

LECTURE 39 (including page 2, which was missing in the on-line pdf file available before 4/27/05)

MYOGENESIS, ADIPOGENESIS, CHONDROGENESIS, & OSTEOGENESIS

Chapt. 22, p. 1296-1308; Figs. 22-40, 41, 43-45, 49 to -56

SKELETAL MUSCLE: its genesis, modulation & regeneration/repair

- **Fig. 22-40: Four muscle types in vertebrates** (mesoderm deriv., except 4):
 - 1) **Skeletal muscle:** for voluntary movement
 - large, long, multinucleated cells (syncytia) or "muscle fibers"
 - striated: actin & myosin filaments in orderly arrays (sarcomeres)
 - 2) **Heart muscle:** resembles skel. muscle; striated
 - 3) **Smooth muscle:** Unstriated
 - various functions in diff't organs (eg., move food along digestive track)
 - 4) **Myoepithelial muscle:** derived from ectoderm; lie in epithelia; unstriated
 - eg., dilate iris of eye, expel saliva, sweat, milk from various glands

New skeletal muscle forms by fusion of myoblasts into muscle fibers

- **Fig. 22-41: Myoblasts:** proliferating, immature muscle cells
 - derived fr. somites (embryonic mesoderm close to neural tube)
 - commitment reqs combinatorial activities of at least 2 TF families:
 - **MyoD/myogenic** family of bHLH TF's
 - **MEF2/MADS box** family TF's
 - FGF or HGF req to remain proliferating, undifferentiated myoblasts in culture
 - **Removal of FGF/HGF:** myoblasts stop dividing; fuse to form m. fibers
 - **Substrate/ECM attachment** also important
 - **Differentiation/fusion is cooperative** (differentiating myoblasts secrete factors that recruit other myoblasts to differentiate; community effect)

Number muscle fibers is fixed before birth, but size can be modulated:

- nuclei in m. fibers are differentiated & can't divide; so muscles grow by:
 - recruiting more myoblasts in (from **satellite cells**)
 - bulking up contractile machinery in cytoplasm of each m. fiber
- **Skeletal muscle fibers secrete Myostatin to limit their own size/growth**
 - **Myostatin is a TGFβ family signal;** negative feedback regulation
 - Elevated in AIDS patients w/ muscle-wasting
 - **Fig. 22-43: myostatin -/- mice** have larger muscles (more & larger fibers)
 - **Fig. 17-51: muscle-bound steer w/ myostatin mutation**

Fig. 22-44: Satellite cells are myoblast stem cells

- Normally quiescent; can be recruited to proliferate, differentiate & fuse to muscle fibers to repair damaged muscle
- Mutations in muscle cytoskeletal protein **dystrophin** cause degeneration of muscle fibers (**Muscular Dystrophy**)
 - satellite cells constantly called to repair damage; eventually are depleted; muscle fibers gradually replaced by connective tissue

FIBROBLASTS & THEIR TRANSFORMATIONS: Connective Tissue Cell Family

- **mesodermal deriv.;** central role in **support & repair** of every tissue & organ
- **Fig. 22-45:** Connective tissue (c.t.) cell family of interconvertible cell types: **fibroblasts, cartilage cells, bone cells, fat cells, smooth muscle cell**

Fibroblasts (FBs), cartilage cells, & bone cells secrete collagen-rich extracellular matrix (ECM)

- FBs are least specialized cells in c.t. family
 - dispersed in body c.t.; easy to grow in culture

- secrete non-rigid matrix rich in types I & III collagen
- proliferate & migrate into wound, secrete collagen-matrix to isolate & repair damaged tissue
- Bone marrow stromal cells are FBs that are self-renewing, multipotent (aka **mesenchymal stem cells**)
- Skin/dermis FB's are less plastic, but can undergo some changes:
 - near wound, in response to **TGFβ**, become **myofibroblasts** w/ contractile properties, form collagen-rich scar tissue
 - exposed to bone ECM, become cartilage, later, bone cells
- **BMP's & TGFβ** from bone ECM; injected into live animals, induce cartilage, bone or fibrous material
- **ECM may affect c.t. cell differentiat'n by affecting cell shape & attachmt**
 - **Chondrocytes** (secrete **type II collagen for cartilage**) "dedifferentiate" to **FBs** (secrete **type I collagen**) if shifted to monolayer, low density cultures
 - **Dediff'd cells revert to chondrocytes (secrete type II collagen) if moved from plate to agarose** (cell shape change [flat to round]? Loss of anchorage?)
 - Cell shape & attachmt to ECM impact integrin-signaling, focal-contacts
 - c.t. cells make ECM; ECM impacts cell fates; diffus'n of GF's; community effects

Fat cells (aka, adipocytes) develop from FB-like cells

- Fat cell diff'n begins w/ C/EBP & PPAR TF families; maintain expr'n via cross- & auto-regulatory loops (like MyoD & MEF TFs in myoblast diff'n)
- **Fig. 22-47:** Diff'n program: produce enzymes for fatty acid & glucose import, fat (triacylglycerol mostly) synthesis & degrad'n (lipases).
- Fat cells can change their vol by 1000X by accumulating or releasing lipid
- **they secrete Leptin into bloodstr. in negative feedback to inhibit eating**
- **Fig. 22-49:** mutant mice lacking leptin or its receptor overeat & are obese
- Leptin acts on many tissues, including brain to regulate eating behavior
- Negative-feedback role resembles that of myostatin in muscle
- Most obese people have high leptin; over-riding factors poorly understood

Fig. 22-52 & 22-54: Bone (b.) is continually remodeled by cells within it

- Dense specialized ECM/c.t.; plywood-like layers of type I collagen fibers embedded w/ calcium phosphate crystals
- **~15% of vol. is living cells** that continuously turnover/replace bone matrix:
 - **osteoblasts** (related to FBs): deposit new b. matrix (osteoid, chiefly type I collagen) at b. surface; rapidly conv to hard bone by add'n of calcium phosph., traps some osteoblasts which become **osteocytes**
 - **osteoclasts** (**Figs. 22-53:** multin. macrophages formed by fusion of monocytes at b. resorp'n sites); erode b. matrix from w/in
- **limb bones form by replacing cartilage "scale models" during fetal dev**
- **achondroplasia** (commonest form of dwarfism, Fig. 22-50): dominant mutation in **FGFR3** reduces cartilage form'n (chondrogenesis) in limbs
- **Fig. 22-54: osteoclasts excavate tunnel in bone @50 um/day, capillary & osteoblasts follow, latter fill tunnel w/new bone (10-15% new bone/yr in mammal); BMPs in bone matrix may help guide remodeling**
- **Long bone dev (Fig. 22-56):** chondrocytes in cartilage die leaving cavities; o'clasts & bv's invade; cartil. removed by o'clasts; bone deposited by o'blasts
- **osteoporosis:** excessive bone erosion/weakening of bone
- **osteopetrosis:** excessively dense/thick bone