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Immunometabolic Pathways in Hepatotoxicity: Cross-Talk Between the Liver and Peripheral Immune Cells

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ABSTRACT

Hepatotoxicity arises from a complex interplay of metabolic dysregulation, immune activation, and inflammatory signaling within the liver and beyond. The liver is not only the primary organ for xenobiotic metabolism but also a central immunological hub that constantly interacts with peripheral immune cells through cytokines, chemokines, metabolites, and damage-associated molecular patterns. Immunometabolism—the integration of metabolic pathways with immune cell function-has emerged as a critical framework for understanding liver injury induced by drugs, toxins, infections, and metabolic stress. Alterations in hepatic metabolism can shape immune cell phenotypes, while immune-derived signals profoundly influence hepatocellular function, mitochondrial activity, and redox balance. This bidirectional cross-talk plays a decisive role in determining whether liver injury resolves or progresses to chronic inflammation, fibrosis, or liver failure. This review synthesizes current knowledge on immunometabolic pathways involved in hepatotoxicity, focusing on the interactions between hepatocytes, Kupffer cells, hepatic stellate cells, and peripheral immune populations such as monocytes, neutrophils, and lymphocytes. Key metabolic regulators, including mitochondrial function, lipid and glucose metabolism, amino acid sensing, and redox signaling, are discussed in the context of immune modulation. Understanding these integrated pathways provides new opportunities for biomarker discovery and therapeutic strategies aimed at mitigating hepatotoxicity while preserving essential immune functions.

Keywords: Immunometabolism; Hepatotoxicity; Liver–immune cross-talk; Peripheral immune cells; Inflammatory signaling

INTRODUCTION

The liver plays a pivotal role in maintaining metabolic homeostasis and immune tolerance while simultaneously serving as the body's primary site for detoxification[1-4]. As a consequence of this dual function, the liver is particularly vulnerable to injury from drugs, environmental toxins, metabolic overload, and infectious agents [5-8]. Hepatotoxicity encompasses a wide spectrum of liver damage, ranging from transient enzyme elevations to acute liver failure and chronic liver disease. Traditionally, hepatotoxicity has been viewed through the lens of direct cellular injury caused by reactive metabolites and oxidative stress [3,9-13]. However, growing evidence indicates that immune-mediated mechanisms and systemic metabolic alterations are equally critical determinants of liver injury outcomes. Immunometabolism, a field that examines how metabolic pathways regulate immune cell function and vice versa, has reshaped our understanding of liver pathology [14-18]. Hepatic injury alters metabolic fluxes within hepatocytes, leading to the release of inflammatory mediators and metabolites that influence immune cell behavior. At the same time, peripheral immune cells infiltrating the liver can reprogram

hepatocellular metabolism, amplifying or resolving injury [19-25]. This dynamic cross-talk underlies both adaptive repair processes and maladaptive chronic inflammation. This review explores the immunometabolic mechanisms that govern hepatotoxicity, emphasizing interactions between the liver and peripheral immune cells. By integrating metabolic and immunological perspectives, it highlights how systemic immune responses shape liver injury and identifies emerging therapeutic implications.

2. The Liver as an Immunometabolic Organ

The liver occupies a central position at the crossroads of systemic metabolism and immune regulation, making it uniquely susceptible to immunometabolic disturbances during toxic injury[6, 26-28]. Hepatocytes execute essential metabolic functions, including glucose storage and release, lipid synthesis and oxidation, and amino acid turnover, while simultaneously contributing to innate immune surveillance [7,29-34]. These parenchymal cells express pattern recognition receptors capable of sensing microbial components and endogenous danger signals, allowing metabolic activity and immune sensing to be tightly integrated[8,35-40]. Alongside hepatocytes, the liver hosts a diverse population of resident immune cells, such as Kupffer cells, dendritic cells, natural killer cells, and innate-like T lymphocytes, which collectively shape local immune responses[41-45]. Under physiological conditions, the liver maintains a predominantly tolerogenic immune environment despite constant exposure to gut-derived antigens[46-49]. This immune tolerance is supported by metabolic signals, including bile acids, lipid mediators, and controlled exposure to microbial products that promote anti-inflammatory immune phenotypes[50]. However, hepatotoxic stress disrupts this equilibrium. Injury to hepatocytes results in the release of damage-associated molecular patterns, altered metabolic intermediates, and reactive oxygen species[51-54]. These signals activate resident immune cells and promote the recruitment of circulating leukocytes, shifting the hepatic environment from immune tolerance toward inflammation.

At the cellular level, hepatotoxicity is closely linked to profound alterations in hepatocellular metabolism[55-57]. Mitochondrial dysfunction is a central feature, leading to impaired oxidative phosphorylation, reduced ATP generation, and excessive production of reactive oxygen species. Beyond causing direct cellular damage, oxidative stress serves as a potent signaling mechanism that activates redox-sensitive transcription factors, such as NF-κB and AP-1, thereby inducing the expression of pro-inflammatory cytokines and chemokines[14, 58-59]. Disrupted lipid metabolism further amplifies immune activation during hepatotoxicity. Accumulation of free fatty acids and toxic lipid intermediates induces lipotoxic stress and endoplasmic reticulum dysfunction, which intensify inflammatory signaling pathways[60-61]. These metabolic disturbances promote the secretion of chemotactic factors that attract monocytes, neutrophils, and other peripheral immune cells into the liver[58-60]. In addition, hepatocyte-derived metabolites such as lactate, succinate, and bile acids actively modulate immune cell metabolism and function. Succinate enhances inflammatory cytokine production in macrophages, while bile acids influence T cell differentiation and innate immune activation[17, 60-61]. Together, these processes illustrate how hepatocellular metabolic dysfunction directly drives immune activation, shaping the severity and progression of hepatotoxic liver injury.

3. Role of Kupffer Cells and Monocyte-Derived Macrophages

Kupffer cells serve as the primary sentinels of the hepatic immune system and are central to the regulation of immunometabolic responses during hepatotoxic injury[18]. As liver-resident macrophages strategically located within the hepatic sinusoids, they continuously monitor blood-borne antigens, metabolites, and cellular debris[19]. Upon hepatocellular stress or injury, Kupffer cells are rapidly activated and undergo pronounced metabolic reprogramming. This shift is characterized by enhanced glycolytic flux, changes in lipid uptake and processing, and altered mitochondrial function, all of which support the energetic and biosynthetic demands of an inflammatory phenotype[20]. Activated Kupffer cells produce a broad spectrum of pro-inflammatory mediators, including tumor necrosis factor-α, interleukin-1β, and interleukin-6, which directly exacerbate hepatocyte injury by impairing mitochondrial function and promoting oxidative stress[21]. In parallel, these cytokines and chemokines facilitate the recruitment of circulating monocytes from the peripheral blood. Once recruited to the liver, monocytes differentiate into monocyte-derived macrophages that adopt functional and metabolic profiles shaped by the local microenvironment[22]. These newly differentiated macrophages further amplify inflammation, participate in the clearance of dead cells, and influence extracellular matrix remodeling. The metabolic phenotype of both resident and recruited macrophages plays a decisive role in determining disease outcomes[23]. Pro-inflammatory macrophages preferentially rely on glycolysis to sustain rapid cytokine production, while anti-inflammatory and reparative macrophages depend on oxidative phosphorylation and fatty

acid oxidation. Failure to appropriately transition between these metabolic states results in sustained inflammatory signaling, impaired resolution of injury, and progression toward fibrosis.

Beyond macrophages, peripheral immune cells contribute extensively to liver–immune cross-talk in hepatotoxicity[24]. Neutrophils are rapidly mobilized to sites of liver injury, where they release reactive oxygen species, proteolytic enzymes, and neutrophil extracellular traps that can intensify tissue damage. Their activation and survival are tightly linked to metabolic factors such as glucose availability and mitochondrial integrity[25]. Lymphocyte populations, including T cells and natural killer cells, also influence hepatotoxic outcomes through metabolically regulated effector functions. Effector T cells rely predominantly on glycolysis to support proliferation and cytokine secretion, whereas regulatory T cells utilize lipid oxidation and mitochondrial respiration to maintain immune tolerance[26]. Hepatic metabolic signals can shift this balance, promoting either immune regulation or pathological inflammation. Importantly, systemic metabolic disorders such as obesity and insulin resistance precondition peripheral immune cells toward pro-inflammatory metabolic states, increasing their pathogenic potential upon liver infiltration and heightening susceptibility to hepatotoxic injury.

4. Cytokines, Metabolites, and Redox Signaling as Mediators of Cross-Talk

Therapeutic and Biomarker Implications: Cytokines, metabolites, and redox signals form an integrated communication network that governs the bidirectional cross-talk between hepatocytes and immune cells during hepatotoxicity[27]. Pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β, and interleukin-6 play central roles in amplifying liver injury by disrupting insulin signaling, impairing mitochondrial respiration, and promoting oxidative stress within hepatocytes[28]. These cytokines not only exacerbate metabolic dysfunction but also establish a feed-forward loop that sustains immune activation. In parallel, hepatocyte-derived cytokines and growth factors influence immune cell metabolism, survival, and differentiation, thereby shaping the magnitude and quality of hepatic immune responses[29]. Beyond cytokines, metabolites act as potent signaling mediators that bridge metabolic and immune pathways. Alterations in hepatic glucose, lipid, and amino acid metabolism during injury result in changes in the extracellular availability of key metabolites[30]. Amino acids such as arginine and glutamine are particularly important for immune cell proliferation, nitric oxide synthesis, and redox balance[31]. Disruption of hepatic amino acid handling can therefore reprogram immune cell function, favoring pro-inflammatory phenotypes. Similarly, metabolites generated during mitochondrial stress, including succinate and lactate, can modulate macrophage activation and cytokine production, reinforcing inflammatory circuits within the injured liver[32].

Redox signaling represents another critical layer of immunometabolic regulation. Physiological levels of reactive oxygen species are essential for intracellular signaling and host defense, but excessive or sustained oxidative stress promotes hepatocyte death and inflammatory immune activation[33]. The liver's antioxidant systems, including glutathione-dependent pathways, normally buffer redox imbalances and limit immune-driven injury. Failure of these protective mechanisms enhances immune cell activation and perpetuates hepatotoxic damage[34]. When hepatotoxic insults persist, these interconnected signaling pathways drive the transition from acute inflammation to chronic liver disease[35]. Chronic hepatotoxicity is characterized by immunometabolic remodeling involving sustained alterations in glucose and lipid metabolism, continuous immune cell infiltration, and long-lasting changes in gene expression mediated by epigenetic mechanisms[36]. Hepatic stellate cells are activated by cytokines and metabolic cues derived from both damaged hepatocytes and immune cells, leading to excessive extracellular matrix deposition and fibrosis. Over time, this fibrogenic environment increases the risk of cirrhosis and hepatocellular carcinoma[37].

Recognition of these immunometabolic processes has important therapeutic and biomarker implications. Targeting metabolic pathways in hepatocytes or immune cells offers opportunities to dampen pathological inflammation while preserving essential immune functions[38]. Interventions aimed at improving mitochondrial efficiency, normalizing lipid metabolism, or restoring redox homeostasis are under active investigation. In parallel, biomarkers reflecting immunometabolic status, including circulating metabolites, cytokine signatures, and immune cell metabolic profiles, hold promise for early detection of hepatotoxicity and for guiding personalized therapeutic strategies.

CONCLUSION

Hepatotoxicity is a multifaceted process driven by intricate interactions between hepatic metabolism and immune responses. The cross-talk between the liver and peripheral immune cells, mediated by cytokines, metabolites, and redox signals, determines the severity and outcome of liver injury. Immunometabolic pathways provide a unifying framework to understand these interactions and reveal novel targets for therapeutic intervention. Continued

research integrating metabolism and immunology will be essential for advancing the prevention and treatment of hepatotoxic liver diseases.

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