

· 基础研究 ·

## 岩藻多糖对炎症性肠病的作用及其机制

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**[摘要]** **目的:**探讨岩藻多糖抑制炎症性肠病(inflammatory bowel disease, IBD)的作用及其机制。**方法:**将小鼠随机分为实验组和对照组(每组5只),实验组给予岩藻多糖灌胃2周,对照组给予饮用水灌胃2周,随后两组小鼠均自由饮用溶有葡聚糖硫酸钠(dextran sulfate sodium salt, DSS)的水溶液,构建IBD小鼠模型。检测小鼠体重、脾脏重量、结肠长度及重量,HE染色观察结肠组织病理变化,观察大便性状并评分;运用实时荧光定量PCR(real-time fluorescence quantitative PCR, qPCR)检测炎症因子、趋化因子和紧密连接蛋白的mRNA水平变化。**结果:**岩藻多糖处理的实验组小鼠肠炎相关指标显著优于对照组,炎症程度减弱。**结论:**岩藻多糖能够预防和抑制IBD的发生,为预防和治疗IBD提供新方法和依据。

**[关键词]** 岩藻多糖;炎症性肠病**[中图分类号]** R574.6**[文献标志码]** A**[文章编号]** 1007-4368(2019)09-1304-05**doi:** 10.7655/NYDXBNS20190908

## The effects and mechanism of fucoidan on inflammatory bowel disease

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**[Abstract]** **Objective:** This study aims to investigate the effect and mechanism of fucoidan inhibiting inflammatory bowel disease (IBD). **Methods:** Mice were randomly divided into experimental group and control group ( $n=5$ , each group). The experimental group was intragastrically with fucoidan, meanwhile, the control group was given drinking water. Two weeks later, both groups drank dextran sulfate sodium salt (DSS) to make mouse model of IBD. Body weight, spleen weight, colon length and weight of mouse were measured. Pathological changes of colon tissue was observed by HE staining, stool property was observed and scored, and mRNAs of inflammatory factors, chemokines and tight junction proteins were detected by real-time fluorescence quantitative PCR. **Results:** Intestinal inflammation related indexes were better in experimental group treated with fucoidan than in the control group, and the degree of inflammation was reduced. **Conclusion:** Fucoidan can prevent and inhibit the occurrence of IBD. This study will provide a new method and evidence for the prevention and treatment of IBD.

**[Key words]** fucoidan; inflammatory bowel disease

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炎症性肠病(inflammatory bowel disease, IBD)是一种与肠道黏膜免疫系统异常、环境、遗传、感染等相关的特发性肠道炎症性疾病<sup>[1-2]</sup>。IBD主要分为克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC)两类<sup>[1,3]</sup>。IBD患者多表现为

腹痛、腹泻、血便、呕吐等消化道症状。IBD的传统治疗方法主要包括糖皮质激素、水杨酸制剂及免疫抑制剂,但这些治疗方法无法明显缩短IBD病程,且长期使用以上药物会给患者带来难以克服的不良反应<sup>[4]</sup>。因此,迫切需要寻找新的药物,安全有效地抑制肠炎发生,降低肠炎发病率。岩藻多糖是一种富含岩藻糖的硫酸盐聚合物,存在于可食用的大型褐藻和棘皮动物中,可作为膳食补充剂使用<sup>[5]</sup>。已有研究证明,岩藻多糖具有抗凝血、抗肿瘤、抗炎、

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调节免疫功能、调节肠道菌群等作用<sup>[6]</sup>。因此,我们推测岩藻多糖可能对IBD有一定抑制效果,本课题采用口服岩藻多糖的方法,探讨岩藻多糖对肠炎的预防和抑制作用,以期对IBD的预防和治疗提供新思路和方法。

## 1 材料和方法

### 1.1 材料

#### 1.1.1 药品及试剂

岩藻多糖(CAS:9072-19-9, Cool chemistry公司,美国);葡聚糖硫酸钠(dextran sulfate sodium salt, DSS)(DB001-36, TdB Consultancy公司,美国);苏木精伊红(HE)染色试剂盒(C0105, 杭州碧云天公司)。

#### 1.1.2 实验动物

雄性健康C57BL/6J小鼠,SPF级,6~8周龄,体重18~25 g,购自南京医科大学医药实验动物中心。本研究经实验动物伦理委员会批准。

### 1.2 方法

#### 1.2.1 小鼠模型的制备

C57BL/6J小鼠按随机数字表法分为实验组( $n=5$ )和对照组( $n=5$ ),实验组通过灌胃提前给予岩藻多糖(200 mg/kg),每天灌胃1次,持续2周<sup>[7]</sup>,同时对对照组按同样方法予饮用水灌胃2周。2周后,两组小鼠均饮用浓度2.5% DSS溶液7 d,诱发急性溃疡性结肠炎,然后正常饮水2 d后处死小鼠。

#### 1.2.2 测量指标和方法

从DSS诱发IBD模型第1天起,每天记录小鼠体重,观察粪便性状及肉眼血便情况<sup>[8]</sup>。实验第9天处死小鼠,采集小鼠脾脏并称重,剖腹观察结肠外观,进行长度测量,沿肠系膜侧剖开结肠,行组织学大体评分<sup>[9]</sup>。剪开结肠后冲洗干净,称重后固定于硬塑胶平板上,做瑞士卷,用4%多聚甲醛溶液固定24 h,切片,HE染色,行病理组织学观察并评分<sup>[10]</sup>。

#### 1.2.3 评分标准

小鼠体重变化评分:体重下降>0~5%为0.5分,体重下降>5%~10%为1分,体重下降>10%~15%为2分,体重下降>15%为3分;腹泻便血评分:大便颜色及性状正常为0分,大便性状变软无隐血为1分,大便性状变软有隐血为2分,大便变稀且明显便血为3分;具体参考文献<sup>[11]</sup>。组织病理学炎症评分主要依据炎性细胞浸润程度和肠道组织损伤情况来评分:炎性细胞浸润黏膜为1分,浸润黏膜及黏膜下层为2分,透壁浸润为3分,肠道上皮局灶性糜烂为1分,局灶性溃疡为2分,肠道上皮延长溃疡并有

肉芽组织和息肉为3分;病理组织学炎症评分为炎性细胞浸润程度和肠道组织损伤情况评分之和,具体参考文献<sup>[11]</sup>。

#### 1.2.4 RNA、逆转录和实时定量PCR分析

采用TRIzol试剂盒提取小鼠肠道组织总RNA,逆转录后,使用qPCR检测炎症因子:肿瘤坏死因子(tumor necrosis factor, TNF)- $\alpha$ 、白介素(interleukin, IL)-1 $\beta$ 、IL-6、IL-13、干扰素(interferon, IFN)- $\gamma$ ;抗炎因子:IL-10;趋化因子:单核细胞趋化因子(monocyte chemoattractant protein, MCP)-1、巨噬细胞炎症蛋白(macrophage inflammatory protein, MIP)-1、MIP-2;紧密连接蛋白:闭合蛋白(Claudin)-1、Claudin-2、Claudin-5、咬合蛋白(Occludin)-1、闭合小环蛋白(zonula occludens, ZO)-1的mRNA水平,内参为GAPDH。反应条件为95℃预变性5 min;95℃ 10 s, 60℃ 10 s, 72℃ 10 s,共40个循环。结果采用比较阈值法进行定量分析。引物序列见表1。

### 1.3 统计学方法

采用SPSS17.0软件进行统计学分析,实验数据以均数 $\pm$ 标准差( $\bar{x} \pm s$ )表示,组间比较采用两样本独立 $t$ 检验。首先确保实验开始时,实验组和对照组数据基本一致,之后按不同时间点分别比较实验组与对照组,根据结果描述从某个时间点开始,或某一段时间内两组数据的差异有统计学意义,以此来说明在特定时间段内实验组和对照组变化幅度的不同。 $P \leq 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 口服岩藻多糖改善DSS诱导的肠炎症状

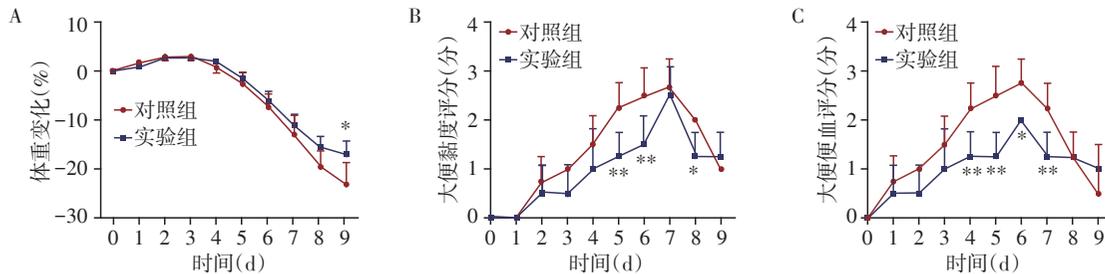
与对照组相比,实验组在第9天体重变化显著,差异有统计学意义( $P < 0.05$ ,图1A)。从第5天开始实验组小鼠大便黏度评分低于对照组小鼠,差异有统计学意义( $P < 0.01$ ),第6天差异也比较明显( $P < 0.01$ ),第8天对照组和实验组大便黏度差异变小,但差异仍有统计学意义( $P < 0.05$ ,图1B)。从第4天开始实验组小鼠大便便血评分比对照组小鼠明显降低,第5天和第7天差异显著( $P < 0.01$ ),第6天对照组和实验组大便便血差异变小,但差异仍有统计学意义( $P < 0.05$ ,图1C)。以上数据表明,口服岩藻多糖能缓解和减轻腹泻和便血现象,对肠道具有保护性。

### 2.2 口服岩藻多糖减轻DSS诱导的结肠萎缩、水肿和脾脏肿大

观察DSS模型第9天的小鼠结肠,形态学分析

表1 引物序列  
Table 1 Sequences of primers

基因	上游(5'→3')	下游(5'→3')
mGAPDH	GGGTGTGAACCACGAGAAATATG	TGTGAGGGAGATGCTCAGTGTTG
mTNF-α	TCAGCCTCTTCTCATTCCTG	CAGGCTTGTACTCGAATTT
mINF-γ	GCGTCATTGAATCACACCTG	TGAGCTCATTGAATGCTTGG
mIL-6	CCTCTCTGCAAGAGACTTCCA	AGAATTGCCATTGCACAACCTCT
mIL-1β	CCAAAAGATGAAGGGCTGCT	ACAGAGGATGGGCTCTTCTT
mIL-13	CAGCATGGTATGGAGTGTGG	TGGGCTACTTCGATTTTGGT
IL-10	GCTCTTACTGACTGGCATGAG	CGCAGCTCTAGGAGCATGTG
mMIP-1	CTTCTCTGTACCATGACACTCTGC	CCTCCAAGACTCTCAGGCATTC
mMIP-2	CCCAGACAGAAGTCATAGCCA	AGTGAACTCTCAGACAGCGA
mMCP-1	GTGCAGAGAGCCAGACGGGA	GGCATCACAGTCCGAGTCACA
mZO-1	CCACCTCTGTCCAGCTCTTC	CACCGGAGTGTGGTTTTCT
mOccludin1	CCTCCAATGGCAAAGTGAAT	CTCCCCACCTGTCTGTAGT
mClaudin-2	TATGTTGGTGCCAGCATTGT	TCATGCCACCACAGAGATA
mClaudin-5	GCTCTCAGAGTCCGTTGACC	CTGCCCTTTCAGGTTAGCAG
mClaudin-1	GATGTGGATGGCTGTCATTG	CGTGGTGTGGGTAAGAGGT



A: 实验组与对照组小鼠体重变化统计图; B: 大便黏度评分统计图; C: 大便便血评分统计图。与对照组比较, \* $P < 0.05$ , \*\* $P < 0.01$  ( $n=5$ )。

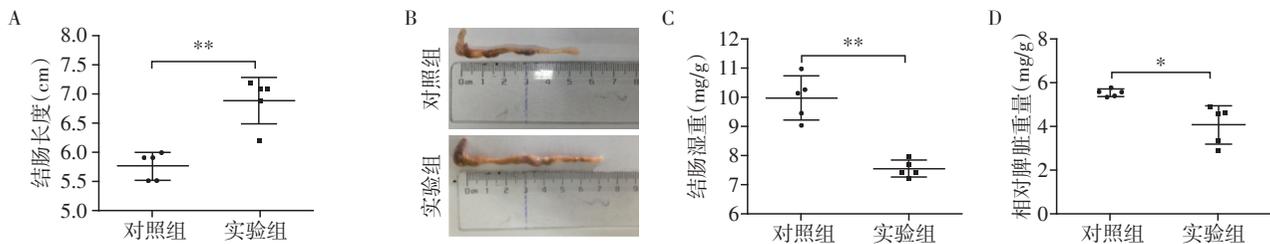
图1 口服岩藻多糖能够改善DSS肠炎模型小鼠的肠炎症状

Figure 1 Taking fucoidan orally can ameliorate enteritis symptoms in DSS model mice

表明,对照组小鼠结肠有明显的粪便淤积和肠粘连现象,结肠长度 $[(5.7 \pm 0.5)\text{cm}]$ 明显短于实验组小鼠结肠 $[(6.9 \pm 0.7)\text{cm}]$ ,差异有统计学意义( $P < 0.001$ ,图2A、B)。

结肠的湿重是肠道水肿和炎症的指标,以结肠重量与体重的比值(mg/g)表示。对照组结肠湿重 $[(9.9 \pm 1.2)\text{mg/g}]$ 高于实验组 $[(7.5 \pm 0.9)\text{mg/g}]$ ,差

异有统计学意义( $P < 0.001$ ,图2C)。通常情况下,肠道炎症会引起脾肿大<sup>[12]</sup>,检测小鼠脾脏重量,实验数据表明,实验组小鼠的相对脾脏重量[脾脏重量(mg)/体重(g)]为 $(4.2 \pm 1.2)\text{mg/g}$ ,低于对照组小鼠 $[(5.9 \pm 2.0)\text{mg/g}]$ ,差异有统计学意义( $P < 0.01$ ,图2D)。以上数据说明,在DSS肠炎模型中,口服岩藻多糖可以改善肠道水肿以及肠道萎缩,并且能



A: 小鼠结肠长度分析; B: 小鼠结肠形态学分析; C: 小鼠结肠湿重分析; D: 脾脏称重。两组比较, \* $P < 0.01$ , \*\* $P < 0.001$  ( $n=5$ )。

图2 口服岩藻多糖改善DSS肠炎模型小鼠的结肠萎缩、水肿及脾脏肿大

Figure 2 Taking fucoidan orally can ameliorate colonic atrophy, edema and splenomegaly in DSS model mice

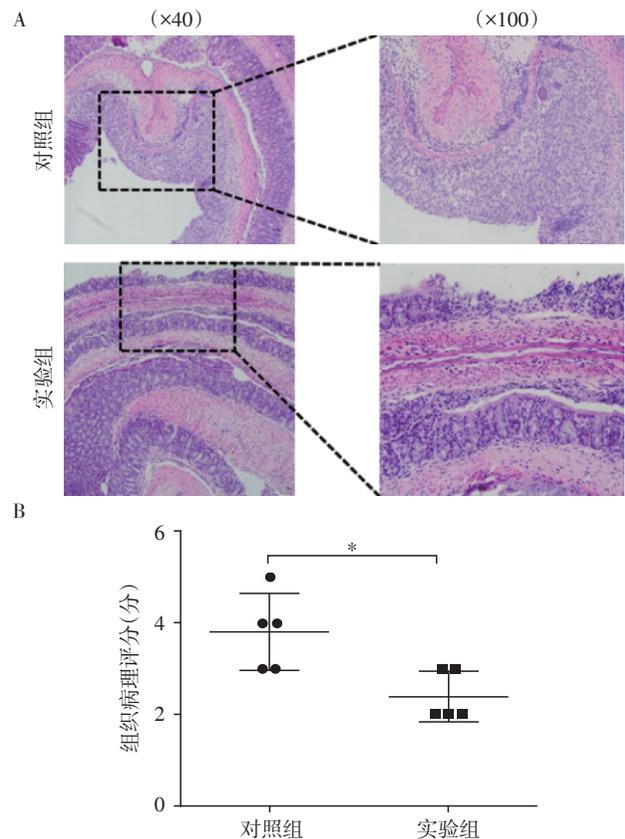
有效防止脾脏肿大。

### 2.3 口服岩藻多糖减轻DSS诱导的结肠病理损伤及炎症细胞浸润

进一步采用组织学分析,通过HE染色可以观察到对照组小鼠结肠上皮糜烂或破坏、隐窝变形、杯状细胞丢失、黏膜下水肿、结肠壁厚度增加和结肠内炎症细胞浸润;而口服岩藻多糖的实验组其结肠结构保留,炎症细胞浸润减少,黏膜下层水肿减少(图3A)。对照组结肠组织学损害评分平均为4分,实验组小鼠结肠组织学损害评分平均为2分(图3B),两组差异有统计学意义( $P < 0.05$ ,图3B)。

### 2.4 口服岩藻多糖能降低炎症细胞因子和趋化因子的mRNA水平,提高紧密连接蛋白的mRNA表达水平

为了进一步研究岩藻多糖的作用机制,采用qPCR检测了结肠组织中炎症细胞因子水平。与对照组相比,实验组促炎因子IL-1 $\beta$ 、IL-13、TNF- $\alpha$ 、IL-6、IFN- $\gamma$ 等mRNA水平受到明显抑制,而抑炎因子IL-10 mRNA水平明显升高(图4A)。趋化因子作为能够吸引白细胞移行到感染部位的细胞因子,在炎症反应中具有重要作用<sup>[13-14]</sup>,进一步检测了趋化因子MIP-1、MIP-2、MCP-1,结果显示它们在实验组的mRNA表达水平明显低于对照组(图4B)。肠上皮细胞紧密连接(tight junction, TJ)蛋白在肠道黏膜屏障中起着重要作用,其主要包括咬合蛋白(Occludin)、闭合蛋白(Claudins)、连接黏附分子及闭合小环蛋白(ZO,一种胞浆蛋白)<sup>[15-17]</sup>。进而检测了紧密连接蛋白ZO-1、Claudin-1、Claudin-2、Claudin-5、Occludin-1在肠组织中的mRNA表达水平。结果显示,实验组中相关紧密连接蛋白的mRNA水平明显高于对照组(图4C)。以上数据表明,岩藻多糖可以通过抑制炎症因子和趋化因子,促进肠上皮紧密连接蛋白



A:小鼠结肠组织切片HE染色;B:小鼠结肠病理学评分。两组比较, $P < 0.05$ ( $n=5$ )。

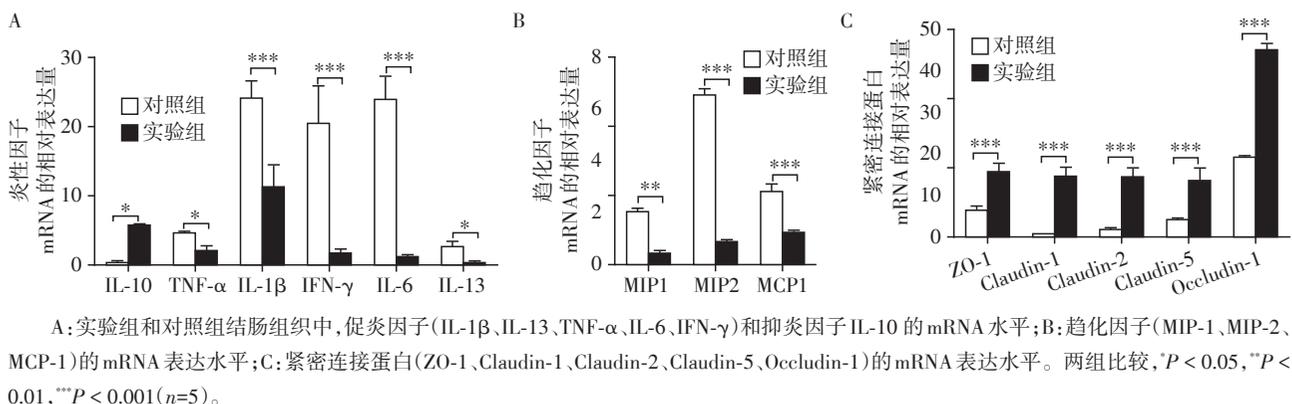
图3 口服岩藻多糖改善DSS诱导的结肠病理损伤及炎症细胞浸润

Figure 3 Taking fucoidan orally can ameliorate DSS-induced colonic pathological damage and inflammatory cell infiltration

的表达,从而抑制IBD的发生。

## 3 讨论

岩藻多糖是一种水溶性多糖,具有来源广泛、成本低的优点。研究表明它具有抑菌和抗炎



A:实验组和对照组结肠组织中,促炎因子(IL-1 $\beta$ 、IL-13、TNF- $\alpha$ 、IL-6、IFN- $\gamma$ )和抑炎因子IL-10的mRNA水平;B:趋化因子(MIP-1、MIP-2、MCP-1)的mRNA表达水平;C:紧密连接蛋白(ZO-1、Claudin-1、Claudin-2、Claudin-5、Occludin-1)的mRNA表达水平。两组比较, $P < 0.05$ ,\*\* $P < 0.01$ ,\*\*\* $P < 0.001$ ( $n=5$ )。

图4 口服岩藻多糖对炎症细胞因子、趋化因子、紧密连接蛋白mRNA表达的影响

Figure 4 Effect of taking fucoidan orally on mRNAs of inflammatory factors, chemokines and tight junction proteins

作用<sup>[18-21]</sup>。而IBD是一组反复发作的慢性炎症性肠道疾病,我们推测岩藻多糖可能对IBD有一定抑制效果。本课题采用口服岩藻多糖的方法,检测其对IBD的预防效果,旨在探索有效使用岩藻多糖防御IBD的可行性和机制,为推广使用岩藻多糖,降低IBD发病率提供新途径。

本研究表明,口服岩藻多糖不仅减轻了IBD所致体重减轻和腹泻便血等病理指标,而且明显减轻了肠道炎症。研究表明,肠道中的细胞因子形成一个复杂网络,参与调控IBD的发病<sup>[3,22]</sup>,也影响上皮完整性<sup>[22-24]</sup>。本研究发现岩藻多糖抑制巨噬细胞分泌炎症因子,如IL-1 $\beta$ 、IL-13、TNF- $\alpha$ 、IL-6、IFN- $\gamma$ <sup>[25]</sup>。特别是TNF- $\alpha$ 被认为在炎症细胞信号转导中起着重要作用,临床应用TNF- $\alpha$ 抑制剂能够改善急性结肠炎症状<sup>[5]</sup>。与此一致的是,岩藻多糖能阻断体外共培养的肠道炎症模型中巨噬细胞源性TNF- $\alpha$ 的产生,对TNF- $\alpha$ 信号有抑制作用<sup>[26]</sup>。趋化因子在炎症反应中具有重要作用,趋化因子的主要作用是趋化细胞的迁移,进一步研究发现口服岩藻多糖抑制趋化因子的表达。肠上皮细胞紧密连接蛋白在肠道黏膜屏障中起着重要作用,其受损会导致细胞间的通透性增加,肠腔内的细菌、毒素等物质可穿透肠黏膜而进入其他组织、器官或循环系统,导致疾病。本研究发现口服岩藻多糖能上调这些紧密连接蛋白的表达,保护肠上皮的完整性。由于本研究中岩藻多糖给药是在DSS动物模型构建之前,因此研究结果只能说明岩藻多糖对肠炎发生有预防作用,其是否可以治疗IBD还有待于进一步研究。

本研究从动物和分子水平探讨口服岩藻多糖对IBD的作用,发现其能够抑制炎症、保持肠上皮完整性,减缓炎症性肠病发生,拓展了目前对口服岩藻多糖预防IBD的认识,为预防IBD的发生提供了依据和新途径。

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