Dynamic regulation and targeted intervention of neutrophils in hepatic ischemia-reperfusion injury (Review)

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Received December 17, 2025; Accepted February 12, 2026

DOI: 10.3892/ijmm.2026.5780

Abstract. Ischemia-reperfusion injury (IRI) is a complex pathophysiological process characterized by oxidative stress, inflammatory response and cell death during tissue reperfusion, leading to organ dysfunction. In liver transplantation, hepatic ischemia-reperfusion injury (HIRI) can result in irreversible liver failure and subsequently trigger rejection. Neutrophils, as the first recruited innate immune cells, play a central role in the initiation, progression and resolution stages of HIRI. However, current research predominantly focuses on their pro-inflammatory and damaging mechanisms, lacking a theoretical framework that systematically integrates their dual functions. Based on a systematic review of key processes involving neutrophils in HIRI, including recruitment, adhesion, migration, neutrophil extracellular trap (NET) formation and phenotypic polarization, the present review proposed the 'injury-repair balance' theory. It emphasized that neutrophils are dynamically regulated by the hepatic microenvironment and can undergo functional conversion between pro-inflammatory N1 and anti-inflammatory/repair N2 phenotypes. Their polarization state is a critical factor determining the progression and recovery of HIRI. The present review further explores multi-dimensional intervention strategies targeting neutrophils, including inhibiting excessive recruitment and activation, regulating migration to reduce local accumulation, suppressing NET formation and promoting their clearance, as well as combining antioxidant and anti-inflammatory therapies to reestablish immune homeostasis. Additionally, extracellular vesicles, due to their excellent targeting delivery and immunomodulatory capabilities, have emerged as potential tools for precise regulation of neutrophil function. Notably, current research on neutrophil polarization mechanisms remains incomplete. Future studies should delve into the temporal regulatory mechanisms of polarization and explore the possibility of driving neutrophils toward an N2-like reparative phenotype through pharmacological or biological interventions. This strategy is expected to shift the treatment paradigm for HIRI from traditional 'cell suppression' to a more precise 'functional reprogramming,' transforming the approach from merely mitigating injury to actively promoting tissue regeneration.

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Abbreviations: IRI, ischemia-reperfusion injury; HIRI, hepatic ischemia-reperfusion injury; NETs, neutrophil extracellular traps; EVs, extracellular vesicles; DAMPs, damage-associated molecular patterns; LSECs, liver sinusoidal endothelial cells; ROS, reactive oxygen species; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor alpha; IFN-β, interferon beta; IFN-γ, interferon gamma; VEGF, vascular endothelial growth factor; MPO, myeloperoxidase; NE, neutrophil elastase; PGI2, prostacyclin I2; NKT, natural killer T cells; APCs, antigen-presenting cells; PRRs, pattern recognition receptors; TLRs, Toll-like receptors; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; DNase, deoxyribonuclease

Key words: neutrophils, ischemia-reperfusion injury, hepatic ischemia-reperfusion injury, neutrophil extracellular traps, inflammation response, neutrophil polarization, therapeutic application

Contents

1. Introduction

Hepatic ischemia-reperfusion injury (HIRI) represents a critical clinical challenge in liver transplantation and major hepatectomy, serving as a key determinant of postoperative liver dysfunction, graft rejection and patient mortality (1,2). HIRI pathogenesis mainly involves hypoxic damage during the ischemic phase, which is subsequently dominated by a robust sterile inflammatory response triggered upon reperfusion. This response manifests as oxidative stress, activation of immune cells and programmed cell death (3). During this process, neutrophils, as the earliest immune cells recruited to the injury site, react swiftly and play a complex, multi-layered role in the progression of HIRI. Traditionally, neutrophils have been considered primary executors of tissue damage, exacerbating HIRI through the generation of reactive oxygen species (ROS), release of granular proteases and formation of neutrophil extracellular traps (NETs) (4,5). Notably, NETs not only possess antibacterial functions but also can entrap host cells and release damage-associated molecular patterns (DAMPs), thereby further amplifying inflammatory responses and thrombosis, which intensifies tissue damage and microcirculatory dysfunction.

However, with the continuous development of immunomodulatory strategies and advances in cell tracking technologies (6), the understanding of neutrophil roles in HIRI has gradually shifted. Studies have revealed that neutrophils are not merely terminal effector cells participating in damage but also act as dynamic regulators in the processes of injury and repair (7-10). The functional fate of neutrophils, whether they polarize towards a pro-inflammatory (N1) or an anti-inflammatory (N2) phenotype, plays a pivotal role in the course of HIRI. This phenotypic shift determines whether HIRI is exacerbated or alleviated (11,12). Although some progress has been made regarding neutrophil functions and their mechanisms in HIRI, significant research gaps remain in this field (13,14). Currently, the most critical questions are: What are the key molecules regulating the transition from the N1 to the N2 phenotype? More importantly, how can this mechanism be translated into therapeutic strategies that precisely modulate neutrophil function, moving beyond simple immune cell depletion? The present review aimed to address these conceptual gaps by proposing and elaborating an 'injury-repair balance' theoretical framework to reinterpret the multifaceted roles of neutrophils in HIRI. Furthermore, the present review explored the potential of emerging therapeutic strategies, such as targeting neutrophil phenotypic regulation, intervening in NETs formation and utilizing neutrophil-derived vesicles. These investigations not only provide a novel perspective for understanding HIRI but also establish a theoretical foundation for precise immunomodulatory interventions, potentially paving new avenues for future therapeutic strategies.

2. Pathological mechanism of HIRI

HIRI refers to the interruption of blood flow to the liver during the ischemic phase, causing liver cells to lose oxygen and nutrients. Subsequently, upon the restoration of blood flow (reperfusion phase), the liver undergoes sterile inflammatory damage caused by excessive oxidative stress and inflammatory responses (15). In liver transplantation, HIRI not only leads to functional impairment of the donor liver but also exacerbates the issue of donor shortage (16). Healthy livers and marginal donor livers are both susceptible to IRI. Reducing the occurrence of HIRI can help improve the success rate of transplantation and expand the available donor pool. Although the success rate of liver transplantation has increased in recent years, the persistent growth in the number of patients awaiting a liver means that HIRI remains a pressing clinical challenge (17).

The liver is composed of parenchymal cells (such as hepatocytes) and non-parenchymal cells [such as Kupffer cells, liver sinusoidal endothelial cells (LSECs) and stellate cells]. HIRI can be divided into warm IRI and cold IRI (1,4,18,19). Warm IRI primarily occurs in situations such as liver surgery, liver transplantation, hypovolemic shock, certain toxic liver injuries, venous embolic diseases and Budd-Chiari syndrome. On the other hand, cold IRI occurs mainly during the preservation process of donor livers before transplantation. Although both types of HIRI share similar pathological mechanisms, their specific mechanisms differ. The present review focused on the pathogenesis of warm IRI (Fig. 1).

In the pathogenesis of HIRI, hepatocyte necrosis is the primary manifestation of cellular damage. During the ischemic phase, hepatocytes suffer from a lack of oxygen and nutrients, leading to suppressed metabolism, inhibited ATP synthesis and a gradual accumulation of an acidic intracellular environment, ultimately causing structural and functional damage to the liver cells (20-22). However, although the restoration of blood flow is essential during reperfusion, it is accompanied by a dramatic increase in oxidative stress and produce excessive ROS that damage cell membranes, mitochondria and DNA (23-25). This oxidative damage-induced cell death affects hepatocytes and involves LSECs and cholangiocytes. ROS generation can directly damage the parenchymal liver cells and activate immune cells and endothelial cells, leading to the release of various inflammatory factors such as tumor necrosis factor alpha (TNF-α), interferon beta and gamma, interleukins (IL-1β, IL-6) and vascular endothelial growth factor (VEGF). This further exacerbates tissue injury. It has been reported that the alternating effects of ischemia and reperfusion can induce oxidative damage to cell membranes, lipid peroxidation, endothelial dysfunction, intracellular calcium overload and cell cycle arrest, all of which contribute to liver injury (26-28).

During the HIRI process, immune responses are one of the key factors in the pathological progression. The immune cascade involves the activation of Kupffer cells in the liver and the infiltration of circulating lymphocytes, neutrophils and monocytes. Macrophages are strategically distributed

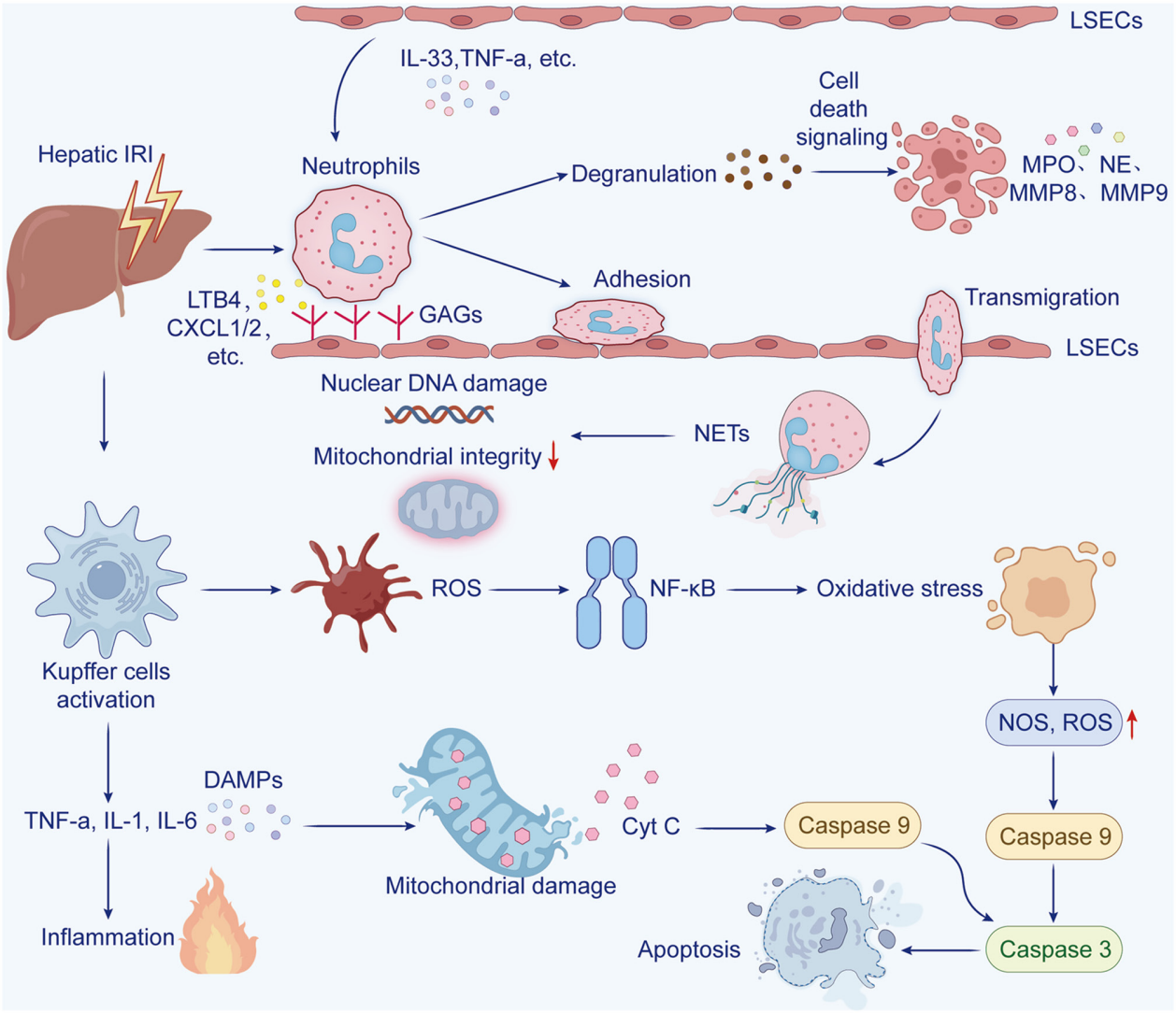

Figure 1. The pathological mechanism of HIRI and the role of neutrophils in HIRI. HIRI, hepatic ischemia-reperfusion injury; IRI, ischemia-reperfusion injury; LSECs, liver sinusoidal endothelial cells; GAGs, glycosaminoglycans; DAMP, damage associated molecular pattern; NETs, neutrophil extracellular traps; ROS, reactive oxygen species; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor alpha; LTB4, leukotriene B4; MPO, myeloperoxidase; NE, neutrophil elastase; MMP8, matrix metallopeptidase 8; MMP9, matrix metallopeptidase 9; NOS, nitric oxide synthase; Cyt C, Cytochrome *c*.

throughout the body, phagocytosing dead cells and debris. Liver contains a large number of macrophages, which play a crucial role in the mechanism of HIRI. They sense the initial damage-associated signals, triggering inflammation and recruiting host immune cells and promote inflammation resolution and tissue repair for maintaining homeostasis. Neutrophils, a major immune cell in steady-state blood circulation, serve as the first line of defense against invading pathogens. They are recruited to the injury site where they enhance hepatocyte damage and act as a biomarker for the severity of HIRI (29) as 'non-specialized' innate effector cells. In ischemic tissue, neutrophils produce hydrogen peroxide and myeloperoxidase (MPO) (30). Hydrogen peroxide induces intracellular oxidative stress within hepatocytes by directly diffusing into the cells. MPO utilizes hydrogen peroxide to produce hypochlorous acid, which enters target cells and causes damage. Activated neutrophils also release neutrophil elastase (NE), which inhibits the production of prostacyclin I2 (PGI2). PGI2 is a vasodilator released from endothelial cells that plays a protective role by maintaining normal hepatic circulation during liver ischemia-reperfusion. When activated neutrophils release NE, the protective effect of PGI2 is suppressed and liver damage ensues (31,32).

Additionally, T lymphocytes and natural killer T (NKT) cells play important roles in the immune response during HIRI (33-35). Deficiency of T cells or disruption of their infiltration markedly reduces HIRI injury, while NKT cells exacerbate inflammation by secreting IFN-γ. The activation of T cells, particularly $CD4^+$ Th1 and $CD8^+$ T cells, relies on the classical 'two-signal' model: T cell receptor recognition of the peptide-MHC complex presented by antigen-presenting cells (APCs) (first signal), along with co-stimulatory signals (such as B7-CD28 interactions) provided by APCs. In HIRI, hepatic APCs (e.g., Kupffer cells, dendritic cells) upregulate co-stimulatory molecules upon activation, thereby driving T cell clonal expansion and effector function differentiation. Activated T cells aggravate hepatocyte damage directly or indirectly by releasing cytokines such as IFN-γ and TNF-α, as

well as cytotoxic mediators such as granzyme/perforin (36). Studies have shown that sulfonylurea-mediated activation of type II NKT cells can reduce the secretion of INF-γ by type I NKT cells, thus alleviating HIRI damage (37,38).

Following ischemia, the hypoxic local environment in the liver leads to the release of large amounts of DAMPs into the bloodstream. These DAMPs activate the innate immune response via pattern recognition receptors (PRRs). The activation of receptors such as Toll-like receptors (TLRs) and NOD-like receptors (39) triggers intracellular signaling pathways, which in turn activate inflammatory transcription factors such as nuclear factor-kappa B (NF-κB) and promote the production of various inflammatory cytokines (40,41). Moreover, among various PRRs, the recently characterized cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling pathway has emerged as a key mediator of inflammation and innate immune responses in HIRI. cGAS-STING activation occurs in response to cytoplasmic DNA, which becomes abundant during ischemia-reperfusion due to mitochondrial dysfunction and cellular damage. Once activated, STING initiates downstream signaling pathways such as TANK-binding kinase-1 (TBK1)-interferon regulatory factor-3 (IRF3) and NF-κB, not only enhancing the generation of ROS but also amplifying inflammatory responses by promoting the adhesion and migration of immune cells (42). Furthermore, the interplay between the cGAS-STING pathway and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is increasingly recognized as a critical axis under various conditions (43,44). Activation of the NLRP3 inflammasome represents a key step in IL-1β production during HIRI, further promoting neutrophil recruitment and amplification of the inflammatory response (45). The STING-NLRP3 axis links innate immune sensing to pyroptosis, a form of programmed cell death, which exacerbates hepatocyte injury and enhances the recruitment of immune cells to the liver. Activation of this axis has been shown to contribute markedly to endothelial dysfunction, hepatocyte necrosis and impaired liver regeneration in HIRI. Therefore, targeting the inflammasome and the production of inflammatory factors represents a potential therapeutic strategy.

Microcirculatory dysfunction is also a significant manifestation in the pathological process of HIRI (46). During ischemia, LSECs undergo vacuolization and swelling due to energy depletion and ion transport dysfunction, leading to the narrowing of the sinusoidal lumen and obstructing smooth blood flow (47). Although the restoration of blood flow during reperfusion helps provide oxygen, it may exacerbate the microcirculatory disorder, further aggravating liver damage. Preliminary studies suggested that the adhesion and accumulation of neutrophils may be a major cause of microcirculatory dysfunction. However, subsequent research indicated that despite accumulating in the microcirculation, neutrophils do not directly cause severe obstruction of sinusoidal perfusion (48). The isolated rat liver model has also demonstrated that the accumulation of neutrophils within the microcirculation does not significantly affect hepatic sinusoidal perfusion (49). Subsequently, local vasoconstrictors such as endothelin have been identified as the primary cause of post-ischemic microcirculatory dysfunction. Agonists of the adenosine or nitric oxide pathways, endothelin antagonists and prostaglandins can exert protective effects by regulating the sinusoidal diameter, preventing neutrophil adhesion, inhibiting platelet aggregation and scavenging ROS (50).

Furthermore, the renin-angiotensin-aldosterone system (RAAS) plays a key role in the pathophysiology of HIRI. During reperfusion, blood recirculates into the ischemic liver tissue, triggering a surge in ROS and pro-inflammatory mediators, thereby activating the RAAS. Angiotensin II (Ang II) is a key effector of the RAAS, exerting pro-inflammatory, pro-fibrotic and vasoconstrictive effects through its interaction with the angiotensin II type 1 receptor (AT1R). Upon binding to AT1R, Ang II primarily activates Gq proteins, leading to the activation of phospholipase C and the generation of second messengers IP3 and DAG. This results in intracellular calcium release and protein kinase C (PKC) activation. PKC further activates NADPH oxidase, producing large amounts of ROS and activating the NF-κB and AP-1 pathways, thereby forming a positive feedback loop of ROS and inflammation (51). Ang II promotes the recruitment of inflammatory cells, increases oxidative stress, stimulates the production of cytokines such as TNF-α and IL-1β and further exacerbates hepatocyte damage. Aldosterone, another key component of the RAAS, amplifies infection and fibrosis formation, worsening liver injury volume. Abouzed *et al* (52) demonstrated that using angiotensin receptor blockers, such as valsartan, to inhibit the RAAS and LCZ696 to inhibit neprilysin reduced liver IRI damage in a mouse model.

In summary, the initiation and progression of HIRI are orchestrated by a complex network of cytokines, primarily released by early-activated Kupffer cells and later-infiltrating neutrophils (Fig. 2). Mechanistically, TNF-α acts as a central mediator by binding to its receptor tumor necrosis factor receptor 1, subsequently triggering the activation of NF-κB, mitogen-activated protein kinases (MAPKs) and c-Jun N-terminal kinase (JNK) pathways (53). Furthermore, TNF-α enhances the expression of adhesion molecules on sinusoidal endothelial cells, particularly intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1(VCAM-1), promoting firm adhesion and aggregation of neutrophils and aggravating microvascular obstruction and tissue damage (54). In addition to TNF-α, a series of interleukins contribute to the immunopathology of HIRI. IL-6, IL-12, IL-23, VEGF and hepatocyte growth factor (HGF) play critical yet distinct roles (55). Pro-inflammatory interleukins such as IL-12 and IL-23 stimulate $CD4^+$ T cells to secrete IL-17, a potent chemoattractant for neutrophils, creating a positive feedback loop that exacerbates liver injury (51). Moreover, IL-12 and IL-23 increase TNF-α production via NF-κB activation, while IL-23 further activates the IFN-γ/IRF-1 axis, promoting the propagation of inflammation. Conversely, the post-inflammatory phase is mediated by counter-regulatory cytokines. IL-6, VEGF and HGF exhibit protective and regenerative properties. IL-6 promotes hepatocyte proliferation and alleviates oxidative stress by enhancing glutathione synthesis and activating the STAT3 signaling pathway (56). VEGF demonstrates a dual role in IRI; while endogenous VEGF may promote injury initiation, exogenous administration has been shown to facilitate angiogenesis and regeneration in post-ischemic liver (57). Similarly, HGF exerts potent protective effects by inhibiting oxidative stress, stimulating hepatocyte proliferation via

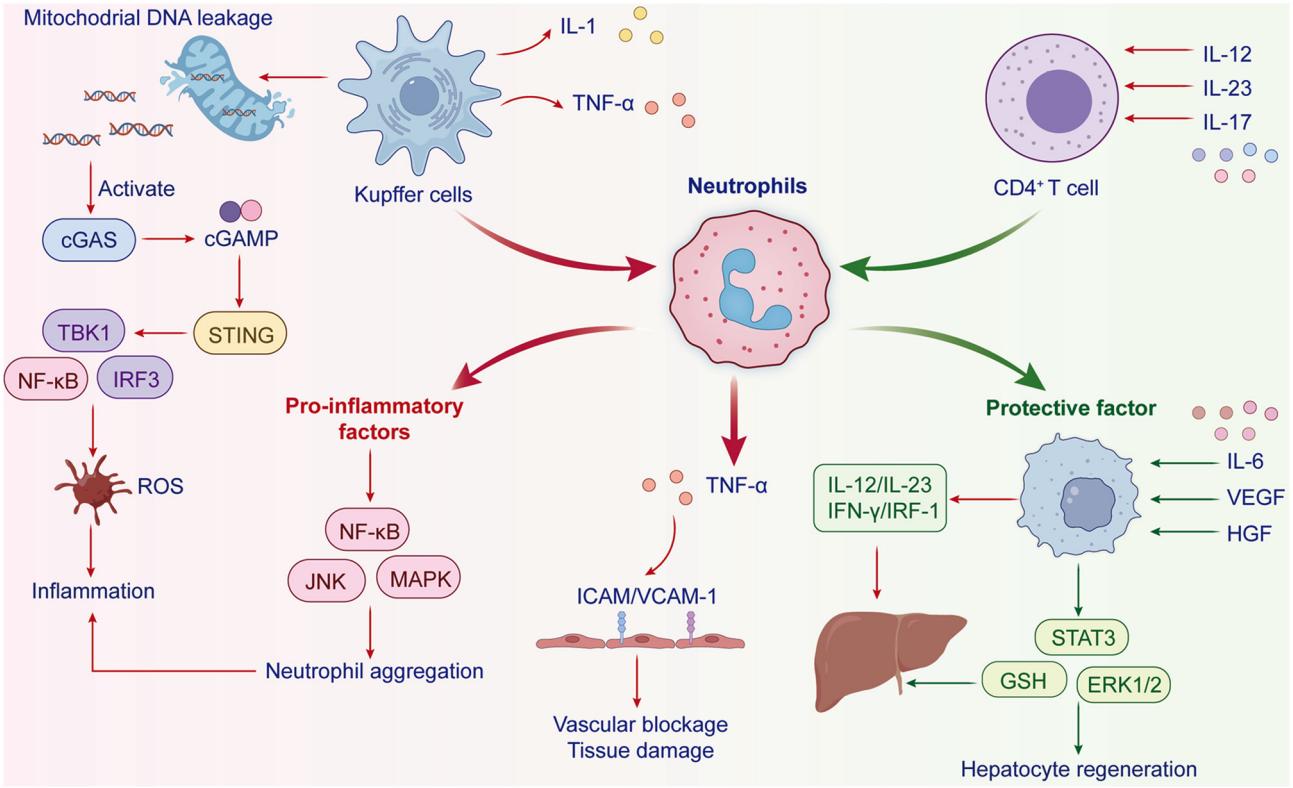

Figure 2. Integrated signaling network in HIRI: Inflammation amplification via cGAS-STING and cytokine crosstalk. mtDNA release activates cGAS-STING, driving TBK1-IRF3/NF-κB to enhance ROS and immune cell recruitment. Kupffer cell/neutrophil-derived IL-1/TNF-α and IL-12/IL-23/IL-17 axes promote inflammation, while IL-6, VEGF and HGF support regeneration via STAT3/ERK1/2, antioxidant effects and reduced adhesion. HIRI, hepatic ischemia-reperfusion injury; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; NF-κB, nuclear factor-kappa B; IRF3, interferon regulatory factor 3; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor ; STAT3, signal transducer and activator of transcription 3; GSH, glutathione.

ERK1/2 activation, upregulating glutathione and down-regulating ICAM-1 expression, thereby suppressing neutrophil adhesion and migration (58). In conclusion, the pathogenesis of HIRI is a complex, multi-factorial and multi-stage process involving interactions among oxidative stress, immune cell activation, cytokine release, microcirculatory dysfunction and damage-repair mechanisms. Although our understanding of its pathological mechanisms has advanced, effectively intervening in and treating HIRI, particularly in clinical settings such as liver transplantation, remains a key focus of current research.

3. The key role of neutrophils in HIRI

In HIRI, neutrophils play a central and dynamic role as effector cells. Their function is not fixed but evolves in an orderly manner along with the injury process. During the early phase, neutrophils are rapidly recruited to the ischemic liver, where they directly mediate hepatocyte damage by releasing ROS and proteases and form NETs, thereby amplifying local inflammation and microcirculatory dysfunction (4,5,59). As the pathological process progresses, neutrophils exhibit remarkable functional plasticity (60,61). A subset of these cells can undergo phenotypic switching, enhancing phagocytic activity to clear necrotic debris and secreting anti-inflammatory cytokines, thereby actively contributing to inflammation resolution and tissue repair (11). Ultimately, neutrophils are cleared from the inflammatory site through controlled processes such as programmed apoptosis, NETosis, or reverse transendothelial migration (rTEM) (62,63). Therefore, neutrophils are not merely terminal effectors but are deeply integrated into a coordinated immune response program. The dynamic balance between their pro-damage and pro-repair functions directly determines whether the tissue outcome shifts toward sustained injury or initiates orderly repair. This core mechanism establishes neutrophils as a key therapeutic target in HIRI. Future intervention strategies should focus on precisely modulating the nodes of their functional transition rather than applying non-specific suppression.

Neutrophil activation and recruitment. In the early phase of HIRI, DAMPs activate resident immune cells in the liver, particularly Kupffer cells and LSECs, which subsequently induce the production of various inflammatory mediators such as chemokines (CXCL1, CXCL2), cytokines (TNF-α, IL-1β) and ROS (64). This cascade of reactions collectively promotes the directed recruitment of neutrophils to the liver and initiates a systemic inflammatory response. Notably, the extent of neutrophil recruitment is markedly associated with the duration of ischemia, the longer the ischemic period, the more intense the local and systemic inflammatory responses, ultimately leading to aggravated liver injury.

During the HIRI process, leukotriene B4 (LTB4) is one of the earliest neutrophil chemokines to be released and its strong chemotactic effect plays a crucial role in the early inflammatory response (65). In addition, FMIT released from mitochondria binds to the formyl peptide receptor 1 (FPR1) receptor on the surface of neutrophils during cell necrosis, promoting their migration to the necrotic area. Neutrophils play a role in HIRI in the initial immune response and by activating the complement system, which further enhances the inflammatory response. C5a in the complement system is one of the strongest chemotactic factors (65) and promotes neutrophil recruitment and infiltration to the damage site by binding to the C5aR1 receptor on the neutrophil surface (66). Zhang *et al* (67) reduced neutrophil recruitment and ROS production by using single-stranded oligonucleotides with high affinity for C5a, coupled to nanoparticles, thus alleviating inflammation and damage associated with HIRI.

LSECs upregulate the expression of CXCL1 during HIRI, which not only promotes neutrophil NETs formation but also exacerbates the formation of liver sinusoids and the occurrence of portal hypertension (68). However, chemokines alone are insufficient for efficient neutrophil recruitment. For optimal chemotactic effects, the concentration of chemokines must be maintained within a precise range, a process depends on the expression of glycosaminoglycans (GAGs) on LSECs (69). GAGs can bind chemokines via their sulfated domains, anchoring them to the endothelial surface and thereby establishing and maintaining a local high-concentration chemokine gradient, which is essential for the specific recruitment of neutrophils (70,71). Research shows that blocking the expression of heparan sulfate significantly inhibits chemokine-mediated neutrophil migration (72); similarly, disrupting the interaction between GAGs and chemokines effectively suppresses neutrophil extravasation in gout models (73). In summary, chemokines, cytokines, the complement system and GAGs form a synergistic regulatory network that precisely controls the activation and recruitment of neutrophils in the early stage of HIRI.

Neutrophil adhesion in the sinusoids. After reperfusion, neutrophils are activated and adhere to LSECs to enter the injury area. The unique structure of LSECs determines the specificity of neutrophil migration. Unlike capillaries in other organs, LSECs possess a porous structure, have relatively little subendothelial basement membrane material and lack intercellular junctions. These structural characteristics allow large molecules such as lipoproteins to pass through, but prevent the passage of chylomicrons (74). Additionally, LSECs in the liver do not express Weibel-Palade bodies and are devoid of E- and P-selectins (75). As a result, selectin-mediated neutrophil rolling is not observed on LSECs (76). This feature indicates that the accumulation of neutrophils in the hepatic sinusoids is less dependent on these adhesion molecules. *In vivo* microscopic observations show that ~80% of neutrophils adhere to LSECs, while 20% adhere to post-sinusoidal venules, highlighting the critical role of LSECs in adhesion (77). Among these, CD44-mediated interactions between hyaluronic acid (HA) receptors play an important role in neutrophil adhesion to LSECs. The binding of CD44 to the extracellular matrix (ECM) of LSECs enhances neutrophil contact with the liver microenvironment (78,79). In models of endotoxin-induced liver injury, blocking the CD44-HA interaction markedly inhibits neutrophil adhesion in the sinusoids but does not markedly affect adhesion in post-sinusoidal venules. This indicates that the CD44-HA pathway has a specific role in HIRI. CD44 activates the p38 MAPK and PI3K/Akt pathways, mediates cytoskeletal rearrangement and strengthens firm adhesion, while upregulating integrin expression to stabilize neutrophil-endothelial interactions (78).

In HIRI models, neutrophil interactions with LSECs involve the binding of the integrin molecule Mac-1 (CD11b/CD18) with ICAM-1 on LSECs. After ischemic injury, LSECs can sense DAMPs through Toll-like receptor 9, thereby directly inducing the release of IL-1β and IL-18. The upregulation of these cytokines further enhances ICAM-1 expression, promoting neutrophil migration to the liver sinusoidal spaces (80).

Neutrophil transendothelial migration (TEM) and rTEM in the liver sinusoids. Neutrophils migrate into the liver parenchyma via TEM, a process that occurs mainly through paracellular or transcellular routes, with the paracellular pathway dominating in peripheral circulation (81). A key step in TEM is the binding of β2-integrin (CD11b/CD18) to VCAM-1 (82). Under acute inflammatory conditions, LSECs rapidly activate the endothelial Notch signaling pathway (83), increasing the expression of TNF-α and IL-33, which further exacerbates liver damage (84).

Additionally, after neutrophils cross the vascular endothelium, their migration within the ECM depends on the dynamic balance of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). MMPs are responsible for hydrolyzing ECM components, while TIMPs regulate MMP activity. Among them, gelatinases (MMP2-MMP9) play an important role in HIRI (85). Fibronectin is a key component of the ECM glycoprotein family and activates the integrin α4β1 receptor on neutrophils in HIRI mice, leading to the production of MMP9. Inhibitors of MMP9 markedly reduce neutrophil infiltration and alleviate liver damage. Alterations in the MMP-TIMP balance are associated with pathological processes involving ECM degradation, such as tumor invasion, angiogenesis and tissue repair. Duarte *et al* (86) verified that animals lacking TIMP1 suffered more severe liver dysfunction and tissue damage. In this model, the mortality rate of TIMP1 double-knockout mice following reperfusion was 60%, while all wild-type mice survived (86). Additionally, the lack of TIMP1 was associated with increased MMP9 activity, which facilitated neutrophil migration across the vascular barrier during liver IRI. Indeed, TIMP double knockout mice exhibited marked neutrophil infiltration in the liver, accompanied by upregulation of proinflammatory mediators such as TNF-α, IFN-γ and inducible nitric oxide synthase. Therefore, MMPs and TIMPs play crucial roles in maintaining liver homeostasis and can serve as therapeutic targets for improving liver injury.

Beyond TEM, increasing evidence with the advance of imaging techniques suggests that neutrophils can also undergo rTEM (63). Neutrophils can migrate within tissues and subsequently clear the infection site through this mechanism. However, dysregulation of this process may trigger systemic inflammatory responses. The mechanisms of rTEM are still under active investigation. Some studies have identified potential regulatory factors that play key roles in neutrophil

rTEM. For example, increased levels of chemokines ultimately lead to neutrophil migration in the opposite direction along the microvenular wall (87), suggesting that the concentration of chemotactic factors is one of the main determinants of accelerating neutrophil rTEM. Furthermore, dynamic regulation of chemokine receptor expression on the neutrophil surface or its sensitivity to corresponding ligands is critical for neutrophil rTEM (88). In addition to these chemokine- and receptor-mediated events, junctional adhesion molecule-C (JAM-C) is the most widely studied molecule regulating neutrophil rTEM and has been widely expressed on endothelial cells (EC). JAM-C knockout mice exhibited increased rTEM neutrophils, with more than 50% of total transendothelial migration events, compared with ~10% observed in wild-type animals (80). This group also described the JAM-C-mediated leukocyte rTEM regulation mechanism mediated by the LTB4 and NE axis (89).

It is worth noting that, since neutrophil rTEM functions by clearing excess neutrophils from local tissues, regulating T and B cell proliferation, NET formation and inducing systemic inflammation and immune system interactions (81,90-92), targeting neutrophil rTEM may represent a new therapeutic strategy to address inflammation. Future research strategies may focus on modulating chemokine gradients, stabilizing endothelial junctions, or targeting the MMP-TIMP axis to achieve this balance, offering novel avenues for treating HIRI and other inflammatory diseases.

NETs. Another important function of neutrophils in HIRI is the formation of NETs. NETs consist of an extracellular scaffold of nuclear DNA loaded with histones and granular proteins such as NE and MPO. The mechanism of NET formation involves NADPH oxidase- and peptidylarginine deiminase 4 (PAD4)-mediated citrullination of histones, translocation of neutrophil NE and MPO to the nucleus, chromatin decondensation and extracellular DNA release promoted by proteolysis of histones.

Neutrophils produce and release NETs through a process called NETosis. While NETs serve as a beneficial defense strategy against pathogens by trapping and combating bacteria, fungi and protozoa (92), in sterile inflammation such as HIRI, 'suicidal NETosis' (that is, neutrophil programmed death associated with NET release) predominantly occurs. By exposing intracellular proteins to the extracellular space, NETosis promotes the presentation of autoantigens and the release of DAMPs, thereby amplifying the ongoing inflammatory response. Research (93) shows that in liver transplantation-associated HIRI, plasma levels of NET markers were markedly elevated in LT recipients, peaking at the end of transplantation and correlating with coagulation activation. Compared with healthy controls, levels of the more specific NET marker MPO-DNA complexes were already markedly increased at the beginning of transplantation (94). Besides plasma, NETs were detected in liver tissue 30 min after reperfusion. Excessive NET formation exacerbates tissue damage.

The dual role of neutrophils in HIRI: From inflammatory effector to repair and regulation. In recent years, the dual role of neutrophils in sterile inflammation, both driving tissue injury and promoting inflammation resolution and tissue repair, has garnered widespread attention. Traditionally viewed as 'first responders' that promote inflammation and tissue destruction, growing evidence indicates that neutrophils possess high functional plasticity. Under specific microenvironmental regulation, they can shift toward anti-inflammatory, pro-repair phenotypes and participate in steering HIRI from a 'damage-dominant' to a 'repair-dominant' transition. In liver-related injury models, the reparative functions of neutrophils have been preliminarily revealed. For instance, Wang *et al* (7) found that in a fully repaired sterile thermal liver injury model, neutrophils also penetrated the injury site, performing critical tasks such as dismantling damaged vessels and creating channels for new vascular regrowth. These neutrophils performing key repair functions neither died nor were phagocytosed. Instead, they returned to the circulation via rTEM, likely became inactivated or reprogrammed and then migrated selectively to the bone marrow via CXCR4 to end their life cycle. Deng *et al* (8) further elucidated how the post-injury liver signals the bone marrow to release neutrophils and how reparative neutrophils signal hepatocytes to re-enter the cell cycle. Using liver-specific leukemia inhibitory factor receptor (LIFR) knockout mice, the authors demonstrated that hepatocyte LIFR promotes the secretion of CXCL1 and cholesterol in a STAT3-dependent manner, recruiting and activating neutrophils. These neutrophils, in turn, secrete the hepatocyte mitogen HGF, accelerating liver injury repair and regeneration. Lin *et al* (9) discovered that during allogeneic tissue transplantation (mouse heart, kidney and human cardiac tissue), neutrophils are indispensable for creating new vascular networks, further confirming their pivotal role in tissue repair. Marques *et al* (10) found that compared with Kupffer cell depletion, neutrophil depletion using anti-Ly-6G alleviated acetaminophen-induced liver injury. In this liver injury model, a small number of neutrophils contributed to the clearance of cellular debris, whereas a large number enhanced liver injury and inflammation. Thus, the role of neutrophils in this process is determined by the quantity of toxic substances in the liver and the number of infiltrating neutrophils. Consequently, how to regulate neutrophil function to promote the shift from injury to repair has become a focus of our attention.

Neutrophil polarization. Similar to macrophages, the diverse biological functions of neutrophils are influenced by timing and specific tissue environments. Analogous to the ability of macrophages to polarize toward M1/M2 phenotypes under different stimuli (95), studies indicate that specific microenvironments can also drive neutrophils toward distinct phenotypes such as N1/N2 (60,61,96,97). Currently, N1 and N2 neutrophil populations are primarily defined by their functional phenotypes, based on their capacities for degranulation, cytokine release and migration. The same phenotypes have been identified as pro-inflammatory (N1) and anti-inflammatory (N2) neutrophils. Mihaila *et al* (98) characterized phenotypic and functional differences between N1 and N2 neutrophils *in vitro* based on transcriptomics and functional assays. The authors found that compared with N2 neutrophils, N1 neutrophils exhibited higher levels of ROS and oxidative burst, greater MPO and MMP-9 activity and stronger chemotactic responses. N1 neutrophils also showed elevated expression of NADPH oxidase subunits and activation of signaling molecules ERK

and the p65 subunit of NF-κB. Furthermore, they identified for the first time that the alarmin S100A8/9, abundantly secreted by activated neutrophils, serves as a critical promoter of the aggressive pro-inflammatory N1 phenotype through an autocrine mechanism.

Although no direct studies have explicitly identified N2-type neutrophils or systematically resolved their polarization trajectory in HIRI models, multiple cross-disease model studies provide strong support for this hypothesis (11,12,99). In the early phase of HIRI, initially infiltrating neutrophils mostly exhibit an 'N1-like' phenotype with high activity, ROS production and strong chemotactic capacity, releasing mediators such as MPO, NE and NETs that exacerbate oxidative stress and microcirculatory dysfunction. As reperfusion time extends, the microenvironment gradually shifts from pro-inflammatory to pro-repair and some neutrophils begin to display anti-inflammatory, pro-angiogenic and immunomodulatory characteristics, suggesting the occurrence of functional polarization. This functional duality makes neutrophil polarization a central node in the 'injury-resolution balance,' directly influencing the prognosis of HIRI. This theory has been corroborated in ischemia models of the heart and brain. In a myocardial infarction model, the predominant neutrophil subset in the infarct area was N1-type neutrophils rich in pro-inflammatory factors, peaking on day 1; subsequently increased N2-type neutrophils corresponded to the anti-inflammatory phenotype after infarction (11). In a mouse stroke model, peripheral blood neutrophil counts peaked at 12 h after cerebral ischemia, with peak brain injury occurring 1-2 days later. In stroke lesions, neutrophil clearance peaked 2 days post-stroke and extracellular traps were mostly detected 2-3 days after stroke. Among neutrophils infiltrating stroke lesions, N2-phenotype neutrophils promoted macrophage-mediated neutrophil clearance. These processes are highly similar to the pathological progression of HIRI, that is, the dynamic transition from early inflammatory storm to later repair and regeneration (12). Therefore, it is reasonable to hypothesize that a similar neutrophil phenotypic switch exists in HIRI, though it has not yet been systematically identified and deeply explored.

Currently, research on neutrophil polarization and repair primarily focuses on cancer models (100). However, the role of neutrophil polarization in tissue repair is also gradually emerging in non-neoplastic diseases. In a mouse brain inflammation model, rosiglitazone treatment shifted the neutrophil population toward an N2 phenotype, suppressing inflammatory responses, promoting neutrophil clearance and reducing brain injury (101).

In summary, although direct evidence for N1/N2 polarization switching in HIRI is currently lacking, multisystem, cross-disease studies consistently indicate that neutrophil function is highly dynamic and context-dependent. Their shift from 'pro-inflammatory effectors' to 'repair coordinators' may be a critical node determining the prognosis of HIRI. Therefore, promoting neutrophil polarization toward an N2-like phenotype could be a potential therapeutic strategy to alleviate HIRI and foster liver regeneration. Future research should focus on the specific mechanisms of N1/N2 polarization, including whether a polarization process exists and whether it is driven by 'transcriptional reprogramming' of existing neutrophils or by 'epigenetic remodeling' of newly recruited cells due to environmental changes.

4. Targeted neutrophil therapy strategies

The role of neutrophils in the initiation and progression of various pathological conditions makes them an attractive therapeutic target. However, the critical requirement of neutrophils for antimicrobial host defense limits the utility of therapies that broadly reduce neutrophil numbers or functional responses. Current treatments targeting single inflammatory mediators may have limited efficacy due to redundancy within the innate immune system and the potential for eventual immunosuppression. Arguably, the ideal therapeutic strategy would be to prevent or reverse neutrophil-mediated tissue damage without compromising their ability to control microbial invasion. Furthermore, one innovative approach for developing treatments for inflammatory disorders is to harness the biological properties of neutrophils to enhance the resolution of inflammation. Based on the functional plasticity of neutrophils, the present review proposed the 'injury-repair balance' theoretical framework. This framework leverages the evolving multifunctional roles of neutrophils in HIRI, from a 'pro-inflammatory (N1)' to an 'anti-inflammatory/reparative (N2)' phenotype, to design alternative therapies for pro-inflammatory diseases. By preventing N1 polarization or inducing N2 polarization, this approach opens new therapeutic avenues for achieving precise immunomodulation and developing highly effective, low-toxicity organ-protective strategies in the future. Building on this, the present review further explore multi-dimensional intervention strategies targeting neutrophils. These include inhibiting excessive recruitment and activation, regulating migration to reduce local accumulation, suppressing NET formation and promoting their clearance, as well as combining antioxidant and anti-inflammatory treatments to re-establish immune homeostasis. Additionally, EVs, owing to their excellent targeted delivery and immunomodulatory capabilities, have emerged as a potential tool for achieving precise regulation of neutrophil function (Fig. 3).

Chemokine receptors and complement inhibitors. Chemokine receptors, as core targets regulating neutrophil recruitment, have become an important direction in HIRI treatment. Chemokines such as CXCL1 and CXCL2 precisely guide neutrophils toward inflammatory sites by binding to the CXCR2 receptor. Currently, drug development targeting CXCR2 has achieved phased progress. In animal models, the dual-target inhibitor Ladarixin (targeting CXCR1 and CXCR2) has been shown to effectively block neutrophil infiltration across the vascular basement membrane while preserving their rolling and adhesion functions, thereby suppressing the inflammatory response (102). Furthermore, small-molecule CXCR2 antagonists such as Repertaxin, Navarixin, Danirixin and AZD5069 have also demonstrated potential in reducing neutrophil recruitment in animal disease models (103), showing significant efficacy particularly in sustained inflammatory conditions such as cystic fibrosis, severe asthma and chronic obstructive pulmonary disease (COPD). It is noteworthy that CXCR2-selective inhibitors have not caused significant impairment to neutrophil host defense

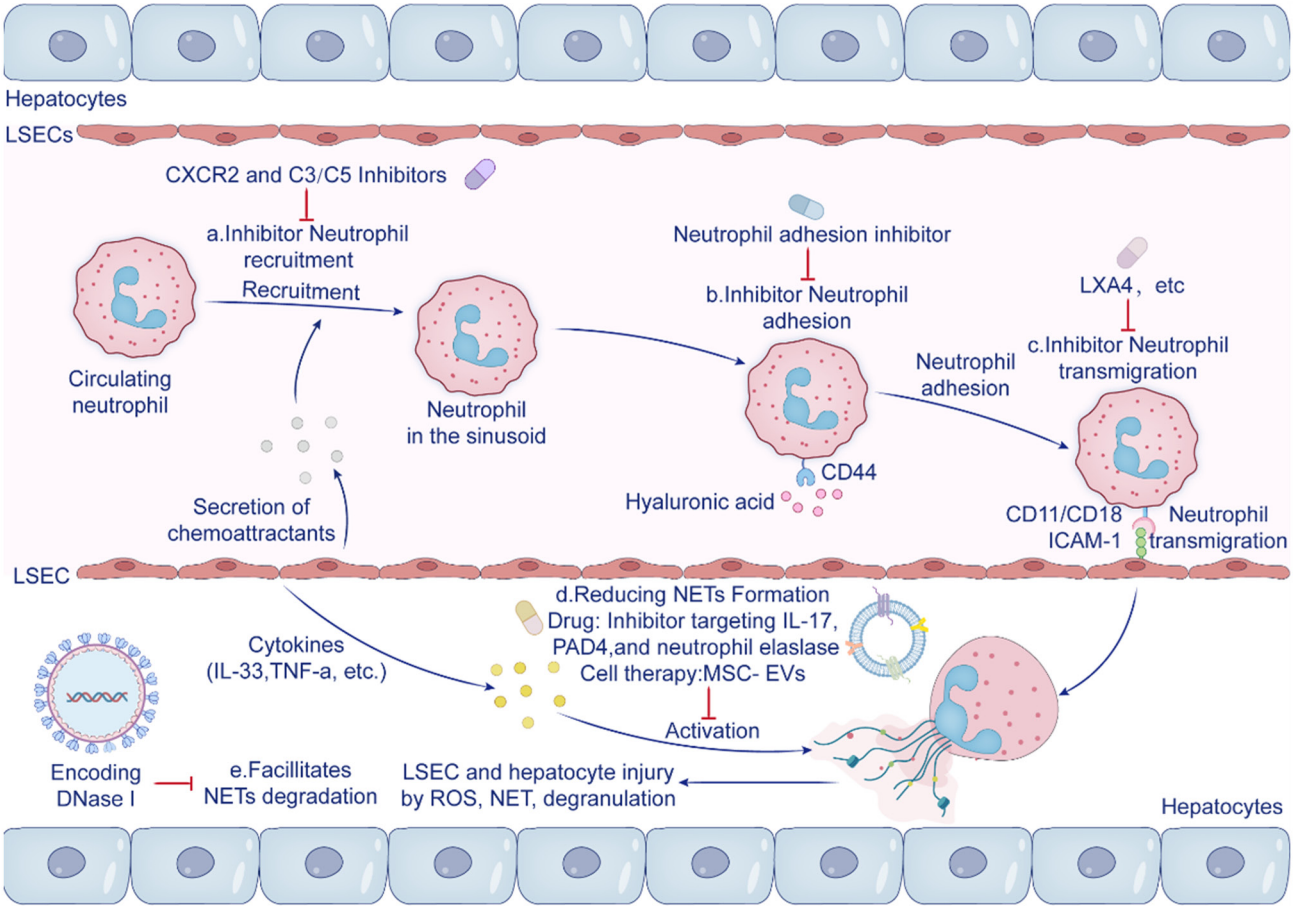

Figure 3. Neutrophil-targeted therapeutic strategies for hepatic ischemia-reperfusion injury. Strategies include targeting chemokine receptors and complement inhibitors to regulate neutrophil recruitment, anti-adhesion and migration therapies to prevent neutrophil accumulation, reducing NETs formation and enhancing their degradation, antioxidant and anti-inflammatory treatments to mitigate oxidative stress and the application of extracellular vesicles as a novel approach for targeted therapeutic delivery. LSECs, liver sinusoidal endothelial cells; LXA4, lipoxin A4; ICAM-1, intercellular adhesion molecule-1; NETs, neutrophil extracellular traps; PAD4, peptidylarginine deiminase 4; MSCs-EVs, mesenchymal stem cells-extracellular vesicles; TNF-α, tumor necrosis factor alpha; ROS, reactive oxygen species; DNase I, Deoxyribonuclease I.

functions, providing a key basis for their safety profile. Most of these drugs are still in clinical development (such as, Phase II trial NCT001006616 for COPD) (104), indicating that preliminary human safety data are being accumulated. However, no clinical trials targeting HIRI have yet been reported. Clinical investigations of CXCR2-selective inhibitors for other diseases are ongoing, such as studies on their role in combination with oseltamivir for influenza treatment (105). These preliminary results have validated the feasibility of the strategy to inhibit neutrophil recruitment by targeting chemokine receptors.

The complement system represents another key regulatory network for neutrophil recruitment, demonstrating unique advantages in mitigating HIRI when suppressed. C3a, C5a and the membrane attack complex (MAC) play central roles in liver IRI by activating the complement cascade and exacerbating tissue damage. Preclinical studies have confirmed that multi-strategy interventions targeting the complement system (such as blocking C3, C5, or enhancing endogenous regulatory mechanisms) can markedly improve liver injury outcomes. For example, the humanized monoclonal antibody Eculizumab (targeting C5), an approved drug, has established its safety profile in diseases such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (106). However, its application for human HIRI has not been reported. For mouse models, anti-C5 monoclonal antibody (BB5.1) treatment not only reduced ALT levels and inhibited the expression of inflammatory mediators such as IL-6 and TNF-α, but also provided cellular protection by reducing neutrophil infiltration and oxidative stress at both early (2 h) and late (6 h) reperfusion stages (66). Furthermore, C3 inhibitors such as the compstatin analog AMY-101, by blocking C3 convertase, reduced kidney damage and systemic inflammation in hemorrhagic shock models. The mechanism involves inhibiting the production of anaphylatoxins, regulating Kupffer cell phagocytosis and blocking the complement positive feedback loop (107,108). A promising strategy involves using recombinant regulatory molecules to mimic endogenous regulatory mechanisms [such as soluble CR1 (sCR1) and CR2-CD59 fusion proteins] (109,110), which can precisely modulate complement activation without inducing immunosuppression. In liver IRI models, these approaches have shown the potential to reduce MAC deposition, protect microvascular integrity and preserve C3a/C5a-mediated regenerative signaling. While clinical evidence for complement inhibitors in cardiac surgery has accumulated (110), targeted clinical trials are still needed to validate efficacy in humans for hepatic IRI. Nevertheless,

existing data strongly support their potential as breakthrough therapies for surgery- and transplant-associated liver injury.

Anti-adhesion and migration molecule therapy. Neutrophil adhesion and migration depend on interactions with adhesion molecules on endothelial cells, such as ICAM-1 and P-selectin. Therefore, anti-adhesion molecule therapy has become an important strategy for targeting neutrophils. ICAM-1 blockers reduce inflammation in rat pancreatic transplant models and improve microvascular perfusion (111). In rat models, NE inhibitor sivelestat sodium inhibits neutrophil migration to the vessel wall, reducing HIRI (112). In 2025, Xia *et al* (113) developed a macrophage membrane-disguised manganese-based anti-aging nanzyme (MB@LM) for targeted delivery and oxidative stress relief in acute kidney injury (AKI) treatment. MB@LM selectively targets damaged kidney tissue overexpressing adhesion molecules such as ICAM-1 and VCAM-1, promoting enhanced accumulation at the injury site. In an AKI mouse model, MB@LM treatment markedly reduced renal injury, restored microvascular perfusion assessed by ultrasound imaging and alleviated inflammation, demonstrating marked therapeutic efficacy. The present review provides strong support for the treatment of liver injury.

In addition to conventional systemic immunosuppressive therapies, some studies have proposed local immunosuppressive strategies that involve the topical administration of immunosuppressants or regulatory factors to reduce neutrophil activation. For example, the use of specific pro-resolving mediators such as lipoxin A4 (LXA4) can inhibit neutrophil activation and migration (114,115), thereby alleviating hepatic inflammatory responses. LXA4 acts by activating the ALX/FPR2 receptor, suppressing ROS production and NETs formation by neutrophils and thus reducing liver inflammation induced by reperfusion injury. The LXA4/FPR2 signaling pathway mitigates ferroptosis in alveolar epithelial cells during lung IRI via an NRF2-pathway-dependent mechanism (116), which may offer a novel therapeutic target for HIRI.

Reducing NETs formation and promoting clearance. In addition to regulating neutrophil activation and migration, targeting the inhibition of NETs formation and promoting their degradation is also an important direction for treating HIRI. The formation of NETs relies on neutrophil oxidative stress and the synergistic regulation of multiple molecular signaling pathways, making drug interventions targeting the NETosis process a potential therapeutic target for alleviating HIRI. Superoxide induces NET release through the TLR4/NOX pathway and the combination of allopurinol (superoxide inhibitor) and diphenyl iodinium (NOX inhibitor) can markedly suppress NET formation in mice and alleviate liver injury (117). Elevated serum IL-17 levels are directly associated with increased neutrophil infiltration and NET formation in the liver, suggesting that IL-17 is a potent NET inducer (118). Similarly, in the kidney IRI mouse model, infiltrated neutrophils were the main source of IL-17 production, further promoting neutrophil migration (119). Moreover, research by Lin *et al* (120) indicates that IL-17-positive neutrophils, abundant in human psoriatic lesions, can release IL-17 through the induction of NETs. Therefore, targeting IL-17 with neutralizing antibodies can reduce NET formation and mitigate IR-induced damage. Histone citrullinase PAD4 is a key mediator of NET formation and its inhibitors (YW3-56 and YW4-03) can markedly reduce liver injury in HIRI mice (40). Similar effects were observed in mouse models when targeting NE or using specific MPO inhibitors. Compared with wild-type animals, NE inhibitor-treated PAD4KO or wild-type animals showed markedly smaller tumors, reduced neutrophil infiltration and fewer NETs (121), suggesting that anti-PAD4 strategies may provide a new pathway for HIRI treatment. Yang *et al* (122) found that Aldh2 deficiency induced NOX2-dependent NETosis through the endoplasmic reticulum stress/GST2/LTC4 pathway and the LTC4 receptor antagonist montelukast might be a potential therapeutic option. Other studies have indicated that acrolein promotes NET formation by activating the NOX2/P38MAPK signaling pathway, delaying postoperative liver recovery (123). Targeting NOX2 and P38MAPK pathways can suppress NET generation in chronic liver disease patients but improve postoperative liver function (123). These strategies effectively block the source of NET formation and reduce liver tissue damage. However, excessive NET accumulation can still trigger localized inflammatory damage, making the promotion of NET degradation a key aspect of treatment. Under physiological conditions, serum deoxyribonuclease (DNase; e.g., DNase1) is the main nuclease responsible for degrading NETs (124,125). Liu *et al* (126) innovatively constructed a stroke-homing peptide (SHp) fused with DNase1 (SHp-DNase1), which enhances DNase stability and targets NETs in thromboembolism events. Combined with ceftriaxone sodium therapy, this approach synergistically controls inflammation and resolves NET-induced microcirculatory impairment. The validation of these multidimensional intervention strategies in the HIRI model provides an innovative direction for precisely regulating NET biology and overcoming the therapeutic bottleneck in HIRI treatment.

Antioxidant and anti-inflammatory therapy. Neutrophils contribute to liver reperfusion injury through migration and release of inflammatory mediators and by generating ROS, which exacerbate tissue damage. Excess ROS can attack cell membrane lipids, mitochondrial structures and DNA, triggering oxidative stress, leading to hepatocyte apoptosis or necrosis, worsening inflammation and impairing liver function (127). Hence, targeting neutrophil-mediated oxidative stress has emerged as a key strategy for preventing and treating HIRI, with antioxidant therapies gaining increasing attention.

Antioxidants can effectively alleviate liver reperfusion injury by scavenging free radicals and reducing oxidative stress (127). In animal models, various antioxidants have shown protective effects, including N-acetylcysteine (NAC) (117), vitamin E, vitamin C (128). NAC, as a precursor for glutathione (GSH) synthesis, replenishes intracellular cysteine, promotes GSH production and enhances endogenous antioxidant capacity, thereby reducing ROS-induced liver damage (117). Vitamin E, a lipid-soluble antioxidant primarily localized in cell membranes, interrupts the chain reaction of lipid peroxidation. Vitamin C, a water-soluble antioxidant, directly neutralizes free radicals and regenerates vitamin E, synergistically exerting protective effects (128).

In recent years, nano-selenium (nano-Se) has gained popularity in antioxidant therapy due to its high efficiency

and low toxicity. Selenium is a necessary cofactor for various antioxidant enzymes, such as glutathione peroxidase, superoxide dismutase and catalase and it helps regulate cellular redox balance. Nano-Se not only directly scavenges free radicals such as DPPH and ABTS but also enhances the activity of the endogenous antioxidant system (129). Nano-Se particles modified with chitosan of different molecular weights exhibit superior free radical scavenging capacity and concentration-dependent ROS inhibition in skin and intestinal cells, higher selenium concentrations yield stronger inhibitory effects (130). Compared with traditional selenium preparations, nano-Se has higher bioavailability and targeting potential. It exerts hepatoprotective effects through multiple mechanisms, including ROS clearance, enzyme activity enhancement and apoptosis inhibition, with lower toxicity, showing broad potential in preventing and treating HIRI (131).

However, single antioxidant therapy is insufficient to comprehensively control the complex pathological process of HIRI. Regarding the interplay between oxidative stress and inflammation, which forms a 'vicious cycle' (51), combined antioxidant and anti-inflammatory therapy strategies are considered more advantageous (132). On the one hand, antioxidants can alleviate oxidative stress and inhibit neutrophil activation and infiltration; on the other hand, anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs or corticosteroids, can effectively reduce local liver inflammation (133,134). Their synergistic effects hold promises for more efficiently mitigating liver tissue damage and promoting functional recovery (132).

Notably, following HIRI, the expression of polo-like kinase 2 was markedly upregulated, indicating its involvement in regulating the injury process. Biocompatible Prussian blue (PB) scavengers possess ROS-scavenging and anti-inflammatory properties (135) and may be used for HIRI treatment. PB scavengers are primarily distributed in the liver and have good alleviating effects on cell apoptosis, tissue damage and organ dysfunction following HIRI. In 2025, Shen *et al* (136) developed a PB nanzyme carrier system (met@PBN@Neu-CVs) based on neutrophil membrane coating for the delivery of metformin. This biomimetic nanoplatform utilizes the chemotactic properties of neutrophil membranes to actively target the inflamed liver, markedly enhancing drug accumulation in damaged tissues. This system can efficiently clear ROS, suppress inflammation and promote macrophage polarization toward the anti-inflammatory M2 phenotype. Consequently, it reduces HIRI-induced liver injury in a multidimensional manner, demonstrating strong therapeutic potential. The present review provided conceptual support for liver injury therapy; however, direct evidence regarding its role in HIRI still comes from animal models.

In conclusion, targeting neutrophil-driven oxidative stress and inflammation cascades, developing nano-antioxidant-based therapies combined with anti-inflammatory interventions, offers new approaches and effective methods for clinical prevention and treatment of liver reperfusion injury.

Application of extracellular vesicles: a new strategy for targeted treatment of IRI. Nano-scale targeted drug delivery systems have shown broad application prospects in reducing IRI and promoting tissue function recovery. Biomimetic nanoparticles inherit the surface antigen profiles of their source cells and possess multiple biological functions, including precise targeted delivery, high accumulation in lesion sites and the ability to regulate the immune microenvironment (137). As key effector cells in inflammation, neutrophils play a central role in recognizing and responding to tissue damage. Their surface expresses various adhesion molecules, chemokine receptors and damage-associated molecular patterns, allowing them to migrate directionally and accumulate at inflammation sites (25). Based on this characteristic, neutrophil membrane-coated liposome delivery systems can effectively bind to local chemokines. For example, neutrophil membrane-coated liposome drug delivery systems effectively target and accumulate at rheumatoid arthritis lesion sites with joint-specific precision (138) and neutrophil membrane-wrapped therapeutic liposomes can target acute lung injury treatment (139).

Furthermore, *in vitro* and *in vivo* studies have shown that neutrophil-derived extracellular vesicles not only efficiently load therapeutic drugs but also specifically bind to damaged endothelial cells, markedly alleviating endothelial dysfunction and improving sepsis-induced lung injury. Yuan *et al* (140) developed a ROS-responsive neutrophil-derived vesicle system (SOD2-Fer-1@CVs), which could specifically accumulate in inflammation tissues with high oxidative stress, thus enabling the controlled release of superoxide dismutase 2 (SOD2) and ferroptosis inhibitor Fer-1 upon ROS stimulation. SOD2-Fer-1@CVs intervene in the core pathological processes of IRI from multiple dimensions: alleviating oxidative stress, adsorbing and neutralizing pro-inflammatory cytokines, inhibiting ferroptosis, restoring endothelial barrier integrity and promoting macrophage polarization to the anti-inflammatory M2 phenotype. Ultimately, it markedly alleviates IRI following lung transplantation, demonstrating strong multi-effect synergistic therapeutic potential.

At the same time, stem cell therapy, as an important direction in regenerative medicine, has shown great potential in various disease fields. In liver IRI, mesenchymal stem cells (MSCs) have garnered widespread attention due to their immune regulatory, anti-inflammatory and tissue repair functions. MSCs can secrete anti-inflammatory factors such as IL-10 and TGF-β, regulating neutrophil activation and reducing their infiltration in the liver, thereby inhibiting excessive inflammatory responses. Additionally, MSCs can promote hepatocyte proliferation and regeneration, alleviating liver failure caused by reperfusion. Notably, EVs secreted by MSCs, particularly exosomes, are gradually being regarded as a cell-free alternative to full-cell therapies and are entering the clinical translation stage for liver disease treatment. These nano-sized vesicles are rich in bioactive components such as microRNA, proteins, lipids and functional mitochondria and can modulate immune responses through intercellular communication mechanisms. Research has demonstrated that human umbilical cord-derived MSC-EVs (hUC-MSC-EVs) effectively inhibit the formation of neutrophil extracellular traps (NETs) in mouse models (141), thereby ameliorating HIRI. The mechanism involves hUC-MSC-EVs transferring functional mitochondria to liver neutrophils, triggering mitochondrial fusion processes, repairing damaged mitochondrial structure and function and subsequently inhibiting abnormal NET release. This 'mitochondrial rescue' strategy reveals a

novel protective mechanism whereby MSC-EVs exert effects by modulating the neutrophil metabolic-immune axis.

5. Hope and challenges

Although targeting neutrophils has shown therapeutic potential in animal models of HIRI, clinical translation still faces significant challenges. These challenges stem not only from inherent interspecies differences in immunobiology but also from an insufficient understanding of the functional complexity of neutrophils. There is an urgent need to re-frame research paradigms and intervention strategies under the guidance of the 'injury-repair balance' theory.

The primary challenge lies in the significant heterogeneity between human and mouse neutrophil biology. Studies indicate that human neutrophils constitute a much higher proportion (40-70%) of circulating leukocytes compared with mice (10-20%) and their phenotypic characteristics and functions differ markedly (142). For instance, whether human neutrophils express key inflammatory cytokines such as IL-4 and IL-6 remains debated, while the expression patterns of surface molecules (such as TLRs, MHC-II) and chemokine receptors also diverge substantially from those in mice (142). Such phylogenetic and regulatory discrepancies often lead to therapeutic deviations or failures when rodent-model-based interventions are applied to humans. Moreover, HIRI is a dynamic process involving the coordinated participation of multiple cell types, including intricate signaling crosstalk among LSECs, Kupffer cells, platelets and parenchymal cells. The current systematic understanding of this interactive network remains incomplete. Therefore, establishing research models that more closely mimic human pathophysiology, such as humanized mice, organoid co-culture systems, or single-cell spatiotemporal atlas platforms, is a critical step in bridging the 'translational gap' between basic research and clinical application.

Secondly, existing therapeutic strategies generally lack spatiotemporal specificity and functional selectivity. Most conventional approaches rely on systemic immunosuppression or broad-spectrum anti-inflammatory interventions, which, while capable of mitigating tissue injury to some extent, inevitably carry the risk of immune imbalance due to off-target effects. For example, broadly blocking the complement pathway may compromise host defense, increase postoperative infection rates and interfere with liver regeneration. Notably, the complement cascade is rapidly activated within minutes after reperfusion, requiring therapeutic intervention to be precisely timed within a minute-level window, posing a major challenge for clinical dosing regimen design. Although emerging strategies such as C5aR antagonists or CR2-CD59 fusion proteins have demonstrated in animal models the ability to achieve tissue-specific inhibition by targeting the C5a-C5aR axis, thereby reducing inflammatory damage while preserving physiological complement functions (143), their clinical translation is still hampered by difficulties in target validation, substantial inter-individual variability in response and a lack of long-term safety data. Consequently, developing targeted drugs with both high selectivity and efficacy remains a critical bottleneck. Emerging strategies are now focusing on targeted or pathway-specific inhibition, such as C5aR antagonists or fusion proteins such as CR2-CD59, which enable selective inhibition of tissue-damaging pathways while preserving beneficial complement functions. These approaches also reduce systemic side effects and offer more personalized treatment options, particularly in patients with variable complement activation due to pre-existing liver disease, steatosis, or autoimmune backgrounds (144).

A deeper challenge arises from the multifaceted functionality and phenotypic plasticity of neutrophils themselves. Neutrophil polarization reflects a spatiotemporally coordinated, microenvironment-driven process transitioning from a damage-promoting state to a repair-promoting state. The 'injury-repair balance' model we propose for neutrophils in HIRI argues against comprehensive neutrophil depletion and instead advocates for stage-specific interventions targeting the polarization process. Potential therapeutic strategies include inhibiting early N1-driving factors, administering pro-resolving mediators to promote an N2 shift and facilitating the conversion to an N2 phenotype during the recovery phase. A study has shown that through specific interventions, it is possible to promote the transition of neutrophils from the N1 to the N2 phenotype. For instance, combining IFN-γ and lipopolysaccharide (LPS) can successfully induce polarization toward an N1 phenotype, whereas induction with TGF-β or IL-4 can promote their conversion to an N2 phenotype (12). Although *in vitro* models offer valuable insights, the dynamics of neutrophils *in vivo* are far more complex. Cells *in vivo* do not simply switch to one of two polarized phenotypes but instead exhibit a spectrum of lineages with overlapping functions. Some studies indicate that N2 polarization of neutrophils may involve multiple signaling pathways. For example, the miR-193a-5p/TLR4/JNK/p38 MAPK pathway has been found to skew neutrophils toward an N2 anti-inflammatory phenotype (13). Another study demonstrated that activating the STAT6/SOCS1 signaling pathway promotes anti-inflammatory polarization of neutrophils and suppresses their pro-inflammatory polarization (14). While these studies provide strong clues for understanding neutrophil polarization, the interactions and synergistic effects among different signaling pathways remain an important area for future exploration. Therefore, further research is needed to elucidate the precise mechanisms of these pathways and how to effectively modulate neutrophil polarization to achieve precise inflammation control and tissue repair.

Future breakthroughs will depend on achieving 'precision reprogramming' of neutrophil function rather than simple depletion. This requires the development of high-dimensional dynamic monitoring technologies, such as single-cell multi-omics, spatial transcriptomics, live imaging, or multiparameter flow analysis, to resolve in real time the distribution, interactions and functional states of neutrophil subsets across different disease stages. Furthermore, intervention strategies based on the 'injury-repair balance' framework should enable precise modulation according to the features of each phase, thereby shifting from 'passive suppression' to 'active regulation'. Hence, developing technologies that can dynamically monitor the distribution and functional states of neutrophil subsets and designing subset-specific regulatory strategies, such as promoting the polarization of protective subsets or targeting the clearance of harmful subsets, will be key

to achieving precision therapy. Additionally, integrating advances in targeted delivery systems and smart responsive materials can enable spatiotemporally controlled drug release within specific cell subsets or microenvironments, thereby minimizing off-target effects.

In summary, the dual role of neutrophils in HIRI makes them both a therapeutic target and a potential source of therapeutic risk. Future therapeutic strategies should no longer focus merely on whether to target neutrophils but should instead concentrate on when to target, which state to target and how to modulate their fate. Guided by the 'injury-repair balance' theory, the ideal intervention would be a stage-specific, phenotype-directed and microenvironment-responsive integration, inhibiting N1 polarization and NET formation in the early phase, regulating inflammation resolution in the middle phase and promoting N2-mediated tissue regeneration in the late phase. Achieving this goal demands a deeper understanding of neutrophil fate-determining mechanisms in basic research, particularly at the levels of metabolic reprogramming, intercellular communication and epigenetic regulation; promoting the development of high-precision monitoring tools and intelligent delivery systems in translational research; and formulating personalized dosing regimens based on dynamic biomarkers in clinical trial design. Only in this way can we advance clinical management from 'attenuating injury' to 'actively promoting regeneration', ushering HIRI treatment into a new era of precise immune modulation.

Acknowledgements

Not applicable.

Funding

The present review was supported by the Natural Science Foundation of Chongqing (grant no. CSTB2022NSCQ-MSX1509) and the China Foundation for International Medical Exchange (grant no. z-2016-23-2101-05).

Availability of data and materials

Not applicable.

Authors' contributions

SL was responsible for conceptualization, formal analysis, investigation and writing the original draft. JT was responsible for conceptualization, funding acquisition, project administration, resources, supervision, writing, reviewing and editing. JJ was responsible for data curation, investigation, visualization, writing, reviewing and editing. QZ was responsible for data curation, investigation, visualization, writing, reviewing and editing. YH was responsible for conceptualization, supervision and writing the original draft. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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