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REVIEW ARTICLE

The response of the hepatocyte to ischemia

M. Massip-Salcedo[1], J. Roselló-Catafau[1], J. Prieto[2], M. A. Avíla[2] and C. Peralta[3]

1 Experimental Hepatic Ischemia-Reperfusion Unit, Instituto de Investigaciones Biomédicas de Barcelona-Consejo Superior de Investigaciones Científicas, Instituto de Investigaciones Biomédicas August Pi i Sunyer, Barcelona, Spain
2 Hepatology and Gene Therapy Division, CIMA, University of Navarra, Navarra, Spain
3 Agzesción Biológica y Mecanismosde Respuesta, Instituto de Investigaciones Biomédicas August Pi i Sunyer, Barcelona, Spain

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Correspondence
Dr. Joan Roselló-Catafau, Experimental Hepatic Ischemia-Reperfusion Unit, IIBB-CSIC, C/Rosellón 161, 7th floor, 08036-Barcelona, Spain.
Tel: +34 933 638 333
Fax: +34 933638301
e-mail: jrcbam@iibb.csic.es

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Abstract:
Background: Ischemia-reperfusion (I/R) injury associated with hepatic resections and liver transplantation remains a serious complication in clinical practice, in spite of several attempts to solve the problem. *Aims:* To evaluate the response of the hepatocyte to ischemia *Methods:* Published data are thus revised. *Results:* The response of the hepatocyte to ischemia is based on the sensitivity of hepatocytes to different types of ischemia, the kind of cell death of the hepatocyte when it is subjected to ischemia, and on the response of the hepatocyte to the different times and extents of ischemia. Clinical factors including starvation, graft, age, and hepatic steatosis, all of which contribute to enhancing liver susceptibility to ischemia/reperfusion injury. *Conclusion:* Ischemic preconditioning, based on the induction of a brief ischemia to the liver prior to a prolonged ischemia, has been applied in tumor hepatic resections for reducing hepatic I/R injury and recent clinical studies suggest that this surgical strategy could be appropriate for liver transplantation.

Ischemia-reperfusion (I/R) injury is a phenomenon whereby cellular damage in a hypoxic organ is accentuated following the restoration of oxygen delivery (1–3) (Fig. 1). In the liver, this form of injury was recognized as a clinically important pathological disorder by Toledo-Pereyra et al. in 1975 during studies of experimental liver transplantation (LT). However, it was not until the mid-1980s that the term reperfusion injury was generally used in the literature on LT (1, 4).

The lack of oxygen to hepatocytes during ischemia causes mitochondrial de-energization, ATP depletion, alterations of H^+, Na^+, Ca^{2+} homeostasis that activate hydrolytic enzymes and impair cell volume regulation and sinusoidal endothelial cells (SEC) as well as Kupffer cells (KC) swelling (5–8). This fact together with the imbalance between nitric oxide (NO) and endothelin (ET) production, contributes to narrowing of the sinusoidal lumen and thus to microcirculatory dysfunction. Capillary narrowing also contributes to hepatic neutrophil accumulation (9, 10). Concomitantly, the activation of KC releases reactive oxygen species (ROS) and proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) (11, 12). Like KC, ROS can derive from mitochondria and xanthine oxidase of activated SEC and hepatocytes. Cytokines release throughout the induction of adhesion molecules (intercellular cell adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM)) and chemokines promote neutrophil activation and accumulation, thereby contributing to the progression of parenchymal injury by releasing ROS and proteases (2, 3, 11). Besides, IL-1 and TNF-α recruit and activate CD4+T-lymphocytes, which produce granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon γ (INF-γ) and tumor necrosis factor β (TNF-β). These cytokines amplify KC activation and TNF-α and IL-1 secretion and promote neutrophil recruitment and adherence into the liver sinusoids (13–15). Platelet activating factor (PAF) can prime neutrophils for superoxide generation, whereas leukotriene B4 (LTB4) contributes to the amplification of the neutrophil response (2, 3).

Due to the complexity of hepatic I/R injury, the present review summarizes established basic concepts of the mechanisms and cell types involved in this

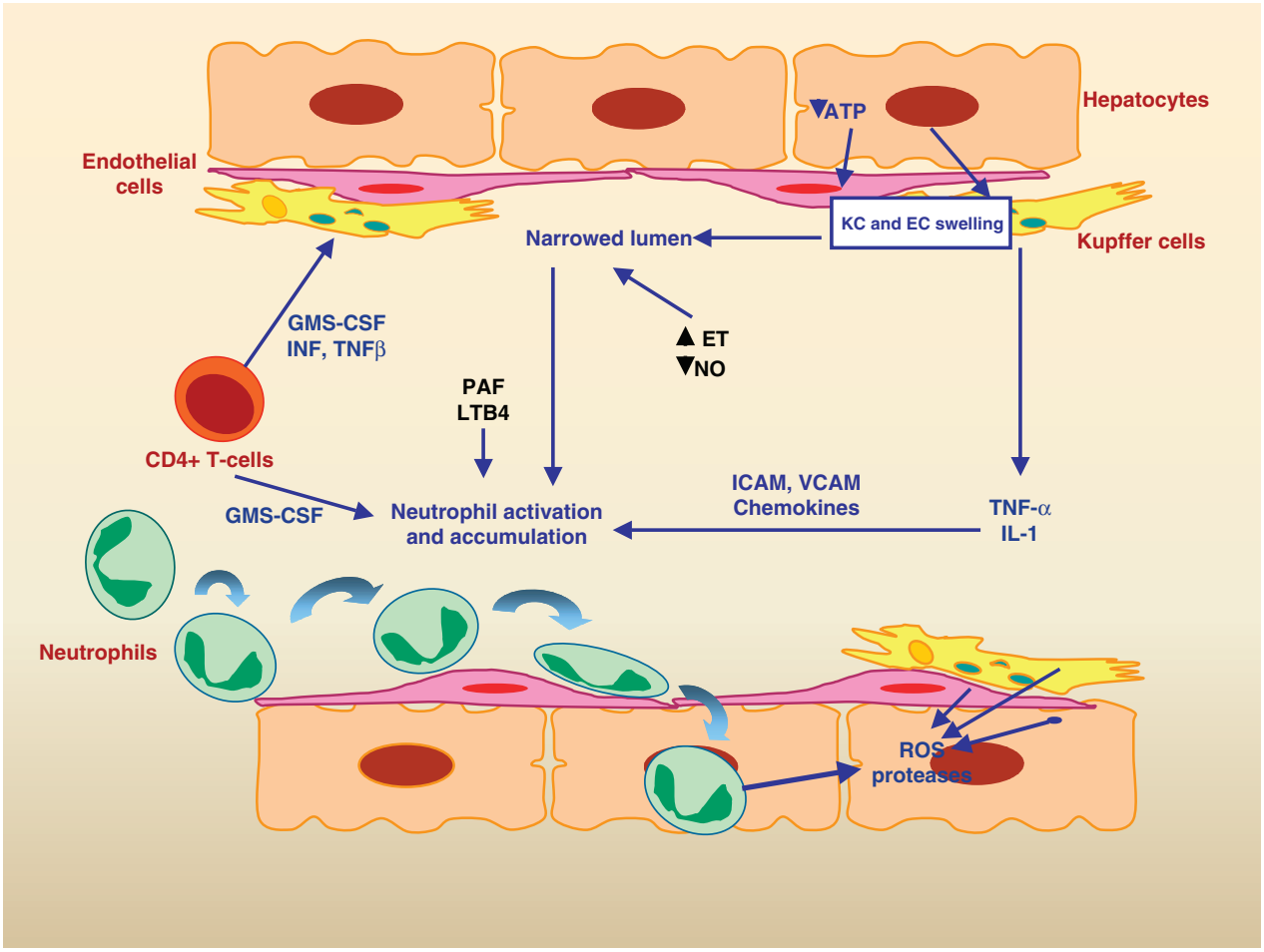

Fig. 1. Mechanisms involved in the pathophysiology of ischemia-reperfusion injury.

process. To prevent or minimize graft dysfunction and posttransplantation complications and the risks associated with I/R in hepatic resections, it is essential to fully understand the importance of individual liver cell types in I/R injury induced by cold storage and warm ischemia. The present review is mainly focused on the response of the hepatocyte to ischemia.

Sensitivity of the hepatocyte to the different types of ischemia

The main victims of ischemic injury are the hepatocytes and SECs. These two cell types show different responses to different types of ischemia: hepatocytes are more sensitive to warm ischemia and SECs to cold ischemia (12, 16, 17). Although, most hepatocytes remain viable after 48 h of cold preservation and reperfusion, SECs suffer severe damage following reperfusion (40% non-viable) (18). The result of this sinusoidal damage is the subsequent microcirculatory abnormalities upon reperfusion, resulting in hepatocyte injury and dysfunction (16, 19). This contributes to the development of primary nonfunction or impaired primary function after LT. However, some studies have called the importance of sinusoidal injury into question. Huet et al. (20) have demonstrated that damage to the extracellular matrix from prolonged preservation and reperfusion appears to be the critical factor in graft failure (21). In addition, it is possible that perturbations in hepatocyte levels of adenine nucleotides during cold storage can trigger proteolytic events that contribute to damage in the liver graft and subsequently compromise hepatic functions after LT (22). Moreover, cold ischemia profoundly disturb several key hepatocellular functions, such as volume and pH homeostasis, as well as solute transport and drug metabolism, protein synthesis and mitochondrial function. This contribute to preservation injury of the liver graft. Therefore, these observations indicate that aside from reducing endothelial cell damage, LT therapy may benefit from strategies aimed at improving

the maintenance of appropriate hepatocyte functions (22, 23).

What kind of cell death occurs when the hepatocyte is subjected to isquemia?

The exact mechanism of cell death in hepatic I/R injury remains uncertain. Apoptosis has been regarded as the fate of cells experiencing I/R injury (24). In this line, different studies have demonstrated apoptotic death in hepatocytes and/or SECs after both cold and warm ischemia of the rat liver (25–27). All of the aforementioned studies (24–27) used TdT-mediated dUTP-biotin nick and labelling (TUNEL staining) for DNA ladders to demonstrate apoptosis. However, the ability of TUNEL staining to distinguish between apoptosis and necrosis has been called into question (28). The activation of caspases has also been used to demonstrate apoptosis in rat SECs following cold I/R (29, 30). Indeed, use of pan-caspase inhibitors protected rat liver SECs (31) and hepatocytes (32) against I/R injury after prolonged periods of both cold and warm ischemia. On the other hand, the groups of Jaeschke and Lemasters oppose the view that the majority of cells undergo apoptosis in response to either warm or cold I/R injury, believing that necrosis is the principle form of cell death. They believe that in a number of studies the proportion of cells undergoing apoptosis is not of significant magnitude and that the degree of caspase activation does not correlate with the number of SECs and hepatocytes supposedly undergoing apoptosis (33). It is postulated that a shared intracellular pathway, which can lead to either apoptosis or necrosis, is an explanation for these conflicting findings (21, 34). The new term 'necrapoptosis' has been coined to describe a process that begins with a common death signal and which culminates in either cell lysis (necrotic cell death) or programmed cellular resorption (apoptosis), depending on factors such as the decline of cellular adenosine triphosphate levels (35, 36).

What is the response of hepatocytes to the times and extent of hepatic ischemia?

The severity of hepatocyte damage depends on the length of time the ischemia lasts. It appears that short periods (60 min) of warm ischemia result in reversible cell injury in which liver oxygen consumption returns to control levels when oxygen is resupplied after ischemia. Reperfusion after more prolonged periods of warm ischemia (120–180 min) results in irreversible cell damage. These observations agree with a previous report on rat liver subjected to I/R, indicating a cellular end point for hepatocytes after 90 min of ischemia (37, 38). In human LT, a long ischemic period is a predicting factor for posttransplantation graft dysfunction, and some transplantation groups hesitate to transplant liver grafts preserved for more than 10 h (39, 40). Some studies in experimental models of LT indicate that 24 h of cold ischemia induces low survival at 24 h after LT. However, at shorter ischemic periods, LT may also result in primary organ dysfunction. For animals subjected to 8 h of cold ischemia, an ischemic period associated with high survival, the histological study of the liver at 24 h after LT showed multifocal and extensive areas of hepatocyte coagulative necrosis with neutrophil infiltration and hemorrhage (39, 41).

In regard to the extent of hepatic ischemia, previous reports indicate that the extent of hepatic injury as well as the hepatic I/R mechanisms, including the recovery of the blood flow and energy charge during hepatic reperfusion, is dependent on the extent of ischemia, depending on whether a total or a partial hepatic ischemia of 70% is applied (42–44). The authors have suggested that this fact could be explained by the stealing phenomenon. In contrast to 100% hepatic ischemia, during ischemia to the left and median lobes, the flow is shunted via the right lobes and following the release of the occlusion to the left and median lobes, a significant amount of shunting via right lobes will continue during reperfusion until vascular resistance in the postischemic lobes decreases. This is due to the fact that blood will flow through the path of least resistance. The reasons for this may be cellular swelling endothelial, stasis, or other changes. Thus, the recovery of blood flow and hepatic perfusion of the preischemic lobe is later in the case of 70% than to 100% of hepatic ischemia (45–47). In line with these observations, different studies have shown that infusion of ATP–$MgCl_2$ following 60 or 90 min of total hepatic ischemia in rats restored the depressed reticuloendothelial function and improved hepatocellular function (42, 48, 49). However the benefits of ATP–$MgCl_2$ were dependent of the extent of hepatic ischemia used. Thus, when the ischemia applied was 70%, this drug had no benefits on mitochondrial function or hepatic blood flow in the postischemic lobes as the postischemic lobes were not reached by any great amounts of the drug under these conditions (45).

Do all hepatocytes respond in the same way to ischemia?

A variety of clinical factors including starvation, graft age, and steatosis contribute to enhance liver

susceptibility to I/R injury, further increasing the patient risks related to reperfusion injury (50). In clinical LT, starvation of the donor, due to prolonged intensive care unit hospitalization or lack of an adequate nutritional support, increases the incidence of hepatocellular injury and primary nonfunction (51, 52). It is well-known that the shortage of organs has led care centers to expand their criteria for the acceptance of marginal donors. Some of these criteria include the use of organs from aged donors and steatotic liver grafts (53–55). However, I/R injury is the underpinning factor of graft dysfunction that is seen in the marginal organ. Donor age of more than 70 years was found to be associated with lower patient and graft survival (56, 57). Additionally, these donors also have an increased incidence of steatosis, which may potentiate cold preservation injury (56, 58–60). Moreover, increased rates of primary non-function have been reported when using donor livers with moderate steatosis compared with non-steatotic livers. As such, hepatic steatosis is the major cause of rejected grafts for LT and exacerbates the organ shortage problem (54, 61, 62). Therefore, minimizing the adverse effects of I/R injury could increase the number of both suitable transplantation grafts and of patients who successfully recover from LT. The first step towards achieving this objective is a full understanding of the mechanisms involved in I/R injury in these marginal organs.

Starvation

The preexistent nutritional status is a major determinant of hepatocyte injury associated with I/R. Based on the nutritional status, several studies in experimental animals and in man support the hypothesis that the availability of glycolytic substrates is important for maintenance of hepatic ATP levels during ischemia and functional recovery during reperfusion (63–65). Fasting exacerbates I/R injury because the low content of glycogen stores results in a more rapid ATP fall during ischemia, when the oxidative phosphorylation is inhibited and glycogen must supply glucose for glycolytic ATP generation (5, 66). In addition, fasting causes alteration in tissue antioxidant defenses, accelerates the conversion of xanthine dehydrogenase to xanthine oxidase during hypoxia and induces mitochondrial alterations. In fact, Caraceni et al. (67) have shown that mitochondrial damage is greatly enhanced by fasting which decreases the hepatic content of antioxidants and therefore sensitizes the mitochondria to the injurious actions of ROS (51, 68). An important observation is the close association between the nutritional status and the mitochondrial content of the catalytic F_1 subunit of the F_0F_1-ATP synthase, an enzymatic complex involved in ATP synthesis (69). The fasting-induced exacerbation of oxidative stress is likely to have contributed to the very low levels of the F_1 subunit observed in starved rats. Indeed, under fasting conditions, the fall of mitochondrial GSH affects the protein sulfhydril pool, whose reduced form is necessary for the preservation of proteins (70) and which can, in turn, predispose to the oxidation of enzymes containing functional sulfhydril groups, such as β-F_1 subunit (71). Taking these observations into account, it has been suggested that an artificial nutritional support, which may also include an adequate content of antioxidants, may represent a new approach for the prevention of reperfusion injury in fasted livers (66). On the other hand, it has been reported that fasting can improve organ viability and survival (72–74). Fasting reduces phagocytosis and the generation of TNF-α; both parameters indicate impaired KC function in fasted livers. Because activation of KC is important for reperfusion injury, metabolic inactivation of these cells can be beneficial (72). Although these reports appear to contradict the other reports mentioned above, which indicated the injurious effects induced by fasting conditions, it is important to consider the different experimental conditions in these investigations. A beneficial effect of high glycogen content can mainly be expected under conditions of long preservation times and long periods of warm ischemia. Under these conditions, high metabolic reserves of the liver may attenuate ischemic cell injury and preserve defense functions against cytotoxic mediators of KC. On the other hand, short ischemic periods require lower metabolic reserves, and the extent of KC activation can be the dominant factor in early graft injury (63).

Aged

A number of distinct age-related alterations have been identified in the hepatic inflammatory response to hepatic I/R, including cell-specific alterations in the activation of inflammatory transcription factors and expression of cytoprotective proteins (75–78). Under warm hepatic ischemia, mature adult mice had a much increased neutrophil function, increased intracellular oxidants and decreased mitochondrial function, compared with young adult mice. These alterations contributed to the increased liver injury after I/R in mature adult mice compared with young adult mice Specifically, mature adult mice had much lower hepatic expression of the cytoprotective protein, heat shock

protein (HSP) 70 (HSP70), than did young adult mice. In contrast, serum HSP70 levels which have been linked to subsequent tissue injury, were higher in mature adult mice than in young adult mice (78). The age appears to be a condition which influences the sensitivity of the liver to oxidative stress (75–78). The results obtained in an experimental model of isolated perfused liver indicate that, during reperfusion, livers obtained from old rats generate an amount of oxyradicals lower than livers from young rats. This fact could be explained by the lower KC activity, the reduction of liver blood flow, and the impaired functions and structural alterations observed in the livers of old rats (75). In fact, in hepatocytes from mature adult mice, delayed activation of NF-κB in response to TNF-α and virtually no production of MIP-2 has been detected, which may be due to an age-related defect in hepatocytes (78).

Steatosis

Several hypothesis have been suggested to explain the decreased tolerance of steatotic liver to I/R injury compared with non-steatotic livers. Besides the impairment of the microcirculation, which is considered a major event of reperfusion injury in steatotic livers (66, 79–81), hepatocyte damage appears remarkably higher in steatotic livers than in non-steatotic livers (82, 83). Several evidences indicate that an increased sensitivity of fatty hepatocytes to the injurious effects of ROS could explain the poor tolerance of steatotic livers to I/R (84–86). Mitochondrial ROS generation dramatically increases during reperfusion and mitochondrial structures are exposed to the attack of the ROS generated both outside and inside these organelles leading eventually to the dysfunction of important mitochondrial processes including those responsible for the ATP synthesis. It is well-known that steatotic livers synthesise less ATP than non-steatotic livers during postischemic reperfusion (87). Different works have been focused on preventing the increased oxidative stress observed in steatotic livers (85, 88, 89). However, until now, data about the effectiveness of the administration of antioxidants on the deleterious effects of ROS in steatotic livers was controversial. Some studies in obese Zucker rats, a well-characterized model of nutritionally induced obesity, indicated that the administration of tocopherol, which possesses antioxidant properties, improved tolerance to warm ischemia. However, other experimental studies in steatotic livers, induced by a choline–methionine-deficient diet, show that the administration of GSH precursors, such as *N*-acetylcysteine, could help to restore hepatocellular integrity in the steatotic liver but without scavenging free radical. In addition, both dietary high fat and alcohol exposure produced SOD/catalase-insensitive ROS that may be involved in the mechanism of failure of steatotic livers after orthotopic LT (85, 88–90). The difficulties that have been found when attempting to prevent I/R injury in steatotic livers with therapies aimed at inhibiting ROS production have also been evidenced with caspase inhibitors (32, 82), No donors (91) and heme-oxygenase-1 (HO-1) activators (92). Results obtained under warm hepatic ischemia indicate that apoptosis was the predominant form of hepatocyte death in the ischemic non-steatotic liver, whereas the steatotic livers developed massive necrosis after an ischemic insult. Thus, caspase inhibition, a highly protective strategy in non-steatotic livers, had no effect on hepatocyte injury in steatotic livers (82). In the experimental model of LT, exogenous no protected non-steatotic grafts but was ineffective in presence of steatosis. The injurious effects of exogenous NO donors on hepatic injury and oxidative stress in steatotic grafts could be explained by peroxinitrite generation caused by ROS overproduction (91). HO-1 activators such as cobalt(III) protoporphyrin IX, might protect both liver types against warm I/R injury. However, a lower dose of HO-1 activator was required to protect steatotic livers effectively, as steatotic livers undergoing I/R showed higher HO-1 levels than non-steatotic livers (92).

In regard to the mechanisms involved in hepatic I/R injury in relation to the type of steatosis, neutrophils have been involved in the increased vulnerability of steatotic livers to I/R injury, especially in alcoholic steatotic livers. However, neutrophils do not account for the differentially greater injury in the non-alcoholic steatotic liver during the early or late hours of reperfusion. Similarly, the role of TNF in the vulnerability of steatotic livers to I/R injury may be dependent on the type of steatosis (88, 93). These observations could be of clinical interest because pharmacological strategies that could be effective in alcoholic fatty livers by reducing the neutrophil infiltration and or TNF action may not be sufficient to reduce the hepatic I/R injury in non-alcoholic fatty livers.

All the aforementioned results point up the fact that the different mechanisms of cell death in steatotic vs. non-steatotic livers as well the differences in the mechanisms involved in hepatic I/R injury in terms of the type of esteatosis could explain the difficulties in effectively preventing steatotic livers from I/R injury.

Thus, therapies which are effective in non-steatotic livers may either prove useless in the presence of steatosis or the effective drug dose may differ between the two types of grafts (13, 91, 92). On the other hand, there may be drugs that would only be effective in steatotic livers (94, 95).

What is the response of the hepatocyte to a brief period of ischemia before a prolonged ischemia?

The response of hepatocyte to ischemia never ceases to be surprising. In fact, contrary to what might be expected, the induction of consecutive periods of ischemia to the liver does not provoke an additive effect in terms of the hepatocyte lesion. Murry et al. (96) have reported that ischemic preconditioning (IP) based on a brief period of ischemia followed by a short interval of reperfusion before a prolonged ischemic stress protects against I/R injury (Fig. 2). The molecular basis for IP consists of a sequence of events: in response to the triggers of IP, a signal must be rapidly generated which is then transduced into an intracellular message leading to the amplification of the effector mechanism of protection (97, 98). As in the pathophysiology of hepatic I/R, in the modulation of hepatic injury induced by IP there is a complex interaction between different cell types. The present review is focused on some of the proposed mechanisms leading to the development of hepatocyte resistance to I/R injury following hepatic IP. Experimental studies in isolated hepatocytes indicate that the stimulation by adenosine of adenosine A_2 receptors induces a network of signals involving Gi proteins, phospholipase C (PLC) and phosphatidylinositol 3-kinase (PI3K) that mediate that sequential activation of protein kinase C (PKC) and p38. No release through the activation of guanylate cyclase (cG-S) can also stimulate p38 MAPK (99, 100). In addition, the generation of AMP by IP could induce the activation

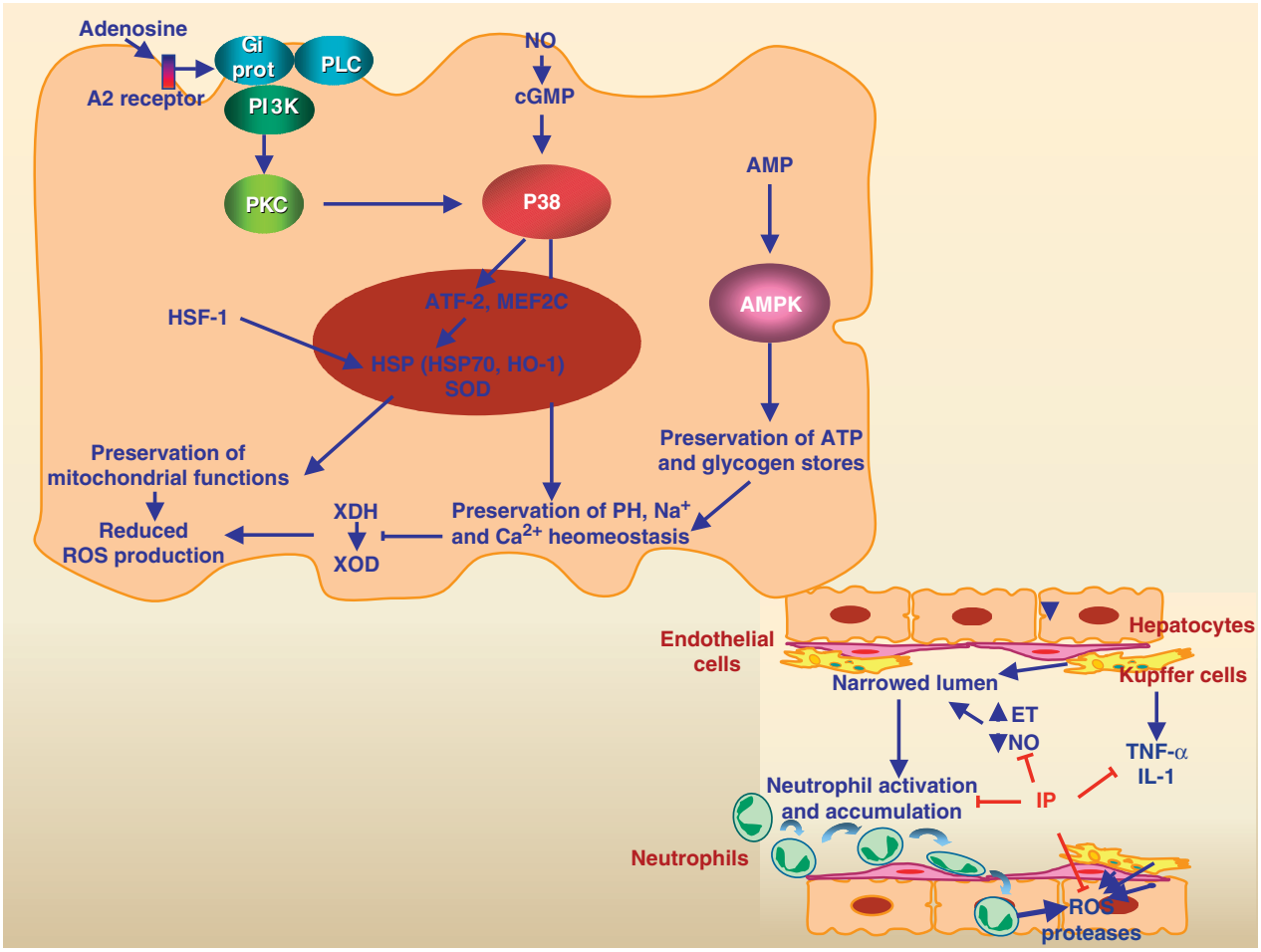

Fig. 2. Proposed mechanisms involved in the benefits of ischemic preconditioning on hepatic ischemia-reperfusion injury.

of AMP-dependent kinase (AMPK) (101, 102). The signals transduced by p38 MAPK, protein kinase B (PKB/Akt) and AMPK can activate a variety of mechanisms able to preserve energy metabolism, mitochondrial functions, pH and ion homeostasis as well as to reduce oxidative stress (99). IP via AMPK activation, reduced the ATP depletion thus attenuating the accumulation of glycolytic intermediates and lactate production during hepatic sustained ischemia (101, 102). The benefits of IP on oxidative stress could be explained by the induction of antioxidants, such as SOD and HSPs (15, 97, 99, 103) as well as by its effect on xanthine dehydrogenase/xanthine oxidase. IP reduced the accumulation of xanthine during ischemia and prevented the conversion of XDH to XOD, thus preventing the deleterious effect of this ROS generating system on liver (39, 97, 104). It is possible that nuclear factor κB (NFκB) and p38MAPK-regulated transcription factors (ATF-2 and MEF2C) might be responsible for inducing the expression of protective genes, including SOD (99, 105). IP signals also activate heat shock transcription factor 1 (HSF1), and its binding to specific heat shock recognition sequences (HES) in the DNA leads to the production of HSP27, HSP70, and HO-1. It is also possible that HSPs might contribute to improve membrane potential and respiratory control in hepatic mitochondria, allowing a faster recovery of ATP on reoxygenation (99, 106, 107). The modulation of inflammatory response by hepatic IP has been also reported in different experimental models of warm and cold hepatic ischemia. IP reduces neutrophil accumulation, and the generation of ROS and proinflammatory cytokines including TNF and IL-1 from KC (13, 97, 98, 108, 109). The benefits of IP were also observed on hepatic microcirculation by inhibiting the effects of different vasoconstrictor mediators such as ETs, thus ameliorating sinusoidal perfusion and microvascular dysfunction (10, 110). The combination of these effects decreases liver cell susceptibility to necrosis and/or apoptosis in response to I/R.

The benefits of IP observed in experimental models of hepatic warm and cold ischemia created the need for human trials of IP. To date, IP has been successfully applied in human liver resections in both steatotic and non-steatotic livers (21, 104). The effectiveness of IP in hepatic surgery was first reported by Clavien, but unfortunately, in this study, it proved ineffective in elderly patients (111, 112). Prevention of posthepatectomy liver insufficiency by IP, particularly in patients with cirrhotic or steatotic livers has also been demonstrated (113). A recent clinical study by Koneru and colleagues shows no effects of IP on cadaveric donor livers compared with controls. However, the study consisted of clamping the hepatic vessels for a period of 5 min and, as the authors concluded, that may be insufficient time to obtain a beneficial effect from IP (84). Another clinical study carried out by Azoulay and colleagues using the model of cadaveric whole LT has shown that IP based on 10 min of ischemia was associated with better tolerance to ischemia. However, this was at the price of decreased early function (114). Jassem and colleagues have concluded that 10 min of preconditioning is effective to protect cadaveric donor allografts from cold ischemia, reduces inflammatory response and results in better graft function (115). Further randomized clinical studies are necessary to confirm whether IP is appropriate for LT in clinical practice. The potential applications of IP in human LT are numerous. IP also has the potential to increase the number of organs suitable for LT as it can improve the outcome for marginal grafts that would not otherwise have been transplanted. Its benefits to reduce the vulnerability of steatotic grafts to I/R injury have also been reported in different experimental studies of LT (54, 91). Again, IP may also have a role in the transplantation of small grafts whose pathophysiology overlaps with I/R injury. In fact, a study published by Barrier et al. (116)in 2005 has shown the benefits of IP in transplantation from living human liver donors.

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