Cartilage Tissue Engineering; the search for chondrogenic progenitor cells and associated signalling pathways

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i Hjärtats aula, Vita stråket 12, Sahlgrenska Universitetssjukhuset, måndagen den 1 juni 2009 kl 13.00

av

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Avhandlingen baseras på följande delarbeten**:**

I. Julia Asp*, **Maria Thornemo***, Sven Inerot, Anders Lindahl. The helix-loop-helix transcription factors Id1 and Id3 have a functional role in control of cell division in human normal and neoplastic chondrocytes. *FEBS Letters* 1998;438: 85-90. *These authors contributed equally and should both be considered first authors.

II. Brittberg M, Sjogren-Jansson E, **Thornemo M**, Faber B, Tarkowski A, Peterson L, Lindahl A. Clonal growth of human articular cartilage and the functional role of the periosteum in chondrogenesis. *Osteoarthritis Cartilage* 2005;Feb;13(2):146-53.

III. **M Thornemo**, T Tallheden, E Sjögren- Jansson, A Larsson, K Lövstedt, U Nannmark, M Brittberg, A Lindahl. Clonal populations of chondrocytes with progenitor properties identified within human articular cartilage. *Cells Tissues Organs* 2005;180(3): 141-50.

IV. Camilla Karlsson*, **Maria Thornemo***, Helena Barreto Henriksson, Anders Lindahl. Identification of a stem cell niche in the zone of Ranvier. An experimental study in the rabbit. *Submitted to Journal of Anatomy, under revision.* *These authors contributed equally and should both be considered first authors.

V. **Thornemo M**, Barreto H, Karlsson C, Concaro S, Stenhamre H, Lindahl A. Expression of the stem cell associated proteins Stro-1 and Bcrp1 and the Wnt and Notch signalling pathways in regenerated and repaired human articular cartilage. *Manuscript.*

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ABSTRACT

The socioeconomic cost of articular cartilage related diseases in the Western world is very high. The suffering of the individual patient is even more problematic. Different methods are used today to treat this large, heterogeneous group of patients, one of which has been in use for more than 20 years: cell based autologous chondrocyte implantation (ACI). Irrespective of treatment method, a great deal remains to be done to improve our knowledge of what occurs at molecular and cellular levels. The overall aim of this thesis was therefore to find chondrocytes with stem cell properties in cartilage used for ACI, and to study the associated molecular signalling pathways.

The helix-loop-helix (HLH) transcription factor Id1 was demonstrated to play a role in regulating proliferation of cultured human articular chondrocytes, indicating a role for the family of HLH proteins in chondrocytes. Human articular chondrocytes cultured in agarose suspension demonstrated subpopulations with different growth potential. Some showed mesenchymal stem cell (MSC) properties. To be able to locate potential stem cells *in vivo,* a rabbit BrdU model, identifying slow cycling cells was used. Stem cells were not only identified in the articular cartilage but also in the groove of Ranvier located in the periphery of the epiphyseal growth plate. The groove of Ranvier also exhibited properties as a stem cell niche structure. Further biopsies from human normal articular cartilage, as well as regenerated and repaired cartilage after ACI were studied. The human normal articular cartilage demonstrated expression of the stem cell associated markers STRO-1 and Bcrp1 in cells in the superficial zone, and activity of the fundamental Wnt (Wingless-related proteins) and Notch signalling pathways. The distribution showed a distinct zonal pattern in the normal cartilage. In biopsies from regenerated cartilage with almost normal histological architecture, the markers and pathways studied demonstrated a distinct zonal pattern similar to that in normal cartilage. Biopsies taken from repaired cartilage with more or less fibrocartilage formation and with a disorganized matrix, showed increased Stro-1 expression and activity for the Wnt pathway throughout the biopsies. The supposed stem cell marker Bcrp1 was expressed in a sparse population of cells independently of cartilage tissue studied.

This thesis demonstrates that in cartilage there are subpopulations of cells with mesenchymal stem cell properties, and that it is possible to identify and select these populations for further study of their properties as stem cells and their usefulness for transplantation. The HLH, Wnt- and Notch signalling pathways are closely involved in articular cartilage repair and regeneration. The stem cells and signalling pathways may represent potential drug targets or valuable tools in the tissue engineering of joint tissue.

Key words: stem cell, progenitor cell, tissue engineering, articular cartilage, chondrocytes

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