**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