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Effects of oxaliplatin on inflammation and intestinal floras in rats with colorectal cancer

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Abstract. – OBJECTIVE: The aim of this study was to investigate the effects of oxaliplatin on intestinal floras, inflammation level, apoptosis-related gene expressions and oxidative stress in rats with colorectal cancer.

MATERIALS AND METHODS: A total of 30 adult Sprague-Dawley (SD) rats were selected as research objects and were divided into control group, model group and oxaliplatin group. Rats in control group were raised normally, without any treatment. Rats in model group were subcutaneously injected with dimethylhydrazine (25 mg/kg) to establish the model of colorectal cancer. Meanwhile, rats in oxaliplatin group were injected with oxaliplatin (15 mg/kg) once every 2 weeks for 12 consecutive weeks. Peripheral blood, intestinal tumor tissues and feces were collected from rats. In addition, inflammatory indexes [tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), interleukin-4 (IL-4) and IL-1β], oxidative stress indexes [catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH) and total antioxidant capacity (T-AOC)], expressions of apoptosis-related genes [apoptotic protease activating factor-1 (Apaf1), Caspase-9, Survivin and B-cell lymphoma-2 (Bcl-2)] and intestinal floras were detected.

RESULTS: The abundance of microorganisms such as *Sphaerobacterales, Adlercreutzia* and *Coriobacterium glomerans* increased significantly in the intestines in control group ($p<0.05$). However, the abundance of *Bifidobacterium, Rikenellaceae* and *Paraprevotella* in the intestines was obviously higher in model group ($p<0.05$). Oxaliplatin group exhibited remarkably higher abundance of such microorganisms as *Cyanobacteria, Alistipes* and *Metascardovia* in rat intestines ($p<0.05$). The content of Alistipes was the highest in oxaliplatin group, followed by control group and model group, and the difference was statistically significant ($p<0.05$). The levels of serum TNF-α, CRP and IL-1β were remarkably higher in model group than those in control group ($p<0.05$). Oxaliplatin group exhibited notably lower levels of serum TNF-α, CRP and IL-1β ($p<0.05$) and higher IL-4 level than model group ($p<0.05$). The content of serum CAT, SOD, GSH and T-AOC was markedly elevated in model group compared with control group ($p<0.05$). However, it was significantly reduced in oxaliplatin group in comparison with model group ($p<0.05$). Compared with control group, model group had distinctly lower expressions of Apaf1, Caspase-9 and Survivin but an evidently higher expression level of Bcl-2 in tumor tissues ($p<0.05$). Moreover, the expressions of Apaf1, Caspase-9 and Survivin were clearly higher, while that of Bcl-2 was prominently lower in tumor tissues in oxaliplatin group than model group ($p<0.05$).

CONCLUSIONS: Oxaliplatin exerts significant effects on the inflammation, oxidative stress, apoptosis-related genes and intestinal floras in rats with CRC.

Key Words:
Colorectal cancer, Intestinal floras, Oxaliplatin.

Introduction

Colorectal cancer (CRC) is the most common tumor in the digestive tract, whose morbidity and mortality rates rank top five among all the tumors worldwide[1,2]. In China, however, the morbidity rate of colorectal cancer ranks third, which is higher than the average level. Meanwhile, it has shown a constantly increasing trend[3,4]. Due to the low prevalence rate of early diagnosis and screening, colorectal cancer has already been in the advanced stage when first diagnosed and it is difficult to be treated[5,6]. Therefore, searching for efficacious therapeutic methods for CRC can significantly reduce the number of deaths and lower its mortality rate.

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Oxaliplatin, a new third generation platinum anti-tumor drug, has been proven to exert favorable therapeutic effects on multiple tumors[7]. Oxaliplatin can be used in the treatment of patients with CRC, meanwhile, it is an adjunctive drug therapy for operation[8]. Current studies[9,10] have shown that such a drug can help improve the effect of colorectal cancer surgery, which is certainly effective for advanced cases. Nevertheless, the specific action mechanism of oxaliplatin in colorectal cancer has not been clarified yet.

In the present study, 30 adult Sprague-Dawley (SD) rats were selected as research objects. Meanwhile, they were prepared into models of colorectal cancer by subcutaneous injection with dimethylhydrazine (25 mg/kg). After treatment with oxaliplatin injection (15 mg/kg), changes in the composition and proportion of intestinal floras were compared among groups. The influences of oxaliplatin on rats with colorectal cancer were explored combined with the levels of inflammatory indexes [tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), interleukin-4 (IL-4) and IL-1β], oxidative stress indexes [catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH) and total antioxidant capacity (T-AOC)] and expressions of apoptosis-related genes [apoptotic protease activating factor-1 (Apaf1), Caspase-9, Survivin and B-cell lymphoma-2 (Bcl-2)]. All our findings might help to provide a solid theoretical basis for the clinical treatment of colorectal cancer with oxaliplatin.

Materials and Methods

Grouping of Laboratory Animals

A total of 30 Specific Pathogen Free (SPF)-grade male Sprague-Dawley (SD) rats (280-320 g) provided by the Laboratory Animal Center of the university were enrolled as research objects in this study. All rats were routinely fed according to standardized processes, and the food and padding were replaced by special personnel. All rats were randomly divided into 3 groups, with 10 rats in each group. This investigation was approved by the Animal Ethics Committee of Shandong University Animal Center.

Establishment of Model

Rats were randomly assigned into three groups, including control group, model group and oxaliplatin group. Rats in control group were raised routinely. In model group, dimethylhydrazine (25 mg/kg) (Sigma-Aldrich, St. Louis, MO, USA) was subcutaneously injected into the neck and back of rats once a week for 1 month to establish the model of CRC. Based on the treatment in model group, rats in oxaliplatin group were injected with oxaliplatin (15 mg/kg) (Sigma-Aldrich, St. Louis, MO, USA) once every 2 weeks for 3 months.

Detection of Intestinal Floras

Feces of rats in control group, model group and oxaliplatin group was first collected and frozen in liquid nitrogen. All collected samples were sent to TinyGen Biotechnology Co., LTD (TinyGen, Shanghai, China) for analysis and detection of intestinal microorganisms in rats. Genomic deoxyribonucleic acid (DNA) was extracted from the microorganisms and amplified, and the genomic DNA database was established. Subsequently, the genomic DNA was labeled and subjected to high-throughput sequencing using Illumina MiSeq and Ion Torrent PGM. Next, the category and relative abundance of microorganisms in feces samples in each group were tested and analyzed. Bioinformatics analysis was conducted on Galaxy website (http://huttenhower.sph.harvard.edu/galaxy/). Experimental data of intestinal floras in each group were uploaded to the website and analyzed using linear discriminant analysis (LDA) effect size (LEfSe). The composition of intestinal floras in each group was finally detected and visualized.

Detection of Inflammatory Indexes and Oxidative Stress Indexes

Enzyme-linked immunosorbent assay (ELISA) was applied to determine the changes in the content of inflammatory indexes TNF-α, CRP, IL-4 and IL-1β in control group, model group and oxaliplatin group. The content of these molecules in the serum was analyzed strictly according to the instructions of commercial ELISA kits (BD, Franklin Lakes, NJ, USA). Specifically, peripheral blood of rats in control group, model group and oxaliplatin group were centrifuged at 3,500 rpm for 5 min. The supernatant was taken for detection. With 4 replicate wells in each group, absorbance at 450 nm was detected using a micro-plate reader (Bio-Rad, Hercules, CA, USA). Next, it was converted into actual concentrations of TNF-α, CRP, IL-4 and IL-1β by means of standard curves. Fur-

thermore, oxidative stress indexes CAT, SOD, GSH and T-AOC in control group, model group and oxaliplatin group were measured *via* chemical colorimetry.

Detection of Expressions of Apoptosis-Related Genes in Intestinal Tissues

The expressions of apoptosis-related genes in intestinal tumor tissues, including Apaf1, Caspase-9, Survivin and Bcl-2, in control group, model group and oxaliplatin group were examined through quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Total RNA was extracted from intestinal tumor tissues *via* TRIzol method (Invitrogen, Carlsbad, CA, USA). Subsequently, extracted RNA was reversely transcribed into complementary deoxyribose nucleic acid (cDNA). Gene expression was detected *via* qRT-PCR, with GAPDH as an internal reference. Primers were designed, synthesized and verified by Sangon Biotech (Shanghai, China) Co., Ltd (Table I). Reaction conditions were set as follows: 95°C for 5 min, (95°C for 30 s, 55°C for 45 s and 72°C for 40 s) × 40 cycles, and 72°C for 5 min.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 23.0 software (IBM, Armonk, NY, USA) was utilized for statistical processing, ANOVA was adopted for comparison of measurement data among multiple groups, followed by Post-Hoc Test (Least Significant Difference). The *t*-test was performed for comparison between two groups. $p<0.05$ was considered statistically significant.

Results

Analysis Results of Intestinal Floras in Control Group, Model Group and Oxaliplatin Group

The analysis results of intestinal floras in control group, model group and oxaliplatin group were shown in Figures 1-2. LDA scores were displayed in Figure 1, and LEfSe results were exhibited in Figure 2. The abundance of microorganisms such as *Sphaerobacterales*, *Adlercreutzia* and *Coriobacterium glomerans* in the intestines was significantly higher in control group ($p<0.05$). However, the abundance of *Bifidobacterium*, *Rikenellaceae* and *Paraprevotella* in the intestines was higher in model group ($p<0.05$). Oxaliplatin group exhibited remarkably higher abundance of such microorganisms as *Cyanobacteria*, *Alistipes* and *Metascardovia* in rat intestines ($p<0.05$).

Abundance of Intestinal Alistipes Among Control Group, Model Group and Oxaliplatin Group

According to the comparison of abundance of intestinal *Alistipes* among control group, model group and oxaliplatin group (Figure 3), the content of *Alistipes* was the highest in oxaliplatin group, followed by control group and model group, and the difference was statistically significant ($p<0.05$).

Levels of Inflammatory Indexes in Control Group, Model Group and Oxaliplatin Group

Based on the comparisons of the levels of inflammatory indexes TNF-α, CRP, IL-4 and IL-1β in the serum among control group, model group and oxaliplatin group (Table II), the levels of

Table I. Primer sequences for PCR.

	Forward/reverse primer	Primer sequence
Apaf1	Forward primer	TCGATGAGCACTACGAGTACC
	Reverse primer	CCATCCTAGACTCTGTTGGACAC
Caspase-9	Forward primer	TACTTCGATGAGCACTACGAGT
	Reverse primer	AAGAGAAGAATATGCGGTTCTGG
Survivin	Forward primer	TCCATTGCTCTTAGCGACTGT
	Reverse primer	GGGGTTCAATCCCATAACTCG
Bcl-2	Forward primer	TCTTGCCACAGACCCGGTAT
	Reverse primer	ATCTCCAGTCCAACTAGCACA
GAPDH	Forward primer	GCTAGTTGGACTGGAGATTTGG
	Reverse primer	GTGGCTCCTTGAACACACTG

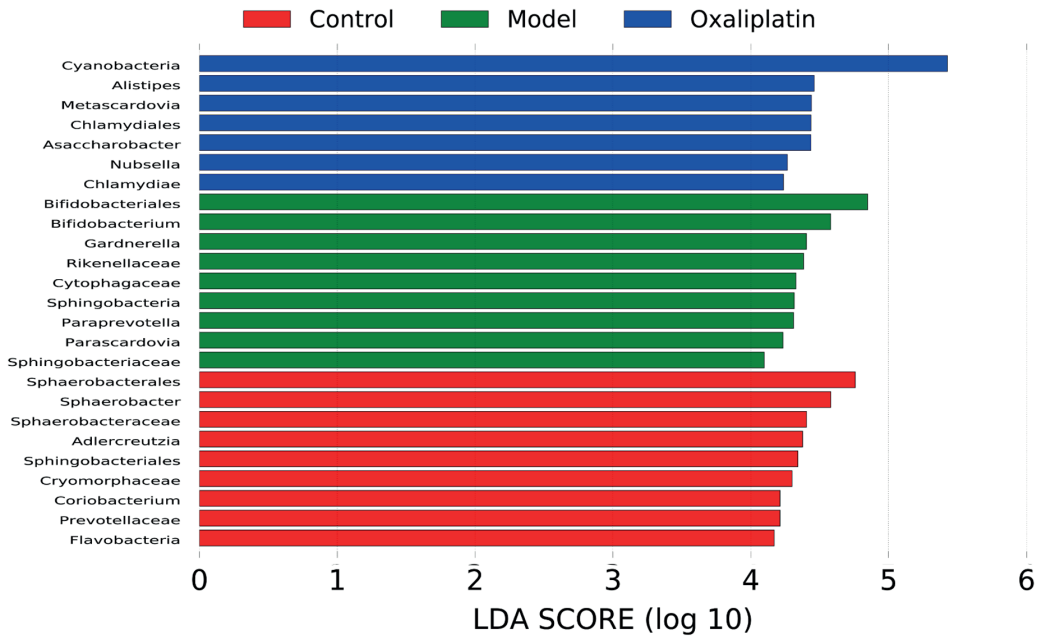

Figure 1. LDA scores of intestinal floras in control group, model group and oxaliplatin group.

serum TNF-α, CRP and IL-1β were significantly higher in model group than those in control group (p<0.05). Oxaliplatin group exhibited notably lower levels of serum TNF-α, CRP and IL-1β (p<0.05) but higher level of IL-4 than model group (p<0.05).

Levels of Oxidative Stress Indexes in Control Group, Model Group and Oxaliplatin Group

The content of oxidative stress indexes such as CAT, SOD, GSH and T-AOC in control group, model group and oxaliplatin group was listed in Table III. The results indicated that the content of serum CAT, SOD, GSH and T-AOC was markedly elevated in model group compared with control group (p<0.05). However, it decreased remarkably in oxaliplatin group in comparison with model group (p<0.05).

Expressions of Apoptotic Molecules in Control Group, Model Group and Oxaliplatin Group

As shown in Figure 4, compared with control group, model group had distinctly lower expressions of Apaf1, Caspase-9 and Survivin but evidently higher expression level of Bcl-2 in intestinal tumor tissues (p<0.05). Moreover, the expressions of Apaf1, Caspase-9 and Survivin were clearly higher, while that of Bcl-2 was prominently lower in intestinal tumor tissues in oxaliplatin group than those in model group (p<0.05).

Discussion

With the development of social economy and the improvement of living standards, the morbidity rate of colorectal cancer is increasing rapid-

Table II. Levels of serum inflammatory factors in each group of rats.

	n	CRP (ng/L)	IL-4 (ng/L)	TNF-α (ng/L)	IL-1β (ng/L)
Control group	10	1.24±0.12	3.21±0.45	13.46±2.72	2.14±0.24
Model group	10	6.83±1.01[a]	2.15±0.87	47.56±3.18[a]	7.43±2.74[a]
Oxaliplatin group	10	3.45±0.66[b]	4.11±1.13[b]	27.24±2.98[b]	4.11±1.26[b]

Note: [a]p<0.05 *vs*. control group, and [b]p<0.05 *vs* model group, *t*-test.

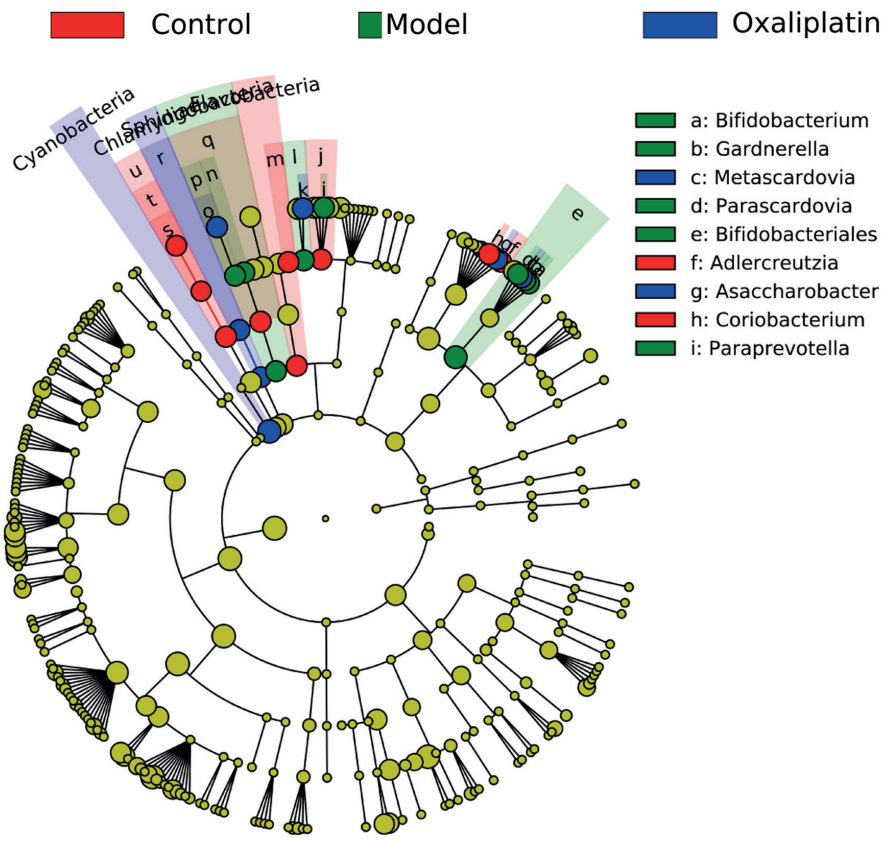

Figure 2. LEfSe results of intestinal floras in control group, model group and oxaliplatin group.

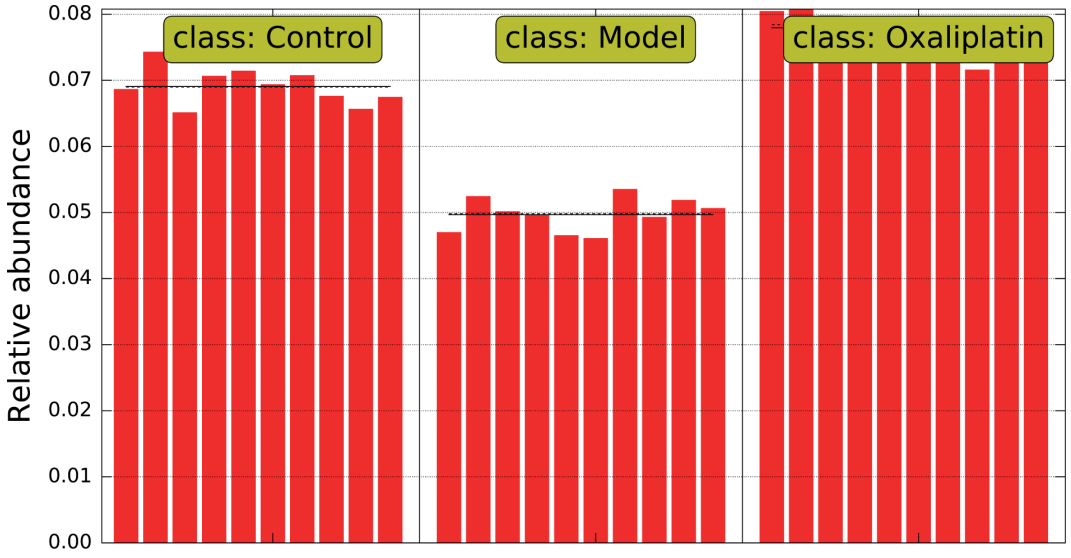

Figure 3. Comparison of abundance of intestinal *Alistipes* among control group, model group and oxaliplatin group.

ly. Meanwhile, its mortality rate remains high in recent years[11,12]. The incidence rate of colorectal cancer is higher in developed cities than that in less developed cities. This is mainly attributed to different diet styles such as high fat, high protein and low fiber[13,14]. In addition, family heredity, age

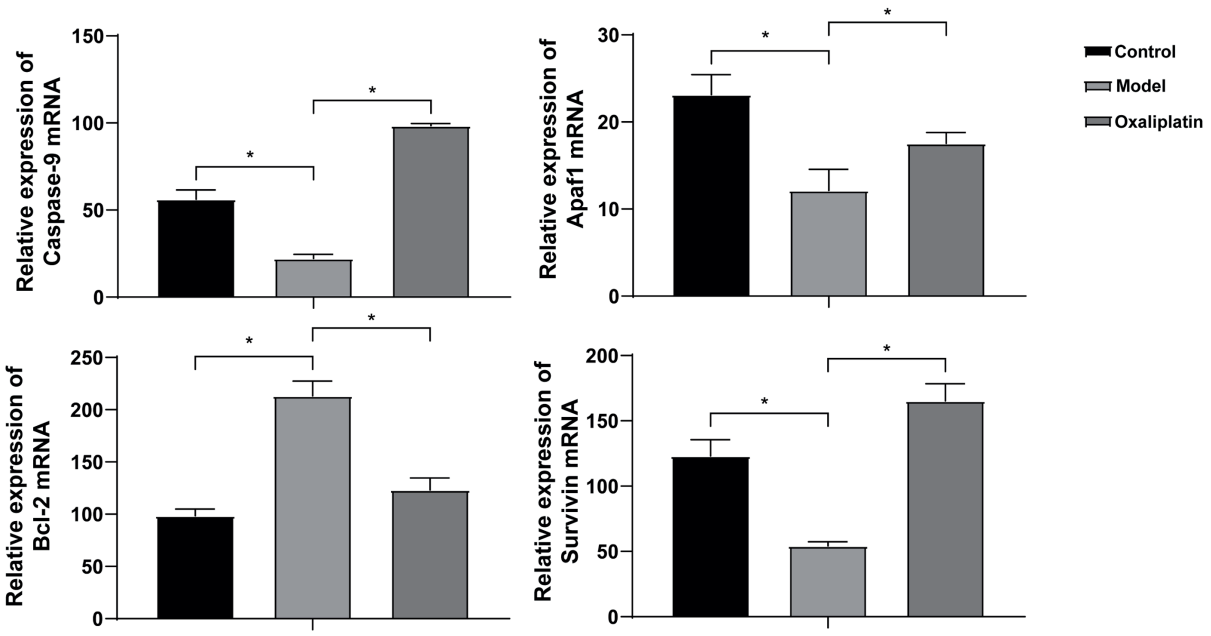

Figure 4. Expressions of apoptotic molecules in control group, model group and oxaliplatin group.

Table III. Levels of oxidative stress indexes in each group of rats.

	n	CAT (U/mL)	SOD (U/mL)	GSH (mg/L)	T-AOC (U/mL)
Control group	10	8.32±0.84	345.35±23.15	15.33±1.45	8.94±1.27
Model group	10	6.32±0.41[a]	267.25±31.25[a]	7.86±0.19[a]	2.76±0.87[a]
Oxaliplatin group	10	7.73±0.78[b]	302.57±28.76[b]	12.23±1.31[b]	5.34±1.02[b]

Note: [a]$p<0.05$ *vs*. control group, and [b]$p<0.05$ *vs* model group, *t*-test.

above 40 years old and chronic intestinal diseases are crucial contributing factors for the incidence of colorectal cancer. Surgical resection assisted with proper chemotherapy is the preferred treatment currently. Meanwhile, chemotherapy is the most important method for patients with advanced and metastatic colorectal cancer[15]. Chemotherapy drugs including 5-Fu and irinotecan can inhibit the proliferation and development of colorectal cancer cells primarily by interfering in DNA synthesis in cells. However, they can kill normal cells *in vivo*. Due to great side effects, patients are prone to stopping treatment due to intolerance[16]. Therefore, seeking for new mechanisms of chemotherapy drugs for colorectal cancer is conducive to changing and optimizing the chemotherapy regimens, so as to obtain better efficacy.

Chemotherapy has been considered as one of the effective treatment methods for tumors. It can not only assist surgical treatments in improving the efficacy, but also treat patients with advanced tumors[17]. It is argued that oxaliplatin, a novel chemotherapy drug following cisplatin and carboplatin, has satisfactory killing effects on tumor cells. Meanwhile, it can vigorously inhibit tumor growth during the treatment of such tumors as breast cancer[18] and gastric cancer[19]. El-Fatatry et al[20] demonstrated that the mechanism of oxaliplatin in the treatment of tumors may be realized by multiple mechanisms, including the regulation of molecular expressions in key signaling pathways. In the case of colorectal cancer, oxaliplatin has been confirmed to have strong killing effects on tumor cells both *in vitro* and *in vivo*[21]. In contrast with carboplatin, irinotecan and other chemotherapy drugs, oxaliplatin possesses remarkably fewer side effects (including lower hepatotoxicity and nephrotoxicity) in the treatment of colorectal

cancer. Therefore, it is more applicable to affected patients[22]. However, the specific action mechanism of oxaliplatin in colorectal cancer has not been fully elucidated yet. Hence, exploring its mechanism in killing tumor cells can facilitate its better utilization. Moreover, combination therapy with other potential drugs can achieve more favorable efficacy. In the present study, the rat model of CRC was established and treated with oxaliplatin injection (15 mg/kg). It was found that the drug had certain effects on intestinal floras in rats with CRC. Control group had significantly higher abundance of intestinal microorganisms *Sphaerobacterales*, *Adlercreutzia* and *Coriobacterium glomerans*. Model group displayed higher abundance of *Bifidobacterium*, *Rikenellaceae* and *Paraprevotella* in the intestines.Oxaliplatin group exhibited higher abundance of such intestinal microorganisms as *Cyanobacteria*, *Alistipes* and *Metascardovia*. Besides, oxaliplatin group exhibited the highest content of *Alistipes*, followed by control group and model group, with statistically significant differences ($p<0.05$). All these results illustrate that microorganisms including *Bifidobacterium*, *Rikenellaceae* and *Paraprevotella* may have important significance in the occurrence and development of colorectal cancer and is worthy of further study. Other results suggest that microorganisms *Cyanobacteria*, *Alistipes* and *Metascardovia* probably compose the intestinal microbial mechanism of oxaliplatin in treating CRC, which will be investigated through experiments in subsequent studies.

In this study, the influences of oxaliplatin on the levels of inflammation and oxidative stress in colorectal cancer were compared. It was discovered that the levels of serum TNF-α, CRP and IL-1β rose evidently in model group in comparison with control group ($p<0.05$). The levels of serum TNF-α, CRP and IL-1β were reduced prominently ($p<0.05$), while that of IL-4 was markedly elevated in oxaliplatin group in contrast with model group ($p<0.05$). Furthermore, model group exhibited remarkably higher content of serum CAT, SOD, GSH and T-AOC than both control group ($p<0.05$) and oxaliplatin group ($p<0.05$). These findings imply that oxaliplatin may kill colorectal cancer cells by improving the level of inflammation or altering the level of oxidative stress in organisms.

Finally, the impact of oxaliplatin on the apoptosis level in CRC tissues was explored. The results revealed that the expressions of Apaf1, Caspase-9 and Survivin in the intestinal tumor tissues were remarkably lowered, whereas that of Bcl-2 was clearly elevated in model group compared with control group ($p<0.05$). The opposite results were observed between oxaliplatin group and model group ($p<0.05$). All these results indicate that oxaliplatin may indirectly stimulate the expressions of apoptosis-related genes in tumor cells and increase the percentage of apoptotic cells through various pathways (e.g., changing the inflammation or oxidative stress level in organisms), thereby killing tumor cells.

Conclusions

The novelty of this study was that Oxaliplatin has significant effects on the inflammation, oxidative stress, apoptosis-related genes and intestinal floras in rats with CRC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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