3. Inducible cartilage-specific PPARgamma-deficient mice exhibit accelerated experimentally-induced osteoarthritis associated with defective autophagy and mTOR signaling.

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Objectives: Our previous studies showed that germ-line PPAR-□ knockout (KO) mice exhibit cartilage and bone developmental defects and during aging they exhibit spontaneous cartilage degradation. To bypass these developmental defects associated with germ-line PPAR□ KO mice, in the present study we generated inducible-cartilage-specific PPAR□ KO mice and subjected these mice to destabilization of medial meniscus (DMM) model of osteoarthritis (OA). The main objective of this study was to identify the specific in vivo role of PPAR□ in OA using DMM murine model.

Methods: Inducible cartilage-specific PPAR□ KO mice were generated using the LoxP/Cre system in which Cre expression was induced by doxycycline treatment in 4 weeks old mouse. 10 weeks old mice were subjected to DMM model of OA.

Results: Histomorphometric analysis of mice knee joints 5 and 10 weeks post OA surgery showed that inducible cartilage-specific PPAR□ KO mice when compared to WT mice, exhibited accelerated OA (significantly increased OARSI histopathological scoring) associated with enhanced cartilage degradation, hypocellularity, synovial inflammation, mononuclear cell influx and increased expression of catabolic factors (MMP-13 and ADAMTS-5, accompanied by decrease in the expression of aggrecan and type II collagen. Our results also showed that PPAR□ deficient cartilage exhibited enhanced expression of mammalian target of rapamycin (mTOR) associated with decreased expression of autophagy specific genes including ULK1 (most up stream autophagy inducer), LC3B (critical factor for autophagy vacuole formation) and ATG5 (required for autophagosome formation). Treatment of PPAR□ deficient chondrocytes with PPAR□ plasmid rescued the expression of aggrecan and type II collagen and downregulated the expression of MMP-13 and ADAMTS-5. Interestingly, PPAR□ plasmid was able to rescue the expression of autophagy-specific genes (ULK1, LC3B and ATG5) in PPAR□ deficient.

Conclusion: Loss of PPAR□ in the cartilage and subsequent increase in mTOR expression and decreased autophagy signalling could be responsible for decreased chondroprotection and accelerated cartilage degradation.