Bone and Cartilage Regeneration

Wnt Signaling Pathway in Healing

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. Thorfve. A, Dehne, T, Lindahl, A, Brittberg, M, Pruss. A, Ringe. J, Sittinger. M, and Karlsson. C, *Characteristic Markers of the Wnt Sgnaling Pathways Are Differentially Expressed in Osteoarthtitic Cartilage*. Cartilage 2012; 3: 43-57.

II. Svala. E, Thorfve. A, Ley. C, Barreto Henriksson. H, Synnergren. J, Lindahl. A, Ekman. S, and Skiöldebrand. E, *Effects of Interleukin-6 and Interleukin-1β on Expression of Growth Differentiation Factor-5 and Wnt Signaling Pathway Genes in Equine Chondrocytes.* Am J Vet Res 2014; 75: 132-140.

III. Thorfve. A, Lindahl. C, Xia. W, Igawa. K, Lindahl. A, Thomsen. P, Palmquist. A, and Tengvall. P, *Hydroxyapatite Coating Affects the Wnt Signaling Pathway during Peri-implant Healing in vivo.* Acta Biomater 2014; 10: 1451-1462.

IV. Thorfve. A, Bergstrand. A, Ekström. K, Lindahl. A, Thomsen. P, Larsson. A, and Tengvall. P, *Gene Expression Profiling of Peri-implant Healing of PLGA-Li^{+} Implants Reveals an Activated Wnt Signaling Pathway in vivo.* In manuscript, submitted to PLOS ONE.

UNIVERSITY OF GOTHENBURG

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Wnt Signaling Pathway in Healing

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Abstract

The Wnt signaling pathway plays a central role in bone and cartilage embryonic development, processes that are recapitulated during regeneration. Imbalance in such well conserved and complex system often contributes to numerous diseases, whereas controlled modulation of the Wnt signaling activity is an attractive target e.g. for improved fracture healing therapies.

The first aim of the present thesis was to increase the knowledge of the underlying mechanisms that lead to cellular alterations in osteoarthritis (OA), resulting in cartilage degeneration. In particular, we investigated the genome-wide expression profile of Wnt related markers in human OA cartilage and the effect of the pro-inflammatory cytokines IL-1β and IL-6 in the context of Wnt signaling pathway, thereby revealing mechanisms for OA modulation therapies.

As a second aim, we studied if a local release of the canonical Wnt activator Li^+ from hydroxyapatite (HA) or poly(lactic-co-glycolic acid) (PLGA) modulated the Wnt pathway and subsequently enhanced the bone regeneration around the implants.

The results indicated that the Wnt signaling pathways were dysregulated in OA cartilage, with a partly inhibited canonical Wnt signaling and an active non-canonical Wnt cascade. We were able to demonstrate that WNT5A was excessively expressed in degenerative cartilage, and that the pro-inflammatory cytokine IL-6 possessed cartilage protective properties by reducing β-catenin and canonical Wnt signaling. The canonical Wnt pathway was activated by HA but the osteoinductivity of HA itself overridden the Wnt modulating capacity of Li^+. Finally, a global gene expression profiling demonstrated that the controlled release of Li^+ from PLGA activated the canonical Wnt signaling.

In conclusion, the present findings may be used to develop gene targeted OA treatments and serve as a basis for further improvement of Li^+ based therapies associated to fracture repair. This thesis sheds further light on the ambiguous influence of Wnt signaling in osteochondral homeostasis and repair mechanisms.

Keywords: Wnt signaling pathway, osteoarthritis, bone regeneration, lithium

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