Title: Proteomics study of articular cartilage catabolism

Background
Osteoarthritis (OA) is a severe chronic disabling disease characterized by an abnormal destruction of articular cartilage. It is the most common joint disease, and there is currently no disease-modifying treatment available. The knowledge about the early development of OA and the involved disease mechanisms is poor; hence there is a lack of diagnostics that could identify the disease in an early stage.

Aim
We aim to better understand cartilage biology and identify molecular alterations and their mechanisms in pathology that are central to development in joint failure; as well as to develop novel biomarkers of joint tissue turnover allowing earlier detection and better disease monitoring. We will use two ex-vivo catabolic models of cartilage breakdown and discovery mass spectrometry (MS) in combination with histology analysis and molecular biology techniques.

Preliminary results
In one project, we have studied the effect of two pro-inflammatory cytokine treatments: interleukin-17A (IL-17A), and oncostatin M in combination with tumor necrosis factor alpha (OSM+TNF) on articular cartilage integrity. Discovery proteomics methods combined with bioinformatics analysis revealed 45 upregulated proteins in IL-17A-treated explant secretome, and over 70 upregulated proteins in OSM+TNF secretome when compared to untreated cartilage. GO terms analysis using PANTHER-db revealed that majority of proteins identified in the secretomes were extracellular region proteins with binding and catalytic activities, and that there were cytokine-specific differences. In another pilot project, we investigated the endogenous, soluble protein fragment generation by these treatments, and the suitability of these fragments as cartilage breakdown biomarkers. Currently, 4 neo-epitopes (3 x COL2A1, 1 x COL12A1) with catabolic profiles have been selected for quantitative ELISA biomarker assay development.

Significance
Neo-epitope search led to 4 new biomarker development programs being initiated and a possibility for complementary MRM assay development for detecting protein fragments specific to IL-17A- or OSM+TNF-mediated cartilage breakdown. This is a first proteomics study done on IL-17A effect on articular cartilage – IL-17A is a known player in psoriatic arthritis, ankylosing spondylitis and rheumatoid arthritis, thus better understanding of IL-17A effect on articular cartilage will also contribute to better understanding of the inflammatory arthritis pathogenesis.

Granskare: Docent Robin Kahn (IKVL) samt docent Lotta Happonen (IKVL)

Huvudhandledare: Patrik Önnerfjord

Bihandledare: Anne-Christine Bay-Jensen (Nordic Bioscience, Copenhagen), Anders Aspberg (IKVL) samt Yi He (Nordic Bioscience, Copenhagen)