Effect of *Candida albicans* on Intestinal Ischemia-reperfusion Injury in Rats

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Abstract

Background: Inflammation is supposed to play a key role in the pathophysiological processes of intestinal ischemia-reperfusion injury (IIRI), and *Candida albicans* in human gut commonly elevates inflammatory cytokines in intestinal mucosa. This study aimed to explore the effect of *C. albicans* on IIRI.

Methods: Fifty female Wistar rats were divided into five groups according to the status of *C. albicans* infection and IIRI operation: group blank and sham; group blank and IIRI; group cefoperazone plus IIRI; group *C. albicans* plus cefoperazone and IIRI (CCI); and group *C. albicans* plus cefoperazone and sham. The levels of inflammatory factors tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, and diamine oxidase (DAO) measured by enzyme-linked immunosorbent assay were used to evaluate the inflammation reactivity as well as the integrity of small intestine. Histological scores were used to assess the mucosal damage, and the *C. albicans* blood translocation was detected to judge the permeability of intestinal mucosal barrier.

Results: The levels of inflammatory factors TNF-α, IL-6, and IL-1β in serum and intestine were higher in rats undergone both *C. albicans* infection and IIRI operation compared with rats in other groups. The levels of DAO (serum: 44.13 ± 4.30 pg/ml, intestine: 346.21 ± 37.03 pg/g) and Chiu scores (3.41 ± 1.09) which reflected intestinal mucosal disruption were highest in group CCI after the operation. The number of *C. albicans* translocated into blood was most in group CCI ([33.80 ± 6.60] ×10⁵ colony forming unit (CFU)/ml).

Conclusion: Intestinal *C. albicans* infection worsened the IIRI-induced disruption of intestinal mucosal barrier and facilitated the subsequent *C. albicans* translocation and dissemination.

Key words: *Candida albicans*; Infection; Inflammation; Intestinal Mucosa Barrier; Ischemia-reperfusion Injury

INTRODUCTION

Intestinal ischemia-reperfusion injury (IIRI) in human is a frequent event entailing high morbidity and mortality, representing a pivotal complication in many clinical cases and surgical procedures such as small bowel transplantation, cardiopulmonary bypass, strangulated hernias, abdominal aortic aneurysm surgery, and neonatal necrotizing enterocolitis. Ischemia-reperfusion (IR) is detrimental to the intestine not only for disrupted nutrient absorption by the mucosa but also for damaged barrier integrity, leading to possible translocation of pathogenic microorganisms across the gut wall and consequently systemic sepsis. As an essential part of the intestinal mucosa, epithelial enterocytes and tight junction proteins are vulnerable to IIRI, causing inflammatory activation of the innate immune response. Inflammatory factors, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β, are produced in the intestine during IIRI and contribute to a local and systemic inflammatory response, leading to damages to local and remote organs, such as gastrointestinal (GI) tract and lungs, causing multiple organ failure and death, resulting in up to 80% mortality.

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**Candida albicans** is an opportunistic fungal pathogen commonly found in human GI tract.[5] Under physiological conditions, there is a dynamic balance between microorganisms in the intestinal lumen and the multifactorial host defense mechanisms. However, when the balance is lost, yeast can break through the intestinal mucosal barrier and cause invasive candidiasis and candidemia.[7] In many clinical cases, such as excessive use of antibiotics, immunosuppression, and organ transplantation, the load of **C. albicans** in GI tract would rise rapidly. The fungal infection was accompanied by the significant elevation of inflammatory cytokines.[8] Early during **C. albicans** infection, inflammatory cytokines such as TNF-α, IL-6, and IL-1β participate in the control of fungus.[9] However, these inflammatory cytokines produced in IIRI also participated in organ disruption.[5] Recent microbiological studies have been focused on the pathogenic roles of intestinal bacteria in IIRI; however, the presence and activity of fungi have not been extensively studied. Marotta et al. had shown that protein-calorie malnutrition aggravates the gut translocation of **C. albicans** triggered by mesenteric IR injury in a mice model.[10] However, whether **C. albicans** in GI tract would aggravate IIRI and systemic inflammatory response syndrome (SIRS) has puzzled the researchers for years. Therefore, the present study aimed to explore the effect of inflammation caused by intestinal **C. albicans** infection on the pathophysiology of IIRI.

**Methods**

**Experimental animals and grouping**

**Animals**

The experimental protocol and procedures used in this study were approved by the Experimental Animal Ethics Committee of Fudan University, and in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Fifty specific pathogen-free female Wistar rats (body weight, 170–220 g) were collectively housed in cages in the experimental room for at least 3 days before the start of the experiments (male rats are prone to fight with each other, which would result in trauma and infection and affect the results of research). The rats were maintained at 22°C under a 12:12 h light–dark cycle. They were provided with clean laboratory diet and tap water ad libitum and housed in a clean-air and pathogen-free room with restricted access.

**Experimental design**

The rats were randomly assigned to five treatment groups according to computer-generated random numbers as the following:

I. Blank and sham (BS) (n = 10): Rats were given purified water during the entire experiment. They were exposed to laparotomy without clamping the superior mesenteric artery (SMA) when undergoing surgery on the 16th day.

II. Blank and IIRI (BI) (n = 10): Rats were given purified water during the entire experiment. On the 16th day, they were exposed to laparotomy with occlusion of the SMA for 60 min, followed by 120 min of reperfusion period.

III. Cefoperazone plus IIRI (CI) (n = 10): Rats were given 2% cefoperazone in drinking water from the 1st to 16th day.[11] On the 16th day, they were exposed to laparotomy with occlusion of the SMA for 60 min, followed by 120 min of reperfusion period.

IV. **C. albicans** plus cefoperazone and IIRI (CCI) (n = 10): Rats were given 2% cefoperazone in drinking water from the 1st to 16th day. They were inoculated with 1 ml 0.9% NaCl containing 10^6 CFU live **C. albicans** cells by oral gavage on the 5th day. On the 16th day, they were exposed to laparotomy with occlusion of the SMA for 60 min, followed by 120 min of reperfusion period.

V. **C. albicans** plus cefoperazone and sham (CCS) (n = 10): Rats were given 2% cefoperazone in drinking water from the 1st to 16th day. They were inoculated with 1 ml 0.9% NaCl containing 10^6 CFU live **C. albicans** cells by oral gavage on the 5th day and were exposed to laparotomy without clamping the SMA when undergoing surgery on the 16th day.

**Microorganism**

**C. albicans** isolates (American Type Culture Collection [ATCC] 10231) were obtained from the ATCC. All of the microorganisms were cultured aerobically at 37°C for 48 h. At the end of the incubation, microorganisms were harvested by centrifugation, washed three times in 0.9% NaCl, and adjusted to a concentration of 10^8 colony forming unit (CFU)/ml in 0.9% NaCl.

**Rat model of intestinal ischemia-reperfusion injury**

During all the procedures, the animals had spontaneous breathing and the body temperature was maintained at 37°C using a water-circulating heating pad. A midline laparotomy was performed under deep anesthesia with sodium pentobarbital. The SMA was identified and isolated; then, a small nontraumatic vascular clamp was applied for 1 h.[12-13] Ischemia was recognized by lack of pulse or by pale color of the intestine. After the ischemic phase, the clamp was removed and the intestine was allowed to reperfusion for 2 h. The return of the pulses, the reestablishment of the pink color, and enhanced intestinal peristalsis were taken as the signs of intestinal reperfusion. In BS and CCS groups, SMA was isolated but not clamped. After 2 h, the blood and small intestine were sampled for analysis.

**Histologic changes of intestinal mucosa and injury score**

After sacrifice of the animals, the removed small intestinal tissue samples were immediately fixed in 10% neutral-buffered formalin, embedded in paraffin, and sectioned. The sections were processed by hematoxylin-eosin (HE) staining and examined under light microscopy. Histological scores were evaluated by two independent investigators who were blind to the grouping; two sections were observed per rat. The degree of histopathological changes was graded semiquantitatively using the histological injury scale described by Chiu et al.[14] as follows: 0 - normal mucosal villi; 1 - development of...
Figure infected animals, the presence of fungal were observed infiltrating in the mucosal epithelial layer [14]. The intestine of rats in group BS displayed smooth mucosal inflammation and injury score statistically significant if the total tissues and blood were compared between groups. The percentages of culture-positive samples among the homogenized tissues and blood were plated on Sabouraud dextrose agar (Bianzhen Biological Technology, Nanjing, China). Colonies of C. albicans were observed after 48-h incubation at 37°C. To obtain Colony-Forming Units, we calculated the number of colonies on the medium.

Measurement of inflammatory mediators and diamine oxidase
After 120 min of removing of the vascular clamp, blood was collected into heparinized tubes and plasma was isolated via centrifugation (3000 ×g for 10 min). As soon as the experimental rats were sacrificed, their intestinal tissues were quickly removed and cleaned with phosphate-buffered saline (PBS). The tissues were homogenized with PBS and centrifuged at 3000 ×g for 10 min. The tissue supernatants and plasma were stored at −20°C until further assays, respectively. The levels of TNF-α, IL-6, IL-1β, and diamine oxidase (DAO) were determined by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer’s instructions (R&D, USA), and the concentrations of cytokines were determined spectrophotometrically by the absorbance at 450 nm. A standard curve was constructed using the cytokine standards available in the ELISA kit. The cytokine concentrations for unknown samples were calculated according to the standard curve.

The presence of Candida albicans in gastrointestinal tract and blood
The homogenized tissues and blood were plated on Sabouraud dextrose agar (Bianzhen Biological Technology, Nanjing, China). Colonies of C. albicans were observed after 48-h incubation at 37°C. To obtain Colony-Forming Units, we calculated the number of colonies on the medium.

Statistical methods
Data were entered and analyzed using Statistical Package for Social Sciences version 21.0 (IBM, USA, New York). All data were presented as means ± standard error (SE). If the data of cytokines met the standards of both normal distribution and homogeneity of variance, they were analyzed by the one-way analysis of variance with the least significant difference test used as post hoc analysis. Otherwise, they were analyzed using Kruskal–Wallis test followed by post hoc Wilcoxon rank-sum tests and Bonferroni correction. The percentages of culture-positive samples among the total tissues and blood were compared between groups with Fisher’s exact test. Differences were considered to be statistically significant if the P < 0.05.

Results
Mucosal inflammation and injury score
The intestine of rats in group BS displayed smooth villus and healthy glands with few inflammatory cells infiltrating in the mucosal epithelial layer [Figure 1a]. Compared with sham groups, damaged intestinal wall, loss of villous structure, and severe necrosis were observed in group BI [Figure 1b]. The rats of group CCI showed denuded villi, ulceration, hemorrhage, and inflammatory cells infiltrating near the basement membrane of the intestine [Figure 1d]. Hence, the mucosal injury scores were highest in group CCI. Animals in group CI exhibited milder mucosal damage than those in group CCI whereas the lifting of epithelial layer from lamina propria and the ulceration were still observed [Figure 1c].

Consistent with the histologic changes of intestinal mucosa, the intestinal injury scores were significantly higher in IIRI groups compared with sham groups, and infection of C. albicans increased the histologic scores [Figure 1f].

In Candida-infected animals, the presence of fungal hyphae indicated the colonization of fungi in the intestinal mucosa [Figure 1, arrows]. Infectious C. albicans hyphae were present in the lumen in groups CCS, CCI, and CI [Figure 1d and 1e]. Taking advantage of the disruption of intestinal mucosa after IIRI, some fungi, in the form of hyphae or pseudohyphae, even invaded into small intestinal wall, laying the foundation for the subsequent candidemia and disseminated candidiasis.

Changes of inflammatory mediators and diamine oxidase
Inflammatory cytokines such as TNF-α, IL-6, and IL-1β may
be important mediators in IIRI and may also contribute to the defense mechanisms of the host in response to *C. albicans* infection.\[^{[5,9]}\] As shown in Figure 2, the levels of TNF-α, IL-6, and IL-1β in serum and intestinal tissue significantly increased after IIRI compared with those in sham groups. Excessive *C. albicans* infection in the gut increased the serum and intestinal IL-6 and TNF-α compared to the blank groups (IL-6: \(\mu = 5.11, 3.21\); TNF-α: \(\mu = 4.30, 3.23\), \(P < 0.01\)) [Figure 2a, 2b, 2e, and 2f]. We found that the levels of IL-1β in serum from the *C. albicans* infection group (CCS: 10.28 ± 1.07 pg/ml) were similar to those in the blank group (BS: 9.88 ± 1.16 pg/ml) [Figure 2c]. With the double strikes of IIRI and *C. albicans* infection, the levels of TNF-α, IL-6, and IL-1β in both serum and intestine increased significantly in group CCI than that of other groups. However, no statistical difference was found in TNF-α and IL-6 was found between groups CI and BI (IL-6: \(\mu = 1.11, 1.27\); TNF-α: \(\mu = 0.73, 1.23, P > 0.01\)).

DAO is an enzyme synthesized primarily in GI mucosal cells, and the level of DAO has been used as an indicator of the integrity and functional mass of the intestinal mucosa.\[^{[15-17]}\] Compared with groups BS (10.43 ± 3.56 pg/ml, 94.82 ± 4.12 pg/g) and CCS (12.03 ± 2.14 pg/ml, 96.52 ± 5.24 pg/g), the serum and intestinal DAO activity significantly increased in groups BI (38.47 ± 1.49 pg/ml, 297.93 ± 18.70 pg/g), CI (36.47 ± 5.70 pg/ml, 282.51 ± 35.50 pg/g), and CCI (44.13 ± 4.30 pg/ml, 346.21 ± 37.03 pg/g). However, no statistical difference was found between CI and BI groups (\(\mu = 0.75, 1.06, P > 0.05\)). Meanwhile, *C. albicans* infection seemed to have no significant influence on the levels of DAO in group CCS compared with group BS (\(\mu = 1.51, 0.69, P > 0.05\)) [Figure 3].

**Presence of Candida albicans in gastrointestinal tract and blood**

After 48-h incubation at 37°C, pure *C. albicans* was isolated...
from the intestines of all rats in groups CCS, CCI, and CI. The rates of positive-culture from blood of groups CCS, CCI, and CI were 10%, 40%, and 20%, respectively. As for groups BS and BI, C. albicans was not isolated from either intestine or blood [Figure 4]. The number of C. albicans colonies in blood and intestine is shown in Table 1.

**DISCUSSION**

In this research, intestinal C. albicans infection increased the inflammatory factors, such as TNF-α, IL-6, and IL-1β, worsened the IRI-induced disruption of intestinal mucosal barrier, had a bad influence on the damaged intestinal mucosa, and facilitated the subsequent C. albicans dissemination. This devastating effect could be found in pathological changes of intestine, e.g., inflammatory cells accumulated in the areas infected by C. albicans. As a result, C. albicans broke through intestinal mucosa barrier and translocated into blood.

II RI in human is a common event in a variety of clinical conditions, such as small bowel transplantation, trauma, burn injuries, septic shock, and heart and aortic surgery. The pathophysiological processes of IRI in vivo are complex, and inflammation may play an important role. Our results showed that the levels of TNF-α, IL-6, and IL-1β increased sharply after IIRI in rats. Previous researches have shown that in the early stages of IRI, the production of oxygen-free radicals causes polymorphonuclear neutrophils (PMN) activation and inflammatory cytokine production. The activation of PMN and inflammatory cytokines further lead to the release of oxygen-free radicals, thereby contributing to intestinal injury. Inflammation involves a sequential activation of signaling pathways which results in the production of pro- and anti-inflammatory mediators during IIRI. Among the proinflammatory mediators, TNF-α and TNF-αR1 systems play central roles in the physiological regulation of intestinal barrier function and TNF-α can induce intestinal epithelial barrier dysfunction. TNF-α also acts as an initiator to induce the expression of other cytokines such as IL-6. IL-6 and IL-1β are a triad of cytokines involved in inflammation and innate response activation triggered by tissue damage. Meanwhile, IL-1β is considered as a marker of acute inflammation, resulting in the activation of macrophages during early stages of tissue injury. These cytokines all play important roles in the pathophysiology of IIRI, which could explain the sharp increase of cytokines after IIRI compared with sham groups.

In this study, cefoperazone was added into drinking water to inhibit intestinal commensal bacteria, which might create proper conditions for C. albicans proliferation. Meanwhile, our research showed that...
IIRI strongly promoted *C. albicans* infection [Figure 4 and Table 1]. Conversely, *C. albicans* augments the inflammation after IIRI too [Figure 2]. Galectin-3 is an intestinal lectin that binds to specific *C. albicans* glycans and involved in inflammation.[23] Compared with rats in Group BS, *C. albicans* infection in group CCS triggered TNF-α, IL-6, and IL-1β expression and production. It is suggested that these cytokines contribute to the defense mechanisms of the host in response to microbial colonization and invasion.[25-28] TNF-α is one of the major secretory products of macrophages with an important role in host defense against disseminated candidiasis.[29,30] IL-1β is an important proinflammatory cytokine that is required for the induction of immune responses involving IL-17-producing helper T-cells that are integral to antifungal defense by mobilizing neutrophils.[28] IL-6 is a regulator of the cellular response to *C. albicans* infection, which may have a proinflammatory effect by inhibiting the suppressor activity of CD4+ CD25+ regulatory T-cells or by affecting the differentiation of T lymphocytes to IL-17-producing T-cells.[31-33] In view of the complex role of cytokines in the host defenses against infection and in the tissue-destructive effects of inflammation on the hosts, we sought to explore their effect on aggravating IRI of intestine with *C. albicans* infection. In our research, the levels of TNF-α, IL-6, and IL-1β reached the highest values in animals under both *C. albicans* infection and IIRI operation. Compared with rats in the CCS group, rats in CCI group also got IIRI operation; therefore, the intestinal inflammation and pathological results of group CCI showed the additional effect of IIRI.

Our studies also suggested that *C. albicans* enteral infection may aggravate local or SIRS after IIRI, which would have a bad influence on the recovery of damaged intestinal mucosa and increase mortality of patients after operation. This devastating effect could be found in pathological changes of intestine, e.g., inflammatory cells accumulated in the areas infected by *C. albicans*.[18] Histological evaluation of the disruption of intestinal mucosal barrier [Figure 1] showed that the histological damage index reached the highest values in animals suffered from both *C. albicans* infection and IIRI [Figure 1].

DAO regulates cell proliferation through degradation of polyamine, an indispensable substance for mitosis and meiosis. DAO also rapidly detoxifies dietary histamine, preventing the allergy-like symptoms of histamine excess.[16,17] The activity of DAO is associated with the maturation and integrity of small intestinal mucosa.[16,17] In our study, with the increase of inflammation mediators, the levels of DAO reached the peak in group CCI after IIRI. As similar to histological damage index, the levels of DAO increased in IIRI groups compared with the sham groups.

Results of experimental studies indicated that significant *C. albicans* infection of the rat intestine would aggravate the disruption of intestinal mucosal barrier after IIRI, and this effect could attribute to the aggravation of inflammatory reaction. Meanwhile, systemic inflammation would also increase intestinal permeability.[19] In addition, IIRI damages the integrity of intestinal barrier. The disruption of intestinal barrier would be a sally port for the pathogenic microorganism to invade into blood and translocate to the distant organs. Therefore, in this research, blood *C. albicans* cultures were positive in groups CCI and C1. The preoperative anesthetics might also decrease the intestinal blood flow, resulting in aggravated disruption and delayed recovery of intestinal mucosa.[15] Therefore, an increase in intestinal permeability due to anesthetics might explain the systemic invasion of *C. albicans* in group CCS. With the double blow of IRI operation, the load of *C. albicans* in the blood in group CCI would be more than those in other groups at the same time point [Table 1].

Several limitations were encountered in our study. First of all, in our research, *C. albicans* intestinal infection trigger inflammation was on the contrary to previous reports by Mason et al.[30] A major reason is that Mason et al. only examined HE-stained histological samples of intestine without detecting inflammatory mediator. Hence, they believe that colonization with *C. albicans* during antibiotic treatment does not trigger overt inflammation in the murine cecum. Besides, *C. albicans* load in the intestine in our research is much more than that in research by Mason et al. Second, the short term *C. albicans* colonization in the rat model does not correctly reflect the situation of clinical patients. Indeed, the amount of *C. albicans* in intestine cannot be substantially sustained over time in patients as already described elsewhere.[37] Further prospective study to elucidate the role of *C. albicans* might be needed in the clinical field. Finally, the precise microbial and host factors which favor *C. albicans* as a cause of GI and systemic candidiasis were not studied.

In conclusion, the results of our experimental studies demonstrated that a significant fungal infection of the intestinal mucosa could aggravate the disruption of intestinal mucosal barrier after IIRI and facilitate the subsequent translocation and dissemination of *C. albicans*. Our study indicated that ecological imbalance in the intestinal flora may worsen IIRI and facilitate the development of SIRS. However, more detailed researches are needed to further elucidate the molecular mechanism underlying the disruption of intestinal mucosal barrier and the enterogenous invasion of *C. albicans* during IIRI.

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Conflicts of interest

There are no conflicts of interest.

References

1. Grootjans J, Lenaerts K, Derikx JP, Matthijisen RA, de Bruïne AP, van Bijnen AA, et al. Human intestinal ischemia-reperfusion-induced inflammation characterized: Experiences from a new translational model. Am J Pathol 2010;176:2283-91. doi: 10.2353/ajpath.2010.091069.

2. Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. Anesthesiology 2001;94:1133-8. doi: 10.1097/00000542-200106000-00030.

3. Erling Junior N, Montero EF, Sanomiyami P, Poli-de-Figueiredo LF. Local and remote ischemic preconditioning protect against intestinal ischemic/reperfusion injury after supraceliac aortic clamping. Clinics (Sao Paulo) 2013;68:1548-54. doi: 10.6061/clinics(2013(12)12.

4. Tsoulfas G, Agorastou P. Ischemia reperfusion injury and the immune system. J Surg Res 2014;186:114-5. doi: 10.1016/j.jss.2013.05.094.

5. Tóth S Jr., Pekárová T, Varga J, Tomceková V, Tóth S, Lakový L, et al. Trehalase as a possible marker of intestinal candidiasis – Reperfusion injury. Acta Biochim Pol 2013;60:411-6.

6. Nucci M, Anaissie E. Revisiting the source of candidemia: Skin or gastrointestinal tract? Arch Surg 2006;141:E53-4. doi: 10.1001/archsurg.141.9.e53.

7. Yan L, Yang C, Tang J. Disruption of the intestinal mucosal barrier during ischemia-reperfusion injury supervening on protein-calorie malnutrition. Chin J Dig Dis 2006;7:33-8. doi: 10.1111/j.1443-9573.2006.00241.x.

8. Rodriguez-Galán MC, Sotomayor C, Costamagna ME, Cabanillas AM, Marotta F, Barreto R, Kawakita S, Minelli E, Pavasuthipaisit K, et al. Colonization of mice by Candida albicans in late-onset neonatal sepsis. Mycoses 2011;54:212-6. doi: 10.1111/j.1.8764-0674.00375-7.

9. Yang X, Bai H, Cai W, Li J, Zhou Q, Wang Y, et al. Lycium barbarum polysaccharides reduce intestinal ischemia/reperfusion injuries in rats. Chem Biol Interact 2013;204:166-72. doi: 10.1016/j.cbi.2013.05.010.

10. Mallick H, Yang W, Winslet MC, Seifalian AM. Ischemia-reperfusion injury of the intestine and protective strategies against injury. Dig Dis Sci 2004;49:1539-77. doi: 10.1023/B:DDAS.0000002322.98927.91.

11. Shen ZY, Zhang J, Song HL, Zheng WP. Bone-marrow mesenchymal stem cells reduce rat intestinal ischemia-reperfusion injury, ZO-1 downregulation and tight junction disruption via a TNF-a-regulated mechanism. World J Gastroenterol 2013;19:3583-95. doi: 10.3748/wjg.v19.i23.3583.

12. Cicora F, Roberti J, Lasauda N, González P, Guerrieri D, Stringa P, et al. Donor preconditioning with rabbit anti-rat thymocyte immunoglobulin ameliorates ischemia reperfusion injury in rat kidney transplantation. Transpl Immunol 2012;27:1-7. doi: 10.1016/j.trim.2012.03.004.

13. Fukumoto I, Kobayashi M, Dabanaka K, Maeda H, Okamoto K, Okabayashi T, et al. Diamine oxidase as a marker of intestinal mucosal injury and the effect of soluble dietary fiber on gastrointestinal tract toxicity after intravenous 5-fluorouracil treatment in rats. Med Mol Morphol 2014;47:100-7. doi: 10.1007/s00795-013-0555-7.

14. Deng Y, Ren X, Yang L, Lin Y, Wu X. A JNK-dependent pathway is required for TNFalpha-induced apoptosis. Cell 2003;115:61-70. doi: 10.1016/S0092-8674(03)00757-7.

15. Liu XH, Yang YW, Dai HT, Cai SW, Chen RH, Ye ZQ. Protective immunocompetence of Candida albican cell wall. Cell Immunol 1991;134:65-76. doi: 10.1016/0092-8674(91)90054-P.

16. Tóth S Jr., Pekárová T, Varga J, Tomceková V, Tóth S, Lakový L, et al. Trehalase as a possible marker of intestinal candidiasis – Reperfusion injury. Acta Biochim Pol 2013;60:411-6.

17. Rodriguez-Galán MC, Sotomayor C, Costamagna ME, Cabanillas AM, Rentería BS, Masini-Repiso AM, et al. Role of adiponectin in a rat model of intestinal ischemia reperfusion injury. J Microbiol Immunol Infect 2011;44:369-75. doi: 10.1016/j.jmii.2010.08.010.

18. Vecchiarelli A, Puliti M, Torosantucci A, Cassone A, Bistoni F. In vitro production of tumor necrosis factor by murine splenic macrophages stimulated with mannoprotein constituents of Candida albicans cell wall. Cell Immunol 1991;134:65-76. doi: 10.1016/0092-8674(91)90031-5.

19. Grootjans J, Lenaerts K, Derikx JP, Matthijisen RA, de Bruïne AP, van Bijnen AA, et al. Human intestinal ischemia-reperfusion-induced inflammation characterized: Experiences from a new translational model. Am J Pathol 2010;176:2283-91. doi: 10.2353/ajpath.2010.091069.

20. Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. Anesthesiology 2001;94:1133-8. doi: 10.1097/00000542-200106000-00030.

21. Erling Junior N, Montero EF, Sanomiyami P, Poli-de-Figueiredo LF. Local and remote ischemic preconditioning protect against intestinal ischemic/reperfusion injury after supraceliac aortic clamping. Clinics (Sao Paulo) 2013;68:1548-54. doi: 10.6061/clinics(2013(12)12.

22. Tsoulfas G, Agorastou P. Ischemia reperfusion injury and the immune system. J Surg Res 2014;186:114-5. doi: 10.1016/j.jss.2013.05.094.

23. Rodriguez-Galán MC, Sotomayor C, Costamagna ME, Cabanillas AM, Rentería BS, Masini-Repiso AM, et al. Role of adiponectin in a rat model of intestinal ischemia reperfusion injury. J Microbiol Immunol Infect 2011;44:369-75. doi: 10.1016/j.jmii.2010.08.010.

24. Vecchiarelli A, Puliti M, Torosantucci A, Cassone A, Bistoni F. In vitro production of tumor necrosis factor by murine splenic macrophages stimulated with mannoprotein constituents of Candida albicans cell wall. Cell Immunol 1991;134:65-76. doi: 10.1016/0092-8674(91)90031-5.

25. Gringhuis SI, Kaptein TM, Wevers BA, Theelen B, van der Vlist M, Boekhout T, et al. Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1ß via a noncanonical caspase-8 mechanism. J Immunol 2008;180:972-80. doi: 10.4049/jimmunol.1000789.

26. Zhou J, Guo J, Jiang T, Li Q, Wang X, et al. Local and remote ischemic preconditioning protect against intestinal ischemia-reperfusion injury in rats. J Int J Exp Med 2015;8:1768-79.

27. Chiu CJ, McArindle AH, Brown R, Scott HJ, Gurd FN. Intestinal mucosal lesion in low-flow states. I. A morphological, hemodynamic, and metabolic reappraisal. Arch Surg 1970;101:478-83. doi: 10.1001/archsurg.1970.01304280030009.

28. Wang SH, Ling YH, Li Y, Li C, Liu JX, Li YS, et al. Ischemic postconditioning during reperfusion attenuates oxidative stress and intestinal mucosal apoptosis induced by intestinal ischemia/reperfusion via aldose reductase. Surgery 2013;153:555-64. doi: 10.1016/j.surg.2012.09.017.

29. Calinescu C, Mondovi B, Federico R, Ispas-Szabo P, Mateescu MA. Carbosxymethyl starch: Chitosan monolitic matrices containing diamine oxidase and catalase for intestinal delivery. Int J Pharm 2012;428:48-56. doi: 10.1016/j.ijpharm.2012.02.032.
recruitment during inflammation. Trends Immunol 2003;24:25-9. doi: 10.1016/S1471-4906(02)00013-3.
34. Schäper J, Wagner A, Enigk F, Brell B, Mousa SA, Habazettl H, et al. Regional sympathetic blockade attenuates activation of intestinal macrophages and reduces gut barrier failure. Anesthesiology 2013;118:134-42. doi: 10.1097/ALN.0b013e3182784c93.
35. Tverskoy M, Gelman S, Fowler KC, Bradley EL. Intestinal circulation during inhalation anesthesia. Anesthesiology 1985;62:462-9. doi: 10.1097/00000542-198504000-00015097/0000542-198504000-00015.
36. Mason KL, Erb Downward JR, Mason KD, Falkowski NR, Eaton KA, Kao JV, et al. Candida albicans and bacterial microbiota interactions in the cecum during recolonization following broad-spectrum antibiotic therapy. Infect Immun 2012;80:3371-80. doi: 10.1128/IAI.00449-12.
37. Spanakis EK, Kourkoumpetis TK, Livanis G, Peleg AY, Mylonakis E. Statin therapy and decreased incidence of positive Candida cultures among patients with type 2 diabetes mellitus undergoing gastrointestinal surgery. Mayo Clin Proc 2010;85:1073-9. doi: 10.4065/mcp.2010.0447.