

LECTURE 37

ENDOTHELIAL CELLS, ANGIOGENESIS (formation of blood vessels) and HEMATOPOIESIS (generation of blood cell types)

Chapt. 22, p. 1279-1288

Figs. 22-22 to -33; Table 22-1.

BLOOD VESSELS (bv's): all tissues, even tumors, need bv's to supply blood

- make up the **vascular system**
- **mesodermally derived** (m. also generates body's connective tissues, muscles, blood cells, kidney, other structures)
- lined by **endothelial cells (ec's)** (in layer called the **endothelium**)
 - **fundamental cell type** in all bv's
 - **responsible for dev/growth & remodeling** of bv during repair
 - **basal lamina (bl)** separates endothelium from surrounding tissue
 - **regulates exchange/passage** of material & white blood cell types betw/ blood & tissues
- **FIG. 22-22: cross section of small artery**
 - **arteries & veins:** largest bv's, w/ connective tissue wall & smooth muscle (sm)
 - dev during embryogenesis from small vessels containing **ONLY ec's & bl**
 - pericytes, connect. tissue & sm added later as a. or v. grows
- **capillaries & sinusoids (Fig. 22-23):** finest branches of vasc. system, w/ ec's, bl & pericytes
- **pericytes**
 - related to vasc. smooth muscle cells
 - wrap around bv
 - recruited by PDGF secreted by ec
 - bv's w/out pericytes dev. microaneurysms (microscopic ruptures)

FORMATION OF NEW CAPILLARIES (cap's)

New ec's are generated by duplication of existing ec's

- **lifetime of ec:** months to years in adult mouse liver & brain, respectively (3H-thymidine into DNA)
- embryonic ec's proliferate more frequently

Fig. 22-25: New cap's form by sprouting from existing small bv: Angiogenesis

- new bv's in adult originate as **cap's:**
 - sprout begins with long **pseudopodial process** extended from ec
 - sprouted cap. **hollows out, forms tube**
 - **sprout continues to grow** out until cap finds & connects to another bv

Fig. 22-26: New cap formation in vitro

- cap. ec's alone in culture spontaneously form cap. tubes (dependent on GF's & substrate)
 - cultured cap. ec's proliferate, internal vacuoles form @ ~20d; these join up from cell to cell, branching occurs, form network
 - ec's secrete laminin, promotes tube formation
- blood flow & pressure not required for cap. formation

Angiogenesis is controlled by factors released by surrounding tissues

- almost every cell in vertebrate animal is 50-100 μm from cap
- **Fig. 22-27: New capillary formation in response to wounding**
- proliferation of caps induced by:
 - wounding, to meet high metabolic requirement of repair process

- local irritants & infection/inflam'n (these caps regress later)
- experimental: implant tumor tissue in cornea
- **Fig. 22-28:** The homeostatic regulatory mechanism controlling blood vessel growth according to the tissue's oxygen requirement:
 - **invading ec's respond to signals from tissue**
 - **VEGF**, key signal (related to PDGF)
 - Regulated transcriptionally (& also via mRNA stability)
 - O₂-shortage (hypoxia) elevates intracell. **HIF-1 (hypoxia-inducible factor 1)**; HIF-1 activates transcr of VEGF & other genes req in low O₂
 - secreted VEGF acts on nearby ec causing them to:
 - 1) produce proteases, degrade bl of parent cap/venule
 - 2) migrate/chemotax to signal source
 - 3) proliferate
 - 4) form tubes, differentiate
 - as O₂ rises, HIF-1 & VEGF product'n drops, angiogen. stops
- **Under normal conditions, HIF-1 is degraded rapidly**
 - Reqs **ubiquitylation** of HIF-1
 - **Von Hippel-Lindau** patients are +/- for recess. gene for factor in HIF-1 ubiq. pathway; dev **hemangioblastoma tumors** (dense masses of bv's) where -/- somatic cells arise via mitotic recomb'n; w/ high HIF-1 & VEGF; new bv's promote prolif of -/-, HIF-1+ cells; tumor growth escalates

BLOOD CELL FORMATION: Renewal by Multipotent Stem Cell

- **common features of blood cells:**
 - limited life spans
 - produced thruout life of animal
 - all generated from common precursor
 - **hemopoietic stem cell:** in bone marrow, for blood cells & bone osteoclasts
- Table 22-1**
- Red blood cells (erythrocytes)
 - White blood cells types (wbc) (**Fig. 22-30**)
 - granulocytes –
 - neutrophils: phagocytic, role in innat immunity
 - eosinophils: destroy parasites, modulate allergic inflam.
 - basophils: release histamine, help mediate inflam responses; related to mast cells
 - monocytes – become tissue macrophages
 - lymphocytes: B & T
 - natural killer (NK) cells – kill virus-infected & some tumor cells
 - Platelets: from megakaryocytes; initiate blood clotting
 - **Fig. 22-31: migration of wbc out of bloodstream during inflam. response**
 - Initiated by signals from connective tissue & ec or via complement reaction (Ch. 24, 25); decrease ec:ec adherence, induce ec to express glycoproteins in their pm that recognize **selectins in pm of wbc**; **chemokines** secreted by damaged tissue & ec attract wbc's; wbc req. **integrins** to crawl betw/ ec, into tissue
 - **Fig. 22-32: Bone marrow**
 - **Fig. 22-33: Megakaryocytes:** bone marrow cell that produces **platelets**