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ORIGINAL ARTICLE

Inflammation of Mesenteric Adipose Tissue Correlates with Intestinal Injury and Disease Severity in Rats with Severe Acute Pancreatitis

Qing Huang[1] · Jiawen Liu[1] · Zhiyong Zhou[1] · Mingjun Zhang[1] · Yutang Ren[1] · Xuan Jiang[1] · Bo Jiang[1]

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Abstract

Background Visceral adipose tissue (VAT) is related to SAP prognosis. As a depot of VAT, mesenteric adipose tissue (MAT) resides between pancreas and gut, which might affect SAP and the secondary intestinal injury.

Aims To investigate the changes of MAT in SAP.

Methods 24 SD rats were randomly divided into four groups. 18 rats in SAP group were euthanized in time gradients (6 h, 24 h, and 48 h after modeling) and the others in control group. Blood samples and tissues of pancreas, gut, and MAT were taken for analysis.

Results Compared to the control group, SAP rats appeared MAT inflammation, presenting higher mRNA expression of TNF-α and IL-6 and lower IL-10, and histological changes after 6 h of modeling, which became worse over time. Flow cytometry showed that B lymphocytes increased in MAT after 24 h of SAP modeling and lasted up to 48 h, earlier than the changes of T lymphocytes and macrophages. The intestinal barrier integrity was damaged after 6 h of modeling, presenting lower mRNA and protein expression of ZO-1 and occludin, higher serum levels of LPS and DAO, with pathological changes, which gradually aggravated after 24 h and 48 h. SAP rats had higher serum levels of inflammatory indicators and revealed histological inflammation of pancreas, the severity of which increased with the passage of modeling time.

Conclusion MAT appeared inflammation in early-stage SAP, and became worse over time, with the same trend as the intestinal barrier injury and the severity of pancreatitis. B lymphocytes infiltrated early in MAT, which might promote the MAT inflammation.

Keywords Acute pancreatitis · Mesenteric adipose tissue · Intestinal barrier · B lymphocyte

Introduction

Approximately one-fifth of all patients with acute pancreatitis (AP) will develop to severe AP (SAP) characterized by organ dysfunction and pancreatic necrosis with high mortality rate [1]. Intestinal barrier injury is the most common systematic complication in SAP patients, which may lead to bacterial translocation and secondary infection [2]. Intestinal function is of great significance in disease severity and prognosis of SAP. However, the pathogenesis of secondary intestinal injury is complicated. Several factors, like intestinal microcirculation disorder, excessive release of inflammatory mediators, ischemia–reperfusion injury, pyroptosis, intestinal nutrition deficiency, and dysbacteriosis are supposed to be involved [3]. To clarify the mechanism of intestinal injury will provide new methods for early-stage evaluation and targeted therapy of SAP.

The increasing amount of visceral adipose tissue (VAT) would lead to poorer prognosis in AP patients [4]. VAT was found to be thicker in AP patients compared with healthy people, with no difference in body mass index [5]. However, which depot of VAT plays the most important role has not been clear. VAT mainly consists of mesenteric, perirenal, retroperitoneal, epididymal and omental adipose tissue, among others. All these adipose tissues locate in an individual microenvironment and maintain various functions, which should be evaluated individually.

✉ Xuan Jiang
jxa01998@btch.edu.cn

Qing Huang
hqa03058@btch.edu.cn

[1] Department of Gastroenterology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 102218, China

Mesenteric adipose tissue (MAT), as a depot of VAT, resides between pancreas and gut, surrounded by blood vessels, lymphatic vessels and nerves, making it possible to affect contiguous tissues by secreting inflammatory cytokines and adipocytokines, etc. [6]. Gea-Sorli et al. [7] found that AP induced a strong inflammatory response in MAT, while no changes were found in retroperitoneal adipose tissue. Furthermore, MAT played an important role in intestinal injury in Crohn's disease [8] and nonalcoholic fatty liver disease (NAFLD) [9]. These results indicated that MAT might play an important role in SAP and the related intestinal barrier damage.

In the present study, we aimed to investigate the changes of MAT in SAP rats. Our results showed that MAT appeared inflammatory response in early-stage SAP and became worse over time, with B lymphocytes infiltration in MAT. The MAT inflammation correlated with the intestinal injury and the severity of pancreatitis. The early infiltration of B lymphocytes might promote the MAT inflammation.

Materials and Methods

Animals and SAP Model

About 250 g male Sprague Dawley (SD) rats of 4–6-week-old were supplied by Beijing Vital River Laboratory Animal Technology (Beijing, China) and raised in a specific pathogen-free facility with constant temperature and humidity. After 5 days of adaptive feeding, rats were free to drink but fasted for about 12 h before modeling. 24 male SD rats were randomly divided into four groups: (1) SAP 6 h group, (2) SAP 24 h group, (3) SAP 48 h group, and (4) control group. 18 rats in the SAP group were anesthetized with isoflurane and their abdomen was exposed along the midline. They received retrograde pumping of 5% sodium taurocholate (0.1 ml/100 g) into pancreaticobiliary duct, and then placed back into position. Rats in the SAP group were euthanized in time gradients (6 h, 24 h, and 48 h after modeling). The others in the control group were anesthetized and their abdomen was exposed along midline. Their duodenum and pancreas were pulled out and touched by sterile swabs for 4–5 times, and then placed back into position. Rats in the control group were euthanized in 6 h after modeling. Serum and various tissues were collected, including pancreas, gut, and MAT.

Histological Analysis

Samples of pancreas, gut, and MAT were sliced into 4-μm cross-sections and stained with hematoxylin–eosin (HE) for histological analysis. The sections were observed under a light microscope. Two pathologists used double-blind method to evaluate the inflammatory status of tissues in the experiment. The pancreatic pathology was assessed according to the scoring criteria proposed by Schmidt [10]. The intestinal pathology was scored according to the criteria described by Chiu [11]. The histological assessment of MAT was to count the number of "crown-like structure" (CLS), which was defined as one adipocyte surrounded by at least five macrophages.

Real-Time Polymerase Chain Reaction (RT-PCR)

Total RNA was extracted using an RNA extraction kit (Qiangen, Hilden, Germany) according to the manufacturer's protocol. cDNA was synthesized using an cDNA Synthesis kit (Thermo Fisher Scientific, Vilnius, Lithuania) according to the manufacture's protocol. RT-PCR was carried out with a StepOne PT-PCR System (Applied Biosystems, Waltham, MA) using SYBR premix EX Taq II kit (Takara, Tokyo, Japan). The sequences of primers were as follows: zonula occludens-1 (ZO-1) forward, GCCGCTAAGAGCACA GCAA and reverse, GCCCTCCTTTTAACACATCAGA; occludin forward, GCTTATCTTGGGAGCCTGGACA and reverse, GTCATTGCTTGGTGCATAATGATTG; and tumor necrosis factor-α (TNF-α) forward, CAGGCGGTGCCTATG TCTC and reverse, CGATCACCCCGAAGTTCAGTAG; and interleukin-6 (IL-6) forward, CTGCAAGAGACT TCCATCCAG and reverse, AGTGGTATAGACAGGTCT GTTGG; and IL-10 forward, CTTACTGACTGGCATGAG GATCA and reverse, GCAGCTCTAGGAGCATGTGG; and acetyl-coenzyme A carboxylase 1 (ACC-1) forward, GGC GACTTACGTTCCTAGTTG and reverse, AGATGTCGA TAAATGCGGTCC; and peroxisome proliferators activated receptor α (PPAR-α) forward, AACATCGAGTGTCGAATA TGTGG and reverse, CCGAATAGTTCGCCGAAAGAA; and leptin forward, ACCTGGCATATCCAATCTCTCC and reverse, TTCAAAGCCGAGGCATTGTTT; and adiponectin forward, TGTTCCTCTTAATCCTGCCCA and reverse, CCAACCTGCACAAGTTCCCTT.

Flow Cytometry

Immune cells were labeled with CD45-PE, CD19-APC, CD3-FITC, and F4/80-PerCP/Cy5.5 antibodies (Biolegend, San Diego, CA, USA) and measured using a FACS Calibur flow cytometer (BD Immunocytometry Systems, Frnklin Lakes, NJ). Data analysis was used Flowjo 10.

Western Blot Analysis

Protein was extracted from intestinal tissue and the protein concentrations were measured. 60 μg protein was separated using sodium dodecyl sulfate–polyacrylamide gel electrophoresis and transferred to a nitrocellulose filter membrane. The protein was then incubated at 4 ℃ overnight in primary

antibody on a shaking table. The primary antibodies were as follows: anti-occludin and anti-ZO-1 (Abcam; 1:1000). After extensive washing, the second antibody was used. Glyceraldehyde phosphate dehydrogenase (GAPDH) was used as an internal control and the protein bands were scanned by Image-Pro Plus 6.0 software.

Enzyme-Linked Immunosorbent Assay (ELISA)

Levels of C-reactive protein (CRP), lipopolysaccharide (LPS), and diamine oxidase (DAO) in serum were detected using ELISA. The ELISA kits were obtained from R&D Systems (Minneapolis, MN, USA).

Blood Routine and Biochemistry Detection

The blood cells counts were detected using an automatic whole blood counter. The concentrations of amylase (AMY) and lipase were detected using an automatic biochemical detector-Labospect 008.

Statistical Analysis

Data are presented as mean ± standard deviation. Two-tailed student's t test or one-way ANOVA were used to compare values between groups. All the analyses were conducted using SPSS version 26 software. GraphPad Prism 8.3 was used to plot graphs. *P*-value < 0.05 was considered statistically significant.

Results

MAT Appeared Inflammatory Response in Early-Stage SAP, and Became Worse Over Time, with the Same Trend as the Severity of Pancreatitis

Firstly, we investigated the pancreatitis of rats. The counts of white blood cells (WBC) ($P < 0.01$) and the ratio of neutrophil (NE) ($P < 0.01$) were statistically higher in SAP groups than that in the control group (Fig. 1A, B). The serum levels of CRP were also higher ($P < 0.01$) (Fig. 1C). The serum concentrations of AMY were significantly higher ($P < 0.01$) in SAP groups (Fig. 1D). All these inflammatory indicators of AP had significant increasing tendencies with the passage of SAP modeling time. While the serum levels of lipase did not increase statistically until 48 h of SAP modeling ($P < 0.01$) (Fig. 1E). The pancreas tissue exhibited interstitial edema and leukocyte infiltration in SAP groups. The inflammation became gradually obvious over time (Fig. 2A). And the pathological scores increased significantly in sequence in the control group, SAP 6 h, 24 h, and 48 h group ($P < 0.01$) (Fig. 2B).

Secondly, to clarify the changes of MAT in SAP, we explored inflammatory, lipometabolic, and endocrine status of MAT. In the SAP 6 h group, the mRNA expression of inflammatory cytokines (TNF-α and IL-6) within MAT were significantly higher than that in the control group ($P < 0.01$). And the mRNA expression of TNF-α and IL-6 further increased in the SAP 24 h and 48 h group in

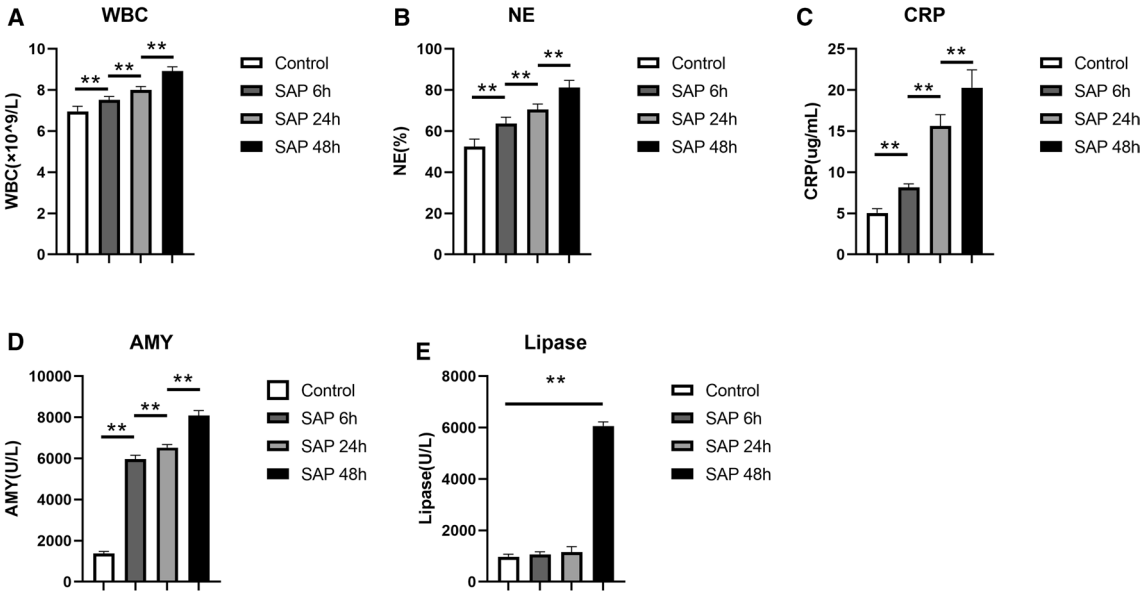

Fig. 1 Time-course analysis of pancreatic inflammation. The counts of WBC (**A**), the ratio of NE (**B**), and the serum levels of CRP (**C**) in rats. The serum levels of AMY (**D**) and lipase (**E**) in rats. Values represent means ± standard deviation. $^{**}P < 0.01$. *SAP* severe acute pancreatitis, *WBC* white blood cells, *NE* neutrophil, *CRP* C-reactive protein, *AMY* amylase

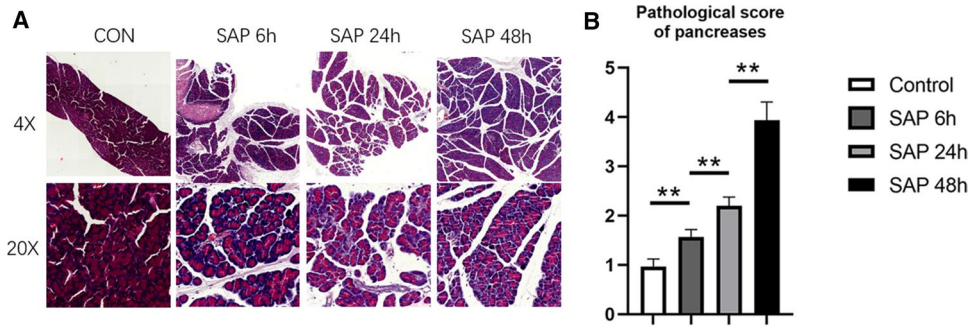

Fig. 2 Time-course histological analysis of pancreas tissue. **A** Representative hematoxylin–eosin staining of rats' pancreas in each group. **B** The pathological scores of pancreas tissues. Values represent means ± standard deviation. $^{**}P < 0.01$

sequence ($P < 0.01$) (Fig. 3A, B). Meanwhile, the mRNA expression of IL-10 presented statistical declining trend in sequence in the control, 6 h, 24 h, and 48 h SAP group ($P < 0.01$) (Fig. 3C). By contrast, the mRNA expression of neither lipometabolic factors (ACC-1 and PPAR-α) nor endocrine factors (leptin and adiponectin) differed in early stage of SAP from the control group (Fig. 3D, E). In the histological assessment of MAT, the number of CLSs was statistically more in the SAP 6 h group than that in the control group. The numbers of CLSs in the SAP 24 h and 48 h group significantly increased with the passage of modeling time (Fig. 4A, B). These findings indicated that MAT appeared inflammation in early-stage of SAP, and became worse over time, with the same trend as the severity of pancreatitis.

B Lymphocytes Infiltrated Earlier in MAT of SAP Rats Than T Lymphocytes and Macrophages

To explore the infiltration of immune cells in MAT of SAP rats, we detected them at multiple timepoints (6 h, 24 h, and 48 h) using flow cytometry. The gating strategy of flow cytometry for the MAT is shown in Fig. 5A. CD45 + CD19 + lymphocytes were considered as B lymphocytes, CD45 + CD3 + lymphocytes were considered as T lymphocytes and CD45 + F4/80 + lymphocytes were considered as macrophages. Compared with the control group, CD45 + CD19 + B lymphocytes in MAT increased significantly after 24 h of SAP modeling ($P < 0.01$), and lasted up to 48 h of SAP modeling ($P < 0.05$) (Fig. 5B). CD45 + CD3 + T lymphocytes in MAT decreased statistically in the SAP 24 h group ($P < 0.01$) (Fig. 5C), and

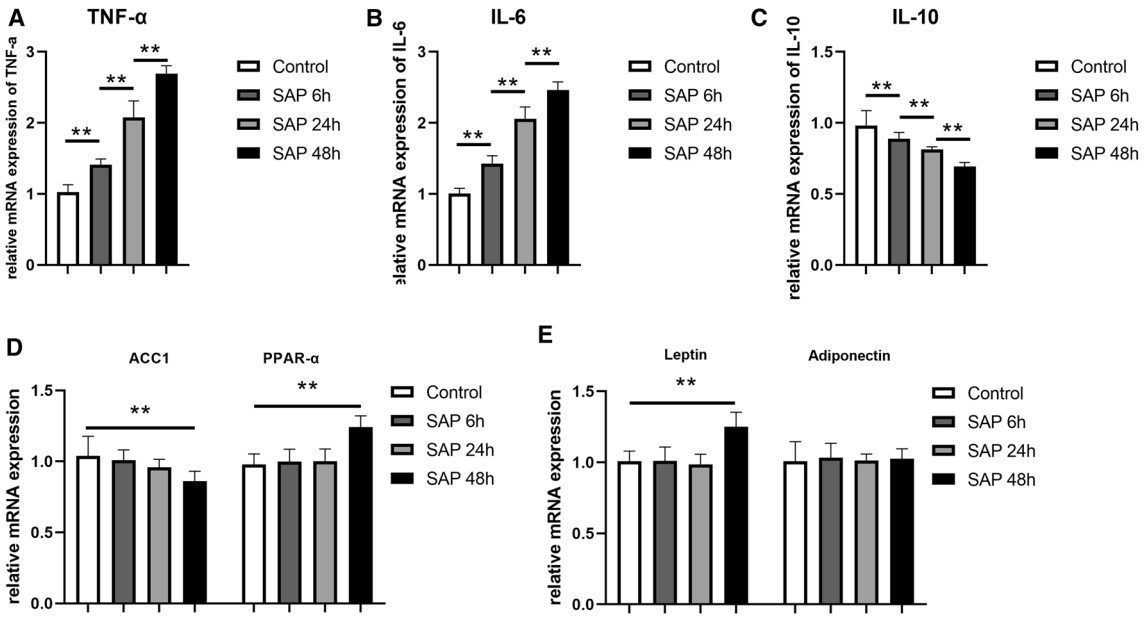

Fig. 3 Time-course analysis of inflammatory, lipometabolic, and endocrine status of MAT. Expression of mRNA responsible for MAT inflammation, specifically, TNF-α (**A**), IL-6 (**B**), and IL-10 (**C**). Expression of mRNA responsible for MAT lipometabolic status, specifically, ACC1 and PPAR-α (**D**). Expression of mRNA responsible for MAT endocrine status, specifically, leptin and adiponectin (**E**). Values represent means ± standard deviation. $^{**}P < 0.01$. *MAT* mesenteric adipose tissue, *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6, *IL-10* interleukin-10, *ACC1* acetyl-coenzyme A carboxylase 1; *PPAR-α* peroxisome proliferators activated receptor α

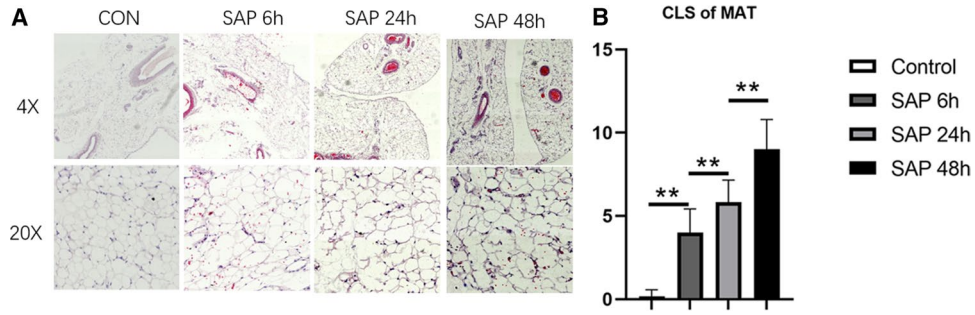

Fig. 4 Time-course histological analysis of MAT. **A** Representative hematoxylin–eosin staining of rats' MAT in each group. **B** The numbers of CLS in MAT. Values represent means ± standard deviation. $^{**}P < 0.01$. *CLS* crown-like structure

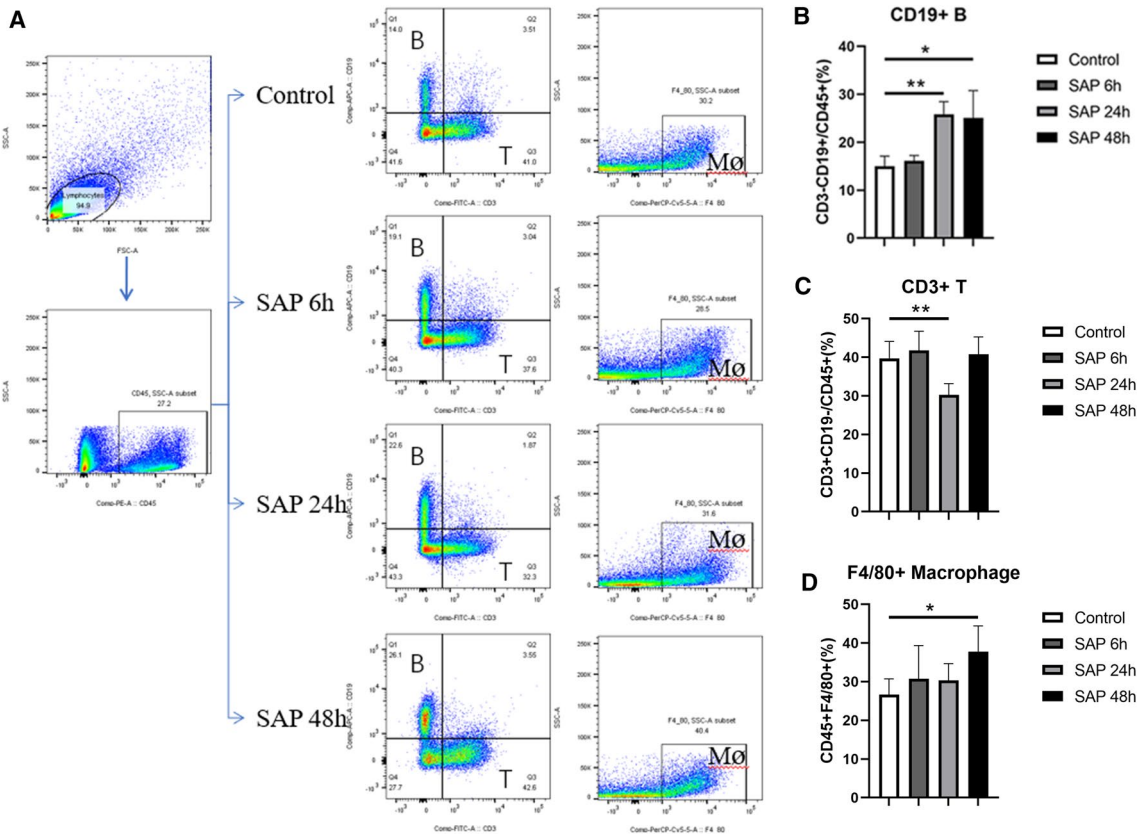

Fig. 5 B lymphocytes infiltrated early in MAT of SAP rats. **A** The gating strategy of flow cytometry for the MAT. The proportion of CD45 + CD19 + B lymphocytes (**B**), CD45 + CD3 + T lymphocytes (**C**), and CD45 + F4/80 + macrophages (**D**) in the MAT. Values represent means ± standard deviation. $^{**}P < 0.01$, $^{*}P < 0.05$

CD45 + F4/80 + macrophages did not increase in MAT until 48 h after SAP modeling ($P < 0.05$) (Fig. 5D). The early accumulation within MAT indicated that B lymphocytes might promote MAT inflammatory response in SAP.

SAP Rats Presented Intestinal Barrier Injury in the Early Phase, with the Same Trend as the Inflammation of MAT

To evaluate the intestinal barrier function in SAP, we detected the mRNA and protein expression of intestinal tight junction (ZO-1 and occludin) and the levels of serum endotoxin (LPS and DAO). In the SAP 6 h group, the mRNA expression of ZO-1 ($P < 0.01$) and occludin ($P < 0.01$) significantly decreased, compared to the control group. The mRNA expression of tight junction decreased statistically ($P < 0.01$) with time gradients of modeling (Fig. 6A). Similarly, the protein expression of ZO-1 and occludin declined in sequence with the passage of SAP modeling time (Fig. 6B). Compared to the control group, the serum levels of LPS and DAO were statistically higher in the SAP 6 h group ($P < 0.01$) and increased gradually in the SAP 24 h and 48 h group ($P < 0.01$) (Fig. 6C, D). Histological assessment of gut showed structural damage in the SAP 6 h

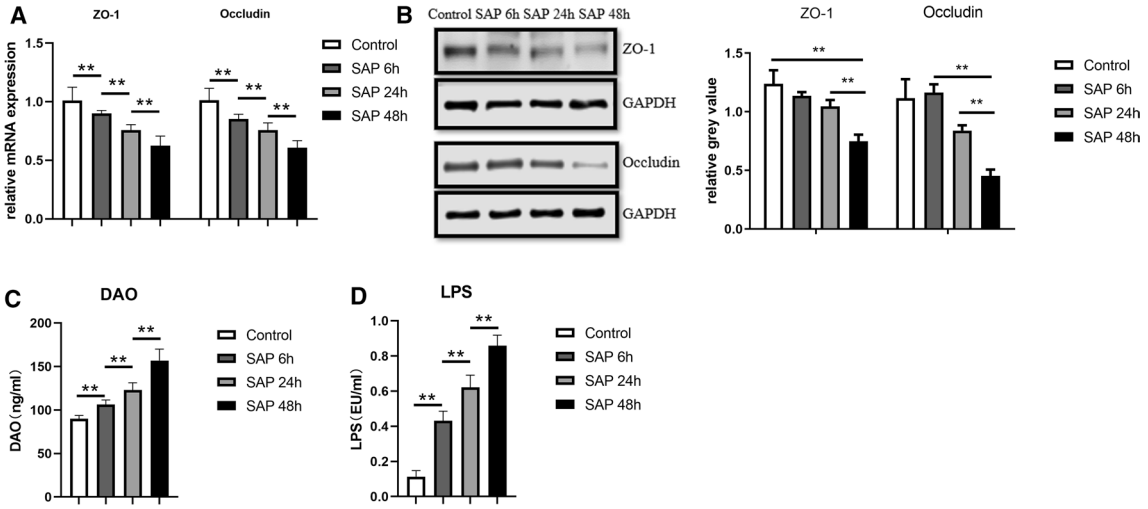

Fig. 6 Time-course analysis of intestinal barrier permeability. Expression of mRNA (**A**) and proteins (**B**) responsible for intestinal tight junction. Levels of serum endotoxins DAO (**C**) and LPS (**D**). Values represent means ± standard deviation. $^{**}P < 0.01$. *ZO-1* zonula occludens-1, *GAPDH* glyceraldehyde phosphate dehydrogenase, *DAO* diamine oxidase, *LPS* lipopolysaccharide

group compared to the control group, which became gradually obvious in the SAP 24 h and 48 h group (Fig. 7A). The representative signs of intestinal injury in the SAP groups included edema, bleeding, villus breakage, exposure of lamina propria capillaries and infiltration of inflammatory cells. Consistent with the trends of serum endotoxin, the pathological score of gut orderly increased in the control, SAP 6 h ($P < 0.01$), 24 h ($P < 0.05$), and 48 h group (Fig. 7B). Collectively, the above results revealed that SAP rats presented intestinal barrier damage in the early stage, with the same trend as the inflammation of MAT.

Discussion

AP is manifested by a spectrum of severity, from mild AP (MAP) in the majority of patients to SAP in 10–20% patients. SAP patients suffer from severe local and systemic complications and organ dysfunction. Majority of AP patients will present acute gastrointestinal malfunction and intestinal barrier injury. Secondary bacterial translocation to the blood circulation and to distant tissue often ensues, resulting in poorer prognosis [12]. Improving intestinal permeability of SAP patients would lead to better prognosis [13]. Nevertheless, the mechanism of secondary intestinal injury is complicated, which several factors are proposed to participate in. The volume of VAT is an important prognostic indicator for the severity of AP [4]. O'Leary et al. [14] used CT scan to estimate the volume of VAT and revealed a strong association between VAT, AP and the subsequent complications. Although these results implied that VAT contributed to the development of AP, which depot of VAT played the most important role had not been clear. VAT mainly consists of mesenteric, perirenal, retroperitoneal, epididymal and omental adipose tissue, among others [15]. All these adipose tissues locate in an individual microenvironment and maintain various functions [16], which should be evaluated individually.

As a depot of VAT, MAT resides between pancreas and gut, wrapping around blood vessels, lymphatic vessels and nerves, etc. In terms of homologous embryonic development, intestinal muscular layer connects directly with

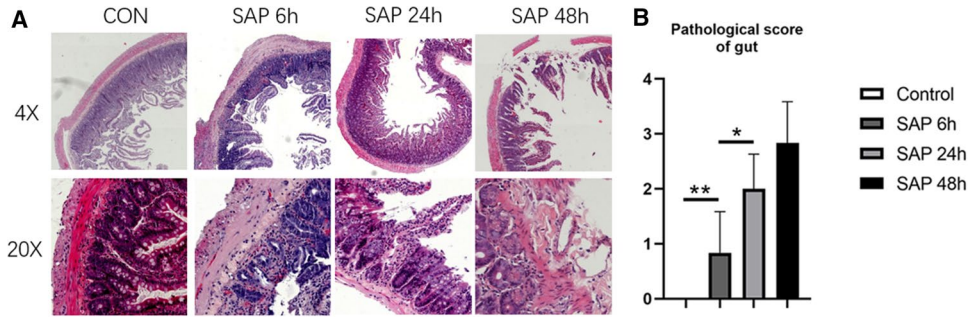

Fig. 7 Time-course histological analysis of intestinal tissue. **A** Representative hematoxylin–eosin staining of rats' intestine in each group. **B** The pathological scores of intestinal tissues. Values represent means ± standard deviation. $^{**}P < 0.01$, $^{*}P < 0.05$

MAT. These anatomical and physiological structural foundation provides opportunities for communication between pancreas, gut, and MAT. In addition, local inflammatory response would proliferate and spread to distant tissue along the abundant communicating vessels of MAT rapidly. Besides, MAT was considered to be more capable of inflammatory cytokines secretion. Wueest et al. [17] found that mesenteric adipocytes isolated from high-fat-diet fed mice secreted more IL-6 and monocyte chemoattractant protein 1 (MCP-1), compared to perigonadal adipocytes. Previous studies demonstrated that MAT was of great significance in pathogenesis of insulin resistance related diseases. Ko et al. [18] revealed that the incidence of NAFLD increased significantly with MAT thickened. Catalano et al. [19] reported the positive relationship between insulin resistance and changes in MAT thickness. However, there are few studies focusing on the role of MAT in the pathogenesis of SAP.

In the present study, MAT appeared inflammation in the early phase of SAP, and became worse over time, with the same tendency as the severity of pancreatitis. These results indicated that the inflammatory response of MAT might have potential impact on the course of SAP. In the past, the effect of VAT lipotoxicity on the pathogenesis of AP received more attention. Navina et al. [20] explored that an increasing volume of intrapancreatic adipocytes was associated with more extensive pancreatic necrosis and multisystem organ failure (MOF) in AP. Inhibition of lipolysis in AP mice would prevent a rise in serum unsaturated fatty acids (UFA) and prevent MOF, pancreatic necrosis, and mortality. Durgampudi et al. [21] reached the similar conclusion by analyzing human post-AP necrotic collections for UFA. Lin et al. [22] demonstrated that NAFLD aggravated AP via affecting pancreas cholesterol metabolism in mice. Conversely, in our study, the mRNA expression of neither lipometabolic factors nor endocrine factors in MAT increased obviously in early-stage of SAP. These findings implied that lipotoxicity of MAT might not be the critical characteristics in the early phase of SAP.

On the other hand, the inflammation of MAT might affect the function of intestinal barrier, considering about the adjacent location of MAT and gut. MAT was reported to have substantial effect on the intestinal barrier integrity and pathogenesis of Crohn's disease in numerous studies. As a potent producer of cytokines, adipokines, and fatty acids, MAT was believed to play an important role in intestinal immune and inflammatory regulation. MAT had strong relationship with the changes in the bowel wall, such as muscular hypertrophy, fibrosis, and stricture formation [8]. Furthermore, MAT contributed to the intestinal barrier integrity in NAFLD mice. MAT removal damaged the intestinal barrier, promoted the bacterial translocation to the liver and aggravated NAFLD [9]. Despite the above, only a few researches concerning about the influence of MAT on the intestinal injury. In the present study, SAP rats presented intestinal barrier injury in the early stage, and became worse over time, with the same trend as the MAT inflammation. Based on the above results, MAT inflammation might participate in the development of SAP via affecting the intestinal barrier function.

In the present study, we also detected the infiltration of immune cells, especially the accumulation order in MAT. The accumulation of B lymphocytes appeared after 24 h of SAP modeling and lasted up to 48 h, earlier than macrophage and T lymphocytes in MAT, which indicated the potential role of B lymphocytes in the MAT inflammation. MAT consists of a variety of cells, such as adipocytes, fibrocytes and nearly all types of lymphocytes [23]. In addition, MAT possesses more B lymphocytes than other VATs [24]. Previous studies reported that B lymphocytes could promote tissue inflammation via producing cytokines, secreting immunoglobulin, and interacting T lymphocytes and macrophages [25–27]. Wu et al. [28] demonstrated that B cells infiltrated early in MAT and promoted MAT inflammation by regulating macrophages, resulting in migrating to the liver and inducing hepatocytes inflammation in NAFLD. In our study, the mechanism of B lymphocytes involving in the MAT inflammation was not clear. Further profound studies are required, which may provide new methods for the therapy and management of SAP.

In this study, MAT appeared inflammation in early stage of SAP, and became worse over time, with the same trend as the intestinal barrier injury and the severity of pancreatitis. B lymphocytes infiltrated early in MAT, which might promote the MAT inflammation.

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Declarations

Competing interest All authors declare no competing interests.

Ethical approval All protocols were approved by the Beijing Tsinghua Changgung Hospital Ethics Committee (22271-4-01).

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