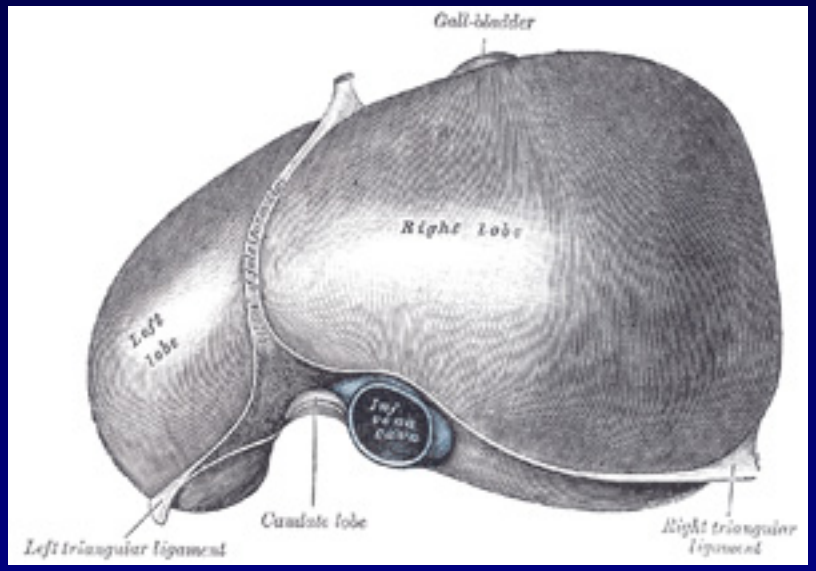
Liver Anatomy and Histology

Arlin Rogers
Comparative Pathology Laboratory
Division of Comparative Medicine

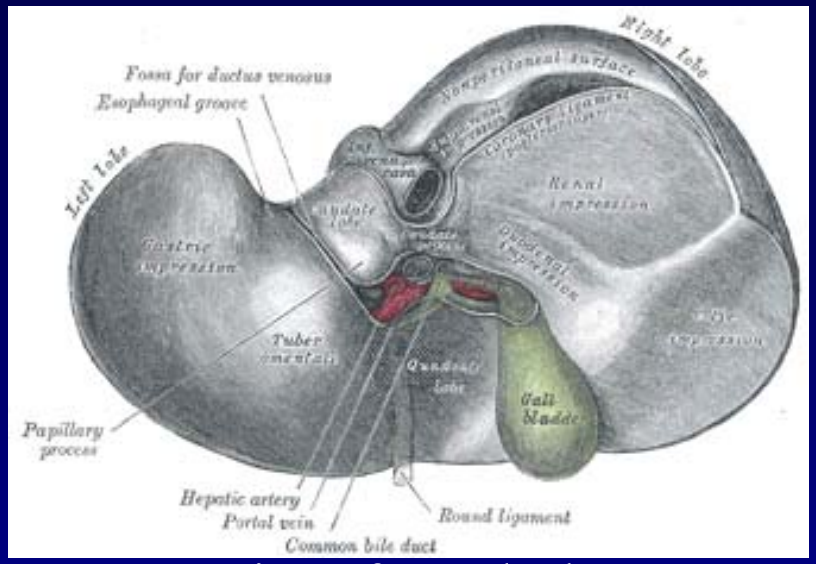
Comparative liver macroanatomy

- Human
  - Lobes: Right, left, caudate, quadrate
  - Majority of liver on R side cranial abdomen
  - Subdivided into 9 discrete units based on vasculoductular supply - important in surgery
- Rodent
  - Lobes: Right, left, median, caudate
  - More evenly spaced across cranial abdomen
  - Rats lack gallbladder

Gross anatomy



View from above



View from below

image courtesy of CM North, Michigan State University. Source: Wikipedia.

Perfused rat liver

Surgical segments	
Lobe	**Couinaud segments**
Caudate	1
Left	2, 3
Quadrate	4
Right	5, 6, 7, 8

Several diagrams of liver structure removed for copyright reasons. (Vertical and horiztonal section, anterior and interior surfaces, and a detail cutaway showing interior ducts.)

Mouse liver lobes

Images removed for copyright reasons.

Source: Figures 2 and 3 in Harada, T., et al. "Liver and Gallbladder." Chapter 7 in *Pathology of the Mouse*. Edited by Robert Maronpot. Vienna, IL: Cache River Press, 1999. ISBN: 188989902X.

Liver functional unit classification schemes

- Lobule first described by Weppler, 1665
- Functional anatomy still not fully known!
- Three main models:
  - Classical lobule
  - Rappaport's acinus model
  - Matsumoto's primary lobule

Classical lobule

- Central vein & peripheral portal triads
- Roughly hexagonal outline
- Blood flows from portal triads to central vein
- Species differences
  - Pigs have well outlined lobules due to ↑ portal fibrous connective tissue (many anatomy studies done with this species as a result)
  - Humans and nonhuman primates have discernible lobules
  - Mice have poorly visualized lobules

Two photos removed for copyright reasons.
Fig. 10-74 and 10-75 from unknown source.

Lobule--reticulin stain

Figure removed for copyright reasons.
Source: Figure 1.33 in [MacSween].
MacSween, R., et al. Pathology of the Liver, 4th ed.
Philadelphia, PA: Elsevier, 2002

Lobular division

Figure removed for copyright reasons.
Source: Figure 1.4 in [MacSween].

Hepatic acinus

- Rappaport, 1950's
- Portal tracts are headwater, elliptical zones spread to terminal hepatic (central) vein
  - Zone 1: Periportal, high enzyme & O2
  - Zone 2: Intermediate
  - Zone 3: Perivenular, low O2, most susceptible to hypoxic injury
- Simple & complex acini in berry-like bunches

Classical lobule vs. acini

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Source: Figure 1.7 in [MacSween].

Comparison of Lobular and Acinar Terminologies

Lobular	Acinar
Central; centrilobular; centrizonal	Perivenular; acinar zone 3
Mid-zonal	Acinar zone 2
Peripheral; periportal	Periportal; acinar zone 1
Multilobular	Multiacinar
Panlobular	Panacinar
Central/central (necrosis or bridging)	Peri-acinar (complex) (necrosis or bridging)
Central/portal (necrosis or bridging)	Peri-acinar (simple), peripheral acinar, zone 3 (necrosis or bridging)
Portal/portal (necrosis or bridging)	Portal-portal (necrosis or bridging)

Figure by MIT OCW.

Matsumoto's Primary Lobule

- Similar to classical lobule, but incorporates current knowledge of vascular supply
- "Sickle zone" of complex periportal branching
- Otherwise a hybrid of classical & acinar models

Figure removed for copyright reasons.
Source: Figure 1.9 in [MacSween].

Primary vs. classical lobule: vascular network models

Matsumoto
Primary
Lobule

Figures removed for copyright reasons.
Source: Figures 1.10-1.12 in [MacSween].

Classical Lobule

Arteriovenous connections in adult liver

Figure removed for copyright reasons.
Source: Figure 1.6 in [MacSween].

Hepatic functional unit

- Kidney-Nephron (glomerulus to collecting duct)
- Liver-Not as well defined
  - Choleon: hepatocytes drained by a single canal of Herring
  - Hepaton: hepatocytes served by a single vascular twig
  - Choleohepaton: hybrid of above

Hepatic microcirculatory subunit

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Source: Figure 1.14 in [MacSween].

Zonal heterogeneity

- Hepatocytes in different zones of lobule have different morphology, gene expression, and function
  - O2 concentration
  - Matrix proteoglycans
  - Bile concentration
  - Endothelial & Kuffer cell adhesion molecules and cytokines

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Source: Figure 1.5 in [MacSween].

Biliary Tree

- Canaliculi
- Canals of Herring
- Bile ductules
- Intrahepatic bile ducts
- Extrahepatic bile ducts
- Gallbladder
- Common bile duct

Canaliculi

- Interhepatocytic channels for bile flow
- 1-2 um diameter
- Bounded by zonula occludentes and zonulae and maculae adherentes
- Microfilaments in microvilli provide motility
- Bile flows opposite direction of blood

Figures removed for copyright reasons.
Source: Figure 1.23, 1.24 (Canal of Herring), 1.39 (Portal Triad) and 1.26 in [MacSween].

Gallbladder

- Sac for bile storage
- Empties into common bile duct under hormonal stimulation (e.g. cholecystikinin)
- Absent in rat and horse

Image removed for copyright reasons.

Source: Figure 9 in Harada, T., et al. "Liver and Gallbladder." Chapter 7 in *Pathology of the Mouse*. Edited by Robert Maronpot. Vienna, IL: Cache River Press, 1999. ISBN: 188989902X.

Hepatic sinusoids

- ~10 um diameter
- Fenestrated endothelium
- Space of Disse between endothelium and hepatocyte membrane - exchange of molecules
  - small frequent pores periportally “sieve plate”
  - large pores centrilobularly
  - pore size affected by hormones and alcohol

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Source: Figure 1.31 in [MacSween].

Resident Cells of the Liver

- Hepatocytes
- Biliary epithelium
- Endothelial
  - Blood vessels
  - Sinusoids
  - Lymphatics
- Hepatic stellate (Ito) cells
- Kupffer cells (resident MØ)
- Liver-associated lymphocytes
- Nerves & connective tissue cells

Hepatocytes

- 30-40 um, polyhedral
- Polarized
  - Apical - canalicular region
  - Lateral - adjacent to canaliculi
  - Basolateral - facing sinusoids
- Endocrine and exocrine function
- Round open nuclei with dispersed and aggregated chromatin and prominent nucleoli
- Polyploidy is common, increases with age

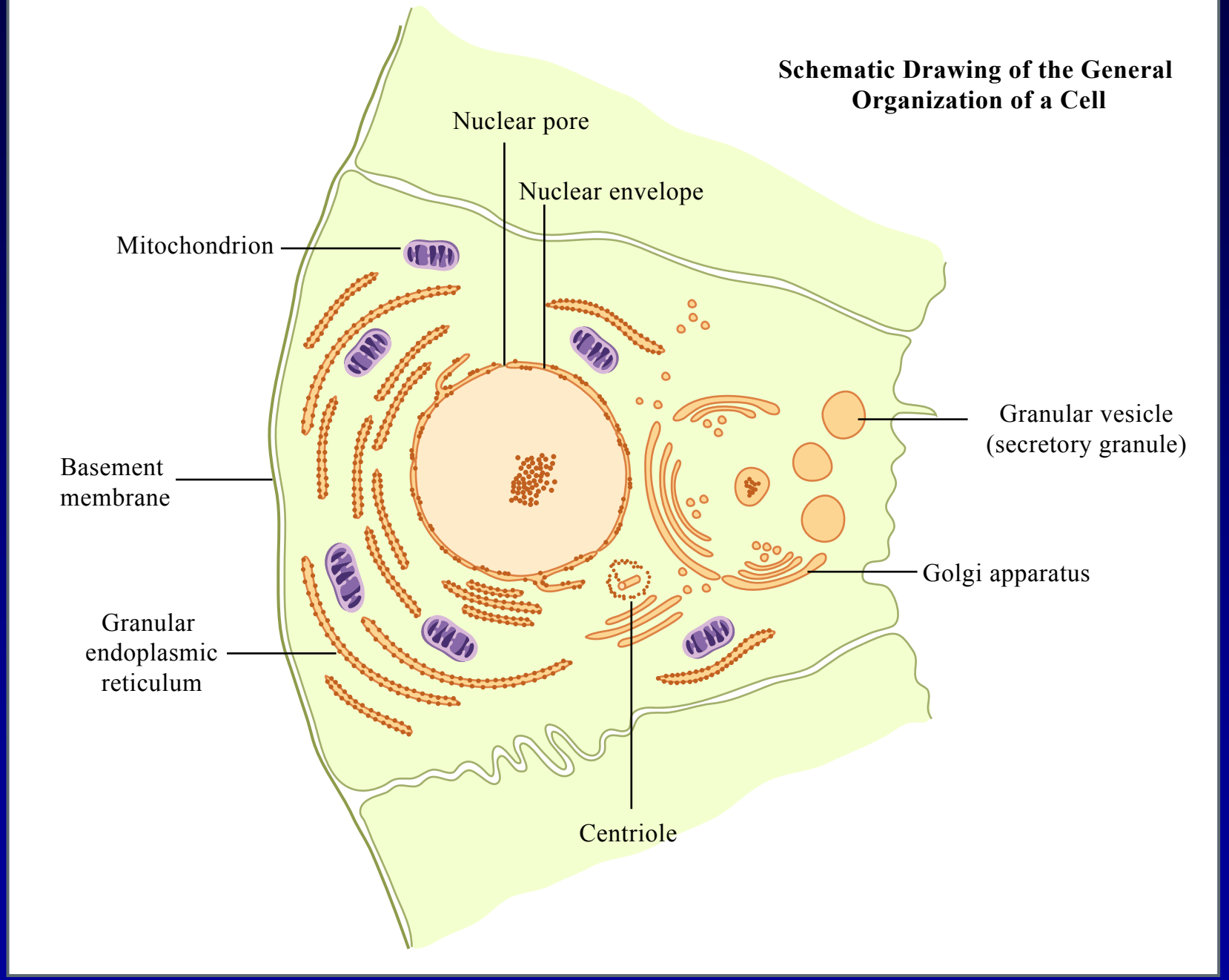

Figure by MIT OCW.

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Source: Figure 1.1 in [Cheville] Cheville, N.F. *Ultrastructural Pathology: An introduction to interpretation*. Ames, IA: Blackwell Publishing, 1994. ISBN: 0813823986.

Hepatocyte organelles: nucleus

- Large, 5--10% of cell volume
- Double-layered membrane with many pores
- Polyploidy (humans)
  - Birth: Nearly 100% diploid
  - 8 years: 90% diploid
  - 15 years: <85% diploid
- Cytoplasm doubles in volume for each nucleus, maintaining steady ratio of genetic material to cell size
- Mitoses infrequent in adults

Figure removed for copyright reasons.
Source: Figure 1.18 in [MacSween].

Hepatocyte organelles: ER

- Cisternal network of membrane lined tubes
- In general rough ER (ribosomes bound) more concentrated at periphery, smooth ER centrally merging into perinuclear Golgi
  - Parallels protein processing
- Zonal variation
  - Centrilobular hepatocytes 2X SER vs periportal
- Important site of enzymatic activity
  - SER significantly expands following toxic exposures
- ER can be isolated in vitro by density gradient centrifugation = “microsomes”

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Source: Figure 1.7 from unknown source.

Hepatocyte organelles: Golgi

- Up to 50 interconnected Golgi zones
- Stacks of curved membrane-bound sacs
  - convex (outer) surface = cis
  - concave (inner) surface = trans
- Raw proteins arrive from SER on cis face
- Processed glyco- & lipoproteins bleb from trans face for trafficking to cellular site of function or secretion into blood or bile

Hepatocyte organelles: lysosomes

- Landfills of the cell
- Primary lysosomes contain hydrolytic enzymes (acid phosphatase, etc)
- Fuse with phagocytic vesicles to form 2o lysosomes or effete cell products to form autophagic vacuoles
- Enzymes degrade contents
- Subunits recycled, excreted (e.g. into bile), or retained for long periods (sometimes with pathologic consequences)

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Source: Figure 1.36 in [Cheville].

Hepatocyte organelles: peroxisomes (microbodies)

- Ovoid membrane-bound granules 0.2-1 um
- Fatty acid beta-oxidases
- Upregulated by peroxisome proliferator-activated receptor -alpha (PPARa)
- Peroxisome proliferator compounds (PPC)
  - Phthalate plasticizers, hypolipidemic fibrate drugs (e.g. clofibrate), Wy 14,643
- Rodents are exquisitely sensitive to PPC (tumors)
- Humans and other species (e.g. guinea pig) resistant

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Source: Figure 1.19 in [MacSween].

Hepatocyte organelles: mitochondria

- “Powerhouse of cell”
- Outer membrane with lipid transport proteins
- Inner folded membrane (cristae) with oxidative enzymes
- Main function to produce ATP
- Also important in apoptosis (mitochondrial permeability transition, MPT, cytochrome c, Bcl family)
- Highly mobile organelles
- Comprise 20% of hepatocyte volume

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Source: Figure 1.22 in [Cheville].

Other hepatocyte contents

- Cytoplasm (hyaloplasm)
- Glycogen
  - alpha-rosettes
  - beta-particles
- Liposomes
- Free ribosomes
- Other

Glycogen in the non-Atkins liver

Figure removed for copyright reasons.
Source: Figure 1.35 in [MacSween].

Glycogen - fasting vs. fed mice

Images removed for copyright reasons.

Source: Figures 5 and 6 in Harada, T., et al. "Liver and Gallbladder." Chapter 7 in *Pathology of the Mouse*. Edited by Robert Maronpot. Vienna, IL: Cache River Press, 1999. ISBN: 188989902X.

Cell debris

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Source: Figure 1. 36 in [MacSween].

Hepatocyte organelles: cytoskeleton

- Microfilaments (6 nm)
  - Fibrous (F) actin polymerized fibrils
  - Globular (G) actin monomers
- Intermediate filaments (cytokeratins; 8-10 nm)
  - Hepatocyte Ck 8 & 18
  - Biliary epithelium add Ck 7 & 19
- Microtubules (20 nm)
  - Polymers of alpha & beta tubulin
  - Part of mitotic spindle apparatus & cyotplasmic centrioles
  - Scaffold for rigidity and directed organelle trafficking

Junctional complexes

- Desmosome (macula adherens)
  - button-like connector between cytokeratin filaments of adjacent cellls
- Intermediate junction (zonula adherens)
  - continous belt-like junction below tight jxns
  - Ca2+ dependent adherins incl beta catenin
- Tight junction (zonula occludens)
  - sealing belt separates canaliculus from intercellular space

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Source: Figure 1-22, 1-23 in unknown source.

Canalicular membrane

- Specialized region of hepatocyte membrane
- Bile canaliculus bounded by apposing hepatocyte hemicanaliculi
- Finger-like projectios (microvilli)
  - actin/myosin etc for bile propulsion
- Canalicular-rich enzymes
  - gamma glutamyl transpeptidase (GGT)
  - alkaline phosphatase (ALP)
  - backflow into blood during cholestasis (bile sludging)

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Source: Figure 1.16 in [MacSween].

Bile secretory apparatus-Uptake

- Conjugated bilirubin uptake from blood via high affinity receptors
  - **Sodium taurocholate cotransporting polypeptide** (NTPC)
  - Organic anion and cation transporting proteins (Oat1 & 2, Oct1 & 2)
- Most bile taken up by periportal hepatocytes (decreasing bile gradient in sinusoids approaching central vein)
- Hepatocyte receptor for unconjugated bilirubin unknown

Bile secretory apparatus-Vesicle transport

- Endocytosis of ligand-bound receptors (larger than clathrin-coated pits)
- Endosome contents acidified (releases ligand)
- Most endosome contents (80%) returned to cell membrane
- ~18% directed to lysosomes
- ~2% secreted into bile
- Vesicular trafficking along microtubules accounts for 95% of blood-to-bile transport

Bile secretory apparatus-excretion

- Bile salt export pump (BSEP)
  - Other names: canalicular bile salt transporter (CSBT), sister of P glycoprotein (SPGP)
  - rate-limiting step of bile outflow
  - absent in progressive familial intrahepatic cholestasis type 2 (PFIC 2)
  - important in drug excretion
- Other known or putative bile export molecules
  - Multidrug-resistance associated protein 2 (MRP2)
  - Multidrug resistance proteins 1 & 3 (MDR1,3)

Biliary epithelium

- Cuboidal or columnar w/microvilli
- Actively secrete substances and resorb bile
  - cholehepatic shunt pathway
- Peribiliary glands (human)
  - intramural mucous glands communicate w/lumen
  - extramural mixed seromucous glands form tubuloalveoli that connect to lumen via ducts
- Duct epithelium secretes IgA and IgM
- Stimulated by secretin and inhibited by somatostatin

Bile ductule

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Source: Figure 1.25 in [MacSween].

Endothelial cells

- Specialized for compartment & function
- Display unique cell adhesion molecules & cytokine production based on location
- Sinusoidal endothelium fenestrated
  - frequent small pores periportally (sieve plate)
  - infrequent large pores centrally (fixation artifact?)
  - no basement membrane; hepatocytes bathed in filtered plasma

Figures removed for copyright reasons.
Source: Figure 1.27, 1.28 in [MacSween].

Hepatic stellate (Ito) cells

- In space of Disse; inapparent w/stndrd stains
- Long thin cellular projections
- Important in lipid and vitamin A storage
- 4 main functions:
  - extracellular matrix proteins
  - pericytic - microvascular tone
  - Vitamin A and retinyl storage
  - cytokines (HGF-alpha in response to IGF-2)

Figure removed for copyright reasons.
Source: Figure 1.29 in [MacSween].

Kupffer cells

- Resident macrophages line sinusoids
- Clearance of gut derived toxins (e.g. LPS)
- Secrete cytokines
  - IL-1
  - IL-6
  - TNF-alpha
- Express class II MHC- antigen presentation
- At least partially derived from bone marrow monocytes

Figure removed for copyright reasons.
Source: Figure 1.30 in [MacSween].

Liver-associated lymphocytes

- Normal human liver has $1x10^{10}$ lymphoid cells
- Predominantly in portal regions but also scattered
- Predominant classes
  - NKT cells
  - gamma-delta T cells (most g/d T cells of any organ)
  - CD8+ T cells
- Immune function of liver comparable to that of GI tract

Lymphatics

- Liver is single largest source of lymph
  - 15-20% overall volume
  - 25-50% thoracic duct flow
- Very high protein content
- ~80% lymphoid cells & 20% MØ
- Terminal twigs of lymphatic channels accompany hepatic arterioles
  - dilated w/visible cells in some disease states
- Continuous with subcapsular lymphatic sinus
- Drains fluid collected in space of Disse

Nerve supply

- Liver is richly innervated although difficult to see neural structures histologically
- Nerve fibers demonstrated by immunohistochemistry
- Sympathetic and parasympathetic signals affect vascular tone and metabolism
- Successful transplant engraftment, however, suggests neural control is dispensible to overall function

Hepatic embryonic development

- Human embryos: Hepatic bud @ 3 wk
- Endoderm - pouch off of future duodenum
- Cues from mesenchyma guide hepatic differentiation
  - Septum transversum
  - Coelomic lining
- Hepatic diverticulum invades stroma, induces sinusoidal plexus formation from vitelline veins

Figure removed for copyright reasons.
Source: Figure 1.1 in [MacSween].

Development (cont'd)

- Epithelial bud breaks into anastomosing parallel sheets around sinusoids
- Caudal bud forms cystic duct & gallbladder
- Growing liver fills available space, displacing stomach & duodenum from septum transversum
- Hepatic stalk migrates with duodenum to form extrahepatic bile ducts

Figure removed for copyright reasons.
Source: Figure 1.2 in [MacSween].

Hepatic plate development

- Anastamosing sheets of hepatocytes
  - Muralium multiplex ("mural" = wall) - several cells thick
    - Birth
  - Muralium duplex - 2 cells thick
    - 5 months
  - Muralium simplex - 1 cell thick
    - 5 years
- Not all species have well organized single-cell thick hepatic cords (e.g. mice)

Figure removed for copyright reasons.
Source: Figure 1.34 in [MacSween].

Fetal hepatocyte functions

- α-fetoprotein (AFP)
  - Albumin-like serum protein, carrier & circulatory osmotic potential
  - Secreted from earliest stages of liver development (human gest. day 25-30—birth)
  - Reappears in ~70% of adult hepatocellular carcinoma (serum diagnostic test)
- Glycogen present at 8 wk
  - Hepatic glycogenesis begins 12 wk
  - Large fetal glyocogen reserve at birth
    - rapidly metabolized first few days after birth

Fetal hepatocyte functions (cont'd)

- Hemosiderin (iron) deposits early in development
  - Increased during hepatic hematopoiesis (12--18 wks gestation), then decrease
  - Mostly periportal; also site of copper storage
- Sinusoidal endothelial, Kupffer & stellate cells appear @ 10-12 wk

Biliary functional development

- Bile acid synthesis begins 5--9 wk
- Secretion 12 wk
- However, canalicular excretion & transport remains immature until 4--6 wk postpartum
- Bile excretion across placenta is important for fetus

Developing ductal plate Cytokeratin IHC

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Source: Figure 1.3 in [MacSween].

Summary

- Liver main functions
  - Catabolism
  - Metabolism
  - Detoxification
  - Bile production
- Several ways to classify liver based on histology, physiology & vascular supply
- Species differences in anatomy and physiology
- Knowledge of liver functional anatomy informs hypotheses about disease pathogenesis

Sources

Kumar, Vinay, Abul K. Abbas, and Nelson Fausto, eds. *Robbins and Cotran Pathologic Basis of Disease*. 7th ed. Philadelphia, PA: Elsevier Saunders, 2005.

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