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Genes and Joints

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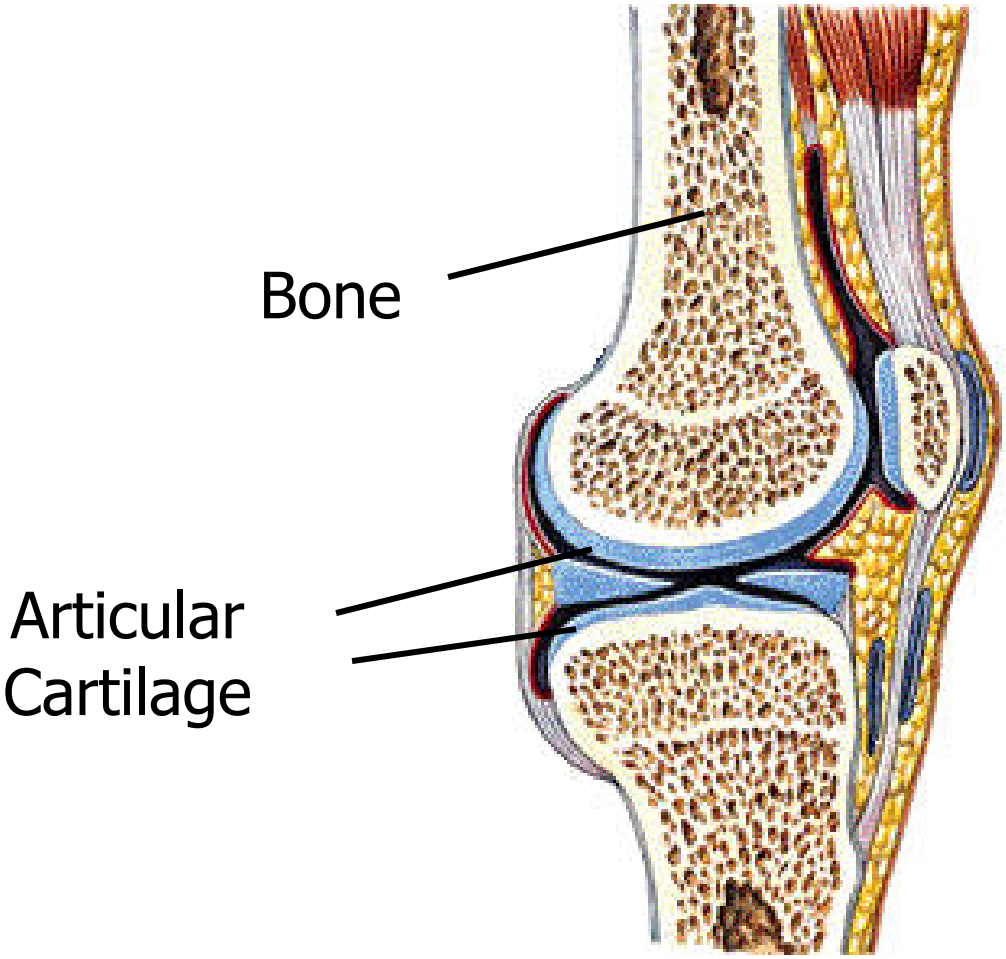
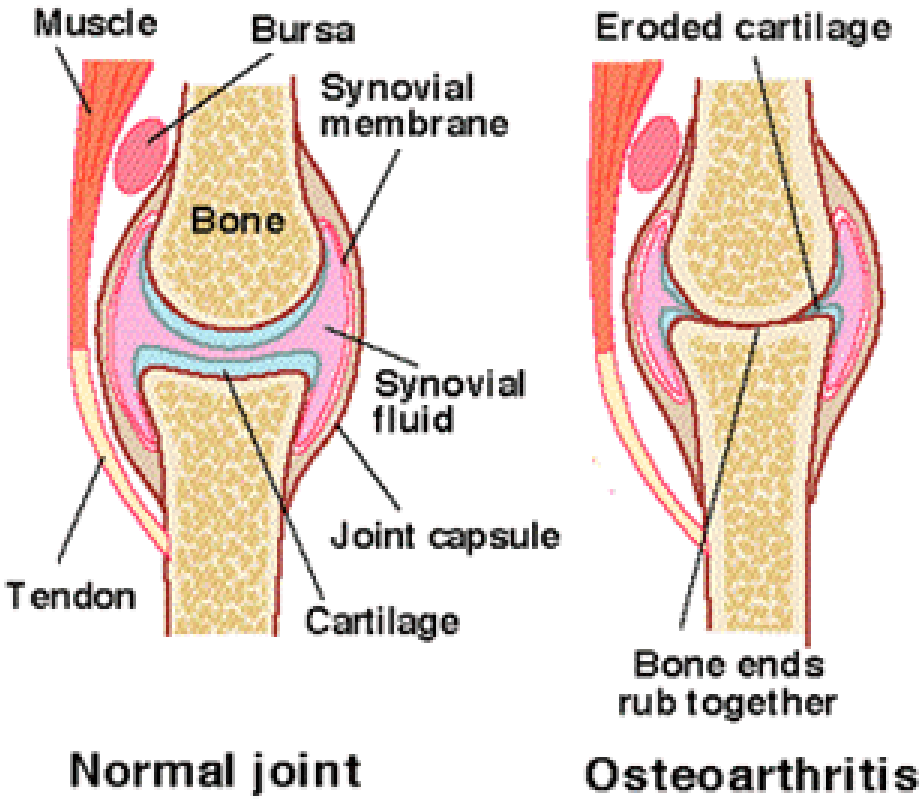
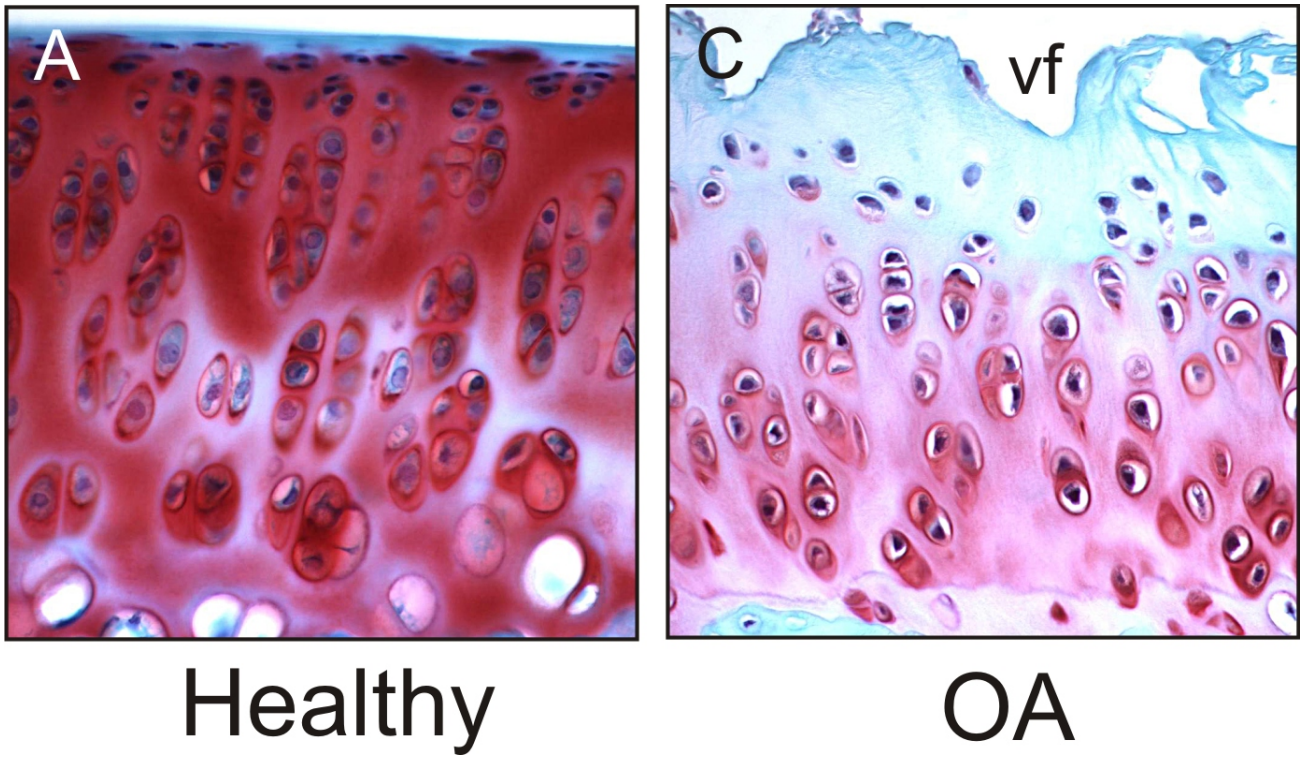
Tissues of the Joint



Joint changes in Osteoarthritis

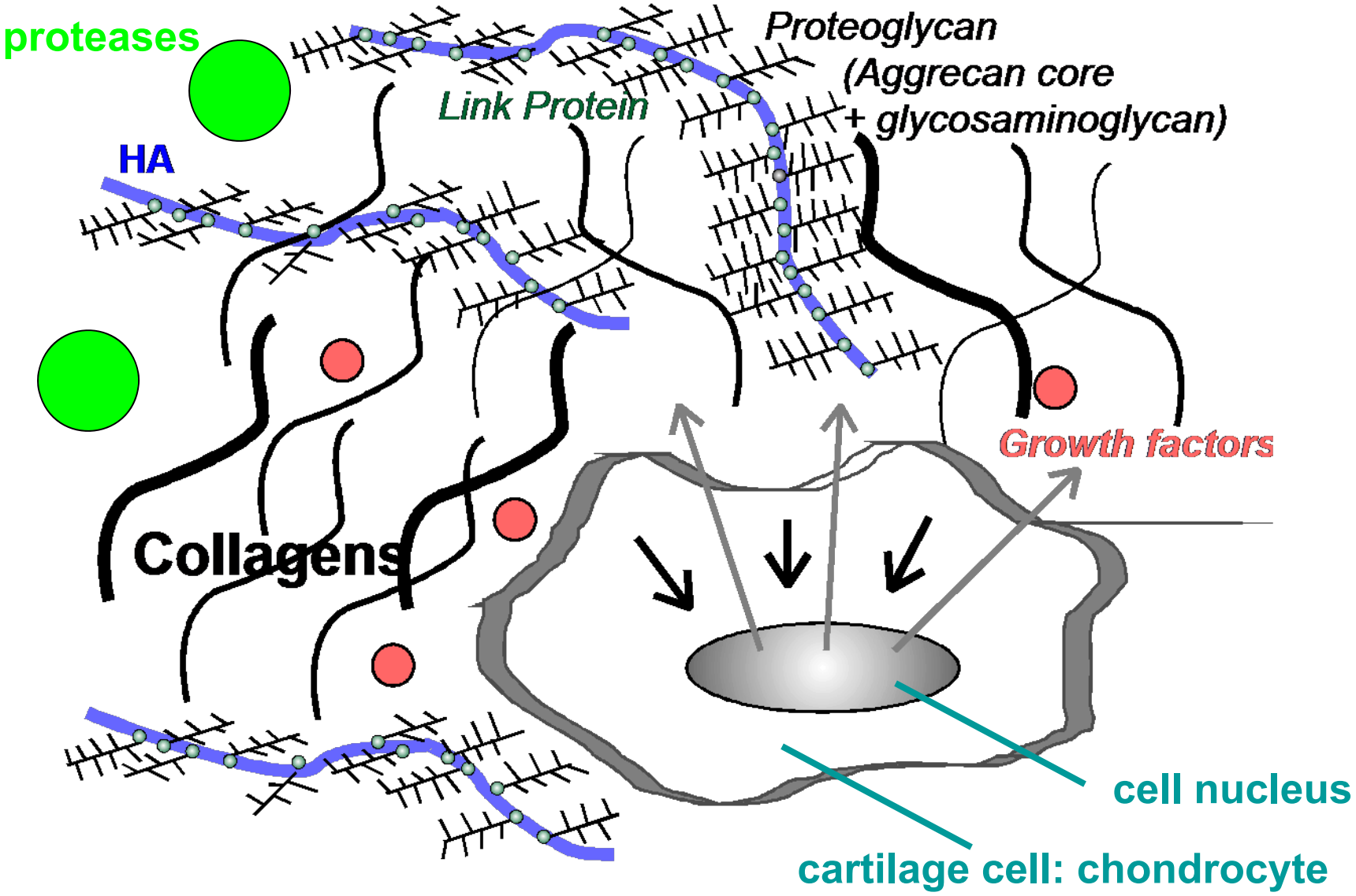


Osteoarthritis at the histological level

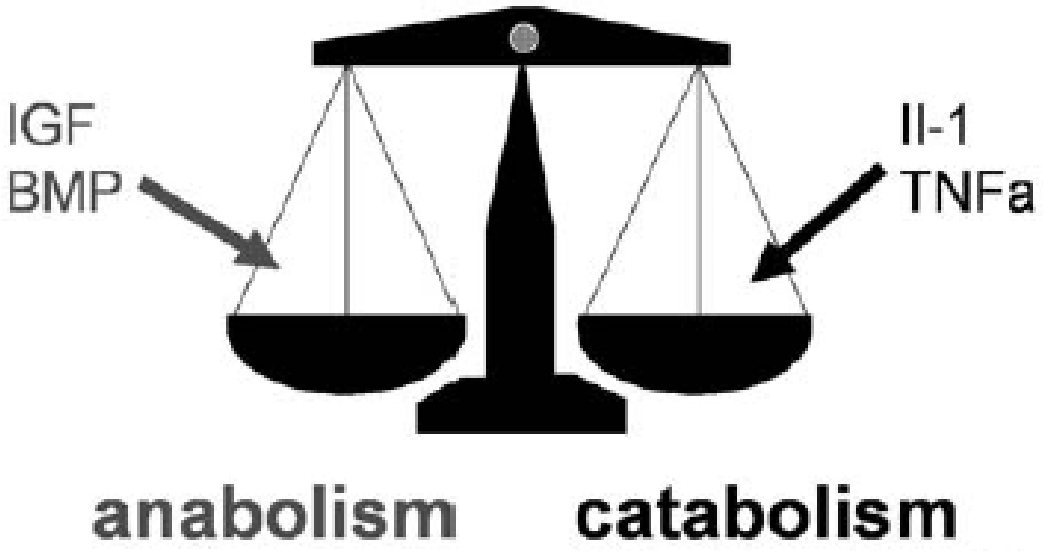


Loss of cells and extracellular matrix
(increased breakdown and lack of replacement)

Organization of Cartilage



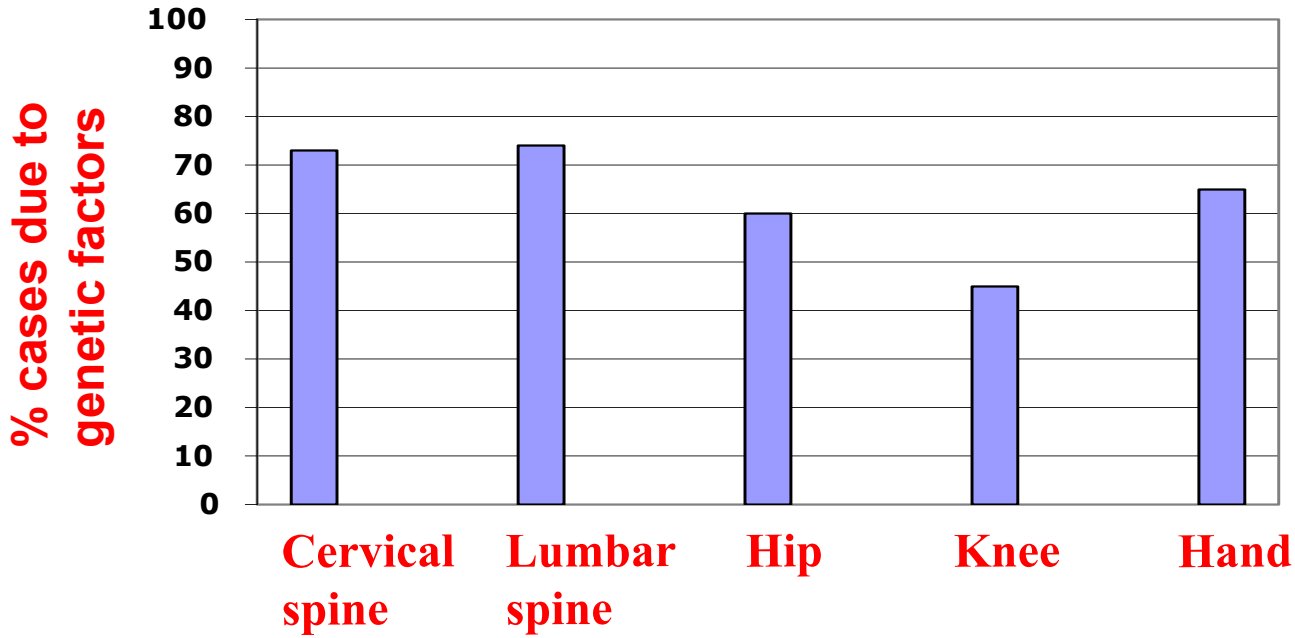
Balance of anabolism & catabolism



(Aigner et al., Eur. Cell Mater. 2006)

Genes and Osteoarthritis

Genetic factors contribute to a large proportion of OA cases



(Spector and MacGregor, Osteoarthritis and Cartilage 2003)

Genes are in control!

- **Architecture of the joint**
- **Strength of the tissues**
- **Division of cells**
- **Function of cells**

Genetic Information

- **stored and inherited as sequence of letters (nucleotides) in DNA**

- **in humans, the genetic information consists of three billion letters distributed over 46 strands of DNA (chromosomes)**

- **0.1 % of these letters are different in two randomly chosen humans**

- **Humans have approximately 20,000 genes**

The Human Genome

2 pairs of 23 chromosomes

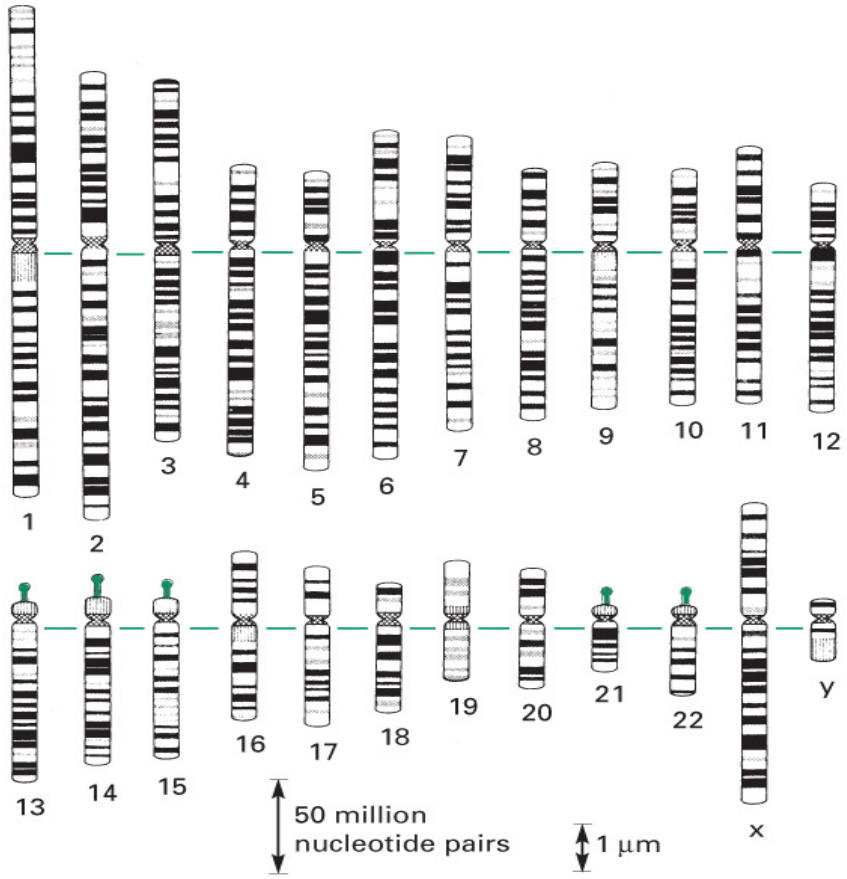


Figure 4–11. Molecular Biology of the Cell, 4th Edition.

DNA

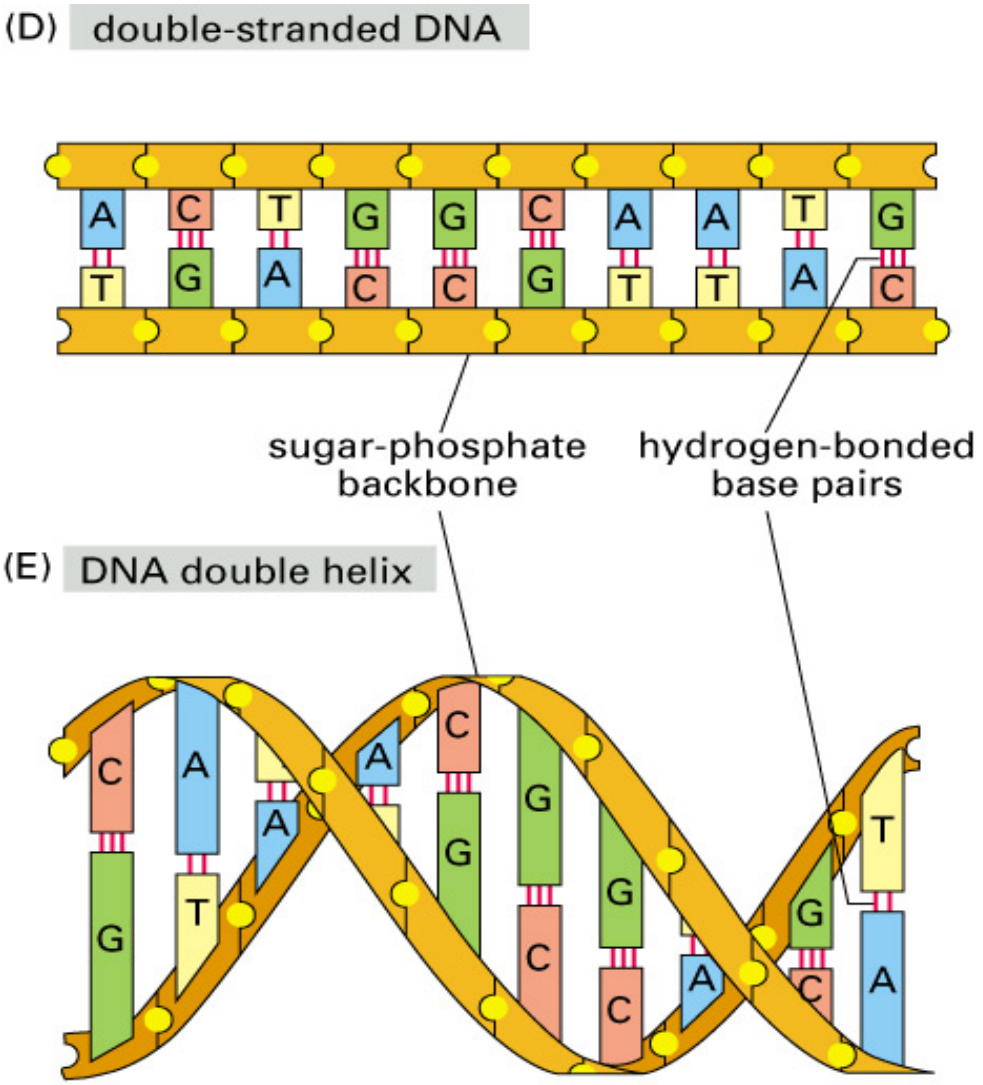


Figure 1–2 part 2 of 2. Molecular Biology of the Cell. 4th Edition.

Genes

- genes contain the information for all proteins in the body
- all tissues within the body have the same genes
- differences between tissues are due to the patterns of genes that are active (make proteins)
- similarly, differences between healthy and diseased tissues are connected to the patterns of gene activity

How does genetics contribute to osteoarthritis?

1) **Differences in nucleotide sequence change the function or the expression of a gene**
   - for example, a matrix molecule that is less stable or produced at a lower level

2) **Genetically controlled pathways determine how cells respond to their environment**
   - for example, changes in joint loading can increase production of proteases, causing cartilage destruction

Genes and Osteoarthritis

- genes that contribute to development of osteoarthritis remain to be identified

- different genes appear to contribute to arthritis at different anatomical sites, in males and females etc.

- many cases of arthritis likely involve changes in two or more genes (multifactoral disease)

- Genetic effects often work together with environmental factors to determine risk of osteoarthritis

Genes and Osteoarthritis: Current Approaches

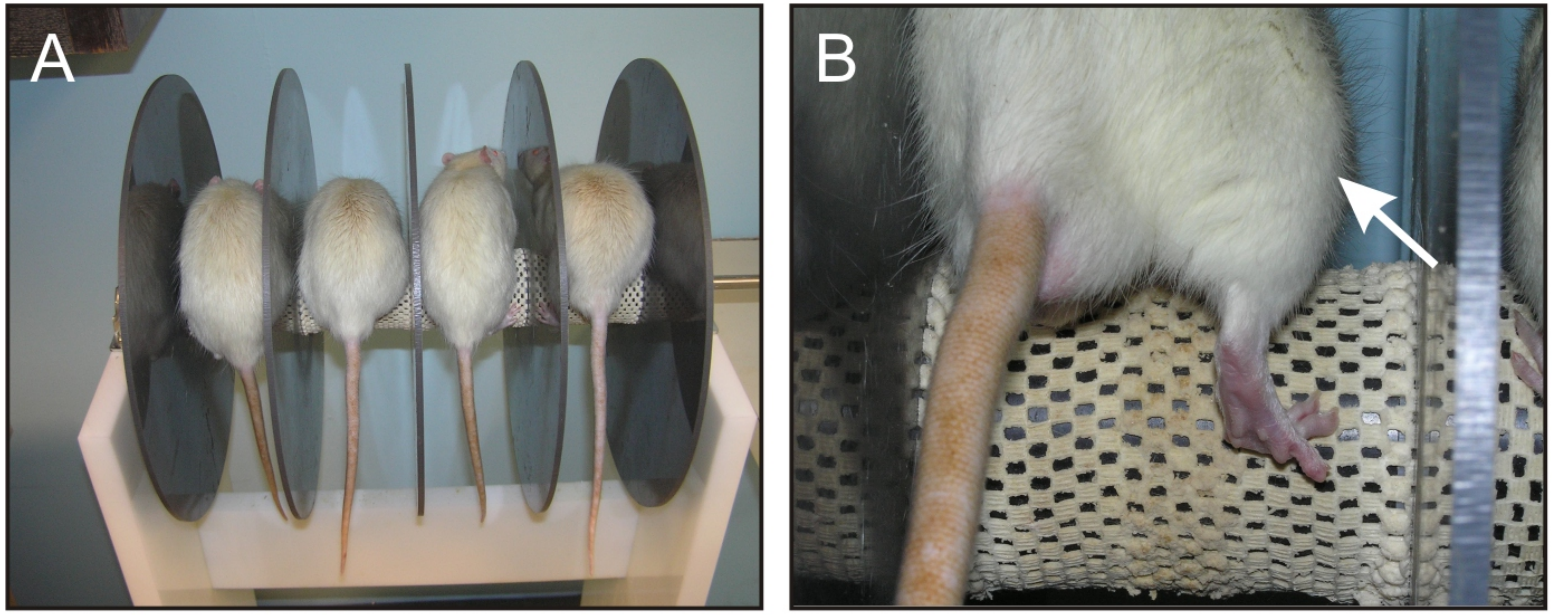
1) Identify genetic variations involved in the development of osteoarthritis

2) Identify changes in patterns of gene activity in osteoarthritis

3) Test the effects of these alterations on joint and cartilage function

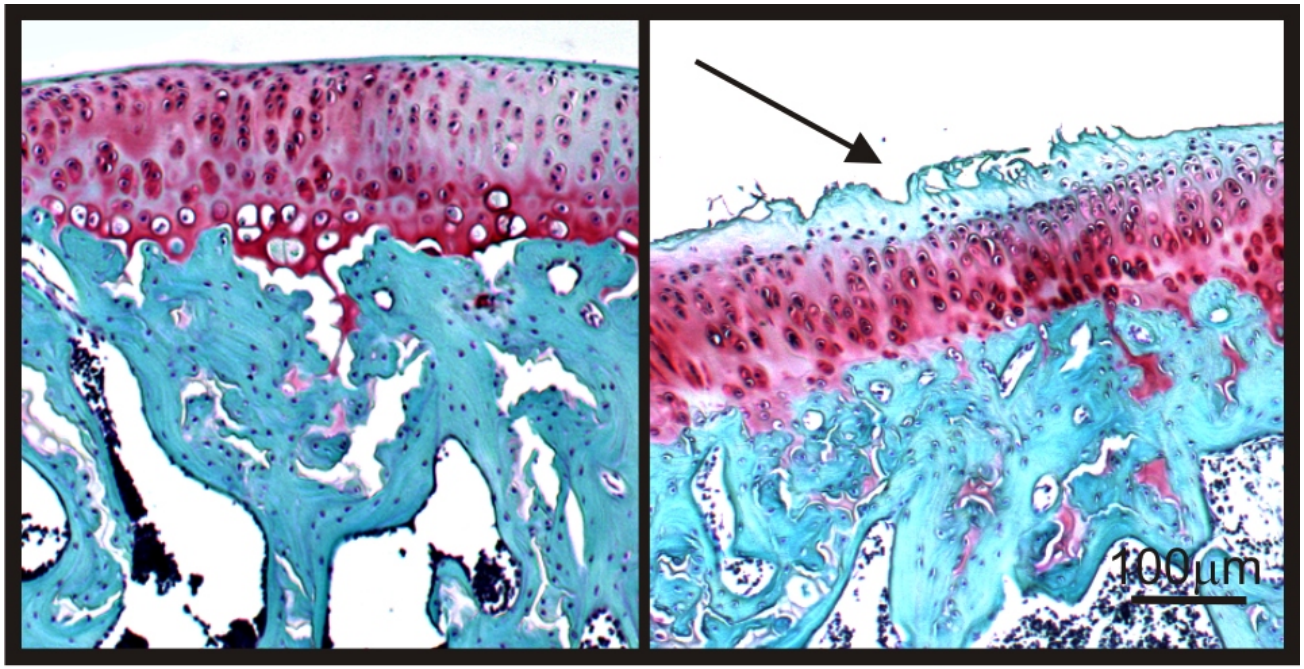
→ **Identification of novel preventive, diagnostic and therapeutic targets**

Rat Model of Osteoarthritis



Appleton et al., Arthr. Res. Ther. 2007

Early Osteoarthritis in our Model



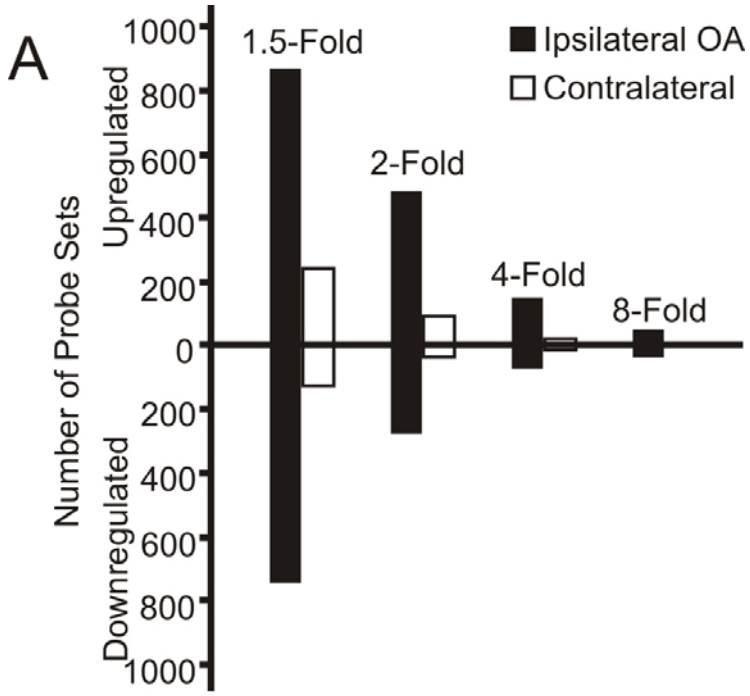
Appleton et al., Arthr. Res. Ther. 2007

Large Scale Analyses of Gene Activity: GeneChips or Microarrays

- allows analyses of activity of thousands of genes in one experiment, thereby accelerating scientific progress

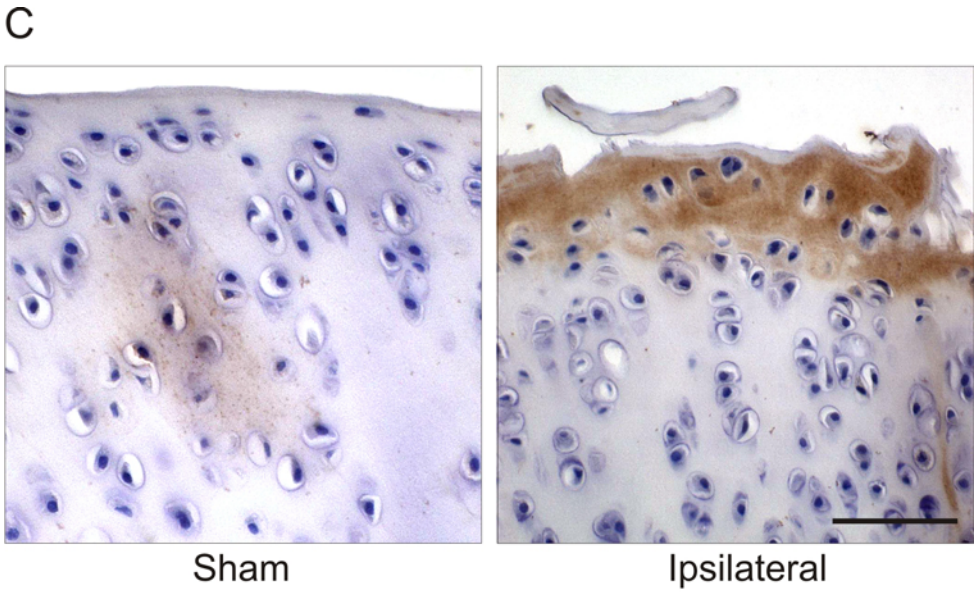
- in conjunction with computer programs permits identification of pathways and regulatory networks

Microarray Analyses of our Osteoarthritis Model



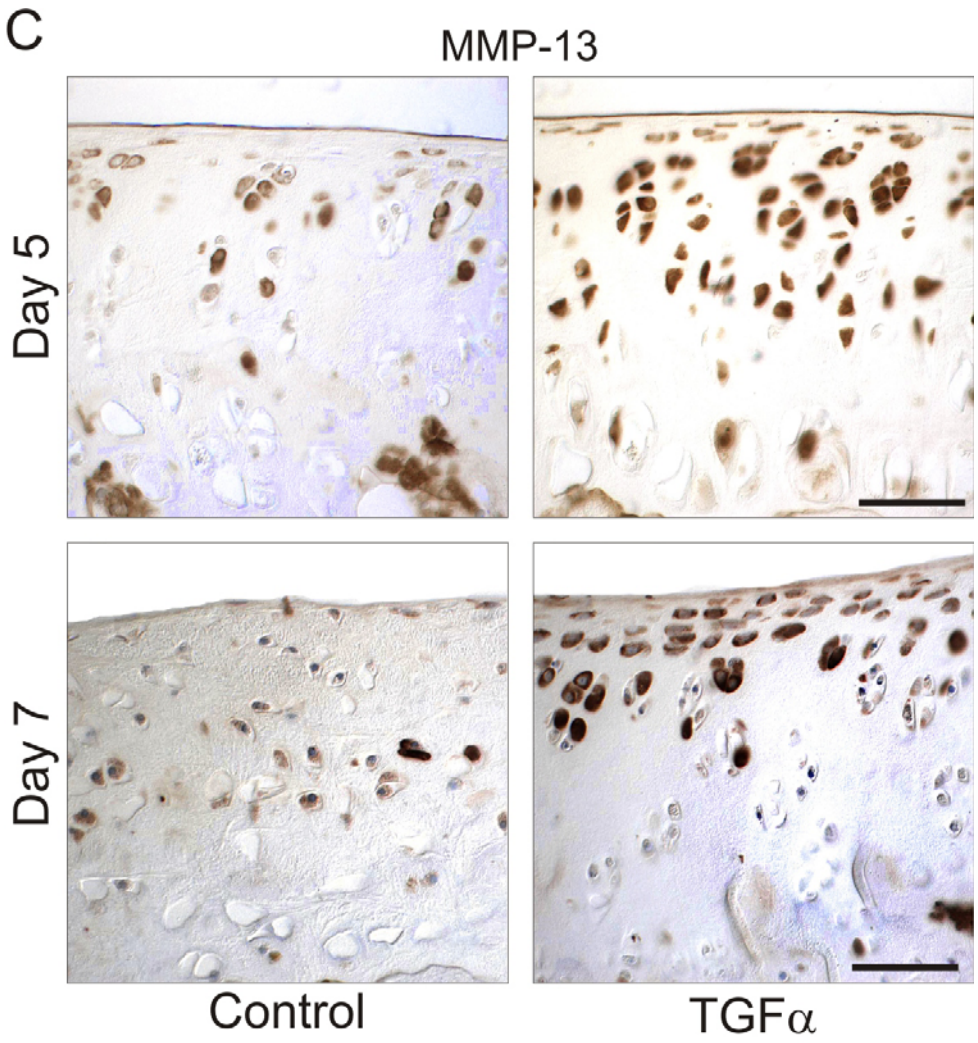
Appleton et al., Arthr. & Rheum. 2007a

Example for an identified gene: TGFα is activated in Osteoarthritis

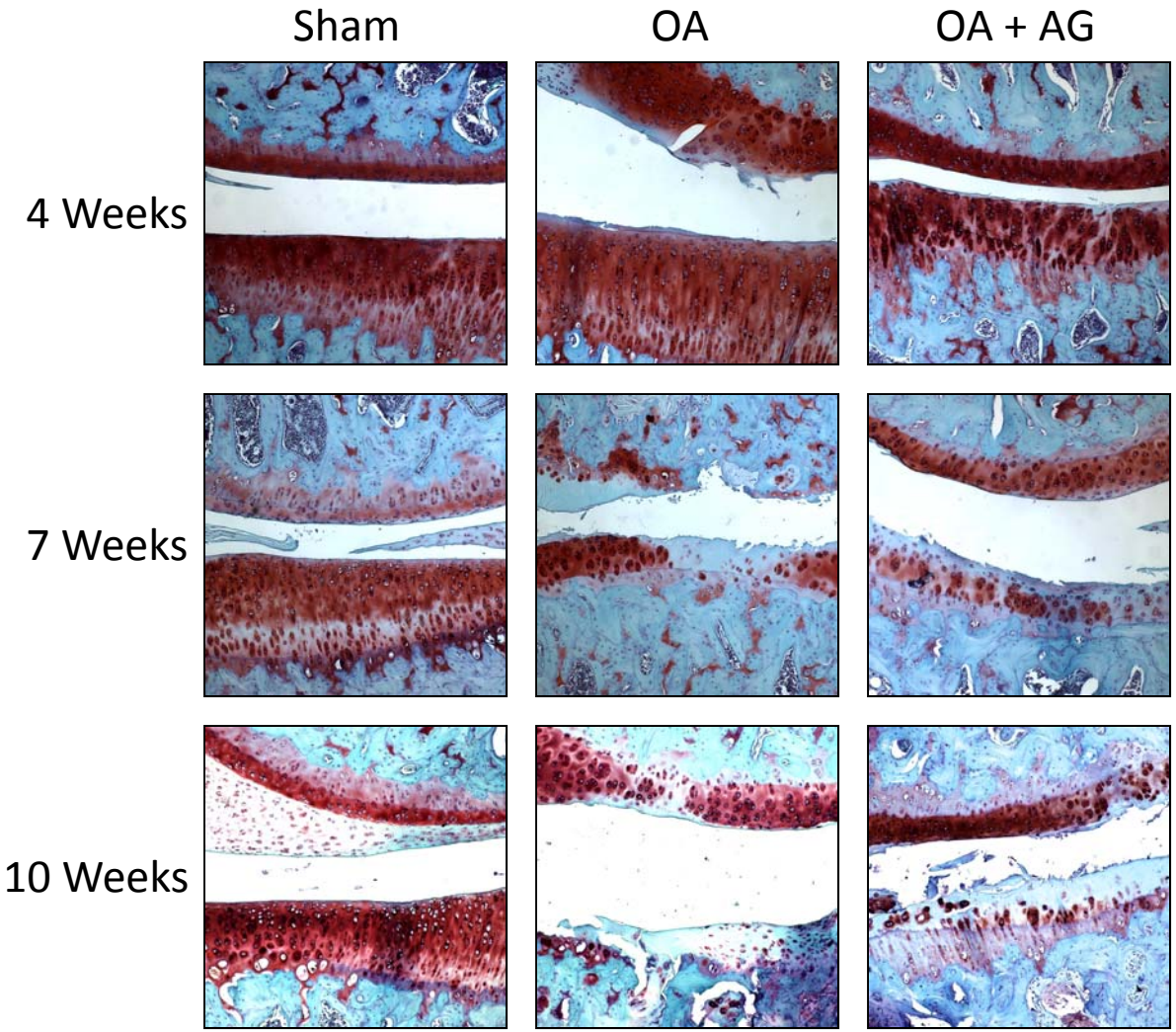


Appleton et al., Arthr. & Rheum. 2007b

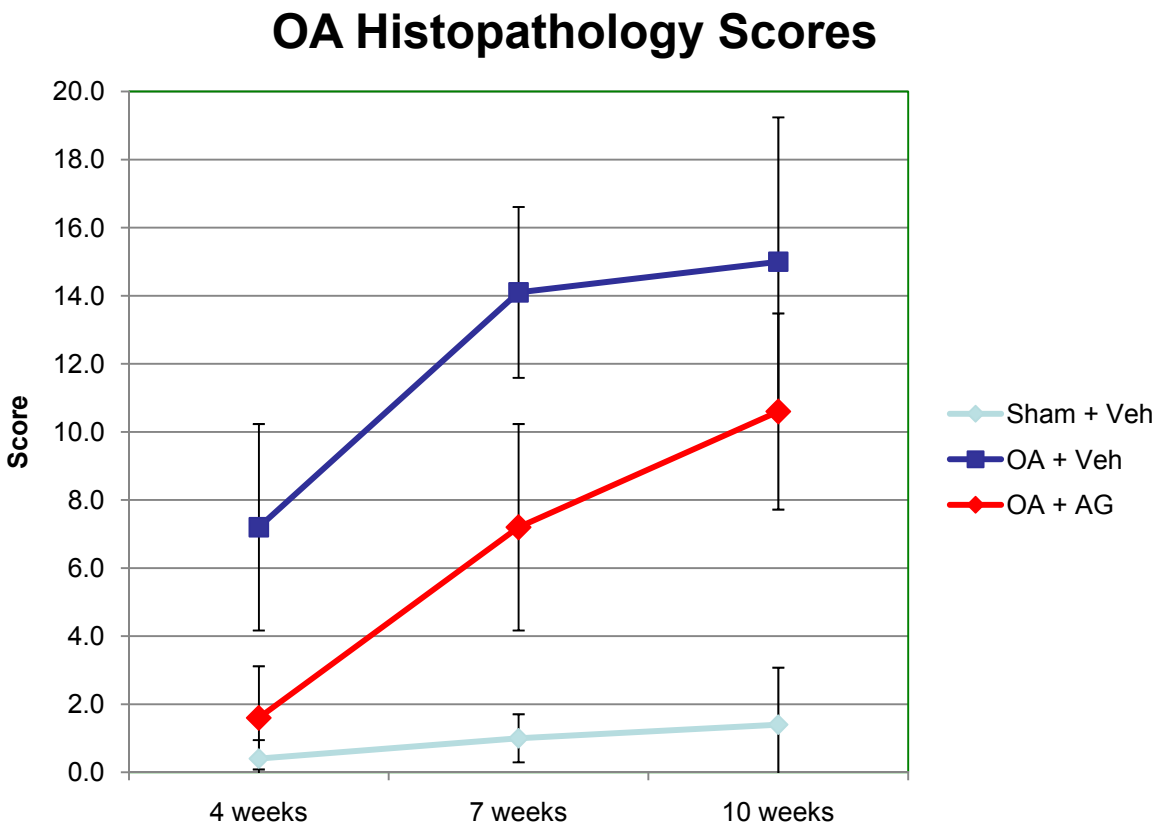
TGFα induces features of Osteoarthritis



Inhibition of TGFα signaling reduces OA severity in our rat model



Inhibition of TGFα signaling reduces OA severity



Tom Appleton

What next?

- **Is TGFα involved in human osteoarthritis?**
- **How does TGFα work in cartilage?**
- **What is the role of the many other genes and proteins identified in our gene chip studies?**

Thanks to

Lab

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Thank you for listening!!