

## Chondrocyte Gene Expression in A Rat Model Of Osteoarthritis

[C.T.G. Appleton](#)<sup>1,2</sup>, [D.D. McErlain](#)<sup>4</sup>, [V. Pitelka](#)<sup>1,2</sup>, [J.L. Henry](#)<sup>3</sup>,  
[D. Holdsworth](#)<sup>4</sup>, and [F. Beier](#)<sup>1,2</sup>

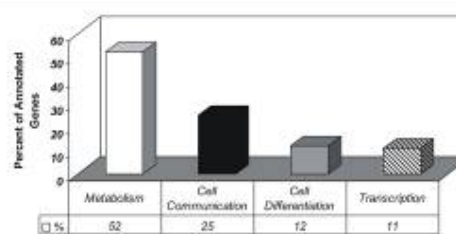
<sup>1</sup>[CIHR Group in Skeletal Development & Remodeling, Schulich School of Medicine & Dentistry, University of Western Ontario, London, CAN](#), <sup>2</sup>[Department of Physiology & Pharmacology, University of Western Ontario, London, CAN](#), <sup>3</sup>[McMaster University, Hamilton, CAN](#), <sup>4</sup>[Imaging Research Group, Robarts Research Institute, London, CAN](#)

**INTRODUCTION:** Osteoarthritis (OA) is a complex degenerative disease that results in architectural changes to both the articular cartilage and subchondral bone of synovial joints. A common characteristic of OA is cartilage degradation. Studies have shown that much of the degradation is due to the misexpression of proteases, cytokines, chemokines, growth factors, and other secreted factors<sup>1,2</sup>. Accordingly, we hypothesized that altered expression of growth factors in articular cartilage causes cartilage degradation in OA.

**METHODS:** Total RNA was harvested directly from the articular knee cartilage of rats that had undergone anterior cruciate ligament transection (ACL-T) and partial medial meniscectomy (PM) (to induce OA), or Sham surgery (control), followed by 28 days of 30-minute forced mobilization sessions 3 times per week on a rota-rod apparatus. Affymetrix microarrays (RAE230\_2.0 GeneChips<sup>®</sup>) were used to assess changes in articular chondrocyte gene expression due to OA stimuli (n = 5). Data were subsequently categorized using Gene Ontology classifications. The expression patterns of genes known to play a role in OA pathogenesis (e.g. *Mmp13*)<sup>2</sup> and genes novel to the study of OA were also confirmed using real-time PCR. Functional studies are being carried out with identified growth factors to determine their effects on primary chondrocyte gene expression, morphology, and phenotype.

**RESULTS:** After data normalization and statistical analysis, 1,619 gene probe sets showed at least 1.5-fold changes in expression between operated knees and sham controls. Several growth factors were among these, and many of the regulated genes are implicated in metabolism, cell signal transduction, cell differentiation, and transcriptional regulation as indicated by GeneOntology annotations (Figure 1). Consistent changes in gene expression were also observed in the contralateral knee. Novel factors identified included endothelin type A

receptor (*Edrna*), kit-ligand (*Kitl*), and several members of the cathepsin family of proteases including cathepsin S (*Ctss*). Further, groups of related genes were also dynamically regulated including many ECM genes, members of the TGF- $\beta$  superfamily and the insulin-like growth factor (IFG) axis.



*Fig. 1: Distribution of genes across metabolic (52%), cell communication (25%), cell differentiation (12%), and transcription (11%) functional classifications.*

**DISCUSSION & CONCLUSIONS:** Overall, these results implicate dysregulated expression of growth factors (and other types of genes) in cartilage degradation and support the contention that multifactorial influences contribute to OA pathogenesis. Several avenues of research into the causes and potential therapeutic targets of OA will stem from this exciting pool of candidate genes.

**REFERENCES:** <sup>1</sup> E.V. Tchetina, G. Squires, and A.R. Poole (2005). *J Rheumatol* **32**:876-86.  
<sup>2</sup> G. Tardif, P. Reboul, M. Dupuis, C. Geng, N. Duval, J.P. Pelletier, J. Martel-Pelletier (2001) *J Rheumatol* **28**:1631-9.

**ACKNOWLEDGEMENTS:** This project was funded by the Canadian Institutes of Health Research and the Canadian Arthritis Network.