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Biodegradable magnesium implants, immunomodulation and tissue repair/regeneration

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen. våning 5, BIOTECH Center, Arvid Wallgrens Backe 20, fredagen den 17 november, klockan 9:00

av

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Avhandlingen baseras på följande delarbeten

I. Ben Amara H, Martinez DC, Shah FA, Johansson Loo A, Emanuelsson L, Norlindh B, Willumeit-Römer R, Plocinski T, Swieszkowski W, Palmquist A, Omar O, Thomsen P.
Magnesium implant degradation provides immunomodulatory and proangiogenic effects and attenuates peri-implant fibrosis in soft tissues
Bioact Mater 2023; 26:353-369

II. Ben Amara H, Martinez DC, Iskhakova K, Emanuelsson L, Norlindh B, Johansson Loo A, Wieland DCE, Zeller Plumhoff B, Willumeit-Römer R, Plocinski T, Swieszkowski W, Shah FA, Palmquist A, Omar O, Thomsen P.
Magnesium implant degradation tunes inflammation and bone repair at the implant interface and beyond
Submitted for publication

III. Ben Amara H, Shah FA, Emanuelsson L, Norlindh B, Palmquist A, Omar O, Thomsen P.
Gas bubbles derived from magnesium implants provide mechanosensitive and proinflammatory stimuli in both soft tissue and bone
In manuscript

SAHLGRENSKA AKADEMIN
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Biodegradable magnesium implants, immunomodulation and tissue repair/regeneration

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Abstract

The century-old paradigm of holding fractures with a metallic implant to enable bone repair, known as osteosynthesis, is still used today without alteration. Patients are increasingly being treated with metallic implants made of magnesium (Mg) that secure osteosynthesis and are reabsorbed in situ without the surgical re-entry that requires their permanent analogs. Often, Mg implants achieve osteosynthesis. However, when failure occurs, aberrant inflammation in overlaying soft tissue and persistent peri-implant radiolucencies generated by gas release from the implants are common. How can this be reconciled with popular concepts predestining Mg implants to promote bone formation by mitigating inflammation and bone resorption? This thesis investigated the sequence of biological processes prompting soft tissue and bone to accommodate Mg implants with different degradation behaviors from early to relatively long healing. Detailed studies of cells and their molecular circuits during inflammation were undertaken in different but related biological compartments surrounding the implants. Complementary analytical microscopy and compositional spectroscopy were performed to characterize tissue assembly at the interface with the implants and beyond. Compared to nondegradable titanium implants, Mg implants amplify initial inflammation in soft tissue and bone. The rapid release of degradation products, including Mg^{2+} and gas, correlatively induces a strong, transient proinflammatory environment that fosters mRNA and protein programs associated with macrophage polarization, chemotaxis, osteoclastogenesis, and neovascularization but without cytotoxic effects. Thereafter, inflammation markedly subsides. The transition to soft tissue and bone repair coincides with the attenuation of Mg^{2+} concentrations and gas void generation in the peri-implant milieu in tandem with an enrichment in calcium and phosphorous on the implant surface. Immunomodulation by Mg implants, reflected by a shift from proinflammatory to prohealing macrophage activation, reinforces their anchorage in bone and alleviates fibrotic encapsulation in soft tissue. However, this restorative effect is not equal in response to the various Mg degradation behaviors. Pure Mg implants, which degrade faster than clinical-grade alloyed Mg implants, alter the composition of interfacial bone and result in a previously unknown proadipogenic response in the bone marrow beyond the bone–implant interface. This increased adiposity is closely associated with persistent gas voids in bone marrow. Gas voids encourage inflammation in their microenvironment, trigger mechanosensation, and may induce local bone matrix deposition. In conclusion, Mg implants in different tissues transiently amplify the initial immune reaction, and degradation product escape creates an inflammatory microenvironment at the tissue–implant interface and beyond. An appropriate reparative response is obtained but can be impaired by the uncontrolled implant degradation. Above the demand for rigorous tailoring of Mg implants, healing monitoring needs to expand to tissues outside the confines of the implant interface, with pending questions on the fate of tissues under compromised conditions.

Keywords: *Adipose tissue; Biodegradable implants; Bone–implant interface; Bone marrow; Inflammation; Cellular mechanotransduction; Gene expression; Immunohistochemistry; Magnesium; Neovascularization; Osseointegration; Soft tissue injuries.*

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