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CXC Chemokines play a critical role in Liver Injury, Recovery and Regeneration

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Abstract

Background—Hepatic ischemia/reperfusion (I/R) injury is a principal consideration of trauma, resectional liver surgery and transplantation. Despite improvements in supportive care hepatic I/R injury continues to negatively impact patient outcomes due to significant tissue damage and organ dysfunction. CXC chemokines have been implicated as key mediators in the deleterious inflammatory cascade following hepatic I/R and also as important, beneficial regulators of liver recovery and regeneration. As such, their potential to mediate both beneficial and detrimental effects on hepatocytes makes them a key target for therapy. Herein, we provide a review of the inflammatory mechanisms of hepatic I/R injury, with a focus on the divergent functions of CXC chemokines in this response compared to other liver insults, and offer an explanation of this apparent paradox.

Data sources—MEDLINE and PubMed

Conclusions—CXC chemokines are key mediators of both the inflammatory response to hepatic I/R as well as the recovery from this injury. Their contrasting functions in the regeneration of liver mass after an ischemic insult indicates that therapeutic manipulation of these mediator pathways should differ depending on the surgical milieu.

Keywords

Ischemia/reperfusion; chemokines; inflammation; liver regeneration

INTRODUCTION

Hepatic ischemia/reperfusion (I/R) injury is a major complication of major trauma, liver resection, and transplantation.^{1–3} It occurs when blood flow to liver parenchyma is interrupted for a period of time and subsequently reperfused. This results in the induction of an acute inflammatory response that can lead to significant tissue damage and organ dysfunction both locally and remotely.^{3–5} The mechanisms of acute inflammation in hepatic ischemia/reperfusion injury has been widely investigated in animal models and has increased our understanding of the pathogenesis of this inflammatory cascade and guided clinical investigations aimed at preventing or minimizing hepatic ischemia/reperfusion injury. Additionally, these experimental models have discovered new functions of soluble mediators elaborated during I/R injury that may govern the ability of the hepatic parenchyma to recover

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and regenerate after significant injury. This review will summarize our current knowledge of the inflammatory response that contributes to the pathophysiology of hepatic I/R injury. More specifically, we will focus on an important class of small proteins, called CXC chemokines, that regulate both the injury and recovery from I/R and offer intriguing new ideas regarding the relevance of experimental discoveries to the clinical management of transplantation and resection surgery.

MECHANISMS OF HEPATIC I/R INJURY: EARLY PHASE

Jaeschke et al. first described and characterized two distinct phases of liver injury after hepatic ischemia/reperfusion injury. The first phase occurs during the initial few hours after reperfusion and is a Kupffer cell-mediated response augmented by complement activation.^{6,7} These liver-resident macrophages produce reactive oxygen species which cause oxidant induced stress and cell damage to the surrounding hepatocytes.^{7,8} This phase is associated with modest hepatocellular injury marked by moderate increases in serum transaminase levels but preserved hepatic architecture. Despite the limited degree of injury during this phase, the oxidant stress results in the release of a number of proinflammatory cytokines that serve to initiate and propagate an intense secondary inflammatory response.^{4,5} The most proximal of these cytokines is interleukin-12 (IL-12), which is increased during the period of ischemia and early reperfusion.⁹ While the precise cellular source of IL-12 remains unknown, neutralization of IL-12 using antibodies or IL-12 knockout mice results in impaired TNF- α production and diminished subsequent inflammation.⁹ TNF- α is thought to be the primary factor that propagates the inflammatory response throughout the liver,^{10,11,12} while another major early-response cytokine, IL-1, is expressed after TNF- α and likely serves an accessory role in neutrophil recruitment.¹³ Expression of these proinflammatory cytokines is mediated by activation of transcription factors, including HIF-1 α and NF- κ B, as studies have shown associations between HIF-1 α and Kupffer cell cytokine production.^{14,15} In this manner, the initial injury phase gives rise to a later, inflammation-mediated phase of injury (Figure 1).

MECHANISMS OF HEPATIC I/R INJURY: LATE PHASE

The second phase of liver injury after ischemia/reperfusion is characterized by the recruitment of activated neutrophils into the liver parenchyma.¹⁶ As discussed above, TNF- α plays a principal role in the induction of mechanisms leading to neutrophil accumulation^{11,12,13}. TNF- α induces the production and release of neutrophil chemoattractants, particularly CXC chemokines, from Kupffer cells and hepatocytes.^{17,18} In addition, it stimulates hepatic microvascular endothelial cells to increase their expression of adhesion molecules.¹¹ There are three main classes of adhesion molecules. The selectin family of adhesion molecules is expressed on both leukocytes and endothelial cells and function in the initial capture and transient adhesion of neutrophils to the endothelium.^{19,22} By bringing neutrophils in close proximity to the endothelial cell surface and reducing their velocity, selectins allow other adhesion molecules expressed on neutrophils and endothelial cells to interact. Specifically, integrins (e.g. MAC-1) expressed on neutrophil surfaces and immunoglobulin molecules (e.g. ICAM-1 and VCAM-1) on endothelial cells mediate firm adhesion and diapedesis of the neutrophil from the vascular space to the interstitium.^{23–25}

Neutrophils that are adherent to the vascular endothelium are activated by CXC chemokines expressed at the site of injury.^{26,27} (Figure 2). Furthermore, the chemotaxis of these activated neutrophils to the liver parenchyma is directed by a gradient of CXC chemokines.^{17,18} Accumulated neutrophils damage hepatocytes via elaboration of oxidants and proteases. Neutrophil release of reactive oxygen radicals such as superoxide anion (O₂[•]) and hydroxyl radical (HO[•]) lead to hepatocyte cell death.^{28,29} Additionally, release of proteases (e.g. collagenase, elastase, cathepsin G, heparanase) from neutrophil granules also directly damage

hepatocytes.^{30,31} The resulting injury is severe and is characterized by marked hepatocyte necrosis histologically as well as highly elevated levels of ALT in the circulation.

ANTI-INFLAMMATORY REGULATORS OF HEPATIC I/R INJURY

In order to prevent an overwhelming and possible lethal inflammatory response to hepatic I/R, endogenous anti-inflammatory mediators are expressed that serve to maintain a homeostatic balance. Several key players have been identified including IL-6, IL-13 and secretory leukocyte protease inhibitor (SLPI). IL-6 has been shown to be protective in hepatic I/R by reducing expression of TNF- α and c-reactive protein, thereby limiting hepatocellular injury and promoting hepatocyte regeneration.³² The role of IL-13 is less clearly understood. Administration of exogenous IL-13 protects against hepatic I/R injury by STAT6, a transcription factor that inhibits the transcription of TNF- α and MIP-2.³³ However, IL-13 knockout mice show a greater degree of cellular injury after hepatic I/R with no significant change in TNF- α expression and with decreased tissue neutrophil accumulation due to less VCAM-1 hepatic expression.³⁴ SLPI is a protease inhibitor produced by a various cells in response to I/R.^{35–37} In hepatic I/R, endogenous SLPI suppresses the expression of proinflammatory cytokines and reduces local and remote organ injury.³⁷

HEPATIC RECOVERY FROM I/R INJURY

Hepatic I/R is commonly encountered in trauma surgery as well as liver transplantation and resection. This directly affects patient outcomes by impacting liver function and viability as well as remote organ injury from inflammation. Experimental models of liver I/R injury have shown that peak hepatocellular injury occurs within 12 hours after reperfusion.^{38,39} By 48 hours after reperfusion the liver enters a proliferative phase with nearly complete recovery of hepatocellular architecture within 96 hours of reperfusion.^{38,39}

STAT3 and NF- κ B are transcription factors known to be critical to liver regeneration.^{40–42} In experimental models of hepatectomy they have been shown to be upregulated in response to IL-6 and other cytokines to induce liver regeneration.⁴⁰ STAT3 and NF- κ B are also thought to play essential roles in the protective mechanisms of ischemic preconditioning and ischemic hypothermia in hepatocytes.^{43,44} Both transcription factors are also activated during the recovery from I/R injury and are important for the proliferative/repairative response observed after 48 hours of reperfusion.^{15,39} Other cell cycle regulators have also been implicated in the recovery phase, including p53, p21, CDK.³⁸

IMPORTANCE OF CXC CHEMOKINES IN LIVER RECOVERY AND REGENERATION

CXC chemokines are critical mediators involved in the recruitment of neutrophils to the liver after I/R.^{4,17,18} CXC chemokines represent one of four branches of the chemokine superfamily. Chemokine nomenclature is based on a conserved, cysteine-containing amino acid sequence at the amino terminus of each molecule: C, CC, CXC, and CX₃C (where X is any amino acid). Very little is known about the C and CX₃C branches however they are believed to mediate chemotaxis of precursor T cell and natural killer cells respectively.⁴⁵ The CC family has been widely studied and at least 27 distinct ligands have been identified which serve as potent chemoattractants for monocytes.⁴⁵

CXC chemokines are further subdivided into two subsets based on the presence or absence of a Glu-Leu-Arg (ELR) amino acid motif at the amino terminus of the peptide. CXC chemokines possessing the ELR motif bind to the receptors CXCR1 and/or CXCR2, while ELR-negative chemokines bind to CXCR3, CXCR4, CXCR5 and CXCR6.^{46,47} Table I lists CXC

chemokines, their receptors and target cells expressing the different receptors. The ELR-positive CXC chemokines are relevant to liver injury, with CXCR1 and CXCR2 being expressed by neutrophils, endothelial cells and hepatocytes.^{46,47,48} The effects of CXC chemokines on neutrophils are well-known and include stimulation of chemotaxis as well as induction of respiratory burst activity.⁴⁹ In endothelial cells, the binding of CXC chemokines to CXCR2 results in proliferation and chemotaxis in a manner facilitating angiogenesis.^{50,51} CXC chemokines have also been shown to induce proliferation in hepatocytes.^{52,53} These findings led to the examination of the role of CXC chemokines during liver regeneration after partial hepatectomy.

Colletti et al were the first to define the effects of CXC chemokines on hepatocytes *in vitro*.⁵² They noted hepatocyte proliferation in response to increasing concentrations of ELR-positive CXC chemokines. Subsequently, they investigated the function of CXC chemokines *in vivo* during liver regeneration using a murine model of 70% hepatectomy. They reported that expression of CXC chemokines was elevated after hepatectomy and that when these chemokines were neutralized using antibodies, there was a significant reduction in liver mass.⁵² Conversely, treatment of mice with the CXC chemokine, macrophage inflammatory protein-2 (MIP-2), increased hepatocyte proliferation and liver regeneration after partial hepatectomy.⁵³

However, we have recently found that the role of CXC chemokines in liver recovery after I/R is far different from their role in regeneration after partial hepatectomy. We found that genetic deletion or pharmacological antagonism of CXCR2 after I/R injury resulted in augmented hepatocyte proliferation and accelerated recovery from injury.³⁹ While the precise mechanism of the divergent effects of CXC chemokines on liver regeneration between I/R and partial hepatectomy models is unclear, we have preliminary data that suggests that the differences are related to the amount of CXC chemokines produced during these insults. We have found that levels of CXC chemokines are increased 3 to 5-fold after 70% hepatectomy. Similar expression levels were reported by others in this model.⁵² In contrast, after I/R, levels of CXC chemokines increase 25 to 50-fold.³⁹ We postulate that moderate increases in CXCR2 ligands, as occurs after partial hepatectomy, may promote liver regeneration, whereas much larger increases in expression of CXCR2 ligands, as occurs after I/R injury, may be hepatotoxic and/or oppose hepatocyte proliferation and regeneration (Figure 3). This concept was supported by *in vitro* studies in which hepatocytes were treated with varying concentrations of MIP-2. Low concentrations of MIP-2 had hepatoprotective effects, whereas high concentrations induced significant cytotoxicity.³⁹ When hepatocytes isolated from CXCR2-knockout mice were used for the same studies, there was no effect of any dose of chemokine, suggesting that CXCR2 may mediate both protective and cytotoxic signaling.

While these studies suggest dynamic and contrasting functions for signaling through CXCR2 in liver recovery after hepatectomy or I/R, they do not define the mechanism(s) by which CXCR2 functions in hepatocytes. Similarly, they have not investigated the potential role of CXCR1, the other receptor that binds ELR-positive CXC chemokines. The signaling pathways utilized by CXCR1 and CXCR2 have been well-studied in neutrophils. However, nothing is known regarding the signaling pathways used by these receptors in hepatocytes. Given the potential clinical impact of these receptors and their ligands, this represents an important gap in our knowledge that warrants further investigation.

SUMMARY

Hepatic ischemia/reperfusion injury continues to impact patient mortality and morbidity despite advances in supportive care and strategies aimed at minimizing tissue injury such as ischemic pre-conditioning and pharmacologic administration of *N*-acetylcysteine,

prostaglandins or prostacyclin.^{54–57} Consequently, there is still much to gain from therapeutic modalities aimed at suppressing the acute inflammatory response and subsequent organ injury seen after I/R. Several targets have been identified in pre-clinical studies including TNF α , adhesion molecules, and protease inhibitors. Others have identified transcription factors that regulate hepatic I/R injury, such as NF- κ B and STAT-6.^{58–61} CXC chemokines and their receptors, CXCR1 and CXCR2, now appear to also be important mediators that regulate both the inflammatory response and the recovery and regeneration of liver parenchyma after I/R. Our recent work suggests there is a divergent hepatic response to CXC chemokines that is directly related to the level of expression. Since pharmacological antagonists to CXCR1/CXCR2 are in clinical trials for treatment of other inflammatory diseases, the role a greater understanding of the function of these chemokines in the liver may have significant impact on potential therapeutic modulation of liver trauma, transplantation or surgical oncology.

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Figure 1. Hepatic ischemia/reperfusion injury inflammatory pathway: the initial phase mediated by Kupffer cells and TNF- α production gives rise to an inflammation-mediated late phase of injury highlighted by neutrophil accumulation and CXC chemokine production.

Table I

CXC chemokine ligands, corresponding receptors and target cells. Murine CXC chemokine common names and are italicized next to their human equivalents.

Chemokines		Chemokine Receptor	ELR Status Target Cells
Old Nomenclature	New Nomenclature		
GRO α / <i>KC</i>	CXCL1	CXCR1, CXCR2	ELR + Neutrophils
GRO β / <i>MIP-2</i>	CXCL2	CXCR1, CXCR2	
GRO γ	CXCL3	CXCR1, CXCR2	
ENA-78/ <i>LIX</i>	CXCL5	CXCR2	
GCP-2	CXCL6	CXCR1, CXCR2	
NAP-2	CXCL7	CXCR1, CXCR2	
IL-8	CXCL8	CXCR1, CXCR2	
PF-4	CXCL4	CXCR3b	ELR – Lymphocytes
MIG	CXCL9	CXCR3a, CXCR3b	
IP-10	CXCL10	CXCR3a, CXCR3b	
ITAC	CXCL11	CXCR3a, CXCR3b	
SDF-1	CXCL12	CXCR4	
BCA-1	CXCL13	CXCR5	
BRAK	CXCL14	Unknown	
-	CXCL16	CXCR6	