The liver in sepsis: patterns of response and injury

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Purpose of review
Sepsis elicits profound changes in the concentrations of plasma proteins synthesized by liver parenchymal cells referred to as acute-phase proteins. Mechanisms controlling this orchestrated response include release of cytokines that induce acute-phase proteins, while other ‘house-keeping’ genes are downregulated.

Recent findings
Although some acute-phase proteins help to control damage, functions of many other acute-phase reactants remain obscure. Changes in acute-phase gene expression are primarily subject to transcriptional regulation and can be comprehensively monitored by array techniques. Emerging evidence from such strategies implies that in addition to a ‘common host response’ also highly specific pathways are induced in specific disease contexts. Applying a systems biology approach to the integrated response of the hepatocyte to infection would suggest that the reprogramming of metabolic functions occurs in parallel with a severity-dependent disruption of phase I and II biotransformation and canalicular transport, that is, excretory failure. Although traditionally bilirubin serves to monitor excretion, emerging evidence suggests that bile acids indicate liver dysfunction with higher sensitivity and specificity.

Summary
Sepsis induces reprogramming of the hepatic transcriptome. This includes induction of adaptive acute-phase proteins but also repression of phase I, II metabolism and transport with important implications for monitoring and pharmacotherapy.

Keywords
acute phase, biotransformation, cholestasis, stress response, transcriptomics

INTRODUCTION
Liver dysfunction and jaundice are redoubtable manifestations of critical illness. Extrahepatic bacterial infection and sepsis account for approximately 20% of jaundice cases only surpassed by malignant compression of the bile duct as cause [1]. As the liver plays a pivotal role in metabolic and immunological homeostasis, alterations in its function can acutely promote – in an ill-defined manner – progression of multiple organ failure. In a large Austrian multicentric cohort, early increase of plasma bilirubin (>2 mg/dl), noted in approximately 10% of critically ill intensive care patients of whom many were septic, was a strong independent risk factor for subsequent mortality [2], a pattern that has been confirmed in the year reviewed [3]. Furthermore, prolonged hepatic dysfunction impairs neutrophil phagocytic activity, burst, and killing but also the interplay with the adaptive immune system [4]. Thus, preexisting liver disease is a risk factor for the progression of bacterial infections to sepsis, for example, in community-acquired pneumonia with increased odds ratios for hospitalization, ICU admission, and death [5]. Vice versa, development of jaundice as a manifestation of sepsis was only observed with the widespread establishment of ICUs in the 1960s related at least in part to prototypical therapeutic ICU interventions, such as multiple transfusions, parenteral nutrition, and potentially hepatotoxic medications [6]. As a consequence, patients with septic complications in the presence of chronic liver disease, most notably cirrhosis, have a poor prognosis.

PATTERNS OF RESPONSE TO INFECTION: ACUTE PHASE AND BEYOND
Sepsis elicits profound changes in the plasma proteome. Many of the proteins affected are
predominantly synthesized in liver parenchymal cells and named acute-phase proteins. This response reflects a highly regulated process as part of a more generalized reprogramming of signaling events across the body primarily under the influence of cytokines released in response to pathogen-associated molecular patterns. These mediators, for example, interleukin-6 (IL-6), affect subsets of acute-phase genes and can either synergistically enhance or inhibit their respective effects acting on a transcriptional and, to a lesser extent, post-transcriptional level. These signaling events may result in an upregulation (as in the case of C-reactive protein) or downregulation of proteins (as in the case of albumin). Although some acute-phase proteins have been shown to control damage and to participate in tissue repair, the role of many acute-phase reactants remains speculative. In the clinical setting, measurements of acute-phase proteins are primarily of diagnostic or prognostic value. From a pathophysiological point of view, understanding of this highly conserved adaptive mechanism might help to unravel novel therapeutic avenues. The shift in gene expression patterns due to sepsis is reflected in a large group of proteins that are conserved across pathogens and sites of infection, but there are in addition specific response patterns. Within the year of review, several promising candidates have been unraveled, for instance, induction of S-nitrosated alpha-1-acid glycoprotein [7] as well as angiotensin-2 [8] was shown to confer protection in true microbial sepsis, even against multidrug-resistant bacteria. Furthermore, augmenter of liver regeneration (ALR) protein, an important factor to promote liver regeneration, maintains hepatocellular viability and having an important role in parenchymal/nonparenchymal cross-talk is inducible both by endotoxin and microbial sepsis [9]. Vice versa, a lack of hepatic c-Met and gp130 are associated with a substantially attenuated acute-phase response, which is paralleled by impaired innate immunity and antibacterial defense during cholestatic conditions [10].

The primarily transcriptional control and the complex regulatory interplay of various mediators render gene expression profiling techniques, such as microarray and next generation sequencing, promising candidates to describe patterns of response to sepsis and infection.

‘OMICS-TECHNOLOGIES’ AND APPROACHES OF SYSTEMS BIOLOGY

Modern ‘highly parallel’ techniques allow assessing thousands of biomolecules simultaneously and can describe the genome, transcriptome, proteome, or metabolome of cells or tissues in an integrative manner. Since the pioneering work of Cobb et al. in 2002 [11], several groups have applied these ‘omics’-techniques to assess the response of the liver in the context of complex diseases and syndromes, including systemic inflammatory response syndrome (SIRS) and sepsis. This approach might be extended beyond protein-coding transcripts to identify regulatory micro-RNAs and long noncoding RNAs [12]. Within the year of review, differences in the response to surgery per se (SIRS) and sepsis were monitored by array and identified significant differences regarding kinetics/resolution of the response as well as regarding specific effector functions [13]. Applying a similar transcriptomic and metabolomic approach across tissues, hepatic induction of cholesterol biosynthesis was identified as a remote, pathogen-specific adaptive response to pneumococcal disease [14].

These strategies can also be applied to assess gene expression patterns as they relate to outcome. A model developed by Rudiger et al. [15] predicting mortality that occurred between day 2 and 3 in septic peritonitis as early as 6h after infection, was applied to study associated changes in the liver. With regard to the physiological regulation of hepatobiliary transport and bile secretion, phosphatidylinositol-3-kinase (PI3K) is essential for intracellular trafficking and has been shown to selectively regulate ATP-dependent canalicular transporters in health and disease. A failure of hepatobiliary transport processes was observed in animals predicted to die due to septic peritonitis and resulted in hepatocellular retention of bile acids, bilirubin, and xenobiotics. PI3K signaling that had received considerable attention in the context of bile acid-mediated apoptosis was also observed to affect hepatic phase I and II metabolism of bile acids. Moreover, altered handling of bile acids was observed to perform superiorly as a biomarker compared to the clinical standard, bilirubin [16] (Fig. 1).
MECHANISMS AND MANIFESTATION OF HEPATIC PARENCHYMAL INJURY

Of the varied liver partial functions, the hepatobiliary excretory machinery appears exceptionally sensitive to inflammation [17]. Pathogen-associated molecular patterns (PAMPs) including lipopolysaccharides (LPSs, endotoxin) of Gram-negative bacteria trigger Toll-like receptor (TLR)-dependent release of cytokines and other inflammatory mediators by Kupffer and other primarily nonparenchymal cells. Interest continues in the role of nitric oxide as perpetuator of injury in particular in the presence of oxidative stress with the potential formation of reactive oxygen and nitrogen species, including peroxynitrite [18]. This well described mechanism of hepatic inflammatory injury seems to be subject to alterations depending on the hormonal milieu [19] and contributes to the sexual dimorphism characterized by a higher susceptibility of male individuals for and protection against sepsis-associated liver injury by female hormones [20,21]. Interestingly, a novel protective role for non-myeloid cell MyD88 has been reported in septic peritonitis, whereas myeloid MyD88 had the expected pro-inflammatory effect [22].

Gaseous mediators of cellular function beyond nitric oxide may include not only carbon monoxide and hydrogen sulphide but also molecular hydrogen at low concentrations presumably preventing oxidative stress. Inhalation of H₂ allowed to safely apply hyperoxia (a therapeutic option that is hampered by its toxic side-effects), thereby increasing survival in the cecal ligation and puncture model substantially [23]. Interest continues in assessing the role of gaseous mediators of microcirculatory and mitochondrial dysfunction in sepsis-associated liver injury. Unlike in models of ischemia and reperfusion, H₂S seems to contribute to liver injury in sepsis acting in part via its vasoactive properties that differentially affect sinusoidal and extrasinusoidal vessels [24].

Influx of polymorphonuclear neutrophils (PMNs) represents a prominent feature of sepsis-associated tissue injury, potentially perpetuating hepatic excretory dysfunction [25,26]. These factors impair the downstream expression and functional integrity of hepatocellular transport proteins, most notably the energy-dependent canalicular ATP-binding cassette (ABC) transporters required for normal bile secretion [27] underlying sepsis-associated cholestasis [28]. Interest continues in the role of preexisting liver disease, such as bile duct obstruction or alcoholic liver disease, in the development of hepatic dysfunction [29,30]. Many of these concepts have been derived based on the use of endotoxin-induced systemic inflammation or even shock

FIGURE 1. Liver failure and potential underlying signaling events in sepsis. Overexpressed PI3Kgamma is associated with downregulation of cytochromes and other enzymes involved in biotransformation. As a consequence, xenobiotics may accumulate in hepatocytes, which results in increased hepatotoxicity in sepsis. Further, PI3Kgamma-related signaling also causes internalization of the basolateral actin-rich brush borders, wherein the proteins of the excretory apparatus (e.g., Mrp2) are located. Indeed, the morphology as well as the physiology may be recovered by the inhibition of PI3Kgamma. To put it in a nutshell, PI3Kgamma serves as a molecular switch for liver failure in sepsis and is a potential target structure for novel therapy for liver dysfunction (xenobiotics, PI3Kgamma, enzymes involved in biotransformation).
associated with high doses of endotoxin by far exceeding those amounts observed in liver disease or sepsis. Recent evidence would suggest that amounts of endotoxin that induce significant cholestasis also induce injury/demise of hepatocytes (reflected in increases in transaminases) and of bile duct epithelia (reflected by increased alkaline phosphatase and gamma-glutamyl-transferase). In contrast, cholestasis is even more pronounced in polymicrobial sepsis in the absence of significant amounts of cytokines, oxidative stress, and ensuing conventional liver cell injury [31] casting doubt on the suitability of endotoxin models to unravel pathogenesis of sepsis-induced cholestasis. Similarly, an adaptive role for influx of PMNs unravels pathogenesis of sepsis-induced cholestasis. Hence, postacute phase of sepsis in which patients often receive a multitude of different drugs daily. A study by Vanwijngaarden et al. [36] that appeared in the year of review would indicate that hyperbilirubinemia in these patients indeed reflects cholestasis as it is associated with a disrupted expression pattern of the export machinery and a concomitant increase in serum bile acid levels.

CONCLUSION
Severe infections elicit profound changes in the concentrations of plasma proteins synthesized by liver parenchymal cells and referred to as acute-phase proteins. Underlying mechanisms controlling this orchestrated response include the remote or paracrine release of mediators, such as IL-6, that in turn affect subsets of acute-phase genes. Although some of these proteins have been shown to minimize tissue damage or to participate in hemostasis and repair, functions of many other acute-phase reactants remain obscure. Changes in acute-phase protein gene expression are primarily subject to transcriptional regulation and can be comprehensively monitored by array or sequencing techniques. Emerging evidence from such strategies implies that in addition to a ‘common host response’ also highly specific pathways are induced in specific disease contexts. Applying a systems biology approach to the integrated response of the hepatocyte to infection and tissue injury would suggest that the reprogramming of metabolic functions occurs in parallel with a severity-dependent disruption of phase I and II biotransformation and canalicular transport, that is, excretory failure. Progress has been made during the year of review regarding understanding of potential mechanisms of liver dysfunction in the critically ill septic host. The role of neutrophils as perpetrators of injury must be revisited and extended by a potential beneficial role as a contributor to bacterial clearance. Similarly, there is emerging evidence that models of endotoxemia are not exactly modeling the mechanism of injury of sepsis-induced liver dysfunction. Although traditionally bilirubin has been used to monitor the excretory system, it is becoming increasingly clear that this diagnostic approach underestimates the problem and ignores the pathophysiologically important bile acids that indicate liver dysfunction with higher sensitivity and specificity. Thus, liver dysfunction with impaired phase I, II metabolism and transport reflects an early and poor prognostic event in the critically ill with important implications for monitoring and pharmacotherapy in the ICU.

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Conflicts of interest
The authors have no conflicts of interest to declare.
REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■ of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 164).

A prospective clinical trial that characterizes the function of circulating neutrophils in septic patients with acute and subacute liver failure.
S-nitrosation of a prototypical hepatic stress protein, alpha-1-acid glycoprotein variant A (SNO-AGPvA), and formation of SNO-AGPvA may serve to inhibit growth of multidrug-resistant bacteria. This was also confirmed in a mouse sepsis model.
In this study, ALR protein is pointed out to be a potential marker for hepatocellular stress and/or acute inflammatory conditions. ALR levels and mRNA expression of tumor necrosis factor and IL-6 are elevated in early inflammatory, induced in a LPS model, Gram-negative sepsis model, or due to surgery. The increase in ALR level preceded the loss of cell viability and/or inhibition of DNA synthesis.
Interesting insights into the cooperative role of HGF/c-Met and IL-6/gp130 pathways during the onset of cholestatic liver injury in sepsis by regulating antibacterial, immune response, and control of acute-phase response.
miRNAs were found to be novel regulators of the innate immune response to LPS by investigating the role of the transcription factor E2F1, involved in the regulation of inflammatory response to TLR ligands.
A nice systems biology approach providing insights into the unique dynamics of transcriptional changes following the induction of the inflammatory response to surgery and infection.

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