Strategies to improve outcome after partial liver resection

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Interleukin-10 attenuates inflammation and apoptosis and promotes hepatocyte proliferation in hepatic ischemia/reperfusion injury

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Abstract

Introduction. One of the most important determinants of the outcome of hepatic ischemia and reperfusion (I/R) injury is the onset of the inflammatory response. Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine. It inhibits the production of interleukin-6 (IL-6), which however, also is involved in priming hepatocyte proliferation. The aim of this study was to examine the protective effects and the influence on the regenerative response of exogenous as well as endogenous IL-10 in a rat model of hepatic I/R injury.

Animals and Methods. 70% Liver I/R was induced in male Wistar rats by clamping of the vessels to the median and left-lateral lobes for 60 min and allowing subsequent reperfusion during 24 hours. One group underwent a midline laparotomy with recombinant rat (rr)IL-10 administration (SHAM+IL-10). The other groups underwent 60 minutes ischemia with administration of saline (I/R+saline), rrIL-10 [at two different time-points, i.e. I/R+IL-10pre(ischemia) and I/R+IL-10end(ischemia)] or anti-rat IL-10 antibody (I/R+antiIL-10, reflecting the contribution of endogenous IL-10).

Results. Parenchymal damage, as assessed by plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST), was significantly reduced by rrIL-10 and by endogenous IL-10 (p<0.05). Also, rrIL-10 significantly reduced IL-6 production and the accumulation of neutrophils in liver and lung tissue, as measured by myeloperoxidase (MPO) activity. Necrosis and apoptosis were significantly reduced and hepatocyte proliferation was stimulated by rrIL-10.

Conclusion. RrIL-10 and to a lesser extent endogenous IL-10, attenuate damage and inflammation, while rrIL-10 also promotes proliferation after hepatic I/R injury in rats. Therefore, rrIL-10 has potential use to prevent I/R injury and to promote liver regeneration after partial liver resection with temporary inflow occlusion.
Introduction

Hepatic inflow occlusion (Pringle's manoeuvre) can be applied to reduce blood loss during liver resection. This will result in ischemic liver injury which is aggravated by restoration of oxygenated blood flow (reperfusion), depending on the duration of ischemia. One of the most important determinants of the outcome of hepatic, posts ischemic reperfusion (I/R) injury is the onset of the inflammatory response. This inflammatory response is caused by the activation of Kupffer cells, which constitutes the main source of reactive oxygen species (ROS) formation during the initial reperfusion period. ROS cause injury to the hepatocytes and endothelial cells potentially resulting in microcirculatory failure. Kupffer cell activation also leads to the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-6, as well as chemokines, which are mainly responsible for the induction of neutrophil sequestration in the liver. This causes further tissue injury several hours after the initiation of reperfusion. Tissue injury can lead to necrosis or apoptosis, ultimately resulting in functional loss.

The effect of IL-10 administration has been studied in various models of I/R injury. In most of these studies, IL-10 appears to have an attenuating effect on organ damage caused by I/R. IL-10 is a potent anti-inflammatory cytokine, which inhibits the production of proinflammatory cytokines such as IL-6, as well as of chemokines released by activated monocytes, macrophages and neutrophils. Furthermore, IL-10 suppresses the expression of adhesion molecules on endothelial cells.

Besides mediating the inflammatory response, TNF-α and IL-6 are also involved in priming hepatocyte proliferation when functional liver mass is lost. It is also known that IL-6 has anti-apoptotic activity by maintaining adequate levels of intracellular anti-apoptotic proteins. This leads to the question whether IL-10, by inhibiting production of IL-6, also inhibits priming of proliferation after major loss of functional parenchymal cells due to I/R injury. This study tested the hypothesis that because of its anti-inflammatory action, IL-10 administration reduces hepatic injury in a rat model of hepatic I/R. In addition, the role of endogenous IL-10 and of IL-6 was examined in relation with necrosis and apoptosis on the one hand, and proliferation on the other hand.

Materials and Methods

Animals

This study was approved by the Animal Experiment Committee of the Academic Medical Center, University of Amsterdam, The Netherlands. Male Wistar rats (Harlan, Horst, The Netherlands), weighing 320-340 gram, were used. All rats were allowed to adapt to the laboratory environment for 7 days with free access to water and standard laboratory chow (Hope Farms, Woerden, The Netherlands). Rats were housed under standard environmental conditions with a 12-hour light-dark cycle. Before use in experiments, rats were fasted overnight with free access to water.
Experimental design

33 rats were randomly appointed to 5 experimental groups. Group 1 received 50 µg/kg rrIL-10 (Cell Sciences, Norwood, MA, USA) and underwent a midline laparotomy (SHAM+IL-10, n=5). Group 2-5 underwent 60 minutes ischemia. Group 2 received saline solution prior to ischemia (I/R+saline, n=7), group 3 received 500 µg/kg rabbit (polyclonal) anti-rat IL-10 antibody (Biosource International, Camarillo, USA) pre-ischemically to inhibit endogenous IL-10 (I/R+antiIL-10, n=7), group 4 received 50 µg/kg rrIL-10 prior to ischemia (I/R+IL-10pre, n=7) and group 5 received 50 µg/kg rrIL-10 at the end of the ischemic period (I/R+IL-10end, n=7). The chosen dose of 50 µg/kg rrIL-10 was obtained from literature. A reperfusion period of 24 hours was applied in all animals.

Anesthesia

All animals were anesthetized via inhalation of a mixture of O₂:N₂O (1:1 L/min) and isoflurane 3-4% (Florene®, Abbott Laboratories Ltd., Queensborough, Kent, UK). After endotracheal intubation, rats were ventilated (Zoovent ventilator, Instruvet, Amerongen, The Netherlands) and anesthesia was maintained with a mixture of O₂:N₂O (1:1 L/min) and isoflurane 2-3%. Tidal volume was adjusted according to end-tidal CO₂ levels. A polyethylene catheter (Ø 0.9 mm, Braun, Melsungen, Germany) was introduced into the right carotid artery and tunneled subcutaneously to the back of the rats for assessment of hemodynamic parameters during operation as well as for withdrawal of blood samples. Arterial blood pressure was maintained at approximately preoperative levels by adjustment of isoflurane levels. The animals were kept in supine position on a heating pad and rectal temperature was maintained at 37°C with the use of a heating lamp.

Surgical procedure

A midline laparotomy was performed and the afferent vessels to the median and left lateral lobes of the liver were exposed. An a-traumatic vascular clip was applied to these vessels to induce partial hepatic ischemia (70%) for 60 minutes, after which the clip was removed and subsequent reperfusion initiated. After surgical closure of the abdomen, rats were allowed to recover and were provided with water and food. After 24 hours of reperfusion the rats were anesthetized with above mentioned anesthesia. A polyethylene catheter (Ø 0.4 mm) was inserted into the distal bile duct and bile was collected during 15 minutes. The rats were subsequently sacrificed under anesthesia, and liver biopsies were taken, frozen in liquid nitrogen and stored at -80°C or fixed in 4% (W/V) formaldehyde for further analysis.

Hepatocellular damage

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined in heparinized plasma by routine spectrophotometry using alpha-ketoglutaric acid and pyridoxal phosphate (General Clinical Chemistry Laboratory, AMC, The Netherlands).
**Inflammatory response**

Plasma IL-6 and IL-10 concentrations were assessed using commercial ELISA kits (Pierce Endogen, Rockford, IL, USA). Manufacturer's instructions were followed. Samples were assessed in duplicate and concentrations were calculated using a standard curve. MPO activity, an index of neutrophil infiltration, was measured in liver and lung homogenates as described by Krawisz et al. with some modifications \(^20\). Briefly, tissue samples were homogenized (Heidolph, Diax 900, Berlin, Germany) in 5 mM phosphate buffer (pH 6.0). After a sample was taken from the homogenate for protein content determination (BCA protein assay, Pierce Endogen, Rockford, IL, USA), the sample was centrifuged for 10 minutes at 12,000 g and 4°C. The pellet was homogenized in 0.5% hexadecyltrimethyl ammonium bromide (HTAB) (Sigma chemicals, Munich, Germany) and 10 mM EDTA in 50 mM phosphate buffer (pH 6.0). Homogenates were freeze-thawed three times, pottered 10 times (Bellco 20, RW 20.n IKA Labortechnik, Staufen, Germany), sonicated for 10 sec and centrifugated at 10,000 rpm at 4°C for 10 minutes. The supernatants were collected and assayed for MPO activity by addition of 0.167 mg/ml o-dianisidine dihydrochloride (Sigma chemicals, Munich, Germany) and 0.001% H₂O₂ (Sigma chemicals, Munich, Germany) in 50 mM sodium phosphate buffer (pH 6.0). The change in absorbance was measured spectrophotometrically (Victor³, Wallec 1420, PerkinElmer Life Sciences, Boston, MA, USA) at 450 nm during 10 min at 37°C. One Unit is defined as the amount of enzyme necessary to produce a change in absorbance of 1.0 per minute. The MPO activity is expressed as Units per mg protein.

**Proliferation and apoptosis**

Liver biopsies of the middle and left lateral liver lobes taken 24 hours after ischemia were analyzed. For caspase-3 immunohistochemistry, sections were incubated with cleaved caspase-3 antibody (9661, dilution 1:200, Cell Signaling Technology, Inc., Beverly, MA, USA) for 1 hour at room temperature. Hereafter, sections were exposed to secondary antibody (dilution 1:1, Sigma chemicals, Munich, Germany) and peroxidase activity was detected by DAB and counterstained with haematoxylin. Cleaved caspase-3 positive cells were counted by two independent observers in a blinded fashion and expressed as number of positive cells per 30 microscopic fields (40 x).

A MIB-5 antibody was used to determine hepatocyte proliferation. MIB-5 is a rat equivalent of human Ki-67 antibody which detects all active parts of the cell cycle (G1, S, G2 and mitosis) and shows a strong positive correlation with proliferating antigen expression, bromodeoxyuridine incorporation and thymidine incorporation \(^21\). Briefly, after formaldehyde fixation and paraffin-embedding, 4 μm sections were deparaffinized and immersed in citric acid pH 6.0, preheated and boiled (2 bar, 120°C, 20 min) in a pressure cooker. Sections were then incubated with a MIB-5 antibody (dilution 1:50, DAKOCytomation, Glostrup, Denmark) for 60 min. After incubation with a secondary antibody (dilution 1:1, Poly-HRP, Invitrogen, Carlsbad, US) 3,3-diaminobezidine (DAB) (Sigma chemicals, Munich, Germany) was used to visualize the peroxidase complexes together with haematoxylin counterstaining. The proliferative index was determined in 30 microscopic fields (40 x).
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Histolopathology
H&E sections were analyzed semi-quantitatively by two independent observers in a blinded fashion. Tissue damage and inflammation was scored by examining necrosis, hepatocellular vacuolization and inflammation. Necrosis and hepatocellular vacuolization were scored as percentage of cells per 30 microscopic fields (20x enlargements). A score of 0 to 5 was used as follows: 0=0%, 1=1-10%, 2=11-20%, 3=21-30%, 4=31-50% and 5=51-100%. Inflammation was determined in 30 microscopic fields (40x enlargement) as follows: 1= focal collections of mononuclear cells, 2= diffuse infiltrates of mononuclear cells, 3= focal collections of polymorphonuclear cells in addition to mononuclear cells, 4= diffuse infiltrates of polymorphonuclear cells. Apoptotic activity was measured by counting cells that expressed hepatocellular nuclear condensation, hepatocellular nuclear fragmentation and hepatocellular nuclear fading. Mitotic activity was assessed by counting mitotic bodies. Cell counts were performed on 30 H&E slides (40x enlargement).

Statistical analysis
Results are expressed as mean ± standard error of the mean (SEM). Student T-test or one-way ANOVA, followed by Bonferroni post-test were used for differences between groups. Repeated measures ANOVA was used for measurements at multiple time-points followed by Bonferroni post-test for differences between groups or paired T-test for differences within groups at different time points (GraphPad Software, San Diego, California, USA). A p-value of < 0.05 was considered significant.

Results
Hepatocellular damage
In all I/R groups, a significant increase in AST and ALT was found at all time points after ischemia compared to SHAM+IL-10 (Fig. 1a+b). This increase was most pronounced in I/R+antiIL-10. AST values in I/R+antiIL-10 were significantly higher as compared to all other groups at all time points after ischemia. After 6 hours reperfusion, AST increased to 10,310 ± 1,483 in I/R+antiIL-10 as compared to 5,225 ± 943 in I/R+saline. AST values in the I/R+saline group were significantly higher than in the I/R+IL-10pre group, after 6 and 24 hours of reperfusion. ALT values were significantly higher in I/R+antiIL-10 compared to I/R+IL-10pre and I/R+IL-10end at all time points after ischemia. After 24 hours reperfusion, ALT values were significantly higher in I/R+saline compared to both I/R+IL-10pre and I/R+IL-10end.

Bile production
Bile production, measured during 15 min at the end of the 24 hour reperfusion period, was 4.9 ± 0.3 and 4.8 ± 0.2 μL/min/100g liver weight in SHAM+IL-10 and I/R+IL-10pre, respectively (Fig. 2). Bile production was significantly higher in these groups, when compared to I/R+saline, I/R+antiIL-10 and I/R+IL-10end.
Figure 1. Plasma AST (A), ALT (B) and IL-6 (C) values measured before ischemia (t=0) and during 24 hours reperfusion.

AST and ALT values were significantly higher in the I/R groups compared to SHAM+IL-10 at all time points after reperfusion (p<0.05). After 0.5 hour (t=0.5), IL-6 values were significantly higher in the I/R groups compared to SHAM+IL-10 (p<0.05). After 6 hours (t=6), IL-6 values were significantly higher in I/R+antiIL-10 and I/R+saline compared to SHAM+IL-10 (p<0.01). After 24 hours (t=24), IL-6 values were significantly higher in I/R+antiIL-10 compared to SHAM+IL-10 (p<0.05). ** Significantly higher compared to I/R+IL-10pre, I/R+IL-10end and I/R+saline (p<0.05). * Significantly different from I/R+IL-10pre and I/R+IL-10end (p<0.05).

Figure 2. Bile production after 24 hours of reperfusion.

SHAM+IL-10 and I/R+IL-10pre ischemia had significantly more bile production than I/R+IL-10end ischemia, I/R+saline and I/R+antiIL-10. * Significantly higher compared to I/R+IL-10end, I/R+saline and I/R+antiIL-10 (p<0.05).
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Inflammatory response

The inflammatory response was evaluated by measuring plasma IL-6 levels and MPO activity in liver and lung homogenates. IL-6 levels were significantly increased in all I/R groups compared to SHAM+IL-10, 30 min. after ischemia (Fig. 1c). Six hours after ischemia, IL-6 declined to significantly lower levels in I/R+IL-10pre and I/R+IL-10end as compared to I/R+saline and I/R+antiIL-10. After 24 hours reperfusion, IL-6 levels were still significantly elevated in I/R+antiIL-10 as compared to SHAM+IL-10, I/R+IL-10pre and I/R+IL-10end. Separate values of endogenous and rrIL-10 could not be determined by ELISA. IL-10 levels were significantly more elevated in I/R+saline compared to I/R+antiIL-10 at all time points after ischemia (data not shown). In the I/R+saline group, IL-10 levels reached peak values of 147.0±31.5 pg/mL, after 30 min reperfusion. Administration of anti IL-10 resulted in IL-10 levels falling below the detection level (data not shown).

Hepatic MPO activity was significantly elevated in all I/R groups compared to SHAM+IL-10 24 hours after ischemia (Fig. 3a). MPO levels were significantly decreased in the I/R+IL-10pre and I/R+IL-10end groups as compared to the I/R+antiIL-10 group, but not when compared to the I/R+saline group. To evaluate distant organ damage and inflammation, MPO activity was measured in lung homogenates (Fig. 3b). No significant increase was detected in both I/R+IL-
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10pre and I/R+IL-10end compared to SHAM+IL-10. Compared to I/R+saline, MPO activity in the lungs was significantly lower in SHAM+IL-10 and I/R+IL-10end. Compared to I/R+antiIL-10, MPO activity was significantly lower in SHAM+IL-10, I/R+IL-10pre and I/R+IL-10end.

Figure 4. Histopathology scores after 24 hours of reperfusion

A semiquantitative score (0-14) was used for assessment of necrosis (0-5), hepatocellular vacuolization (0-5) and leukocyte accumulation (0-4). Histopathology scores were significantly higher in all I/R groups compared to SHAM+IL-10 (p<0.05). ** Significantly higher compared to I/R+IL-10pre ischemia, I/R+IL-10end ischemia and I/R+saline (p<0.01). * Significantly different from I/R+IL-10pre and I/R+IL-10end (p<0.02).

Figure 5. Apoptosis (rate of cleaved caspase-3 positive cells, A) and hepatocyte proliferation (rate of MIB-5 positive cells, B), after 24 hours of reperfusion

The rate of apoptotic cells was significantly higher in all I/R groups compared to SHAM+IL-10, except I/R+IL-10pre ischemia (p<0.02). The rate of proliferating cells was significantly higher in I/R+IL-10pre ischemia compared to SHAM+IL-10 (p<0.05). * Significantly different from I/R+IL-10pre ischemia and I/R+IL-10end ischemia (p<0.05). # Significantly different from I/R+IL-10pre ischemia (p<0.05). & Significantly different from I/R+saline and I/R+antiIL-10 (p<0.05).
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Histopathology score

The histopathology score was significantly elevated in all I/R groups compared to SHAM+IL-10 24 hours after ischemia (Fig. 4). All groups had a significantly lower score compared to I/R+antiIL-10. Compared to I/R+saline, all groups had a significantly lower score, except I/R+antiIL-10. Necrosis, when detectable, was located periportally as well as pericentrally, showing clear demarcation between healthy and necrotic tissue. Vacuolization occurred mainly in hepatocytes between healthy and necrotic parenchyma. Leukocyte accumulation was found around as well as within necrotic areas (Fig. 6).

Apoptotic activity

24 Hours after ischemia, the rate of cleaved caspase-3 positive cells was significantly increased in all groups except in I/R+IL-10pre, compared to SHAM+IL-10 (Fig. 5a). I/R+saline showed significantly more caspase-3 positive cells compared to I/R+IL-10pre. I/R+antiIL-10 showed more caspase-3 positive cells compared to I/R+IL-10pre and I/R+IL-10end, but not when compared to I/R+saline (Fig. 6). In addition, there was a trend towards increased apoptotic activity in H&E slides of the I/R+antiIL-10 group (data not shown).

Figure 6. Micrographs of H&E and cleaved caspase-3 stained sections

(A) (F) (B) (G)
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Letters represent the following: A+F: SHAM+IL-10, B+G: I/R+saline, C+H: I/R+antiIL-10, D+I: I/R+IL-10pre ischemia and E+J: I/R+IL-10end ischemia. H&E sections (A-E) show necrosis (N), hepatocellular vacuolization (V) and leukocyte accumulation (arrow), mainly in B and C. Necrotic areas appear well demarcated (B). Vacuolization is mainly found between healthy and necrotic tissue. Leukocyte accumulation occurs around as well as within necrotic areas. Apoptotic hepatocytes (F-J) are mainly found in B and C.

Hepatocyte proliferation

Hepatocyte proliferation, as measured by MIB-5 positive hepatocytes, was significantly higher in I/R+IL-10pre compared to SHAM+IL-10, I/R+saline and I/R+antiIL-10 (Fig 5b). No significant differences were found after 24 hours reperfusion in I/R+saline, I/R+antiIL-10
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or I/R+IL-10end compared to SHAM+IL-10. In addition, in H&E slides, mitotic bodies were also primarily found in the I/R+IL-10pre group (data not shown).

Discussion

In this study, the effect of exogenous as well as endogenous IL-10 was examined in a rat model of 70% liver ischemia and reperfusion. Special attention was paid to the onset of the inflammatory response and the balance between apoptosis and proliferation after I/R. The role of endogenous IL-10 in attenuating organ damage after I/R is controversial. In an IL-10-/- knockout model, several studies report a beneficial effect of endogenous IL-10 on I/R injury. However, endogenous IL-10 was not protective in a study focusing on intestinal I/R injury. In the present study, blocking endogenous IL-10 by IL-10 neutralizing antibody resulted in a significant increase in AST/ALT values after ischemia compared to control I/R animals. Also, damage and inflammation on microscopical examination was significantly worse in anti-IL-10 treated animals as compared to all other groups. IL-6 production was not higher in anti-IL-10 treated animals suggesting that the protective effect of endogenous IL-10 is not accompanied by less IL-6 production. Therefore, IL-6 does not seem to play an important role in the inflammatory response leading to more tissue damage when endogenous IL-10 is blocked.

In a number of studies on intestinal I/R, exogenous IL-10 seemed to protect intestinal mucosa, but on the other hand increased hepatocellular injury after I/R. In contrast, IL-10 administration diminished liver damage in a mouse model of hepatic I/R. In the present study, the administration of exogenous IL-10 resulted in less liver parenchymal damage as compared to anti-IL-10 treated animals as well as control I/R animals. These differences were most pronounced after 24 hours reperfusion. Also, the inflammatory response measured by IL-6 levels and tissue MPO levels, was attenuated by exogenous IL-10 treatment. Exogenous IL-10, however, did not have additional effect on leukocyte accumulation in the liver, as measured by liver MPO levels, compared to endogenous IL-10.

It is known that hepatic I/R injury can lead to inflammatory changes in distant organs, predominantly in the lungs. In humans, this can lead to the adult respiratory distress syndrome (ARDS). Eventually, inflammatory changes can give rise to injury in other organs, culminating in multiple organ failure (MOF) and even death. In the present study, lung MPO levels were 10 times more elevated than liver MPO levels, and were significantly reduced by exogenous IL-10, when administered at the end of the ischemic period. It should be taken into account that besides distant inflammation caused by I/R, ventilation of the animals also may causes an inflammatory reaction in the lungs. However, it is unlikely that differences in lung MPO levels between groups in this study was caused by ventilation, because all animals were equally ventilated. Previous studies from our laboratory have clearly shown the advantages of ventilation by maintaining adequate end-tidal CO₂ levels and normal pH.

It has been shown that ischemic preconditioning before I/R reduces tissue injury through IL-10 overproduction. Ischemic preconditioning also impairs liver regeneration after ischemia combined with partial liver resection. IL-6, on the other hand, has been reported to promote hepatocyte proliferation after I/R in rodents and reverses impaired liver
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regeneration after partial liver transplantation preceded by cold ischemia. These studies suggest that IL-10, by inhibiting IL-6 production, also inhibits the regenerative response after hepatic I/R. In this study, however, I/R combined with rrIL-10 administration resulted in an increased regenerative response compared to rrIL-10 administration without ischemia. Also, significantly more MIB-5 positive cells were found in the I/R+IL-10 groups as compared to I/R+saline. Hence, exogenous IL-10 administration did not impair hepatocyte proliferation, but on the contrary, enhanced hepatocellular proliferation. Along with increased proliferation, apoptosis was inhibited by I/R+IL-10 administration as compared to the I/R+saline and I/R+antiIL-10 groups. It can therefore, be concluded that rrIL-10, by inhibiting IL-6, did not prevent proliferation, nor stimulate apoptosis after I/R. This suggests that other systems under the influence of IL-10, play a role in the proliferation and apoptosis pathways during hepatic I/R. RrIL-10 was administered at two different time points in this study. These were chosen to examine whether rrIL-10 can be used to prevent I/R induced injury, and whether rrIL-10 produces better results when administered after the ischemic insult, just before reperfusion. While parameters such as AST/ALT and MIB-5 showed a trend, bile production showed a significant advantage of rrIL-10 administration prior to ischemia compared to rrIL-10 administration at the end of the ischemic period. As mentioned above, MPO levels, however, were lower in I/R+IL-10end, although not statistically significant. Therefore, no clear advantage for either time point of administration was found.

In conclusion, the results of this study clearly demonstrate the protective effect of endogenous IL-10 and even more of exogenous rrIL-10 in a rat model of hepatic I/R. RrIL-10 administration, in contrast to what has been reported in literature, also sustains a regenerative response after I/R of the liver. RrIL-10 administration can therefore be useful to prevent I/R injury and to promote liver regeneration after partial liver resection with temporary inflow occlusion.

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Reference list


