68 EFFECTS OF VIDEO-BASED HOME EXERCISE ON CLINICAL AND RADIOGRAPHIC OUTCOMES IN ADULTS WITH KNEE OSTEOARTHRITIS: A ONE-YEAR RANDOMIZED CONTROLLED TRIAL

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Purpose: Previous systematic reviews conclude that exercise therapy has beneficial effects on pain and physical function of the population with osteoarthritis (OA) of the knee. However, its positive post-treatment effects on pain and physical function decline over time. Exercise adherence has been shown to be an important predictor of long-term outcome in exercise therapy. Video media can be an effective means of delivering exercise instruction. Therefore, use of a home exercise video could enhance adherence to prescribed exercise program. No published research to date has investigated the effectiveness of a home exercise video for patients with knee OA compared with conventional home exercise without video media. Then we have hypothesized that video-based home exercise could enhance adherence to prescribed exercise program and produce substantial improvements in pain, physical function and quality of life in patients with knee OA and also prevent radiographic progression of knee OA compared with conventional home exercises. 

Methods: One hundred and seven subjects who fitted the following criteria were randomized to a DVD-based exercise (DVD) group or a control group by a computer-generated random number. Entry criteria were defined as knee pain, age over 50 years old, and radiographic evidence of OA (Kellgren-Lawrence Grade 2, 3, or 4). Subjects in the DVD group received a DVD-based program encompassing muscle stretching, active ROM exercises, and five forms of muscle strengthening and use it during home exercise. Subjects in the control group initially received detailed verbal and hands-on instruction in a home-based program of a quadriceps exercise program. Subjects in both groups were evaluated after 3, 6, and 12 months and compared with the baseline scores. 

Results: Concerning exercise adherence, subjects in the DVD group performed the prescribed exercise 5.3, 5.6 and 3.8 times in a week at 3, 6 and 12 months, while those in the control group performed the prescribed exercise 3.9, 3.7 and 4.1 times, respectively. The numbers of exercise times in the DVD group were significantly higher than those in the control group at 3 and 6 months, although there was no significant difference between groups at 12 months. The reduction in walking pain was significantly greater in the DVD group than in the control group at 3, 6, and 12 months. The improvements in all categories of WOMAC and physical component summary of SF-8 were significantly greater in the DVD group than in the control group at 3, 6, and 12 months. The reduction in pain was significantly greater in the DVD group than in the control group at 3, 6, and 12 months. Regarding radiographic OA progression of the knee, the DVD group showed significant increase in FTA at 12 months compared with the baseline values, while we could not find significant progression in the medial minimum joint space width, medial joint space area, or medial osteophyte area. There were no significant differences in the SF-8 mental component summary or BMI between two groups at 3, 6, or 12 months. Regarding radiographic OA progression of the knee, the DVD group showed significant increase in FTA at 12 months compared with the baseline values, while we could not find significant progression in the medial minimum joint space width, medial joint space area, or medial osteophyte area. There were no significant differences in radiographic OA parameters (i.e. medial minimum joint space width, medial joint space area, medial osteophyte area, and femorotibial angle (FTA)) using the knee osteoarthritis computer-aided diagnosis (KOACAD) measuring system.

Conclusion: The present one-year randomized controlled trial showed that video-based home exercise can enhance adherence to prescribed exercise program for 6 months and can produce substantial improvements in pain, physical function and quality of life in patients with knee OA at one year. However, this video-based home exercise cannot prevent radiographic progression of the knee OA.
accelerated synovial joint formation at E14.5, although the joint structure appeared similar to controls at E18.5. By 2-weeks of age the mutant mice exhibit delays in the formation of the secondary center of ossification as assessed by histology and ISH, although the surface articular cartilage appears mostly normal. Micro-CT analyses at 2-, 4-, and 8-months of age demonstrated an early increase in mineralization in both the subchondral and trabecular bone regions that was followed by a progressive loss of bone. Additionally, mutant mice developed osteophytes and excessive mineralization of the menisci as compared to controls. Histology, histomorphometric, ISH, and IHC analyses of 2-, 4-, and 8-month old knee joint sections revealed that mutant mice show early and progressive signs of OA. Analyses of alcian blue stained sections from mutant mice displayed a progressive degeneration and fibrosis of the articular cartilage and menisci, subchondral bone sclerosis, osteophyte formation, and synovial expansion. By 8-months of age the articular cartilage of mutant mice exhibit severe cellular and molecular changes consistent with OA, such as fibrosis and fibrillation, near complete loss of Prg4 expression, decreased Col2a1 and enhanced Col10a1 and Mmp13 immunoreactivity, and enhanced cell death. Polarized light microscopy on all mutant and control adult knee sections further demonstrated a loss of normal collagen fibrils within the subchondral bone and articular cartilage extracellular matrix of mutant mice.

Conclusions: Our data demonstrate for the first time that RBPjk-dependent Notch signaling is critical in maintaining post-natal articular cartilage and joint maintenance, but is dispensable for the formation of synovial joints during embryonic development.

71 NOTCH/RBPJ/HES1 SIGNAL IN CHONDROCYTES MODULATES TERMINAL STAGE OF ENDOCHONDRAL OSSIFICATION DURING SKELETAL GROWTH AND OSTEOARTHRITIS DEVELOPMENT

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Purpose: The Notch signaling pathway, a potent modulator of cell differentiation in many organs, is regulated by several molecules: the Notch receptors, the intracellular domains (ICD), the transcriptional effector Rbpj, and the target transcription factor Hes/Hey family members. Here we have examined the roles of these molecules in chondrocytes during the endochondral ossification process which is essential for skeletal growth and osteoarthritis (OA) development.

Methods: In vitro expression patterns were examined by real-time RT-PCR and Western blotting in cultures of mouse chondrogenic ATDC5 cells with the differentiation medium (insulin, transferrin, and sodium selenite) and primary chondrocytes isolated from the ribs of mouse embryos. In vivo expression patterns were examined by immunohistochemistry of the limb cartilage of mouse embryos and knee OA joint cartilage of the mouse experimental model. The OA model was created surgically by inducing instability in the knee joints of 8-week-old mice, and OA severity was quantified by the OARSI histopathology grade. Tissue-specific knockout mice of Rbpj were generated by mating Sox9 or Col2a1 promoter-driven Cre-transgenic mice (Sox9-Cre or Col2a1-Cre) with mice homozygous for a floxed Rbpj allele (Rbpjfl/fl), and the phenotype was compared with respective Rbpjfl/fl littermates. For functional analyses, we created stable lines of ATDC5 cells with retroviral overexpression of the genes. Transcriptional regulation was examined by luciferase assay using ATDC5 cells transfected with the reporter construct containing a promoter fragment of the marker genes.

Results: In cultures of ATDC5 cells and primary chondrocytes, Notch1, 2, Rbpj, and Hes1 were strongly expressed in the initial differentiation stages during Mmp13 and Vegf expression, while Notch3, 4 and other Hes/Hey members were little expressed throughout the differentiation stages. In the mouse limb cartilage and in the knee OA joint cartilage, ICDs of Notch1, 2 were localized in the nucleus of highly differentiated chondrocytes in the hypertrophic zone and in the degraded cartilage, respectively, while they remained in the cytoplasm of less differentiated chondrocytes of the proliferative zone and undegraded cartilage. Rbpj and Hes1 were also co-expressed in the nucleus of highly differentiated chondrocytes, while other Notch ICDs and Hes/Hey family members were not detected in either cartilage. The conditional knockout mice of Rbpj in chondroprogenitor cells (Sox9-Cre;Rbpjfl/fl) died shortly after birth; however, the embryos exhibited dwarfism with impaired matrix degradation and vascular invasion into the cartilage primordia due to decreases of Mmp13 and Vegf expression. Contrarily, the conditional knockout mice of Rbpj in chondrocytes (Col2a1-Cre;Rbpjfl/fl) exhibited diverse skeletal phenotypes depending on mouse lines with various levels of Rbpj inactivation. When we created the experimental OA model in a Col2a1-Cre;Rbpjfl/fl mouse line with partial Rbpj inactivation causing normal skeletal growth, the ability was suppressed as compared to the Rbpjfl/fl littermates, with prevention of the terminal stage of endochondral ossification, similar to the Sox9-Cre;Rbpjfl/fl limb cartilage. To know the underlying mechanism, we established stable lines of ATDC5 cells with retroviral transfection of Notch1-ICD and Notch2-ICD, and found that both overexpressions stimulated Alizarin red S and ALP stainings, as well as Mmp13, Vegf, and Hes1 expression. These stimulations were inhibited by addition of a Notch inhibitor DAPT. Luciferase analyses revealed that the Hes1 transfection enhanced the Mmp13 and Vegf promoter activity most potently among the Hes/Hey members.

Conclusions: The Notch/Rbpj/Hes1 signal in chondrocytes modulates the terminal stage of endochondral ossification during skeletal growth and OA development, indicating it to be a possible therapeutic target of OA.

72 ERG AND PTHRP GENETICALLY COOPERATE TO MAINTAIN ARTICULAR CARTILAGE LONG-TERM FUNCTION


Purpose: During embryogenesis, chondrocytes located at the ephysseal ends of long bone anlagen acquire a permanent articular phenotype, while those located in the shaft become organized in growth plates, undergo maturation and hypertrophy and are replaced by bone. The mechanisms regulating such critical developmental bifurcation remain unclear.

We previously showed that the ets transcription factor family member Erg is preferentially expressed in developing articular cartilage and that targeted over-expression of Erg in the embryonic cartilage suppresses chondrocyte maturation and ossification. In addition, majority of chondrocytes in an entire skeleton exhibited immature articular-chondrocyte like phenotype. Developing joints are also known to express parathyroid hormone-related protein (PTHRp), that share the ability with Erg to suppress chondrocyte maturation. Recent large-scale transcriptome analysis revealed that two genes are often expressed in variety of tissue. In this study, we asked whether Erg is required for articular cartilage development and maintenance. We also asked if Erg and PTHrp functionally and/or genetically cooperate in articular chondrocytes.

Methods: 1) Transgenic mice. Floxed Erg mice were generated by a conventional procedure. The mouse carries loxP-flanked exon5 that encodes part of the pointed domain and removal of this exon resulted in mice that lacked the entire Ets1 gene. Our in vivo data demonstrate for the first time that RBPjk-fl mice demonstrated similar phenotypes to controls at E18.5. By 2-weeks of age the mutant mice displayed accelerated synovial joint formation at E14.5, although the joint structure appeared similar to controls at E18.5. By 2-weeks of age the mutant mice exhibit near complete loss of Prg4 expression, decreased Col2a1 and enhanced Col10a1 and Mmp13 immunoreactivity, and enhanced cell death. Polarized light microscopy on all mutant and control adult knee sections further demonstrated a loss of normal collagen fibrils within the subchondral bone and articular cartilage extracellular matrix of mutant mice.

2) Over-expression of Erg in cultured chondrocytes up-regulated PTHrp expression, while siRNA inhibition of Erg strongly suppressed PTHrp expression in explant mouse limbs.

3) Over-expression of Erg increased the activity of a PTHrp P2 promoter reporter, the main PTHrp promoter in cartilage and, interestingly, such