Inhibition of CaMKK2 Decreases Progression of Post-traumatic Osteoarthritis in a Rabbit ACL Transection Model

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Background and Hypothesis:
Post-traumatic osteoarthritis (PTOA) is a multifactorial degenerative disease of the joint affecting 20-50% of all joint injuries with a total annual cost of $15 billion. There are no current disease-modifying therapies for PTOA. Mechanical stress due to ligament tear or impact injury triggers the release of inflammatory mediators in the joint. Resulting collagen damage, loss of proteoglycans, and cell death triggers further release of inflammatory mediators and reactive oxygen species. This cycle of inflammation leads to PTOA. We hypothesize that inhibition of Ca^{2+}/CaM dependent protein kinase kinase 2 (CaMKK2), a kinase associated with the inflammatory effects in PTOA, will mitigate the disease-propagating mechanisms.

Methods:
We utilized a rabbit model of PTOA which involved surgical transection of the anterior cruciate ligament (ACL) to generate joint instability. Rabbits were then treated tri-weekly with either STO-609 (CaMKK2 inhibitor, 0.033 mg/kg) or saline (control) for 16 weeks. Rabbits were sacrificed at 16 weeks post-surgery. Tibiofemoral joints were harvested for staining with safranin O fast green (SO) and PTOA grading via Osteoarthritis Research Society International (OARSI) guidelines. Apoptosis was assessed with terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL). RNA isolation of cartilage and subchondral bone tissue was conducted for qRT-PCR. Gene expression of *MMP-13, IL-6, IL-1B, ACAN, COL2A1* was quantified and normalized to *GAPDH*.

Results:
Histology and gross morphology showed increased PTOA severity in saline controls compared to STO-609 treated rabbits. There was no significant difference in chondrocyte apoptosis in STO-609 treated rabbits compared to saline controls based on TUNEL staining. Gene expression analyses are in progress.

Potential Impact:
This study addresses the unmet clinical need for novel disease-modifying therapeutics for PTOA. Preliminary results show that inhibition of CaMKK2 has the potential to decrease cartilage degradation after joint injuries.