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On osseointegration in response to controlled surface nanotopography

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Föreläsningssalen, Biotech Center, Arvid Wallgrens Backe 20, Göteborg, fredagen den 11 juni 2021, klockan 13:00

av Dimitrios Karazisis

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Avhandlingen baseras på följande delarbeten

I. Karazisis D, Ballo AM, Petronis S, Agheli H, Emanuelsson L, Thomsen P, Omar O. ***The role of well-defined nanotopography of titanium implants on osseointegration: cellular and molecular events in vivo.*** *Int J Nanomedicine. 2016;11:1367-82.*

II. Karazisis D, Petronis S, Agheli H, Emanuelsson L, Norlindh B, Johansson A, Rasmusson L, Thomsen P, Omar O**.** ***The influence of controlled surface nanotopography on the early biological events of osseointegration.*** *Acta Biomater. 2017;53:559-571.*

III. Karazisis D, Rasmusson L, Petronis S, Palmquist A, Furqan A. Shah FA, Aghelie H, Emanuelsson L, Johansson A, Omar O, Thomsen P. ***The effects of controlled nanotopography, machined topography and their combination on the molecular activities, bone formation and biomechanical stability during osseointegration.*** *Manuscript Submitted.*

IV. Karazisis D, Omar O, Petronis S, Thomsen P, Rasmusson L. ***The molecular response to nanopatterned implants in human jaw bone.*** *Manuscript Submitted.*

SAHLGRENSKA AKADEMIN
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On osseointegration in response to controlled surface nanotopography

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Abstract

Knowledge about the biological responses provoked by the surface modification of titanium implants on the nanoscale is still in its infancy. Although *in vitro* studies claim superior effects considering higher adhesion and proliferation of osteoblasts in the short term and even differentiation towards the osteogenic cell lineage in the long term, these responses do not necessarily reflect the actual outcome in the complex *in vivo* environment. Therefore, the main aim of this thesis was to evaluate the biological responses at the bone interface to titanium implants with controlled surface nanotopography. Both very early and late healing events were considered, and the phases of acute inflammation, bone regeneration and bone remodeling were evaluated, first in the rat tibia and thereafter in human maxillary bone. This was performed by screening and quantification of genes of interest, representing the different healing phases, by quantitative polymerase chain reaction (qPCR), and correlating these molecular events to morphological (histology and histomorphometry) and biomechanical (removal torque) outcomes of osseointegration.

The first study used a specially designed implant with nanopatterns only at the cylindrical part facing the bone marrow and not the threads that were engaging the cortical bone. Analyses showed that the gene expression of the proinflammatory cytokine tumor necrosis factor alpha (TNF-α) and osteoclast marker cathepsin K (CatK) was downregulated at the nanopatterned implants at 3 and 6 days, respectively. This finding was consistent with fewer CD163-positive macrophages in the peri-implant tissue. Due to improved methodology, the nanopatterns could be applied to complex screw-shaped implants resembling clinical dental implants and used in the second, third and fourth studies. In the second study, evaluating the very early tissue-implant interactions, nanotopography downregulated the expression of monocyte chemoattractant protein-1 (MCP-1) at 12 hours and triggered the expression of osteocalcin (OC) at 3 days. This was in parallel with a relatively lower number of CD68-positive monocytes and a higher proportion of early-formed bone. In the third study, it was demonstrated that the nanotopography could downregulate the expression of the proinflammatory cytokine TNF-α even after 21 days. Osteoclastogenesis molecular activity was down-regulated at implants with combined nano- and microtopography at 6 days. A synergistic effect was disclosed, with the combination of micro- and nanotopography further attenuating the inflammatory response via TNF-α downregulation and resulting in an increased biomechanical stability, as judged by higher removal torque values. A human study showed that implants with nanotopography significantly increased the expression of all the targeted osteoblastic markers, namely, Runt-related transcription factor 2 (RUNX2), alkaline phosphatase (ALP) and OC, suggesting the promotion of bone formation.

In conclusion, nanotopography *per se*, attenuates the initial inflammatory response and increases bone formation while down-regulating osteoclastogenesis and bone resorption molecular activities. Furthermore, the combined effect of micro- and nanotopography can further attenuate the inflammatory response and enhance the mechanical stability of the implants.

Keywords: in vivo, nanotopography, osseointegration, titanium

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