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Elevated IRF9 raised cell apoptosis and tissue damages through suppressing SIRT1 in hyperlipidemia acute pancreatitis with liver injury

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Abstract

Background Hyperlipidemia is a vital etiology of acute pancreatitis (AP), 12 to 20% of which have a history of hyperlipidemia. Multiple organ failure is the major cause of the high mortality rate of AP. Liver injury has been discovered in 80% of AP patients. The relationship and role of IRF9 and SIRT1 have not been presented in AP and hyperlipidemia AP (HLAP) with liver injury. This investigation was designed to explore the function and relationship of IRF9 and SIRT1.

Methods HLAP model in vivo was performed by feeding high-fat forage and induced by peritoneal injection with 20% L-arginine. The severity of pancreas and liver tissues was assessed. Cell apoptosis in the liver was determined by the TUNEL experiment. IRF9, SIRT1, p53, and acetylated p53 (Ac-p53) expression levels in liver tissues were detected by qRT-PCR and Western blot. The association of IRF9 expression with SIRT1 levels was evaluated. The relevance of triglyceride level to tissue damage was analyzed.

Results Our observation exhibited more distinct liver damage, a large number of hepatic cell apoptosis, marked raised IRF9, Ac-p53, and sharply dropped SIRT1 in the AP and HLAP groups. Compared with other groups, HLAP showed the most significant changes in liver injury, hepatic cell apoptosis, protein, and mRNA levels. The declined expression of SIRT1 was correlated with the elevated expression of IRF9. The damage of the pancreas and liver exacerbated with the increase in triglyceride levels.

Conclusion Elevated IRF9 in pancreatitis with liver injury raised cell apoptosis and tissue damage by decreasing SIRT1 expression.

Keywords IRF9, SIRT1, HLAP, Liver injury, Apoptosis

Introduction

Acute pancreatitis is a clinically common inflammatory disease caused by over-activation of pancreatic enzymes, which will not only lead to pancreatic tissue damage but also usually accompanied by damage to outside pancreatic organs including the liver, lung, kidney, and heart [1, 2]. The mortality rate of AP is about 10–15%, but the probability increases to 20–30 % in severe AP (SAP) due to early systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF) [3–6]. Most of the current investigation has focused on pulmonary,

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renal, or heart failure in AP, while relatively less attention is paid to liver injury. Generally, blood flowing out of the pancreas is processed by the liver before returning to the heart. In the course of AP, SIRS may affect remote organs such as the liver and lung and promote the development of distant organ failure. The liver is a major organ beside the pancreas that is frequently affected in AP patients. Liver injury has been reported in 80% of AP patients, and its severity is positively correlated with AP progression. Significant pathological changes can be observed in the liver cells of patients with AP [7]. Abnormalities of signal intensity on in-phase (IP)/out-of-phase (OP) images in the liver are positively related to MR severity index (MRSI) score in AP patients with fatty liver [8]. The perfusion computed tomography (CT) revealed that AP caused very marked perfusion abnormalities of liver tissue [9]. In a group of 260 cases of AP, severe complications appeared in 23.1% of cases, and acute hepatocellular failure occurs in 5.0% of cases, which invariably leads to death [10]. A study has presented that the highest mortality in patients with SAP is associated with liver (83%) failure [11]. Clinically, liver injury is a great index of AP severity and has significant application values for the prognosis of AP [12].

Twelve to 20% of AP patients have a history of hyperlipidemia [13]. Hyperlipidemia has gradually become one of the most common causes after biliary and alcoholic etiology. Previous studies have suggested that hyperlipidemia acute pancreatitis (HLAP) has more complications, longer disease duration, and higher recurrence rates than other types of pancreatitis [14]. An investigation about the morbidity of AP in China has shown that HLAP accounts for about 8.2–12.6% of total cases, and the incidence is increasing every year [15, 16]. The pathogenesis of HLAP is not entirely clear and may be related to pancreatic damage, severe inflammation, and microcirculation disorder caused by excess free fatty acids (FFAs) which are produced by the decomposition of triglycerides (TG) [17].

Interferon regulatory factor 9 (IRF9) is a member of IRF family transcriptional regulators, which mediates the expression of interferon-stimulated genes (ISGs). IRF family members have been demonstrated playing a vital role in many physiological processes, including cell development and differentiation, apoptosis and proliferation, antiviral response, innate and adaptive immune responses, and inflammation [18–27]. Relevant literatures show that IRF9 involved in the occurrence and development of many diseases such as cardiovascular disease, ischemic stroke, hepatic ischemia/reperfusion injury, myocardial ischemia/reperfusion injury, rheumatoid arthritis, human acute myeloid leukemia, and other diseases by directly downregulating NAD+-dependent deacetylase SIRT1[28–33]. SIRT1 is an important member of the sirtuin (SIRT) protein family, which is first discovered as the homology of the silencing information regulator (SIR) protein family in mammals [34–37]. SIRT1 has been proved to perform a vital role in a variety of biological processes by deacetylating mutiple proteins, both histone and nonhistone proteins [36–43]. However, the role of SIRT1 and IRF9 in HLAP with liver injury has not been reported so far. Our study aimed to investigate whether the negative regulation of SIRT1 by IRF9 existed in HLAP with liver injury. Finally, this study will provide theoretical guidance for the diagnosis and treatment of the disease.

Methods

Establishment of AP and HLAP rat model

Thirty-six healthy adult male Sprague-Dawley rats (weighting 250~300 g) were obtained from the experimental animal center of Anhui Medical University and divided into four groups: normal control (NC, $n = 9$), AP group ($n = 9$), hyperlipidemia normal control (HLNC, $n = 9$), and HLAP group ($n = 9$). NC and AP group rats used general diet, and HLNC and HLAP group rats were fed with high-fat diet. All rats were raised in a standard condition (25 ± 1 °C, light/dark12 h alternated). When the blood lipid levels in HLNC and HLAP groups were significantly elevated, pancreatitis models were constructed. Before building the model, all rats were fasted for 12 h. The rats in AP and HLAP groups were intraperitoneally injected with 20% L-arginine (2000 mg/kg), while the rats in NC and HLNC groups were replaced by the same dosage of normal saline. Twenty-four hours after the last injection, the animals were anesthetized and sacrificed. Blood was collected from the heart, and the tissue samples from the pancreas and liver were collected. The experimental protocol was approved by the Animal Ethics Committee of Anhui Medical University (No. LLSC20200404).

Determination of pathological changes of pancreatic and liver tissues

The tissue samples were fixed by 4% paraformaldehyde, embedded in paraffin, and sectioned and stained with hematoxylin-eosin to observe histopathological changes under the light microscope. The tissue damage severities of the pancreas and liver were assessed by two blinded investigators according to the method as previously described [44, 45].

Measurement of serum *indicator*

The serum concentration of triglycerides (TG), amylase, alanine transaminase (ALT), and aspartate aminotransferase (AST) was measured with commercial

kits (Nanjing Jiancheng Biological Engineering Institute, Nanjing, China) according to the manufacturer's protocols. Enzyme-linked immunosorbent assay kits for interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α) (Nanjing Jiancheng Biological Engineering Institute, Nanjing, China) were used to determine inflammatory cytokines levels in serum according to the manufacturer's instructions.

TUNEL staining

Apoptosis of liver tissues was detected using DeadEnd™ Fluorometric TUNEL System (Promega, USA) according to the manufacturer's instructions.

Western blot analysis

Total proteins in liver samples from each group rat were extracted using RIPA lysis buffer (Beyotime, Shanghai, China), and the concentration was detected by BCA Protein Assay Kit (Beyotime, Shanghai, China). Proteins in each group were electrophoresed by SDS-PAGE (Beyotime, Shanghai, China) and transferred onto PVDF membranes (0.45 μm, Merckmillipore, Germany). Then, the membranes were blocked with 5% nonfat milk for 3 h at room temperature and immunoblotted with primary antibodies (anti-IRF9, SIRT1, P53, Ac-p53, and GAPDH (Affinity Biosciences, Jiangsu, China) at 4 °C. Subsequently, the membranes were washed by TBST buffer at least five times and incubated with secondary antibody to detect the immunoreactive proteins by enhanced chemiluminescence (Advansta, USA).

Quantitative real-time PCR (qRT-PCR)

Total RNA was isolated from liver samples using TRIzol reagent (Beyotime, Shanghai, China) and then reserved transcribed into cDNA using the reverse transcription system (Beyotime, Shanghai, China). Then, qRT-PCR amplification was performed using SYBR Green reagent (Vazyme, Nanjing, Jiangsu, China). The primer pairs used in this study were as follows: SIRT1-sense: 5′AGCAGGT TGCAGGAATCCAAAGG3′, SIRT1-antisense: 5′CACCTA GGACACCGAGGAACTACC3′, IRF9-sense: 5′CTCGCTGC TGCTCACCTTCATC3′, IRF9-antisense: 5′AGCCACAAGC CGACAGTCTAGG3′, GAPDH-sense: 5′GCTGGTGCC GAGTATGTT3′, and GAPDH-antisense: 5′CAGAAG GTGCGGAGATGA3′. The relative mRNA expression levels of target genes were calculated using the 2-ΔΔCT method [46].

Data analysis

The statistical analysis of the data was performed using the SPSS software (version 19.0), and results were expressed as mean ± standard deviation. Differences between different groups were analyzed by *t*-test. Three biological replicates were performed. A *P*-value less than 0.05 was represented statistically significant.

Results

Alterations of pancreatic histopathology and serum indicator.

In order to verify the successful construction of the AP and HLAP rat model, HE staining was performed on pancreatic tissues, and serum indicators (TG, amylase, IL-1β, and TNF-α) were measured. Representative HE staining images showed that compared with the NC group, pancreas tissues in the HLNC group presented a few inflammatory cell infiltration and hyperemia; the AP group exhibited local inflammatory cell infiltration, edema, hyperemia, and necrosis; and HLAP group showed extensive inflammatory cell infiltration, edema, hyperemia, and necrosis (Fig. 1A). Results of pathological score in each group rat revealed that the AP and HLAP groups showed higher damage scores compared with the NC and HLNC groups, and scores in the HLAP group were more higher than the other groups (Fig. 1B). IL-1β and TNF-α levels in the AP and HLAP groups were elevated compared with the NC and HLNC groups, and the inflammatory cytokine levels in the HLAP group were higher than the other groups (Fig. 1C). The TG levels in the HLNC and HLAP groups were raised compared with the NC and AP groups (Fig. 1D), and the amylase levels in the AP and HLAP groups were increased compared with the NC and HLNC groups (Fig. 1E). The above results suggested the AP and HLAP animal models were established successfully.

Changes in *liver pathology and serum indexes*

To prove the liver injury appeared in the AP and HLAP rat models, HE staining of liver tissues and pathological score were evaluated, and serum indicators (ALT and AST) were detected. As compared with the NC group, liver tissues in the HLNC group showed mild congestion and edema; the AP group exhibited partial injury such as inflammatory cell infiltration, congestion, and necrosis; and the HLAP group presented a large area of inflammatory cell infiltration, congestion, and necrosis (Fig. 2A). Results of liver pathological score from each group rat showed that the AP and HLAP groups presented increased damage scores compared with the NC and HLNC groups, and scores in the HLAP group were larger in three groups (Fig. 2B). ALT and AST levels in the AP and HLAP groups were raised compared with the NC and HLNC groups, and the HLAP group were greater than the other groups (Fig. 2C, D). It suggested the animal models of AP and HLAP with liver injury were established successfully.

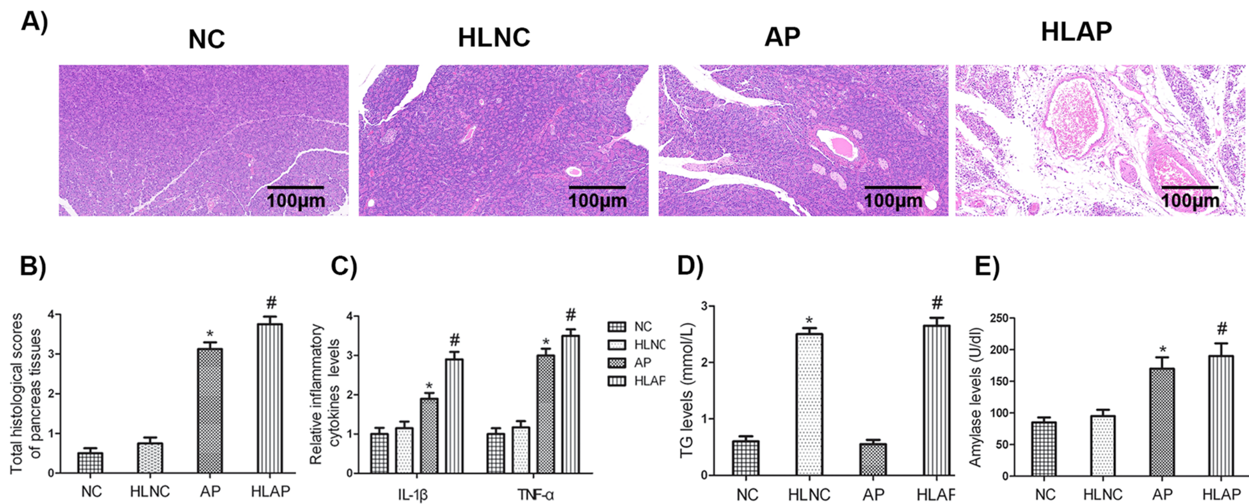

Fig. 1 HE staining, histological scores of pancreas and serum inflammatory cytokines, TG, amylase levels of rats. **A** Pancreatic HE staining, **B** pancreatic histopathological scores, **C** serum inflammatory cytokines (IL-1β and TNF-α), **D** serum TG, and **E** amylase levels of each group rat

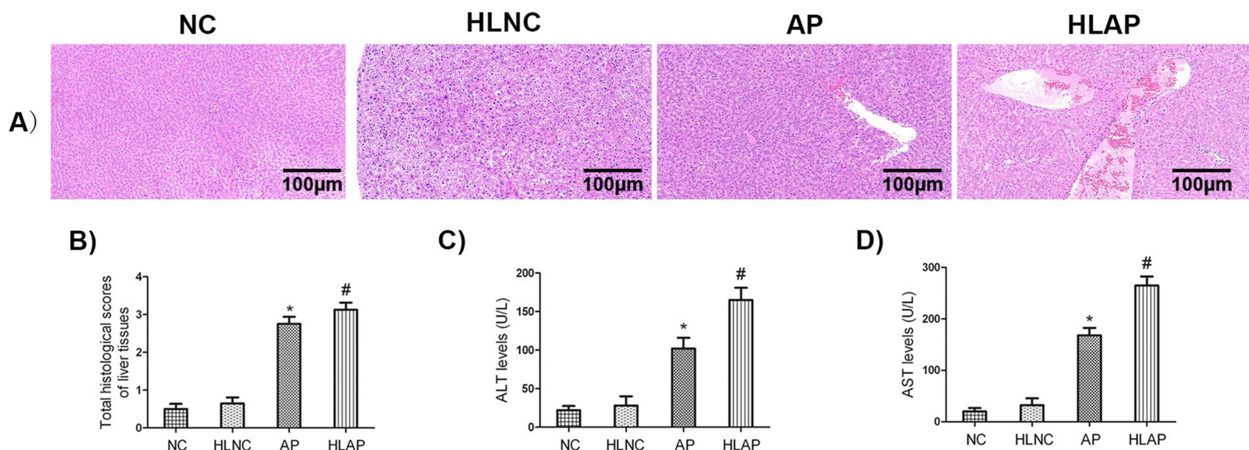

Fig. 2 HE staining, histological scores of liver and serum ALT, AST levels of rats. **A** Liver HE staining, **B** liver histopathological scores, **C** serum ALT, and **D** AST levels of each group rat

TUNEL staining results

TUNEL assay was conducted to determine the condition of hepatic cell apoptosis in each group of rats. Results of liver samples exhibited that cell apoptosis presented in the AP and HLAP groups. The hepatic cell apoptosis of the HLAP group was more obviously compared with the AP group (Fig. 3). The observation demonstrated that hyperlipidemia might elevate hepatic cell apoptosis.

Enhanced IRF9 and *Ac-p53 and decreased SIRT1 protein levels in* the *AP and HLAP groups*

Western blot was performed in liver tissues to detect the expression of IRF9, Ac-p53, and SIRT1 protein levels. The results (Fig. 4A–D) revealed that in the AP and HLAP groups, dramatic increased expressions of IRF9 and Ac-p53 were discovered, while largely dropped expressions of SIRT1 were detected compared with the NC and HLNC groups ($p < 0.05$). HLAP group rats exhibited drastically raised expressions of IRF9 and Ac-p53, while sharply decreased expressions of SIRT1 compared with the AP group ($p < 0.05$).

Elevated IRF9 and decreased SIRT1 mRNA expressions of liver tissues in the *AP and HLAP groups*

qRT-PCR assay was carried out to detect the expression of IRF9, Ac-p53, and SIRT1 mRNA levels in liver tissues. qRT-PCR results (Fig. 4E, F) presented sharply

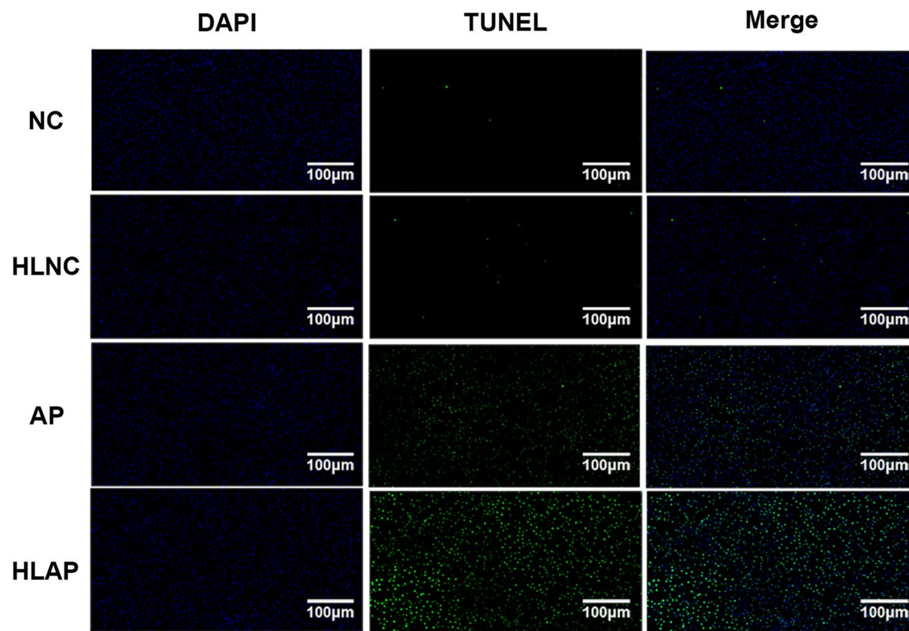

Fig. 3 The hepatic cell apoptosis in liver tissues was stained with TUNEL (green) and DAPI (blue)

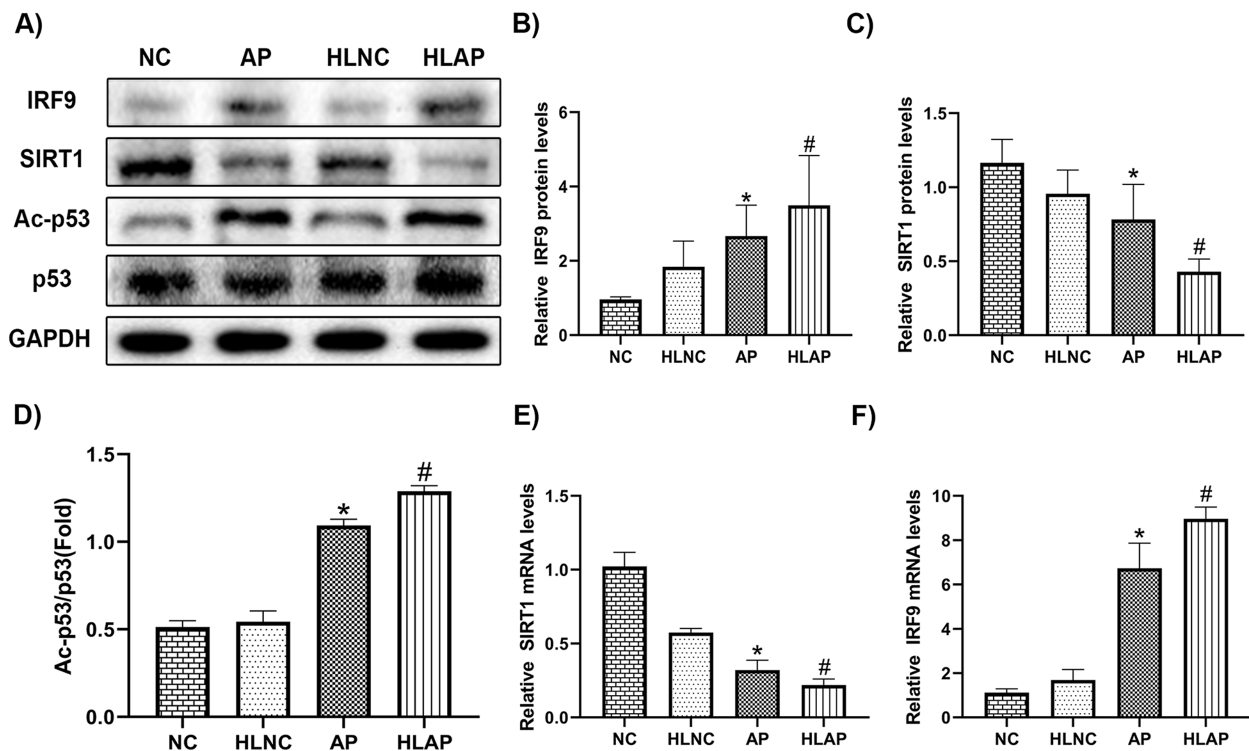

Fig. 4 Enhanced IRF9 and Ac-p53 and decreased SIRT1 levels of liver tissues in the AP and HLAP groups. **A** Representative Western blot images of IRF9, SIRT1, Ac-p53, and p53. **B**–**D** Relative IRF9 (**B**), SIRT1 (**C**), and Ac-p53/p53 (**D**) protein levels. **E**, **F** Relative mRNA levels of SIRT1 (**E**) and IRF9 (**F**)

attenuated mRNA levels of SIRT1 but drastically elevated mRNA levels of IRF9 in the AP and HLAP groups compared with the NC and HLNC groups ($p < 0.05$). The HLAP group showed obviously decreased mRNA levels of SIRT1 but largely elevated mRNA levels of IRF9 compared with the AP group ($p < 0.05$).

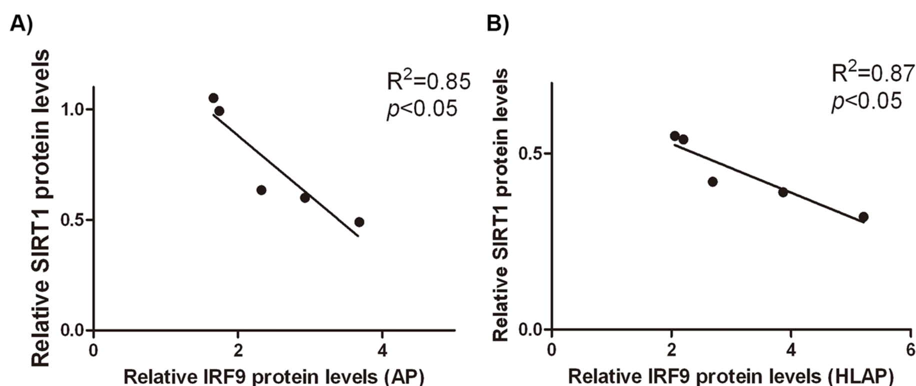

Fig. 5 SIRT1 expressions had an obvious negative relationship with IRF9 in AP and HLAP with liver injury. Correlation analysis between SIRT1 and IRF9 protein levels in AP (**A**) and HLAP (**B**) with liver injury

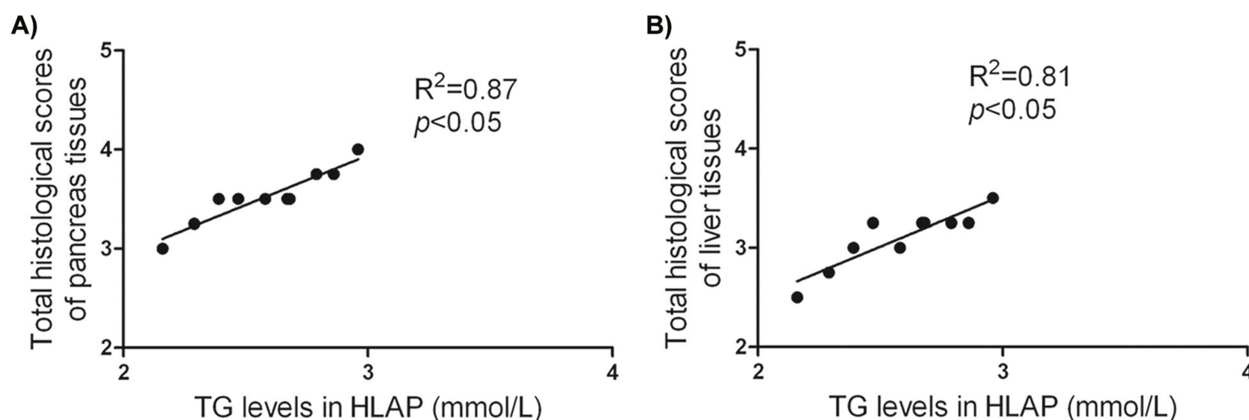

Fig. 6 Pancreatic (**A**) and liver (**B**) damage exacerbated with the increase of triglyceride (TG) level. Correlation analysis between pancreatic (**A**) and liver (**B**) histopathological scores and TG level in HLAP with liver injury

Analysis of the correlativity between SIRT1 and IRF9

Correlation analysis was performed to evaluate the relationship between SIRT1 and IRF9. Results of the correlation analysis were shown in Fig. 5, and it demonstrated that protein levels of SIRT1 in liver tissues decreased as protein levels of IRF9 increased. A negative relationship between the expression of IRF9 and SIRT1 in liver tissues was discovered ($p < 0.05$).

Analysis on the correlativity between hyperlipidemia and damage of pancreas and liver tissues

Correlation analysis was conducted to analyze the correlativity between hyperlipidemia and damage of pancreas and liver tissues. The results of the correlation analysis shown in Fig. 6 revealed that the degree of injury in the pancreas and liver samples became more severe as TG levels raised. A positive relationship between TG levels and total histological scores of the pancreas and liver respectively was observed ($p < 0.05$).

Discussion

AP is a common clinical acute abdomen, which is associated with significant morbidity and mortality. MOF is a major cause of the high mortality rate of AP, and the death rate in patients with SAP associated with liver failure is as high as 83% [47]. Liver injury is a sign of SIRS during AP and is a vital clinical prognostic indicator. A large attention has been focused on acute lung injury and other organ injuries but fewer liver injuries in AP. Our investigation was designed to explore the function of IRF9 and SIRT1 in AP and HLAP with liver injury. As results of the HE staining assay shown in Figs. 1A and 2A, it exhibited that more noticeable injury degree of the pancreatic and liver tissue in the AP and HLAP groups. Histopathological scores in Figs. 1B and 2B revealed raised scores in the AP and HLAP groups, and enhanced TG, inflammatory cytokines (IL-1β and TNF-α), amylase, ALT, and AST levels were observed in the AP and HLAP groups (Figs. 1C-E and 2C, D), indicating animal models

of AP and HLAP with liver injury established successfully. Numerous cell apoptosis in liver tissues was discovered in the AP and HLAP groups. A dramatic raised apoptosis of hepatic cells in the HLAP group was presented compared with the AP group (Fig. 3).

Besides, elevated mRNA and protein expression levels of IRF9 and Ac-p53/p53 in the AP and HLAP groups were exhibited compared with the NC and HLNC groups. Just the inverse, declined mRNA and protein expression levels of SIRT1 in the AP and HLAP groups were appeared compared with the NC and HLNC groups ($p < 0.05$). Moreover, the HLAP group showed largely increased expression levels of IRF9 and Ac-p53/p53 but reduced SIRT1 expression compared with the AP group ($p < 0.05$, Fig. 4). Furthermore, correlation analysis exhibited that SIRT1 expression was dropped when IRF9 expression was raised in the AP and HLAP groups, indicating there was an opposite relationship between SIRT1 and IRF9 ($p < 0.05$, Fig. 5), and a positive connection was discovered between hyperlipidemia and injury degree in the pancreas and liver in the AP and HLAP groups, suggesting the damage degree of pancreas and liver tissues was elevated when TG level was enhanced ($p < 0.05$, Fig. 6).

Hyperlipidemia is an important cause of AP, typically characterized by elevated TG levels. TG can be hydrolyzed by pancreatic lipase to produce FFA, which will be largely raised and excessively accumulated in the pancreas [48, 49]. Excess FFA causes increased inflammation and injury of the pancreas, thus leading to AP [49]. Our study manifested that hyperlipidemia might elevate the damage to pancreas and liver tissues, enhancing hepatic cell apoptosis.

A series of investigations had presented that SIRT1 expression was repressed by IRF9 in a variety of diseases [28–33]. Downregulation of SIRT1 attenuated deacetylase activity and activated p53, thus causing enhanced inflammatory response and apoptosis, and finally aggravated AP [50]. Our previous investigation had elucidated that suppressed SIRT1 by IRF9 raised the expression of acetylated p53 and apoptosis mediated by p53 in AP [51]. In this research, our observations exhibited that SIRT1 expression was declining as IRF9 expression was raised, and the damage degree of pancreas and liver tissues was enhanced when the TG level was elevated in the AP and HLAP groups. These findings suggested that SIRT1 had an obvious negative relationship with IRF9. Hyperlipidemia was positively correlated with the damage degree of the pancreas and liver in the AP group and HLAP groups. The potential mechanism was that the reduced SIRT1 by increased IRF9 raised acetylated p53, aggravated pancreas and liver damages, and enhanced hepatic cell apoptosis in AP and HLAP with liver injury.

The limitation of this work is that it does not in-depth explore the molecular mechanism of these findings, and our future investigation will further study the relevant molecular mechanism in order to provide new ideas for the diagnosis and treatment of clinically related AP and HLAP diseases.

Conclusion

These discoveries hinted that in AP and HLAP with liver injury, the marked increase of IRF9 expression caused an obvious decline of SIRT1, a dramatic rise of acetylated p53, and a massive activation of inflammatory response and cell apoptosis. The above finding might provide an important guidance for expounding the pathogenesis of pancreatitis with liver injury.

Abbreviations

AP	Acute pancreatitis
NC	Normal control
HLNC	Hyperlipidemia normal control
HLAP	Hyperlipidemia acute pancreatitis
SAP	Severe AP
SIRS	Systemic inflammatory response syndrome
MOF	Multiple organ failure
IP	In-phase
OP	Out of phase
IRF	Interferon regulatory factor
SIRT	Sirtuin
TG	Triglycerides
ALT	Alanine transaminase
AST	Aspartate aminotransferase
IL-1β	Interleukin-1β
TNF-α	Tumor necrosis factor α

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Authors' contributions

PJG performed the experiments, analyzed all the data, and was a major contributor in writing the manuscript. RXQ, MXY, HZY, and LZH analyzed the data and were contributors in editing the manuscript. SY analyzed all the data and was a major contributor in writing and editing the manuscript. YWL designed all the experiments, analyzed all the data, and was a major contributor in writing and editing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The experimental protocol was approved by the Animal Ethics Committee of Anhui Medical University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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