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The liver is a metabolic and immunologic organ: a reconsideration of metabolic decompensation due to infection in inborn errors of metabolism (IEM)

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Abstract

Metabolic decompensation in inborn errors of metabolism (IEM) is characterized by a rapid deterioration in metabolic status leading to life-threatening biochemical perturbations (e.g. hypoglycemia, hyperammonemia, acidosis, organ failure). Infection is the major cause of metabolic decompensation in patients with IEM. We hypothesized that activation of the immune system during infection leads to further perturbations in end-organ metabolism resulting in increased morbidity. To address this, we established model systems of metabolic decompensation due to infection. Using these systems, we have described the pathologic mechanisms of metabolic decompensation as well as changes in hepatic metabolic reserve associated with infection. First and foremost, our studies have demonstrated that the liver experiences a significant local innate immune response during influenza infection that modulates hepatic metabolism. Based on these findings, we are the first to suggest that the role of the liver as a metabolic and immunologic organ is central in the pathophysiology of metabolic decompensation due to infection in IEM. The dual function of the liver as a major metabolic regulator and a lymphoid organ responsible for immunosurveillance places this organ at risk for hepatotoxicity. Mobilization of hepatic reserve and the regenerative capacity of a healthy liver compensates for this calculated risk. However, activation of the hepatic innate immune system may be deleterious in IEM. Based on this assertion, strategies aimed at modulating the innate immune response may be a viable target for intervention in the treatment of hepatic metabolic decompensation.

1. Introduction

Ongoing care for patients with inborn errors of metabolism (IEM) requires judicious monitoring of growth and developmental parameters, as well as nutritional and biochemical status [1–3]. Despite strict adherence to practice standards, patients with IEM may still experience periodic episodes of metabolic decompensation [4–6]. Although no formal definition exists, metabolic decompensation is part of the IEM lexicon and is appreciated

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clinically as a functional deterioration in patients with a tenuous biochemical equilibrium at baseline due to an inherited deficiency in intermediary metabolism. Subpopulations of IEM patients are recognized as being more metabolically fragile, i.e. more prone to metabolic decompensation, and include the organic acidemias, amino acid disorders, urea cycle disorders, fatty acid oxidation disorders and mitochondrial disorders [7]. In general, metabolic decompensation is potentially life threatening, displays high rates of morbidity, and can result in long-term sequelae [4, 8–10].

Despite multiple etiologies, intercurrent infection is recognized as the leading cause of metabolic decompensation in patients with IEM. In a cohort of patients with methylmalonic and propionic acidemia, intercurrent infection preceded metabolic decompensation in 29% and 44% of unscheduled clinic visits respectively [11, 12]. Intercurrent infection is also the most common precipitant of acute hyperammonemia in urea cycle disorders, accounting for >34% of episodes, and is associated with increased morbidity versus other precipitants [13, 14]. Although formal data on metabolic decompensation in other IEM are difficult to find in the medical literature, the role of infection in precipitating metabolic decompensation is well appreciated in the IEM community [15].

Regardless of the diverse pathophysiology and biochemistry associated with different IEM, during metabolic decompensation due to infection, one aspect remains equivalent: activation of the immune system. Although the immune system is necessary for clearance of an organ specific viral pathogen (e.g. influenza), the initial response is oftentimes systemic with far-reaching bystander effects in organs via the actions of migrating immune cells, tissue resident immune cells, and soluble mediators.

From personal experience, few things frighten metabolic physicians more than a discussion of the immune system. Hyperbole aside, immunology is a complicated discipline for understanding disease, with its own language, standards and methods of investigation. Metabolism also shares this same level of intricacy and literacy. To complicate matters further, recently there has been a resurgence of the cross-disciplinary field of immunometabolism. Depending on your audience, immunometabolism holds different meanings [16]. In the spirit of this Minireview, immunometabolism refers to the study of metabolism in organs in response to immune activation. It should be noted that pathophysiologic studies on metabolic decompensation in mouse or human IEM systems are generally absent from the medical literature, with the exception of our work. Based on published animal and human models of infection and sepsis, and our own published studies on viral infection and end-organ metabolism, we will explore how the immune system may play a role in metabolic decompensation.

2. Hepatic metabolic decompensation

During metabolic decompensation, disease-specific biochemical perturbations occur and include acidosis (e.g. organic acidemias), hyperammonemia (e.g. UCD), hypoglycemia (e.g. FAOD), bioenergetic failure and end-organ dysfunction (e.g. mitochondrial disease). The liver is a critical organ in many IEM, as evidenced by the amelioration of metabolic abnormalities following liver transplantation [17–20]. Many of the life-threatening

biochemical perturbations seen on clinical testing during metabolic decompensation (i.e. hyperammonemia, acidosis, hypoglycemia) can be traced to impaired intermediary metabolism in the liver, prompting a reconsideration of this biochemical instability as hepatic metabolic decompensation. The liver in various IEM (e.g., organic acidemias, mitochondrial disease, fatty acid oxidation defects, urea cycle disorders) is often vulnerable to toxic insults (e.g. valproic acid induced steatosis and acute liver toxicity) [21]. Whether immune activation in response to infection also results in a toxic insult to the IEM liver causing metabolic decompensation is just beginning to be explored [22, 23].

3. Respiratory viral infections can cause hepatitis

Viral infections, particularly respiratory type, may precipitate and prolong episodes of metabolic decompensation in IEM patients. However, the mechanisms by which this occurs are largely unknown, but may be related to toxic insults perpetuated by the immune system. Indeed, hepatic damage due to respiratory viral infection has been described in healthy individuals. Liver involvement ranging from mild hepatitis to liver failure can occur with influenza, RSV, SARS, and adenovirus [24–30]. Enhanced toxicity may also be associated with certain viral strains. In a study of patients affected by pandemic *H1N1* admitted to the ICU, ~45% had elevations of liver aminotransferases with 16–18% reaching >2X the upper limit of the normal range [29]. The abnormalities in liver biochemistry observed during respiratory viral infection were self-limited and resolved after successful clearance of the virus [31]. Since respiratory viruses are not hepatotropic, immune mechanisms of collateral damage have been proposed [32]. Immune mediated hepatotoxicity may be enacted by the systemic release of immune mediators, however, the cellular makeup of the liver and its unique role as a secondary lymphoid organ also plays a role.

4. The liver is a metabolic and immunologic organ

The role played by the immune system in metabolic decompensation may be related to the multiple physiologic functions assumed by the liver. The microarchitecture of the liver is characterized by small hexagonal lobules oriented around the central vein, which allows this organ to carry out its various metabolic functions. The points of the hexagonal lobules are punctuated by the portal triad, a structure composed of the bile duct, hepatic artery and portal vein. Blood flows from the hepatic artery and portal vein through the sinusoids, which are formed by parallel sheets or cords of hepatocytes and discontinuous/fenestrated endothelia. From the sinusoids, the hepatocytes encounter mixed venous (i.e. digestive tract) and arterial (i.e. periphery) blood and metabolize carbohydrates, amino acids and fat, and detoxify endogenous waste products and xenobiotics. Numerous major metabolic pathways occur in the liver and are relevant to IEM including glycolysis, the tricarboxylic acid cycle, oxidative phosphorylation, fatty acid oxidation, amino acid catabolism and ureagenesis.

In addition to the critical metabolic functions outlined above, the liver also plays a less recognized role in immunosurveillance. Although the spleen is considered a critical mediator in the clearance of blood pathogens, this function overlaps with the liver. With its dual blood supply from the hepatic artery and portal vein, the liver receives 30% of the total blood volume per minute [33], marking it as an ideal organ for immunosurveillance. The

major immunologic role of the liver appreciated by most is the production of acute phase proteins during inflammatory reactions. Often overlooked, the liver also contains a sizable population of immune cells, including T- and B-lymphocytes, Kupffer cells, liver-adapted natural killer (NK) cells, natural killer cells expressing T-cell receptor (NKT cells), stellate cells, and dendritic cells [34]. Within this diverse collection of immune cells, Kupffer cells occupy a central position as the gatekeeper of the hepatic innate immune response and hepatotoxicity.

5. Kupffer cells play a role in systemic and local immune reactions

As the largest organ in the body, the liver contains the greatest population of resident macrophages, Kupffer cells. Kupffer cells account for up to 35% of non-parenchymal cells in the liver and 80–90% of all tissue macrophages in the body [35]. Functionally, Kupffer cells act as scavengers, removing particulate matter from portal circulation via phagocytosis and lysosomal activity, and occupy a niche at the interface with the gut microbiome [36]. In addition to local immune responses, Kupffer cells also play a role in systemic immunity. During systemic infection, blood supply to the liver is increased and hepatic sinusoids dilate, leading to prolonged exposure to blood borne pathogens by Kupffer cells [37]. The importance of Kupffer cells in combating systemic infections is highlighted by depletion studies. Mice treated with liposomal clodronate to deplete Kupffer cells during *L. monocytogenes* and *B. burgdorferi* infections experienced increased lethality [38, 39]. In addition to bacterial infections, Kupffer cells also play a role in viral infections. During influenza infection in mice, Kupffer cell depletion leads to increased lung viral titers (unpublished data).

In addition to playing a role in systemic immunity, Kupffer cells play a role in inflammatory hepatotoxicity. Several well established experimental systems such as concanavalin hepatotoxicity, alcoholic liver disease, acetaminophen hepatotoxicity and non-alcoholic fatty liver disease have all demonstrated the central role of Kupffer cells in these toxin induced conditions [40]. In addition to chemical precipitants, Kupffer cells may also mediate hepatic damage in response to infection. In influenza-associated hepatitis, hepatocytes adjacent to the sinusoids undergo damage and apoptosis due to Kupffer cell activation, a bystander effect [26]. This mechanism likely accounts for the transient hepatitis seen during influenza infection in humans described above [32].

6. Cytokines modulate hepatic metabolism and toxicity

A term related to metabolic decompensation is metabolic reserve. Metabolic reserve may be defined as normal physiologic adaptations to perturbations in homeostasis (e.g. infection) that involves a reprioritization of metabolism due to changes in metabolic flux. These physiologic adaptations represent a response to pathogens as well as endogenous signals. For example, infection with the liver parasite *toxoplasma gondii* leads to a downregulation of proteins involved in OXPHOS, fatty acid and lipid metabolism, and xenobiotic metabolism in mice [41]. Intraperitoneal injection with chlamydia pneumoniae results in dysregulated hepatic cholesterol and triglyceride metabolism in mice [42]. Hepatitis B infection induces upregulation of glutamate dehydrogenase 1 and isocitrate dehydrogenase,

and the transcriptional up-regulation of genes involved in lipid biosynthesis [43, 44]. Changes in metabolic reserve can also be seen with non-hepatic viral infections. Previous work by our group demonstrated a depression of urea cycle enzymes and fatty acid oxidation during influenza infection in wild-type mice in the absence of hepatocyte death [22, 23]. These changes in metabolic reserve were linked to the actions of inflammatory cytokines on hepatocytes, particularly TNF α [23]. By our definition, metabolic decompensation is not just limited to patients with IEM. In addition to mediating changes in metabolic reserve, at its extreme, inflammation can also produce metabolic decompensation and organ dysfunction (i.e. multi-organ dysfunction syndrome, MODS) in individuals not affected by an IEM. This paradigm of metabolic decompensation in non-IEM patients provides a potential framework for understanding the interplay between inflammatory cytokines and metabolism. Significant hepatotoxicity has been noted in many experimental systems and clinical states whose pathology is mediated by cytokines: paraneoplastic phenomena, limb ischemia, sepsis and endotoxemia [45–48]. The hepatic biochemical abnormalities observed during these systemic inflammatory reactions in non-IEM patients are mediated by inflammatory cytokines such IL-1, IL-6 and TNF α [23, 49, 50] and may include hypoglycemia, lactic acidosis and hepatic encephalopathy [51, 52]. In addition to mediating organ dysfunction, cytokines may serve as outcome markers; IL-6, IL-8, IL-10 and TNF- α concentrations are accurate predictors of hepatic dysfunction [53, 54]. Generally, changes in hepatic metabolic reserve or metabolic decompensation involves signals from the immune system with inflammatory cytokines likely playing a major role.

7. Is metabolic decompensation due to infection immune mediated?

The dual function of the liver as a major metabolic regulator and a secondary lymphoid organ responsible for immunosurveillance places this organ at risk for hepatotoxicity. The regenerative capacity of a healthy liver compensates for this calculated risk. Since the immune system plays a role in acute toxicity and modulates hepatic metabolism in a variety of scenarios, we hypothesized that the immune system, via the secretion of local and systemic cytokines, leads to exacerbation of inherited biochemical perturbations and depressed metabolic reserve resulting in metabolic decompensation (Figure 1). As suggested above, metabolic decompensation is not unique to IEM. In healthy livers, low levels of inflammatory cytokines promote changes in metabolic reserve to cope with the challenges to homeostasis brought about by infection [22, 23]. As inflammation increases, organs may progress along a continuum of dysfunction and metabolic decompensation. If unabated, inflammation may progress to cell death and organ failure. In the IEM liver, we hypothesize that the process is similar except that metabolic reserve is limited and the inflammatory threshold for developing metabolic decompensation is much lower due to an inherited deficiency in intermediary metabolism.

To address these fundamental questions regarding metabolic reserve and metabolic decompensation in response to viral infection, we established a model system using mouse adapted PR8 influenza combined with pair-feeding to minimize the effects of differences in food intake [22, 23]. In our model, although the liver is distant from the site of PR8 influenza infection (i.e. lung), profiling of hepatic mRNA transcription suggested activation of the innate immune response [22, 23]. Several innate immune pathways involved in the

anti-viral response were upregulated including pattern recognition receptor signaling (toll like receptors, (TLRs)), viral nucleic acid sensing (RIG-I, MDA5) and interferon signaling (type I interferons) [23, 55]. Influenza is not a hepatotropic virus, suggesting that the hepatic innate immune response may be driven by exogenous or endogenous signals.

Transient viremia can serve as a signal for activating the hepatic innate immune response [56]. In humans, viruses such as rhinovirus, adenovirus, respiratory syncytial virus and enterovirus may be associated with viremia [57–60]. Seasonal influenza can also lead to viremia, particularly early in the infection and before the appearance of clinical symptoms [61]. In addition, viremia associated with more pathogenic strains such as pandemic H1N1 and avian H5N1 is well recognized [62, 63]. During infection, virus enters the blood stream through capillaries in the infected tissue leading to viremia and localization to distant tissues (Figure 2). Non-permissive (i.e. non-replicative) influenza viral infection of the brain and liver have been reported in the mouse supporting this model of transient viremia [64, 65].

In addition to recognition of whole influenza virus by the hepatic innate immune system, pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) may also serve as signals [66]. PAMPs are derived from microorganisms and recognized by innate immune cells bearing pattern recognition receptors. In the case of influenza, viral PAMPs include envelope proteins as well as viral nucleic acids (e.g. ssRNA). Consistent with the recognition of influenza viral nucleic acids, we observed an up regulation of antiviral pattern recognition systems RIG-I and MDA5 [23, 55]. The result is mobilization of an antiviral immune response which involves the secretion of inflammatory cytokines and interferons to combat the virus. In contrast to PAMPs, DAMPs are cell-derived endogenous danger signals that alert the immune system to infection or cell death. Examples of DAMPs include ATP, DNA, uric acid and high-mobility group box-1 protein (HMGB1) which are released from dying or dead cells. These products are then recognized by their respective pattern recognition receptors. For example, HMGB1 stimulates Kupffer cells to produce IL-1 and TNF α via the engagement of toll like receptors 2 and 4 (TLR2, TLR4) [67]. Ultimately, the initiation of the hepatic innate immune response involves the recognition of both exogenous and endogenous signals.

Mice experience a systemic and local hepatic response to PR8 influenza infection [22, 23]. Systemically, plasma inflammatory cytokines such as IFN α , IFN β , IL-1, IL-6 and TNF α are elevated with infection [68]. Locally, Kupffer cells can become activated and release inflammatory cytokines upon hepatocytes, while monocytes and neutrophils infiltrate the liver augmenting the response [23]. Inflammatory cytokines such as IL-1 and TNF α produced systemically and by the Kupffer cells inhibit various aspects of metabolism including fatty acid oxidation (manuscript in preparation and [23]), ureagenesis [22] and respiratory chain metabolism (manuscript in preparation) in WT and IEM models *in vitro* and *in vivo*. Although systemic cytokines play a role in the modulation of hepatic metabolism, Kupffer cells and their cytokines are a critical node for initiating changes in hepatic metabolic reserve as evidenced by our depletion studies. Targeting Kupffer cells with liposomal clodronate can partially ameliorate many of the metabolic changes observed, such as the depression of fatty acid oxidation [23].

Based on our studies and the literature, we propose the following model of hepatic metabolic decompensation due to viral infection (Figure 2). Beginning in the lung, influenza causes a local immune reaction followed by systemic immune activation. Immune signals such as interferons, cytokines, PAMPs (e.g. virus or viral components), and DAMPs are carried in the blood to the liver. In the sinusoids, the immune signal encounters Kupffer cells which become activated, increase in number, and secreting interferons and inflammatory cytokines. These systemic and local “text messages” instruct the hepatocytes to initiate changes in their metabolism (metabolic reserve). In IEM, metabolic decompensation occurs due to the inability of IEM hepatocytes to tolerate or accomplish the required changes in metabolic reserve (Figure 1). As a result, hepatocytes develop the disease specific hallmarks of metabolic decompensation such as the accumulation of toxic metabolic intermediates, decreased production of critical metabolites, proceeding to bioenergetic failure, and even cell death.

8. Conclusions

The liver is ideally positioned at a hemodynamic confluence to carry out the tasks of a metabolic and immunologic organ. Based on our findings, we are the first to suggest that this dual role of the liver is central in the pathophysiology of metabolic decompensation in IEM due to infection. The liver is a critical organ in IEM and is responsible for many of the biochemical perturbations seen during metabolic decompensation. During infection, systemic cytokines and the hepatic innate immune system play a role in precipitating metabolic decompensation. As such, strategies aimed at modulating the immune response may be a viable target for intervention in the treatment of hepatic metabolic decompensation and requires further investigation.

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Highlights

- Metabolic decompensation is an acute deterioration in biochemical status that can be life-threatening or result in long-term or permanent sequelae.
- Infection is the most common cause of metabolic decompensation in inborn errors of metabolism and is associated with increased morbidity.
- The liver is a critical organ in inborn errors of metabolism and many of the biochemical perturbations seen during metabolic decompensation can be traced to the liver.
- The liver is a metabolic and immunologic organ, and co-localization of these two activities places this organ at risk for hepatotoxicity resulting in metabolic decompensation.

Figure 1. Metabolic reserve and metabolic decompensation

In response to increasing inflammation, both IEM and Non-IEM patients may undergo metabolic decompensation. IEM patients have depressed metabolic reserve and a lower inflammatory threshold for metabolic decompensation. See text for details.

Figure 2. The hepatic innate immune response and metabolic decompensation

Signals such as cytokines, virus, PAMPs and DAMPs activate Kupffer cells in the liver. Interferons (e.g. IFNα) and inflammatory cytokines (e.g. IL-1, IL-6, TNFα) produced systemically or locally mediate changes in metabolic reserve and precipitate or exacerbate metabolic decompensation. Kupffer cell depletion studies have highlighted their role as a major node in this immune reaction. See text for details.