Int J Clin Exp Med 2016;9(11):20719-20726
www.ijcem.com /ISSN:1940-5901/IJCEM0027640

Review Article

Molecular mechanism of the migration of neutrophils in liver ischemia/reperfusion injury

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Received March 7, 2016; Accepted June 5, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Liver Ischemia/reperfusion (IR) injury is an innate immune response which is unavoidable during liver transplantation. Neutrophils, the primary leukocyte of human are recruited into the inflammatory sites during the process. However neutrophils possess a vast arsenal of hydrolytic, oxidative, and pore-forming molecules capable of causing profound collateral tissue destruction. Thus understanding the molecular mechanism of the migration of neutrophils to the injured locations during IR injury is very important.

Keywords: Liver ischemia/reperfusion injury, neutrophil, damage-associated molecular patterns, chemokines, cytokines

Introduction

Polymorphonuclear neutrophils (PMN), the key components of the first line of defense against microbial pathogens play an important role in innate immunity. PMNs are chemotaxis cells, can be attracted by chemical or drug concentration gradient and possess myeloperoxidase, lysozyme, hydrolase, etc. Once the host get injured or infected the PMNs can migrate to the insult to remove fragments and eliminate the pathogenic microorganism by producing reactive oxygen species (ROS). However the redundant PMNs can generate lots of toxicity ROS that destroy tissue and organ. Liver Ischemia/reperfusion (IR) injury is an innate immune response caused by physical and chemical factors without bacterial infections, but it also can attracted immune cells just like sepsis. Once the IR injury begins, PMNs are attracted to the insult through many molecules: Small amounts of ROS released by injured hepatocytes [1], damage-associated molecular patterns (DAMPs) like: HMGB1, Mitochondrial DAMPs, Mitochondrial DNA [2], chemokines such as IL-8 and so on. The process is complicated, the leukocytes with the help of interactions between integrin-a (Mac1) and intercellular adhesion molecule-1 (ICAM-1) can adhere to the hepatic sinusoids and craw slowly along the vascular wall. Interestingly the PMNs do not migrate to the insult in a shortest way extravascular but creep intravascula. When they get to the position, through the intravascular gradient of the chemokines and proinflammatory protein [3], the PMNs move towards the injured areas and then adhere to the vascular endothelial cells (VEC) and interact with the VEC, increasing the endothelial permeability with the help of Mitochondrial DAMPs [4] and leak into the extravascular. Then the PMNs get to the injured sites to release ROS, etc and to cause tissue destruction [5]. The whole process needs DAMPs, adherence factors, chemokines, Toll-Like Receptors (TLR), NOD-like receptors (NLR), phosphokinase and so on to participate in.

DAMPs

During pathogenic microorganisms infection, the PMNs can recognize the structures present amongst microbes called pathogen-associated molecular patterns (PAMPs), through this way the immune cells can approach the infected areas and heal the wound. The recruitment of PMNs also can be observed in sterile immunity

Table 1. DAMPs, their receptors and the functions in recruiting neutrophils to the insult

DAMPs		Receptors	Functions	
HMGB1		TLR4, TLR9, RAGE	Active Kupffer cells; up-regulate adhesion Molecules	
			Increase F-actin content; shed L -selectin enzyme	
MTDs	Formyl peptides	FPR-1	Guide PMN to the insult	Promote PMN Ca^+ flux and phosphorylation of MAP kinases
	Mitochondrial DNA	TLR-9	Increase Endothelial Permeability	
ATP		P2X7 P2Y2	Induce cytokine production and initiate neutrophil recruitment	
Histone		TLR9	Modulate inflammatory signaling pathways	

like IR injure mediated by DAMPs released from necrotic hepatocytes and endothelial cells during ischemic injury. High mobility group box 1 (HMGB1) released from necrotic hepatocytes can activate Kupffer cells [6] and adjust the migration of PMNs [7]. HMGB1 effects on PMNs migration depends on its concentration [8]. In a whole-blood conditions experiment, high concentration HMGB1 can promote the migration of PMNS by increasing the PMN F-actin content which is very important for migratory phenotype in PMN [9], however the light concentration has the opposite function. Neutrophils recruitment, mediated by integrins [10] and adhesion molecules play a key role in liver IR injury. Inhibiting integrins or adhesion molecules can significantly suppress the migration of the PMNs. L-selectin can regulate the leucocytes migration, L-selectin deficiency increases peripheral blood neutrophil and lymphocyte numbers [11]. High concentration HMGB1 can up-regulate the expression of adhesion Molecules [12, 13] and promote the L-selectin enzymatic shedding [8], thus promoting the PMN migration. In addition exogenous HMGB1 could increase the levels of IL-4, IL-5, IL-6, IL-8 and IL-17 that aggravate the inflammation of allergic asthma patients [14]. Similarly Apoptosis-associated speck-like protein (ASC), an adaptor protein for inflammasome receptors can lead to hepatocellular injury by promoting HMGB1 production through TLR-4 dependent path in liver IR injury [15]. Mitochondria are evolutionarily derived from bacteria and are the main cellular sites of ROS generation during IR. Mitochondrial constituents DAMPs (MTDs) include formyl peptides and mitochondrial DNA. The MTDS can promote PMN Ca^+ flux and phosphorylation of mitogen activated protein (MAP) kinases thus promoting the PMNs to migrate to the insult through formyl peptide receptor-1 and Toll-like receptor (TLR) 9, respectively [16]. Besides, study have showed that MTDs can increase endothelial permeability through neutrophil dependent and independent pathways [4]. MTDs induced changes in EC permeability occurred in two phases: a brief, PMN-independent 'spike' in permeability was followed by a prolonged PMN-dependent increase in permeability. Exposure to mtDNA caused PMN-EC adherence by activating expression of adherence molecule expression in both cell types. Cellular activation was manifested as an increase in PMN calcium flux and EC MAPK phosphorylation. In IR injury, chemokines can induce the PMNs to the surrounding area of the insult flowing chemokine gradient but formyl peptide can guide the PMNs pass the final few hundred microns to the injured sites through neutrophil formyl-peptide receptor 1 (FPR1). That means the FPR can accelerate the PMNs to the destination and hierarchically override chemokines signaling in the last phases [17-19]. Adenosine triphosphate (ATP), realeased into the extracellular by apoptotic cells [20] or necrotic cells [4] has been identified as an important DAMP [20-22]. It can act as an "find me" signal to recruit the PMNs through P2X7 and P2Y2 receptors. All P2X receptors as well as P2Y2 are activated by ATP, previous studies has showed that as endothelial cells such as human umbilical vein endothelial cells (HUVECs) express various P2Y receptor subtypes (P2Y1, P2Y2, P2Y4, P2Y6, and P2Y11), the P2Y2R activates endothelial p38 MAPK and incerase the expression of ICAM-1 [23] and inducing the production and release of TNF-α, CXCL8, and CCL2 [24]. P2X7 receptor is expressed in immune cells, it requires high concentrations (millimolar range) of ATP to be activated. Activation of P2X7 receptor induces caspase-1 activation, IL-1β, TNF-α, HMGB1 release and cell death [25-27]. The chemokines and proteins above can stimulate the PMNs migration and exacerbate the inflammatory response. A study have found that ATP is required for IL-8 to induce neutrophils migration [28]. However all the researchers hold the same view that ATP danger signals activate a pathway that initiates neutrophil adhesion but do not guide neutro-

phils' chemotaxis toward necrotic cells [3, 21]. **Table 1** list some DAMPs and their functions in IR injury. In conclusion, DAMPs trigger the immune response through been detected by PMNs and act on other cells like EC to release chemokines that can guide the PMNs migration.

Chemokines and cytokines

Ischemia/reperfusion (IR) injury is comprised of two distinct phases. In the ischemic phase, insult induces oxidant stress within the liver resulting in Kupffer cells activation and oxidant mediated injury to hepatocytes [29]. The activation of Kupffer cells results in their production of the early responsecytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β [30] and IL-12 [31]. TNF-α was initially reported to be a neutrophil chemotaxin [32], but following studies showed that TNF-α is not directly chemotactic for neutrophils [33]. However TNF-α is known to upregulate liver expression of vascular endothelial cell adhesion molecules and CXC chemokines, such as epithelial neutrophil-activating protein and macrophage inflammatory protein-2 (MIP-2) [34-36]. Inhibition of TNF-α can effectively prevent IR injury and may be a therapeutic target to prevent IR injury [30, 37, 38]. Recent studies have revealed that TNF-α promotes hepatic IR injury through an NF-κB-dependent pathway [38, 39]. By the way TNF-α can mediate hepatocellular apoptosis in the murine Ischemic Liver and aggravate the liver injury [40]. IL-1β is one of the proinflammatory cytokines involved in infection, reperfusion injury [41] and various inflammatory diseases and is also produced by activated Kupffer cells after ischemia/reperfusion. In a rat model, blocking the IL-1β receptor can reduce TNF-α production and tissue injury [42]. A study by Kato, et al [43] showed that, reduced hepatic neutrophils accumulation as well as reduced MIP-2 Expression and NF-κB activation in IL-1 receptor type I-deficient mice during IR injury. In a zebrafish study [44], IL-Iβ-myd88 axis and NADPH oxidase-mediated ROS have a different effect on the basal random movement and injury induced directional migration of neutrophils, the IL-1β-myd88 axis regulates the neutrophils directional migration by controlling cxcl8 production, which in turn establishes the polarity of PI3K activity through the G-protein-coupled receptors CXCR1 and CXCR2. By the way, MyD88 is an important adaptor protein for IL-β to activate the NF-κB [45] and graded MIP-2 expression [3]. In mice liver IRI model, IL-12 can be expressed by hepatocyte, blockade of endogenous IL-12 by administration of neutralizing antibody greatly reduced the appearance of TNF-α and IFN-γ in serum suggesting that IL-12 may be an integral component of the acute hepatic response to ischemia and reperfusion [31]. IL-8, KC and macrophage inflammatory protein (MIP-2) are chemokines of C-X-C family. In liver IR injury, Both TNF-α and IL-1 can upregulate Mac-1 (CD11b/CD18) adhesion proteins on neutrophils and induce IL-8 synthesis [46, 47]. IL-8 is a major chemokine for neutrophils which is largely responsible for the recruitment of these cells at sites of inflammation/infection in human [48]. In a whole-blood conditions experiment, high concentration HMGB1 also can significantly increased IL-8 production. HMGB1-induced increase in PMN migration was totally reversed by using the anti-IL-8 antibody into whole-blood samples [8]. MIP has been shown not only to regulate PMNs recruitment from the vascular to the insult tissue [3], but also to cause PMN activation, including induction of Mac-1 up-regulation [49]. In liver cold-ischemia time, enhanced C-X-C chemokines, especially MIP-2 expression, might be strongly associated with PMN accumulation in sinusoids and subsequent PMN-mediated graft injury after liver transplantation [50]. In warm ischemia and reperfusion phase, the MIP is upregulated and contributing to hepatic neutrophils accumulation and ensuing liver injury [36], thus MIP-2 is an important mediator involved in hepatic injury induced by ischemia and reperfusion. To summarize, neutrophils are chemotactic cells, intravascular chemokine gradient of the chemokines can guide the PMNs through their ligands from the sinusoids to the insults.

Receptors

Neutrophils express various receptors, these receptors take an important role during IR injury. Toll-like receptors (TLRs) are pattern recognition receptor serve as a common pathway for immune recognition of microbial invasion and tissue injury. During IR injury, DAMPS can be recognized by the TLRs of PMNs and innit the innate immune activation. Hepatic warm IR injury and inflammation is largely TLR4 dependent [51], HMGB1 released by hepatocytes is an active, regulated process that occurs through a mechanism promoted by TLR4-de-

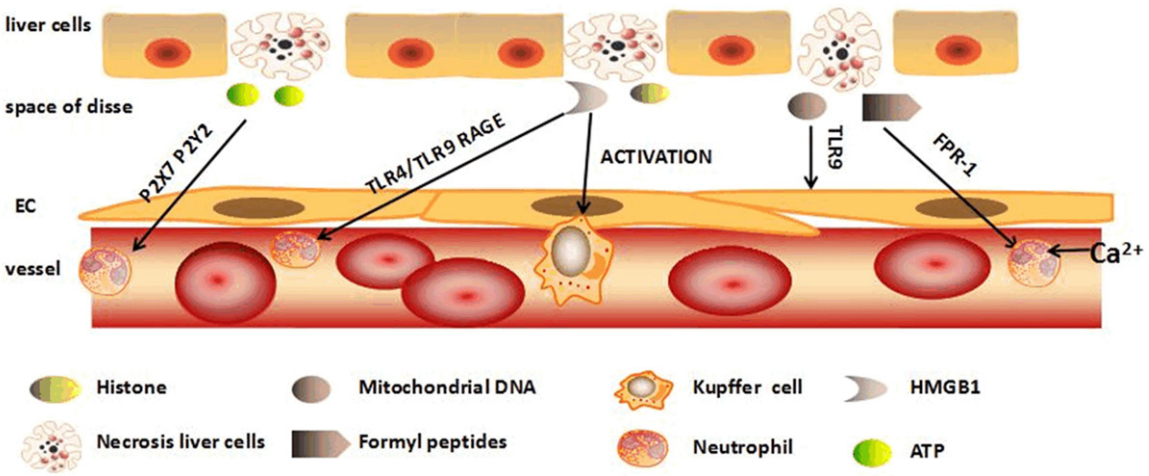

Figure 1. Ischemia injury causes liver cells necrosis and releasing DAMPs, chemokines and cytokines. During reperfusion phases, the DAMPs, chemokines and cytokines are recognized by the receptors on neutrophils thus promoting the PMNs to migrate to the insult.

pendent ROS production [52]. Besides, TLR4 engagement on actively phagocytic nonparenchymal cells such as Kupffer cells is required for warm I/R-induced injury and inflammation in the liver [53]. TLR9 is an endosomal protein that recognizes bacterial CpG as well as self-DNA [54, 55]. During IRI TLR9 can also recognize HMGB1, blockade of HMGB1 and TLR9 confers the protection from I/R injury [56]. Extracellular histones similar to HMGB1 and DNA contribute to hepatic I/R injury, the detrimental effects of exogenous histones in hepatic I/R are dependent on the activation of TLR9 signaling and may also mediate sterile inflammation after hepatic I/R injury by enhancing the DNA-activated TLR9 signaling cascade [57]. Similarly, nucleotide-binding oligomerization domain-like receptor 3 (NLP3), regulates chemokine-mediated neutrophil signaling and functions and contribute to neutrophils recruitment in the I/R liver and subsequent tissue injury [58]. The receptor for advanced glycation end products (RAGE), is associated with the p44/42, p38, and SAPK/JN MAPK and triggers a deleterious inflammatory response rapidly after acute liver I/R [59]. Rage is also the receptor of HMGB1 can mediate the IR injury [60] and modulate neutrophils adhesion and migration [61]. Cell migration depends on the ability of leukocytes to sense an external gradient of chemotactic proteins produced during inflammation. These proteins include chemokines, complement factors, and some acute phase proteins. Chemokines are important players in the migration of leukocytes to sites of injury, the receptors of them can help the PMNs recognize the chemokines and migrate to the insults through the concentration gradient [3]. CXCR inhibitors can inhibited human and rat PMN migration thus relief the injury during IR [62]. As described in this paper, formyl peptides released from necrotic cells and damaged tissues can direct neutrophils migration and instigate the oxidative burst. Formyl peptide receptors (FPRs), which are G-protein-coupled receptors, present on the membrane of neutrophils. FPR1 is critical for directing migrating neutrophils towards infections [63] or sterile insults [3] and neutrophils can migrate to the injuried sites overriding CXCR2 signals trough FPR1 during the last few micrometers surrounding injury. Over all, the receptors present on the membrane of neutrophils have different functions and they are essential for neutrophils to recruit and release the toxicity components.

Conclusion and future directions

Ischemia-reperfusion (IR) injury is an important cause of liver damage occurring during surgical procedures including hepatic resection and liver transplantation, and represents the main underlying cause of graft dysfunction post-transplantation. Neutrophils are essential effector cells of the innate immune response and the major source of ROS at the site of tissue damage in later reperfusion stages. Once at their target sites neutrophils help initiate the

inflammatory response by producing ROS, etc, even when tissues are damaged by non-infectious agents. The proper inflammatory response can help heal the "wound", however overexuberant neutrophils are recruitment during liver IR injury and enhance the tissue damage. **Figure 1** shows that a variety of molecules and mechanisms are involved during the process help neutrophils to extravasate from sinusoid and present to the site of injury. Necrotic cells release amount DAMPs, which act as initial factors trigger the immune response and induce the liver parenchymal cells and non-parenchymal cells to release chemokines. Chemokines act as guides to promote neutrophils to the injury through the chemokine gradient. However the last few micrometers surrounding injury, the chemotatic effect of the DAMPs beyond the chemokines and finally help the neutrophils to the insults. Neutrophils form the first line of defense against bacterial and fungal pathogens, so we cannot handle them as the target to treat the liver IR injury directly. However we can find the solution if we understand the mechanisms of the migration of them. For example different concentration HMGB1 has opposite effect on neutrophils migration. Downregulate the concentration of HMGB1 in blood may significantly decrease the migration of neutrophils and do not change the circulation neutrophils quantity. Changing the concentration of the DAMPs, adjusting the distribution of the chemokines and using the receptor inhibitors against the neutrophils may be useful to relief the IR injury.

Disclosure of conflict of interest

None.

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