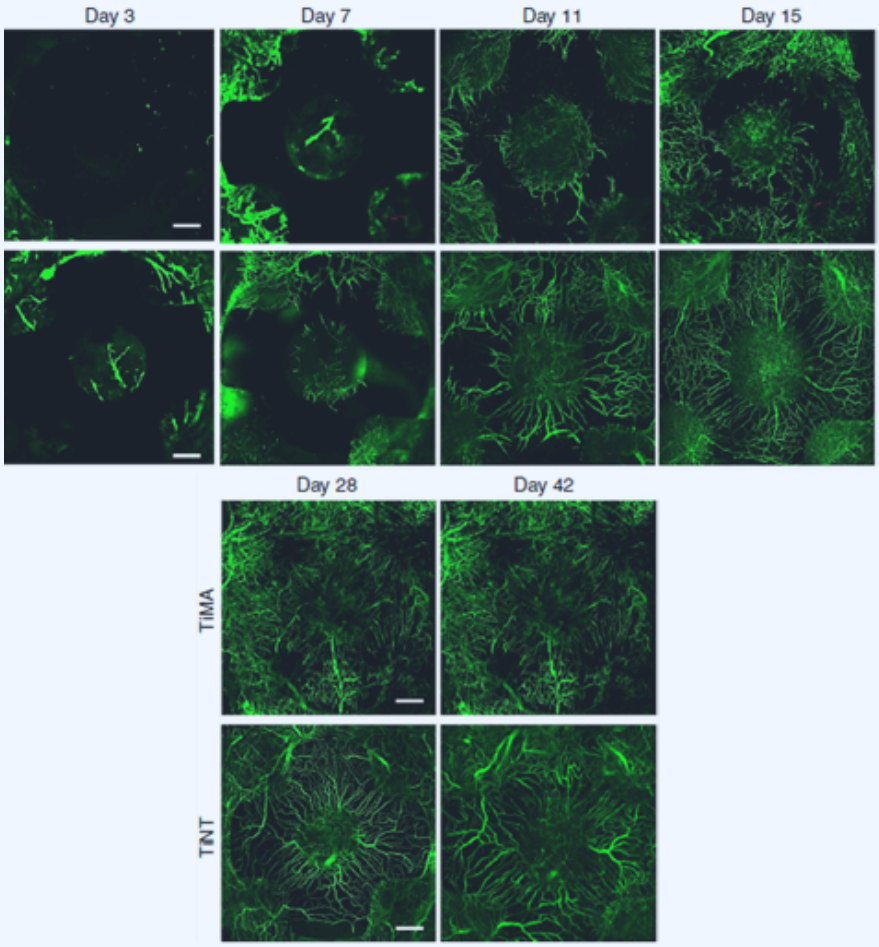

Figure 2: In vivo longitudinal microvascular response to TiMA and TiNT cranial implants. Representative images demonstrating formation and development of the peri-implant neovascular network from Day 3 to Day 42 around the TiMA surface and the TiNT surfaced implants. Scale bars: 500 µm. Images are stacks of tiled scans of the entire craniotomy at the maximum intensity projection; the depth of the field is 0.5 mm, which is equal to the thickness of the implant. This image is modified from the work of Khosravi et al[1].

Results

The vascular growth onto the titanium implants with nanotubes (TiNT) occurred more quickly than on the control machine finished surface (TiMA) on Day 3, Day 7, Day 11, and Day 15. Higher vascular density was observed on the TiNT surface than the TiMA surface at all time points. Vessel coverage was also complete at an earlier timepoint (Day 15) on nanotubes, as shown in Figure 2. Hierarchical vessel maturation was also evident on the nanotube surface at Day 11, with continued maturation out to 42 days. The TiMA surface showed delayed vessel maturation relative to the nanotube surfaces. There was also greater bone-to-implant contact (76% vs. 11%) and higher bone volume (35% vs. 10%) for the TiNT surface compared with the TiMA surface, as shown in the corresponding graphs available in the full publication1.

Discussion

Nanotube surfaces have been shown to modify the in vivo behavior of multiple tissue types, including vasculature and bone[1-7]. There are multiple studies by various peer reviewed groups that have shown the benefits of nanotube surfaces in vitro[4-7]. But in vitro studies cannot replicate the complexity of what happens in vivo. This study allows a literal window into the process of vascular growth onto implants that results in new bone formation. Improvements in vascularization with nanotube surfaces on implants will directly benefit patients by allowing more complete osseointegration.

Conclusion

The authors of this publication demonstrated that nanotube modified surfaces (TiNT) have a significant advantage over machine finished surfaces (TiMA) in vivo. In this study, nanotubes were shown to be better at recruiting vasculature sooner and growing bone more quickly.

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