Molecular and structural patterns of guided bone regeneration (GBR)

Experimental studies on the role of GBR membrane and bone substitute materials

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. Elgali I, Igawa K, Palmquist A, Lennerås M, Xia W, Choi S, Chung UI, Omar O, Thomsen P. Molecular and structural patterns of bone regeneration in surgically created defects containing bone substitutes. Biomaterials. 2014; 35: 3229–3242.

II. Cardemil C[#], Elgali I[#], Xia W, Emanuelsson L, Norlindh B, Omar O, Thomsen P. Strontium-doped calcium phosphate and hydroxyapatite granules promote different inflammatory and bone remodelling responses in normal and ovariectomised rats. PLoS One. 2013; 8: e84932.

III. Turri A[#], Elgali I[#], Vazirisani F, Johansson A, Emanuelsson L, Dahlin C, Thomsen P, Omar O. Guided bone regeneration is promoted by the molecular events in the membrane compartment. Submitted.

IV. Elgali I[#], Turri A[#], Xia W, Norlindh B, Johansson A, Dahlin C, Thomsen P, Omar O. Guided bone regeneration using resorbable membrane and different bone substitutes: early histological and molecular events. Submitted.

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ABSTRACT

The mechanisms of guided bone regeneration (GBR) and bone healing with calcium phosphate (CaP) bone substitutes are not fully understood. The major aim of this thesis was to determine the relationship between the bone formation in bone defects and the cellular distribution and activities in association with CaP materials and/or with GBR membrane. The objectives were, firstly, to examine if the different CaP substitutes induce different cellular and molecular activities, and, secondly, to investigate the mechanisms of GBR with focus on the role of the barrier membrane in the bone healing process. A series of studies were performed in a rat trabecular bone defect model using a set of molecular (e.g. qPCR) and morphological (e.g. histology & histomorphometry) techniques.

Deproteinized bovine bone (DBB) and octa-CaP (TetraB) granules promoted bone regeneration and restitution of the defect. DBB was osteoconductive and elicited low resorption activity. TetraB induced early osteogenic and osteoclastic activities, resulting in greater bone formation than DBB. Strontium (Sr) doping of the CaP granules reduced the expression of osteoclastic resorption genes in comparison to hydroxyapatite (HA). Applying a collagen-based membrane on the defect promoted higher bone formation at all time periods. This was in parallel with upregulation of genes denoting cell recruitment and coupled bone formation and resorption (i.e. remodeling). The membrane was found to accumulate cells that expressed and released different pro-osteogenic growth factors (e.g. BMP-2). When the defect was simultaneously treated with the membrane and bone substitutes (DBB, HA, SrHA), more bone and an inhibitory effect of Sr on osteoclasts was demonstrated in the SrHA treated defect.

In conclusion, different calcium phosphate bone substitutes induce specific molecular cascades involved in the different processes of bone healing, including early inflammation, bone formation and remodeling. This promotes bone regeneration and defect restitution in comparison with the sham defect. Strontium incorporation in a synthetic CaP substitute reduces the osteoclastic resorptive activities, and promotes bone formation. Furthermore, the present results provide cellular and molecular evidence *in vivo* suggesting a novel role for the membrane during GBR, by acting as a bioactive compartment rather than as a passive barrier. The results provide new opportunities for the design of a new generation of materials to enhance bone regeneration.

Keywords: Regenerative medicine; biomaterials; bone substitute; calcium phosphate; guided bone regeneration; membrane; strontium; bone defect; bone remodeling; inflammation; cytokines; chemokines; growth factors; gene expression; histomorphometry; *in vivo*.

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