Endogenous Mechanisms of Cartilage Healing

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Cartilage Regeneration in OA

Exogenous regeneration
Provide exogenous cells, scaffolds, molecules to the joint

Endogenous regeneration
Stimulate cells in the joint to regenerate joint tissues

Correct OA stimulus

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Can cartilage regenerate?

- Evidence for precursor cells in cartilage and joint (reviewed in Jiang & Tan, NRR 2015)
- Repair of articular defects in mice is dependent on genetic background and age (Eltawil et al, OAC 2009)
Control of chondrocyte phenotype

Senescence → Precursor cell → Apoptosis → Hypertrophy

X

X

X

X
Challenges

• Can we control cartilage regeneration while preventing hypertrophy, dedifferentiation etc?

• It will not be sufficient to generate more chondrocytes; need to create the right kind of chondrocyte (e.g. superficial vs deep) and proper cartilage organization

• This will require a better understanding of how articular cartilage is formed in the first place (during development)
The TGFalpha-EGFR pathway as promoter of OA

Appleton et al., 2007
Tgfa KO mice are protected in a surgical OA model

Usmani et al., in revision
EGFR inhibition (AG1478) reduces OA severity in a rat model of OA

Sham  OA  OA + AG

Appleton et al., in revision
Does EGFR activation cause OA?
Cartilage-specific KO mice for Mig6
No overt phenotype in cartilage-specific Mig6 KO mice

Pest et al., 2014
Gait is unaffected in KO animals

Catwalk Gait Analysis

KO
Control

WT
KO

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Western
Ectopic endochondral ossification in joint periphery of Mig6 KO knees

Control

KO

Pest et al., 2014
Increased articular cartilage thickness in cartilage-specific Mig6 KO mice
Increased articular cartilage thickness in cartilage-specific Mig6 KO mice
Articular cartilage thickness in Mig6 KO mice

Control  KO

4 weeks

21 months
Articular cartilage thickness in Mig6 KO mice

36 Weeks

Control

KO

21 months

Control

KO
Cartilage markers in Mig6 KO mice

12 Weeks

A  Control
SOX9

B  KO
COL2A1

C  KO
pEGFR
Increased chondrocyte proliferation in cartilage-specific Mig6 KO mice
Conclusions so far

• Mig6 deletion in cartilage leads to increased proliferation of articular chondrocytes and increased articular cartilage thickness in multiple joints

• This appears at odds with the catabolic function of EGFR signaling in OA – time-/context-dependent effects? EGFR-independent effects?

• Mig6 deletion leads to endochondral ossification in peri-articular tissues of the knee, but not most other joints
Is inhibition of Mig6 a potential strategy to promote articular cartilage growth?

- Post-natal KO of the Mig6 gene in cartilage
- Col2Cre-ER(T2) driver (Di Chen)
- Induction of Cre activity in chondrocytes at 3 weeks of age
What happens when we delete Mig-6 from postnatal chondrocytes?
Not much happens when we delete Mig-6 from postnatal chondrocytes
Nothing in the elbows either

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Cre (-)</th>
<th>Cre (+)</th>
</tr>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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![Image](image3.png)
Recombination occurs, but not in all cells

→ Different tamoxifen time course?

→ Aggrecan-CreER(T2) driver
Does deletion of TGFalpha counteract the effects of Mig6 loss?
Anabolic effects of Mig6 deletion do not require TGFalpha

\[ \text{Mig}6^{fl/fl} \text{Tgfa}^{-/-} \quad \text{Mig}6^{fl/fl} \text{Col2Cre Tgfa}^{-/-} \]
Is Mig6 a potential target for cartilage repair?

- Developmental deletion of Mig6 from cartilage promotes articular cartilage growth
- Transient suppression of Mig6 signaling might be one therapeutic avenue, but it is not clear yet whether this mechanism is effective in adult cartilage
- Data indicate that this role of Mig6 in cartilage might be independent of EGFR signaling
- Mig6 suppression can also promote ectopic endochondral ossification which is detrimental to articular cartilage
- Too early to say whether Mig6 is promising target; however, it is clearly an important player in joint and cartilage biology
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