Small Animal models of Osteoarthritis: Testing Emerging treatments, drug delivery and mechanisms of action

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Stem cell Therapy

Two possible therapeutic options

Targeting Autophagy
Approximately 190 million people worldwide are suffering from osteoarthritis. Osteoarthritis affects 10 to 15% of the world population.

- 68% of women over 65 have osteoarthritis.
- 58% of men over 65 have osteoarthritis.
Joint Structures affected in OA

Normal Human Cartilage

Normal Human OA Cartilage

Normal subchondral bone

Normal Synovium

Human OA Cartilage

OA Subchondral bone

OA Synovium
Pathophysiology of Osteoarthritis

Small Animal models of Osteoarthritis
Small animal models of OA

**Spontaneous age-related Models**
- Mouse: C57BL/6, STR/ort, BALB/c, DBA/1
- Guinea Pig: Hartley Guinea Pig

**Model of rapidly progressive OA**
- Induced Models:
  - Intraarticular injections (MIA)
  - Surgically induced models: Meniscectomy and/or anterior cruciate ligament transection
  - Ovariectomy

**Genetic Models**
- MMP-13 over expression
- TIMP-3 deficient mice
- COL2A1 gene deletion
- TGF-β deficient mice
- Integrin α1 KO mice
- Cartilage-specific PPARgamma deficiency
Spontaneous OA model

Cartilage-specific PPARγ KO mice exhibit spontaneous OA phenotype.
Cartilage-specific deletion of PPARγ results in accelerated OA like characteristics during aging.

Aged PPARγ KO mice exhibit increased synovial inflammation and macrophage influx

Control Heterozygote KO Homozygote KO

Hematoxylin and Eosin stain

Enhanced synovial inflammation

14 months old mice synovium

Control Heterozygote KO Homozygous KO

Macrophage marker stain

Enhanced macrophage influx in synovium
Destabilization of Medial Meniscus OA model

Surgical Model of Osteoarthritis in Mice
DMM Model of OA

- Destablization of medial meniscus: Resulting moderate OA-like phenotype

- This surgery results in a modest degree of OA (partial cartilage erosion and fissures, proteoglycan depletion, synovial inflammation, synovial fibrosis as well as some degree of subchondral bone remodeling.

- This model of relatively slow progression of OA is more reflective of human pathogenesis.

Zhang et al., Kapoor M. Annals of Rheumatic Diseases 2014
DMM model: Effects on articular cartilage and subchondral bone

- Mild degree of proteoglycan loss
- Some loss of articular cartilage cellularity (mostly superficial layer)
- Mild degree of articular cartilage roughening
- No significant bone changes at this time point

OA Characteristics

- Moderate degree of proteoglycan loss
- Significant loss of articular cartilage cellularity
- Moderate degree of cartilage degeneration
- Mild-Moderate degree of subchondral bone remodelling
- Signs of fibrosis in the cartilage

Cell Death
Catabolic Activity
Collagen Type II Breakdown

- TUNEL
- MMP-13
- CI,2C
DMM model: Synovial Inflammation and Fibrosis

- Significant amount of synovial fibrosis
- Increased TGF-beta/Smad signalling
- Synovial fibroblasts activation (Myofibroblast like phenotype)
- Significant influx of inflammatory cells (Monocytes/Macrophages)
MIDMM (Minimally Invasive Destabilization of Medial Meniscus) Model of OA In Mouse

• This model closely resembles human OA by limiting surgical exposure to minimum.

• There is a learning curve associated with the technique.

• MMTL transection is carried out using micro-surgical techniques under direct vision.

• This model results in mild OA at 8 weeks post surgery.

• Application in transgenic mice & evaluation of DMOADs.
Method

- 1mm skin incision is made over antero-medial region of knee.
- Arthrotomy is carried out and fat pad over medial meniscus dissected.
- MMTL is identified and transected under direct vision with special micro-surgical knife.
- Joint irrigation and closure is done.
Minimally Invasive Model
Notes

• The technique utilized an in house custom knife with blunt tip to reduce surgical trauma.

• To our knowledge, this is the only mouse OA model with:
  – minimum surgical trauma
  – early mouse weight bearing
Histopathology
Cell Therapy: Small animal models of OA Feasibility and challenges

Characterization of Cells
Type, amount, route of administration

Intra-articular injection (DMM Model)
Ongoing testing of new therapies to treat Osteoarthritis
In my lab
Deliver autophagy specific gene ULK1 in mouse OA cartilage (intra-articularly)

ULK1 adenovirus
Intra-articular injection

(Concentration 50 MOI, 5ul injection, 2 times)
1st injection: 10 days post surgery
2nd Injection: 20 days post surgery
Evaluate severity of OA 10 weeks post surgery

OA surgery
Deliver bone marrow derived MSCs intra-articularly

Stem cell therapy

Animal Models
Clinical trial
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