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PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330
Int J Hum Genet, 24(4): 378-391 (2024)
DOI: 10.31901/24566322.2024/24.04.887

UQCRC2 Absence Reduced Mitochondrial Damage of Small Intestinal Epithelial Cells in Sepsis by Nrf2/HO-1 Signaling Pathway

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KEYWORDS Heme oxygenase-1. Mitochondrial Damage. Nuclear factor erythroid 2-related factor 2. Sepsis. Ubiquinol-Cytochrome c Reductase Core Protein 2

ABSTRACT This study was to explore the feasibility of UQCRC2 on mitochondrial damage of small intestinal epithelial cells (SIECs) in a model of sepsis to evaluate its mechanism. UQCRC2 mRNA and protein expression in patients or mice models of sepsis were up-regulated. UQCRC2 up-regulation accelerated mitochondrial damage, increased inflammation and oxidative stress of SIECs in vitro model of sepsis through the inhibition of Nrf2/HO-1 signalling pathway. UQCRC2 absence inhibited mitochondrial damage, and reduced inflammation and oxidative stress of SIECs in vitro model of sepsis. In the mice model of sepsis, sh-UQCRC2 also reduced mitochondrial damage, inflammation and oxidative stress in colon tissue. Taken together, the researchers conclude that UQCRC2 suppressed the Nrf2/HO-1 signalling pathway to promote mitochondrial damage of SIECs in sepsis, and provide molecular insight into the mechanisms by which the UQCRC2 absence regulates mitochondrial damage of SIECs in model of sepsis.

INTRODUCTION

Patients with sepsis are prone to gastrointestinal dysfunction due to uncontrolled inflammatory response, hemodynamic changes, and poor gastrointestinal perfusion (Chen et al. 2023b). Once gastrointestinal dysfunction occurs in sepsis (Asdie et al. 2023). The gastrointestinal tract is considered to be the target organ of sepsis. For gastrointestinal dysfunction in sepsis, Western medicine has no specific treatment methods, mainly focusing on regulating gastrointestinal motility and intestinal flora. However, the clinical effect is not ideal, with a morbidity and mortality rate of nearly one-fifth, making it a serious public health burden globally.

The intestine is at the central stage of the occurrence and development of sepsis, and is also considered the "initiating organ" of multiple organ dysfunction syndrome (MODS). Multiple stressors can cause damage to the intestinal mucosal barrier, leading to an imbalance in the intestinal microbiota, increased epithelial permeability, bacterial and endotoxin translocation, MODS, and even death. Intestinal dysfunction is an important factor leading to the rapid development of sepsis, prolonged hospital stay, and increased mortality, as well as an independent risk factor affecting its prognosis. Protecting intestinal function is an important means to reduce complications and mortality in sepsis, and is a research focus in the field of clinical emergency and critical care.

There is evidence that the release of inflammatory factors, ROS, and mitochondrial respiratory chain fragmentation can all lead to sepsis, but the exact mechanism has not been fully elucidated. Mitochondria are the energy-providing units of cells, and mitochondrial damage can cause the accumulation of oxidative stress products and metabolic disorders in cells, even leading to cell damage and death (He et al. 2023). In China, the incidence rate of sepsis in ICU is 20.6 percent, and the 90-day morbidity and mortality rate is 35.5 percent, which is a serious threat to patients' lives (Napolitano 2018). The intestinal injury caused by sepsis can induce multiorgan failure (MODS), which further increases the death rate (Ghafouri et al. 2023). Normal mitochondria are in a dynamic balance of fusion and fission to maintain the morphology and function of mitochondria in cells. Studies have shown

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that Nrf2 activators reduce neuroinflammation and oxidative stress in SAE rat models and improve cognitive impairment (Esparza et al. 2023).

Sepsis is a common cause of intestinal injury, and its pathogenesis is very complex, including patients causes damage to the mitochondria in the intestinal epithelial cells, which leads to cell death (Wang et al. 2023a; Lu et al. 2022). At the same time, the mitochondria are the main organelles for the dysfunction of mitochondria aggravates the intestinal injury (Wang et al. 2021). Mitochondria are more affected by reactive oxygen species than other organelles (Li et al. 2022).

Nrf2 is considered to be the main regulatory factor for endogenous antioxidant defense and mitochondrial biogenesis. Nrf2 is an important transcription factor and a major regulatory factor in antioxidant defense. Upregulation of HO-1 expression under stimuli such as inflammation and oxidative stress helps promote macrophages to transition to an anti-inflammatory phenotype and exert anti-inflammatory effects. HO-1 has anti-inflammatory, antioxidant, and anti apoptotic properties and plays a crucial role in regulating redox homeostasis. The Nrf2/HO-1 pathways is one of the signalling pathways that endogenously regulates the oxidative stress, providing negative feedback to modulate the oxidative stress (Zhang et al. 2023a). In addition to regulating cellular antioxidant defense, HO-1 also has certain anti-inflammatory functions (Zhao et al. 2017; Tang et al. 2022). HO-1 negatively regulates inflammatory responses and oxidative stress (Shen et al. 2021).

Reactive oxygen species (ROS) are mainly derived from mitochondrial respiration, and excessive ROS will damage the structure and function of mitochondria (Zou et al. 2019; Zhang et al. 2021a). Therefore, it is extremely important for health to maintain the oxidative and antioxidant systems in the cell (redox balance) (Chen et al. 2023a; Liu et al. 2021). The antioxidant system slows down or inhibits cellular oxidation by scavenging ROS, chelating metal ions, bursting unilinear oxygen species, and lowering oxygen concentration (Wang et al. 2023a; Zou et al. 2022). The importance of oxidative and antioxidant balance for health will be described in terms of cellular oxidative stress, oxidative stress and mitochondrial damage, and antioxidant defence systems, providing new ideas for promoting health and preventing disease (Zou et al. 2019; Liu et al. 2022).

Ubiquitin cytochrome C reductase core protein 2 (UQCRC2) forms part of the mitochondrial respiratory chain (Wang et al. 2020). Mitochondrial complex III deficiency caused by UQCRC2 mutations can lead to abnormal liver function, lactic acidosis, hypoglycaemia, ketosis and hyperammonemia (Zhang et al. 2021b). UQCRC2 is involved in oxidative stress and intracellular ROS production, and that deficiency of UQCRC2 induces elevated levels of cellular ROS (Bansept et al. 2023; Zhou et al. 2021).

Objective

This study explored the feasibility of UQCRC2 on mitochondrial damage of small intestinal epithelial cells in a model of sepsis to evaluate its mechanism.

MATERIAL AND METHODS

Patients with Sepsis

This study was approved by the Ethics Committee of *our Hospital*. All the serum samples of patients with Sepsis were immediately snap frozen in liquid nitrogen and stored at -80°C for further using.

Vitro model

HCT-116 cells were incubated in a 5 percent CO_2 atmosphere at 37 °C. Plasmids were transfected into HCT-116 cells using Lipofectamine 2000.

Quantitative Polymerase Chain Reaction (qPCR) and Western Blot

qPCR and Western Blot were executed as according to references (Zhang W et al. 2024). Total RNAs were isolated with RNA isolator total RNA extraction reagent and cDNA was synthesised using PrimeScipt RT Master Mix. qPCR were performed with the ABI Prism 7500 sequence detection system. Relative levels of the sample mRNA expression were calculated and expressed as 2-DDCt.

The membranes were incubated with primary antibodies of UQCRC2 (ab203832, 1:1000, abcam),

Nrf2 (ab62352, 1:1000, abcam) and HO-1 (ab189491, 1:1000, abcam) and â-Actin (ab7817, 1:5000, abcam) after blocking with 5 percent BSA in TBS, followed by incubation with peroxidase-conjugated secondary antibodies (Santa Cruz Biotechnology).

Animal Experiment, Hematoxylin-eosin (H&E) Staining and *Immunofluorescent Staining*

Male C57BL/6 mice (5-6 weeks, 18-20 g) were housed separately under controlled temperature. All animal experiments were performed in accordance with approved protocols for the BCM Institutional Animal Care and Usage Committee of the hospital, were anesthetised by 50 mg/kg pentobarbital sodium (i.p., MedChemExpress, China) and subjected to laparotomy followed by extracorporeal cecum mobilisation and ligation as literature (Zhang et al. 2021a). Tissue was collected and fixed with 4 percent paraformaldehyde for 24 hours at room temperature, and were paraffin-embedded.

Cells were incubated with UQCRC2 (ab203832, 1:100, abcam) and Nrf2 (ab62352, 1:100, abcam) at 4ÚC overnight. Cells were incubated with goat anti-rabbit IgG-cFL 488 or anti-rabbit IgG-cFL 555 antibody (1:100) for 2 hours at room temperature and stained with DAPI for 15 minutes and washed with PBS for 15 minutes. The images were obtained using a Zeiss Axioplan 2 fluorescence microscope (Carl Zeiss AG, Oberkochen, Germany).

Statistical Analyses

Data were analysed using the SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA), and followed using Student's t test or one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. $P < 0.05$ was considered to represent a statistically significant difference.

RESULTS

UQCRC2 Expression in Model of Sepsis

Firstly, this study aimed to investigate UQCRC2 expression in a model of DN. Serum UQCRC2 mRNA expression was up-regulated in patients with sepsis (Fig. 1A, $P = 0.0023$). Serum UQCRC2 mRNA expression has a positive correlation with serum IL-1β and IL-6 mRNA expression in patients with sepsis, and ROC = 0.9896 (Fig. 1B-1D, $P = 0.0232$, $P = 0.0066$, $P < 0.0001$). UQCRC2 mRNA and protein expression was increased in colon tissue of mice model of sepsis (Fig.1E-1F).

UQCRC2 Increased Oxidative Stress in Vitro Model

The study examined the effects of UQCRC2 on oxidative stress in SIECs of vitro model. UQCRC2 plasmid increased UQCRC2 mRNA expression, and si-UQCRC2 plasmid reduced UQCRC2 mRNA expression of SIECs in vitro model of sepsis (Fig. 2A, $P = 0.0028$, $P = 0.0036/0.0011$). UQCRC2 up-regulation increased ROS-induced oxidative stress of SIECs in vitro model of sepsis (Fig. 3B-3E, $P = 0.0086$, $P = 0.0052$, $P = 0.0092$, $P = 0.0077$). UQCRC2 down-regulation decreased ROS-induced oxidative stress of SIECs in vitro model of sepsis (Fig. 3F-3I, $P = 0.0021$, $P = 0.0126$, $P = 0.0034$, $P = 0.0052$).

UQCRC2 Increased ROS-induced Mitochondrial Damage of SIECs

The researchers sought to understand the effects of UQCRC2 on ROS-induced mitochondrial damage of SIECs. UQCRC2 up-regulation reduced JC-1 levels and MPT, and inhibited mitochondrial damage of SIECs in vitro model of sepsis (Fig. 3A-3C, $P = 0.0031/0.0118$, $P = 0.0022/0.0052$). UQCRC2 down-regulation increased JC-1 levels and MPT, and promoted mitochondrial damage of SIECs in vitro model of sepsis (Fig.3A-3C, $P = 0.0031/0.0118$, $P = 0.0022/0.0052$). UQCRC2 up-regulation increased mitochondrial ROS levels, and UQCRC2 down-regulation reduced mitochondrial ROS levels of SIECs in vitro model of sepsis (Fig. 3D, $P = 0.0068/0.0021$).

Mitochondrial Damage Accelerated Colon Injury in Model of Sepsis by UQCRC2

The researchers tested the function of UQCRC2 on mitochondrial damage of SIECs in a model of sepsis. Mitochondrial damage agonists (30 mg/kg of Ciprofloxacin) reversed the effects

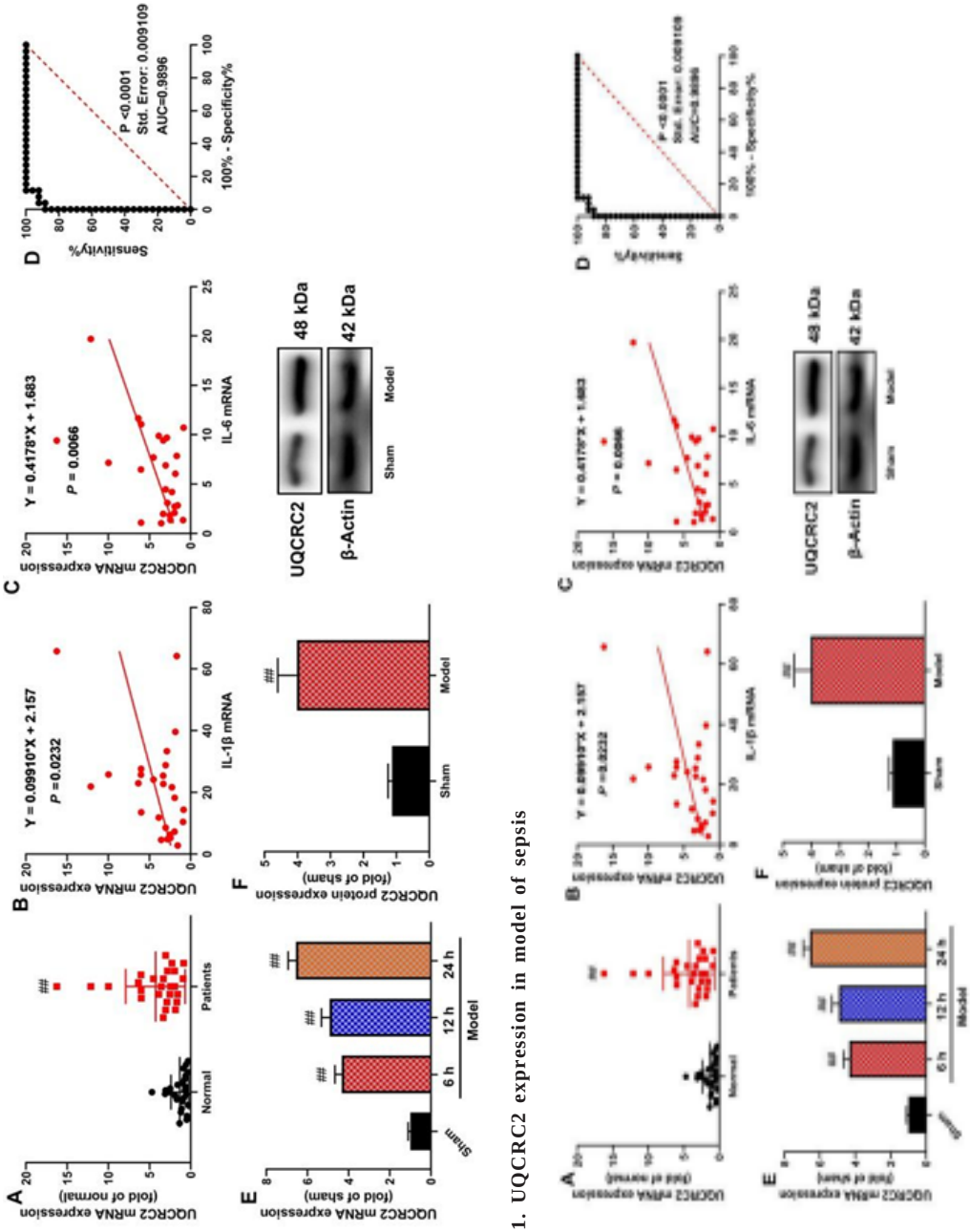

Fig. 1. UQCRC2 expression in model of sepsis

UQCRC2 mRNA expression (A); UQCRC2 mRNA expression was negative correlation with IL-1β (B), IL-6 (C) mRNA expression, ROC (D) in patients with sepsis; UQCRC2 mRNA and protein expression in colon tissue of mice model (E and F)
##p<0.01 vs the normal group or Sham group.

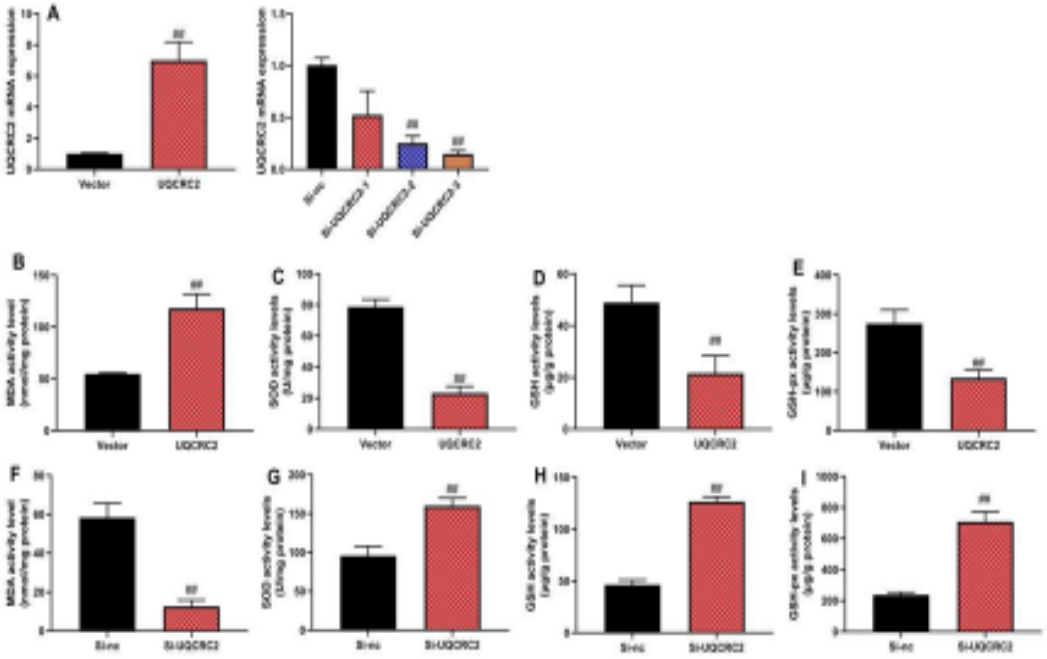

Fig. 2. UQCRC2 increased oxidative stress in vitro model
UQCRC2 mRNA expression (A), MDA/SOD/GSH/GSH-px in vitro model by UQCRC2 (B, C, D and E), MDA/SOD/GSH/GSH-px in vitro model by si-UQCRC2 (F, G, H and I).
$^{\#\#}$p<0.01 vs vector or si-nc group

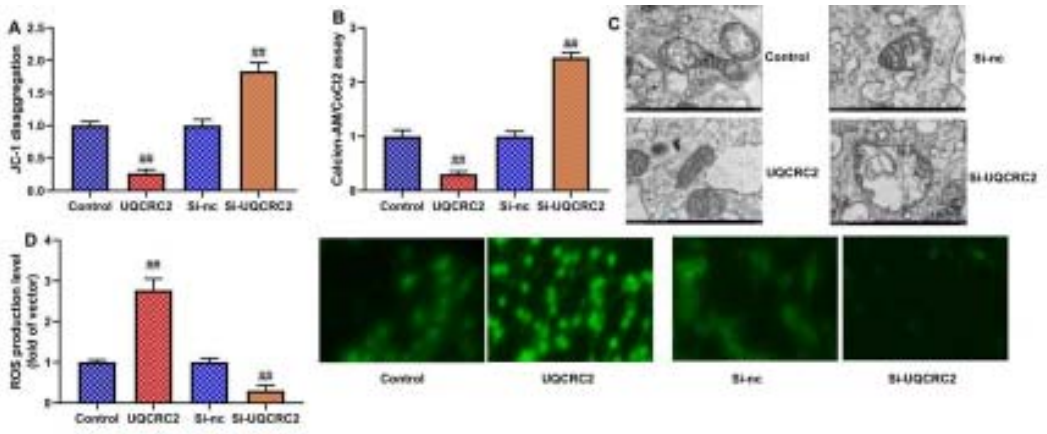

Fig. 3. UQCRC2 increased ROS-induced mitochondrial damage of SIECs
JC-1 levels (A), MPT (B), mitochondrial damage (electron microscope, C), ROS (D).
$^{\#\#}$p<0.01 vs control or si-nc group

of sh-UQCRC2 virus on body weight (P = 0.0162), DAI score (P = 0.0091), the colon epithelial cell injure, inflammation levels (P = 0.0181/0.0117/0.0079/0.0063) and oxidative stress (P = 0.0177/0.0096/0.0082/0.0215) (Fig. 4).

Meanwhile, mitochondrial damage inhibitors (5 mM of Mitoquinone mesylate) reduced ROS-induced mitochondrial damage of SIECs in vitro model by UQCRC2 up-regulation (Fig. 5A-5G, P = 0.0092/0.0115/0.0068/0.0077/0.0275/0.0221). Mitochondrial damage agonists (50 ìg/mL of Ciprofloxacin) reduced ROS-induced mitochondrial damage of SIECs in vitro model by UQCRC2 down-regulation (Fig. 5H-5N, P = 0.0051/0.0093/0.0026/0.0109/0.0132/0.0093/0.0287).

UQCRC2 Suppressed Nrf2/HO-1 Signalling Pathway

The study determined the mechanism of UQCRC2 on mitochondrial damage in SIECs of sepsis model. UQCRC2 over-expression induced UQCRC2 protein expression, and increased Nrf2/HO-1 mRNA and protein expression in SIECs of sepsis model (Fig. 6A-6B, 6E, P < 0.0001, P = 0.0034, P = 0.0176/0.0052/0.211). UQCRC2 down-regulation suppressed UQCRC2 protein expression, and reduced Nrf2/HO-1 mRNA and protein expression in SIECs of sepsis model (Fig. 6C-6D, 6F, P = 0.0017/<0.0001, P <0.0001/<0.0001, P = 0.0096/0.0085/0.0036). Immunofluorescence showed that UQCRC2 over-expression

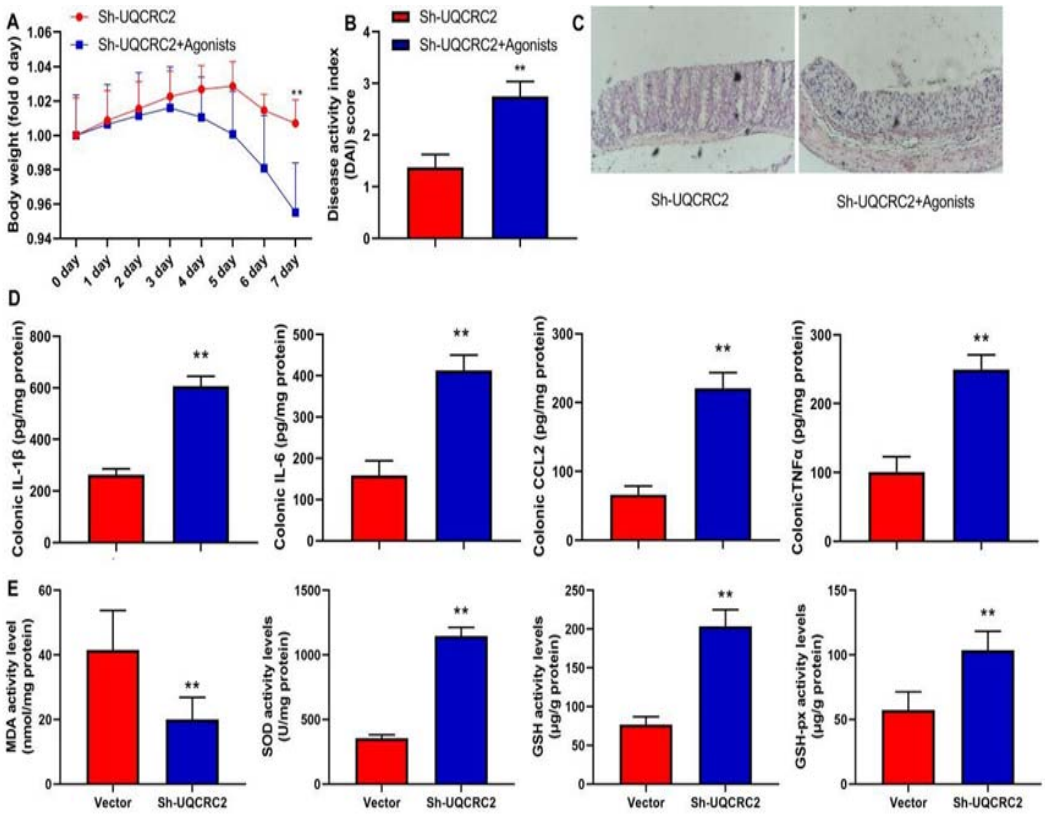

Fig. 4. Mitochondrial damage accelerated colon injury in mice model of sepsis by UQCRC2
Body weight (A), DAI score (B), the colon epithelial cell injure (HE, C), inflammation levels (IL-1β, IL-6, CCL2 and TNFα, D), oxidative stress (MDA, SOD, GSH and GSH-px, F).
****p<0.01 vs sh-UQCRC2 group**

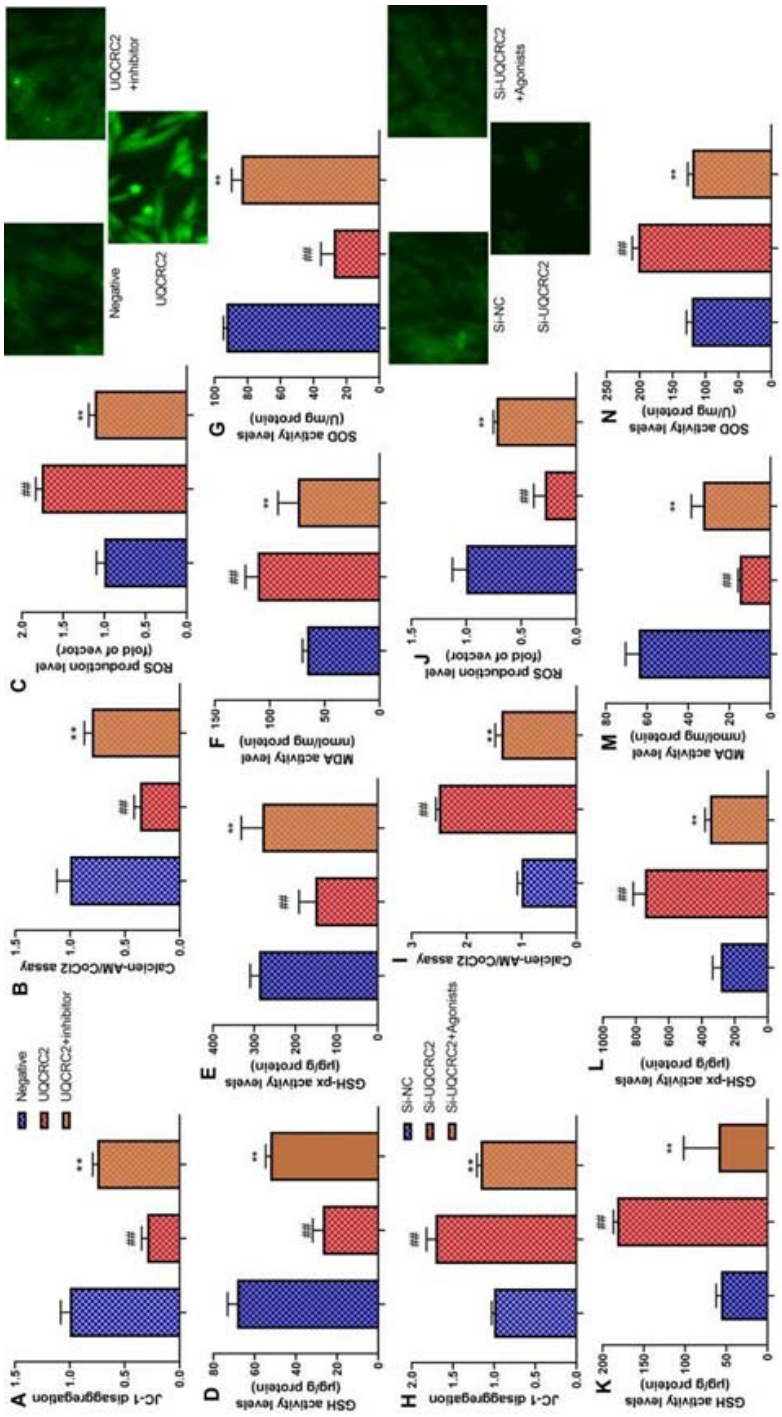

Fig. 5. Mitochondrial damage accelerated colon injury in vitro model of sepsis by UQCRC2
JC-1 levels (A), MPT (B), ROS/GSH/GSH-px/MDA/SOD in vitro model by UQCRC2 (C, D, E, F and G); JC-1 levels (H), MPT (I), ROS/

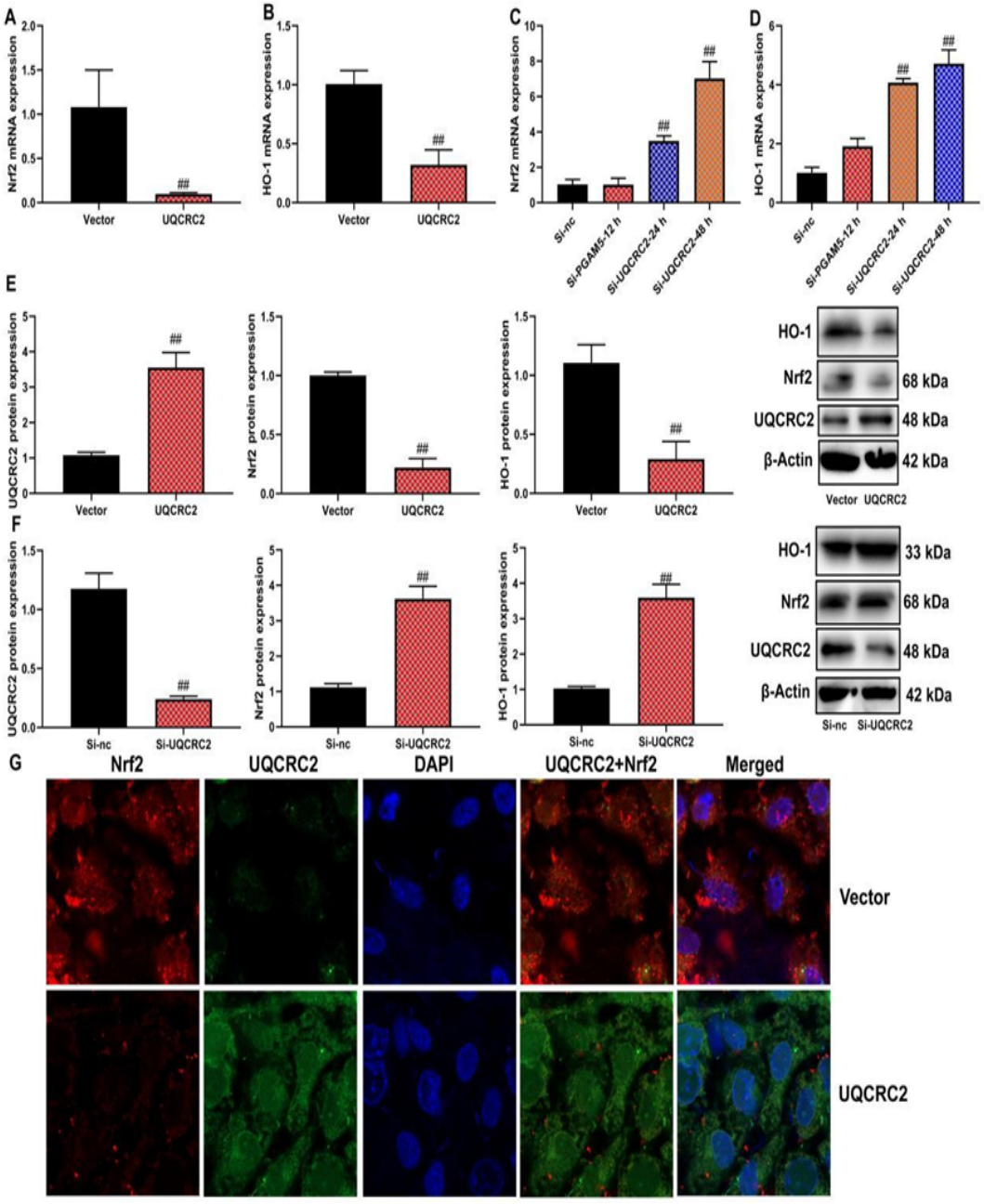

Fig. 6. Mitochondrial damage accelerated colon injury in vitro model of sepsis by UQCRC2 Nrf2/HO-1 mRNA expression (A, B/C, D), UQCRC2/ Nrf2/HO-1 mRNA expression in vitro model by UQCRC2/ si-UQCRC2 (E/F), UQCRC2 and Nrf2 expression (G).
##p<0.01 vs vector or si-nc group

increased UQCRC2 expression, and reduced Nrf2 expression in gastric cancer cells (Fig. 6G).

In the mice model, sh-UQCRC2 virus restored body weight, DAI score, the colon epithelial cell injury, inflammation levels and oxidative stress (Fig. 7A-7C, 7E-7F, P = 0.0175/0.0089/0.0062, P = 0.0091, P = 0.0037/0.0314/0.0081/0.0062, P = 0.0001/0.0185/0.0097/0.0191). Sh-UQCRC2 virus also increased Nrf2/HO-1 protein expression in colon tissue of the sepsis model (Fig.7D, P = 0.0053/0.0081).

More importantly, the researchers confirmed the mechanism of UQCRC2 on colon injury in a model of sepsis by mitochondrial damage. Nrf2 activator (10 μM of NK-252) induced Nrf2/HO-1 protein expression to reduce oxidative stress and mitochondrial damage of SIECs in vitro model of sepsis by UQCRC2 up-regulation (Fig. 8A-8F, P = 0.0088/0.0036, P = 0.0075, P = 0.0021, P = 0.0085, P = 0.0167, P = 0.0038). Nrf2 inhibitor (0.15 μg/mL of Brusatol) suppressed Nrf2/HO-1 protein expression, and expanded ROS-induced oxidative stress and mitochondrial damage of SIECs in vitro model of sepsis by UQCRC2 down-regulation (Fig. 8G-8L, P = 0.0035/0.0082, P = 0.0042, P = 0.0017, P = 0.0079, P = 0.0203, P = 0.0152).

In the mice model, Nrf2 inhibitor (2 mg/kg of Brusatol) suppressed Nrf2/HO-1 protein expression (P = 0.0012/0.0029), and reduced body weight (P = 0.0088/0.0061), DAI score (P = 0.0102), the colon epithelial cell injure, inflammation levels (P

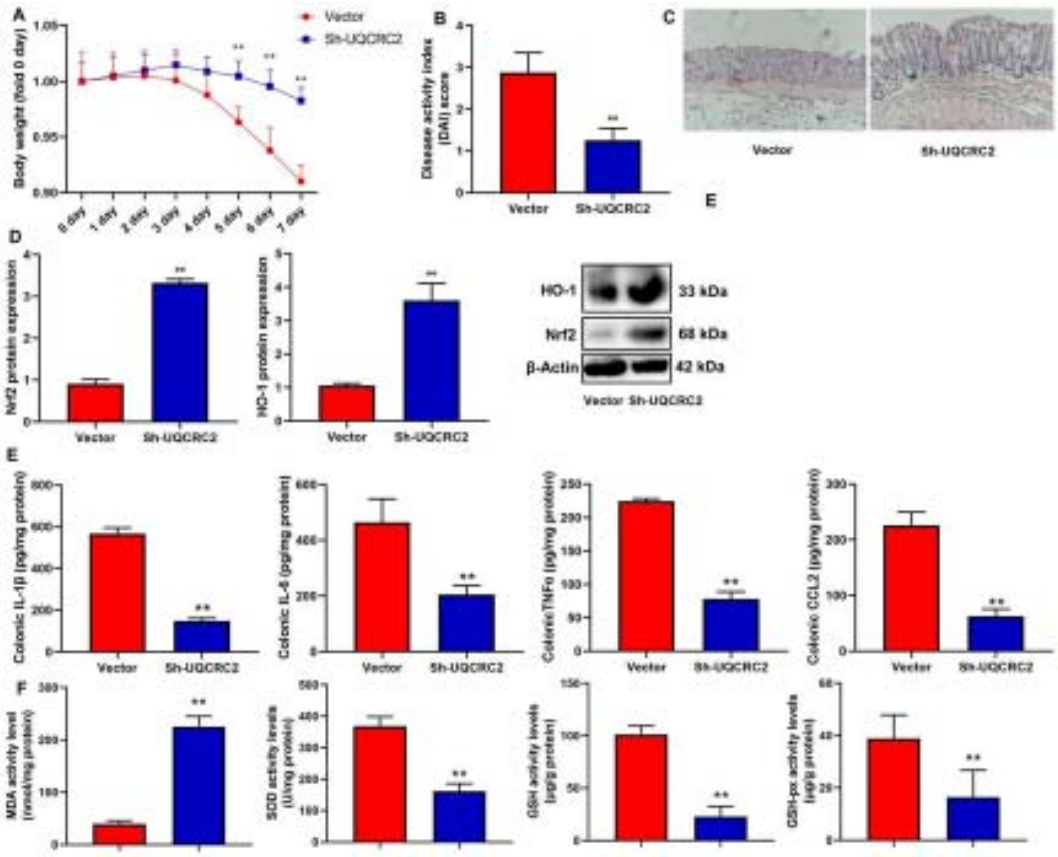

Fig. 7. UQCRC2 suppressed Nrf2/HO-1 signalling pathway in mice model
Body weight (A), DAI score (B), the colon epithelial cell injure (HE, C), Nrf2/HO-1 protein expression (D), and inflammation levels (E), oxidative stress (F). $^{**}p<0.01$ vs Vector group

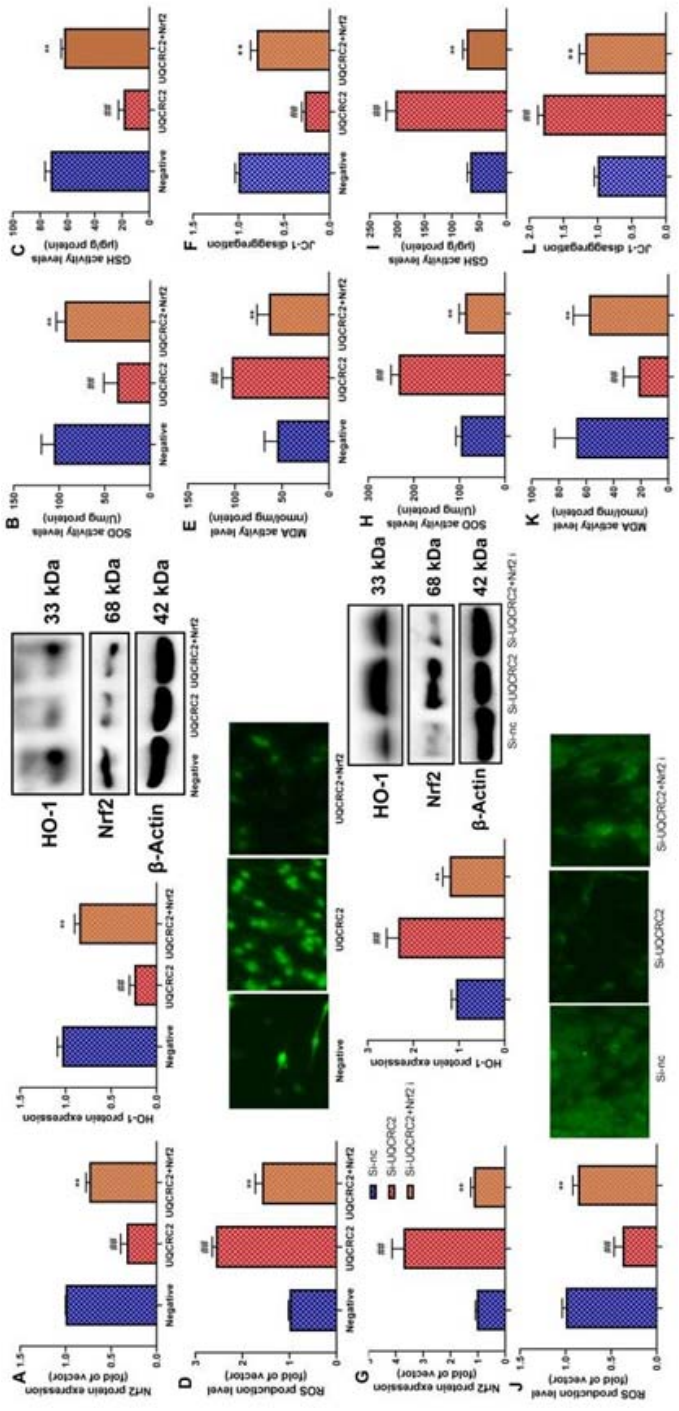

Fig. 8. Nrf2 is target spot for UQCRC2 on colon injury in vitro model of sepsis
Nrf2/HO-1 protein expression (A), SOD/GSH/ROS/MDA/JC-1 (B, C, D, E, F) in vitro model by UQCRC2+Nrf2; Nrf2/HO-1 protein expression (G), SOD/GSH/ROS/MDA/JC-1 (H, I, J, K, L) in vitro model by si-UQCRC2+Nrf2 inhibitor.
$^{\#\#}$p<0.01 vs vector or si-nc group, **p<0.01 vs UQCRC2 or si-UQCRC2 group

= 0.0097/0.0172/0.0052/0.0061) and oxidative stress (P = 0.0085/0.066/0.0117/0.0268) (Fig. 9).

DISCUSSION

Sepsis is still one of the major health problems facing the world (Zhang et al. 2023b). It is characterised by high incidence rate and mortality (Peng et al. 2023). Early identification, effective intervention and prevention of complications are still the key to reduce mortality (Naseri et al. 2023). The gastrointestinal tract is an important digestive and endocrine organ in the human body, carrying various functions such as digestion, absorption, secretion, and immunity, and playing a crucial role in human health. Its etiology and pathogenesis are complex and not yet fully understood. The gastrointestinal tract is most sensitive to stress reactions (Han et al. 2023; Tsuji et al. 2023). In sepsis, the body is in a state of stress, and gastrointestinal blood vessels contract, leading to a state of low perfusion in the gastrointestinal tract (Zhu et al. 2023). The gastrointestinal mucosa undergoes ischemia and hypoxia damage; Severe microcirculatory disorders, treated with fluid resuscitation and other treatments, generate a large amount of oxygen free radicals during reperfusion, attack the human enzyme system, disrupt biofilm permeability, disrupt normal cell metabolism, and cause a series of reperfusion injuries; The systemic inflammatory response disrupts the epithelial cells of the intestinal mucosa, leading to increased apoptosis of intestinal cells or insuffi-

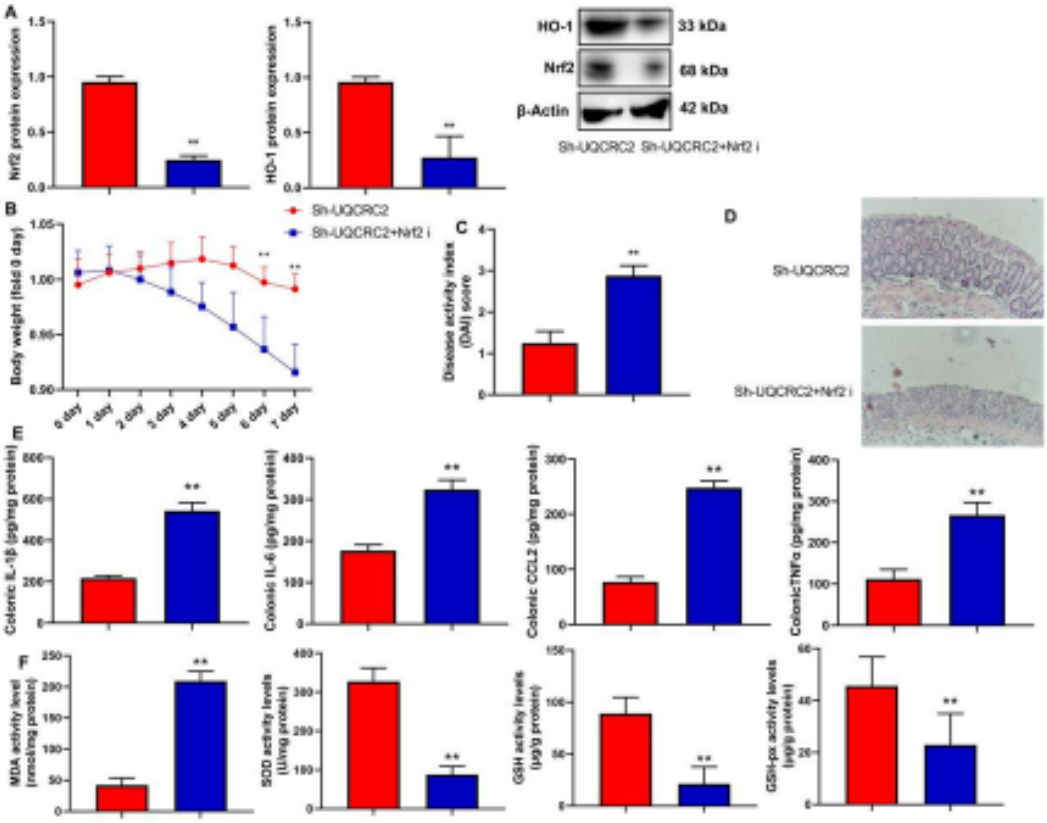

Fig. 9. Nrf2 is target spot for UQCRC2 on colon injury in mice model of sepsis
Nrf2/HO-1 protein expression (A), body weight (B), DAI score (C), the colon epithelial cell injure (HE, D), inflammation levels (E), oxidative stress (F). $^{**}p<0.01$ vs sh-UQCRC2 group

cient gastrointestinal perfusion, necrosis and shedding of villi, and increased mucosal permeability; During sepsis, the secretion of gastrointestinal hormones such as motilin and vasoactive intestinal peptide in the human body is disordered, resulting in decreased gastrointestinal motility, retention of stomach contents, and reduction or disappearance of bowel sounds; Total parenteral nutrition therapy, broad-spectrum antibiotic application, etc., lead to dysbiosis of the intestinal microbiota, damage to the intestinal environment, increased risk of bacterial colonization in the gastrointestinal tract, and increased resistance rate of Enterobacteriaceae (Peng et al. 2023). If the gastrointestinal function is damaged, bacteria and endotoxins can migrate and enter the bloodstream through the intestinal mucosal barrier, leading to serious consequences such as sepsis; In addition, the body's own immune system is weakened, and glutamine deficiency can also lead to gastrointestinal dysfunction. In this study, UQCRC2 mRNA and protein expression was increased in colon tissue of the model of sepsis. Zhang et al. (2021b) showed that Circ-UQCRC2 aggravates inflammatory response and oxidative stress in human bronchial epithelioid cells. UQCRC2 participated in the disease progression of sepsis.

Blood flow infection is a very serious infectious disease, which is due to the existence and proliferation of various pathogenic bacteria in human blood circulation, leading to poisoning, infection and systemic inflammatory reaction (Purcarea and Sovaila 2020). Clinical studies have found that bloodstream infections can quickly cause septic shock in patients, which is also a key reason for the high mortality rate of patients (Rello et al. 2017). In clinical practice, early diagnosis of sepsis, timely anti-infection, fluid replacement, and related supportive treatment are the key to reducing mortality and improving prognosis in sepsis patients (Peng et al. 2023). Research has found that the detection of relevant factors in the body has high clinical value in sepsis (Salomão et al. 2019). The increased intestinal permeability are the initiating factors for the occurrence of MODS in sepsis (Wang et al. 2023b). The researchers found that UQCRC2 increased oxidative stress in vitro models or mice models of sepsis. Zhou et al. (2022) uncovered that UQCRC2 inhibits ROS in alcoholic liver disease. These data instructed that UQCRC2 increased oxidative stress of SIECs in vitro model or mice model of sepsis.

Mitochondria can convert nutrients such as sugars, lipids, and proteins into adenosine triphosphate (ATP) through oxidative phosphorylation, providing energy for biological activities (Gao et al. 2022; van der Slikke et al. 2021). Excessive ROS in the body can lead to impaired mitochondrial function, resulting in dysfunction of cells, tissues, organs, and systems, leading to various diseases such as sepsis and intestinal injury (Zou et al. 2022; Gao et al. 2022). At present, UQCRC2 increased ROS-induced mitochondrial damage of SIECs in vitro model of sepsis. Mitochondrial damage accelerated colon injury in a model of sepsis by UQCRC2. Lu et al. (2021) sought to determine the significance of UQCRC2 in the process of mitophagy in mitochondria. These data indicated that UQCRC2 exacerbates ROS-induced mitochondrial damage in an in vitro model of sepsis in SIECs.

Nrf2/HO-1 is a key pathway for the body to exert antioxidant stress, regulating downstream antioxidant gene transcription, and is considered one of the targets for treating sepsis intestinal injury (Gao et al. 2021). Oxidative stress excessive accumulation of ROS (Feng et al. 2021). Excessive ROS can damage cellular proteins, DNA, and lipids (Qiu et al. 2022) (Shang et al. 2021). Various oxidative stress biomarkers and damage to the antioxidant system of intestinal tissue can be detected in patients with sepsis intestinal injury (Bai et al. 2022). Currently, the researchers found that UQCRC2 suppressed Nrf2/HO-1 signalling pathway of SIECs in vitro model or mice model of sepsis. Lu et al. (2021) found that UQCRC2 regulated the NFE2L2/NRF2 signalling axis in the process of mitophagy in mitochondria. So, UQCRC2 suppressed the NRF2/HO-1 signalling axis of SIECs in the model of sepsis.

CONCLUSION

In conclusion, UQCRC2 accelerated mitochondrial damage of SIECs in the model of sepsis through the ROS production by the NRF2/HO-1 signalling axis. UQCRC2 offers a rationale for enhancing the effectiveness of anti-ROS-induced mitochondrial damage treatment in sepsis. UQCRC2 might benefit the treatment of sepsis.

RECOMMENDATIONS

UQCRC2 offers a rationale for enhancing the effectiveness of anti-ROS-induced mitochondrial damage treatment in sepsis. UQCRC2 might benefit the treatment of sepsis.

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Paper received for publication in
Paper accepted for publication in