

On the immune regulation of bone response to biomaterials.

Akademisk avhandling

Som för avläggande av odontologie doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i F-sal 3, Medicinaregatan 12E, den 15 november 2019, klockan 13.00.

av Ricardo Trindade

Fakultetsopponent:

Andreas Thor, Professor

Uppsala Universitet, Sverige

Avhandlingen baseras på följande delarbeten

- I. Trindade R, Albrektsson T, Tengvall P, Wennerberg A. Foreign body reaction to biomaterials: On mechanisms for buildup and breakdown of osseointegration. *Clin Implant Dent Relat Res* 2016; 18(1):192-203.
- II. Trindade R, Albrektsson T, Galli S, Prgomet Z, Tengvall P, Wennerberg A. (2018). Osseointegration and foreign body reaction: Titanium implants activate the immune system and suppress bone resorption during the first 4 weeks after implantation. *Clin Implant Dent Relat Res* 2018; 20(1):82-91.
- III. Trindade R, Albrektsson T, Galli S, Prgomet Z, Tengvall P, Wennerberg A. Bone Immune Response to Materials, Part I: Titanium, PEEK and Copper in Comparison to Sham at 10 Days in Rabbit Tibia. *J Clin Med* 2018; 7(12):526.
- IV. Trindade R, Albrektsson T, Galli S, Prgomet Z, Tengvall P, Wennerberg A. Bone Immune Response to Materials, Part II: Copper and Polyetheretherketone (PEEK) Compared to Titanium at 10 and 28 Days in Rabbit Tibia. *J Clin Med* 2019; 8(6):814.

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Abstract

Osseointegration is the biological basis for bone anchorage of oral implants, and revolutionized the replacement of lost teeth. It is also applied in bone anchored hearing aids and limb replacement in amputees. In biomaterial science, the *in vivo* mechanisms involved in host-biomaterial interaction - the foreign body reaction (FBR) – have been studied in soft tissues but not in bone. The present thesis aims to explore these important mechanisms in bone.

A literature review of current knowledge in FBR identified the immune system as central for host tissue response to biomaterials: materials modulate the immune system, which in turn directly regulates the local tissue reaction (Paper I). A hypothesis was developed that titanium, rather than inert, is immunomodulatory in bone and osseointegration the result of a specific immune-inflammatory reaction triggered by titanium, in an attempt to isolate the foreign material from the rest of the body.

In vivo animal pilot studies were performed (rabbit model, in femur and tibia bone), to explore the aforementioned immune mechanisms. The methods used were gene expression analysis to explore the cell and molecular mechanisms, and histology to study the bone tissue response.

The first experimental study (Paper II) compared bone healing around titanium versus normal bone healing without a biomaterial (sham), demonstrating that titanium is not inert, rather induces an immune reaction in bone up to at least 28 days.

A second experimental study (Paper III) compared materials titanium (osseointegrating material), copper and PEEK (non osseointegrating) versus sham (natural bone healing) at 10 days, demonstrating that titanium suppresses pro-inflammatory (M1-macrophage) and promotes a reparative reaction (M2-macrophage), whereas the other materials maintain a mixed M1/M2 reaction, i.e. still a pro-inflammatory environment at an early healing stage. These results suggest that osseointegration is defined at an early stage in biomaterial healing; also, that PEEK is not inert.

A final experimental study (Paper IV) compared the 10 days results in Paper III with 28 days (post-inflammatory period) on a copper and PEEK with titanium as a control study; the results showed a continued activation of M1 and M2 around copper and PEEK at 28 days, and also that PEEK may have a specific mechanism that induces adipose tissue formation instead of bone.

In conclusion, bone reaction is specific to the type of implanted material, titanium is immunogenic and osseointegration the result of a specific immune-inflammatory balance triggered by titanium in bone.

Keywords: Biomaterial, immune system, osseointegration, foreign body reaction, immune modulation, titanium, copper, polyether ether ketone, PEEK.

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