

World Journal of *Gastroenterology*

World J Gastroenterol 2015 February 21; 21(7): 2005-2264





FIELD OF VISION

- 2005 Injury-associated reacquiring of intestinal stem cell function
Sipos F, Múzes G

ORIGINAL ARTICLE

Basic Study

- 2011 Gene expression profiling of MYC-driven tumor signatures in porcine liver stem cells by transcriptome sequencing
Aravalli RN, Talbot NC, Steer CJ
- 2030 Negative impact of bone-marrow-derived mesenchymal stem cells on dextran sulfate sodium-induced colitis
Nam YS, Kim N, Im KI, Lim JY, Lee ES, Cho SG
- 2040 Depletion of the *IKBKAP* ortholog in zebrafish leads to hirschsprung disease-like phenotype
Cheng WWC, Tang CSM, Gui HS, So MT, Lui VCH, Tam PKH, Garcia-Barcelo MM
- 2047 Impact of high glucose on metastasis of colon cancer cells
Lin CY, Lee CH, Huang CC, Lee ST, Guo HR, Su SB
- 2058 Mechanism of action of gypenosides on type 2 diabetes and non-alcoholic fatty liver disease in rats
He Q, Li JK, Li F, Li RG, Zhan GQ, Li G, Du WX, Tan HB

Case Control Study

- 2067 Increased inspiratory esophagogastric junction pressure in systemic sclerosis: An add-on to antireflux barrier
Nobre e Souza MÁ, Bezerra PC, Nobre RA, Holanda ESF, Santos AA
- 2073 Chronic hepatitis B in children with or without malignancies: A 13-year follow-up
Usta M, Urgancı N, Yıldırım ZY, Dogan Vural S
- 2080 Clinical significance and usefulness of soluble heparin binding-epidermal growth factor in gastric cancer
Chung HW, Kong HY, Lim JB

Retrospective Cohort Study

- 2089 Natural YMDD-motif mutants affect clinical course of lamivudine in chronic hepatitis B
Tan YW, Ye Y, Ge GH, Zhao W, Gan JH, Zhao Y, Niu ZL, Zhang DJ, Chen L, Yu XJ, Yang LJ

Retrospective Study

- 2096** FOLFIRI plus bevacizumab as a second-line therapy for metastatic intrahepatic cholangiocarcinoma
Guion-Dusserre JF, Lorgis V, Vincent J, Bengrine L, Ghiringhelli F
- 2102** Liver resection for the treatment of post-cholecystectomy biliary stricture with vascular injury
Perini MV, Herman P, Montagnini AL, Jukemura J, Coelho FF, Kruger JA, Bacchella T, Ceconello I
- 2108** Endocytoscopic narrow-band imaging efficiency for evaluation of inflammatory activity in ulcerative colitis
Maeda Y, Ohtsuka K, Kudo S, Wakamura K, Mori Y, Ogata N, Wada Y, Misawa M, Yamauchi A, Hayashi S, Kudo T, Hayashi T, Miyachi H, Yamamura F, Ishida F, Inoue H, Hamatani S
- 2116** Predictors of kidney tubular dysfunction induced by adefovir treatment for chronic hepatitis B
Shimizu M, Furusyo N, Ikezaki H, Ogawa E, Hayashi T, Ihara T, Harada Y, Toyoda K, Murata M, Hayashi J
- 2124** Repeat hepatic resection in patients with colorectal liver metastases
Lee H, Choi SH, Cho YB, Yun SH, Kim HC, Lee WY, Heo JS, Choi DW, Jung KU, Chun HK
- 2131** Determination of surgical priorities in appendicitis based on the probability of undetected appendiceal perforation
Lee SC, Park G, Choi BJ, Kim SJ

Clinical Trials Study

- 2140** Endoscopic measurement of variceal diameter
Li ZQ, Linghu EQ, Hu M, Wang XD, Wang HB, Meng JY, Du H
- 2147** Is intraoperative cholangiography necessary during laparoscopic cholecystectomy for cholelithiasis?
Ding GQ, Cai W, Qin MF

Observational Study

- 2152** Establishing an integrated gastroenterology service between a medical center and the community
Niv Y, Dickman R, Levi Z, Neumann G, Ehrlich D, Bitterman H, Dreier J, Cohen A, Comaneshter D, Halpern E
- 2159** ARID1A expression in gastric adenocarcinoma: Clinicopathological significance and correlation with DNA mismatch repair status
Inada R, Sekine S, Taniguchi H, Tsuda H, Katai H, Fujiwara T, Kushima R
- 2169** Preliminary study of a new pathological evolution-based clinical hepatolithiasis classification
Liu FB, Yu XJ, Wang GB, Zhao YJ, Xie K, Huang F, Cheng JM, Wu XR, Liang CJ, Geng XP

Prospective Study

- 2178** Measurement system that improves the accuracy of polyp size determined at colonoscopy
Leng Q, Jin HY

Randomized Controlled Trial

- 2183 MicroRNA profiling of the intestine during hypothermic circulatory arrest in swine
Lin WB, Liang MY, Chen GX, Yang X, Qin H, Yao JP, Feng KN, Wu ZK

Randomized Clinical Trial

- 2191 Semaphorin 4D and hypoxia-inducible factor-1 α overexpression is related to prognosis in colorectal carcinoma
Wang JS, Jing CQ, Shan KS, Chen YZ, Guo XB, Cao ZX, Mu LJ, Peng LP, Zhou ML, Li LP

EVIDENCE-BASED MEDICINE

- 2199 New cancer suppressor gene for colorectal adenocarcinoma: Filamin A
Tian ZQ, Shi JW, Wang XR, Li Z, Wang GY

CASE REPORT

- 2206 Lymphangitic spread from appendiceal adenocarcinoma to ileocecal valve, mimicking Crohn's disease
Murdock T, Lim N, Zenali M
- 2210 Human papillomavirus-related squamous cell carcinoma of the anal canal with papillary features
Leon ME, Shamekh R, Coppola D
- 2214 Combined glucocorticoid and antiviral therapy of hepatitis B virus-related liver failure
Bockmann JH, Dandri M, Lüth S, Pannicke N, Lohse AW
- 2220 Resection of multiple rectal carcinoids with transanal endoscopic microsurgery: Case report
Zhou JL, Lin GL, Zhao DC, Zhong GX, Qiu HZ
- 2225 Gastroduodenal intussusception due to gastric schwannoma treated by billroth II distal gastrectomy: One case report
Yang JH, Zhang M, Zhao ZH, Shu Y, Hong J, Cao YJ
- 2229 Portal hypertension induced by congenital hepatic arterioportal fistula: Report of four clinical cases and review of the literature
Zhang DY, Weng SQ, Dong L, Shen XZ, Qu XD
- 2236 Autoimmune hepatitis-primary biliary cirrhosis concurrent with biliary stricture after liver transplantation
Kang YZ, Sun XY, Liu YH, Shen ZY
- 2242 Gastric myeloid sarcoma without acute myeloblastic leukemia
Huang XL, Tao J, Li JZ, Chen XL, Chen JN, Shao CK, Wu B
- 2249 Stent displacement in endoscopic pancreatic pseudocyst drainage and endoscopic management
Wang GX, Liu X, Wang S, Ge N, Guo JT, Liu W, Sun SY

- 2254** Mixed adenoneuroendocrine carcinoma of the ampulla: Two case reports

Huang Z, Xiao WD, Li Y, Huang S, Cai J, Ao J

LETTERS TO THE EDITOR

- 2260** Adalimumab-induced interstitial pneumonia in a patient with Crohn's disease

Casanova MJ, Chaparro M, Valenzuela C, Cisneros C, Gisbert JP

- 2263** Hepatitis B reactivation and timing for prophylaxis

Tuna N, Karabay O

ABOUT COVER

Associate Editor of *World Journal of Gastroenterology*, Yung-Jue Bang, MD, PhD, Professor, Department of Internal Medicine, Seoul National University College of Medicine, Seoul 110-744, South Korea

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1379 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, Digital Object Identifier, and Directory of Open Access Journals. ISI, Journal Citation Reports®, Gastroenterology and Hepatology, 2013 Impact Factor: 2.433 (36/74); Total Cites: 20957 (6/74); Current Articles: 1205 (1/74); and Eigenfactor® Score: 0.05116 (6/74).

FLYLEAF

I-IX Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Xiao-Mei Liu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Yuan Qi*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

Salah A Naser, PhD, Professor, Burnett School of Biomedical Sciences, College of Medicine, University of Central Florida, Orlando, FL 32816, United States

Stephen C Strom, PhD, Professor, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach, CA 90822, United States

EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Gastroenterology
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgooffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

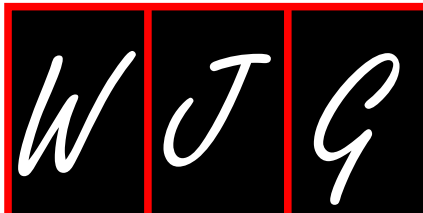
PUBLICATION DATE
February 21, 2015

COPYRIGHT
© 2015 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1007-9327/g_info_20100315215714.htm

ONLINE SUBMISSION
<http://www.wjgnet.com/esps/>



Randomized Controlled Trial

MicroRNA profiling of the intestine during hypothermic circulatory arrest in swine

Wei-Bin Lin, Meng-Ya Liang, Guang-Xian Chen, Xiao Yang, Han Qin, Jian-Ping Yao, Kang-Ni Feng, Zhong-Kai Wu

Wei-Bin Lin, Meng-Ya Liang, Guang-Xian Chen, Xiao Yang, Han Qin, Jian-Ping Yao, Kang-Ni Feng, Zhong-Kai Wu, 2nd Department of Cardiac Surgery, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China

Author contributions: Lin WB conducted the molecular studies, analyzed the data and drafted the manuscript; Chen GX, Liang MY and Yao JP participated in establishing the cardiopulmonary bypass model; Feng KN and Qin H participated in the design of the study and performed the statistical analysis; Wu ZK and Yang X conceived the study, participated in its design and coordination and helped to draft the manuscript; all authors read and approved the final manuscript.

Supported by National Basic Research Program of China (973 Program), No. 2010CB5295007; Pearl River Scholar Program, No. 80000-3210003; and Natural Science Fund of China, No. 81370215.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Zhong-Kai Wu, MD, PhD, 2nd Department of Cardiac surgery, the First Affiliated Hospital of Sun Yat-Sen University, 58 Zhongshan II Road, Guangzhou 510080, Guangdong Province, China. wuzhk@mail.sysu.edu.cn

Telephone: +86-20-87755766

Fax: +86-20-87750632

Received: May 31, 2014

Peer-review started: June 1, 2014

First decision: July 21, 2014

Revised: August 12, 2014

Accepted: September 5, 2014

Article in press: September 5, 2014

Published online: February 21, 2015

Abstract

AIM: To perform a profiling analysis of changes in intestinal microRNA (miRNA) expression during hypothermic circulatory arrest (HCA).

METHODS: A total of eight piglets were randomly divided into HCA and sham operation (SO) groups. Under general anesthesia, swine in the HCA group were subjected to hypothermic cardiopulmonary bypass at 24 °C followed by 80 min of circulatory arrest, and the reperfusion lasted for 180 min after cross-clamp removal. The counterparts in the SO group were only subjected to median sternotomy. Histopathological analysis was used to detect mucosal injury, and Pick-and-Mix custom miRNA real-time polymerase chain reaction (PCR) panels containing 306 unique primer sets were utilized to assay unpooled intestinal samples harvested from the two groups.

RESULTS: The intestinal mucosa of the animals that were subjected to 24 °C HCA exhibited representative ischemic reperfusion injury of grade 2 or 3 according to the Chiu score. Such intestinal mucosal injuries, with the subepithelial space and epithelial layer lifting away from the lamina propria, were accompanied by shortened and irregular villi. On the contrary, the intestinal mucosa remained normal in the sham-operated animals. In total, twenty-five miRNAs were differentially expressed between the two groups (15 upregulated and 10 downregulated in the HCA group). Among these, eight miRNAs (miR-122, miR-221-5p, miR-31, miR-421-5p, miR-4333, miR-499-3p, miR-542 and let-7d-3p) were significantly dysregulated (four higher and four lower). The expression of miR-122 was significantly (5.37-fold) increased in the HCA group vs the SO group, indicating that it may play a key role in

HCA-induced mucosal injury.

CONCLUSION: Exposure to HCA caused intestinal miRNA dysregulation and barrier dysfunction in swine. These altered miRNAs might be related to the protection or destruction of the intestinal barrier.

Key words: Reperfusion injury; Cardiopulmonary bypass; Animal model; Barrier function; Randomized controlled trial; MicroRNA

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Swine intestine was subjected to hypothermia, cardiopulmonary bypass and ischemia/reperfusion following hypothermic circulatory arrest (HCA). These factors caused barrier dysfunction, resulting in gastrointestinal complications. Histopathological and microRNA (miRNA) array analyses were used to investigate the effects of HCA on the gut barrier. HCA was found to disturb barrier function in the small intestine and influence the miRNA levels in swine. Our results contribute to the body of research examining gut barrier function following HCA *in vivo*.

Lin WB, Liang MY, Chen GX, Yang X, Qin H, Yao JP, Feng KN, Wu ZK. MicroRNA profiling of the intestine during hypothermic circulatory arrest in swine. *World J Gastroenterol* 2015; 21(7): 2183-2190 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i7/2183.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i7.2183>

INTRODUCTION

Since Bigelow performed the first experiments on hypothermic circulatory arrest (HCA) in 1950, HCA has become a vital technique in surgery for aortic and congenital heart disease. HCA can decrease the metabolic rate of tissues throughout the body and provides a bloodless surgical field while increasing complications such as edema formation, coagulopathy and organ dysfunction. On the grounds that the brain is the organ that is the most sensitive to ischemia, many studies have focused on neurological impairment associated with HCA, while only a few studies have focused on other organs, such as the kidney, intestines and spinal cord.

The prognosis after cardiopulmonary bypass (CPB) is closely related to the degree of gastrointestinal complications^[1]. Even simple CPB will impair gastrointestinal function^[2]. Although the underlying mechanism remains unclear, possible explanations for these complications include gastrointestinal hypoperfusion^[3,4], gut barrier dysfunction, preoperative immune function defects, the change in the blood capillary permeability of the intestinal wall, and the systemic inflammatory

response. Furthermore, HCA may increase the risk associated with gut barrier dysfunction^[5]. Due to HCA, the intestines suffer from ischemic reperfusion injury (IRI).

MicroRNAs (miRNAs) are small noncoding RNAs that are capable of silencing gene expression post-transcriptionally. In recent years, research on miRNA has been mainly focused on cancer, while miRNA expression following IRI has remained poorly understood. Growing evidence indicates that some miRNAs are related to IRI, such as miRNA expression in the liver^[6], kidney^[7], muscle^[8] and flap^[9]; however, there are no reports on miRNA expression in intestinal IRI following HCA.

We postulated that miRNA is also associated with intestinal IRI during HCA. The present study aims to identify the influence of HCA on microRNA expression in the intestine by using miRNA polymerase chain reaction (PCR) arrays in swine.

MATERIALS AND METHODS

Animals and study design

A total of 8 Wuzhishan pigs (6 to 8-wk-old, weight 9.7-13 kg, average 11.66 kg) were randomly assigned into HCA 24 °C and sham operation (SO) groups. The experiment was conducted in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1996) and the Guidelines for Animal Experimentation, which were issued by the First Affiliated Hospital of Sun Yat-sen University.

Anesthesia

The animals were sedated with intramuscular ketamine hydrochloride and maintained on IV infusions of ketamine (40 mg/kg) and fentanyl (2 µg/kg per hour) after endotracheal intubation *via* tracheotomy. Following this step, an arterial pressure catheter was inserted into the right femoral artery for pressure monitoring and blood sampling. Then, an 8-Fr central venous catheter was inserted *via* the left femoral vein for fluid administration and central venous pressure monitoring.

CPB and sham operation

A median sternotomy was performed in both groups. Next, each of the piglets in the HCA group was administered heparin sodium (400 IU/kg). The ascending aorta was cannulated with a single 10F arterial cannula, and the superior and inferior vena cava were both cannulated with 12F cannulas. The CPB circuit consisted of a roller pump, a membrane oxygenator (SK3301, Medtronic Inc, Minneapolis, MN, United States), and a heat exchanger (Sarns Heater

Cooler, Ann Arbor, MI, United States). The circuit was primed with electrolyte solution, blood from a donor pig and heparin (3 mg/100 mL total fluid). A mean arterial pressure of 50 to 80 mmHg was maintained by keeping the CPB flow rate between 75 mL/kg per minute and 80 mL/kg per minute in the CPB group.

HCA

After initiation of CPB, the animals were cooled to a target nasopharyngeal temperature of 30 °C by a heat exchanger (Sarns, Ann Arbor, MI, United States). After the body temperature lowered to 30 °C, the ascending aorta was cross-clamped, and the cardioplegia solution was administered. Topical ice slush was used to cool the surface of the heart throughout the HCA procedure. The heat exchanger operated until the body temperature was cooled down to 24 °C. Then, the roller pumps were turned off, and HCA was performed for the next 80 min. Next, the aorta was declamped, and the animal was rewarmed to normothermia in 60 min using a temperature gradient of 8 °C. For the hearts that encountered deleterious arrhythmia after de-clamping, direct-current defibrillation was used to restore the sinus rhythm. The animals were weaned off from CPB when the hemodynamic data became steady after partial perfusion, and the reperfusion lasted for 180 min following the removal of the cross-clamping. When the experiment was complete, midline laparotomy was performed to obtain specimens from the terminal ileum, which were preserved at -80 °C.

Real-time PCR profiling of microRNAs

RNA was isolated from cryopreserved tissue using TRIzol (Invitrogen Life Technologies, Carlsbad, CA, United States) and subsequently precipitated, washed and redissolved. The RNA purity was measured using a NanoDrop ND-1000 spectrophotometer (Wilmington, DE, United States). cDNA was generated from 20 µL of RNA using the buffer and the enzymes that were provided in the Qiagen kit (Exiqon, Denmark). Pick-and-Mix custom panels (Exiqon, Denmark) containing 306 primer sets uniquely designed for microRNAs were chosen for miRNA expression profiling. The cDNA was diluted × 110 and assayed in 10-µL PCR reactions according to the protocol for miRCURY LNA TM Universal RT microRNA PCR. PCR was performed using the ABI PRISM 7900 system (Applied Biosystems, Inc., Foster City, CA, United States). The miRNA expression was normalized relative to the expression of U6 using the $\Delta\Delta C_t$ method. Then, the fold change was calculated by using the ratio of miRNA_{HCA}/miRNA_{SO} or miRNA_{SO}/miRNA_{HCA} (when miRNA_{HCA} was down-regulated).

Histopathological analysis

Hematoxylin and eosin-stained sections from formalin-fixed and paraffin-embedded intestinal samples were

assessed by two pathologists who were blinded to the study protocol according to Chiu's method^[10]. All samples were observed under a stereomicroscope (DM 2500B, Leica, Germany) at × 200 magnification using an objective lens with an aperture of 22 mm. Photomicrographs were obtained using the Leica Application Suite (Leica Microsystems, Wetzlar, Germany) and edited with Adobe Photoshop 12.0 (Adobe Systems Inc., San Jose, United States).

Statistical analysis

Significant differences between the two groups were tested using Student's *t*-test, with a significance threshold of $P < 0.05$. miRNAs with expression changes of > 2-fold were considered to be differentially expressed. The statistical program SPSS 20.0 (SPSS Inc., Chicago, IL, United States) was used for statistical analysis.

RESULTS

Morphological changes in the intestine following HCA

No significant differences were observed in the intestinal mucosa between the two groups based on observations with the naked eye. However, histological tissue evaluations revealed that the structures of the mucosal epithelial layer and the lamina propria were well preserved in the SO group (Figure 1A). In contrast, the intestinal mucosa of the animals that were subjected to HCA demonstrated representative IRI of grade 2 or 3 according to the Chiu score (Figure 1B). This result indicates that the gut barrier function was interrupted following 80 min of ischemia and 180 min of reperfusion despite exposure to 24 °C hypothermia.

MiRNA real-time PCR array

Relative to the SO group, miRNA profiling revealed that 25 miRNAs were differentially expressed ($P < 0.05$) in the intestine after 80 min of ischemia and 180 min of reperfusion (Figure 2 and Table 1). Of the 25 miRNAs, miR-122, -542-5p, -499-3p, -421, let-7d-3p, miR-31, -221-5p and -4333 were diversely expressed between the HCA and SO groups for $P < 0.05$ and a fold change > 2 levels of significance. In Table 2, we summarize six miRNAs that were previously implicated in IRI. Although these six miRNAs were not significantly expressed in the intestine, a lower miR-192 level was observed compared to the SO group (Table 2).

DISCUSSION

To date, no data are available regarding the intestinal miRNA expression profile during an HCA procedure. In the present study, we detected twenty-five dys-regulated miRNAs and injury to the mucosa barrier in the intestine following HCA. The factors that may have

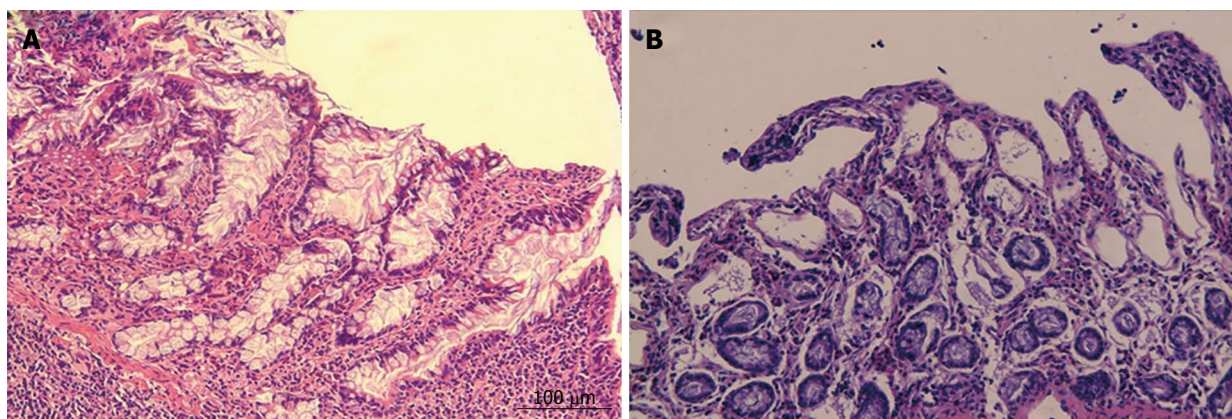


Figure 1 Histopathological changes in the mucosa in each group. A: Epithelial layer and the lamina propria of the intestinal mucosa in the SO group were normal; B: Shortened and irregular villi as well as subepithelial space were observed; some lifting of the epithelial layer of the lamina propria was observed in mucosa exposed to HCA (magnification × 200).

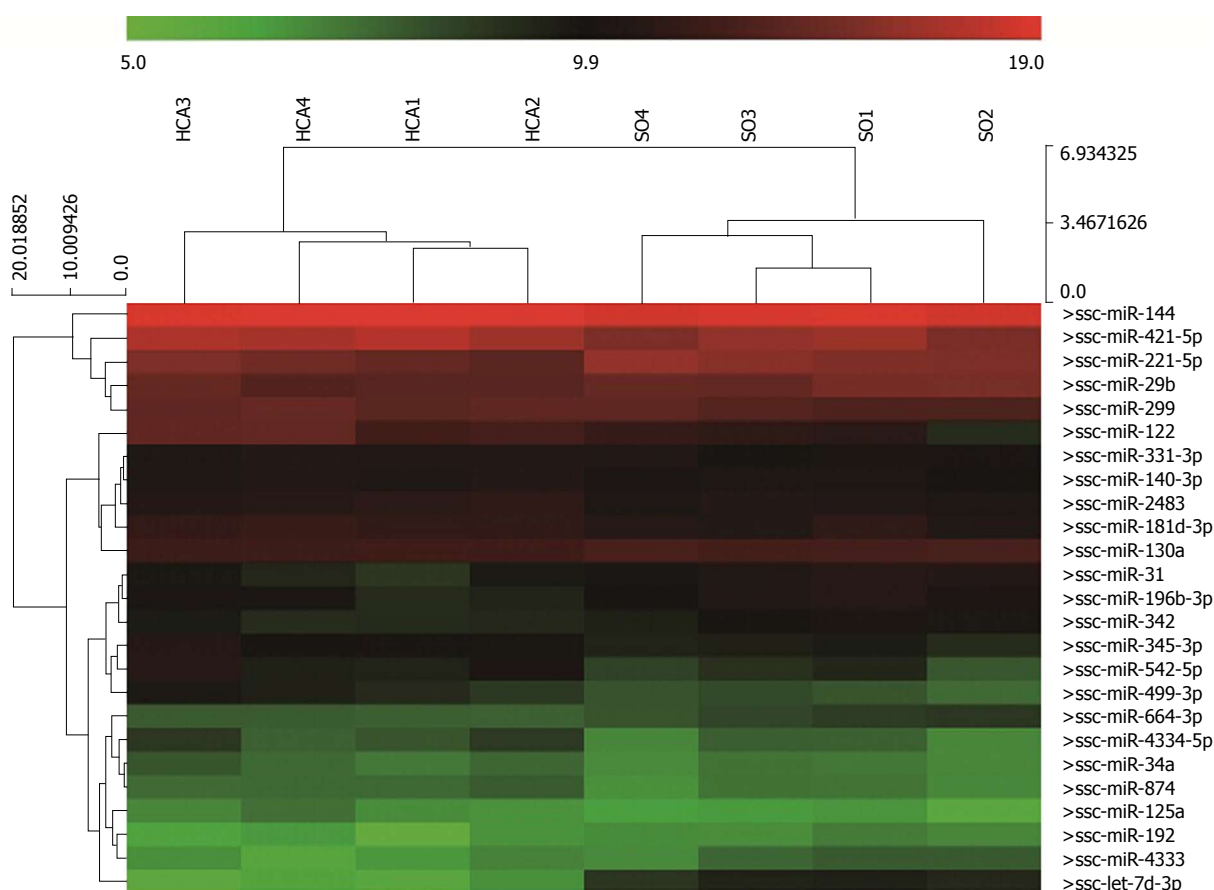


Figure 2 Heat maps of the differentially expressed microRNAs. Twenty-five dysregulated microRNAs were detected between the HCA and SO groups ($P < 0.05$) in this study. HCA: Hypothermic circulatory arrest; SO: Sham operation.

influenced miRNA expression in this study included hypothermia, CPB and circulatory arrest. Firstly, hypothermia may induce miRNA dysregulation. For example, higher miR-21 expression levels have been detected in skeletal muscle and liver at -3°C compared to 5°C *in vivo*^[11]. Interestingly, in another tissue miRNA study performed in a traumatic brain injury rat model, miR-874 was markedly differentially expressed under hypothermia conditions (33°C) compared to

normothermia (37°C)^[12]. Specifically, temperature-dependent miRNA modulation was mediated by RNA-binding motif protein 3^[13]. These studies were not performed at 24°C ; nevertheless, they reflected the effect of hypothermia on miRNA. Therefore, the modulated miRNAs in our study (let-7d-3p, miR-29b, miR-125a, miR-130a, miR-874) may be temperature-dependent miRNAs that are affected by HCA. Secondly, changes in the miR-499 levels

Table 1 MicroRNAs that were dysregulated in the hypothermic circulatory arrest group vs the sham operation group

	Up-regulation	FC	P value	Down-regulation	FC	P value
1	miR-122	5.37	0.0193	let-7d-3p	8.73	0.0000
2	miR-542-5p	2.64	0.0273	miR-31	2.33	0.0141
3	miR-499-3p	2.47	0.0026	miR-221-5p	2.18	0.0248
4	miR-421-5p	2.41	0.0141	miR-4333	2.01	0.0219
5	miR-4334-5p	1.95	0.0344	miR-29b	1.89	0.0213
6	miR-345-3p	1.73	0.0212	miR-196b-3p	1.79	0.0440
7	miR-181d-3p	1.63	0.0211	miR-192	1.63	0.0494
8	miR-2483	1.59	0.0074	miR-664-3p	1.55	0.0085
9	miR-125a	1.52	0.0487	miR-342	1.49	0.0266
10	miR-874	1.48	0.0226	miR-130a	1.40	0.0006
11	miR-299	1.47	0.0440			
12	miR-34a	1.41	0.0489			
13	miR-331-3p	1.38	0.0392			
14	miR-140-3p	1.36	0.0232			
15	miR-144	1.35	0.0166			

Among the 25 aberrantly expressed miRNAs, only eight miRNAs showed significant changes. miR-4333 expression was found to overlap with that of the well-conserved SNORA53 based on information retrieved from miRBase 20.

in the myocardium during CPB were reported^[14]; however, no change about miR-499 was reported in the intestine. miR-499 is an acute myocardial infarction marker that is overexpressed in cardiac IRI. In a study by Reddy *et al*^[15], the authors stated that miR-499 is cardiac cell-specific in swine and cannot be detected in other organs; however, only the stomach was included in this previous study, and the intestine was not analyzed. Our data revealed differential miR-499 expression between the normal and experimental intestines, indicating that miR-499 may be a marker of IRI in the intestine, distinct from the heart. However, with the present study design, we cannot differentiate among the hypothermia-induced, CPB-induced and IRI-induced miRNA changes. Therefore, additional studies are needed to assess the individual impact of these factors. Thirdly, few studies examining alterations in the expression of miRNAs in the intestine subjected to IRI have been reported, although miRNAs were found to be altered in other organs subjected to IRI. Nevertheless, the dysregulation of several miRNAs was found in other organs subjected to IRI^[9,16-18], including the liver (miR-146), kidney (miR-10a, miR-30d), and skin flap (miR-21, miR-96, miR-193-3p, miR-210). However, the miRNA expression found in our study was quite different than in other IRI studies. The decreased levels of miR-192 that we detected were consistent with a previous report on renal IRI^[18]. This phenomenon also suggests that IRI is not the only factor related to intestinal miRNA changes following HCA. Consequently, this finding suggests that the superior mesenteric artery ligation model may not be suitable to mimic the intestinal pathophysiology changes in cardiac surgery.

The histological change of the intestinal mucosa

is one of the key factors used to evaluate gut barrier function. Our results suggest that the gut barrier function was compromised in animals subjected to 24 °C HCA. Altered levels of several miRNAs were associated with barrier dysfunction, indicating that they may play a protective/detrimental role in HCA. Cytokines, such as IL-6 and IL-10, are key inflammation regulators of CPB-induced intestinal dysfunction mediated by the NF-κB pathway. Let-7d^[19,20] and miR-421^[21] were hypothesized to promote gut barrier conservation by reducing the cytokine level. However, in the present study, the let-7d expression level decreased, while the miR-421 level increased in response to HCA. Therefore, although high miR-421 levels may benefit the intestinal mucosa, reduced let-7d-3p levels are likely to negatively affect the intestinal mucosa.

Our morphological results also confirmed that IRI caused by HCA leads to barrier dysfunction. Hypoxia inducible factor (HIF) is activated by IRI^[22], resulting in intestinal mucosa barrier dysfunction^[23]. HIF is down-regulated by factor inhibiting HIF (FIH-1)^[24], a target gene of miR-31^[25], suggesting that the decreased miR-31 expression observed in our study may protect the intestinal barrier. The CPB procedure activates several pathways, including oxidative stress, which dysregulates senescence-associated miR-542 expression^[26] and inhibits cell proliferation *in vitro*^[27]. Ultimately, high miR-542 levels might injure the mucosa in our model. miR-122 showed significantly (5.37-fold) increased expression in the HCA group vs the SO group. During myocardial IRI, the activity of myocardial p38-MAPK may lead to the down-regulation of miR-122^[28,29], suggesting that miR-122 may also show similar changes during IRI in other organs. On the contrary, miR-122 was shown to be up-regulated in intestinal IRI in our study, which may be due to a different activated sub-family of p38-MAPK or organ differences. In a recent study by Ye *et al*^[30], it was shown that TNF-α may lead to increased miR-122 levels in the intestine, suggesting that miR-122 may be involved in TNF-α induced intestinal barrier dysfunction. However, *NOD2* and *TNF-α* are two gut function-associated target genes of miR-122. Lower *NOD2* levels protect intestinal epithelial cells by increasing anti-inflammatory cytokines^[31], and reduced TNF-α levels alleviate intestinal IRI^[32,33]. In contrast, elevated miR-122 levels are postulated to protect barrier function in our HCA model.

IRI can lead to increased miR-221 expression through the high-mobility group box 1 protein pathway^[34,35]; however, the miR-221 level was decreased in HCA, suggesting that hypothermia or CPB influence the expression of miR-221 in HCA. Low miR-221 expression is related to high TNF mRNA expression^[36,37]; therefore, miR-221 down-regulation may be detrimental to intestinal epithelial cells *via* activation of the NF-κB pathway^[38].

Table 2 ischemic reperfusion injury-associated miRNA expression in hypothermic circulatory arrest and sham operation groups

miRNA	miR-10a-3p	miR-10a-5p	miR-21	miR-193a-3p	miR-210	miR-205
FC	-1.23	-1.16	-1.11	-1.11	-1.41	-1.17
P value	0.3752	0.5034	0.6219	0.7919	0.0952	0.6146

Six previously reported ischemic reperfusion injury-associated miRNAs showed nonsignificant changes.

There are several advantages of the swine model, such as steady hemodynamics, tolerance of long duration circulatory arrest and similarity to human beings. Furthermore, the age of six to eight weeks in swine likely corresponds to the relevant age in human infants for congenital heart disease. This model more closely resembles the real disease state in human beings, while animals such as rats, canines and rabbits have failed to match closely with real disease states. Therefore, we selected the swine as a model of HCA. Little is known about mucosa injuries caused by circulatory arrest. Karhausen reported that 45 min of circulatory arrest can lead to obvious rat intestinal mucosa IRI^[39]. Although the duration of ischemia was longer in our study, minor microscopic changes were found. A possible explanation might be that the rat intestine is more sensitive to ischemia or temperature changes than it is to the duration of the ischemia.

One limitation of this study is that we did not set up groups of cardiopulmonary hypothermia without circulatory arrest or circulatory arrest at normal temperatures. Therefore, although intestinal miRNA could be influenced by HCA, we were not able to detect the most significant factor among hypothermia, CPB and circulatory arrest during HCA. However, the animal model that we aim to establish can be used to simulate the clinical surgical process. Therefore, circulatory arrest following atmospheric temperature and superior mesenteric artery ligation without CPB may not provide useful information. Another limitation of our study is that we did not link the dysregulated miRNAs with significant changes in pathological characteristics. Although many candidate genes are potentially targeted by the 7 identified miRNAs, only a few of these target genes were validated in other studies. We assessed the mutual target genes of these miRNAs, but the results we obtained are not ideal for determining the connection between miRNAs and the gut barrier, suggesting that the direct relationship between the genes and the pathological characteristics shown in our figures is difficult to identify. We hope that the initial data provided by our study may inspire other researchers to determine the connection between these miRNAs and the gut barrier.

In summary, intestinal barrier dysfunction and miRNA deregulation occurred when the swine were subjected to 24 °C HCA. Among these miRNAs, altered miR-122, miR-31 and miR-421-5p levels may protect

barrier function, while altered miR-542-5p, let-7d-3p and miR-221-5p levels may negatively affect barrier function. Furthermore, miR-499 may be a marker of IRI in the intestine.

ACKNOWLEDGMENTS

We would like to acknowledge the Key Laboratory on Assisted Circulation and KangChen Bio-tech Inc. for experimental assistance.

COMMENTS

Background

Although the incidence of gastrointestinal complications is low following cardiopulmonary bypass (CPB) during cardiac surgery, the complications may be serious. Hypothermic circulatory arrest (HCA), a special technique in CPB, may increase the risk associated with gut barrier dysfunction.

Research frontiers

Due to HCA, ischemic reperfusion injury (IRI) occurs in the intestine. The study aimed to determine the influence of reperfusion injury during HCA on microRNA expression in the intestine.

Innovations and breakthroughs

The injury to the mucosal barrier in the intestine following HCA was validated in swine, which are large animals. Furthermore, miRNA dysregulation was observed following the HCA procedure.

Applications

A better understanding of the miRNAs involved in HCA related to intestinal mucosal injury may be helpful in developing strategies to protect organ function.

Terminology

CPB is a technique that enables blood circulation throughout the body when the heart is stopped during cardiac surgery. HCA is a brief period during CPB in which the systemic circulation is shut down while maintaining heart and brain perfusion.

Peer-review

This manuscript concerns HCA-regulated miRNA expression in swine intestine. By conducting a miRNA array experiment, the authors targeted some miRNAs which might be significant in HCA or I/R-induced tissue injury. Overall, the research design is very decent with adequate animal experiment, miRNA sample preparation, and array profiling.

REFERENCES

- Mangi AA**, Christison-Lagay ER, Torchiana DF, Warshaw AL, Berger DL. Gastrointestinal complications in patients undergoing heart operation: an analysis of 8709 consecutive cardiac surgical patients. *Ann Surg* 2005; **241**: 895-901; discussion 901-904 [PMID: 15912039 DOI: 10.1097/01.sla.0000164173.05762.32]
- Haverich A**, Hagl C. Organ protection during hypothermic circulatory arrest. *J Thorac Cardiovasc Surg* 2003; **125**: 460-462 [PMID: 12658185 DOI: 10.1067/mtc.2003.291]
- Croome KP**, Kiaii B, Fox S, Quantz M, McKenzie N, Novick RJ. Comparison of gastrointestinal complications in on-pump versus off-pump coronary artery bypass grafting. *Can J Surg* 2009; **52**: 125-128 [PMID: 19399207]

- 4 **Dong GH**, Wang CT, Li Y, Xu B, Qian JJ, Wu HW, Jing H. Cardiopulmonary bypass induced microcirculatory injury of the small bowel in rats. *World J Gastroenterol* 2009; **15**: 3166-3172 [PMID: 19575498 DOI: 10.3748/wjg.15.3166]
- 5 **McMonagle MP**, Halpenny M, McCarthy A, Mortell A, Manning F, Kilty C, Mannion D, Wood AE, Corbally MT. Alpha glutathione S-transferase: a potential marker of ischemia-reperfusion injury of the intestine after cardiac surgery? *J Pediatr Surg* 2006; **41**: 1526-1531 [PMID: 16952586 DOI: 10.1016/j.jpedsurg.2006.05.017]
- 6 **Chen Q**, Kong L, Xu X, Geng Q, Tang W, Jiang W. Down-regulation of microRNA-146a in the early stage of liver ischemia-reperfusion injury. *Transplant Proc* 2013; **45**: 492-496 [PMID: 23498784 DOI: 10.1016/j.transproceed.2012.10.045]
- 7 **Wang N**, Zhou Y, Jiang L, Li D, Yang J, Zhang CY, Zen K. Urinary microRNA-10a and microRNA-30d serve as novel, sensitive and specific biomarkers for kidney injury. *PLoS One* 2012; **7**: e51140 [PMID: 23272089 DOI: 10.1371/journal.pone.0051140]
- 8 **Hsieh CH**, Jeng JC, Jeng SF, Wu CJ, Lu TH, Liliang PC, Rau CS, Chen YC, Lin CJ. MicroRNA profiling in ischemic injury of the gracilis muscle in rats. *BMC Musculoskelet Disord* 2010; **11**: 123 [PMID: 20553627 DOI: 10.1186/1471-2474-11-123]
- 9 **Chang KP**, Lai CS. Micro-RNA profiling as biomarkers in flap ischemia-reperfusion injury. *Microsurgery* 2012; **32**: 642-648 [PMID: 23097335 DOI: 10.1002/micr.22046]
- 10 **Chiu CJ**, McArdle AH, Brown R, Scott HJ, Gurd FN. Intestinal mucosal lesion in low-flow states. I. A morphological, hemodynamic, and metabolic reappraisal. *Arch Surg* 1970; **101**: 478-483 [PMID: 5457245 DOI: 10.1001/archsurg.1970.01340280030009]
- 11 **Biggar KK**, Dubuc A, Storey K. MicroRNA regulation below zero: differential expression of miRNA-21 and miRNA-16 during freezing in wood frogs. *Cryobiology* 2009; **59**: 317-321 [PMID: 19735650 DOI: 10.1016/j.cryobiol.2009.08.009]
- 12 **Truettner JS**, Alonso OF, Bramlett HM, Dietrich WD. Therapeutic hypothermia alters microRNA responses to traumatic brain injury in rats. *J Cereb Blood Flow Metab* 2011; **31**: 1897-1907 [PMID: 21505482 DOI: 10.1038/jcbfm.2011.33]
- 13 **Pilotte J**, Dupont-Versteegden EE, Vanderklish PW. Widespread regulation of miRNA biogenesis at the Dicer step by the cold-inducible RNA-binding protein, RBM3. *PLoS One* 2011; **6**: e28446 [PMID: 22145045 DOI: 10.1371/journal.pone.0028446]
- 14 **Qin H**, Chen GX, Liang MY, Rong J, Yao JP, Liu H, Wu ZK. The altered expression profile of microRNAs in cardiopulmonary bypass canine models and the effects of mir-499 on myocardial ischemic reperfusion injury. *J Transl Med* 2013; **11**: 154 [PMID: 23800236 DOI: 10.1186/1479-5876-11-154]
- 15 **Reddy AM**, Zheng Y, Jagadeeswaran G, Macmil SL, Graham WB, Roe BA, Desilva U, Zhang W, Sunkar R. Cloning, characterization and expression analysis of porcine microRNAs. *BMC Genomics* 2009; **10**: 65 [PMID: 19196471 DOI: 10.1186/1471-2164-10-65]
- 16 **Liu F**, Lou YL, Wu J, Ruan QF, Xie A, Guo F, Cui SP, Deng ZF, Wang Y. Upregulation of microRNA-210 regulates renal angiogenesis mediated by activation of VEGF signaling pathway under ischemia/perfusion injury in vivo and in vitro. *Kidney Blood Press Res* 2012; **35**: 182-191 [PMID: 22123256 DOI: 10.1159/000331054]
- 17 **Chang KP**, Lee HC, Huang SH, Lee SS, Lai CS, Lin SD. MicroRNA signatures in ischemia-reperfusion injury. *Ann Plast Surg* 2012; **69**: 668-671 [PMID: 23154340 DOI: 10.1097/SAP.0b013e3182742e45]
- 18 **Godwin JG**, Ge X, Stephan K, Jurisch A, Tullius SG, Iacomini J. Identification of a microRNA signature of renal ischemia reperfusion injury. *Proc Natl Acad Sci USA* 2010; **107**: 14339-14344 [PMID: 20651252 DOI: 10.1073/pnas.0912701107]
- 19 **Iliopoulos D**, Jaeger SA, Hirsch HA, Bulyk ML, Struhl K. STAT3 activation of miR-21 and miR-181b-1 via PTEN and CYLD are part of the epigenetic switch linking inflammation to cancer. *Mol Cell* 2010; **39**: 493-506 [PMID: 20797623 DOI: 10.1016/j.molcel.2010.07.023]
- 20 **Jiang L**, Cheng Z, Qiu S, Que Z, Bao W, Jiang C, Zou F, Liu P, Liu J. Altered let-7 expression in Myasthenia gravis and let-7c mediated regulation of IL-10 by directly targeting IL-10 in Jurkat cells. *Int Immunopharmacol* 2012; **14**: 217-223 [PMID: 22835429 DOI: 10.1016/j.intimp.2012.07.003]
- 21 **Spinelli SV**, Diaz A, D'Attilio L, Marchesini MM, Bogue C, Bay ML, Bottasso OA. Altered microRNA expression levels in mononuclear cells of patients with pulmonary and pleural tuberculosis and their relation with components of the immune response. *Mol Immunol* 2013; **53**: 265-269 [PMID: 22964481 DOI: 10.1016/j.molimm.2012.08.008]
- 22 **Majmundar AJ**, Wong WJ, Simon MC. Hypoxia-inducible factors and the response to hypoxic stress. *Mol Cell* 2010; **40**: 294-309 [PMID: 20965423 DOI: 10.1016/j.molcel.2010.09.022]
- 23 **Feinman R**, Deitch EA, Watkins AC, Abungu B, Colorado I, Kannan KB, Sheth SU, Caputo FJ, Lu Q, Ramanathan M, Attan S, Badami CD, Doucet D, Barlos D, Bosch-Marce M, Semenza GL, Xu DZ. HIF-1 mediates pathogenic inflammatory responses to intestinal ischemia-reperfusion injury. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G833-G843 [PMID: 20689059 DOI: 10.1152/ajpgi.00065.2010]
- 24 **Mahon PC**, Hirota K, Semenza GL. FIH-1: a novel protein that interacts with HIF-1alpha and VHL to mediate repression of HIF-1 transcriptional activity. *Genes Dev* 2001; **15**: 2675-2686 [PMID: 11641274 DOI: 10.1038/sj.emboj.7600196]
- 25 **Olaru AV**, Selaru FM, Mori Y, Vazquez C, David S, Paun B, Cheng Y, Jin Z, Yang J, Agarwal R, Abraham JM, Dassopoulos T, Harris M, Bayless TM, Kwon J, Harpaz N, Livak F, Meltzer SJ. Dynamic changes in the expression of MicroRNA-31 during inflammatory bowel disease-associated neoplastic transformation. *Inflamm Bowel Dis* 2011; **17**: 221-231 [PMID: 20848542 DOI: 10.1002/ibd.21359]
- 26 **Faraonio R**, Salerno P, Passaro F, Sedia C, Iaccio A, Bellelli R, Nappi TC, Comegna M, Romano S, Salvatore G, Santoro M, Cimino F. A set of miRNAs participates in the cellular senescence program in human diploid fibroblasts. *Cell Death Differ* 2012; **19**: 713-721 [PMID: 22052189 DOI: 10.1038/cdd.2011.143]
- 27 **Yoon S**, Choi YC, Lee S, Jeong Y, Yoon J, Baek K. Induction of growth arrest by miR-542-3p that targets survivin. *FEBS Lett* 2010; **584**: 4048-4052 [PMID: 20728447 DOI: 10.1016/j.febslet.2010.08.025]
- 28 **Thomas CJ**, Ng DC, Patsikatheodorou N, Limengka Y, Lee MW, Darby IA, Woodman OL, May CN. Cardioprotection from ischaemia-reperfusion injury by a novel flavonol that reduces activation of p38 MAPK. *Eur J Pharmacol* 2011; **658**: 160-167 [PMID: 21371449 DOI: 10.1016/j.ejphar.2011.02.041]
- 29 **Chen YJ**, Chang LS. Hydroquinone-induced miR-122 down-regulation elicits ADAM17 up-regulation, leading to increased soluble TNF- α production in human leukemic cells with expressed Bcr/Abl. *Biochem Pharmacol* 2013; **86**: 620-631 [PMID: 23791922 DOI: 10.1016/j.bcp.2013.06.009]
- 30 **Ye D**, Guo S, Al-Sadi R, Ma TY. MicroRNA regulation of intestinal epithelial tight junction permeability. *Gastroenterology* 2011; **141**: 1323-1333 [PMID: 21763238 DOI: 10.1053/j.gastro.2011.07.005]
- 31 **Chen Y**, Wang C, Liu Y, Tang L, Zheng M, Xu C, Song J, Meng X. miR-122 targets NOD2 to decrease intestinal epithelial cell injury in Crohn's disease. *Biochem Biophys Res Commun* 2013; **438**: 133-139 [PMID: 23872065 DOI: 10.1016/j.bbrc.2013.07.040]
- 32 **Esposito E**, Mazzon E, Muià C, Meli R, Sessa E, Cuzzocrea S. Splanchnic ischemia and reperfusion injury is reduced by genetic or pharmacological inhibition of TNF- α . *J Leukoc Biol* 2007; **81**: 1032-1043 [PMID: 17210619 DOI: 10.1189/jlb.0706480]
- 33 **Chen LW**, Chang WJ, Chen PH, Liu WC, Hsu CM. TLR ligand decreases mesenteric ischemia and reperfusion injury-induced gut damage through TNF- α signaling. *Shock* 2008; **30**: 563-570 [PMID: 18317407 DOI: 10.1097/SHK.0b013e31816a3458]
- 34 **Tetteh HA**. The role of HMGB1 in ischemia-reperfusion injury in the rat small intestine. *J Surg Res* 2013; **183**: 96-97 [PMID: 22560848 DOI: 10.1016/j.jss.2012.04.004]
- 35 **Galardi S**, Mercatelli N, Farace MG, Ciafrè SA. NF- κ B and c-Jun induce the expression of the oncogenic miR-221 and miR-222 in prostate carcinoma and glioblastoma cells. *Nucleic Acids Res* 2011;

- 39: 3892-3902 [PMID: 21245048 DOI: 10.1093/nar/gkr006]
- 36 **Chou WW**, Wang YT, Liao YC, Chuang SC, Wang SN, Juo SH. Decreased microRNA-221 is associated with high levels of TNF- α in human adipose tissue-derived mesenchymal stem cells from obese woman. *Cell Physiol Biochem* 2013; **32**: 127-137 [PMID: 23867206 DOI: 10.1159/000350131]
- 37 **El Gazzar M**, McCall CE. MicroRNAs distinguish translational from transcriptional silencing during endotoxin tolerance. *J Biol Chem* 2010; **285**: 20940-20951 [PMID: 20435889 DOI: 10.1074/jbc.M110.115063]
- 38 **Mallick IH**, Yang W, Winslet MC, Seifalian AM. Ischemia-reperfusion injury of the intestine and protective strategies against injury. *Dig Dis Sci* 2004; **49**: 1359-1377 [PMID: 15481305]
- 39 **Karhausen J**, Qing M, Gibson A, Moeser AJ, Griefingholt H, Hale LP, Abraham SN, Mackensen GB. Intestinal mast cells mediate gut injury and systemic inflammation in a rat model of deep hypothermic circulatory arrest. *Crit Care Med* 2013; **41**: e200-e210 [PMID: 23478660 DOI: 10.1097/CCM.0b013e31827cac7a]

P- Reviewer: Hwang KC, Nasir O, Tsai YH **S- Editor:** Ma YJ
L- Editor: Logan S **E- Editor:** Zhang DN





Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>



ISSN 1007-9327

