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Genes and Joints

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Genes and Joints

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Tissues of the Joint

Bone

Articular Cartilage
Joint changes in Osteoarthritis

![Diagram showing normal joint and osteoarthritis joint with labels: Muscle, Bursa, Synovial membrane, Synovial fluid, Joint capsule, Tendon, Cartilage, Eroded cartilage, Bone ends rub together.](image)
Osteoarthritis at the histological level

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

proteases

HA

Proteoglycan
(AGgrecan core + glycosaminoglycan)

Link Protein

Collagens

cell nucleus

cartilage cell: chondrocyte

Growth factors
Balance of anabolism & catabolism

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.
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 (multifactorial 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

Sham  OA

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.

Sham | OA | OA + AG

4 Weeks

7 Weeks

10 Weeks
Inhibition of TGFα signaling reduces OA severity

OA Histopathology Scores

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?
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