On the role of signalling pathways in the pathogenesis of osteoarthritis

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i aula Hjärtat
Vita Stråket 12, Göteborg,
torsdagen den 10 april, 2014 kl. 09.00

Johan Stenberg

Fakultetsopponent:
Professor **Anthony Hollander**
Faculty of Medical and Veterinary Sciences, School of Cellular and Molecular Medicine, University of Bristol, Bristol, United Kingdom

The thesis is based on the following studies,
referred to in the text by their Roman numerals:

I. **Quantitative proteomics reveals regulatory differences in the chondrocyte secretome from human medial and lateral femoral condyles in osteoarthritic patients** Stenberg J, Rüetschi U, Skiöldebrand E, Kärrholm J, Lindahl A. *Proteome Sci* (2013) 11:43.

II. **Clinical outcome three years after autologous chondrocyte implantation does not correlate with the expression of a predefined gene marker set in chondrocytes prior to implantation but is associated with critical signaling pathways** Stenberg J, de Windt T, Synnergren J, Hynsjö L, van der Lee J, Saris D, Brittberg M, Peterson L, Lindahl A. Manuscript.

III. **GDF5 reduces MMP13 expression in human chondrocytes via DKK1 mediated canonical Wnt signaling inhibition** Enochson L, Stenberg J, Brittberg M, Lindahl A. Osteoarthritis and cartilage (2014). doi:10.1016/j.joca.2014.02.004

IV. **Sustained embryoid body formation and culture in a non-laborious three dimensional culture system for human embryonic stem cells** Stenberg J, Elovsson M, Strehl R, Kilmare E, Hyllner J, Lindahl A. Cytotechnology (2011) 63:227–237

UNIVERSITY OF GOTHENBURG

On the role of signalling pathways in the pathogenesis of osteoarthritis

Johan Stenberg
Department of Clinical Chemistry and Transfusion Medicine,
Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden

Abstract

The problem with degenerating cartilage tissues is one of the major causes for disability worldwide. The aetiology of the cartilage degenerating disease osteoarthritis is elusive and considered to be multifactorial. The aim of the present thesis was to find new hypotheses regarding the aetiology of osteoarthritis with focus on signalling pathways. In particular, the conducted studies described expressional differences in different grades of cartilage extracellular matrix degradation and in chondrocytes used in successful and failed autologous chondrocyte implantations. These studies were conducted in order to generate new targets for studies of osteoarthritis aetiology and investigate putative biomarkers that could predict clinical outcome of autologous chondrocyte implantation. Further, the role of the osteoarthritis associated growth factor growth differentiation factor 5 in cartilage homeostasis was investigated. Finally, a non-laborious embryoid body culture system for further investigation of the effects of different factors on chondrogenesis was developed.

The different grades of cartilage tissue degradation revealed expressional patterns that may add to the knowledge regarding osteoarthritis aetiology and/or be further investigated for their role as diagnostic markers. There are no apparent differences in gene expressions between chondrocytes used in successful or failed autologous chondrocyte implantations indicating that the cells are seemingly alike before the procedure, which questions the demand for a potency measurement on the cells based on gene expression. Growth differentiation factor 5 showed to balance degenerative processes in differentiated chondrocytes through inhibiting the collagen II degrading enzyme matrix metallopeptidase 13 via inhibition of the canonical Wnt signalling pathway. This finding further emphasizes the putative role of growth differentiation factor 5 as a future disease-modifying drug against osteoarthritis. The developed three-dimensional culture system improved the formation efficiency and stability of embryoid bodies in a non-laborious way. The culture system may be useful when investigating the role of signalling pathways in early chondrogenesis in the future.

The present thesis adds to descriptions and explanations of the mechanisms behind osteoarthritis and presents a non-laborious embryoid body culture system to investigate questions that can be raised based on results from this thesis.

Keywords: Cartilage, regeneration, osteoarthritis, induced pluripotent stem cells, factorial design, growth factors

ISBN: 978-91-628-8967-8