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Review

Anatomy of rodent and human livers: What are the differences?☆

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ABSTRACT

The size of the liver of terrestrial mammals obeys the allometric scaling law over a weight range of $> 3 * 10^6$. Since scaling reflects adaptive changes in size or scale among otherwise similar animals, we can expect to observe more similarities than differences between rodent and human livers. Obvious differences, such as the presence (rodents) or absence (humans) of lobation and the presence (mice, humans) or absence (rats) of a gallbladder, suggest qualitative differences between the livers of these species. After review, however, we conclude that these dissimilarities represent relatively small quantitative differences. The microarchitecture of the liver is very similar among mammalian species and best represented by the lobular concept, with the biggest difference present in the degree of connective tissue development in the portal tracts. Although larger mammals have larger lobules, increasing size of the liver is mainly accomplished by increasing the number of lobules. The increasing role of the hepatic artery in lobular perfusion of larger species is, perhaps, the most important and least known difference between small and large livers, because it profoundly affects not only interventions like liver transplantations, but also calculations of liver function.

1. Introduction

The size of the liver of terrestrial mammals obeys the allometric scaling law for animals as small as the Etruscan shrew (~1.8 g) and as large as the African elephant (~6600 kg) [1]. Since scaling deals with "structural and functional consequences of changes in size or scale among otherwise similar animals" [2], we can expect more similarities than differences between rodent and human livers. We will address the following topics:

1. Lobar architecture
2. The presence or absence of a gallbladder
3. Lobular architecture
4. Lobular perfusion

2. Lobar architecture

2.1. Murine liver

The first partial hepatectomy in rats was described in 1932 [3], whereas the first one in humans was performed only 20 years later [4], that is, ~70 years after major surgical interventions on the intestines were first reported. The reason is that rodents have a lobated liver, of which individual lobes can be easily ligated and removed, whereas humans have a non-lobated liver. Since the lobar architecture represents the basic architecture of the liver, we will elaborate on this type of liver before comparing it to non-lobated livers.

Liver lobes in species with a lobated liver become visible shortly after the appearance of the liver bud in embryos [5]. These species develop 2 dorsolateral lobes which, upon expansion, engulf the vitelline veins that drain blood from the yolk sac (Fig. 1). Shortly thereafter, both umbilical veins, which drain blood from the developing placenta, become engulfed by the hepatocytes of the single ventromedial lobe. This ventromedial lobe typically has an incomplete median fissure, which divides it into left and right portions. The gallbladder is embedded and, especially when empty, often partly hidden in this fissure. Finally, the dorsally located caudate or Spieghel's lobe forms (Fig. 1). The caudate lobe is special in that its draining hepatic vein forms the intrahepatic portion of the inferior caval vein [6]. In agreement, the intrahepatic caval vein occupies a central position in the caudate lobe of species, in which this lobe is well separated from the right dorsolateral lobe [7,8]. The formal names of these 4 lobes in adult liver are

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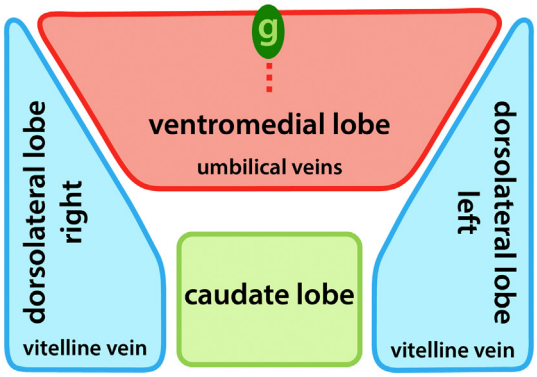

Fig. 1. The lobar building plan of the liver (modified from [35]). The vitelline and umbilical veins are embryonic veins that are associated with the dorsolateral and ventromedial lobes, respectively. The caudate lobe develops only after the 6th week of development in humans [5].

the right and left lateral lobes (developed from both embryonic dorsolateral lobes), the right and left medial lobes (developed from the incompletely divided ventromedial lobe), and the caudate lobe [9,10]. This basic architecture can change by further subdivisions of the lobes or by the merging of the fissures. Thus, the caudate lobe often has caudate and papillary processes, and the right lateral lobe upper and lower sublobes [11–14]. In contrast, in non-lobated livers, such as that of humans, fissures are usually not present, except those demarcating the caudate lobe dorsally, but (partial) lobation of human livers is occasionally reported [15,16]. Interestingly, a 5th lobe, the quadrate lobe, which is found between the gallbladder and the round ligament (postnatal remnant of the umbilical vein), is very variable in its development between species: it is virtually absent in rodents [11–14], small in pigs, and well developed in dogs, cows, and horses [17]. In humans, a quadrate lobe is normally present, but quantitative differences, including complete absence, have been reported [18–20]. Nevertheless, the quadrate lobe is one of the 4 officially acknowledged lobes that make up a human liver ([21]; see next section).

2.2. Human liver

Human liver differs markedly from rodent livers because of its non-lobated architecture. According to the official International Anatomical Terminology [21], the human liver is divided into left, right, caudate and quadrate lobes. This terminology does only partially correspond with that used for quadrupeds [10] (Table 1). Furthermore, the caudate and quadrate lobes are well-defined entities on the visceral aspect of the liver but have no representation on its ventral aspect. In practice, the classical nomenclature is no longer used. Instead, Couinaud's liver model with 8 segments has become the standard [22]. Approximately 70 years ago, anatomists were searching for avascular planes in the afferent vessels to the liver to enable hepatic surgery without fatal blood loss (Fig. 2) [23–25]. The resulting models differ in that Hjortsjö based his model on the branching pattern of the bile ducts [23], Healey and Schroy theirs on that of the hepatic arteries [24], and Couinaud his on that of the portal veins [25]. Corrosion casts in all three approaches revealed that the portal vein divides the liver into left and right perfusion areas ("hemi-livers"; Table 1) and that the plane of separation coincides with the "Rex-Cantlie line", a plane through the gallbladder and intrahepatic portion of the inferior caval vein established well over a century ago [26,27]. Planes through the intrahepatic portion of the inferior caval vein and right, middle, or left hepatic veins separate the perfusion domains ("sectors") of the main branches of the portal vein, hepatic artery, or bile duct (Table 1). In Couinaud's and Healey's models the two sectors of the right hemi-liver were each subdivided into 2 "segments" by a transverse plane through the first bifurcation of the portal vein. In Healey's model, this line also included sector IV, which contains the quadrate lobe. The liver segments that resulted from the three approaches are very similar (Fig. 2), with arguments mainly centering on whether the right hemi-liver has two (Healey and Couinaud) or three sectors (Hjortsjö) and whether the segment III in the left hemi-liver belongs to the lateral (Healey) or medial sector (Couinaud). Clearly, classical anatomy of the liver has changed into surgical anatomy of the liver.

Couinaud's basic assumption, the regular hierarchical bifurcation of the portal vein, has come under scrutiny. Platzer and Maurer showed that the smooth and predictable boundaries of the sectors and segments were an illusion [28], while Fasel confirmed that the right hemi-liver contained 3 second-order portal branches (the left and right portal branch represent the first-order vessels), but also that the left hemi-liver contained many more, with an average of 20 [29,30]. Couinaud further claimed that his model had to be preferred, because it had an embryological basis [9] and because the portal veins are the first definitive vessels to develop in the mammalian liver. Since Couinaud's embryological knowledge was solely based on literature [9], we re-investigated his claim and confirmed Fasel's data in human embryos [6]. We further established that the remarkable left-right difference in the branching pattern of the portal vein was due to the origin of these branches from either the intrahepatic portion of the umbilical vein (left hemi-liver) or the portal vein (right hemi-liver). The numerous branches arising from the large umbilical vein are, compared to the parent vessel, relatively small and have large branching angles, whereas the opposite is true for the right hemi-liver: the parent portal vein is relatively small (~50% of its blood supply is dependent on an anastomosis with the umbilical vein [31]) and branches more symmetrically [6]. The left-sided asymmetric branching pattern of the portal vein is typical for a transport ("distributing") vessel, whereas the right-sided symmetrical branching pattern of the portal vein is typical for a tissue-supplying ("delivering") vessel [32]. An asymmetric ("monopodial") branching design appears to minimize pumping power and the size of the vascular tree [33], which represents an important advantage in a venous system. Couinaud's model of surgical liver segments still dominates the textbooks and internet, but hilar transection of "Glissonean pedicles" ([34]; "pedicles" are, in this context, connective tissue tunnels containing the segmental portal vein, hepatic artery and bile duct) and hemostatic dissecting devices have made hepatic surgery less dependent on avascular afferent planes.

Many efforts have been made to translate ("homologize") the lobar and segmental models of liver architecture [6,11–14,35]. These studies agree on the scheme shown in Table 1. The lobar Bauplan as used in veterinary anatomy has an embryological origin and is, therefore, more practical for interspecies comparisons than the human anatomical nomenclature. The description of the dorsolateral lobes in the non-lobated human embryonic liver as its dorsolateral "wings" [36] underscores this

Table 1
Official anatomical terminology of human liver [21], Couinaud's segmental surgical anatomy [22], and official veterinary terminology [10]. Couinaud's model includes a left and right hemi-liver (based on the 1st order portal vein branches), sectors (based on 2nd order portal branches and main hepatic veins) and segments (based on a transverse plane through the 1st bifurcation of the portal vein).

Lobar anatomy (human)	Segmental anatomy (Couinaud)				Lobar anatomy (quadrupeds)
	Hemi-liver	Sector	Segment	#	
Caudate lobe		Dorsal		I	Caudate lobe
Left lobe	Left	Lateral	Superior	II	Left lateral lobe
		Medial	Inferior	III	Left medial lobe
Quadrate lobe			Quadrate lobe	IV	
Right lobe	Right	Anterior	Inferior	V	Right medial lobe
			Superior	VIII	
		Posterior	Inferior	VI	Right lateral lobe
			Superior	VII	

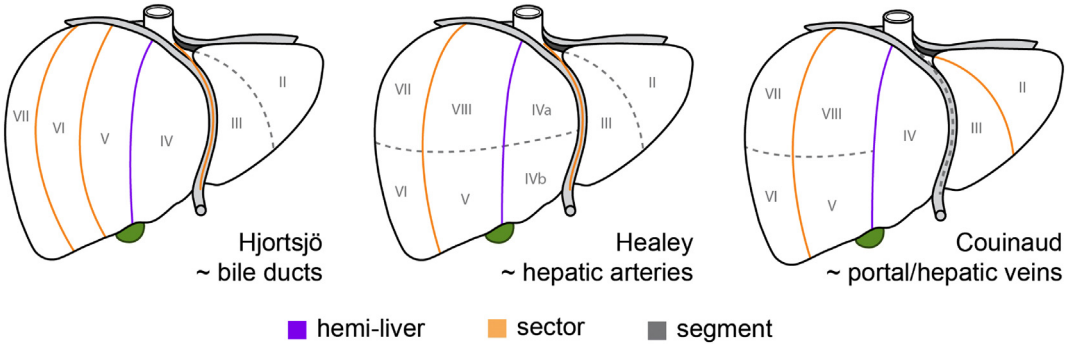

Fig. 2. Hjortsjö's, Healey's, and Couinaud's segmentation concepts of human liver (modified from [22–24]). Segment #1, the caudate lobe, is located on the dorsal side of the liver and, therefore, not visible.

Table 2
Mammalian species with different degrees of lobation of their livers.

Lobated	Intermediate	Non-lobated	Reference
Dog			[17,35,117]
Mouse			[13,14,117]
Rat			[11,12,14,117]
Golden hamster			[35]
Pocket gopher			[117]
Striped gopher			[117]
Pig			[17,35,117,118]
Guinea pig			[35,117,119]
Rabbit			[35,117,120]
Cat			[35,117]
Hedgehog			[35]
	Cynomolgus		[8]
	Macaque		[35,121]
	Rhesus		[117]
	Elephant		[122]
	Horse		[17,117,123]
	Sheep		[117]
	Goat		[117]
	Deer		[117]
		Human	[35]
		Dolphin	[124]
		Whale	[125]
		Cattle	[17,35,117]
		Water buffalo	https://scialert.net/fulltext/?doi=ajava.2011.508.516

argument. A nomenclature that is based on the distribution of the hepatic vessels is not used because of the perceived variability of their branching pattern. This is partly due to definition: a serial bifurcation with just a few millimeters difference between the consecutive branches is no longer a “trifurcation” [8,37]. If such surgically important, but functionally less relevant variations are not taken into consideration, the distribution of the portal veins [37] and that of the hepatic veins just peripheral of their entrance into the caval vein [6,38,39] is quite predictable. Again, this characteristic is more easily visible in lobated (rodent) livers, because there is one portal and one hepatic vein for each lobe [9]. As a result, the branching pattern of the portal and hepatic veins in such livers is serial [11–14]. Together, these data have convinced us that the veterinary concept with 2 dorsolateral, a ventromedial and a caudate lobe best represents the basic architecture of the liver across mammalian species [6]. Table 2 gives a non-exhaustive list of species with non-lobated, partially lobated and lobated livers.

3. How important is the presence of a gallbladder?

Bile salts are detergents that aid in the absorption of dietary lipids, but also serve as signaling molecules. The gallbladder concentrates and stores bile between meals [40], which seems a potential trait for natural selection. The presence or absence of a gallbladder across mammalian species, nevertheless, resembles a checkerboard (Table 3). Although the list is not exhaustive (for more data, see [41,42]), a few trends can be found. Firstly, primates and carnivores seem to be obligatorily outfitted with a gallbladder, possibly because of their relatively high-fat diets. On the other hand, herbivorous odd-toed ungulates have, with the exception of manatees, no gallbladder. However, no predictions are possible for the equally herbivorous even-toed ungulates and the omnivorous rodents. Perhaps the most interesting examples are mice and rats, because these species belong to the same subfamily (Murinae). The early development of the caudal foregut and its glands is very similar in mice and rats, except that the biliary bud is missing ab initio in the rat [43,44]. The murine biliary bud epithelium expresses the gallbladder master regulator *Sox17*, whereas no *Sox17* expression is identifiable in the hepatobiliary primordia of the rat [44]. Since *Sox17* is expressed in rat embryonic stem cells [45,46], the *Sox17*-regulatory region or an upstream regulatory factor must have mutated. These data suggest that just one mutation can cause absence of a gallbladder in species. Since environmental factors, frequency and choice of food intake, and the nature of the bile salts produced are very similar in these species [47,48], a random mutation and little selection pressure seem the best explanation. The Atlantic forest hocicudo appears a case in point: among chromosomally identified specimens of this small South-American species, individuals with and without gallbladder were present [49]. In aggregate, these observations suggest that the presence or absence of a gallbladder does not represent a modification of the Bauplan, but more likely the functional loss of one or at most a few genes.

An obvious, more experimental extension of these observations is to ablate the gallbladder. In humans, cholecystectomy is frequently performed, because 10–15% of the adult western population has bile stones and 1–4% become symptomatic within a year, especially when middle aged [50]. Humans [51] and mice [52–54] do quite well after cholecystectomy. The intervention decreases the bile acid pool, but because secretion rates of bile acids and cholesterol, and the enterohepatic recirculation rate are increased, in particular during fasting, digestion and absorption remain relatively unaffected ([53–56]; for a recent review, see [40]). In fact, the main risk factor of cholecystectomy is age [50]. Solitary absence of the gallbladder, which is a rare feature in humans [57–59], does not seem to increase the risk for bile duct-related problems [57]. These findings, therefore, underscore our argument that the presence of a gallbladder does not represent an advantage in natural selection. The similar response to cholecystectomy in humans and mice is, nevertheless, somewhat surprising since rodent bile is much more hydrophilic than human bile due to their capacity to synthesize muricholic acids. The presence of just one additional gene in rodents, *Cyp2c70*, is responsible for the capacity to synthesize muricholic acid [60]. The capacity of mice and rats to synthesize muricholic acid allows urinary excretion of large amounts of bile acids after bile-duct ligation [61,62] and long-term survival even in the complete absence of intrahepatic bile ducts [63,64].

Table 3
Mammals with and without gallbladder (more examples can be found in [41] and [42]). The species are grouped by taxonomic order.

Species	Gallbladder absent	Gallbladder present
Rodentia	Rat	Mouse
	Altlantic forest hocicudo [49]	Altlantic forest hocicudo [49]
	Montane grass mouse [49]	Cursor grass mouse [49]
		Golden hamster
	Pocket gopher	Ground squirrel
		Guinea pig
Artiodactyla (even-toed ungulates)	Camel	Cattle
	Llama	Sheep
	Giraffe	Goat
	Deer; all except:	Musk deer
		Muntjac
	Common duiker	Antelope
		Pig
		Peccary
		Hippopotamus
Perissodactyla (odd-toed ungulates)	Horse	
	Donkey	
	Zebra	
	Rhinoceros	
	Tapir	
Proboscidea	Elephant	
Cetartiodactyla	Dolphin	
	Whale	
Tubulidentata	Aardvark	
Hyracoidea	Hyrax	
Sirenia		Sea cow (dugong)
Carnivores		Lion
		Tiger
		Cat
		Dog
		Hyena
		Fox
		Bear
		Seal
Primates		Human
		Gorilla
		Chimpanzee
		Orangutan
		Gibbon
		Baboon
		Vervet
		Macaque

4. Lobular architecture

The microscopic architecture of the liver is generally similar in all mammals. The terminal branches of the afferent portal and efferent hepatic veins intertwine, and the sinusoids that bridge the portocentral distance have the most constant spanning distance of any organ in the body [65]. This distance measures 620 μm in pig liver [66], 385 μm in human liver [65], 300 [67] or 355 μm [68] in rat liver, and 210 μm in mouse liver [69]. Despite this strict boundary condition, many concepts of the smallest functional unit in the liver have been formulated. Because the microscopic architecture of the liver is a critical feature for liver function, we will describe the prevailing concepts. Unfortunately, the nomenclature of the structures that contribute to the microarchitecture of the liver is not very consistent between studies. We have chosen that formulated by Crawford [70].

In our view the microarchitecture of the liver is best represented by the classic lobular concept [71,72] (Fig. 3). The lobular concept is usually attributed to Kiernan, who described it in humans, sheep, oxen, rabbits, hares, and squirrels [73], but Kiernan himself referred to earlier histological observations by Malpighi, Mascagni, and Bidloo. The concept is also known as “centri”-lobular, because hepatocytes surround the central (terminal hepatic) vein, while the terminal branches of the portal vein demarcate the periphery of the lobule. Despite the central position of the efferent hepatic vein, it is generally assumed that the fibrous portal septa in the larger species that Kiernan described were a leading feature in the development of his lobular concept. These so-called “portal tracts” contain the terminal branches of the portal vein, hepatic artery and bile duct, and form an isotropic three-dimensional network that in sections generates the typical hexagonal outline of the lobule with 3 portal tracts and 3 areas where the portal “venules” (final branches of a terminal portal vein) end (Fig. 3). It should be kept in mind, however, that the “hexagon” is more a concept than a reality because a lobule is normally bounded by ~6 portal triads ([68,71,74]; see also our description of Matsumoto's unit-concept of the liver lobule). A functional feature that underscores the lobular model is the expression pattern of numerous mRNAs and proteins in the liver: if expressed periportally these gene products form a continuous network and if expressed pericentrally a discrete tree of stained hepatocytes (Fig. 3C), as predicted by the lobular model. We dubbed this concept the “metabolic” lobule [71], because the acinar concept (next paragraph) dominated the field at that time.

The most important alternative structural model is Rappaport's acinar concept [75,76], so named because the arrangement of the liver units resembles a bunch of grapes. The concept is based on the three-dimensional spread of India ink particles dissolved in gelatin (to allow fixation) through the portal vein and the pattern of ischemic pericentral cell death in patients with right-sided cardiac failure. We posit that Rappaport's preparations identify the circulatory periphery under adverse conditions: the viscous gelatin solution causes a rapid drop of perfusion pressure and cardiac failure is associated with an increased

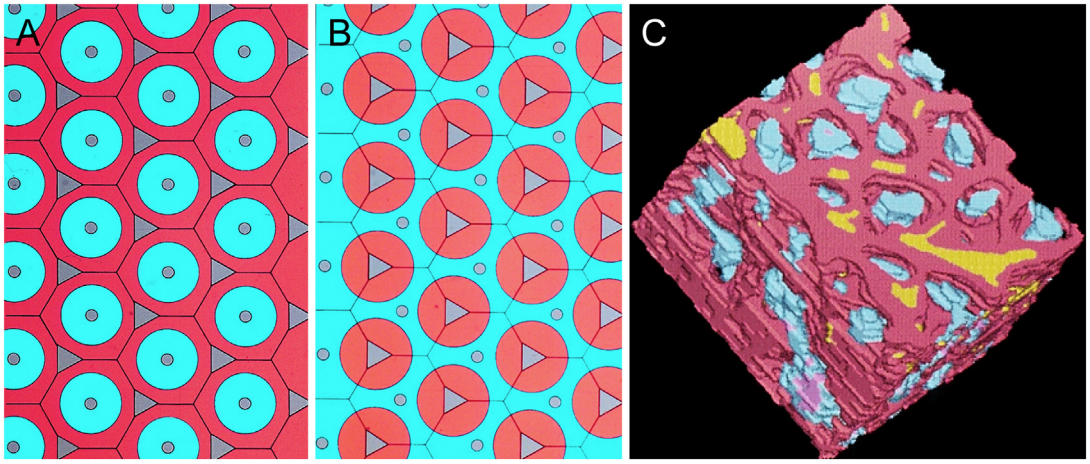

Fig. 3. Lobular (A) and acinar (B) concepts of liver microarchitecture, and 3D reconstruction (C) of human liver stained for the presence of the periportal (upstream) enzyme carbamoylphosphate synthetase (red) and the pericentral (downstream) enzyme glutamine synthetase (blue). Yellow areas in panel C represent portal veins. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

central venous pressure, which in turn affects function and changes the gene-expression pattern of the liver profoundly [77]. In addition, the gene-expression patterns and biochemical functions attributed by Rappaport to acinar zones 1–3 [78] do not correspond to those actually demonstrable in livers. As an example, staining of mouse livers for pimonidazole-protein adducts, which visualizes hypoxic regions, identifies pericentral regions with a discrete [79] rather than continuous distribution as predicted by the acinar model. More definitively, the flavoprotein/pyridine nucleotide redox ratio-scanning technique revealed that the oxidized periportal domains of rat livers form a three-dimensional network, whereas the reduced pericentral domains follow a discrete branching pattern [80]. Upon perfusion with ethanol the continuous, oxidized periportal region shrinks into a discretely branching structure, whereas the discretely branching, reduced pericentral region expands into a continuous three-dimensional network [80]. The rising metabolic demands due to exposure to ethanol apparently transfer the periportal areas near the end of the (septal) portal venules that are sensitive to hypoxia to areas with a pericentral redox ratio and thus establish a typical acinar zonal distribution. For all these reasons we conclude that the acinar concept does not model the microarchitecture of healthy livers and interpret Rappaport's model as one showing a hypoxic or ischemic, that is, pathological liver.

We owe the “comeback” of the lobular concept to Matsumoto [74]. His “unit-concept” divides the portal venous tree into upstream “conducting” and downstream parenchymal (“delivering”) portions with a higher branching frequency (see section on Couinaud's segmental liver model). Typically, ~6 such terminal parenchymal portal twigs, accompanied by arterial and ductular twigs, embrace a piece of parenchyma that has a terminal hepatic vein as its central axis. The terminal portal twigs in the portal tracts typically form three portal venules (“septal” branches) that feed the sinusoids via inlet sinusoids. Because the sinusoids near the terminal portal tracts are more tortuous, whereas those originating from the distal ends of the septal portal venules and those surrounding the central (hepatic) veins are relatively straight, Matsumoto postulated an “inflow (perfusion) front” towards the central vein. The boundary between vital and lethally damaged hepatocytes after controlled digitonin perfusion of the liver [81,82] have underscored the concept of an inflow front. The redox ratio-scanning technique [80] showed, in addition, that the tortuous sinusoids characterize the metabolically robust periportal zone, whereas the straight sinusoids characterize the metabolically sensitive zone. We have hypothesized that the tortuous periportal sinusoids are also responsible for the ability of blood to flow from the portal to the central vein, but not vice versa, whereas a cell-free solution allows bidirectional perfusion [83,84].

The liver lobule has been further subdivided in some concepts, but also combined into compound lobules. In Matsumoto's unit-concept, the classic (≈ “secondary”) lobule consists of ~6 “primary” lobules. A primary lobule represents the part of the secondary lobule that is perfused by a single terminal branch of a parenchymal portal vein [85]. The even smaller “microcirculatory unit” represents the fraction of a lobule that is perfused by one inlet sinusoid [86]. Because the bile that is produced in that microcirculatory unit usually drains into a bile ductule that leaves the hepatic parenchyma near the inlet sinusoid, the microcirculatory unit is also known as “cholehepaton” [87]. Compound parenchymal units, on the other hand, include all lobules served by a parenchymal portal branch [68]. In support of this compound model, we showed that the first 2–4 generations of terminal or “collecting” hepatic veins are surrounded by a rim of glutamine synthetase-containing hepatocytes, whereas the more downstream, larger “conducting” hepatic veins are not [88], probably because their wall is thicker and blocks the transmission of an endothelial signal necessary to express glutamine synthetase [89]. The presence of sinusoid-draining terminal hepatic veins is, therefore, another feature of the compound liver lobule. In our view, the classic lobule is the most versatile functional unit.

Two aspects of lobular architecture that differ quantitatively between small and large mammals are the portocentral distance (vide supra) and the amount of connective tissue that is present in the portal tracts. Furthermore, liver lobules in small mammals like the mouse are more tortuous cylindrical structures [69] than those in pig and human liver [90,91], but too few examples are available to conclude that this is a general feature of size. It is well established that the amount of connective tissue in the portal tract is lowest in rodents, sparse in healthy human liver, better developed in ruminant and equine livers [92,93], and pronounced in pig liver, where it already reaches near-adult levels shortly after weaning [66]. The amount of connective tissue determines the tissue stiffness and “fracture toughness” [94,95], but the adaptive value remains to be established.

5. Lobular perfusion

The reported allometric constant of the relation between mammalian body weight and liver size (0.89) is similar to that between body weight and hepatic blood flow (0.85–0.91; [1,96]), showing that liver perfusion increases concomitantly with liver size. As shown above, the portocentral distance between species also increases with body weight, but the few species for which information could be obtained produce an

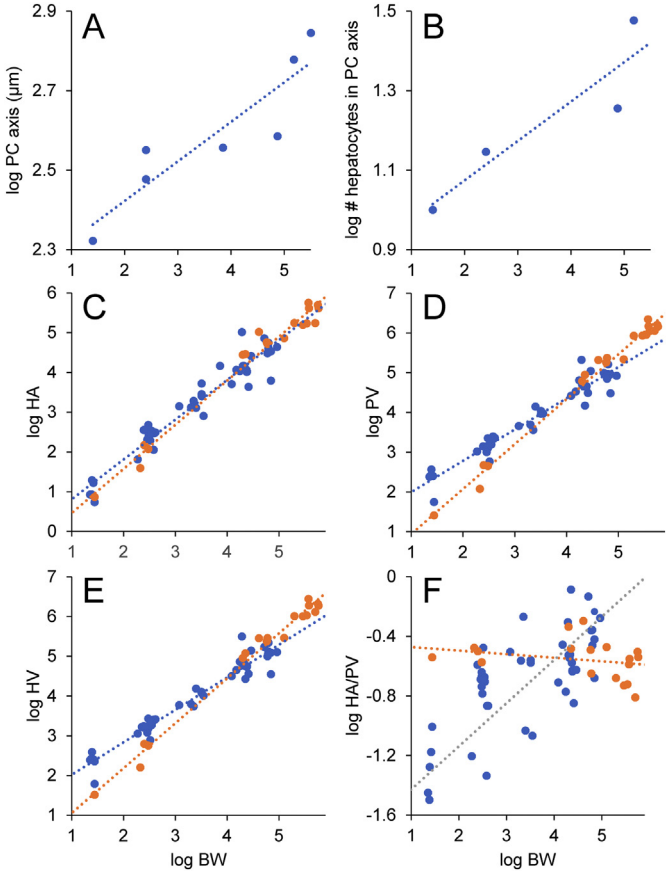

Fig. 4. Allometric scaling of the length of the portocentral axis (A), the number of hepatocytes on a portocentral axis (B), and the contribution of hepatic artery (C), portal vein (D), and hepatic vein (E) to lobular perfusion in mammals. Panel F shows allometric scaling of the ratio of the contribution of hepatic artery and portal vein to liver perfusion. Symbols in panels C–F represent flows based on dilution of para-aminohippuric acid (ochre) or all other methods inventoried (blue; microspheres, ultrasound or electromagnetic probes, hepatic indocyanine green or bromosulfophthalein extraction, or MRI or CT data). Data in panel A are from mice [69], rats [67,68], macaque monkeys [72], men [65], pigs [66], and dolphins [126]. Data in panel B are from mice [69], rats [67], men [71], and pigs [66]. Data in panels C–F are from mice [127–134], rats [103,135–152], rabbits [104,153–157], macaque monkeys [158], dogs [105,159–169], sheep [160,170–172], pigs [173–176], men [177–183] and cattle [184–193]. The allometric constants (R^2 values) are 0.10 (0.82), 0.10 (0.84), 0.29 (0.50), 1.00 (0.94), 0.78 (0.94), and 0.82 (0.95), respectively, for the blue symbols in panels A–F and 0.02 (0.08), 1.09 (0.98), 1.11 (0.99), and 1.11 (0.99), respectively, for the ochre symbols in panels C–F. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

allometric constant of only ~0.10 (Fig. 4A), which implies that the portocentral distance increases only slowly with liver size. Similarly, the allometric constant of the relation between body size and the number of hepatocytes on the portocentral axis is only ~0.10 (Fig. 4B). For most organs the allometric constant for the relation between body weight and cell size, including that of (diploid) hepatocytes, is not different from zero [97], that is, invariant with body size. However, the volume of hepatocytes increases with the degree of ploidy [98] and rodents have a higher percentage of polyploid hepatocytes than larger mammals [98–101], so that fewer rodent hepatocytes fit on the same portocentral distance. For that reason, 0.1 is a high estimate for the allometric constant. The direct relation between liver size and perfusion is, therefore, accomplished by generating more rather than larger lobules. While blood pressure in the hepatic artery is ~120 mm Hg and independent of animal size [106], that in the portal vein is only 6–11 mm Hg and also similar for mice [107,108], rats [108,109], cats [110], dogs [110,111], and humans [112,113]. Hence, we hypothesize that one of the structural limitations for an increase in size of the lobule is its perfusion.

The reported allometric constant for blood flow in the portal vein is, with 0.76, lower than that for the hepatic artery (0.86; [102]), implying that the contribution of the hepatic artery to lobular perfusion increases with increasing size of the mammal. A change in the relative contribution of the hepatic artery and portal vein to liver perfusion will affect the extrapolation of pharmacological data from small to large animal models and humans, if metabolic activity in the liver is determined with the Fick principle, which states that the product of blood flow to an organ and the arteriovenous concentration difference of a substance determine uptake or release of a substance by that organ. Since just one study was available to underscore this hypothesis and since this study compiled data on mice, rats, dogs and humans only [102], we have reviewed the pertinent literature for paired samples of liver perfusion (portal and hepatic vein, or portal vein and hepatic artery). Our review includes mice, rats, rabbits, dogs, pigs, sheep, macaque monkeys, humans, and cattle, that is, mammals with a 10,000-fold range in body mass. Liver blood flow was determined with indicator dilution methods (para-aminohippuric acid (PAH), microspheres, or clearance of indocyanine green or bromosulphtalein), ultrasound or electromagnetic probes, MRI or CT imaging. The PAH-based assay is used in both small and large mammals, but many of these studies in rodents do not provide quantitative data on transhepatic blood flow, so that our PAH sample is somewhat biased to larger mammals. The microsphere technique is, on the other hand, often used in small and intermediate size mammals.

The collected data revealed a pronounced difference between liver perfusion as determined with the PAH-dilution method and all other methods (Fig. 4C–F). The allometric constant of blood flow in the hepatic artery was 1.00–1.09 with all methods used (Fig. 4C; not significantly different), but that in the portal vein was 1.11 for PAH and only 0.79 for all other methods ($P < 0.001$) and similar to that reported earlier [102]. The numbers for the hepatic vein followed that of the portal vein ($P < 0.001$). Fig. 4F, finally, shows that the allometric constant of the ratio of the contribution of the hepatic artery and portal vein to hepatic perfusion is zero for PAH and 0.29 for all other assays ($P = 0.001$). The differences persist when we compare PAH with all other indicator-dilution methods only. We do not know the reason for the observed difference, except that it appears to arise from the portal-vein data. Good correspondence was reported between microsphere- and electromagnetic probe-based estimates of liver perfusion in rats [103], between microspheres- and MRI-based estimates of portal blood flow in rabbits [104], and between electromagnetic probe- and indocyanine-green clearance-based estimates of liver perfusion in dogs [105].

Because the allometric constant for hepatic perfusion via the portal vein as determined with the PAH dilution method is ~0.3 units higher than the previously [102] and presently collected values for all other, technically diverse techniques combined, we tentatively conclude that the PAH data are not representative. Because the regression lines (Fig. 4D) crossed, the PAH-based estimates of portal blood flow in small mammals like mice and rats were low and those in large mammals like cows high relative to reference values. Since the perfusion pressure and flow rate are low in the portal vein and since plasma is a viscous fluid, a potential explanation is incomplete mixing of the injected PAH in between the mesenteric-vein injection site and the portal vein in the smaller mammals (distance > 10-fold longer in cattle than in mice). In large ruminants like cattle, on the other hand, often more than one (frequently two) of the three large tributaries to the portal vein (gastrosplenic, gastroduodenal, anterior mesenteric veins) are cannulated [106] to optimize mixing in the portal vein. Since cannulation of one tributary should suffice according to theory, this protocol suggests that portal blood flow in ruminants can be overestimated.

If we accept that the contribution of the portal vein to hepatic blood flow decreases and that of the hepatic artery increases with increasing size of the mammal (Fig. 4F), it is tempting to speculate that the increased arterial supply serves perfusion of the larger liver lobules with longer portocentral sinusoids, and that of the vasa vasorum of the conducting portal veins and peribiliary plexus of bile ducts [92,107]. It remains to be determined where the terminal branches of the hepatic artery join the sinusoidal network (see e.g. [108,109]) and how they affect sinusoidal perfusion [110]. The increasing significance of the hepatic artery for liver perfusion also seems to explain the finding that liver transplants in mice do not need a hepatic artery to avoid biliary complications [111,112], whereas those in humans do [113,114], with rats taking an intermediate position rat [115,116].

6. Conclusions

Our main conclusion is that the Bauplan of the liver in the mammalian class of vertebrates is invariant and that the main differences are quantitative in nature: the size of the liver determines the number of lobules, and the degree to which fissures have formed determines whether a liver is (partially) lobated or non-lobated. Similarly, the degree of connective tissue development in the portal tracts does not change the architecture of the lobule, but does affect its stiffness (and, hence, suitability for consumption). Even qualitative differences, such as the presence or absence of a gallbladder or the hydrophobic index of the bile, appear to be mediated by the loss or acquisition of only one functional gene. However, quantitative differences can have major implications if not taken into account. An obvious example is the increasing dependence of lobular perfusion on the contribution of the hepatic artery in larger mammals: if hepatic consumption or production of metabolites is calculated from concentrations or enrichments of metabolites in the arteries, and portal and hepatic veins, the contribution of the hepatic artery is > 5-fold higher and that of the portal vein 25% lower in men than in mice.

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