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Research Article

Monocyte-Derived Macrophages Exacerbate Acetaminophen-Induced Liver Injury in Mice through Intrahepatic Hypercoagulation

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Abstract

Objective: The contribution of macrophages to the development of acetaminophen-induced liver injury is controversial. This study was designed to clarify those conflicting results.

Methods: The standard protocol using liposome-encapsulated clodronate suggests that pretreatment should occur 48 h prior to acetaminophen challenge, which appears long enough to allow the infiltration of bone marrow-derived monocytes/macrophages into the liver. To confirm this possibility, we shortened the interval between pretreatment and acetaminophen challenge to 24 h, and influences of two different protocols were examined 24 h after acetaminophen challenge.

Results: Although F4/80-positive Kupffer cells were depleted with pretreatment protocols using liposome-encapsulated clodronate, serum ALT concentrations significantly decreased in the 24-h-interval group compared with the group that did not undergo pretreatment. ALT concentrations increased in the 48-h-interval group, accompanied with infiltration of CD11b-positive cells into centrilobular necrosis areas, increased expression of LDH and tissue factor in hepatocytes surrounding centrilobular necrosis, and increased expression of MCP-1. As infiltration of CD11b-positive cells was not observed in the 24-h-interval group, CD11b-positive cells should be bone marrow-derived macrophages.

Conclusion: Macrophages play a pivotal role in the exacerbation of acetaminophen-induced liver injury through intrahepatic microcirculation disturbance, but they were found to be bone marrow-derived macrophages, and not resident Kupffer cells.

Key words:

Acute liver failure; Clodronate; Tissue factor; Lactate dehydrogenase; Monocyte chemoattractant protein-1

Introduction

Acetaminophen (*N*-acetyl-*p*-aminophenol; APAP) is the most frequent cause of drug-induced liver failure worldwide. APAP is metabolized into *N*-acetyl *p*-benzoquinone imine by CYP2E1 in hepatocytes, which binds to mitochondrial proteins and leads to hepatocyte necrosis [1]. As well as the harmful effects of the metabolite, the involvement of innate cells in the development of APAP-induced liver injury has been studied. Of the innate cells, the role of macrophages is the most studied; however, results remain controversial [2].

It was first reported that depletion of Kupffer cells, resident macrophages in the liver, using gadolinium chloride eliminated APAP-induced hepatotoxicity in mice, suggesting the harmful effect of Kupffer cells on the process of liver injury by APAP [3]. Later research, however, suggested that gadolinium chloride cannot sufficiently deplete Kupffer cells [4,5]. Complete depletion of Kupffer cells was achieved with liposome-encapsulated clodronate (Lip/Cld), which also depleted circulating monocytes and monocyte-derived macrophages [6]. Since pretreatment with Lip/Cld significantly worsened APAP-induced liver injury, the authors concluded that Kupffer cells play a protective role in the disease [4].

In a series of studies using macrophage ablation techniques with Lip/Cld, the observed long period of absence of resident and circulating macrophages/monocytes after ablation suggested that the method was effective. However, soon after the establishment of this method it was reported that bone marrow macrophage precursors were not affected by Lip/Cld[6]. Furthermore, although depletion of macrophages following treatment with Lip/Cld was confirmed using F4/80 antigen in earlier studies, the antigen is expressed in limited amounts on mature macrophages, and is low or absent in selected macrophage populations such as splenic marginal macrophages and osteoclasts [7]. It is therefore possible that the involvement of newly derived macrophages/monocytes from bone marrow after ablation with Lip/Cld has been overlooked.

Administration of APAP is generally performed 48 h after Lip/Cld treatment based on evidence that this time period is associated with the maximum depletion of Kupffer cells [8]. It is not known, however, whether this time interval is appropriate to avoid the influence of bone marrow-derived macrophages/monocytes.Even though a number of prior studies indicated the involvement of innate cells in APAP-induced liver failure, it is still undetermined how innate cells contribute to hepatocyte death.

The most characteristic clinical findings in patients with APAP-induced liver failure is the distinct elevation of serum lactate dehydrogenase (LDH) concentrations in the acute phase, and the existence of pathological centrilobular necrosis. These findings are similar to hypoxic hepatitis, suggesting that the liver could be in a hypoxic state during the exacerbation period of the disease [9].

In a study using a mouse model of APAP-induced liver injury, activation of the coagulation system, including hepatic fibrin deposition and centrilobular necrosis, was found to contribute to the development of liver injury, which was attenuated by pretreatment with heparin [10]. It was also reported that macrophages and T-cells are indispensable in the induction of hepatic hyper-coagulation through upregulation of tissue factor expression in the liver of a mouse model of concanavalin A-induced T-cell-mediated hepatitis [11].

In the current study, we hypothesized that a shorter interval between pretreatment with Lip/Cld and APAP administration is suitable to attenuate the infiltration of bone marrow-derived macrophages/monocytes. In addition, we sought to confirm responses to APAP challenge using a more complete depletion method of intrahepatic macrophages than previously reported, and examine the influence of macrophage elimination upon expression of tissue factor and the subsequent hypoxic state.

Materials and Methods

Mice and protocols for pretreatment and APAP administration

Male C57BL/6 mice (8 weeks old) were purchased from Japan SLC (Hamamatsu, Japan). All studies were performed in accordance with the *Guide for the Care and Use of Laboratory Animals*(National Institutes of Health) and were approved by the Animal Care Committee of Kyushu University (A27-192-0).Mice were fasted for 16 h before APAP administration, and were then injected intraperitoneally with freshly prepared APAP (Sigma-Aldrich, St. Louis, MO) dissolved in phosphate-buffered saline (300 mg/kg body weight). In advance of APAP administration, mice were divided into four groups and underwent different pretreatments. Pretreatments for the first and second groups were intravenous injection of 100 μL liposome-encapsulated phosphate-buffered saline (non-clodronate group), and Lip/Cld(clophosome-A; FormuMax, Sunnyvale, CA) (24-h-interval group) 24 h prior to APAP administration. The third group underwent pretreatment with liposome-encapsulated phosphate-buffered saline simultaneously with the previous groups but phosphate-buffered saline was injected instead of APAP (control group). For the fourth group, 100 μL liposome-encapsulated clodronate was injected 48 h prior to APAP administration (48-h-interval group). At 24 h after APAP challenge, mice were anesthetized, bled, and killed. Sera were isolated for testing alanine aminotransferase (ALT) concentrations. Liver tissues were excised for extracting RNA followed by quantitative real-time polymerase chain reaction (RT-PCR) analysis for LDH, tissue factor, and monocyte chemoattractant protein-1 (MCP-1). Tissues were paraffin-embedded prior to hematoxylin and eosin (H&E) staining and immunohistological analysis.

Immunohistological analysis

Liver tissues were fixed in 4% paraformaldehyde and cut into 5-μm sections. For immunohistological staining, liver sections from tissue blocks were deparaffinized and immersed in methanol containing 0.3% hydrogen peroxide. After boiling at 100°C with antigen retrieval reagent (Dako, Glostrup, Denmark), and preventing nonspecific binding of antibodies with the blocking buffer (NacalaiTesque, Kyoto, Japan), sections were incubated with primary antibodies for F4/80 (1:100; Abcam, Cambridge, UK), CD11b (1:200; Abcam), LDH-5 (1:100; Abcam), tissue factor (1:150; Bioworld Technology, St. Louis Park, MN), CD4 (1:100; Bioss, Woburn, MA) and NK1.1 (1:100; Novus Biologicals, Littleton, CO) at 4°C overnight.

As hepatic LDH comprises four subunits of LDH-A (known as LDH-5 isozyme), specific antibodies were applied. Sections were subsequently incubated with peroxidase-conjugated secondary antibodies for 2 h at room temperature. Reaction products were visualized using a 3,3'-diaminobenzidine staining kit (Nichirei, Tokyo, Japan). Counterstaining was conducted using methyl green.

RNA isolation and quantitative RT-PCR analysis

Total RNA was prepared from all tissues using TRIzol reagent (Invitrogen, Carlsbad, CA) and cDNA was synthesized from 1.0 μg RNA by GeneAmp RNA polymerase chain reaction (Applied Biosystems, Hammonton, NJ) with random hexamers. RT-PCR was performed using LightCyclerFastStart DNA Master SYBR Green I (Roche, Basel, Switzerland). The reaction mixture (20 μL) contained Master SYBR Green I, 4 mmol/L of $MgCl_2$, 0.5 μmol/L of the upstream and downstream PCR primers, and 2 μL of first-strand cDNA as a template. To control for variations in reactions, all PCR data were normalized against glyceraldehyde 3-phosphate dehydrogenase expression. The specific primers used were:

MCP-1: (sense 5′-AGGTCCCTGTCATGCTTCTG-3′; antisense 5′-GCTGCTGGTGATCCTCTTGT-3′)

LDH-A: (sense 5′-TGGCAGCCTCTTCCTTAAAA-3′; antisense 5′-TTTTCCAAGCCACGTAGGTC-3′)

Tissue factor: (sense 5′-TGCTTCTCGACCACAGACAC-3′; antisense 5′-TAAAAACTTTGGGGCGTTTG-3′)

Statistical analysis

Data are presented as mean ± SEM. Comparisons among multiple groups were performed using the Kruskal–Wallis test followed by the Mann–Whitney U test. JMP software (version 11, SAS Institute, Cary, NC) was used for all statistical analyses. A p-value <0.05 was considered statistically significant.

Results

Serum ALT concentrations and pathological findings

The serum ALT concentration 24 h after APAP challenge in the non-clodronate group was 4161.7±259.0 U/L. This decreased to less than half in the 24-h-interval group (2050.0 ± 112.4 U/L), and increased more than 1.8 times in the 48-h-interval group (7627.2 ± 526.2 U/L) (Figure 1).

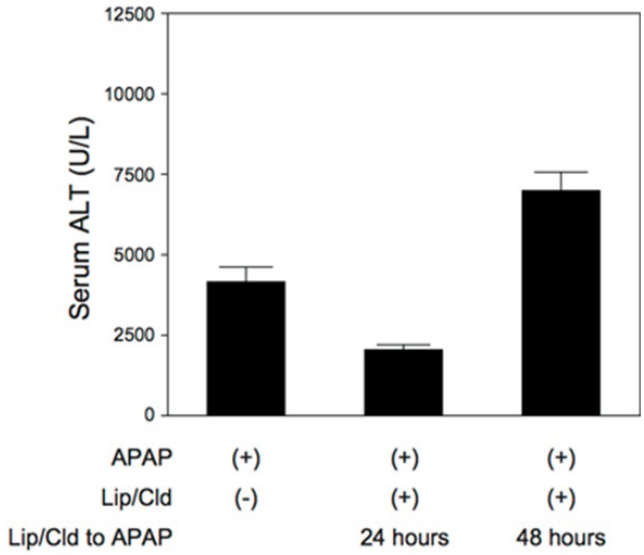

Figure 1: Serum ALT concentrations 24 h after APAP challenge. Even with pretreatment at the same dose of Lip/Cld, ALT concentrations decreased when pretreatment was performed 24 h before APAP challenge. In contrast, ALT concentrations increased when the interval was extended to 48 h.

H&E staining showed geographical centrilobular necrosis in the non-clodronate group, which was also observed in the 48-h-interval group with no significant differences. In contrast, eosinophilic degeneration around centric veins was seen in the 24-h-interval group but centrilobular necrosis was not observed (Figure 2).

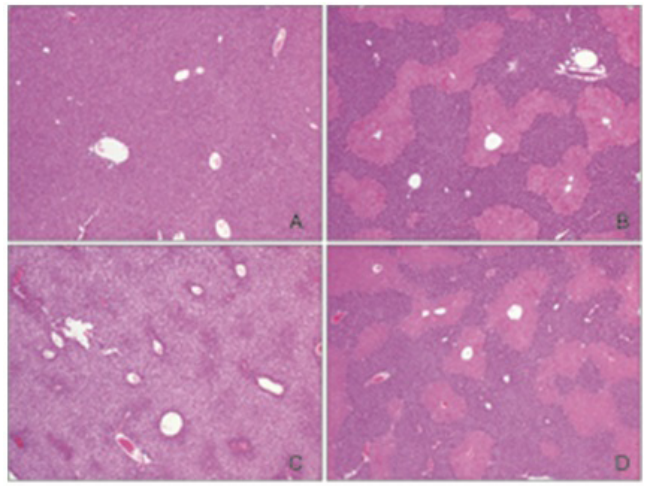

Figure2: Pathological liver injury 24 h after APAP challenge (H&E). (A) Control group, (B) non-clodronate group, (C) 24-h-interval group, (D) 48-h-interval group. Centrilobular necrosis was observed in non-clodronate and 48-h-interval groups. Eosinophilic degeneration around central veins was observed in the 24-h-interval group.

Immunohistological findings

Immunostaining with anti-F4/80 antibodies showed scattered positive cells in sinusoids of control and non-clodronate groups. Positive cells were observed to be evenly dispersed regardless of zones of Rappaport's acinus and centrilobular

necrosis. There were no differences in numbers and distributions of positive cells between these two groups. In groups that underwent pretreatment with clodronate, clear positive cells were not observed. Only in the 48-h-interval group, there were a few dimly stained spindle cells observed in areas of centrilobular necrosis (Figure 3).

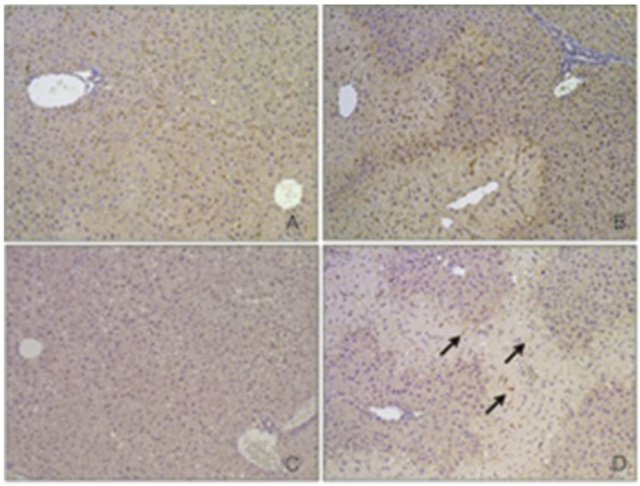

Figure3: Immunological staining with anti-F4/80 antibodies. (A) Control group, (B) non-clodronate group, (C) 24-h-interval group, (D) 48-h-interval group. Although clear positive cells were not observed after pretreatment with Lip/Cld (C, D), a few dimly positive cells were seen in the 48-h-interval group (black arrow).

For immunostaining using anti-CD11b antibodies, a few positive cells were observed scattered across acini in the control group, and a slight increase in the number of positive cells was seen around central veins in the 24-h-interval group. Significantly increased numbers of positive cells were observed centered in areas of centrilobular necrosis in non-clodronate and 48-h-interval groups (Figure 4).

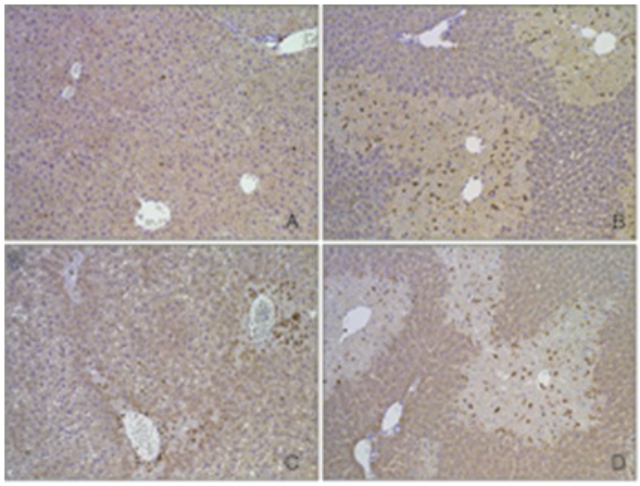

Figure4: Immunological staining with anti-CD11b antibodies. (A) Control group, (B) non-clodronate group, (C) 24-h-interval group, (D) 48-h-interval group. CD11b-positive cell infiltration was observed mainly in areas of centrilobular necrosis after APAP challenge (B, D). Such infiltration was not observed when the interval between pretreatment with Lip/Cld and APAP challenge was shortened (C).

Positive cells stained with anti-LDH-5 and anti-tissue factor antibodies were observed in a similar manner of distribution (Figure 5, 6). Both showed increased expression around central veins in the 24-h-interval group, and significantly strong expression was observed in areas surrounding centrilobular necrosis in control and 48-h-interval groups. LDH expression remained in necrotized hepatocytes and in centrilobular necrosis areas. When stained with anti-CD4 and anti-NK1.1 antibodies, there were no positive cells in areas of centrilobular necrosis after APAP challenge (data not shown).

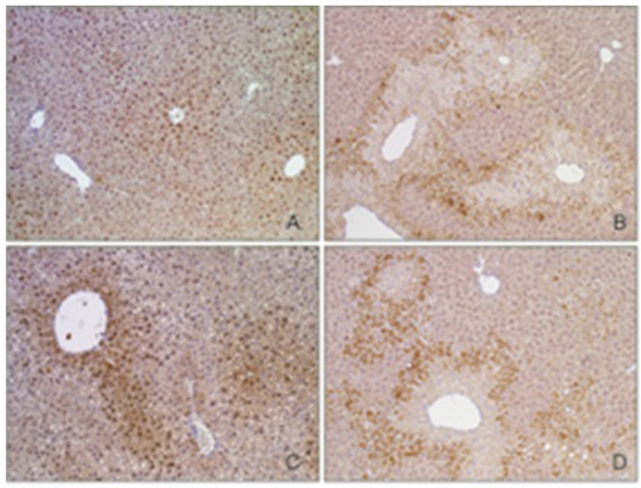

Figure5: Immunological staining with anti-LDH-5 antibodies. (A) Control group, (B) non-clodronate group, (C) 24-h-interval group, (D) 48-h-interval group. Strong staining was observed in hepatocytes surrounding areas of centrilobular necrosis in non-clodronate and 48-h-interval groups. Remnant LDH was also observed in necrotized hepatocytes in centrilobular necrosis. In the 24-h-interval group, increased expression of LDH was observed only around central veins.

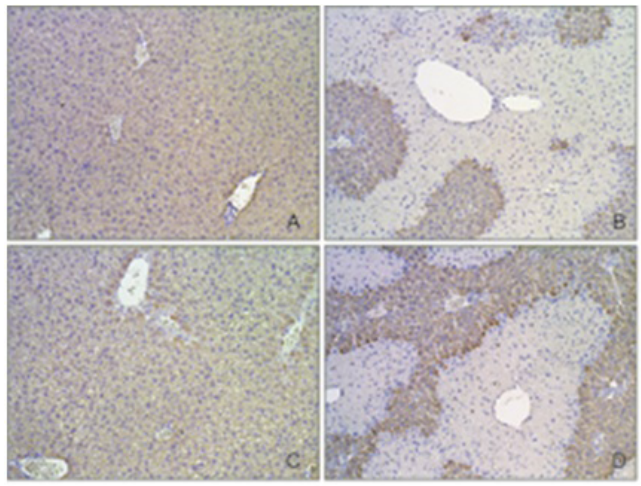

Figure6: Immunological staining with anti-tissue factor antibodies. (A) Control group, (B) non-clodronate group, (C) 24-h-interval group, (D) 48-h-interval group. Hepatocytes with increased expression of tissue factor were distributed in a similar pattern to those expressing LDH.

Quantitative RT-PCR

Differences in LDH and tissue factor expression were examined using quantitative RT-PCR. The 48-h-interval group showed the strongest mRNA expression for LDH-A and tissue factor, followed by the non-clodronate group. These findings were consistent with results from immunostaining (Figure 7A, B).

To investigate the mechanism of CD11b-positive cell infiltration, mRNA expression of MCP-1 was examined. Expression of MCP-1 was scarcely seen in the control group, but appeared to increase after APAP challenge. This increase was especially evident in the 48-h-interval group (Figure 7C).

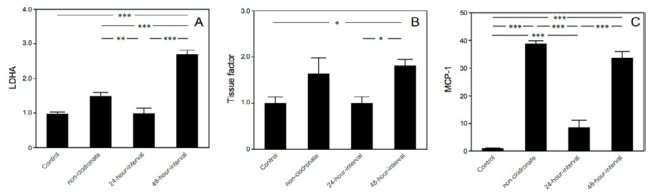

Figure7: mRNA expression in the liver 24 h after APAP challenge. Degree of expression is presented as a ratio to the mean of the control group. The 48-h-interval group showed the highest levels of gene expression of LDH and tissue factor, followed by the non-clodronate group.

Discussion

In this study, we found that the elimination of macrophages markedly attenuated increases in serum ALT concentrations and prevented the formation of centrilobular necrosis in a mouse model of APAP-induced liver injury. This phenomenon was observed when pretreatment with Lip/Cld was performed at 24 h before APAP challenge, but was not evident when performed at 48 h. In both conditions, Kupffer cells clearly positive of F4/80 were completely depleted, which meant Kupffer cells did not play a pivotal role in the exacerbation of APAP-induced liver injury.

CD11b-positive cell infiltration into the liver was observed in the 48-h group but not in the 24-h group. Infiltration of CD11b-positive cells therefore appeared to occur between 24 and 48 h after pretreatment with Lip/Cld, which is considered to contribute to the exacerbation of APAP-induced liver injury. CD11b is expressed on the surface of many leukocytes, including monocytes, macrophages, granulocytes, natural killer cells, and macrophages. CD11b-positive cells that infiltrated the liver were considered to be bone marrow-derived monocytes/macrophages because they were negative for NK1.1 immunostaining and did not show a lobulated nucleus with H&E staining. Furthermore, since Lip/Cld can deplete resident and peripheral monocytes/macrophages without affecting other leucocytes [8], if the CD11b-positive cells observed in the 48-h-interval group had not been monocytes/macrophages, they should also have been observed in the 24-h-interval group. In order to rule out the involvement of Kupffer cells, we stained the 48-h-interval group with the F4/80 antibody, but could only find faint positive cells which might have been part of the CD11b-positive cells.

It has recently been reported that three different macrophage subsets can be distinguished in the injured mouse liver with APAP, these being Kupffer cells, Ly6C^{high} macrophages, and Ly6C^{low} macrophages. It is of note that the Ly6C^{high} macrophage population increased in the liver at 24–72 h after APAP administration [12]. Detailed analyses of CD11b-positive cells will be useful to help clarify the mechanisms of innate cell involvement in liver injury.

When we compared prior conflicting studies that, attempted to eliminate Kupffer cells with gadolinium chloride [3], and completely depleted them with Lip/Cld[4], we found differences in the lengths of intervals between pretreatment and APAP administration, as well as the materials used and the outcomes of liver injury. In the former study, the interval was 24 h, and in the latter it was 48 h. If CD11b-positive cells were the main cause of aggravated liver injury, then using gadolinium chloride could suppress APAP-induced liver injury by depleting circulating monocytes. A recent study reported that gadolinium chloride partially affected resident macrophages but almost completely depleted peripheral monocytes [13]. Therefore, the reported effect of gadolinium chloride pretreatment in reducing APAP-induced liver injury is reasonable, because the depletion of peripheral monocytes could result in a monocyte-derived macrophage-free situation in the liver during APAP toxicity despite the residual Kupffer cells.

Alternatively, the results of the prior study that used the macrophage depletion model with Lip/Cld [4] also coincided with the findings of the current study. The higher concentrations of serum ALT in the 48-h-interval group compared with those in the non-clodronate group can be explained by decreases in suppressive cytokines such as IL-6 and IL-10, which are produced by Kupffer cells [4]. This earlier study [4], however, used anti-F4/80 antibodies to detect macrophages, making it difficult to evaluate infiltration of monocyte-derived macrophages.

Intriguingly, we found that centrilobular necrosis disappeared when macrophages were completely depleted in the 24-h-interval group. In these conditions, serum ALT concentrations decreased to about half than that of the non-clodronate group, and H&E staining showed only eosinophilic degeneration around central veins. We believe these findings were a result of the toxic APAP metabolite *N*-acetyl *p*-benzoquinone imine, suggesting that centrilobular necrosis, a characteristic finding of APAP-induced liver injury, could not develop without the participation of monocytes/macrophages.

Hepatocytes overexpressing LDH were observed around necrotic areas in non-clodronate and 48-h-interval groups. Positivity for LDH also remained in necrotic areas. Because up regulation of LDH reflects a hypoxic state [14], centrilobular necrosis could be caused by hypoxia in zone 3. In addition, the distribution of hepatocytes that strongly express tissue factor was the same as the area of LDH overexpression. These findings support the result of an earlier study that reported significant fibrin depositions in centrilobular areas in a mouse model of APAP-induced liver injury [10]. The authors noted that such fibrin depositions were not seen in mice deficient in tissue factor.

We showed that in the groups that developed centrilobular necrosis, CD11b-positive cells were found mainly in necrotic areas, which indicates that monocyte-derived macrophages might contribute to the initiation of hyper-coagulation in

centrilobular areas. A recent study reported that macrophage production of tissue necrosis factor-α, coupled with T-cell production of interferon-γ, induced expression of tissue factor in the livers of mice with concanavalin A-induced hepatitis, resulting in sinusoidal fibrin deposition and hepatic microvascular disturbance[11]. Considering the finding of increased tissue factor and LDH expression in the current study, a similar mechanism could be assumed. Although we could not confirm CD4-positive T-cell infiltration into zone 3, they might have collapsed with the surrounding necrotic hepatocytes. Further studies examining fragmented intervals between 24 and 48 h after pretreatment might clarify the participation of T-cells.

Besides the role of initiator of microcirculation disturbance, results from MCP-1 gene expression indicated that CD11b-positive cells could contribute to the acceleration of liver injury via recruiting peripheral monocytes into the liver. MCP-1 has been demonstrated to recruit monocytes/macrophages into foci of inflammation, and the major source of MCP-1 is also monocytes/macrophages [15, 16]. It is therefore not surprising that MCP-1 gene expression was significantly suppressed in the 24-h-interval group with complete depletion of monocytes/macrophages. When the non-clodronate group was compared with the 48-h-interval group, MCP-1 gene expression was found to be greater in the former than in the latter; however, the difference was not significant. This suggests that increased MCP-1 gene expression was mainly due to infiltrated CD11b-positive cells, not Kupffer cells. The minor difference might come from the protective effect of Kupffer cells.

In this study, we found that APAP-induced liver injury could be completely avoided by depleting monocytes/macrophages, which was achieved by shortening the interval between Lip/Cld pretreatment and APAP administration to 24 h. A significant elevation in serum ALT concentrations and centrilobular necrosis appeared when the interval was extended to 48 h, accompanied by infiltration of CD11b-positive cells into zone 3 and increased expression of tissue factor and LDH in the same area. These findings suggest that monocyte-derived macrophages, not Kupffer cells, play a pivotal role in the exacerbation of APAP-induced liver injury through intrahepatic hyper-coagulation and subsequent hypoxia. Considering a recent clinical study reporting that tissue factor-positive micro particles are associated with mortality in APAP overdose patients [17], inhibition of monocyte-derived macrophages could be a new target of treatment.

Acknowledgments

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Competing Interests

All authors who have taken part in this study declared that they have nothing to disclose regarding funding or conflict of interest with respect to this manuscript.

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