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Immunomodulation in the Pathogenesis of Hepatotoxicity and Nephrotoxicity: Oxidative Stress as a Converging Mechanism

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ABSTRACT

The liver and kidney are critical organs responsible for metabolism, detoxification, and excretion, making them highly susceptible to toxic injury. Hepatotoxicity and nephrotoxicity arise from diverse insults, including xenobiotics, drugs, environmental chemicals, and metabolic disturbances. Recent insights highlight the pivotal role of immunomodulation in driving organ injury, with oxidative stress serving as a unifying mechanism that bridges immune activation and cellular dysfunction. Excessive generation of reactive oxygen and nitrogen species disrupts mitochondrial homeostasis, induces DNA and protein damage, and amplifies lipid peroxidation, thereby sensitizing hepatic and renal cells to immune-mediated injury. In parallel, immune pathways-such as Toll-like receptor signaling, NLRP3 inflammasome activation, T-cell polarization, and macrophage reprogramming-sustain inflammatory responses that accelerate fibrosis and organ dysfunction. This review synthesizes current evidence on the immunological and redox-dependent drivers of hepatotoxicity and nephrotoxicity, emphasizing shared molecular pathways, organ crosstalk, and the therapeutic potential of antioxidant and immunomodulatory interventions.

Keywords: hepatotoxicity, nephrotoxicity, immunomodulation, oxidative stress, inflammation

INTRODUCTION

The liver and kidney are central to detoxification, nutrient metabolism, and systemic homeostasis. Both organs operate in close physiological coordination: the liver metabolizes and transforms xenobiotics, while the kidney ensures their elimination through filtration and excretion [1]. This synergy protects the body from toxic overload but simultaneously exposes both organs to a wide range of insults. Their high metabolic activity, dependence on mitochondrial function, and constant exposure to reactive intermediates render them particularly susceptible to toxic injury. Clinical examples of overlapping hepatotoxicity and nephrotoxicity are abundant. Drug-induced liver injury (DILI) and drug-induced kidney injury are major causes of hospitalization and mortality worldwide [2]. Acetaminophen overdose, for instance, is the leading cause of acute liver failure, but its metabolites can also impair renal tubular function [3]. Chemotherapeutics such as cisplatin and antibiotics like aminoglycosides primarily target the kidney but often trigger secondary hepatic dysfunction [4]. Environmental exposures including heavy metals such as cadmium and lead, and pesticides simultaneously disrupt liver detoxification pathways and renal filtration [5]. Chronic metabolic disorders such as diabetes, obesity, and metabolic syndrome add another layer of vulnerability by driving oxidative stress and low-grade inflammation, further predisposing individuals to combined liver and kidney injury [6].

Traditional models of toxicity emphasized direct chemical or metabolic damage to hepatocytes and renal tubular epithelial cells. While this paradigm explained some acute injuries, it overlooked the contribution of the host's immune system and oxidative imbalance [7]. Current evidence shows that immune dysregulation and oxidative stress are central to organ injury and often explain why toxicity persists or progresses despite removal of the initial insult [8]. Both the liver and kidney harbor resident immune populations: Kupffer cells and hepatic stellate cells in the liver, and macrophages and dendritic cells in the kidney [9]. These cells continuously monitor for danger-associated molecular patterns (DAMPs) released by stressed cells, and pathogen-associated molecular patterns (PAMPs) from microbes or endotoxins.

When excessively activated, these immune cells secrete cytokines, chemokines, and reactive oxygen species (ROS) that amplify inflammation [10]. This not only injures surrounding parenchymal cells but also recruits neutrophils and lymphocytes, perpetuating chronic inflammation. The end result is a cycle of oxidative bursts, tissue remodeling, and fibrosis. For example, hepatic stellate cells respond to ROS and TGF-β by transforming into myofibroblasts that deposit collagen, a hallmark of liver fibrosis [11]. Similarly, renal fibroblasts activated by cytokines and oxidative stress contribute to interstitial fibrosis, a major determinant of chronic kidney disease progression [12]. Thus, oxidative stress emerges as a converging mechanism linking metabolic disturbances with immune activation. Recognizing the interplay between immunomodulation and redox imbalance is critical for understanding how hepatotoxicity and nephrotoxicity develop in parallel. This knowledge is essential for identifying therapeutic strategies that target shared molecular pathways, offering dual protection for the liver and kidney.

2. Oxidative Stress as a Central Driver of Organ Toxicity

Oxidative stress is defined as an imbalance between the production of reactive oxygen and nitrogen species (ROS/RNS) and the body's antioxidant defense capacity [13]. Both the liver and kidney produce ROS physiologically during mitochondrial respiration, cytochrome P450 metabolism, and peroxisomal oxidation [14]. Under stress conditions, however, these processes accelerate, overwhelming endogenous defenses such as superoxide dismutase, catalase, glutathione peroxidase, and the Nrf2-regulated antioxidant system [14].

In hepatotoxicity, oxidative stress plays a decisive role. Hepatocytes exposed to toxins experience mitochondrial dysfunction and impaired ATP production, which increase ROS release [15]. Lipid peroxidation damages cellular membranes, while oxidized proteins disrupt enzymatic activity. DNA lesions further impair replication and repair, predisposing to apoptosis or necrosis [16]. Acetaminophen overdose illustrates this process: its toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) depletes glutathione, reducing antioxidant capacity and amplifying ROS-driven hepatocyte death [17].

In nephrotoxicity, tubular epithelial cells are highly sensitive to ROS. Mitochondrial dysfunction in these cells triggers apoptosis and necrosis, while lipid peroxidation impairs membrane transporters responsible for reabsorption [18]. DNA damage compromises repair pathways, accelerating tubular atrophy [19]. Cisplatin nephrotoxicity exemplifies oxidative overload, where mitochondrial injury and NADPH oxidase (NOX) activation synergize to drive ROS accumulation and tubular apoptosis [20].

Crucially, oxidative stress is not only a byproduct of toxic metabolism but also an active regulator of immune responses. ROS activate redox-sensitive transcription factors such as NF-κB and MAPKs, upregulating proinflammatory cytokines [21]. Furthermore, ROS promote assembly of inflammasomes like NLRP3, which drive the maturation and release of IL-1β and IL-18 [22]. These mechanisms link oxidative stress to immunomodulation, creating a feedback loop where redox imbalance fuels inflammation, and immune activation perpetuates ROS production [23]. Together, these processes establish oxidative stress as a central driver of hepatotoxicity and nephrotoxicity, converging with immune mechanisms to accelerate tissue injury, fibrosis, and organ dysfunction.

3. Immunomodulation in Hepatotoxicity

The liver occupies a unique position as both a metabolic hub and an immune organ. Constantly exposed to antigens and metabolites from the gut via the portal circulation, it must maintain tolerance while retaining the capacity to mount immune responses. When this balance is disrupted, immune dysregulation contributes to hepatotoxicity, with oxidative stress serving as a major amplifier of injury.

Kupffer cell activation is an early step in immune-mediated liver injury [24]. These resident macrophages recognize damage-associated molecular patterns (DAMPs) released from stressed or necrotic hepatocytes, as well as pathogen-associated molecular patterns (PAMPs) derived from microbial translocation [25]. Activated Kupffer cells secrete tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and reactive oxygen species (ROS) [26]. While these mediators help clear damaged tissue, sustained production perpetuates inflammation, recruits circulating neutrophils, and aggravates hepatocyte injury.

Toll-like receptor (TLR) signaling links gut dysbiosis to hepatic immunopathology [27]. Endotoxins such as lipopolysaccharide (LPS) activate TLR4, while unmethylated bacterial DNA triggers TLR9 [28]. Engagement of these receptors activates NF-κB and MAPK pathways, resulting in cytokine release, oxidative bursts, and hepatocellular apoptosis [29]. Thus, intestinal permeability and microbial imbalance act as indirect drivers of hepatotoxicity through immune activation.

The NLRP3 inflammasome further integrates oxidative stress and immune responses. ROS, mitochondrial DNA fragments, and ATP released from damaged hepatocytes activate NLRP3, which recruits ASC and caspase-1 [30]. This leads to maturation of IL-1β and IL-18, cytokines that intensify hepatocyte apoptosis and amplify inflammatory cascades [31]. Adaptive immunity also contributes significantly. CD4+ helper T cells produce cytokines that polarize macrophages toward inflammatory phenotypes, while CD8+ cytotoxic T cells directly kill hepatocytes presenting antigens [32]. Regulatory T cells (Tregs), which normally suppress excessive immune responses, are

often reduced or functionally impaired in hepatotoxic states, tipping the balance toward uncontrolled inflammation [33].

Finally, fibrogenesis represents the chronic endpoint of immune-driven hepatotoxicity. Hepatic stellate cells, normally quiescent vitamin A–storing cells, are activated by cytokines (e.g., TGF-β, TNF-α) and ROS [34]. Activated stellate cells transform into myofibroblasts that produce collagen and extracellular matrix, leading to fibrosis and eventually cirrhosis [35]. Thus, oxidative stress not only initiates hepatocyte death but also fuels immune-mediated fibrotic remodeling.

4. Immunomodulation in Nephrotoxicity

The kidney is similarly vulnerable to immune dysregulation, owing to its high exposure to circulating toxins, metabolites, and immune mediators [36]. Both glomerular and tubular compartments are affected, with oxidative stress acting in concert with immune signaling to sustain nephrotoxicity.

Tubular immune activation occurs when injured tubular epithelial cells release chemokines such as monocyte chemoattractant protein-1 (MCP-1/CCL2) [37]. These signals recruit monocytes that differentiate into macrophages. M1 macrophages secrete TNF-α, IL-6, and ROS, intensifying local damage, whereas M2 macrophages promote fibrosis by releasing transforming growth factor-beta (TGF-β) and stimulating extracellular matrix deposition [38].

Toll-like receptors (TLRs) play a parallel role in the kidney. Renal epithelial and dendritic cells express TLR2 and TLR4, which detect circulating DAMPs and PAMPs [39]. Their activation leads to NF-κB signaling, driving inflammatory cytokine expression and amplifying ROS production [39]. This mechanism is prominent in sepsis-associated kidney injury and diabetic nephropathy.

Inflammasome activation further perpetuates nephrotoxicity. The NLRP3 inflammasome, triggered by ROS and uric acid crystals, promotes caspase-1–mediated processing of IL-1β and IL-18 [40]. These cytokines recruit additional immune cells and maintain a proinflammatory milieu within the renal interstitium.

T-cell dysregulation also shapes renal injury. Th17 cells release IL-17, which enhances neutrophil recruitment and inflammation, while reduced Treg function diminishes immune tolerance [41]. This imbalance leads to persistent immune-mediated damage of renal tissue. As in the liver, chronic immune activation culminates in fibrosis [42]. Renal fibroblasts activated by TGF-β and ROS proliferate and deposit extracellular matrix proteins, leading to interstitial scarring and progressive loss of function [43].

Clinical models illustrate these mechanisms. Cisplatin nephrotoxicity involves ROS generation, TLR4 activation, and macrophage infiltration, while diabetic kidney disease features chronic oxidative stress, NLRP3 activation, and maladaptive immune responses that sustain fibrosis [44].

Together, hepatotoxicity and nephrotoxicity highlight how immunomodulation and oxidative stress converge to drive organ injury. In both organs, resident immune cells detect stress signals, initiate inflammatory cascades, and promote fibrogenesis. Oxidative stress amplifies these responses, establishing a self-sustaining cycle of injury and dysfunction.

5. Converging Mechanisms Across Liver and Kidney

Although hepatotoxicity and nephrotoxicity often present with organ-specific features, their underlying pathogenesis is driven by overlapping molecular and cellular events. Both the liver and kidney are highly metabolic organs exposed to xenobiotics, metabolic intermediates, and immune stimuli, which explains why they frequently share converging mechanisms of injury [45].

Oxidative stress is a unifying driver in both organs. Excess production of reactive oxygen species (ROS) overwhelms antioxidant defenses, leading to mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and activation of cell death pathways [46]. This redox imbalance not only injures parenchymal cells but also acts as a signal that amplifies immune activation.

Inflammasome signaling is another shared pathway. The NLRP3 inflammasome, triggered by ROS, mitochondrial DNA, or uric acid crystals, mediates caspase-1 activation and release of IL-1β and IL-18 [47]. These cytokines maintain chronic inflammatory states in both hepatocytes and renal epithelial cells.

Cytokine networks play central roles in sustaining cross-organ injury. TNF-α and IL-6 perpetuate inflammatory cascades, while TGF-β serves as a critical mediator of fibrosis by activating hepatic stellate cells and renal fibroblasts [48].

Immune cell infiltration is consistently observed in both settings. Kupffer cells, infiltrating macrophages, and T-cells orchestrate persistent injury in the liver, while similar populations drive glomerular and tubular inflammation in the kidney [49].

Ultimately, these events culminate in fibrosis, a common endpoint of chronic injury. Hepatic stellate cells and renal fibroblasts respond to oxidative and immune cues by depositing extracellular matrix proteins, leading to structural remodeling, functional decline, and progression toward cirrhosis or chronic kidney disease [50].

Taken together, these parallels highlight that hepatotoxicity and nephrotoxicity are not isolated phenomena but interconnected syndromes shaped by shared oxidative–immune mechanisms. This convergence underscores the potential for therapeutic strategies that target common pathogenic pathways to achieve dual organ protection.

CONCLUSION

Hepatotoxicity and nephrotoxicity are not merely outcomes of direct chemical injury but are shaped by intricate interactions between oxidative stress and immunomodulation. Excessive ROS generation primes hepatocytes and renal cells for immune-mediated damage, while immune activation perpetuates oxidative injury and fibrosis. Recognizing oxidative stress as a converging mechanism provides a unifying framework for understanding multi-organ toxicity and developing novel therapies. Integrated approaches targeting both immune and redox pathways hold promise for reducing the global burden of liver and kidney diseases.

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