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The complement system in liver diseases: Evidence-based approach and therapeutic options☆

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ABSTRACT

Complement is usually seen to largely originate from the liver to accomplish its tasks systemically – its return to the production site has long been underestimated. Recent progress in genomics, therapeutic effects on complement, standardised possibilities in medical laboratory tests and involvement of complosome brings the complement system with its three major functions of opsonization, cytolysis and phagocytosis back to liver biology and pathology. The LOINC™ system features 20 entries for the C3 component of complement to anticipate the application of artificial intelligence data banks algorythms of which are fed with patient-specific data connected to standard lab assays for liver function. These advancements now lead to increased vigilance by clinicians. This reassessment article will further elucidate the distribution of synthesis sites to the three germ layer-derived cell systems and the role complement now known to play in embryogenesis, senescence, allotransplantation and autoimmune disease. This establishes the liver as part of the gastro-intestinal system in connection with nosological entities never thought of, such as the microbiota-liver-brain axis. In neurological disease etiology infectious and autoimmune hepatitis play an important role in the context of causative *viz* reactive complement activation. The mosaic of autoimmunity, i.e. multiple combinations of the many factors producing varying clinical pictures, leads to the manifold facets of liver autoimmunity.

1. Introduction

The liver is the major site of protein synthesis, including complement components and excluding gammaglobulins [1,2]. The overlap of inflammatory and autoimmune responses in many diseases is a challenge in the care for patients, especially for the choice among therapeutic options built on basic, epidemiological and clinical studies [3–5]. Sequential recruitment of partakers of the innate and acquired immunity in a disarranged standing, superimposed by reparative processes lead to organ damage and dysfunction, typical of most autoimmune diseases [6,7]. To fulfill diagnostic criteria, autoimmune diseases follow a predilection of particular organs [8] but systemic involvement is not unusual [9,10]. Beyond progress in diagnostic procedures and therapeutic measures, the development in medical laboratory technology make cellular and humoral diagnostics more meaningful in uncovering excessive autoimmune reactions. One of the players, the complement system, scrutinized decennies ago for its role in hepatobiliary diseases [11], is going through a revival in clinical importance, none the least because of an upsurge in therapeutic possibilities; we now have a means to therapeutically monitor opsonic, phagocytic and cytolytic complement functions [10,12], even in rare diseases [13]. Among the various organs, the liver merits particular attention since it produces complement components and at the same time it can be victim of local activation of the same components or by sequestering C3b-coated red blood cells [14].

Through this, the manuscript extends the aspects of autoimmune hepatitis to alcoholic, inflammatory and microbial liver diseases. Nosological entities of liver diseases are scrutinized for the passive

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Abbreviations

AIH	Autoimmune hepatitis
ALD	Alcoholic liver disease
AFLD	Alcoholic fatty liver disease
AFP	Alpha Feto Protein
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
AMA	Anti mitochondrial antibodies
CDT	Carbohydrate-deficient transferrin - marker for alcohol consumption
CD46	Complement regulatory protein
CPW	Classical pathway
CRP	C-reactive protein
CXC	Chemokine receptors
DENV	Dengue Virus
EBV	Epstein Barr virus
EBOV	Ebola Virus
FISH	Fluorescence in situ hybridization
FH	Complement Factor H
FLD	Fatty liver disease
GALT	Gut associated lymphoid system
HCV	Hepatitis C virus
HELLP	Hemolysis, elevated liver enzymes, and low platelet count
IEC	Intestinal Epithelial Cells
ICAP	International Consensus on Antinuclear Antibody Patterns
ILC	Innate lymphoid cells
ILCS	Intestinal innate lymphoid cells
iNKT	invariant Natural Killer T cells
IEC	Intestinal epithelial cells
LC-1	Live cytosol antigen type 1
LKM	Liver kidney microsome
MASP	Mannose-associated serine protease
MAIT	Mucosal-associated invariant T cells
NAFLD	Non-alcoholic fatty liver disease
NASH	Non alcoholic steatotic hepatitis
NLRP	Cryopyrin, a subset of inflammasome (Tschopp naming)
PBC	Primary biliary cholangitis
PCR	Polymerase Chain Reaction
SMA	Smooth muscle antibodies
SLA/LP	Soluble liver antigen/liver pancreas
TCC	Terminal complement complex C5b-9 ~ MAC (membrane attack complex)
TLR	Toll-like receptor
TNF	Tumor necrosis factor
VSM47	Vascular smooth muscle cells from rat (EUROIMMUNE)

involvement or the active role of the complement system in immunopathological damage (Table 1). Furthermore, the current insight into the intracellular complement activation (now alluded to complosome) [15] impinging on metabolic properties of the involved cells make novel approaches into exploration of complement in liver diseases necessary [16–18]. Since complement components are released by the liver into the systemic circulation, blood perfuses them to any given site and within the single site, these components far reach into infrastructural location, the liver itself included. The question then is, which type or group of liver disorder might be a target of complement action. The disease pathogenicity varies largely and may include genetic, metabolic and/or toxic causes.

Design, development and diagnostic strategies in laboratory medicine now allow to decipher subtle differences in organ damage, liver included. The elementary cell types which constitute the liver are derived from tissue layers separating as early as during gastrulation. When it comes to assign single components of complement to particular cell types on board at the liver one may relate them to their cytokine profile (Table 2).

During embryonic development, endodermal pluripotent stem cells (hPSCs) generate hepatocytes broadly expressing surface marker CXCR4 [30,36] (Table 2).

The complement system with its early role in ontogeny [37] may call on signals in liver organogenesis (Fig. 1).

Regeneration and organogenesis share common features in hepatocyte proliferation [38] since breaking and repair of DNA is perpetually associated in both, organogenesis and reformation of all tissues in nature [39–41]. On top is this, stem cell colonization of liver tissue profits from the capacity of this tissue to find its way when deplaced on ectopic environment comes without surprise [31] www.nirm-pitt.net. Regeneration, studied by transcriptomic and metabolomic measurements can be tracked down to complement component C3 cascade through activation of the TNF signaling pathway further triggering acute phase genes such as serum amyloid proteins and orosomucoids [29].

1.1. Synthesis sites of complement components

The Germ-layer differences underlie, hepatocytic- and non-hepatocytic hepatogenic origin of liver anatomy [1,2,42] (Fig. 2). Hepatocytes, and such immune cells as Monocytes/Macrophages, Dendritic Cells, Plasma Cells, Innate Lyphoid cells (ILC) [43,44] and γδ T lymphocytes are derived from different provenience. Components of the complement cascade appear very early in evolution and ontogenesis, some components being expressed as early as the gastrula/neurula phase [45]. Intracellular, i.e. cytoplasmatic activity of complement, has been baptized as 'complosome', the -ending "-ome" or "-omics" used to indicate that complement intervenes in several intracellular functions (15) like used in other designations such as transcriptome or methylome [46] and other -omics [15].

The three pathways of activation, classical, lectin and alternative pathways are listed alongside their activating factors, i.e. immune complexes, ficolin and microorganisms. Some components, such as C1q, C3, C5 and C7, are synthesized, at least in part, in other cells than hepatocytes, i.e. in cells of ectodermal, mesormal and endodermal origin (**see** Table 2) A colour code shows these different ontogenic proveniences (red: endoderm, yellow: mesoderm/neural crest and blue: endoderm). Finally, with the recent insights into complosome activity [15], some sedentary liver cells of the immune system may be involved in liver metabolic processes. Complosome: a relatively recent designation to imply participation of complement components at their very site of production [15]. Complosome interacts during T cell activation [17]. Complement is instrumental in both, T and B cell responses and helps to regulate basic cellular functions, even those of metabolic impact. Some complement components may play a so far undefined developmental role in ontogenesis and in migration of neurons. In the developing brain the lectin/MASP arm of the complement pathway and C3 (Fig. 2), have been found to be required for neuronal migration in the developing brain cortex [47]. An informative way of assessing the contribution of hepatocytes to a protein pool would be to look at liver producing specific/-individual allotypes (Fig. 1). The primary synthesis site for complement components of the liver is extended to such cell types as adipocytes, macrophages, endometrium, and endothelial cells and IEPs [35,48,49]. While most complement components are mainly synthesized or expressed in hepatocytes, for example C1- C9 (except C1q and C7) and fB, others like C1q, C7, D, fD are synthesized and expressed in other cells [2, 32]. The extra-hepatic synthesis of C7 was confirmed in the framework of liver transplantation [50]. The allotypes of C7 present in the circulation of liver recipients do not change to the donor allotype after liver transplantation, assessed by specific typing of allotypes or alleles of the C7

Table 1
List of diagnostic labels for different liver diseases. A large variety of liver diseases affecting different structures of the organ and being caused by a variety of pathogenic triggers.

Liver Diseases	Causes	Risks factors	Involvement of antibodies and/or Complement	Laboratory Assays
Infections	• Hepatitis A • Hepatitis B (+/− D) • Hepatitis C • Hepatitis E	• Injecting drugs using shared needles • Tattoos or body piercings • Blood transfusion before 1992 • Exposure (other people's blood, faeces or body fluids) • Unprotected sex • Poor hygienic conditions	+++++ Immune complexes [19]	Serology and PCR
	• Other pathogens, e.g. tropical virus, bacterium, parasite, fungi	• Exposure (man (see above), animals, environment) • Unproteced sex • Poor hygienic conditions	[20,21]	Serology, PCR, microbial cultures, microscopy & histology
Autoimmunity Immune system abnormality	• Autoimmune hepatitis • Primary sclerosing cholangitis • Primary sclerosing (biliary) • cholangitis	• genetic predisposition and environmental triggers	+++++ Autoantibodies [22]	IIF, ELISA and Immunoblot Ultrasound, Liver biopsy & Transarterial chemoembolization
NAFLD (nonalcoholic fatty liver disease) Including NASH (non alcoholic steatotic hepatitis)	• Fat supplanting liver tissue	• Diabetes typ 2 • Obesity (Metabolic syndrome) • Drug induced (e. g.: Amiodaron) • Genetic predisposition *I148M PNPLA3* (patatin-like phospholipase domain-containing protein 3)	[23] [24]	Gamma – GT ↑ Extended Lab tests: transaminases, lipids, glucose, histology. exclude HBV/HCV
AFLD (alcoholic fatty liver disease)	• Alcoholic abusus	• Alcohol	**C1q** [25] **C3**, **C1q**, **D** [26]	CDT (Carbohydrate-Deficient-Transferrin) ↑Ethylglucuronid ↑ Extended Lab tests: Gamma-GT, IgA, transaminases, cholinesterase, albumin, clotting factors, haemogram
Genetics	Hemochromatosis type 1		• NA	• Genotyping p.C282Y • Increased Iron in Plasma, ELISA • Increased secretion of Bile in Serum • Hypercupriuria
	Hyperoxaluria and oxalosis Wilson's disease		• NA	• PCR, DNA Sequencing Hemodialysis, Increased oxalate in Urine and Plasma. • Low serum ceruloplasmin, decreased serum copper, increased copper in urine, and significantly elevated copper on liver. • Sequence analysis of the ATP7B gene,
	Alpha-1Antitrypsin deficiency		• NA	• Quantitation of protein levels in serum • Phenotyping-determination of specific allelic variants by isoelectric focusing (IEF), • Genotyping-DNA p.E34K (PiZ) p.E264V (PiS) i.e. specific mutations, or proteotyping-using LC-MS/MS. • IEF phenotyping, LC-MS/MS proteotyping, and DNA- genotyping
	Familial intrahepatic cholestasis	Genetic background, Liver transplantation	• C4d deposits [27]	• Sequencing flippase and farnesoid receptors [28]
• Cancer and other growths	• Liver cancer • Bile duct cancer • Liver adenoma	• Exposure to certain chemicals or toxins. • Heavy alcohol use and unknown factors, HCV		• Tumor marker (e. g.: AFP) • High concentration of bile acids in serum
Liver regeneration and other	Drug and poison induced	Drug therapy induced on diverse illnesses and unknowingly contact with poison (e. g.: fungal, heavy metals, carbon tetrachloride)	[29] [30] [31]	• track the initial cause • Transaminases, bilirubin, ammoniac, hematology consultation ..

Footnotes: NA: not applicable.

M/N polymorphism. Thus, the majority of circulating C7 is not hepatocyte-derived. In contrast, the C6 of a C6 A allotyped recipient will change to C6 B after having received a liver from a donor of that allotype. This is important for modulated terminal complement complex (TCC) assembly for which C7 is the limiting molecule. Upon complement activation, circulating C5b6 complexes are provided systemically, but unlike C6 or C8, C7 is differentially provided locally by monocytes and PMNLs at inflammatory sites, which determines the magnitude of complement attack, measured by the amount of TCC.

Symbiontic microbial flora on an individuals body stays at the cusp of major changes in the wake of disruptive approaches such as gene, RNA and cell therapies. These enable therapeutic intervention towards disease in so far unprecedented ways; the pace of these changes is driven by advanced approaches such as CRISPR, which makes it possible to correct errors in DNA or even to tailor otherwise healthy DNA to ones design with relative ease.

1.2. GALT: gut associated lymphoid system: crosstalk with liver

The complement system takes part in the homoeostasis of the intestinal lumen; C3 can be synthesized by intestinal epithelial cells (IEC) [48] an endosomal mucosal cell layer which also produces abundantly IgA.

Table 2
Hepatic cell type realm derived from ontogenetic developments with involvement of complement component.

Origin	Cell type	Cytokin		Crosstalk complement	resident(r) transient (t)	Main function	Literature
		Producing /responsive	cytokine				
Endoderm	Hepatocyte CXC reponders	Hepatocyte growth factor	IL-1β, IL-6 IL-8	C1r/s,C4,C2,C4bp C3, fB C1 –C9 (excl. C1q,C7)	r	Protein synthesis	[32]
	Hepatic sinusoidal cells	Produce IL-6					
Mesoderm	Myeloid		+		r	Innate immune defense	[33]
	Kupffer Stellate Cells (Monocytes/ Macrophages)	Responsive Producing	IL-10	C1q, C7, D, P	r t		[2,34] [35]
	Polymorphonuclear Leukocytes, Adipocytes, Dendritic Cells, NK cells Innate lymphoid cells	TNF, IL-2					
Mesoderm	Lymphoid iNKT		Helper Cells responsive to IL-2 IL-9 produced by helper cells	thymus	t	Innate and acquired immune defense	

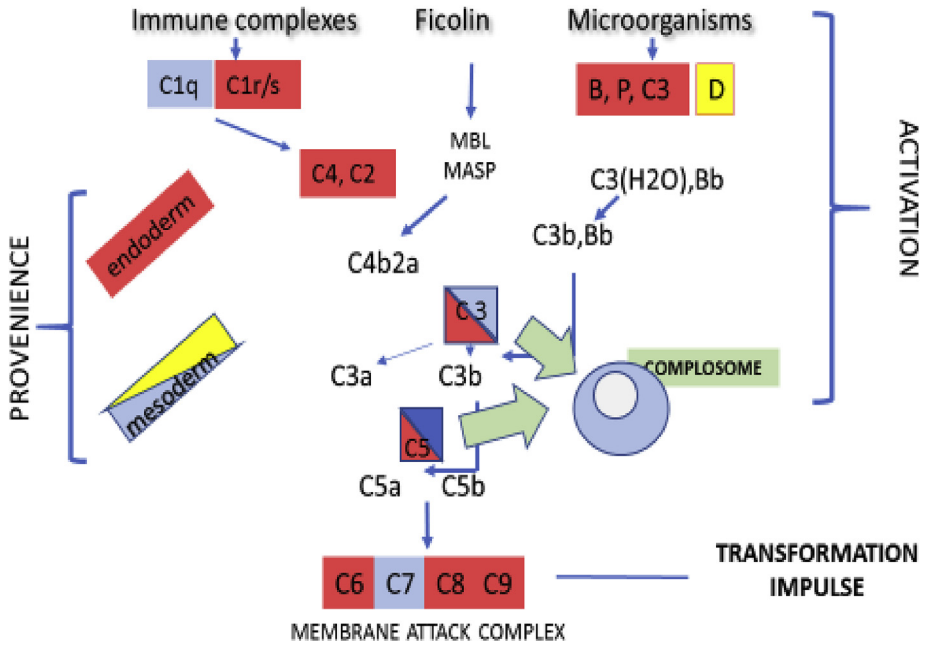

Fig. 1. Cellular origin of different complement components based on ontogenic provenience. red: endoderm, yellow: mesoderm/neural crest and blue: endoderm. Membrane attack complex (terminal complement complex, C5b-9).

The intestinal tract microbiota hosts foreign genome largely defined by two dominant phylotypes, Bacteriodetes and Firmicutes, with minor ones such as Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicrobia completing (Fig. 2). The mature microbiome might drive inflammation in liver disease and governs tolerance to these bacteria [53]. The gut associated lymphoid tissue [51] (GALT) scans microbiata composition:, portal blood reaching the liver will be processed at least in part, by immune recognition. GALT is rich in $CD4^{+}$ T-cells [54] and the Th17 cells functioning under the concurrence of complosome [55]. Ductal pancreatic and healthy intestinal epithelial cells such as enterocytes have been found to express C1q, C4, C3, FB, CD46 and CD59 under basal conditions [56] to different extents. Unexpectedly indeed, a role of the complement system to maintain homeostasis at the host/environmental mucosal interface became apparent when gut intraepithelial cells were found to express and secrete complement components likely to play a role in resolving chronic interstinal inflammation.

2. Complement activation in alcoholic liver diseases (ALD)

2.1. Current appraisal

Some 20 years ago complement activation in acute ALD was demised by such studies as the one published from England [57]. In this work, 20 patients were screened for C3 and factor B serum levels as well as with C3d/C3, C4df/C4 and Fa/factor B ratios which were not different from healthy controls. Presently, literature reviews fail to relate alcoholic damage with complement activation. Fatty transformation or inflammation reveal involvement of complement activation be it causative or as a consequence of histopathological evidence for organ damage C3 levels are increased in patients with hepatic steatosis [58].

2.2. Currently available lab analyses

Before prescribing lab tests we need to exclude drug-induced liver

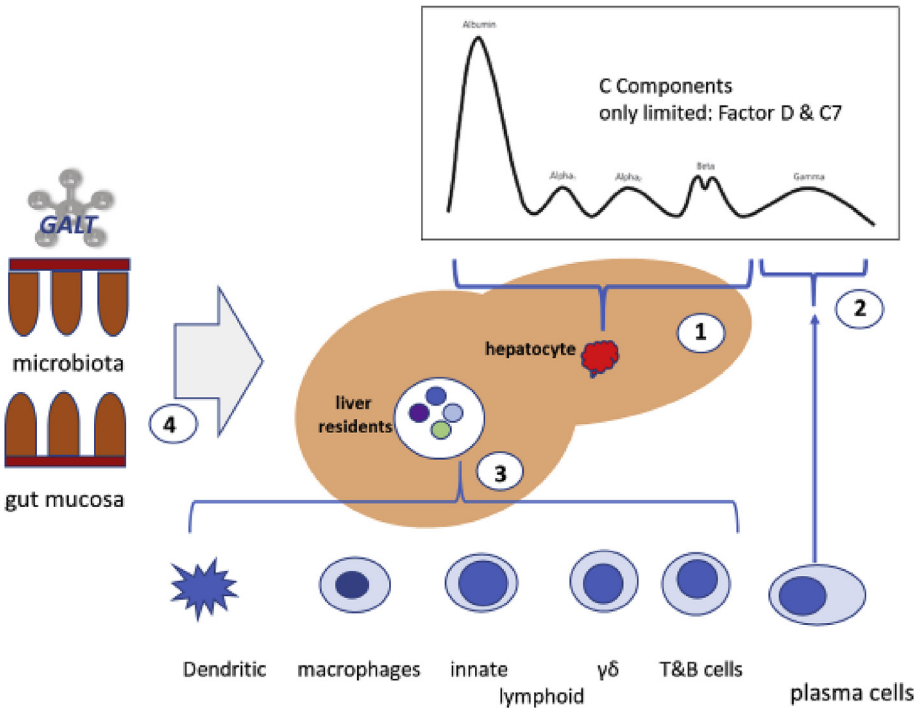

Fig. 2. Hepatocytic and non-hepatocytic liver resident cells synthesizing proteins completed with influence by gut microbiota. 1:1 hepatocytes contribute majority of proteins 2 plasma cells replenish immunoglobulins 3 mesodermal lymphoid cells contriute a whole array of innate and acquired immune humoral components. The orchestration by microbiota, in connection with 4.GALT [4,51,52] is addressed in the text.

damage which may mimick alcohol damage. In addition, non-alcoholic fatty liver disease (NAFLD), hemochromatosis, M. Wilson or alpha1-antitrypsin deficiency need exclusion.

The calibration of laboratory assays for complement is under the auspices of the committee for standardisation and quality assessment of complement mesurements. In an effort to produce international comparativity in results the LOINC coding system (search.loinc.org) of Regenstrief™ (Center for Biomedical Informatics, Indianapolis IN, USA) features 20 entries for C3 analysis alone and in the wake of artificial intelligence and electronic patient dossier, the standardisation will have to be pushed further. The data coordination lab at our local University Hospital (IDCL Insel) now uses LOINC coding and is in line with international efforts to make laboratory results comparable [59]. Many complement assays have been confected as commercially available and the producers do contribute to international standardisation. Autoantibodies to complement proteins are also ready for introduction into diagnosis for autoimmune diseases, perhaps for liver autoimmunity as well [8,60] since their involvement in autoimmune disases is now acknowledged [61]. A list of European Diagnostic investigational and routine laboratories that provide detailed complement analyses or are in a position to counsel medics on the development status of regional offers may be consulted on. These labs provide extended analyses important for some patients, such as FH, C1 Inhibitor, and (auto-) antibodies against some components. The assembly of routine lab assays is ascribed to the five mayor disciplines of lab analytics, i.e. clinical chemistry, hematology, immunology, microbiology and embracing the four, genetics.

Genetics of Alcoholic and Non-Alcoholic (fatty) liver diseases are now backed by robust markers, among them the most prominent PNPLA3 (Adiponutrin) [62,63] or TM6SF2 a gene that encodes for reduction of trglyceride hydrolysis, particularly in lipid droplet disease. ADH1B-ADH1C and its variants protect an individual against dependence on alcohol [64]; risk-reducing genes to develop ALD have also been discovered, such as the HSD17B. To more closely narrow down involvement of alcoholic liver damage, search for carbohydrate-deficient-transferrin and ethylglucuronid are now established as reliable markers; the topic of alcohol-abose related disorders has recently been updated elsewhere [65]. Despite substantial efforts to look out for genetics of inflammation, and despite knowledge on the complement system providing for novel insights into inflammation and autoimmune liver diseases [60], a genetic background of liver diseases leaves out the complement system and bears some potential for better understanding AIH non the least because the organ expresses genes of complement components [66]. Participation of complement in acute-or-chronic liver failure, although a very likely event, remains to be explored. In situ imaging with DNA hybridization and fluorescence could focus on complement in liver disease [67].

Few studies have assessed the association between complement and AFLD [25] or in NASH [68]. The linkeage of complement components to lipid metabolism is poorly alluded to in complement research protocols let alone in lipidology. As yet, if a protein can contain a phospholipase domain or express rare variants [44,69] it might express lipolytic properties to hydrolyze phospholipid substrates at specific ester bonds [70]. A recent review on the involvement of complement in AFLD has provided a metaanalysis, mainly with studies in mice, to underscore the involvement of several complement components (C1q, C3, C5 and factor D) in alcoholic liver damage [26]. C3-deficient mice are more susceptible to ethanol-induced hepatic injury and steatosis [71]. In fact the complement system is now acknowledged to be involved in the pathogenesis of liver disorders (6, 68) [72] [73] with some caveats in primary biliary cirrhosis [74]. In addition, immunoreactivity of C5a receptor (C5aR) is enhanced in alcoholic hepatitis [75].

3. Role of complement activation in non-alcoholic liver disease including infectious hepatitis

In our most recent publication, we reported the importance of complement system assays in diagnosing liver diseases [76] without focusing on fatty liver disease (FLD) to which immunology is currently turning increased attention [44].

For inflammatory mediators implicated in ALD and NAFLD please go

back to https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4887345/table/T1/.Table 1.

3.1. Non alcoholic liver damage (NALD)

Nonalcoholic fatty liver disease (NAFLD) comprises a disease spectrum with the common denominator of triglyceride (TG) accumulation in the form of intracellular droplets in hepatocytes causing steatosis and often is part of a systemic disorder [77–79]. NAFLD is a metabolic disorder with alcohol-associated liver disease in individuals who consume little or no alcohol. Steatosis, i.e. excessive intrahepatic fat accumulation, is linked to inflammation, cell death and fibrosis then progressing to nonalcoholic steatohepatitis (NASH). With patatin-like phospholipase domain-containing protein 3 (PNPLA3) being strongly associated with FLD, it has recently been shown that this protein is abundantly accumulated in lipid droplets [80]. NASH thus exceeds simple steatosis: hepatocyte injury (cell swelling & cell death), inflammatory infiltration and collagen deposition contribute to fibrosis. Until recently, we believed that if the complement system has no biochemical linkeage with a chapter in biochemistry, then it is with lipid metabolism. A protein containing a phospholipase domain, will become lipolytic and able to hydrolyze phospholipid substrates at specific ester bonds [70,81]. In a large population, under study on 3000 subjects from China, it was found that serum C3 levels are independently associated with a higher prevalence of NAFLD and AFLD, mostly in males [24]. Scientific evidence is now solid to attribute autoimmune processes to liver diseases, although definite identification of liver-specific autoantigen lags behind when compared to other organ-specific autoimmune diseases, such as in Hashimotos disease [82]. The establishment of a human proteome library to discover autoantibodies against so far unprecendented liver autoantigens might open the door to use phage display to identify the cause of autoimmune diseases as a whole [83]. Liver tolerance may be broken by viral infections exposing natural liver constituents, e.g. cytochromes [84] and research is ongoing on animal models [85]. Cytochrome P4502D6 has been identified as cross-reacting between virus and itself and intestinal microbiome components sneaking up to the liver might become involved [86]. Currently at the forefront of interest we find the concept of the autoinfectome indeed, to reflect the search of infections which initiate autoimmunity. We have ourselves seen a molecular mimicry between *Campylobacter jujuni* and anti-GM1 autoantibodies [87] an observation still under focus [88].

As recently completed to the concept that molecular mimicry feigned by infectious agents might induce PBC, epidemiological studies observing that patients suffering from this disease have a higher incidence of urinary tract infections; indeed, experiments with laboratory animals infected by E. coli (DHα ATCC 25922 strains) let appear autoimmune cholangitis as evidenced by histopathology and AMA immunoblotting [89]. With acute hepatitis caused by hepatitis E virus (HEV) reported to feign [90] AIH a molecular mimicry linked to hepatic autoantigens must be suspected. Clinicians are in need of a rapid and targeted diagnosis using appropriate lab tests in order to prevent development of such processes into chronic liver diseases Table 3 und Fig. 3. Most cases of hepatocellular carcinoma (HCC) arise in a cirrhotic liver which makes that prevention of cirrhosis is, in fact, also HCC prevention [91].

3.2. Viral hepatitis

The special linking of viruses for the liver depends, at least in part, on complement proteins, but basically remains obscure. What makes a virus type hepatotropic? Is complement involved? Among all viruses, especially hepatitis viruses are implicated with liver disease. Among all hepatitis viruses the involvement of complement in the two usually non-chronic disease-causing viruses, hepatitis A and E appears to be less likely, but there are studies in immunodeficiencies which point towards an interaction with complement.

The wide spectrum of liver diseases caused by Hepatitis B virus (HBV) extends from aggressive virus genotypes of spherical Dane particles surrounding an inner nucleocapsid composed of hepatitis B core antigen (HBcAg) complexed with virally encoded polymerase and the viral double-stranded DNA genome of about 3.2 kilobase pairs [92] to impaired immune defense capacities of the host. Before long, investigators of the complement system have scrutinized the role of this system or of single components thereof in liver immunopathology/inflammation, especially if triggered by viruses. Thanks to genetic characterization of HBV strains by Next-Generation Sequencing and functional analysis of HBV variants combined with up-to-date histological explorations strong evidence of a crucial involvement of complement, at least in some liver diseases, is now appearing [93]. There is evidence from mice studies that C5 may play an important role in maintaining liver homeostasis going as far as to control serum triglyceride and cholesterol [94]. Both, C1q activating immune-complexes formed by HBcAg derived from all HBV strains as well deposits of anaphylatoxins C5a, C3a and C5b-9 (TCC) complexes in diseased liver now strengthen prior suspicions that inflammatory reactions involving complement contribute to hepatic immunopathological damage (Table 4).

In a large cohort of cirrhosis patients, C5a serum concentrations decreased from an original rise in chronically hepatitis B virus infected patients, undergoing liver biopsy, to announce worsening of the disease

Table 3
Potentially complement activating autoantibodies relevant in differential diagnosis of hepatobiliary disorder.

Assay	AIH	PBC	Viral Hepatitis
Transaminases (AST, ALT)	++	(+)[a]	+
Cholestasis (AP, GGT) Bilirubin, Lipids	+++	++	(+)
IgG	++	(+)[b]	+
IgM	(+)[c]	++	–
ANA IIF	+(- for AIH type 2)	+	(+)[d]
ANA IIF different patterns, e.g. ICAP – AC nomenclature[e]	+	e.g.AC-3/6/11/12	(+)[d]
ANA IIF pattern ICAP AC-6 nuclear dots		++[f]	
ANA IIF pattern ICAP, AC-11/AC-12, nuclear membrane		++[g]	
ANA IIF pattern ICAP AC-3 centromer		++[h]	
AMA	(+)[i]	++[j]	
Anti-M2	–	++[k]	
Anti-SMA/actin	++[l]	(+) some cases	(+)[l]
Anti-LKM-1[l]	++[m]	–	
Anti-SLA/LP	++[n]	–	
Anti-LC1[o]	++ (for AIH type 2)	–	
Anti-C4b/C3c	ND	ND	++

[a] overlaps with AIH.
[b] overlaps with AIH.
[c] overlaps with PBC.
[d] non-reactve for AIH-2/unspecifically present in case of infectious, e.g. HEV or toxic processes.
[e] see: www.anapatterns.org.
[f] confirmation by ELISA advised; antigen: sp100.
[g] confirmation by ELISA advised; antigen gp210.
[h] confirmation by ELISA; centromer.
[i] overlaps ith PBC.
[j] *Escherica coli* infection induces AMA, often unspecifically present [89].
[k] serologimarker for PBC: anti-mitochondrial type 2, confirmation marker.
[l] AIH-type: confirmation by blot, IIF on VSM47 cell line; when acute hepatitis E: often unspecifically present (90).
[m] AIH-type: confirmation by ELISA; blot on cytochrom p450 2 D6, possible also with HCV infection CAVE: diagnostic error.
[n] AIH-1 type 1: serologic marker for AIH-1 (earlier for AIH-3): only ELISA, blot available.
[o] AIH-type 2: in IIF overlap by LKM also isolated; confirm with ELISA.

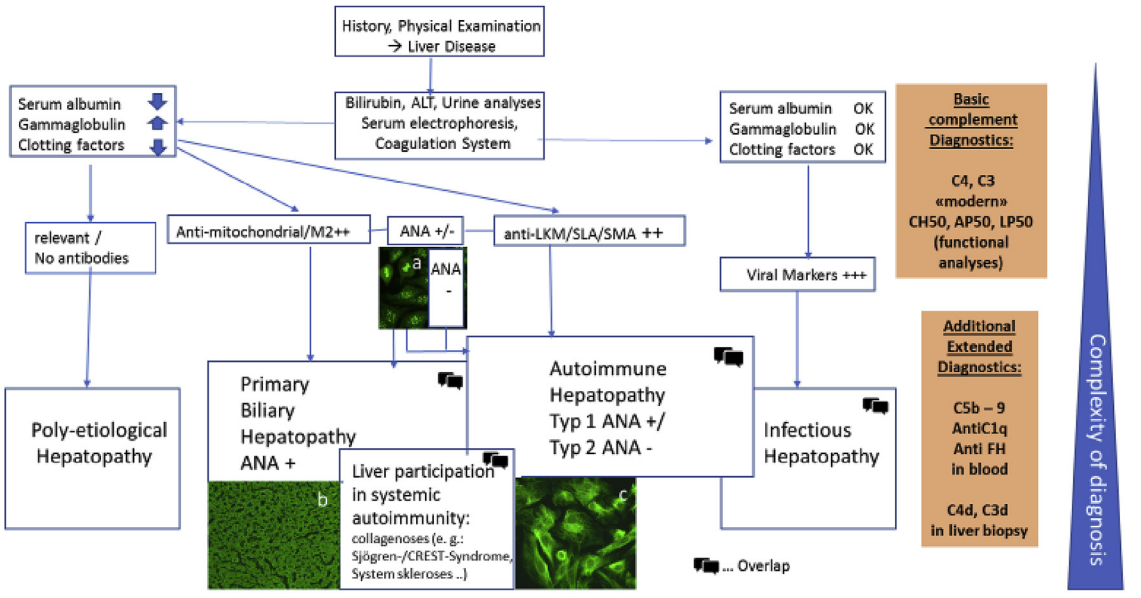

Fig. 3. Standard algorythm to diagnose autoimmune liver diseases The complement system remains unadressed but might promise future refinment of immunopathological damage. (a) ANA centromere (AC-3), (b) liver mitochondria, (c) VSM47 rat cell line (confirmatory assay for anti-actin). Overlap symbols denote squares with limited delineation to other findings.

Table 4
Stepwise lab assays for confirmation of hepatitis B and C infection.

Virus	Lab Test	Extended I	Extended II
Hepatitis B	HBs-Antigen, anti-HBs, anti-HBc (HBe-antigen, anti HBe)	Quantitative PCR, (and genotype), Look for Hepatitis D	C5a[a] [95] HBsAg-anti-HBsAg complexes [96]
Hepatitis C	Anti-HCV, HCV antigen, HCV-PCR Immunoblot	Quantitative PCR (and genotype)	Cryoglobulins, circulating immune complexes [97]

[a] Please note, that in current practice complement analysis is mostly absent.

[95] and reduced C4 and C3 serum levels were observed recently in a clinical study involving over 150 patients suffering from chronic hepatitis B [98]. A further potentially useful, but still to be evaluated assay would be a TCC ELISA.

In the framework of a Swiss-Polish research project scrutinizing epidemiology and infectious pathways in the two countries we have extensively reviewed the ways Hepatitis C (HCV), an RNA virus, is transmitted [99]. The undiagnosed fraction is higher in Switzerland than in Poland, 49% versus 10% which reflects different transmission routes: medical procedures in Poland and drug abuse in Switzerland. The epidemiology of immunodeficiency in Poland lets assume that primary immunodeficiency is more frequent in this country [100]. The prevalence in Switzerland of HCV positivity is 1/1000 inhabitants, of whose 80% are asymptomatic. The interaction with complement occurs in an indirect manner: Cryoglobulinemia, a systemic condition which involves prolonged and excess circulation of soluble immune complexes, is associated with binding of complement components to the complexes. The complexes are then trapped in the liver and induce inflammation [19]. Hepatitis C virus can now be eliminated within a few months – the interferon era has come to a conclusion. Up to this writing, 15.000 patients have been successfullly treated using sofosbuvir, which was introduced in 2014, in combination with adjuvant drugs. Sofosbuvir induces chain fragmentation in the HCV-RNA, thus inactivating the virus. The Swiss Guidelines (SALS 11.2017) are linked to an HCV App Advisor which directs doctors in a constructive direction. The drug interactions potentially causing drug-induced liver damage can be monitored (www.hep-druginteractions.org) and likely do not cause complement activation, but this has yet to be confirmed.

The hepatitis E virus (HEV), after infecting victims through the fecooral route, preferentially persist in immunosuppressed patients, which may lead to chronic hepatitis and accelerated development of cirrhosis [101]. A hepatitis E virus peptide (HEV-p179) represents a conformation-dependent neutralization epitope and the p179-C3d fusion protein enhances antibody responses to HEV [102]. Of 6774 patients hospitalized at the Military Medical Academy Hospital in Sofia, Bulgaria, 2.5% suffered from acute HEV infection [103]. These cases were judged as sporadic autochthonous. It became suspicious that HEV infection, followed by acute hepatitis would mimic AIH. Additional evidence, that 'mimic' could mean 'induce' comes from a recent study on acutely HEV infected patients, who developed anti-nuclear, anti-smooth muscle and/or anti-neutrophil cytoplasmic antibodies (ANCA) [90].

The sexually transmitted Herpes simplex virus 2 (HSV-2) is usually found coated with complement proteins, also in genital fluids. In this instance, complement activation enhances viral attack potential, since complement opsonization of HSV-2 favours infection of dendritic cells, unless opsonization with HSV-2 specific antibodies more or less abolishes HSV-2 infection of dendritic cells [104].

Cytomegalovirus (CMV) may be seen as the prototype of asymptomatic hepatitis virus attack as half of the central European population expresses anti-CMV in their serum, first hand proof of former CMV infection, but most often symptomless. However, first, CMV evades complement as seen in the mouse model, where mouse CMV up-regulates gene expression of complement inhibitors [105], second, even an inapparent infection drives the immune system into immunosenescence [106], and third, CMV is definitely one of the most feared virus infections in transplantation [107].

As for CMV, the majority of the population of first and second world, are also showing anti-EBV antibodies in their serum. As for CMV, however, this is not harmless at all, at least for immunocompromised subjects. This is easily understood when EBV is considered a very deadly virus with the present human race as survivors of a natural selection hundreds of thousands years ago. Immunodeficiency, however, would make all the evolutionary adjustments meaningless and even for immunocompetent subjects the liver is damaged through an infection [108].

Target of immunity is EBV glycoprotein 350/220 (gp350) that

mediates attachment of B cells through complement receptor 2 (CR2/CD21). The elevation of liver enzymes after an attack of febrile, also called Pfeiffer's, disease quite often persists for weeks and months and some authors link this virus with an elevated risk to develop liver disease later in life [109].

Many tropical viruses, both of DNA and RNA types, affect the liver as a priority organ, comprising Yellow fever, Dengue or haemorrhagic fever viruses. Viruses have developed strategies to evade attack by complement or to use complement for invasion of host cells [110,111].

Yellow fever virus can be specifically lysed by complement [112] and causes severe hepatitis [113]. The incidence has recently regressed due to the availability of vaccines. In contrast, Dengue is on the rise. That infection regularly affects the liver. Starting from asymptomatic elevated transaminase levels to acute liver failure, dengue has all the properties of a hepatic illness. In Dengue virus (DENV) infected cells, FH protein is induced by DENV both extra-& intracellularly, but the overall imbalance of the complement system involves an increased C3 deposition on DENV and a hyperreactive alternative pathway of complement, due to increased levels of the acute phase complement protein FB [114].

Ebola virus has been studied in animal models [115] to induce antibodies specific for a plasmid encoding the surface glycoprotein (GP) of the Zaire strain. This enhanced infectivity with model viruses. This phenomenon was downregulated by heat-inactivation of added serum and restored by complement system inhibitors, suggesting that heat-labile factors other than the complement system are also required [116]. Some authors foreshadow that complement-activating anti-EBOV antibodies actually might opsonize the virus, so that it infects target cells more easily [117], whereas the vast majority of antibodies neutralizes the virus.

Marburg virus is also pantropic, but favours the liver. Mannose-binding lectin (MBL), the serum lectin that mediates innate immune functions including activation of the lectin complement pathway, binds to carbohydrates expressed on some viral glycoproteins. Virus pseudotyped with Ebola or Marburg glycoprotein was neutralized by complement, while the Marburg glycoprotein-pseudotyped virus (Ravn strain) was less sensitive to neutralization [118].

3.3. Non-viral infectious hepatitis

For most patients suffering from bacterial, fungal or parasitic infections, the liver takes the position of providing immune defense, producing complement components, many of them in the framework of acute phase response, CRP included. However, quite a number of them attack the liver, making it an important target, complicating the infection.

4. Autoimmune liver diseases and HELLP syndrome

When serum transaminase activity and gamma globulin levels are elevated a suspected diagnosis of AIH will require confirmation with autoantibody diagnostics. Laboratory diagnosis of AIH is largely based on detection of autoantibodies on cell lines (e.g. Hep2-cells) and tissue (e.g. liver, kidney, microsomes) using indirect immunofluorescence assay (IIFA) (see also chapter 3) national and international expert groups issue recommendations for ANA testing and European autoimmunity standardisation initiative representing 15 European countries the IUIS, WHO and CDC supervise autoantibody standardising committees [119]. In addition, consensus is sought on antinuclear antibody patterns, the Hep-2 cells serving reference for a definite nomenclature [120,121]. AIH joins general mechanisms of systemic autoimmune diseases such as SLE or organ specific autoimmune diseases such as thyroiditis. Involvement of the complement system in these diseases is in pursuit of wisdom by animal lab experiments and clinical observations. Since the therapeutic approach of many autoimmune diseases share common protocols one would, at a first sight, not be worried and prescribe to these patients similar therapeutic protocols on the immunosuppressive track: steroids, immunosuppressants, IVIG, plasmapheresis or extracorporeal immunoabsorption. Monoclonal antibody therapy, such as with rituximab would also be considered. As yet, the etiology of AIH may substantially differ from other organs in that the autoinfectome or the Shoenfeld ASIA induction of autoimmune disease [122] might be at work in some patients. With autoinfectome, Dimitrios Petrou Bogdanos has coined the term to reflect the search of infections causing autoimmunity [123]. Some patients with AIH are documented to have passed prior to outbreak a viral infection and the complement system adds up to maintenance of chronic autoimmune inflammation [12].

Separation of autoimmune hepatitis into subgroups might pave the way to more closely see pathogenic processes at work [124]. Gatselis et al., 2015 propose that AIH-1 patients more often present with ANA and/or ASMA and SLA/LP antibodies whereas AIH-2 is more often associeated with LKM-1-specificity. C3 and immunoglobulin A levels were lower in AIH-2 when over 800 children and adolescents with autoimmune hepatitis were reviewed in a Brazilian multicentric survey. Selective removal of pathogenic, complement-activating autoantibodies has been proposed and original procedures are in progress, for the time being confined to laboratory animals [125]. As a matter of fact, our local client doctors rarely ask autoantibody spectrum in combination with complement analytics. Both Th17 cells and the intestinal microbiome have been implicated in AIH. Patients have elevated serum IL-17, an altered microbiota, and increased bacterial translocation. The advances in therapeutics focused on the complement system have been achieved with other diseases than those attacking the liver [10].

In advanced cirrhosis, levels of lectin-complement pathway components in ascitic fluid and blood are lower, which confers low C4 and C3 in serum and ficolin-1 with C3 in ascitic fluid positive predictive values for all-cause mortality independently of liver function especially when cirrhosis is complicated by ascites [126]. When patients suffer from Hemolytic Uremic Syndrome, the gut-liver axis needs to fight against pathogenic microbes; anti-FH autoantibodies have recently been described in this context [127] and patients with dermatomyositis may form circulating immmune complexes with FH as the antigen portion.

The first medical treatment for this incurable disease was ursodeoxycholic acid, approved in 1997 after it was found to delay the progression of liver disease and improve transplantation –free survival [128]. Among the proteins found in the bile fluid, a few belong to the complement system as found be proteomic analyses [129].

Proteomic approaches involving bioinformatics aim to track down evidence for complement tissue-damaging complement activation [21,123]. Antigen enrichment technology was recently applied to capture autoantigens of human intrahepatic biliary epithelial cells (HiBECs) that are recognized by autoantibodies from the sera of PBC patients.

Autoantigen proteins were identified from PBC patient serum. Among them, those analysed by Gene Ontology protein annotations (biological processes, cellular components, and molecular functions) and the Kyoto Encyclopedia of Genes and Genomes pathways were related to mitochondria highly enriched in AMA (antimitochondrial antibody)-positive PBC patients. In this study emanating from the Chinese Academy of Medical Sciences, autoantigens of AMA-negative PBC patients were involved in B-cell activation, NLRP3 inflammasome involvement [130] recognition of phagocytosis, and complement activation [95,131]. These data once again make that anti-M2 assays are important in differentiating AIH from PBC (Table 3). Primary sclerosing cholangitis (PSC), more particularly IgG4-associated cholangitis (IAC) is now well acknowledged to list in the larger group of IgG4 associated autoimmune diseases. The IgG4-associated variety is clearly distinguished from the classical PBC. Because IgG4 does poorly activate complement, it has been proposed that it acts as a blocking agent for binding of the more pathogenic IgG1-3 subclass autoantibodies [132]. The multi-focal bile duct strictures of PSC are rare but stand for an informative experiment of nature; there may be overlaps with coexisting AIH. Seen from the diagnostic laboratory, in absence of conducive markers, some clinicians took care of patients with perinuclear ANCA or x-ANCA, the latter ones reactive with neutrophil

antigens other than myeloperoxidase/proteinases 3. Recent insights into ANCA-associated vasculitis ascribe complement activation a definite role in disease progression.

HELLP (H for hemolysis, EL for elevated liver function tests, and LP for low platelet counts) occurs in approximately 0.5% of pregnancies but reaching up to 10% in those complicated by preeclampsia [133]. We are not yet as far as to be able to make a link between elevated liver enzymes and the participation of complement components in HELLP – however, the successful injection of monoclonal antibodies against C5 (Eculizumab®) into patients with preeclampsia/HELLP (134) for whom complement activation might be a threat [135] rises our degree of attention to include the liver (EL) into the functioning of the complement system.

5. Therapeutic options available to manage complement-induced immunopathology

Complement components produced by the diseased liver, has not seen an uprise in therapeutic options targeting complement such as we have seen it with hematological, ophtalmological, infectious and dermatological diseases. Synthesis by itself cannot be sparked by any means unless by such long known and prescribed nutritional enrichments providing protein synthesis with amino acids. If attacked from the outside by viruses and or by complement-activating immune complexes, virucidal therapy and immune complex/cryoglobulin suppression is adviced using plasma exchange, IVIG therapy based on shifting the antigenantibody ratio in the complexes by anti-idiotypic antibodies contained in IVIG [136]. Impressively, antibody therapeutics not only have spurred the worldwide demand for IVIG [137] preparations but also continue to expand the spectrum of therapeutic monoclonal antibodies (mAbs), of which liver directed therapeutic agents may become an option. The liver may be a target for unwanted effects of mAb therapy with daclizumab used for multiple sclerosis therapy (anti-IL2R, CD25) as prominent example [138]. An update is available on the 'Antibodies to watch' article series in the Mabs Journal. Antibody-drug conjugates and mAb pharmacokinetics continue to improve but definition of complement-activation by Mabs remains a stepchild of companies developing them. The complement system in liver diseases [139] might be involved in a variety of liver disorders indeed. The quest to apply complement therapeutics to hemolytic uremic syndrome or targeting C3b with the compstatin family of C3 inhibitors [13] must be underscored with a better knowledge of what happens with complement-induced damage to the liver [29]. Targeted approaches in AIH go as deep as to modulate intracellular cleavage of C3 and to allow enhancement of tonic metabolic stimulation [140] may become a topic for developing efficacious pharmaceutical agents. The interest in monoclonal antibodies to restore immune systems balance in autoimmune and malignant disease is maintained and drug agencies acknowledge several preparations per year for market access. The clinical efficacy of many a preparation depends on the preparations' capacity to activate complement. Since the first demonstration, backed by immunohistochemical stainings on mouse liver sections to find that the therapeutic activity of Rituximab (anti-CD20) depends on its complement activating capacity, a number of mAbs have been assessed for this property [141].

A focus on modern therapeutic options in liver diseases potentially associated to complement intervention is provided in Table 5. One cannot help to admit that complement therapeutics sidesteps to a large degree the options to remedy liver disease; the present text attempting to reawaken interest into this topic [10].

Liver transplantation has been inspired by kidney transplantation and *vice versa*. The ABO, HLA and other systems identity/compatibility restraints [150] have been broken up since preconditioning of organ recipients with immunmodulatory treatments, plasmaexchange and IVIG conditioning have been introduced. An immunopathological role of complement came to light when organ recipients were regularly followed for signs and symptoms of rejection and graft versus host complications [151]. Ischemia/reperfusion injury in transplants is, at least in part, complement mediated and measures to silence complement activation are under study [152] and could be dampened and are scrutinized to make xenotransplantation possible. The role of complement activation in liver transplantation has been recently updated [153]. Upon liver transplantation, histological detection of C4d-deposits in biopsy samples is announcing mild rejection and forms part of staging as is applied since longer time in kidney transplant rejection [154,155]. In liver regeneration there is now strong evidence that complement, more particularly C1 esterase inhibitor, may favour reconstitutive cell growth [156] in the allotransplant.

For the time being data are sparse when it comes to perceive the involvement of the complement system in immunosenescence. Gene pathways up-regulated by age include complement genes [157]. The risk to develop non-alcoholic fatty liver disease (NAFLD) in old age hikes apparently driven by cellular senescence of hepatocytes [158] as observed in a study with hepatocytes isolated from livers of wild-type mice. An irreversible cell-cycle arrest was associated to secretion of proinflammatory cytokines (notably IL-6) and mitochondrial dysfunction, the latter impinging on both, on aging and obesity-related pathology, especially insulin resistance. Indeed, C4 levels have recently been described to correlate with body mass index and decreased C4 long gene copy number was speculated to be linked to prolonged life span [159] (to be confirmed). Such metabolic processes seem of importance none the least to the pharmaceutical science creating geroprotectors. Senescent cells increase their secretion of a broad repertoire of proinflammatory factors, collectively known as the senescence-associated secretory

Table 5
Selection of liver diseases therapeutic options with emphasis on putative complement systems activation.

Diseases	Standard therapy	Biologicals	Influence of Complement components	References
Alcoholic fatty liver disease	- abstinence	Topiramate (Topomax®) Antabus (Disulfiram®)	+	[142] [143,144]
Non alcoholic fatty liver disease, Non-alcoholic steatotic hepatitis	Medication for Hyperlipidämie/Hyperglykämie Extended: Thiazolidindione/Vitamin E	Anti-TNF therapy Etezimibe (Zetia®) Alisporivir	+	www.drugs.com
Viral hepatitis	Direct-acting antiviral drugs (DAAs)/virostatics Entecavir, Tenofovir, Sofosbuvir	Pegylated-interferon Ribavirin	++	[145] [146]
Non-viral infections	Antibiotics, sulfonamides		+	[147]
AIH	prednisone, IVIG, azathioprine (Azasan, Imuran) plasmapheresis, extracorpoeal immunoabsorption	(anti-CD20) Rituximab	+++	[148] [149]
HELLP	Steroids, plasma exchange	Eculizumab (Soliris®)	++	[134]

phenotype which can induce tissue dysfunction [160,161] driver of age-dependent hepatic steatosis. Inflammaging is driven by proinflammatory cytokines with the complement system at stake [162,163]. Thus, retinal pigment epithelium can modulate expression of complement activation in macrophages – supposedly liver metabolic zonation units (see 1.1) might do the same [162].

Medicine, a profession of lifelong learning now provides evidence for the involvement of the multifaceted complement system, synthesized in a large part by the liver, in diseases of this very same production site. The more we will learn on its immunopathological role complement plays, complosome included, in liver diseases, the more complement therapeutics will take up momentum in helping liver patients.

Contributions

Thomas Lung, Giuseppe Colucci and Urs Nydegger did the medical writing to which.

Reinhard Würzner contributed text & references about involvement of complement in liver physiology and viral diseases; Benjamin Sakem draw the figures and Andreas Cerny with Lorenz Risch provided the auspices of liver pathology and clinical chemistry.

Conflict of interest

All authors have no conflict of interest to declare.

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