2. PPAR Ɣ controls mTOR/autophagy signalling in the articular cartilage.

Faezeh Vasheghani Farahani, Yuo Zhang, Meryam Blati, Hassan Fahmi, Bertrand Lussier, Peter Roughley, Jean-Pierre Pelletier, Johanne Martel-Pelletier, Mohit Kapoor.
Osteoarthritis Research Unit, University of Montreal Hospital research center (CR-CHUM), Notre-Dame Hospital, Montreal, Quebec, Canada

Objectives: In this study we explored the role of peroxisome proliferator activated receptor gamma (PPAR□),a transcription factor, on chondroprotection by determining the effect of PPAR□ genetic deletion in the cartilage on mammalian target of rapamycin (mTOR)/autophagy signaling pathway using mice model of OA.

Methods: We created inducible cartilage-specific PPAR□ knockout (KO) mice and subjected them to mice model of OA.

Results: PPAR□ KO mice exhibit accelerated cartilage destruction, chondrocytes apoptosis, synovial fibrosis and overproduction of OA inflammatory/catabolic factors as well as increased expression of mTOR and suppression of key autophagy genes compare to controls. In vitro rescue experiments using PPAR□ expression vector reduced mTOR expression, increased expression of autophagy genes and reduced the expression of OA inflammatory/catabolic factors, thus reversing the phenotype of PPAR□ KO mice chondrocytes. To validate our in vitro findings in vivo we created cartilage specific PPAR□-mTOR double KO mice. Loss of mTOR in PPAR□ KO mice resulted in increased autophagy signaling and significant protection from OA in mice.

Conclusion: These findings outline PPAR□ and its signaling by mTOR/autophagy as a potential therapeutic target for the treatment of OA.