Post-Traumatic Osteoarthritis: From Bedside to Bench and Beyond

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Disclosures

James L. Cook
- Patents with Royalties: University of Missouri, Arthrex
- Research Support: NIH, DOD, Arthrex, Zimmer, RTI, Nutramax, DePuy Synthes
- Consultant: Arthrex, ConMed, Zimmer, Eli Lilly, Merial, Nutramax
- Board: MTF
- Editorial Board: J Knee Surg

Seth L. Sherman:
- Research Support: Zimmer, Arthrex, RTI
- Consultant: Arthrex, RTI
- Advisory Boards: RTI, SBM, Vericel
- Editorial Board: Arthroscopy Journal, American Journal of Orthopedics, Current Orthopedic Practice
Post-Traumatic Osteoarthritis (PTOA)

- PTOA is arthritis that develops after joint injury

Clinical Diagnosis

- Symptoms
  - Pain, stiffness, decreased function

- Diagnostic Imaging
  - X-ray: joint space narrowing, subchondral sclerosis, osteophytes
  - CT/MRI: Subchondral (BML), chondral, synovitis

(Olson et al. JAAOS 2014)
PTOA is a challenging and disabling disease of the young adult

- 900,000 acute knee injuries/year in the USA
  - 5x higher risk of OA in knee injured population
- Following major knee injury
  - 30% incidence of knee OA by 5 years
  - 50% incidence by 10-20 years (Steibel et al. Journal of Sports Medicine 2014)
- 12% of knee OA cases (Brown et al. JOT 2006)
  - 5.6 million people
  - $3 billion healthcare costs annually

- Multifactorial
  - Progresses rapidly
  - Longer period of joint-related morbidity compared to degenerative OA
  - The joint is an organ!
- No specific classification system or diagnostic criteria versus degenerative OA

(Buckwalter et al. JOSPT 1998)
The Problems
What is needed?

- Decision Making Tools
- Early Diagnosis
- Prevention
- Treatment
- WHOLE ORGAN APPROACH
Research Directions

- Improved methods to measure severity of index injury
- Improved methods to detect “silent” disease in timeframe between initial insult and end-stage PTOA
  - Imaging
  - Biomarkers
- Valid preclinical animal models to test prevention and treatment
- Human registries of joint injuries
  - PTOA risk factors
  - Prospective evaluation of treatment effects

*Anderson JOR 2011*
How do we do this?

- Basic Science
- PreClinical Models
- Clinical Studies
Potential Targets

- **Cytokine Inhibition, Anti-Inflammatory Cytokines**
  - IL-1Ra (animal model, prelim clinical trial)
    - IL-1 inhibition
  - IL-10 (animal model)
    - Anti-inflammatory cytokine
      - Stimulates Collagen II and proteoglycan expression
      - Inhibits MMP and NO expression
      - Protects against apoptosis

- **Caspase inhibitors**
  - Inhibit apoptosis
  - Maintain viable, functional chondrocytes
  - Inhibit IL-1 activation

- **Growth Factors**
  - BMP stimulate mesenchymal cell differentiation and ECM formation
    - BMP-7 (in vitro, animal models)
  - IGF-1 (animal models)
    - Chondroprotective
  - FGF
    - Regulate cartilage development and homeostasis
      - FGF-2, FGF-18 (animal models)

- **Other Targets**
  - Inhibitors of ECM degrading enzymes
    - MMP inhibitors (cartilage explant model)
  - Antioxidants
    - i.e. N-acetylcysteine
  - Aminosugars
    - Glucosamine injection
  - Lubricants
    - Hyaluronan
    - Lubricin

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![Graph](image1.png)

*Anderson et.al. JOR 2011*

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![Graph](image2.png)

*Cook, et.al. JKS, JOR, CORR*
Mizzou PreClinical Model

Development of a Novel Canine Model for Posttraumatic Osteoarthritis of the Knee

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J Knee Surg

2 weeks 12 weeks

60 MPa

Injury 12 weeks

60 MPa

Histology Score

20MPa

40MPa

60MPa

Synovial Histology Cartilage Histology Total Histology
Mizzou Clinical Study
Multimodal Treatment Strategy for PTOA

- Biomechanics
  - Early, effective surgical management
    - Ligament stabilization
    - Meniscal repair/replacement
    - Cartilage restoration
    - Realignment
  - Neuromuscular/Biomechanical Training

- Biology
  - Role of Pharmacologic intervention
    - Aspirate hemarthrosis
    - Decrease inflammatory response
    - Minimize chondrocyte apoptosis
    - Limit matrix degradation of articular cartilage
    - Enhance new ECM production

(Olson et.al. JAAOS 2014)
Conclusions

- PTOA is a major and growing problem
- Biologic and Biomechanical factors influence onset and severity of PTOA
- We know some targets for prevention and treatment but need to figure out detailed whole organ mechanisms of how and why PTOA occurs
- Need concerted, multidisciplinary large scale efforts for classification and standardization, early diagnosis, and therapeutics
Thank You

Teams always defeat Individuals!

International Cartilage Repair Society