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## COST-EFFECTIVENESS ANALYSIS OF ARTHROSCOPIC SURGERY COMPARED TO NON-OPERATIVE MANAGEMENT FOR OSTEOARTHRITIS OF THE KNEE

J. Marsh †, T.B. Birmingham †, J.R. Giffin †, W. Isaranuwatchai ‡, J.S. Hoch ‡, R. Litchfield †, K. Willits †, P. Fowler †. † *Western Univ., London, ON, Canada;* ‡ *St. Michael's Hosp., Toronto, ON, Canada*

**Purpose:** Arthroscopic debridement and partial resection of degenerative joint tissues in patients with knee osteoarthritis (OA) is frequently performed, yet its value is highly debated. The purpose of the present analysis was to determine the cost-effectiveness of arthroscopic surgery compared to non-operative treatment for knee OA.
**Methods:** The present data were collected as part of a previously reported randomized controlled trial. Patients with knee OA were randomly assigned to arthroscopic surgery combined with optimized physical and medical therapy or to treatment with physical and medical therapy alone, and were followed for two years. We used the WOMAC total score and the quality-adjusted life year (QALY) at two years post-operative as the effectiveness measures in our cost-effectiveness analysis. We recorded the total costs for each intervention, as well as all health care resource use at each follow up appointment. All costs are presented in 2012 Canadian dollars. We conducted a cost-effectiveness analysis from a public health payer perspective and a societal perspective. We calculated the incremental cost-effectiveness ratio (ICER), the incremental cost-utility ratio (ICUR), and estimated cost-effectiveness using the net benefit regression framework.
**Results:** A total of 169 patients were included in the cost-effectiveness analysis (88 arthroscopy group, 81 non-operative group). Patients allocated to the arthroscopy group received partial resection of degenerative meniscal tears (81%) and/or debridement of degenerative articular cartilage (97%). The ICER was $13,010 (CAN) (societal), or $11,058 (CAN) (payer) for a clinically important improvement on the WOMAC total score. The ICUR was $107,325 (CAN) (societal) or $91,230 (CAN) (payer) per QALY gained. The incremental net benefit was negative for all willingness-to-pay values, from both the healthcare payer and societal perspectives, suggesting that arthroscopic surgery is not cost-effective compared to non-operative management.
**Conclusions:** The results of the present analysis suggest that arthroscopic debridement for the treatment of knee OA is not cost-effective compared to non-operative management, in terms of disease-specific quality of life and quality adjusted life years, from both a healthcare payer and societal perspective.

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## SUPPRESSION OF REDD1 IN OA CARTILAGE, A NOVEL MECHANISM FOR DYSREGULATED MTOR ACTIVATION

O. Alvarez-Garcia, R. Akagi, Y. Akasaki, K.M. Fisch, A.I. Su, M.K. Lotz. *The Scripps Res. Inst., La Jolla, CA, United States*

**Purpose:** Aging is a main risk factor for the development of osteoarthritis (OA) and the molecular mechanisms underlying the aging-related changes in articular cartilage are beginning to be elucidated. Using genome wide transcriptomic analysis, we identified the PI3K/Akt/mTOR pathway as one of the most dysregulated pathways in OA cartilage, and REDD1, a regulator of cellular stress responses, as the most suppressed gene in this pathway. The PI3K/Akt/mTOR signaling pathway is a major driver of aging in model organisms and its role in OA pathogenesis is emerging with abnormal mTOR activation becoming recognized as an important dysfunction in OA chondrocytes. Therefore, the present study analyzed REDD1 expression in normal and OA cartilage and assessed REDD1 function in cultured human articular chondrocytes.
**Methods:** REDD1 expression was measured in articular cartilage obtained from young healthy donors (38±13 years) or OA donors undergoing knee replacement surgery (71±10 years) by qPCR and immunohistochemistry. For in vitro studies, normal articular chondrocytes were treated with IGF-1, specific inhibitors of the PI3K/Akt/mTOR and ERK pathways, in the presence or absence of REDD1 specific siRNA. REDD1 expression, intracellular signaling pathway activation, and autophagy were measured by western blot using antibodies against REDD1, phospho-AKT, AKT, phospho-ERK, ERK, phospho-S6, S6, phospho-4EBP and LC3, respectively.
**Results:** Human cartilage from normal knee joints expressed high levels of REDD1 mRNA and protein. Immunohistochemistry showed predominant REDD1 expression in the superficial and upper-mid zones as compared with the deep zone of the cartilage. REDD1 expression was significantly reduced in OA cartilage at both mRNA and protein levels. In cultured chondrocytes, REDD1 protein expression was increased by serum and IGF-1 treatment. IGF-1-induced REDD1 expression was blocked by PI3K and mTOR inhibitors, but not by ERK inhibitors. REDD1 knockdown using siRNA resulted in increased S6 and 4EBP phosphorylation, markers of increased mTOR activation. Finally, REDD1 knockdown decreased the LC3-II/GAPDH ratio in human articular chondrocytes.
**Conclusions:** The present study shows that REDD1 is highly expressed in normal human articular cartilage and reduced in OA. Loss of REDD1 in human chondrocytes increases mTOR activity and decreases autophagy activation. Collectively, these results suggest that REDD1 is an important regulator of chondrocyte intracellular signaling and mTOR inhibitor. Reduced REDD1 expression represents a novel mechanism for the increased mTOR activation observed in OA.

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## THE HARWELL AGEING SCREEN: A DISCOVERY PLATFORM FOR GENES AND PATHWAYS ASSOCIATED WITH AGE-RELATED DISEASE

A. Blease †, M.E. Goldsworthy †, A. Haynes †, L. Wisby †, T. Nicol †, S. Falcone †, H. Lad †, T. Vincent ‡, S.D. Brown †, P.K. Potter †. † *Mammalian Genetics Unit, MRC Harwell, United Kingdom;* ‡ *ARUK Ctr. for OA Pathogenesis, Kennedy Institute of Rheumatology, United Kingdom*

**Purpose:** Diseases associated with ageing pose an increasing social and financial burden on society and represent an imperative for research in the biomedical sciences. Despite the complications of genetic background in human populations and the confounds of environment, there have been considerable advances, particularly through Genome-wide association studies (GWAS) in identifying loci involved in diseases of ageing. Nevertheless, this is only a first step towards a more fundamental understanding of the genetic pathways involved. Animal models are required both to test our understanding of these pathways, as well as to provide the tools for developing and assessing therapeutics. We are undertaking the first large-scale project to investigate the interaction between genetic variation and the pleiotropic effects of ageing.
**Methods:** We are employing mutagenesis and phenotyping to specifically generate new mouse models of late onset or age-related disease. The emphasis is on the exploration of the phenotype space in ageing mouse mutant populations providing us with the opportunity to: identify genes and pathways involved in age related disease, scrutinise these models for biomarkers of age related disease, and provide better platforms for preclinical assessment of new therapies for such diseases. Pedigrees are aged to 18 months and undergo comprehensive phenotyping across a wide range of disease areas at several time points throughout the life of the mice. Mutations are mapped initially by a dense SNP panel and then individual mutations identified by whole genome sequencing.
**Results:** To date we have identified lines with age-related hearing loss, cardiovascular disease, retinal degeneration, neurodegeneration, obesity, and bone disease which are being mapped and characterised in detail. We have identified two lines with late onset osteoarthritis. MP-107 was identified as having mild skeletal abnormalities, particularly a curved and wider ischium at 4 months of age. Upon ageing affected mice developed increased boney deposits at the joints, identified by X ray, and upon histopathological analysis showed osteophyte formation and cartilage erosion. This line was mapped as a dominant phenotype and localised to chromosome 11. An existing line (TM-44) also displayed similar ischium abnormalities and also maps to chromosome 11. Whole genome sequencing of MP-107 identified a non-synonymous change (T304M) in ST6galnac2 (ST6(alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2, 6-sialyltransferase 2). A detailed time course of the pathogenesis of disease and functional pathways is now underway in these lines to confirm ST6galnac2T304M as the causative mutation. In the pedigree MPC-227 mice were identified with severe joint deterioration by 15 months of age. The causative mutation was mapped to a missense mutation (A1946V) in aggrecan (Acan). In addition to the joint deterioration these mice exhibited quantitative and qualitative differences in brown and white adipose tissue with ageing, resulting in obesity in ageing mutant mice. Acan mutations in humans have been associated with an increased incidence of osteoarthritis in humans and this mutant line will allow the investigation of pathogenic pathways associated with Acan abnormalities. We are also investigated the role of Acan in adipose tissue.
**Conclusions:** The age challenged mice are an important resource for many research groups, identifying novel genes and pathways resulting