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REVIEW

Burns: The "Fuse" That Ignites Organ Crisis – A Narrative Review of Mechanisms and Crosstalk in Post-Burn MODS

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Abstract: Burns cause skin and deep tissue damage, with ~180,000 annual deaths worldwide, mostly in developing countries. Extensive burn patients are prone to secondary lung, kidney, liver, and heart dysfunctions, and infection-induced sepsis is a major cause of mortality. With August 20, 2025 as the retrieval cutoff, we systematically searched PubMed to review burn-induced organ injury progress. This review elaborates on each organ injury's pathological mechanisms (inflammatory activation, endothelial disruption, pyroptosis, ferroptosis, etc.), clarifies post-burn cross-organ crosstalk, and summarizes emerging therapies (nano-targeted therapy, mitochondrial protection, stem cell intervention) and their clinical potential. It aims to provide a theoretical basis for post-burn organ dysfunction treatment and promote the transformation from single-organ protection to systemic intervention.

Keywords: burns, organ dysfunction, sepsis, lung injury, kidney injury, hepatic injury, cardiac injury, cross-organ crosstalk, treatment

Introduction

Burns are injuries caused by the skin and tissues coming into contact with external heat sources (flames, hot liquids, steam, etc.) or chemical substances.[1] According to data from the World Health Organization in 2023, approximately 180,000 people die from burns globally each year, with the majority from developing countries.[2] The disruption of the skin and superficial barrier is an intuitive manifestation of burns, while subsequent infections can further lead to organ dysfunction (eg, lung, kidney, liver, heart) and even sepsis.[3,4] According to the Sepsis-3.0 consensus, sepsis is defined as a life-threatening condition caused by a systemic inflammatory response syndrome (SIRS) triggered by infection.[5] According to research findings, patients with a total body surface area (TBSA) burn of more than 30% exhibited a significantly higher risk of developing SIRS and multiple organ dysfunction syndrome (MODS), with an incidence approximately three times that of patients with TBSA burns less than 30%.[6] It has been reported that about 60% of burn patients die from post-injury infections.[7] Organ dysfunctions and sepsis pose clinical treatment challenges and are important causes of death in patients with extensive burns.[8] It is noteworthy that organ injuries do not exist independently but form a "pathological alliance" through the neurohumoral system.[9] This "pathological alliance" implies that injuries to various organs do not occur and progress in isolation; instead, they form an interconnected and mutually influential pathological network through multiple pathways such as neurohumoral regulation, inflammatory mediators and hemodynamics. Injury to one organ can act as an inducer to trigger or exacerbate dysfunction of other organs, thereby forming a vicious cycle.

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Although current clinical practice has established comprehensive treatment systems including fluid resuscitation, wound management, and organ support,[10] the incidence and mortality of burn-related organ injuries remain high.[11] Improper fluid resuscitation strategies can significantly increase the risk of complications such as wound deterioration, pulmonary edema, abdominal compartment syndrome, and fluid overload in burn patients.[12,13] Organ support therapies (eg, mechanical ventilation) can only replace organ function, yet fail to repair damaged tissues and cells; prolonged application may induce secondary injuries such as ventilator-associated pneumonia.[14] Therefore, elucidating the pathological mechanisms underlying post-burn organ dysfunction facilitates the exploration of novel therapeutic strategies and has become a research priority in emergency and critical care medicine as well as surgery.

This narrative review focuses on the research progress of burn-induced lung, kidney, liver, and heart injuries. It mainly summarizes the following three sections (Figure 1 and Table 1): 1. The core pathological mechanisms of individual organ injuries, including inflammatory signaling activation, endothelial barrier disruption, and programmed cell death modalities such as pyroptosis and ferroptosis; 2. The pathological crosstalk and "domino effect" among multiple organ injuries; 3. The research advances in emerging therapeutic strategies, including nano-targeted therapy, mitochondrial protection, and stem cell intervention. Compared with existing related reviews,[9,10] this narrative review integrates current basic and clinical findings, providing an important reference for understanding the mechanisms underlying post-burn multiple organ dysfunction and for its clinical prevention and treatment.

This review complies with the TITAN 2025 guidelines for transparency in AI reporting; no AI tools were used to generate text.[89]

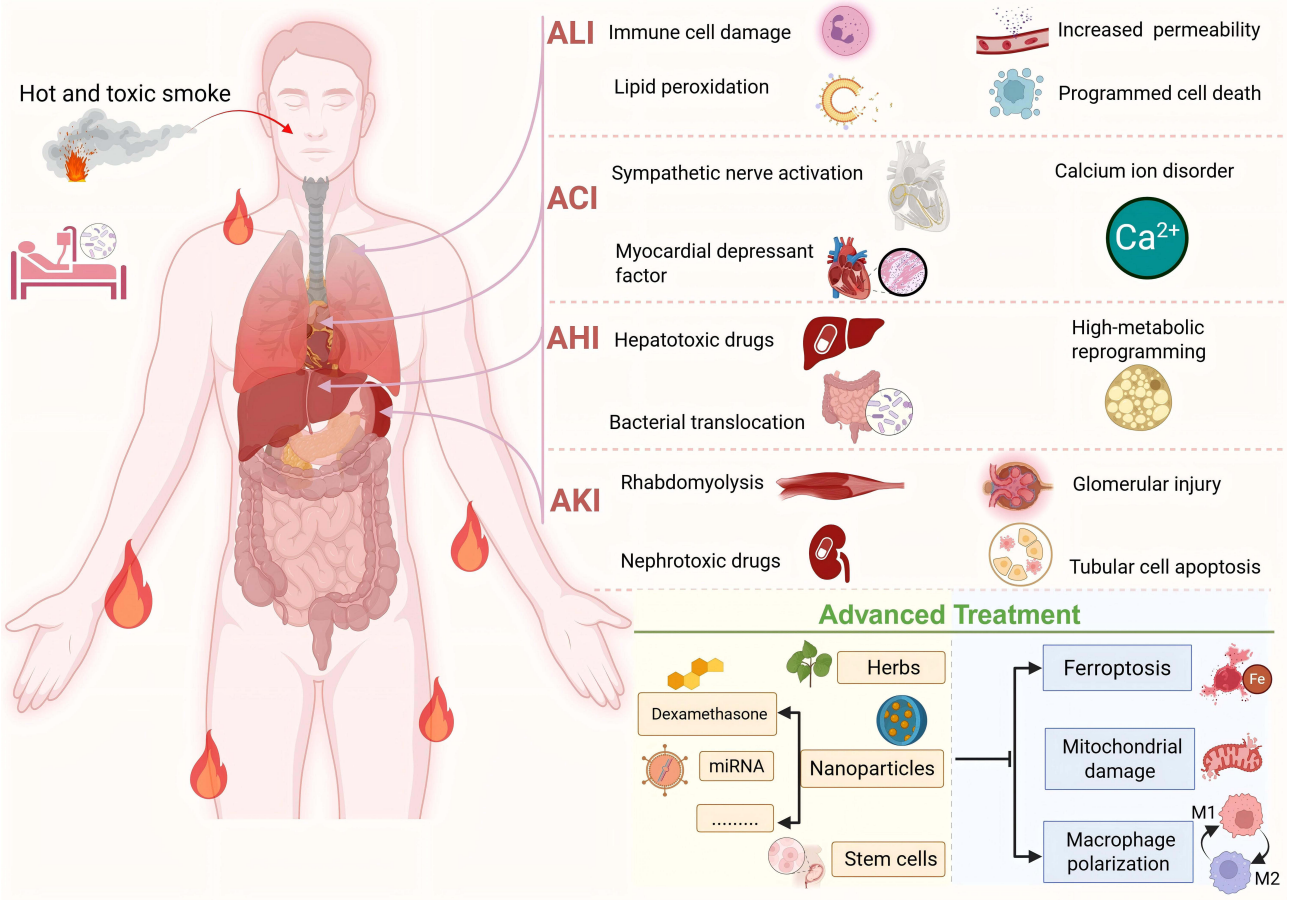

Figure 1 The injury mechanisms and potential intervention methods of four types of organ dysfunction after burns.

Table 1 Main Mechanisms of Single Organ Dysfunction and Crosstalk of Multiple Organ Dysfunction After Burns

Organ	Main Mechanisms of Organ Injury After Burns	References	Year
Lung	Inhalation injury impairs the phagocytic function of macrophages	[15,16]	2023;2025
	Conversion of NO to peroxynitrite causes lipid peroxidation and DNA damage	[17,18]	2001;2003
	Macrophages undergo pyroptosis due to neutrophil-derived exosomes, releasing substantial inflammatory factors	[19,20]	2021;2015
	TNF-α and MMP9 disrupt the endothelial glycocalyx structure, leading to enhanced adhesiveness	[21–23]	2024;2012;2014
	TNF-α remodels the cytoskeleton via upregulating the RhoA/ROCK1/MLC pathway, causing endothelial cell contraction and increased permeability	[24–26]	1992;2023;2003
	VEGF induces VE-cadherin disassembly, increasing permeability	[27,28]	2000;2006
	Macrophages release GBP2, driving endothelial cell ferroptosis via the OTUD5-GPX4 axis	[29]	2025
	Activation of alveolar epithelial cells after injury promotes intrapulmonary fibrin deposition by releasing tissue factor	[30,31]	2008;2007
Kidney	Massive myoglobin released from rhabdomyolysis after severe burns blocks renal tubules	[32–34]	2009;2022;2011
	Stress-induced hyperglycemia impairs mitochondrial function	[10,35]	2020;2013
	Renal ischemia occurs due to fluid loss in the early stage of burns	[10,36]	2020;2021
	Nephrotoxicity of hydroxocobalamin	[37–39]	2019;2016;2017
	STING promotes mitochondrial ROS production and endoplasmic reticulum stress	[40,41]	2024;2020
	LPS causes shedding of glycocalyx in endothelial cells and podocytes, damaging the filtration barrier	[42]	2017
	Fibrin deposition and microthrombi appear in the glomerulus and its surrounding structures	[43,44]	2009;2013
Liver	IL-6 and UCP1 synergistically promote browning of white adipose tissue, mobilizing lipids and accelerating hepatic steatosis	[45]	2019
	Reduced CPT content damages mitochondrial structure and function	[46,47]	2018;1985
	Hepatic toxicity of ketamine during burn treatment	[48]	2024
	Intestinal dysfunction leads to bacterial translocation to the liver, activating Kupffer cells	[49,50]	2018;2020
	LPS disrupts the iNOS-eNOS balance, downregulating the sensitivity of hepatic endothelial cells to acetylcholine and impairing vasodilatory capacity	[51,52]	2014;2017
	MDSCs downregulate the immune response of CD4+ and CD8+ T cells, promoting immunosuppression	[53,54]	2012;2015
	Intrahepatic immune cells develop immune tolerance to long-term LPS stimulation	[55,56]	2011;2015
	In sepsis, inflammatory cells and cytokines inhibit the expression of hepatic bile and bile salt transporters, leading to hepatocellular cholestasis	[57,58]	2000;2005

(*Continued*)

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Table 1 (Continued).

Organ	Main Mechanisms of Organ Injury After Burns	References	Year
Heart	Sustained adrenergic signaling induces myocardial cell apoptosis and accelerates cardiac fibrosis	[59]	2022
	After burns, the concentration of cytokines in myocardial cells is higher than that in peripheral blood, forming an "inflammatory microenvironment"	[60]	1984
	TNF-α promotes ROS production and increases apoptosis by regulating the p38 and ERK1/2 MAPK signals	[61]	2007
	IL-1β mediates the interaction between macrophages and fibroblasts, promoting cardiac fibrosis	[62,63]	2020;2024
	Intracellular calcium concentration in myocardial cells of burned rats increases abnormally, significantly impairing myocardial contractility	[64]	2002
	Myocardial depressant substances exist in sepsis patients	[65]	2007
	Prostaglandin F2α receptor aggravates cardiac fibrosis; thromboxane A2 receptor increases myocardial cell apoptosis by accumulating oxidative stress	[66–68]	2021;2014;2014
	Abnormally expressed NO reduces myocardial contractility by decreasing calcium influx through L-type calcium channels	[69]	1991
	LPS induces myocardial cell ferroptosis	[70]	2020
	STING binds to IRF3, upregulating NLRP3 and driving inflammasome formation and pyroptosis	[71,72]	2019;2011
"Domino effect" of organ dysfunction	In a rabbit burn model, decreased GSH synthesis in the lung and liver weakens the resistance of other organs to post-burn oxidative stress	[73]	2013
	Permissive hypercapnia during ARDS treatment impairs renal function	[74]	2016
	AKI inhibits oxidative phosphorylation in the lung, leading to ATP depletion	[75,76]	2021;2023
	AKI promotes leukocyte aggregation in liver tissue and increases vascular permeability	[77]	2009
	PAD-4 is involved in mediating liver injury after AKI	[78]	2016
	Increased IL-17A and IL-6 levels in AKI patients cause liver injury	[79,80]	2011;2018
	AKI can induce cardiac injury via a Gal-3-dependent pathway	[81–83]	2024;2019;2022
	Liver injury leads to accumulation of endotoxin and TNF-α	[84]	2001
	Bilirubin enters lung tissue, disrupting alveolar surface tension	[85]	2004
	Reduced hepatic synthesis of α-tocopherol weakens the antioxidant function of lung tissue	[86]	2007
	Liver injury activates the RAAS system, causing renal vascular hypoperfusion	[87]	2019
	Liver injury induces myocardial dysfunction by activating the RAS system via AGT	[88]	2021

Methods and Rationale of the Review

All studies included in this review were retrieved from the PubMed medical literature database, encompassing only English-language original research articles and review articles. The search was performed on August 20, 2025. We conducted a literature search using the following search terms: "Burns" OR "Thermal injury" OR "Scald" OR "Burn injury" combined with organ dysfunction-specific terms: (("Lung injury" OR "Acute lung injury" OR "Acute respiratory distress syndrome" OR "ARDS") OR ("Kidney injury" OR "Acute kidney injury" OR "AKI" OR "Renal failure" OR "Acute renal failure") OR ("Liver injury" OR "Hepatic dysfunction" OR "Liver failure" OR "Hepatic failure") OR ("Cardiac injury" OR "Myocardial injury" OR "Cardiac dysfunction" OR "Heart failure") OR ("Multiple organ dysfunction" OR "MODS" OR "Multiple organ failure" OR "Organ crosstalk" OR "Organ interaction")). The referenced articles are closely related to the dysfunction of the lung, kidney, liver, and heart; priority was given to high-quality reviews, animal model studies, and clinical studies in the field, with more than 80% of the included works being research findings published in the past 5–10 years.

This review focuses on the core theme of "post-burn organ dysfunction." It first introduces the mechanisms underlying burn-induced single-organ dysfunction, then integrates the crosstalk among post-burn organ dysfunctions, and finally summarizes the corresponding cutting-edge therapeutic advances based on the aforementioned mechanisms, forming a logical closed loop from mechanisms to treatments. Meanwhile, considering sepsis as a key factor contributing to organ injury after burns, this review elaborates on the mediating injury mechanisms of sepsis in a targeted and scattered manner within the respective sections of each organ dysfunction.

The Mechanisms of Burn-Induced Single-Organ Dysfunction

Acute Lung Injury

During burns, high-temperature airflow and toxic smoke components can cause inhalation injuries. The incidence of burns complicated with inhalation injury is approximately 10%, which is characterized by edema and death of respiratory epithelial cells, and may even cause airway stenosis and obstruction, thereby leading to acute lung injury (ALI).[90] It has been reported that the mortality rate of burn patients with inhalation injury is about 23% higher than that of patients with simple burns.[91] Meanwhile, intervention factors such as respiratory support therapy can also increase the incidence of ventilator-associated lung injury.[92,93] In addition, massive fluid loss, severe stress, and infection can further increase the incidence of ALI.[10] Currently, multiple clinical and basic studies have identified potential biomarkers or indicators predictive of burn-related lung injury,[94–99] providing important clues for the early identification and risk assessment of the disease (Table 2). Although traditional therapeutic approaches for burn-induced ALI (including fluid resuscitation, airway management, and antibiotic therapy) can alleviate symptoms and maintain vital sign stability, they mostly focus on symptomatic support and are difficult to fundamentally block the pathophysiological process of lung injury. Additionally, these approaches may be accompanied by potential risks such as fluid overload and drug-resistant bacterial infections, with limited therapeutic effects in some critically ill patients. Therefore, in-depth exploration of the pathogenesis of burn-related ALI holds significant research value and clinical significance for the innovation of therapeutic strategies.

Lung Injury Induced by Inhalation Injury

Inhalation injury is a direct factor leading to burn-induced ALI. In addition to directly damaging the airway, it impairs the phagocytic function and cytotoxicity of alveolar macrophages, increasing the risk of infection in patients.[15,16] In addition, toxic gases in smoke (such as carbon monoxide, nitric oxide, cyanide, etc.) can also damage the alveoli.[112] Taking nitric oxide (NO) as an example, it can be converted into peroxynitrite in the body, causing lipid peroxidation and cellular DNA damage, thereby increasing the permeability of pulmonary blood vessels, causing pulmonary edema, and reducing gas diffusion efficiency.[17,18] Therefore, removing patients from the burn environment as early as possible can reduce the incidence of burn-induced ALI to a certain extent.

Table 2 Changes in Characteristic Biomarkers of Organ Dysfunction After Burns

Organs with Injury	Study Type	Main Changing Trends of Indicators After Burn Injury	Data Source	References	Year
Lung	Retrospective Cohort Study	Increased: White Blood Cell; Red Blood Cell Index; Neutrophil-to-Lymphocyte Ratio (NLR)	Human	[94]	2024
		Decreased: Eosinophil; Platelet			
	Animal Experimental Study	Increased: HMGB1	Swine	[95]	2023
	Animal Experimental Study	Increased: Caspase-3; Matrix Metalloproteinase-9 (MMP-9); Bronchoalveolar Lavage Fluid (BALF) Albumin	Wistar Rat	[96]	2015
	Animal Experimental Study	Increased: TNF-α; IL-1β; IL-6; Malondialdehyde (MDA); Myeloperoxidase (MPO)	SD Rat	[97,99]	2019;2017
		Decreased: Superoxide Dismutase (SOD)			
	Retrospective Cohort Study	Increased: Lactic Acid; Prothrombin Time (PT)	Human	[98]	2024
		Decreased: Plasma Albumin			
Kidney	Review Study	Increased: Serum Creatinine (Scr); Neutrophil Gelatinase-Associated Lipocalin (NGAL); Cystatin C (Cys C); Kidney Injury Molecule-1 (KIM1); Haptoglobin (Hp); Proenkephalin (ProENK)	/	[81]	2024
		Decreased: Urine Output			
	Animal Experimental Study	Increased: HMGB1	Swine	[100]	2024
	Observational Study	Increased: Neutrophil Gelatinase-Associated Lipocalin (NGAL)	Human	[101]	2020
	Prospective Cohort Study	Increased: Galectin-3 (Gal3); Blood Urea	Human	[102]	2024
		Decreased: Urine Output			
	Retrospective Cohort Study	Increased: Lactate Dehydrogenase (LDH); Blood Urea Nitrogen (BUN); Serum Creatinine (Scr)	Human	[103]	2023
	Clinical Randomized Controlled Trial	Increased: Blood Urea Nitrogen (BUN), Serum Creatinine (Scr), and 24-Hour Urinary Protein; Neutrophil; C-Reactive Protein (CRP); IL-18; IL-6	Human	[104]	2025

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Liver	Prospective Observational Study	Increased: Total Bilirubin; ALT; AST; Globulin; Liver Volume	Human	[105]	2024
		Decreased: Plasma Albumin			
	Clinical Observational and Animal Experimental Study	Increased: ALT; AST; Lactate Dehydrogenase (LDH); Ornithine Carbamoyltransferase (OCT); Triglyceride (TG, Liver Tissue)	Human/SD Rat	[106]	2021
		Decreased: β-Hydroxybutyrate; L-Carnitine			
	Clinical Observational and Animal Experimental Study	Increased: ALT and AST; Liver Triglyceride (TG) Content; Plasma Free Fatty Acid (FFA); Liver Weight	Human/C57 Mouse	[107]	2023
	Animal Experimental Study	Increased: Malondialdehyde (MDA); Intrahepatic Lipid Deposition	C57 Mouse	[108]	2025
Heart	Review Study	Increased: Troponin I (TnI)	/	[109]	2021
	Animal Experimental Study	Increased: IL-1α; IL-1β; IL-6; TNF; C-C Motif Chemokine Ligand 2 (Ccl2); C-X-C Motif Chemokine Ligand 10 (Cxcl10); Toll-Like Receptor (TLR) Family Genes; HMGB1	SD Rat	[110]	2023
		Decreased: IL-1r1; Cluster of Differentiation 14 (Cd14); Toll Interacting Protein (Tollip); Nuclear Receptor Subfamily 2 Group C Member 2 (Nr2c2)			
	Retrospective Cohort Study	Increased: Lactic Acid	Human	[111]	2022

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Lung Injury Caused by Burn Sepsis

As the organ most susceptible to injury under septic conditions, the lung is prone to ALI and even acute respiratory distress syndrome (ARDS).[113] Sepsis-induced ALI has complex mechanisms, among which the functional damage of immune cells and endothelial cells is particularly prominent.[114,115] The interaction between pathogenic microorganisms and immune cells can activate the NF-κB pathway, thereby promoting the massive release of various inflammatory factors, including interleukin (IL), tumor necrosis factor (TNF), etc.[116–118] TNF can serve as an initial stimulus for simulating inflammation in vitro. Studies have shown that with the participation of TNF signaling, macrophages can undergo pyroptosis under the influence of exosomes derived from neutrophils, releasing large amounts of IL-1β and IL-18, exacerbating the inflammatory response of ALI.[19,20] Under the synergistic effect of TNF-α and matrix metalloproteinase 9 (MMP9), the glycocalyx structure, which acts as an important line of defense for the endothelial cell barrier, will detach, leading to increased adhesion of endothelial cells.[21–23] This process promotes the transendothelial migration of white blood cells and aggravates the local inflammatory response.[119] TNF-α can also upregulate the RhoA/ROCK1 (RhoA-associated kinase)/MLC (myosin light chain) pathway, leading to cytoskeletal remodeling, cell contraction, and widened gaps in endothelial cells, increasing cell permeability.[24–26] Cell interaction is also crucial for the progression of ALI. Under the stimulation of lipopolysaccharide (LPS), vascular endothelial growth factor (VEGF) released by polarized macrophages can activate p21 kinase, promoting the disassembly of the cell tight junction molecule VE-cadherin, and increasing the permeability of endothelial cells.[27,28] In addition, macrophages stimulated by LPS can also release guanylate-binding protein 2 (GBP2), which drives ferroptosis of pulmonary vascular endothelial cells by regulating the OTUD5-GPX4 axis,[29] further impairing the function of endothelial cells. In addition to immune cells and endothelial cells, the injury of alveolar epithelial cells also participates in the occurrence and development of ARDS. Lung epithelial cells also have a glycocalyx structure, and their injury and detachment have a pro-inflammatory effect.[120] After the alveolar epithelium is injured and activated, its anticoagulant molecules detach, and the lung epithelium is prompted to release tissue factor into the alveolar cavity.[30,31] Such changes can promote fibrin deposition in the alveoli, thereby promoting the formation of hyaline membranes.

Acute Kidney Injury

Acute kidney injury (AKI) is defined as a short-term decline in renal function (based on glomerular filtration rate, GFR). AKI can also be diagnosed if there is massive accumulation of creatinine, or if oliguria or anuria occurs.[121,122] Burns are closely associated with AKI incidence: 9% to 50% of burn patients develop AKI.[81] Numerous studies have identified potential biomarkers or indicators predictive of burn-related kidney injury, such as neutrophil gelatinase-associated lipocalin (NGAL) and haptoglobin,[10,100–104] providing important evidence for the early diagnosis of the disease (Table 2). Currently, there are various methods for treating and preventing burn-induced AKI, but most of them still focus on symptomatic support. Therefore, in-depth exploration of the intrinsic association mechanisms between burns and AKI remains an important foundation for clinical treatment.

Burn-Induced Kidney Injury

The early injury factors of burns include hypovolemic shock, deep muscle burns, inhalation injury, systemic inflammatory response, and stress; late injuries are closely related to sepsis and drug toxicity.[123] Third-degree burns often extend to muscle layers. Skin carbonization, muscle edema, ischemia, and necrosis may lead to compartment syndrome (similar to fractures) and rhabdomyolysis. Rhabdomyolysis releases myoglobin, causing myoglobinuria and even tubular obstruction.[32–34] Furthermore, burn patients often experience intense stress, insulin resistance, and hypercatabolism, leading to stress-induced hyperglycemia, which may cause AKI by impairing mitochondrial function.[10,35] The kidney is an organ with rich blood flow. In the early burn stage, massive fluid exudation from the wound and extravascular shift of intravascular fluid drastically reduce circulating blood volume, triggering ischemic AKI.[10,36] During fluid resuscitation, ischemic reperfusion injury may occur.[81,124] Hydroxocobalamin is commonly used for the prophylaxis of cyanide poisoning in burn patients with smoke inhalation. However, a recent multicenter observational study found that hydroxocobalamin may have nephrotoxicity and carry a risk of inducing AKI. This may be associated with its ability to increase oxalate levels and its non-selective chelation of NO.[37–39]

Kidney Injury Caused by Burn Sepsis

Sepsis is a critical factor influencing AKI in the late stage of burns. Approximately 50% of AKI cases are associated with sepsis, and about 60% of septic patients develop AKI.[125] Classical theories suggest that sepsis-induced AKI primarily relates to reduced renal blood flow perfusion and tubular epithelial cell death.[126] In a murine sepsis model, GFR begins to decline within the first 2–4 hours, dropping to 80% below normal levels within the subsequent 16 hours.[127] Additionally, blood creatinine and blood urea nitrogen (BUN) levels exceed three times the normal values.[128] Recent studies have found that stimulator of interferon genes (STING) is associated with inflammation and pyroptosis in mouse renal tubular cells induced by LPS. When STING is specifically knocked out in renal tubular cells, inhibition of cell apoptosis and reduction in mitochondrial reactive oxygen species (ROS) production are observed.[40] Endoplasmic reticulum stress is considered to be associated with the pro-injury effect of STING.[41] Endothelial cells are also among the first to undergo adaptive adjustments in sepsis.[129] In a septic environment, endothelial cells express various selectins, adhesion molecules, inflammatory factors, and chemokines, indicating a shift toward a pro-inflammatory phenotype.[130] Stimulation of rats with high-concentration LPS leads to rapid disassembly of VE-cadherin.[131] Electron microscopy reveals detachment of the glycocalyx from endothelial and podocytes, closure of endothelial fenestrae, and gaps forming between podocytes and the glomerular basement membrane.[42] Furthermore, coagulation dysfunction is a key mechanism of septic renal injury. Fibrin deposition occurs in the glomeruli and surrounding structures within 6 hours of LPS stimulation.[43] In a rat cecal ligation and puncture (CLP) model, glomeruli are filled with microthrombi 12 hours post-injury.[44]

Acute Hepatic Injury

The liver plays a pivotal role in systemic metabolism, inflammation, and immune responses. Systemic reactions triggered by burns affect multiple abdominal organs, including the liver.[132] Burn patients exhibit significant morphological changes in the liver, such as enlargement and fatty infiltration.[133] Animal studies have shown that the liver weight in burn groups increases significantly in the early stage compared to control groups.[45] Clinically, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are commonly used as markers for detecting hepatocyte injury.[134] Clinical results indicate that these enzymes peak at 7 days after burns, confirming the occurrence of post-burn liver injury.[135] In addition, several lipid metabolites can also indicate post-burn liver injury (Table 2).[105–108] Notably, burn patients with compromised liver function have a significantly higher incidence of infectious and metabolic complications than those without.[133] Despite ongoing advances in burn research, the pathophysiological mechanisms of burn-induced liver injury remain incompletely understood. Further exploration of these mechanisms is crucial to improving the overall survival rate of burn patients.

Burn-Induced Liver Injury

Hypermetabolic reprogramming is a unique phenomenon in burn research, characterized by the body's consumption of lipids and proteins to maintain function under low-nutrient conditions.[136,137] Studies have found that IL-6 and uncoupling protein 1 (UCP1) synergistically promote the browning of white adipose tissue under burn conditions, enhancing lipolysis and accelerating the progression of hepatic steatosis in mice.[45] The underlying mechanism may involve interactions between endoplasmic reticulum stress and mitochondria in hepatocytes. As an organ rich in mitochondria, the liver's organelle functions are highly susceptible to damage during burn stress.[138,139] Carnitine, a critical cofactor for carnitine palmitoyltransferase (CPT) on the mitochondrial membrane, participates in fatty acid metabolism regulation, redox balance, and inflammatory signaling.[46] However, burn patients show an imbalance of reduced blood carnitine levels and increased excretion.[47] Further studies have found that hepatocyte mitochondria in burned rats exhibit atrophy and decreased membrane potential, indicating dual damage to mitochondrial structure and function.[106] Silencing methyl-CpG binding domain protein J (MCJ, a mitochondrial protein) can improve mitochondrial dysfunction.[140] Additionally, drug-induced liver injury is a non-negligible risk factor. A retrospective burn cohort study involving 279 patients showed that ketamine, used for sedation and analgesia in critically ill patients, has hepatotoxicity and increases the risk of cholestasis in burn patients.[48] These findings suggest that the prevention and treatment of burn-induced liver injury require a multi-target strategy integrating metabolic disorder regulation, mitochondrial protection, and management of drug side effects.

Liver Injury Caused by Burn Sepsis

The liver forms a close anatomical and functional connection with the gastrointestinal tract through the portal venous system. Patients with extensive burns often experience pathological changes such as stress-induced hypersecretion of gastric acid, intestinal motility dysfunction, increased intestinal mucosal permeability, and translocation of intestinal bacteria into the bloodstream.[141–143] When components of pathogens (eg, bacteria) contact hepatic macrophages (Kupffer cells), they activate various pattern recognition receptors including Toll-like receptor 4 (TLR4), inducing immune responses and triggering liver inflammation.[49,50] In burn patients complicated with sepsis, hepatic sinusoidal endothelial cell dysfunction may occur. Studies show that endotoxin-stimulated hepatic endothelial cells exhibit reduced sensitivity to acetylcholine, impairing their vasodilatory capacity, which is closely associated with functional imbalance between inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS).[51,52] The liver is also intimately linked to septic immunosuppression. Hepatic-secreted acute-phase proteins mobilize myeloid-derived suppressor cells (MDSCs), which induce regulatory T cells to downregulate immune responses of CD4+ and CD8+ T cells and secrete anti-inflammatory factors (IL-10 and TGF-β).[53,54] Another immunosuppressive mechanism is endotoxin tolerance: daily LPS stimulation in rats reduces cytokine release and improves survival, and hepatic immune cells (monocytes and macrophages) have been observed to exhibit LPS tolerance in vivo and in vitro.[55,56] Although these findings suggest that immunosuppression can ameliorate multiple organ dysfunction and reduce inflammation, it may also impair pathogen clearance, increasing risks of secondary and multiple infections. Additionally, sepsis patients often develop cholestasis.[144] Animal studies have shown that various inflammatory cells and cytokines in sepsis inhibit the expression of hepatic bile and bile salt transporters, leading to hepatocellular cholestasis.[57,58] The above findings highlight the critical role of the gut-liver axis interaction in septic liver injury after burns, providing new directions for future research on intervention strategies.

Acute Cardiac Injury

Burns significantly and complexly impact cardiac function. Studies have found that hemodynamic disorders, such as decreased cardiac output and increased vascular resistance, occur in the early burn stage. A low cardiac output state upon admission often predicts a poor prognosis.[145,146] In addition to cardiac function parameters, several molecules or proteins (such as troponin, lactate, and interleukins) can also indicate burn-induced cardiac injury (Table 2).[109–111] The pathological mechanisms of post-burn cardiac dysfunction involve multiple factors, including hemodynamic changes, intense inflammatory responses, oxidative stress, and sepsis.

Burn-Induced Cardiac Injury

The hypermetabolic inflammatory response triggered by burns persists for a long time after injury.[136] This response is accompanied by sustained sympathetic activation and massive secretion of stress hormones.[147,148] The early secretion of stress hormones after injury helps patients counteract adverse pathophysiological changes, but prolonged adrenergic signaling induces myocardial cell apoptosis, accelerates cardiac fibrosis, and impairs cardiac function.[59] Additionally, this hypermetabolic response is associated with calcium homeostasis imbalance and massive release of inflammatory mediator.[149,150] Notably, cytokine concentrations in myocardial cells are higher than those in peripheral blood after burns, forming an "inflammatory microenvironment".[60] In vitro experiments on adult myocardial cells show that TNF-α promotes intracellular ROS production via regulating p38 and ERK1/2 MAPK signaling, increasing the proportion of apoptotic cells.[61] IL-1β may drive cardiac fibrosis by inducing arrhythmias and mediating interactions between macrophages and fibroblasts.[62,63] Autonomic dysfunction characterized by reduced heart rate variability during sepsis is closely associated with IL-6.[151] Additionally, in third-degree burned rats, myocardial intracellular calcium concentration abnormally increases, accompanied by significant impairment of myocardial contractility, which can be effectively mitigated by calcium antagonist intervention.[64]

Cardiac Injury Caused by Burn Sepsis

More than 70 years have passed since the first description of sepsis-induced cardiac injury in 1951.[152] The mortality rate exceeds 70% when septic patients exhibit cardiac dysfunction.[153] Studies suggest that myocardial depressant substances

exist in septic patients, including inflammatory cytokines, prostaglandins, endothelin-1, NO, and adhesion molecules.[65] For example, silencing the prostaglandin F2α receptor alleviates myocardial fibrosis, while activating the thromboxane A2 receptor exacerbates myocardial apoptosis via oxidative stress accumulation.[66–68] iNOS is low-expressed in resting myocardial tissue but is activated to synthesize large NO under ischemic and inflammatory conditions.[154,155] Abnormally expressed NO may directly reduce myocardial contractility by decreasing calcium influx through voltage-dependent L-type calcium channels.[69] Septic myocardial injury may also involve multiple cell death forms.[156] Studies show that LPS promotes ferrous iron dissociation from ferritin and translocation to mitochondria, elevating mitochondrial ROS levels and inducing ferroptosis in cardiomyocytes.[70] Additionally, the STING pathway regulates pyroptosis: LPS promotes STING binding and phosphorylation with interferon regulatory factor 3 (IRF3), ultimately upregulating NOD-like receptor protein 3 (NLRP3) expression to drive inflammasome formation and pyroptosis.[71,72] In addition to directly injuring cardiomyocytes, burns can also exert indirect effects on the heart by disrupting vascular homeostasis. Following burn injury, necrotic cells release large amounts of histones, which bind to C-type lectin domain family 2 member D (Clec2d) receptors on vascular endothelial cells, thereby inducing vascular barrier dysfunction.[157] These mechanisms reveal the complexity of septic myocardial injury, offering new perspectives for developing multi-target protective strategies.

The "Domino Effect" of Organ Dysfunction

In 2007, the American Burn Association (ABA) developed a specific definition for burn-related sepsis.[8] This definition covers indicators across multiple organs or systems, including body temperature, blood glucose, tachycardia, tachypnea, and platelet count (Figure 2 and Supporting Information 1). Such a definition reveals that burns are not merely superficial

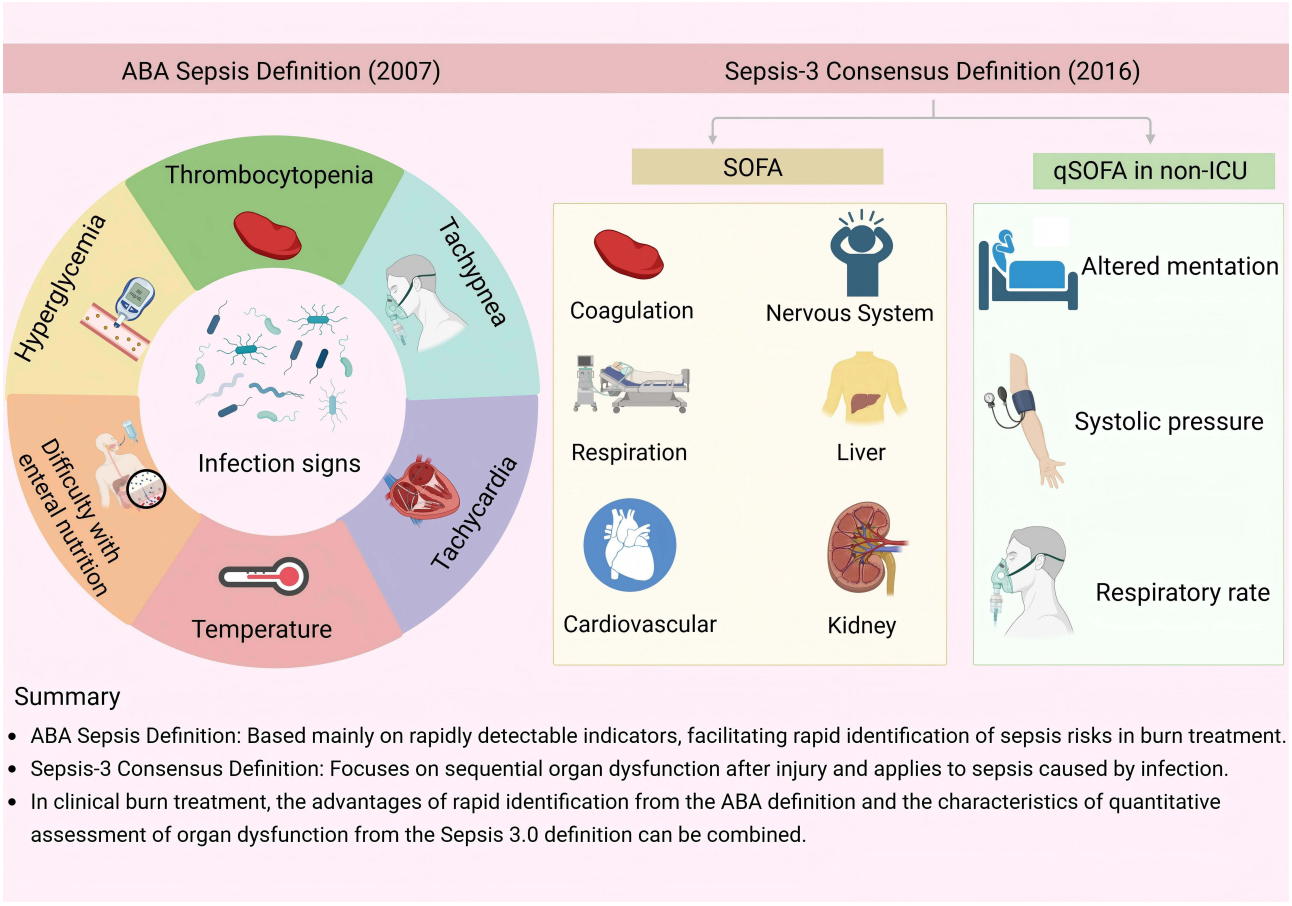

Figure 2 A summary of two clinically commonly used definitions of sepsis.

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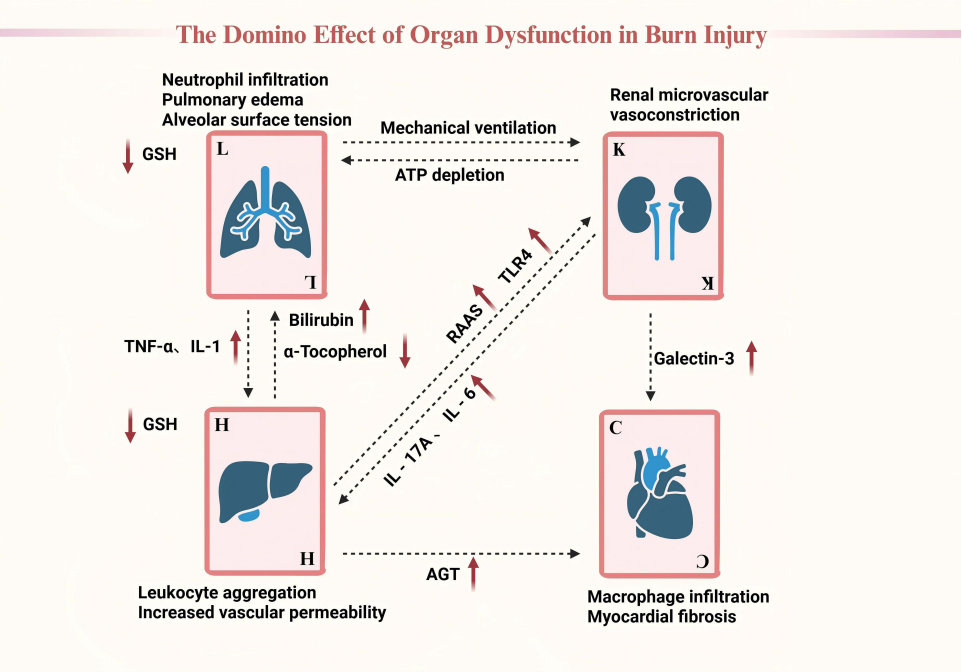

Figure 3 The crosstalk mechanism of injury in four types of organ dysfunction after burns.

tissue injuries but key factors triggering systemic homeostasis imbalance in the body. In the updated Sepsis 3.0 definition of 2016, the Sequential Organ Failure Assessment (SOFA) provides detailed evaluation of sequential organ dysfunction.[5] It involves core dimensions like respiratory, renal, hepatic, and cardiovascular functions (Figure 2 and Supporting Information 2). In 2023, to establish internationally applicable clinical guidelines and reduce global disparities in the management of organ dysfunction associated with burn sepsis, the International Society for Burn Injuries (ISBI) issued the first international clinical practice guideline specifically for sepsis in burn patients: Surviving Sepsis After Burn Campaign (SSABC).[158] Building upon the criteria proposed by the ABA and the Sepsis 3.0 definition, this guideline incorporated diagnostic indicators including wound appearance and procalcitonin, thereby further improving the accuracy of organ dysfunction diagnosis and the targeting of therapeutic interventions. These guidelines indicate that when extensive burns disrupt systemic homeostasis and progress to sepsis, vital organs including the lungs, kidneys, liver, and heart frequently develop dysfunction either sequentially or concurrently. These organs engage in crosstalk via a pathological network consisting of inflammatory cascades, metabolic disturbances, and hemodynamic abnormalities (Figure 3). This acts as a domino effect, continuously exacerbating the overall deterioration of the condition. The reciprocal interaction and coordinated progression of organ dysfunction represent a critical determinant underlying the pathophysiological course and clinical prognosis of burn sepsis.

Inflammatory factors (eg, TNF-α, IL-1β) released by inhalation injury-induced ALI or even ARDS after burns can "remotely attack" other organs via the bloodstream.[74,159] Studies have found that ARDS is closely associated with AKI. When patients present with the hyperinflammatory subtype of ARDS, their serum creatinine levels also increase significantly.[81,160] An observational study involving 8029 patients showed that the incidence of AKI among ARDS patients was 44%, significantly higher than the 27% incidence among patients without ARDS, indicating that ARDS is considered an independent risk factor for AKI.[161] In addition, in an experimental burn model using rabbits, researchers found that the content and synthesis rate of glutathione (GSH) in the lungs and liver decreased significantly. The reduction in GSH synthesis weakens the body's organs' ability to resist oxidative stress after burns.[73] ARDS treatment also increases the risk of kidney injury: positive-pressure mechanical ventilation hinders venous return, leading to right ventricular dysfunction and renal congestion, while reducing renal blood flow, glomerular filtration rate, and urine output. Permissive hypercapnia combined with renal insufficiency exacerbates acid-base imbalance.[74]

Ischemic AKI induces oxidative stress in lung tissue, shifts energy metabolism from oxidative phosphorylation to alternative pathways (eg, amino acid decomposition and pentose phosphate pathway), causes ATP depletion, and accompanies increased circulating cytokines, upregulated lung chemokines, and neutrophil infiltration—thereby triggering pulmonary inflammatory injury and metabolic disorders.[75,76] Clinical data also confirm that burn patients with AKI face an increased risk of respiratory failure.[162] Additional research has found that AKI patients exhibit alterations in drug metabolism, lipid synthesis, and protein synthesis, indicating compromised liver function.[163] Experimental data show that AKI exacerbates oxidative stress and apoptotic processes in hepatocytes, while promoting leukocyte aggregation in liver tissue and increasing vascular permeability.[77] Studies have demonstrated that peptidylarginine deiminase 4 (PAD-4) plays a key regulatory role in liver injury induced by AKI—compared with wild-type mice, PAD-4-deficient mice show significantly reduced hepatic inflammatory responses and injury after renal ischemia-reperfusion injury, suggesting that extrarenal PAD-4 mediates liver injury following AKI.[78] Furthermore, elevated levels of interleukin-17A (IL-17A) and IL-6 in AKI patients can also induce liver damage.[79,80] Additionally, AKI induces cardiac injury via a galectin-3 (Gal-3)-dependent pathway, manifesting as cardiac inflammation, macrophage infiltration, fibrosis, and dysfunction.[81–83] Cardiovascular toxicity arises from uremic toxin accumulation, metabolic acidosis, and electrolyte disorders in AKI, which may increase the risk of myocardial ischemia and fatal arrhythmias.[80]

Acute liver injury reduces the body's ability to clear bacteria and toxins, decreases coagulation factor synthesis/release, causes immune imbalance, and triggers multi-organ injury.[164] In models of bacterial sepsis and secondary hepatic ischemia-reperfusion injury, researchers found that serum levels of endotoxin and TNF-α were significantly higher in the experimental group than in the control group, exacerbating pulmonary neutrophil infiltration and pulmonary edema.[84] Additional studies have shown that elevated bilirubin after liver injury can enter lung tissue and disrupt alveolar surface tension.[85] A study on burn and inhalation injury in sheep confirmed that, in addition to inducing lung tissue damage, the injury leads to abnormally elevated serum transaminase levels. Concurrently, the liver's capacity to synthesize α-tocopherol (the main active component of vitamin E) is significantly reduced, further weakening the antioxidant defense of lung tissue and other organs.[86] Liver injury activates the renin-angiotensin-aldosterone system and sympathetic nervous system; meanwhile, intestinal bacterial translocation induces systemic inflammation, leading to renal microvascular dysfunction and arterial constriction by activating tubular TLR4 and releasing proinflammatory factors—ultimately causing renal hypoperfusion and decreased glomerular filtration rate.[87] Similarly, hepatic angiotensinogen (AGT) induces myocardial dysfunction through the renin-angiotensin system (RAS). Clinical data show a positive correlation between plasma cardiac troponin T (cTnT) levels and AGT concentration in sepsis patients.[88] Cardiac dysfunction primarily impairs pumping capacity, reduces effective circulating blood volume, and further aggravates ischemia in other organs. Current studies show that in the crosstalk of septic organ dysfunction, the heart mainly acts as an affected organ downstream of the domino effect.

In summary, understanding the crosstalk mechanism of post-burn organ dysfunction requires dissecting the injury pathways of individual organs. Furthermore, it requires revealing the laws of cross-organ transmission of pathological signals from a systems biology perspective. This shift in perspective will provide new therapeutic targets for breaking the vicious cycle of multiple organ dysfunction syndrome (MODS). Only by disrupting the "pathological alliance" formed by the lungs, kidneys, liver, and heart through inflammation, metabolism, oxidative stress, and other links—and blocking harmful inter-organ crosstalk—can we truly overcome the clinical bottleneck in burn treatment.

Advanced Treatment

In addition to consuming substantial public resources for society, severe burns inflict dual physical and psychological trauma on patients, which persists for a long time. Although existing expert consensus and treatments (such as prehospital emergency care, wound infection prevention, fluid resuscitation, extracorporeal membrane oxygenation, and continuous renal replacement therapy) have reduced the risk of aggravated conditions in burn patients, they still fail to meet clinicians' therapeutic expectations.[10,165,166] Targeting the pathophysiological mechanisms of burn-induced organ dysfunction, numerous studies have deeply explored potential therapeutic targets, providing a basis for future treatments (Table 3).

Table 3 Translational Therapeutic Research Based on Preclinical Experiments

Target Organ	Types of Experimental Animals and Cells	Materials and Technologies	Therapeutic Mechanism	References	Year
Lung	SD Rat); Amniotic Mesenchymal Stem Cell (AMSC)	Amniotic Mesenchymal Stem Cells Isolated from Human Placenta	Reduce Inflammatory Factors; Promote the Expression of Pulmonary Surfactant Proteins	[167]	2018
	C57BL/6 Mouse; Murine Lung Epithelial Cell 12 (MLE-12 Cell)	N-Acetylcysteine-Loaded Nanoliposomes	Inhibit the Transformation of Macrophages to M1 Proinflammatory Phenotype	[168]	2023
	C57BL/6 Mouse; Human Umbilical Vein Endothelial Cell (HUVECs)	Dexamethasone-Loaded Bovine Serum Albumin Nanoparticles	Targetedly Bind to E-Selectin on the Surface of Endothelial Cells to Reduce Inflammation	[169]	2019
Kidney	C57BL/6 Mouse; Human Embryonic Kidney 293 Cell (HEK-293 Cell)	CB-rDON@AMPs Nanoplatform	Detect Sepsis Biomarker miRNA-21; Scavenge ROS; Antibacterial Activity	[170]	2025
Heart	C57BL/6 Mouse; Rat Ventricular Myocyte; H9c2 Cell; and AC16 Cell	Melanin Nanoparticles	Scavenge ROS; Inhibit Ferroptosis of Cardiomyocytes	[171]	2023
Kidney	C57BL/6 Mouse; Human Proximal Tubular Epithelial Cell (HK2 Cell)	Theabrownin	Inhibit Apoptosis and Ferroptosis of Renal Tubular Epithelial Cells	[172]	2025
Liver	C57BL/6 Mouse; Human Hepatocyte Cell Line LO2 (LO2 Hepatocyte)	Wenqingyin	Antagonize Ferroptosis of Hepatocytes	[173]	2023

Stem Cell Intervention

Stem cells are commonly used in studies on organ injury repair due to their characteristics such as low immunogenicity and strong differentiation ability. In a report on rat inhalational lung injury, researchers treated ALI via caudal vein injection of human amniotic mesenchymal stem cells (hAMSCs) isolated from human placenta.[167] The results showed that stem cell therapy reduced the levels of pro-inflammatory factors such as IL-6 and TNF-α, increased the level of the anti-inflammatory factor IL-10, and promoted the expression of pulmonary surfactant proteins (SP-A, SP-C, SP-D) to alleviate inflammation and repair lung tissue. Moreover, the lung imaging, pathological scores, lung wet-to-dry weight ratio, degree of pulmonary fibrosis, and expression of pulmonary surfactant proteins in the treatment group were all superior to those in the control group. However, the stem cells in this study were derived from clinically discarded placental tissue, which may have unstable sources. Therefore, it is feasible to consider developing biomaterials with similar functions as alternatives and conducting preclinical experiments.

Nano-Targeted Therapy

In recent years, nanoparticles have been widely used as carriers for in vivo targeted therapy due to their good plasticity, stability, and detectability. In studies on burn-induced ALI, nanoparticles constructed from materials like liposomes and pseudocell membranes have been applied to mechanism exploration and therapeutic strategy development.[174] A recent study on regulating the polarization of pulmonary macrophages in mice found that phosphatidylserine-modified nano-liposomes exhibit excellent targeting ability. These liposomes, loaded with the anti-inflammatory agent N-acetylcysteine, significantly inhibit the transformation of macrophages into pro-inflammatory M1 phenotype and promote lung injury repair.[168] Additionally, nanoparticles can carry miRNA-233 to regulate macrophages.[175] In addition to pulmonary macrophages, lung endothelial cell injury is also one of the intervention targets for ALI. In one study, dexamethasone

was encapsulated in bovine serum albumin nanoparticles, which specifically bind to E-selectin on the surface of inflammation-activated endothelial cells, thus targeting dexamethasone to endothelial cells.[169] A latest study developed a nanoplatform named CB-rDON@AMPs based on DNA origami technology. This nanoplatform (CB-rDON@AMPs) relies on sepsis-associated acute kidney injury (SA-AKI)-elevated miRNA-21 to trigger strand displacement reaction for diagnosis, restoring Cy5 fluorescence and inducing photoacoustic signal changes of BHQ3 to achieve bimodal imaging. For therapy, it scavenges ROS via DNA origami, and caspase-1 cleaves peptide bonds to release LL-37 for bactericidal activity. Key preclinical results are remarkable: in a CLP-induced SA-AKI model using male C57 mice (N=3/5), the platform reached peak renal accumulation at 1 hour, enabling detection of early injury. After treatment, BUN and creatinine levels were close to normal, the 7-day survival rate reached 90%, and it exhibited excellent bactericidal efficacy against Escherichia coli and Staphylococcus aureus. In terms of safety, the viability of HEK-293 cells in vitro exceeded 98.7%, liver and kidney function indicators of healthy mice remained normal, no pathological changes were observed in major organs, and biocompatibility was favorable.[170] In addition, a recently developed MRI-visible melanin nanoparticle (MMPP) has been reported for the treatment of septic myocardial injury.[171] The core mechanism of MMPP in alleviating septic myocardial injury is clear: it inhibits ferroptosis through dual pathways of reactive oxygen species (ROS) scavenging and iron ion chelation, while reducing inflammatory responses and protecting mitochondrial homeostasis, exerting a protective effect through multi-target synergy. Its preclinical performance is outstanding: it not only improves the survival rate of male C57 mice with sepsis (N=4), enhances cardiac function and ameliorates myocardial pathological status, but also protects cardiomyocyte viability in vitro, with excellent MRI imaging capability. In terms of safety, it shows no obvious organ or cytotoxicity, is mainly metabolized by the liver and kidneys, and has good biocompatibility. However, it currently only has a foundation in materials and preparation, due to the lack of key data such as pharmacokinetics, it has not yet entered the clinical translation stage.

Mitochondrial Protection Strategy

In recent years, ferroptosis and mitochondrial injury have gained increasing attention as therapeutic targets. In the AKI model induced by dorsal scalding in male BALB/c mice (N=3/6), the herbal component theabrownin (TBs) improved mouse survival and reduced renal injury. Transcriptomic and metabolomic analyses showed that TBs inhibited apoptosis and ferroptosis in renal tubular epithelial cells by increasing the levels of guanosine acetic acid and fumaric acid.[172] In a septic liver injury model induced by intraperitoneal LPS injection in male C57 mice (N=3), researchers found that the traditional Chinese medicine Wenqingyin could alleviate the pathological damage of liver tissue, reduce the levels of ALT and AST as well as the release of inflammatory factors, and restore the mitochondrial membrane potential. Additionally, Wenqingyin showed no cytotoxicity to hepatocytes at the concentrations used in the in-vitro tests. Notably, this therapeutic effect is closely associated with Nrf2-dependent inhibition of hepatocellular ferroptosis.[173] Although these two types of traditional Chinese medicines have shown potential in treating organ injuries or sepsis caused by burns and scalds, these preclinical studies have not comprehensively evaluated in vivo pharmacokinetics and toxicology. Moreover, current conclusions are mainly derived from cell and animal experiments, lacking support from large-sample validation and clinical data, which require further verification in the future.

Conclusion

This review systematically summarizes the pathological mechanisms and emerging therapeutic strategies of dysfunction in four major organs (lung, kidney, liver, and heart) after burns, with the core conclusions clarified as follows: Organ injuries caused by burns are not isolated. Direct injury from high-temperature smoke, sepsis induced by infection, and systemic inflammatory response are the main triggers. Among them, the activation of inflammatory signals (such as the NF-κB pathway), the destruction of the endothelial barrier (glycocalyx structure), and novel cell death patterns including pyroptosis and ferroptosis are the key driving links of injury. Various organs form a “crosstalk effect” through inflammatory cascades, hemodynamic abnormalities, and metabolic disorders. For example, TNF-α released from lung injury can remotely aggravate kidney injury, and AKI in turn acts on the liver through oxidative stress, forming a “pathological alliance” of multiple organ dysfunction. Regarding treatment strategies, the development and exploration of emerging therapeutic approaches, including nanoscale targeted therapy, stem cell intervention, mitochondrial

protection, and ferroptosis inhibition, are all based on the core pathological characteristics of organ injury induced by sepsis. Among these, nanoscale targeted therapy relies on the precise targeting properties of carriers such as liposomes and DNA origami platforms to achieve precise intervention against core targets in the "pathological alliance", including transorgan-activated inflammatory endothelial cells and pro-inflammatory macrophages, thereby blocking the transorgan transmission of inflammatory signals. Human amniotic mesenchymal stem cell intervention can regulate systemic inflammatory homeostasis and promote the repair of damaged organs such as lung tissue, interrupting the vicious cycle of mutual amplification of the multi-organ inflammatory microenvironment within the "pathological alliance". Mitochondrial protection and ferroptosis inhibition mediated by theabrownin, Wenqingyin, and melanin nanoparticles can repair the common mitochondrial dysfunction across multiple organs after burn injury, block the transorgan propagation of programmed cell death such as pyroptosis and ferroptosis, and inhibit the formation and progression of the "pathological alliance" at the source.

The research progress of the above therapeutic strategies confirms that multi-target and systematic intervention targeting the core characteristics of the "pathological alliance" represents a key direction to address the clinical bottleneck in the diagnosis and treatment of post-burn multiple organ dysfunction syndrome, and also provides a clear rationale for subsequent basic research and clinical translation. In the future, it is necessary to develop novel therapeutic regimens with synergistic regulation of multiple organs based on the transorgan crosstalk mechanism of the "pathological alliance", so as to promote the transformation of the therapeutic paradigm for post-burn organ dysfunction from "local symptomatic support" to "systematic and precise intervention".

Current research has limitations in three aspects: First, the population coverage is incomplete, failing to involve special burn groups such as children (with immature organs), the elderly (with declined immune function), and patients with underlying diseases like diabetes and hypertension, thus unable to reflect injury differences under different physiological states. Second, preclinical studies have shortcomings: insufficient reproducibility of nanomaterial preparation, lack of long-term in vivo accumulation toxicity data, poor stability of stem cell sources (eg, placental tissue), and absence of combined efficacy evaluation with traditional therapies such as fluid resuscitation and wound management. Third, there are obstacles to translational implementation: the scarcity of validated biomarkers for organ injury (eg, HMGB1 for lung injury and NGAL for kidney injury), and unclear regulatory standards in the fields of nanomedicine and stem cells, which restrict the translation of achievements into clinical practice.

To promote the development of translational medicine, this review proposes the following research roadmap: At the preclinical research level, it is necessary to prioritize the establishment of standardized preparation processes for nanomaterials, evaluate their safety and toxicity through large animal models (eg, pigs and sheep), optimize stem cell sources (eg, induced pluripotent stem cells), and verify the risk of immune rejection after transplantation. At the level of biomarkers and endpoint indicators, efforts should be made to accelerate the validation of specific biomarkers such as HMGB1 (lung), NGAL (kidney), lipid metabolites (liver), and troponin (heart); trial endpoints should consider both short-term effects (7-day survival rate, organ function indicators) and long-term outcomes (eg, degree of fibrosis). At the level of breaking regulatory barriers, it is essential to collaborate with regulatory authorities to formulate hierarchical approval standards for nanomaterials (based on particle size and targeting mechanism), clarify quality specifications for stem cell preparation (viability, heterocell ratio), and involve regulators in protocol design at the initial stage of clinical trials to shorten the translation cycle.

In the future, by filling the research gaps in special populations, improving the preclinical validation system, and breaking through regulatory barriers, it is expected to translate emerging therapies into clinically accessible protocols. Ultimately, this will enable early warning and precise intervention for organ injuries after burns, significantly reducing patient mortality and improving prognosis.

Abbreviations

AGT, Angiotensinogen; AKI, Acute kidney injury; ALI, Acute lung injury; ALT, Alanine aminotransferase; AMPs, Antimicrobial peptides; ARDS, Acute respiratory distress syndrome; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; CLP, Cecal ligation and puncture; CPT, Carnitine palmitoyltransferase; eNOS, Endothelial nitric oxide synthase; Gal-3, Galectin-3; GBP2, Guanylate-binding protein 2; GFR, Glomerular filtration rate; GSH, Glutathione;

IL, Interleukin; iNOS, Inducible nitric oxide synthase; IRF3, Interferon regulatory factor 3; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinase; MCJ, Methyl-CpG binding domain protein J; MDSCs, Myeloid-derived suppressor cells; MMP9, Matrix metalloproteinase 9; MODS, Multiple organ dysfunction syndrome; NO, Nitric oxide; NLRP3, NOD-like receptor protein 3; Nrf2, Nuclear factor erythroid 2-related factor 2; PAD-4, Peptidylarginine deiminase 4; RAS, Renin-angiotensin system; RhoA, Rho-associated protein kinase; ROCK1, Rho-associated kinase 1; ROS, Reactive oxygen species; SIRS, Systemic inflammatory response syndrome; STING, Stimulator of interferon genes; TBs, Theabrownin; TGF-β, Transforming growth factor-beta; TNF, Tumor necrosis factor; TNF-α, Tumor necrosis factor-alpha; UCP1, Uncoupling protein 1; VEGF, Vascular endothelial growth factor; VE-cadherin, Vascular endothelial cadherin.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

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