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# 溃疡性结肠炎组织中 cingulin、claudin-2 表达量与菌群紊乱、氧化应激及炎症的相关性

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**[摘要]** **目的:**探讨溃疡性结肠炎组织中 cingulin、claudin-2 表达量与菌群紊乱、氧化应激及炎症的相关性。**方法:**选取在本院确诊并作为 UC 组的 UC 患者 70 例, 同期至本院进行肠镜体检的结肠息肉患者 90 例作为结肠息肉组。对比两者肠道病变组织中 cingulin、claudin-2 蛋白表达量以及粪便标本中菌群分布、血清中氧化应激及炎症相关指标的差异。**结果:**UC 组结肠病灶中 cingulin、claudin-2 蛋白表达量高于结肠息肉组; 肠道内大肠杆菌的计数高于结肠息肉组, 双歧杆菌、乳酸杆菌的计数值低于结肠息肉组; 血清中氧化应激指标 GSH-Px、T-AOC 的含量低于结肠息肉组, ROS、LHP 的含量高于结肠息肉组; 血清中炎症因子 IL-4、IL-6、IL-17、IL-23、TGF- $\beta$  的含量均高于结肠息肉组。相关性分析显示: UC 病灶组织中 cingulin、claudin-2 蛋白表达量与菌群紊乱、氧化应激及炎症反应指标均直接相关。**结论:** UC 病灶中存在 cingulin、claudin-2 异常高表达, 可推进机体肠道菌群紊乱及全身炎症应激反应。

**[关键词]** 溃疡性结肠炎; cingulin; claudin-2; 菌群紊乱; 氧化应激反应; 炎症反应

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## Correlation of cingulin and claudin-2 expression in ulcerative colitis tissues with intestinal flora disturbance, oxidative stress and inflammation

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**View from specialist: It is creative, and of certain scientific and educational value.**

**[ABSTRACT]** **Objective:** To investigate the correlation of cingulin and claudin-2 expression in ulcerative colitis tissues with intestinal flora disturbance, oxidative stress and inflammation. **Methods:** 70 patients with UC who were diagnosed in our hospitals between July 2013 and February 2018 were selected as the UC group, and 90 patients with colonic polyps who underwent colonoscopy in our hospitals during the same period were selected as the colon polyps group. The differences in cingulin and claudin-2 protein expression in intestinal lesions, intestinal flora distribution in feces specimens as well as indexes related to oxidative stress and inflammation in serum were compared between the two groups. **Results:** cingulin and claudin-2 protein expression in colon lesions of UC group were higher than those of colon polyps group; Escherichia coli count in intestinal tract was

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higher than that of colon polyps group whereas bifidobacterium and lactobacillus count were lower than those of colon polyps group; oxidative stress indexes GSH-Px and T-AOC contents in serum were lower than those of colon polyps group whereas ROS and LHP contents were higher than those of colon polyps group; inflammatory factors IL-4, IL-6, IL-17, IL-23 and TGF- $\beta$  contents in serum were higher than those of colon polyps group. Correlation analysis showed that the cingulin and claudin-2 protein expression in UC lesion tissues were directly correlated with the intestinal flora disturbance, oxidative stress response indexes and inflammatory response indexes. **Conclusion:** Abnormal high expression of cingulin and claudin-2 in UC lesions can promote the intestinal flora disturbance and systemic inflammatory stress response.

[KEY WORDS] Ulcerative colitis; Cingulin; Claudin-2; Intestinal flora disturbance; Oxidative stress response; Inflammatory response

溃疡性结肠炎(UC)是一种病因尚未完全明晰的结肠、直肠慢性炎症性疾病,该病病程漫长且反复发作,患者可见血性腹泻、腹痛、里急后重、体重减轻等,部分患者可伴有关节炎、肝功能障碍等结肠外表现<sup>[1,2]</sup>。寻找 UC 发病的核心环节是当下疾病研究的重点,cingulin 是维持细胞间紧密连接的重要蛋白,而 UC 存在肠上皮细胞凋亡加剧、黏膜屏障破坏等病理特点,故有学者提出 cingulin 及其下游支配蛋白 claudin-2 可能参与 UC 发生发展<sup>[3,4]</sup>。文中检测 UC 及单纯结肠息肉患者病灶组织中 cingulin、claudin-2 的蛋白表达量,进一步探讨其表达量改变与具体 UC 病情的内在联系,以期明确 cingulin、claudin-2 表达在 UC 病情演进中扮演的角色,为后续临床治疗实践奠定基础。

## 1 资料与方法

### 1.1 一般资料

UC 患者 70 例于 2013 年 7 月~2018 年 2 月间在本院确诊并作为 UC 组,同期至本院进行肠镜体检的结肠息肉患者 90 例作为结肠息肉组。UC 组中男性 37 例,女性 33 例,年龄 22~56 岁;结肠息肉组中男性 36 例,女性 34 例,年龄 24~55 岁。两组患者的上述基础资料分布差异不显著,后续研究计划书得到本院伦理委员会全员投票批准。

入组标准:(1)符合临床 UC 诊断标准;(2)首次确诊 UC,未经相关治疗;(3)结肠息肉患者证实为良性病变;(4)本人签署知情同意书。

排除标准:(1)合并结肠癌等其他病变;(2)合并红斑狼疮等严重自身免疫性疾病;(3)合并肺炎等全身感染性疾病;(4)认知功能正常、检查过程中可进行沟通交流。

### 1.2 结肠病变组织 cingulin、claudin-2 表达量检测

两组行结肠镜检查过程中,获取病变组织标本并冻存于液氮罐中备用。采用 western-blot 法检测其中 cingulin、claudin-2 蛋白表达量。

### 1.3 肠道菌群分布检测

取所有患者清晨新鲜粪便标本,至培养箱中培养 2~3 d,选取生长均匀的 3 块平板计算相应菌落的含菌量,具体纳入研究的菌群包括大肠杆菌、双歧杆菌、乳酸杆菌。

### 1.4 血清氧化应激及炎症相关指标含量检测

入组后(UC 组未经任何药物治疗),留取两组患者的呈 7:00~9:00 空腹外周血标本,抗凝后分离血清备用。采用酶联免疫吸附法检测血清中氧化应激指标、炎症因子的含量,氧化应激指标包括谷胱甘肽过氧化物酶(GSH-Px)、总抗氧化能力(T-AOC)、活性氧(ROS)、脂质过氧化氢(LHP);炎症因子包括白介素-4(IL-4)、白介素-6(IL-6)、白介素-17(IL-17)、白介素-23(IL-23)、转化生长因子  $\beta$ (TGF- $\beta$ )。

### 1.5 统计学处理

所有数据采用 SPSS24.0 统计学软件进行分析处理, $P < 0.05$  为差异有统计学意义。

## 2 结果

### 2.1 结肠病变组织 cingulin、claudin-2 表达量

UC 组结肠病灶中 cingulin、claudin-2 的表达量均显著高于结肠息肉组。两组结肠病灶组织中 cingulin、claudin-2 蛋白表达量的差异有统计学意义( $P < 0.05$ )。见表 1。

表 1 结肠病变组织中 cingulin、claudin-2 表达量的比较( $\bar{x} \pm s$ )

组别	<i>n</i>	cingulin	claudin-2
结肠息肉组	90	84.92 $\pm$ 9.12	102.35 $\pm$ 14.18
UC 组	70	145.07 $\pm$ 16.28	131.18 $\pm$ 14.05
<i>t</i>		15.392	12.058
<i>P</i>		<0.05	<0.05

### 2.2 肠道菌群分布

UC 组肠道内大肠杆菌的计数值高于结肠息肉组,双歧杆菌、乳酸杆菌的计数值低于结肠息肉组。两组肠道内大肠杆菌、双歧杆菌、乳酸杆菌等菌群计数值的差异有统计学意义( $P < 0.05$ )。见表 2。

表 2 两组肠道菌群分布情况比较(IgCFU/g, $\bar{x} \pm s$ )

组别	<i>n</i>	大肠杆菌	双歧杆菌	乳酸杆菌
结肠息肉组	90	7.45 $\pm$ 0.86	8.39 $\pm$ 0.92	7.11 $\pm$ 0.85
UC 组	70	8.97 $\pm$ 0.95	6.41 $\pm$ 0.75	6.07 $\pm$ 0.63
<i>t</i>		7.094	8.862	5.097
<i>P</i>		<0.05	<0.05	<0.05

### 2.3 氧化应激指标

UC 组血清中 GSH-Px、T-AOC 的含量低于结肠息肉

组,ROS、LHP 的含量高于结肠息肉组。两组血清中氧化应激指标 GSH-Px、T-AOC、ROS、LHP 含量的差异有统计学意义( $P < 0.05$ )。见表 3。

#### 2.4 炎症因子

UC 组血清中 IL-4、IL-6、IL-17、IL-23、TGF- $\beta$  的含量均高于结肠息肉组。两组血清中炎症因子 IL-4、IL-6、IL-17、IL-23、TGF- $\beta$  含量的差异有统计学意义( $P < 0.05$ )。见表 4。

表 3 血清中氧化应激指标含量的比较( $\bar{x} \pm s$ )

组别	<i>n</i>	GSH-Px (U/mL)	T-AOC (U/mL)	ROS ( $\mu\text{mol/L}$ )	LHP ( $\mu\text{mol/L}$ )
结肠息肉组	90	45.48 $\pm$ 6.19	27.04 $\pm$ 3.18	16.49 $\pm$ 2.17	71.25 $\pm$ 8.66
UC 组	70	30.17 $\pm$ 4.25	19.72 $\pm$ 2.88	30.75 $\pm$ 3.69	109.26 $\pm$ 14.24
<i>t</i>		13.059	18.261	15.429	11.293
<i>P</i>		<0.05	<0.05	<0.05	<0.05

表 4 血清中炎症因子含量的比较( $\text{pg/mL}$ , $\bar{x} \pm s$ )

Table 4 Comparison of serum inflammatory factor contents ( $\text{pg/mL}$ , $\bar{x} \pm s$ )

组别	<i>n</i>	IL-4	IL-6	IL-17	IL-23	TGF- $\beta$
结肠息肉组	90	10.38 $\pm$ 1.74	8.55 $\pm$ 0.97	11.43 $\pm$ 1.85	6.02 $\pm$ 0.68	9.27 $\pm$ 1.51
UC 组	70	16.92 $\pm$ 2.35	15.87 $\pm$ 1.62	26.57 $\pm$ 3.48	13.47 $\pm$ 1.92	20.04 $\pm$ 2.85
<i>t</i>		9.284	11.251	15.487	10.054	15.473
<i>P</i>		<0.05	<0.05	<0.05	<0.05	<0.05

#### 2.5 相关性分析

Pearson 检验发现,UC 患者病灶中 cingulin、claudin-2 蛋白表达量与肠道菌群中的大肠杆菌计数值呈正相关,双歧杆菌、乳酸杆菌计数值呈负相关;与氧化应激指标 GSH-Px、T-AOC 的含量呈负相关,与 ROS、LHP 的含量呈正相关;与炎症因子 IL-4、IL-6、IL-17、IL-23、TGF- $\beta$  的含量呈正相关( $P < 0.05$ )。见表 5。

表 5 UC 患者病灶组织中 cingulin、claudin-2 蛋白表达量与具体病情的相关关系

Table 5 Correlation of cingulin and claudin-2 protein expression in lesions with the specific illness of patients with UC

指标	cingulin		claudin-2	
	决定系数 <i>r</i>	<i>P</i>	决定系数 <i>r</i>	<i>P</i>
大肠杆菌	0.671	<0.05	0.473	<0.05
双歧杆菌	-0.582	<0.05	-0.598	<0.05
乳酸杆菌	-0.704	<0.05	-0.703	<0.05
GSH-Px	-0.492	<0.05	-0.485	<0.05
T-AOC	-0.708	<0.05	-0.608	<0.05
ROS	0.502	<0.05	0.627	<0.05
LHP	0.653	<0.05	0.530	<0.05
IL-4	0.588	<0.05	0.618	<0.05
IL-6	0.627	<0.05	0.592	<0.05
IL-17	0.711	<0.05	0.612	<0.05
IL-23	0.495	<0.05	0.547	<0.05
TGF- $\beta$	0.695	<0.05	0.409	<0.05

### 3 讨论

UC 是临床多见的肠道慢性炎症性疾病,其反复发作的血便、腹痛等给患者的生活及工作带来巨大负面影响,后期甚至有诱导病灶癌变的风险,寻找疾病发生原因并进行针对性治疗是当下研究的重点<sup>[5,6]</sup>。诸多研究证实,UC 患者存在肠道上皮细胞凋亡加速以及肠黏膜屏障功能异常,而细胞骨架在维持肠黏膜功能完整性方面具有决定性意义,cingulin 作为影响细胞骨架的关键蛋白受到较多关注。

Cingulin 是维持细胞紧密连接完整的重要蛋白,通过 RhoA 信号刺激调控 claudin-2 等紧密蛋白的表达,且研究证实沉默 Cingulin 表达可导致 claudin-2 表达量下降<sup>[7,8]</sup>。文中 UC 组患者病灶中 cingulin、claudin-2 的蛋白表达量均较结肠息肉组高,证实 UC 患者肠黏膜中存在 cingulin、claudin-2 的异常高表达,可能以此增加肠黏膜通透性并破坏肠黏膜屏障完整,加剧 UC 病情进展。关于 cingulin、claudin-2 表达量变化与 UC 具体病情的相关关系,下文中肠道菌群分布、全身氧化应激反应、炎症反应三方面展开阐述。

人体内的肠道菌群是一个复杂的微生态系统,双歧杆菌、乳酸菌等益生菌可产生细菌素等对抗条件致病菌对肠黏膜的侵袭<sup>[9,10]</sup>。UC 患者存在严重肠道菌群失调,具体表现为双歧杆菌、乳酸菌等益生菌的合成减少,而条件致病菌大肠杆菌计数增加,是造成肠黏膜损伤的重要原因之一,也可作为衡量 UC 病情严重程度的可靠参数之一<sup>[11-13]</sup>。文中 UC 组患者粪便标本中大肠杆菌的计数值较结肠息肉组高,双歧杆菌、乳酸菌计数值较低,证实 UC 患者确实存在肠道菌群失调。相关性分析显示,UC 患者病灶组织中 cingulin、claudin-2 蛋白表达量与大肠杆菌计数值呈正相关,与双歧杆菌、乳酸菌计数值呈负相关,说明病灶组织 cingulin、claudin-2 蛋白异常高表达可进一步导致肠道菌群紊乱。

氧化应激反应参与 UC 发生发展,疾病发展过程中大量合成的 ROS 可对病灶局部或者全身组织产生攻击作用,其后经脂质过氧化反应产生更多氧化代谢产物,如 LHP,其含量间接反映组织氧化损伤程度<sup>[14,15]</sup>。UC 患者氧化损伤发生的另一原因是机体抗氧化系统能力下降,ROS 大量产生可与

GSH-Px、T-AOC 等抗氧化指标中和并削弱机体整体抗氧化能力<sup>[16,17]</sup>。文中 UC 组患者血清中 GSH-Px、T-AOC 的含量较低,ROS、LHP 的含量较高,说明 UC 患者存在明显全身氧化应激反应。相关性分析显示,UC 患者病灶中 cingulin、claudin-2 蛋白表达量与 GSH-Px、T-AOC 含量呈负相关,与 ROS、LHP 含量呈正相关,说明异常高表达的 cingulin、claudin-2 蛋白可促进 UC 患者的全身氧化应激反应加剧。

UC 本质上是一种慢性弥漫性炎症性疾病,持续存在的肠道炎症反应可加重患者各项临床表现并导致疾病迁延不愈<sup>[18]</sup>。IL-4、TGF- $\beta$  均是典型的抑炎因子,可抑制单核巨噬细胞的功能并发挥抗炎作用,在全身炎症性疾病中 IL-4、TGF- $\beta$  表达反应性增加以抑制机体炎症反应过度加剧<sup>[19]</sup>。IL-6 也是典型的促炎因子,在炎症反应出现后早期合成增加并释放入血,可刺激其他炎症介质合成。IL-17 由 Th17 细胞分泌,可趋化中性粒细胞、单核巨噬细胞至炎症部位,参与炎症级联反应。IL-23 属于 IL-12 细胞因子家族,具有强效促炎作用,多种研究证实 UC 患者循环血中存在 IL-23 高表达<sup>[20,21]</sup>。文中 UC 患者血清中上述炎症因子的含量均较结肠息肉组高,说明机体存在明显全身炎症反应。相关性分析则进一步明确,UC 患者病灶中 cingulin、claudin-2 蛋白表达量与 IL-4、IL-6、IL-17、IL-23、TGF- $\beta$  等炎症因子的含量呈正相关,说明异常高表达的 cingulin、claudin-2 蛋白可促进 UC 患者的全身炎症反应。

UC 患者结肠病灶组织中存在 cingulin、claudin-2 蛋白异常高表达,可进一步导致机体肠道菌群紊乱并加剧全身炎症应激反应,是 UC 发生发展的重要原因,有望成为日后该病治疗的新靶点。

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