**Articular Cartilage Structure, Composition, & Function:**

Summary of Buckwalter Ch 17

to be read in conjunction with notes/diagrams on hand

*Articular cartilage*

resilient load bearing tissue

forms articulating surfaces of diarthroidal joints

provides these surfaces with low friction, lubrication & wear characteristics

required for repetitive gliding motion

absorbs mechanical shock & spreads the applied load onto subchondral bone

***Structure & Composition:***

consists of:

large extracellular matrix with a sparse highly specialised cells-chondrocytes

ECM- water, proteoglycans, collagens, other proteins/glycoproteins

structure & composition vary throughout depth

*superficial zone* [10-20%]

forms gliding surface

thin fibrils parallel to surface

elongated chondrocytes also parallel

proteoglycans content lowest/ water content highest

*middle(or transition) zone*  [40-60%]

larger diameter less well organised collagen fibres

more rounded chondrocytes

*deep zone*  [30%]

proteoglycans content lowest/ water content highest

large diam collagen organised perpendic to surface

chondrocytes spherical arranged in columns

*calcified zone*

separates hyaline cartilage form subchondral bone

small cells in a cartilaginous matrix encrusted with apatitie salts

tidemark separates deep zone from calcified zone

ECM divided into

*pericellular matrix*

thin layer adjacent to cell membrane & completely surrounds chondrocyte

contains primarily proteoglycans & other non collagenous matrix components

almost no collagen fibrils present

*territorial matrix*

surrounds pericellular matrix

distinct fibrillar network

*inter territorial matrix*

largest of the matrix regions

contributes most of the material properties of artic cartilage

large collagen fibres and majority proteoglycans

Chondron = chondrocyte + its pericellular & territorial matrices

Chondrocytes:

forms & maintains articular cartilage

derived from mesenchymal cells

metabolically active

respond to a variety of environmental stimuli

soluble mediators

growth factors

interleukins

pharmaceutical agents

matrix molecules

mechanical loads & hydrostatic pressure changes

generally maintain stable matrix

limited response to other bodily control mechanisms

no innervation/ cellular & humeral immune response don't penetrate

Matrix Composition:

chondrocytes occupy v small proportion of tissue

normal cartilage

water [65-80%]

may increase in early o/a

some intracellularly, some associated with intrafibrillar space of collagen

most contained in molecular pore space of ECM

inorganic salts dissolved in it - Na Cl Ca K

water concentration greatest at surface [85%] to deep zone [65%]

moves through ECM under pressure gradient or applying a compressive load

two basic mechanisms allow artic cartilage to support high joint loads

frictional resistance

pressurisation of ECM

flow of water through tissue promotes nutrition flow of water across surface aids lubrication

fluid mechanics governed by mechanical & physiochemical laws

v large pressures requ to move water eg 17.5µm/sec - 1MPa ( 143psi)

hydrophilic proteoglycans bind water

depends on Donnan osmotic pressure & entropic tendency of proteogly’s

balance sum these 2 properties vs constraining forces of collagen

result is a strong cohesive solid matrix

macromolecules

*collagen* [ wet 10-20%] [ dry >50%]

major structural macromolecules

at least 15 distinct types [ see other texts/ course notes]

all contain a triple helical structure ( 3 left handed chains)

Type II major collagen [ 90-95%]

provide tensile & sheer properties

immobilise the proteoglycans within the ECM

roles of other collagens in artic cart uncertain [type IX stabilises type II]

cross linked network-> adds to 3D stability/ contributes to tensile prop’s

*aggrecan* [wet 4-7%] [ dry 40%]

complex macromolecule; distributed more to transitional zone

consists of protein core with covalently bound polysaccharides ( glycosaminoglycan)

glycosaminoglycans

consist of long chained repeating disaccharide units

Three major types

*chondroitin SO4* ( 4 & 6 isomers) [ 55-90%]

“4” younger-> “6” older age

*keratan SO4*

*dermatan SO4*

- *hyaluronate*- not sulphated/covalently bound protein core

not part of a proteoglycans

90% of proteoglycans are large aggregating type [aggrecan]

large protein core

distinct complex globular & extended domains

HA binding domain(G1) G2 KS rich region - CS rich region G3

2 small proteoglycans

*decorin*- involved in control fibrillogenesis

*biglycan*

*fibromodulin*

Thus within the ECM, the size, structural rigidity & molecular conformation of the charged proteoglycans trapped within the interfibrillar space will influence the mechanical behaviour of artic cart. The proteoglycans networking and proteoglycan-collagen interactions enhances the ability of artic cart to maintain structural rigidity & adds to stiffness & strength of the ECM. Lack of covalent bonds between proteoglycans & collagen allows collagen fibres to slide though the gel.

Non Collagenous Proteins & Glycoproteins:

help maintain & organise macromolecular structure of ECM

*Anchorin CII*

helps “anchor” chondrocytes to matrix collagen fibrils

*Cartilage Oligomeric Protein COMP*

may bind chondrocytes

found primarily in chondrocyte territorial matrix

*Fibronectin & Tenascin*

poorly understood role

Lipids:

form <1% wet weight

exact function unknown- vary with age and presence o/arthritis

phospholipase A2 - impt in arachnidoic acid metabolism and degradative p/w

***Metabolism:***

chondrocytes rely principally on anaerobic pathway for energy production

chondrocytes synthesise & assemble matrix components & direct their distribution

maintenance of normal ECM depends on chondrocytes being able to balance

rates of synthesis of matrix components, appropriate incorporation into the matrix and the components degradation & release from cartilage

-> do so by responding to the chemical & mechanical environments

- soluble mediators

- matrix composition

- hydrostatic pressure changes

- mechanical loads

- electric fields

Nutrition:

nutrients diffuse thru synovial fluid/underlying bone

diffusion from bone depends on skeletal maturity/ development impermeable tidemark

Proteoglycan Synthesis:

chondrocyte responsible for synthesis, assembly & sulphation of proteoglycan

molecule

can occur at a rapid rate & is affected by numerous endogenous & exogenous environmental stimuli

{ refer texts/notes for diagramatic representation etc}

control mechanisms for proteoglycan synthesis extraordinarily sensitive to biochemical, mechanical& physical stimuli

Proteoglycan Catabolism:

are continually being broken down & released from cartilage

rate of catabolism affected by soluble mediators ( IL 1) & by various types of joint loading ( immobilisation)

major cleavage site of protein core is between G1 & G2domains ( proteolysis)

fragments found in synovial fluid-> taken up by lymphatics

Collagen Synthesis:

collagen network more stable than proteoglycan component

turnover increases in o/arthritic cartilage or laceration injury

hydroxylation requires Vit C as cofactor ( scurvy)

{ refer texts/notes for diagramatic representation etc}

Collagen Catabolism:

little is known,

breakdown may be enzymatic ? metalloproteinase *collagenase* cleaves triple helix

Growth Factors:

role in regulation synthesis normal cartilage

may have greater role in osteoarthritis

IGF-1 & Insulin- compete for cell surface receptor sites

*Platelet-Derived Growth Factor [PDGF]*

mitogenic effect on chondrocytes

glycoprotein

more active in injury/osteoarthritis

*Basic Fibroblast Growth Factor [ bFGF]*

powerful stimulator DNA synthesis, is a peptide

markedly stimulates repair

*Insulin & Insulin Like Growth Factors [ IGF-I, IGF-II]*

stimulate DNA & matrix synthesis, are peptides

? more effective in combination with other factors bFGF

maintains steady state proteoglycan synthesis

*Transforming Growth Factor-Beta [ TGF-ß]*

synthesised locally by chondrocytes, is a protein

stimulates proteoglycan synthesis, suppress Type II collagen synthesis

stimulates formation of *tissue inhibitor of metalloproteinase [TIMP]*

Degradative Enzymes:

proteolytic enzymes synthesised by the chondrocyte; part of the complex orchestration of events to maintain normal cartilage

over activity of some of the se enzymes responsible for cartilage degradation in arthritis

*Metalloproteinases:*

collagenase gelatinase stromelysin

Zinc at active site

*collagenase* only enz to cleave collagen triple helix

*gelatinase* cleaves denatured chains after collagenase action

*stromelysin* also acts on Type II but at non helical domain & IX collagen

major action is to break core protein of aggrecan

?? yet to be defined 4th enzyme

controlled by 2 mechanisms - activation & inhibition

synthesised as latent enzymes - pro....’ase

require activation outside of cell by enzymatic modification

collagenase activated by *plasmin*

plasmin produced from *plasminogen*

stromelysin super activates collagenase

irreversibly inhibited by *TIMP*

ratios of metalloproteinases to TIMP determine net activity

*Cathepsins*:

cathepsin B & D

can degrade aggrecan

operate at low pH ? significance

***Development & Ageing:***

Immature cartilage Adult Cartilage

relatively thick plate for endochondral ossification

high number of cells uniformly distrib

mitotic figures seen virtually none seen

less differentiation in lower zones well defined calcific zone “tidemark”

high water content diminished during skeletal growth;

constant in adulthood

lower collagen content content at adult levels shortly after birth

proteoglycan content high diminishing proteoglyc content with age

longer protein core to Pro’glyc

longer glycosaminoglycan chains

chondroitin 4 sulphate predominates chondroitin 6 sulphate predominates

increasing keratan sulphate to age 30

diminishing aggregation

ch’cyte less responsive to anabolic cytokin

***Biomechanics:***

articular cartilage subjected to

high loads- applied statically, cyclically, repetitively over many decades

best understood as a *biphasic* material

*Solid* phase

*Fluid* phase

cartilage is water permeable

water flows under pressure gradient, also under compression

load carrying capacity of each phase is determined by balancing frictional

drag forces against elastic forces at each point within the tissue

direct relationship betwn permeability and water content

inverse relationship betwn permeability & proteoglycan content

cartilage is *viscoeleastic*

exhibits time dependent behaviour

2 mechanisms:

flow- independent- *pure sheer*

flow - dependent - *creep & stress relaxation*

early o/a changes in human cartilage

increased water/ decreased proteoglyc content

increase tissue permeability-> diminishes fluid pressurisation

diminished fluid pressurisation-> increased solid matrix bearing load

increased solid matrix load bearing-> detrimental to long term survival

random organisation collagen architecture->contributes to sheer properties

sheer stress maximal at tidemark

proteoglycan network maintains spatial form of collagen network but does not provide any appreciable stiffness in sheer

tensile properties

correlates well with collagen content & ratio collagen to proteoglycan

swelling ( physiochemical) derived from ionic charge of proteoglycan

limited by matrix resistance to expansion (predominately collage)

osmotic pressure from fixed & counterion charges

swelling pressure contributes significantly in lightly loaded tissue

highly loaded tissue ( physiological) & dynamical loading interstitial fluid pressurisation predominates

equilibrium state exists

***Response to Loading:***

Mechanosignal transduction

chondrocytes are pressure & deformation sensitive

physical forces act on cell membranes

presumably induce specific gene expression ? how

*integrin* ( spans cell membranes & connect to cytoplasm) are involved

Effects of Joint Motion & Loading

are required to maintain normal articular cartilage

reduced loading-> atrophy & degradation

contact areas-> severe degeneration

non contact areas-> fibrillation, decreased proteoglycan synthesis & content

& altered p/glyc conformation

occur because of decreased nutritive transport from synovial fluid

increased loading -> catabolic effects

either by single impact or repetitive trauma

may serve as initiating factor for progressive degeneration

by disruption intra-articular structures or ligament

decrease in tensile & sheer properties of cartilage obs with ACL rupture

mechanical properties linked to histological & compositional changes

joint instability-> decrease in compressive properties

increase in water permeability

reduction in stress shielding effects

specific mechanisms of joint loading on chondrocyte unknown

unclear which are the most impt signals stimulating catabolic or anabolic activity