

# 世界华人消化杂志®

**WORLD CHINESE  
JOURNAL OF DIGESTOLOGY**

**Shijie Huaren Xiaohua Zazhi**

**2022 年 8 月 8 日      第 30 卷      第 15 期      (Volume 30 Number 15)**



**15 / 2022**

ISSN 1009-3079



9 771009 307056

《世界华人消化杂志》是一本高质量的同行评议、开放获取和在线出版的学术刊物。本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录。



### 述评

- 665 重视HBsAg定量检测在慢性乙型肝炎全程管理中的价值  
封波, 郑佳睿
- 661 葛根芩连汤治疗肠道疾病的研究进展  
舒雁, 惠华英, 谭周进

### 文献综述

- 668 紧密连接蛋白Claudin-3在肝胆疾病中的研究进展  
许祖知, 费书珂
- 674 STING信号通路在肝脏疾病中的作用及研究进展  
魏霞, 张定棋, 张霖璋, 刘伟, 刘平, 徐莹

### 临床实践

- 680 牙线牵引辅助内镜黏膜下挖除术在治疗胃黏膜下肿瘤中的应用  
许捷鸿, 陈志新
- 686 酪酸梭菌活菌片对胆囊结石腹腔镜术后腹泻患者营养状况、Th1/Th2细胞及预后的影响  
王凌, 林霞, 戚国勇

## 消 息

- 660 《腹痛的诊断、鉴别诊断与治疗》书讯  
679 《世界华人消化杂志》修回稿须知  
692 《世界华人消化杂志》性质、刊登内容及目标

## 封面故事

汪昱, 教授, 硕士研究生导师, 上海交通大学附属第六人民医院普外科主任医师, 致力于胃肠道肿瘤的临床诊治及研究30余年, 擅长胃肠道肿瘤的腹腔镜微创手术、开腹手术及手术前后的综合治疗. 主要从事胃肠道肿瘤转移及术后复发的分子机制研究. 主持并完成多项治疗大肠癌的药物临床试验. 主编或参编《胃肠肿瘤治疗学》、《胃肠肿瘤手术学》、《肠屏障功能基础与临床》等著作, 主持或参与完成国家自然科学基金课题2项、上海市科委课题3项. 累计发表SCI及核心期刊论文20余篇.

## 本期责任人

编务 张砚梁; 送审编辑 张砚梁; 组版编辑 张砚梁; 英文编辑 王天奇;  
形式规范审核编辑部主任 李香; 最终清样审核总编辑 马连生

## 世界华人消化杂志

Shijie Huaren Xiaohua Zazhi

吴阶平 题写封面刊名

陈可冀 题写版权刊名

(半月刊)

创 刊 1993-01-15

改 刊 1998-01-25

出 版 2022-08-08

原刊名 新消化病学杂志

期刊名称

世界华人消化杂志

国际标准连续出版物号

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

共同主编

党双锁, 博士, 教授, 研究员, 主任医师, 710004, 陕西省西安市, 西安交通大学医学院第二附属医院感染科

郭晓钟, 博士, 教授, 110840, 辽宁省沈阳市, 北部战区总医院消化内科

霍丽娟, 博士, 主任医师, 030001, 山西省太原市, 山西医科大学第一医院消化内科

江学良, 博士, 教授, 250001, 山东省济南市, 山东中医药大学第二附属医院消化中心

田艳涛, 博士, 教授, 主任医师, 100021, 北京市, 国

家癌症中心/中国医学科学院北京协和医学院肿瘤医院胰胃外科

王小众, 博士, 教授, 350001, 福建省福州市, 福建医科大学附属协和医院消化内科

姚登福, 博士, 教授, 226001, 江苏省南通市, 南通大学附属医院临床医学研究中心

张宗明, 博士, 教授, 100073, 北京市, 首都医科大学北京电力医院普外科

编辑委员会

编辑委员会成员在线名单, 详见:

<https://www.wjgnet.com/1009-3079/editorialboard.htm>

编辑部

王金磊, 主任

《世界华人消化杂志》编辑部

Baishideng Publishing Group Inc

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: [wcjd@wjgnet.com](mailto:wcjd@wjgnet.com)

<http://www.wjgnet.com>

出版

百世登出版集团有限公司

Baishideng Publishing Group Inc

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

<https://www.wjgnet.com>

制作

北京百世登生物医学科技有限公司  
100025, 北京市朝阳区东四环中路  
62号, 远洋国际中心D座903室  
电话: +86-10-85381901

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊出版平台(Superstar Journals Database)》数据库收录.

《世界华人消化杂志》正式开通了在线办公系统(<https://www.baishideng.com>), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

特别声明

本刊刊出的所有文章不代表本刊编辑部和本刊编委会的观点, 除非特别声明. 本刊如有印装质量问题, 请向本刊编辑部调换.

定价

每期136.00元 全年24期3264.00元

© 2022 Baishideng Publishing Group Inc. All rights reserved.



**EDITORIAL**

- 655 Importance of quantitative HBsAg detection in whole course management of patients with chronic hepatitis B  
*Feng B, Zheng JR*
- 661 Progress in treatment of intestinal diseases with Gegen Qinlian decoction  
*Shu Y, Hui Y, Tan ZJ*

**REVIEW**

- 668 Progress in research of tight junction protein claudin-3 in hepatobiliary systemic diseases  
*Xu ZZ, Fei SK*
- 674 Role of STING signaling pathway in liver diseases  
*Wei X, Zhang DQ, Zhang LZ, Liu W, Liu P, Xu Y*

**CLINICAL PRACTICE**

- 680 Application of dental floss traction assisted endoscopic submucosal excision in treatment of gastric submucosal tumors  
*Xu JH, Cheng ZX*
- 686 Effect of live *Clostridium typhimurium* tablets on nutritional status, Th1/Th2 cells, and prognosis of patients with diarrhea after laparoscopic surgery for gallbladder stones  
*Wang L, Lin X, Qi Y*

## Contents

*World Chinese Journal of Digestology*  
Volume 30 Number 15 August 8, 2022

### COVER

Editorial Board Member of *World Chinese Journal of Digestology*, Yu Wang, Chief Physician, Department of Surgery, The Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, No. 600 Yishan Road, Shanghai 200233, China. wangyu11122@sina.com

### Indexed/Abstracted by

Chemical Abstracts, EMBASE/Excerpta Medica, Abstract Journals, Scopus, CNKI, CSTJ and Superstar Journals Database.

### RESPONSIBLE EDITORS FOR THIS ISSUE

Assistant Editor: *Yan-Liang Zhang*

Review Editor: *Yan-Liang Zhang*

Production Editor: *Yan-Liang Zhang*

English Language Editor: *Tian-Qi Wang*

Proof Editor: *Xiang Li*

Layout Reviewer: *Lian-Sheng Ma*

### Shijie Huaren Xiaohua Zazhi

**Founded** on January 15, 1993

**Renamed** on January 25, 1998

**Publication date** August 8, 2022

#### NAME OF JOURNAL

*World Chinese Journal of Digestology*

#### ISSN

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

#### CO-EDITORS-IN-CHIEF

**Shuang-Suo Dang**, Professor, Department of Infectious Diseases, The Second Affiliated Hospital of Medical School of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China

**Xiao-Zhong Guo**, Professor, Department of Gastroenterology, North Theater General Hospital, Shenyang 110840, Liaoning Province, China

**Li-Juan Huo**, Chief Physician, Department of Gastroenterology, The First Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi Province, China

**Xue-Liang Jiang**, Professor, Digestive Center of The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan 250001, Shandong Province, China

**Yan-Tao Tian**, Professor, Chief Physician, National Cancer Center/Department of Pancreatic and Gastric Surgery, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing

100021, China

**Xiao-Zhong Wang**, Professor, Department of Gastroenterology, Union Hospital, Fujian Medical University, Fuzhou 350001, Fujian Province, China

**Deng-Fu Yao**, Professor, Clinical Research Center, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

**Zong-Ming Zhang**, Professor, Department of General Surgery, Beijing Electric Power Hospital, Capital Medical University, Beijing 100073, China

#### EDITORIAL BOARD MEMBERS

All editorial board members resources online at <https://www.wjgnet.com/1009-3079/editorialboard.htm>

#### EDITORIAL OFFICE

Jin-Lei Wang, Director

*World Chinese Journal of Digestology*

Baishideng Publishing Group Inc

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: [wjcd@wjgnet.com](mailto:wjcd@wjgnet.com)

<https://www.wjgnet.com>

#### PUBLISHER

Baishideng Publishing Group Inc

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

<https://www.wjgnet.com>

#### PRODUCTION CENTER

Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China  
Telephone: +86-10-85381901

#### PRINT SUBSCRIPTION

RMB 136 Yuan for each issue

RMB 3264 Yuan for one year

#### COPYRIGHT

© 2022 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, but not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

#### INSTRUCTIONS TO AUTHORS

Full instructions are available online at <https://www.wjgnet.com/1009-3079/Nav/36>. If you do not have web access, please contact the editorial office.

## 紧密连接蛋白Claudin-3在肝胆疾病中的研究进展

许祖知, 费书珂

**许祖知, 费书珂**, 南华大学衡阳医学院附属第二医院肝胆胰脾外科 湖南省衡阳市 421000

许祖知, 硕士研究生, 研究方向为肝胆疾病发病机制.

**基金项目:** 湖南省教育厅优秀青年项目, No. 16B232; 南华大学研究生科研创新项目, No. 203YXC026.

**作者贡献分布:** 本文综述写作由许祖知完成; 费书珂审校.

**通讯作者:** 费书珂, 副主任医师, 副教授, 421000, 湖南省衡阳市蒸湘区解放大道35号, 南华大学衡阳医学院附属第二医院肝胆胰脾外科. pretender8129@hotmail.com

**收稿日期:** 2022-05-12

**修回日期:** 2022-05-31

**接受日期:** 2022-07-26

**在线出版日期:** 2022-08-08

### Research progress of tight junction protein claudin-3 in hepatobiliary systemic diseases

Zu-Zhi Xu, Shu-Ke Fei

**Zu-Zhi Xu, Shu-Ke Fei**, Department of Hepatobiliary, Pancreatic and Splenic Surgery, The Second Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang 421000, Hunan Province, China

**Supported by:** Outstanding Youth Program of Hunan Education Department, No. 16B232; Graduate Research Innovation Project of University of South China, No. 203YXC026.

**Corresponding author:** Shu-Ke Fei, Professor, Department of Hepatobiliary, Pancreatic and Splenic Surgery, The Second Affiliated Hospital, Hengyang Medical School, University of South China, No. 35 Jiefang Road, Zhengxiang District, Hengyang 421000, Hunan Province, China. pretender8129@hotmail.com

**Received:** 2022-05-12

**Revised:** 2022-05-31

**Accepted:** 2022-07-26

**Published online:** 2022-08-08

### Abstract

Claudin-3 is an important member of the claudin family of tight junction proteins and is the most abundant tight junction protein in the hepatobiliary system. It plays an important role in building tight junctions of hepatobiliary cells, and maintaining cellular barrier function and molecular delivery function. Dysregulation of hepatic claudin-3 expression leads to disruption of hepatobiliary system junctions, metabolic function, barrier function, proliferation capacity, and molecular delivery function, and is closely related to the development of various hepatobiliary diseases such as hepatic malignancies, cholesterol stones, and chronic liver diseases. In this paper, we review the progress in the research of claudin-3 in hepatobiliary diseases.

© The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

**Key Words:** Tight junction; Claudin-3; Hepatic systemic diseases

**Citation:** Xu ZZ, Fei SK. Progress in research of tight junction protein claudin-3 in hepatobiliary systemic diseases. Shijie Huaren Xiaohua Zazhi 2022; 30(15): 668-673

**URL:** <https://www.wjgnet.com/1009-3079/full/v30/i15/668.htm>

**DOI:** <https://dx.doi.org/10.11569/wcjd.v30.i15.668>

### 摘要

紧密连接蛋白Claudin-3是紧密连接蛋白家族Claudins的重要成员之一, 是肝胆系统中含量最多的紧密连接蛋白. 在构建肝胆管细胞紧密连接、维持细胞屏障功能和分子传递功能等方面发挥重要的作用. 肝脏Claudin-3的表达失调会导致肝胆系统紧密连接破坏、代谢功能、屏障功能、增殖能力和分子传递功能受损, 与肝脏恶性肿瘤、胆固醇结石、慢性肝病等多种肝胆疾病的发生发展密切相关. 本文就Claudin-3

在肝胆疾病中的研究进展进行综述。

© The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

关键词: 紧密连接; Claudin-3; 肝胆系统疾病

**核心提要:** Claudin-3是机体紧密连接的重要组成部分,也是肝脏中表达最高的紧密连接蛋白。本文主要概述了Claudin-3在肝胆恶性肿瘤、胆固醇结石、慢性肝病等多种肝胆疾病中的作用,在诊断、特异治疗和预后判断等方面有着广泛的应用前景。

**文献来源:** 许祖知, 费书珂. 紧密连接蛋白Claudin-3在肝胆疾病中的研究进展. 世界华人消化杂志 2022; 30(15): 668-673

**URL:** <https://www.wjgnet.com/1009-3079/full/v30/i15/668.htm>

**DOI:** <https://dx.doi.org/10.11569/wjcd.v30.i15.668>

## 0 引言

各种上皮细胞以及内皮细胞之间的相邻面主要由细胞连接构成,这些细胞连接是细胞旁转运的重要组成部分,除了维持细胞屏障的完整性,还限制分子的细胞旁路转运,其主要分为紧密连接(tight junction, TJ)、桥粒、中间连接和缝隙连接等。TJ是主要位于细胞膜最顶端的连接装置,在细胞连接中占主要部分,由3种跨膜蛋白、紧密连接蛋白(Claudins)、闭合蛋白、连接黏附分子以及闭合小环蛋白ZO-1、ZO-2、ZO-3等组成,其中主要结构为Claudins。肝脏紧密连接主要由Claudin-1、-2、-3、-12和-25组成,其中Claudin-3是肝胆系统中含量最多的紧密连接蛋白<sup>[1,2]</sup>。肝脏Claudin-3的表达失调会导致肝胆系统中的紧密连接破坏,代谢功能、屏障功能、增殖能力和分子传递功能受损,与多种肝胆系统疾病的发生发展密切相关。本文就Claudin-3在肝胆疾病中的研究进展进行综述。

## 1 紧密连接蛋白Claudin-3的概述

Claudins由Furuse等<sup>[3]</sup>于1998年首次发现,相对分子质量20 kDa-34 kDa,是紧密连接中最重要的骨架蛋白,也是紧密连接发挥维持细胞屏障完整性功能和限制物质运输的一个关键分子,它的表达数量和分布结构的变化直接影响TJ的结构和功能。Claudins蛋白家族是一种至少拥有27个家族成员的蛋白<sup>[4]</sup>,根据功能的差异可将其分为两类<sup>[5]</sup>:一类与形成屏障功能有关,如Claudin-1、-3、-4和-5等;另一类则与构成特定的通道有关,可通过分子大小及电荷选择决定物质的细胞旁转运,如Claudin-2、-7、-10和-16等。Claudins是一种跨膜蛋白<sup>[6]</sup>,在结构上,Claudins由面向细胞质的N'末端、C'末端,2个细胞外

环、4个跨膜结构域组成,其中面向胞浆的C'末端还含有由80-90个氨基酸残基组成的PDZ结构域,它与ZO1、ZO2、ZO3和多PDZ结构域蛋白1(MUPP1)相互作用,这是紧密连接蛋白复合体与其他多种蛋白的结合位点<sup>[7-9]</sup>。在该结构域还包含与蛋白质翻译后修饰相关的氨基酸残基,如丝氨酸-苏氨酸磷酸化、酪氨酸磷酸化、小泛素化(sumoylation, SUMO)化和棕榈酰化等,这些都可能影响着Claudins的定位和功能<sup>[10-14]</sup>。同时,Claudins调节相邻细胞的离子选择性主要是由于Claudins的细胞外环所携带的氨基酸的带电性质,形成电荷选择性通道<sup>[15]</sup>。例如,Claudin-2的过度表达显著增加了上皮细胞的离子电导,形成阳离子选择性的细胞旁通道<sup>[16]</sup>。Claudin-1、-6、-9的细胞外链可能是丙型肝炎病毒的结合位点<sup>[17]</sup>。Claudin-1缺失可能导致罕见的遗传性疾病(新生儿鱼鳞病)和硬化性胆管炎,由于紧密连接中Claudin-1的缺乏,肝细胞和胆管细胞会出现胆汁的渗漏,这会导致患者出现胆汁淤积,谷草转氨酶(aspartate transaminase, AST)、谷丙转氨酶(alanine transaminase, ALT)、血清γ-谷氨酰转氨酶活性和胆红素明显升高<sup>[18]</sup>。而Claudin-3作为肝脏中表达最多的TJ蛋白,主要在肝细胞和胆管细胞中表达<sup>[19]</sup>。在先天性胆道闭锁的小儿患者中,肝脏内的Claudin-3含量无明显变化,而周围肝细胞和肝脏胆管管腔表面的Claudin-3排列明显紊乱<sup>[20]</sup>。因此,Claudin-3在肝细胞和胆管细胞屏障功能、分泌功能、物质代谢等多个方面发挥重要作用,进而影响肝脏生理,一旦Claudin-3表达失调,则会导致多种肝脏疾病的发生发展。

## 2 紧密连接蛋白Claudin-3的生物学作用

紧密连接蛋白Claudin-3定位于7q11.23,是参与血脑屏障、肠道屏障、血睾屏障构成的重要组成部分<sup>[21]</sup>。同时Claudin-3不仅在人体前列腺、胰腺细胞、肝细胞等多种腺细胞,同时还在乳腺导管上皮、子宫内膜、食管黏膜、肺泡上皮、和胆管上皮细胞等多种上皮细胞内均有表达<sup>[2]</sup>。Claudin-3是TJ的主要跨膜蛋白之一,是细胞间黏附功能的结构基础,并在细胞间的传输转运中发挥着重要的接头作用。除此之外,Claudin-3在维持上皮细胞极性、基因转录、抑制肿瘤、细胞增殖分化、新陈代谢相关的基因和炎症免疫反应等方面有着重大的作用。上皮TJ蛋白组成的复杂变化会影响细胞极性,如Claudin-3的减少与极性复合蛋白(partition defective-3, PAR-3)和丝氨酸/苏氨酸磷酸酶(protein phosphatase-1, PP-1)的定位和表达改变有关<sup>[22]</sup>。有研究表明<sup>[23]</sup>,Claudin-3在不同的肿瘤组织中表达不同,作用也不尽相同。Claudin-3在乳腺癌、前列腺癌、卵巢癌、胃癌等肿瘤中表达增多,而在结直肠癌、食管癌等肿

瘤中的表达则下降<sup>[24-29]</sup>. Claudin-3在胃癌组织中的表达高于癌旁正常组织, 但在胃癌黏膜下侵袭的表面表达较低, 胃癌肿瘤晚期合并远处淋巴转移的患者其Claudin-3表达也低<sup>[30]</sup>. 在增生期子宫内膜进展成为子宫内膜癌的疾病演变过程中, Claudin-3的表达明显升高, 并且其递增与子宫肌层的浸润密切相关<sup>[31]</sup>. Claudin-3除了与肿瘤及增殖相关之外, 还与机体的代谢有着密不可分的关系. 在Claudin-3敲除的小鼠, 其脂肪酸、氨基酸以及脂质的代谢相关基因在肝脏的表达显著下调, 而炎症免疫相关基因表达明显上调. Claudin-3的敲除也会降低肝脏内相关胆汁酸代谢基因(Cyp27a1、Ces1b和Akr1c6)的表达<sup>[32]</sup>. 胆汁酸是脂肪生成的重要调节因子, 胆汁酸代谢改变可能对肝脏能量代谢产生负面影响<sup>[33]</sup>. 所以, 可以推测胆汁酸组成的改变可能是Claudin-3敲除小鼠脂肪酸、脂质等明显下调的一个重要因素.

### 3 紧密连接蛋白Claudin-3与肝胆疾病

**3.1 Claudin-3与肝胆系统恶性肿瘤** 肝胆系统恶性肿瘤主要包括原发性肝癌(hepatocellular carcinoma, HCC)、胆管癌(cholangiocarcinoma, CCA)等, 其中HCC是肝内最常见的恶性肿瘤, 其在我国的发病率以及死亡率居高不下<sup>[34]</sup>. 目前HCC患者术后5年生存率仅为30%左右, 这主要与HCC的高侵袭性和高转移率密切相关<sup>[35]</sup>. E-钙粘蛋白(E-cadherin)的缺失是上皮-间质转化(epithelial-mesenchymal transition, EMT)的标志, 通过EMT, 肿瘤细胞获得了突破基底膜侵入周围组织或转移到远处器官的能力<sup>[36,37]</sup>. Lin等<sup>[38]</sup>的研究表明, 抑制Claudin-3表达可以促进肿瘤体内生长, 其中Claudin-3可能通过维持E-cadherin的表达和限制 $\beta$ -连环蛋白( $\beta$ -catenin)信号转导, 介导了与体内其他细胞的相互作用, 从而抑制了生长和转移潜能. Che等<sup>[39]</sup>研究表明, Claudin-3能够抑制Wnt/ $\beta$ -catenin途径, 进而抑制肿瘤细胞的上皮转移. Jiang等<sup>[40]</sup>研究表明, Claudin-3能够通过下调糖原合成酶激酶3B(glycogen synthase kinase 3B, GSK3B)、钙黏蛋白相关蛋白(catenin beta1, CTNNB1)、锌指家族转录抑制因子2(snail family transcriptional repressor 2, SNAI2)和血管钙黏蛋白(cadherin-2, CDH2)的表达, 使Wnt/ $\beta$ -catenin-EMT转移轴失活, 从而显著抑制肝癌的转移. 基质金属蛋白酶2(matrix metalloproteinase-2, MMP-2)是基质金属蛋白酶家族中的重要一员, 其可能通过降解肿瘤细胞周围的细胞外基质, 从而促进肿瘤的深层浸润, 这其实本质上就是EMT过程<sup>[41]</sup>. 李娟<sup>[42]</sup>等通过临床病例对照研究发现, 与肿瘤周边正常的肝组织相比, HCC组织中Claudin-3阳性表达率降低, MMP-2阳性表达率升高, HCC组织中Claudin-3与MMP-2呈负相关, 这可能是因为HCC组

织中的MMP-2的表达升高, 使上皮组织细胞外基质降解、上皮表型丢失, 导致Claudin-3下降, 最终促进HCC的EMT过程及肿瘤浸润. Bodnar等<sup>[43]</sup>的研究表明, HCC患者Claudin-3的表达与肿瘤的临床分期密切相关, 表明Claudin-3影响了HCC患者的细胞稳定性及肿瘤的演进过程. Claudin-3在HCC组织中的异常表达和分布, 有望成为靶向治疗HCC的新方向. 同时, 既往有研究表明Claudin-3与CCA同样密切相关, Németh<sup>[44]</sup>等通过研究发现, CCA患者Claudin-3的表达明显降低. 最近, 在Ikeda<sup>[45]</sup>等的研究中发现, CCA患者组的胆汁细胞外小泡(extracellular vesicles, EVS)中的Claudin-3较结石组相比显著升高, 其敏感性为87.5%, 特异性为87.5%, AUC值为0.945(95%可信区间: 0.84-1). 这表明了人胆汁来源的EVS中的Claudin-3可能是胆管癌的一种新的生物标志物, 具有重大的临床意义.

**3.2 Claudin-3与胆固醇结石** 胆管结石是消化系统常见的一种疾病, 其主要分为胆固醇结石(cholesterol gallstone disease, GSD)、胆色素结石和磷酸盐结石等. 既往的研究表明, 胆固醇的过饱和为GSD的主要原因, 在GSD形成的过程中, 胆固醇结石核心发现的磷酸钙沉淀也促进了GSD的形成<sup>[46]</sup>. Tanaka等<sup>[47]</sup>研究表明, Claudin-3在小鼠的GSD的形成中起着重要的作用. Claudin-3特异性敲除会明显增加小鼠的胆汁流量, 稀释胆汁中胆固醇、磷脂、胆汁酸、胆红素的浓度, 其主要通过增加肝上皮细胞TJ对水的细胞旁通透性. 同时, Claudin-3的缺乏会影响小鼠肝胆管上皮中磷酸根离子( $\text{PO}_4^{3-}$ )的细胞旁转运, 同时增加胆汁中钙离子( $\text{Ca}^{2+}$ )的浓度, 导致磷酸钙核心形成, 诱发GSD形成. Claudin-3敲除的小鼠会自发的形成黑色的磷酸盐结石, 用红外吸收分光光度法分析胆结石的成分发现其超过98%为磷酸钙的组成<sup>[47]</sup>. 在高胆固醇致石饮食的饲养条件下, Claudin-3特异性敲除的小鼠形成的胆囊结石, 主要成分同样为过饱和的胆固醇结晶形成的胆固醇结石, 但是通过红外吸收分光光度法分析发现结石核心仍为磷酸钙沉淀<sup>[47]</sup>. 所以, Claudin-3影响着GSD的形成, 同时Claudin-3在小鼠肝脏中的表达随着年龄的增加而逐渐降低, 这有助于我们更好地理解GSD的发病率与年龄之间的关系<sup>[48]</sup>.

**3.3 Claudin-3与肝部分切除术后** 在临床诊治中, 部分肝内外胆管结石的患者以及原发性肝癌患者, 行肝部分切除手术(partial hepatectomy, PHX)是有必要的<sup>[49]</sup>. 除了术中的精细操作, 术前患者的肝功能情况、以及患者的基础身体条件之外, 肝脏部分切除术后肝功能的恢复以及残肝的再生对于患者的恢复同样也起着至关重要的作用. Claudin-3是识别肝干细胞的标志物之一, Claudin-3在肝细胞增殖再生中的起着不可或缺

的作用<sup>[50]</sup>. Zhang<sup>[51]</sup>等研究表面, 层粘连蛋白 $\alpha$ -3(laminin alpha-3)和血小板反应蛋白-1(thrombospondin-1)通过影响Claudin-3来改变局部组织微环境, 促进患病肝脏的再生. Ando等<sup>[52]</sup>研究表明, PHX术后的大鼠, 在机械应力作用下, 肝细胞和Kupffer细胞立即释放细胞外ATP, 促进肝再生. 这表明在行PHX术后, 肝脏的增殖能力会代偿性的升高, 其增殖分数会明显升高. Baier等<sup>[32]</sup>的研究表明, 野生小鼠在肝脏部分切除(PHX)后, Claudin-3mRNA和蛋白的表达在术后3-6 h后下降, 并在24 h后开始高于初始水平. 而Claudin-3敲除的小鼠行PHX术后, 相比于正常野生型PHX小鼠, 其增殖指数(Ki67)明显降低. 在PHX小鼠中, 与细胞分裂、细胞周期调节、胆固醇合成和葡萄糖代谢相关的基因在Claudin-3敲除小鼠肝中的表达水平较低, 而与昼夜节律、代谢负调控、脂质分解代谢、钙离子结合以及其他相关基因的表达上调. 所以, 在肝再生以及再生肝代谢调节中, Claudin-3起着重要的作用<sup>[32]</sup>. 针对Claudin-3这一靶点治疗, 可能成为肝部分切除患者术后恢复治疗的一个非常重要的治疗方式.

**3.4 Claudin-3与慢性肝病** 慢性肝病主要是由于一种或者多种病因, 长期、反复刺激导致肝脏引起的, 其中包括以肝脏弥漫性纤维化、假小叶和再生结节形成为组织学特征的肝硬化(liver cirrhosis, LC), 以肝功能不全、全身炎性反应综合征、免疫麻痹为临床特征的慢急性肝衰竭(acute-on-chronic liver failure, ACLF)等. 肝硬化在我国最常见的病因为慢性乙型病毒性肝炎. 在肝硬化的疾病演变过程中, 门脉高压、免疫功能的异常和肠黏膜屏障功能障碍会导致肠道细菌内毒素入血, 导致肠源性内毒素血症(intestinal endotoxemia, IETM), 肠道细菌易位进入腹腔, 导致自发性腹膜炎等. 同时, 肠道屏障功能还与多种慢性肝病密切相关, 例如非酒精性脂肪肝(nonalcoholic steatosis hepatitis, NASH)<sup>[53]</sup>. Claudin-3缺失被认为是紧密连接断裂和肠通透性(intestinal permeability, IP)改变的标志<sup>[54-55]</sup>, 血浆Claudin-3浓度升高提示肠上皮屏障功能障碍<sup>[56-58]</sup>. Wang的研究表明<sup>[59]</sup>, 包括代偿期LC、失代偿性LC、LC导致的肠源性内毒素血症、ACLF等慢性肝病患者血浆Claudin-3水平均升高, 且与血浆内毒素水平呈正相关. 肠道黏膜的通透性与血浆Claudin-3的水平密切相关, 肠道黏膜的损伤会导致血浆Claudin-3的水平升高, 最终可能导致IETM的发生. 总之, 血浆Claudin-3, 是这各种肝病患者肠黏膜通透性的标志物. 临床干预保护肠道机械屏障免受损伤可能会减少IETM造成的损伤, 应该作为肝病的治疗方法进行研究.

## 4 结论

目前的研究发现Claudin-3在维持机体正常屏障、代

谢、增殖等功能中发挥重要作用. 一旦Claudin-3的表达出现异常, 则可能导致多种疾病的发生发展, 尤其是在肝胆系统相关疾病. 本文主要介绍了Claudin-3在原发性肝癌、胆固醇结石、慢性肝病肠道菌群失调等疾病中的致病机制, 胆管癌中的生物标志物作用, 以及对肝部分切除术后增殖代谢影响, 这表明研究Claudin-3与肝胆系统疾病发生、发展的过程密切相关, 在诊断、特异治疗和预后判断等方面有着广泛的应用前景. 对Claudin-3的表达情况和其调节因子对肝胆系统其他疾病的作用机制的深入探索, 寻找或设计与其特异性结合的靶向因子, 干扰细胞表型从而达到治疗目的, 有待进一步研究和探讨.

## 5 参考文献

- 1 Rahner C, Mitic LL, Anderson JM. Heterogeneity in expression and subcellular localization of claudins 2, 3, 4, and 5 in the rat liver, pancreas, and gut. *Gastroenterology* 2001; 120: 411-422 [PMID: 11159882 DOI: 10.1053/gast.2001.21736]
- 2 Ionescu Popescu C, Liliac L, Ceașu RA, Balan R, Grigoraș A, Căruntu ID, Amălinei C. CLDN3 expression and significance - breast carcinoma versus ovarian carcinoma. *Rom J Morphol Embryol* 2013; 54: 99-106 [PMID: 23529315]
- 3 Furuse M, Fujita K, Hiiragi T, Fujimoto K, Tsukita S. Claudin-1 and -2: novel integral membrane proteins localizing at tight junctions with no sequence similarity to occludin. *J Cell Biol* 1998; 141: 1539-1550 [PMID: 9647647 DOI: 10.1083/jcb.141.7.1539]
- 4 Mineta K, Yamamoto Y, Yamazaki Y, Tanaka H, Tada Y, Saito K, Tamura A, Igarashi M, Endo T, Takeuchi K, Tsukita S. Predicted expansion of the claudin multigene family. *FEBS Lett* 2011; 585: 606-612 [PMID: 21276448 DOI: 10.1016/j.febslet.2011.01.028]
- 5 Krause G, Winkler L, Mueller SL, Haseloff RF, Piontek J, Blasig IE. Structure and function of claudins. *Biochim Biophys Acta* 2008; 1778: 631-645 [PMID: 18036336 DOI: 10.1016/j.bbame.2007.10.018]
- 6 Ding L, Lu Z, Lu Q, Chen YH. The claudin family of proteins in human malignancy: a clinical perspective. *Cancer Manag Res* 2013; 5: 367-375 [PMID: 24232410 DOI: 10.2147/CMAR.S38294]
- 7 Huo L, Wen W, Wang R, Kam C, Xia J, Feng W, Zhang M. Cdc42-dependent formation of the ZO-1/MRCK $\beta$  complex at the leading edge controls cell migration. *EMBO J* 2011; 30: 665-678 [PMID: 21240187 DOI: 10.1038/emboj.2010.353]
- 8 Capaldo CT, Koch S, Kwon M, Laur O, Parkos CA, Nusrat A. Tight junction zonula occludens-3 regulates cyclin D1-dependent cell proliferation. *Mol Biol Cell* 2011; 22: 1677-1685 [PMID: 21411630 DOI: 10.1091/mbc.E10-08-0677]
- 9 Tabariès S, Siegel PM. The role of claudins in cancer metastasis. *Oncogene* 2017; 36: 1176-1190 [PMID: 27524421 DOI: 10.1038/onc.2016.289]
- 10 González-Mariscal L, Tapia R, Chamorro D. Crosstalk of tight junction components with signaling pathways. *Biochim Biophys Acta* 2008; 1778: 729-756 [PMID: 17950242 DOI: 10.1016/j.bbame.2007.08.018]
- 11 Tsukita S, Furuse M, Itoh M. Multifunctional strands in tight junctions. *Nat Rev Mol Cell Biol* 2001; 2: 285-293 [PMID: 11283726 DOI: 10.1038/35067088]
- 12 Van Itallie CM, Gambling TM, Carson JL, Anderson JM. Palmitoylation of claudins is required for efficient tight-junction localization. *J Cell Sci* 2005; 118: 1427-1436 [PMID: 15769849 DOI: 10.1242/jcs.01735]
- 13 Van Itallie CM, Mitic LL, Anderson JM. SUMOylation of claudin-2. *Ann NY Acad Sci* 2012; 1258: 60-64 [PMID: 22731716]

- DOI: 10.1111/j.1749-6632.2012.06541.x]
- 14 Van Itallie CM, Tietgens AJ, LoGrande K, Aponte A, Gucek M, Anderson JM. Phosphorylation of claudin-2 on serine 208 promotes membrane retention and reduces trafficking to lysosomes. *J Cell Sci* 2012; 125: 4902-4912 [PMID: 22825868 DOI: 10.1242/jcs.111237]
- 15 Suzuki H, Tani K, Tamura A, Tsukita S, Fujiyoshi Y. Model for the architecture of claudin-based paracellular ion channels through tight junctions. *J Mol Biol* 2015; 427: 291-297 [PMID: 25451028 DOI: 10.1016/j.jmb.2014.10.020]
- 16 Yu AS, Cheng MH, Angelow S, Günzel D, Kanzawa SA, Schneeberger EE, Fromm M, Coalson RD. Molecular basis for cation selectivity in claudin-2-based paracellular pores: identification of an electrostatic interaction site. *J Gen Physiol* 2009; 133: 111-127 [PMID: 19114638 DOI: 10.1085/jgp.200810154]
- 17 Meertens L, Bertaux C, Cukierman L, Cormier E, Lavillette D, Cosset FL, Dragic T. The tight junction proteins claudin-1, -6, and -9 are entry cofactors for hepatitis C virus. *J Virol* 2008; 82: 3555-3560 [PMID: 18234789 DOI: 10.1128/JVI.01977-07]
- 18 Hadj-Rabia S, Baala L, Vabres P, Hamel-Teillac D, Jacquemin E, Fabre M, Lyonnet S, De Prost Y, Munnich A, Hadchouel M, Smahi A. Claudin-1 gene mutations in neonatal sclerosing cholangitis associated with ichthyosis: a tight junction disease. *Gastroenterology* 2004; 127: 1386-1390 [PMID: 15521008 DOI: 10.1053/j.gastro.2004.07.022]
- 19 Matsumoto K, Imasato M, Yamazaki Y, Tanaka H, Watanabe M, Eguchi H, Nagano H, Hikita H, Tatsumi T, Takehara T, Tamura A, Tsukita S. Claudin 2 deficiency reduces bile flow and increases susceptibility to cholesterol gallstone disease in mice. *Gastroenterology* 2014; 147: 1134-45.e10 [PMID: 25068494 DOI: 10.1053/j.gastro.2014.07.033]
- 20 Zhou Y, Ji H, Xu Q, Zhang X, Cao X, Chen Y, Shao M, Wu Z, Zhang J, Lu C, Yang J, Shi Y, Bu H. Congenital biliary atresia is correlated with disrupted cell junctions and polarity caused by Cdc42 insufficiency in the liver. *Theranostics* 2021; 11: 7262-7275 [PMID: 34158849 DOI: 10.7150/thno.49116]
- 21 Günzel D, Yu AS. Claudins and the modulation of tight junction permeability. *Physiol Rev* 2013; 93: 525-569 [PMID: 23589827 DOI: 10.1152/physrev.00019.2012]
- 22 Schumann M, Günzel D, Buerger N, Richter JF, Troeger H, May C, Fromm A, Sorgenfrei D, Daum S, Bojarski C, Heyman M, Zeitz M, Fromm M, Schulzke JD. Cell polarity-determining proteins Par-3 and PP-1 are involved in epithelial tight junction defects in coeliac disease. *Gut* 2012; 61: 220-228 [PMID: 21865402 DOI: 10.1136/gutjnl-2011-300123]
- 23 Morin PJ. Claudin proteins in human cancer: promising new targets for diagnosis and therapy. *Cancer Res* 2005; 65: 9603-9606 [PMID: 16266975 DOI: 10.1158/0008-5472.CAN-05-2782]
- 24 Szade J, Kunc M, Pieczyńska-Uziębło B, Świerblewski M, Biernat W, Jassem J, Senkus E. Comparison of claudin-3 and claudin-4 expression in bilateral and unilateral breast cancer. *Neoplasma* 2021; 68: 283-289 [PMID: 33147053 DOI: 10.4149/neo\_2020\_200816N867]
- 25 Ye X, Zhao L, Kang J. Expression and significance of PTEN and Claudin-3 in prostate cancer. *Oncol Lett* 2019; 17: 5628-5634 [PMID: 31186785 DOI: 10.3892/ol.2019.10212]
- 26 Yuan M, Chen X, Sun Y, Jiang L, Xia Z, Ye K, Jiang H, Yang B, Ying M, Cao J, He Q. ZDHHC12-mediated claudin-3 S-palmitoylation determines ovarian cancer progression. *Acta Pharm Sin B* 2020; 10: 1426-1439 [PMID: 32963941 DOI: 10.1016/j.apsb.2020.03.008]
- 27 Okugawa T, Oshima T, Chen X, Hori K, Tomita T, Fukui H, Watari J, Matsumoto T, Miwa H. Down-regulation of claudin-3 is associated with proliferative potential in early gastric cancers. *Dig Dis Sci* 2012; 57: 1562-1567 [PMID: 22290341 DOI: 10.1007/s10620-012-2043-5]
- 28 Ahmad R, Kumar B, Chen Z, Chen X, Müller D, Lele SM, Washington MK, Batra SK, Dhawan P, Singh AB. Loss of claudin-3 expression induces IL6/gp130/Stat3 signaling to promote colon cancer malignancy by hyperactivating Wnt/ $\beta$ -catenin signaling. *Oncogene* 2017; 36: 6592-6604 [PMID: 28783170 DOI: 10.1038/onc.2017.259]
- 29 Takala H, Saarnio J, Wiik H, Soini Y. Claudins 1, 3, 4, 5 and 7 in esophageal cancer: loss of claudin 3 and 4 expression is associated with metastatic behavior. *APMIS* 2007; 115: 838-847 [PMID: 17614851 DOI: 10.1111/j.1600-0463.2007.apm\_656.x]
- 30 Zhang Z, Yu W, Chen S, Chen Y, Chen L, Zhang S. Methylation of the claudin-3 promoter predicts the prognosis of advanced gastric adenocarcinoma. *Oncol Rep* 2018; 40: 49-60 [PMID: 29749528 DOI: 10.3892/or.2018.6411]
- 31 Pan XY, Wang B, Che YC, Weng ZP, Dai HY, Peng W. Expression of claudin-3 and claudin-4 in normal, hyperplastic, and malignant endometrial tissue. *Int J Gynecol Cancer* 2007; 17: 233-241 [PMID: 17291259 DOI: 10.1111/j.1525-1438.2006.00748.x]
- 32 Baier FA, Sánchez-Taltavull D, Yarahmadov T, Castellà CG, Jebbawi F, Keogh A, Tombolini R, Odriozola A, Dias MC, Deutsch U, Furuse M, Engelhardt B, Zuber B, Odermatt A, Candinas D, Stroka D. Loss of Claudin-3 Impairs Hepatic Metabolism, Biliary Barrier Function, and Cell Proliferation in the Murine Liver. *Cell Mol Gastroenterol Hepatol* 2021; 12: 745-767 [PMID: 33866021 DOI: 10.1016/j.jcmgh.2021.04.003]
- 33 Herrema H, Meissner M, van Dijk TH, Brufau G, Boverhof R, Oosterveer MH, Reijngoud DJ, Müller M, Stellaard F, Groen AK, Kuipers F. Bile salt sequestration induces hepatic de novo lipogenesis through farnesoid X receptor- and liver X receptor alpha-controlled metabolic pathways in mice. *Hepatology* 2010; 51: 806-816 [PMID: 19998408 DOI: 10.1002/hep.23408]
- 34 Wei KR, Yu X, Zheng RS, Peng XB, Zhang SW, Ji MF, Liang ZH, Ou ZX, Chen WQ. Incidence and mortality of liver cancer in China, 2010. *Chin J Cancer* 2014; 33: 388-394 [PMID: 25104174 DOI: 10.5732/cjc.014.10088]
- 35 Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. *Gastroenterology* 2019; 156: 477-491.e1 [PMID: 30367835 DOI: 10.1053/j.gastro.2018.08.065]
- 36 Tania M, Khan MA, Fu J. Epithelial to mesenchymal transition inducing transcription factors and metastatic cancer. *Tumour Biol* 2014; 35: 7335-7342 [PMID: 24880591 DOI: 10.1007/s13277-014-2163-y]
- 37 Yeung KT, Yang J. Epithelial-mesenchymal transition in tumor metastasis. *Mol Oncol* 2017; 11: 28-39 [PMID: 28085222 DOI: 10.1002/1878-0261.12017]
- 38 Lin X, Shang X, Manorek G, Howell SB. Regulation of the Epithelial-Mesenchymal Transition by Claudin-3 and Claudin-4. *PLoS One* 2013; 8: e67496 [PMID: 23805314 DOI: 10.1371/journal.pone.0067496]
- 39 Che J, Yue D, Zhang B, Zhang H, Huo Y, Gao L, Zhen H, Yang Y, Cao B. Claudin-3 Inhibits Lung Squamous Cell Carcinoma Cell Epithelial-mesenchymal Transition and Invasion via Suppression of the Wnt/ $\beta$ -catenin Signaling Pathway. *Int J Med Sci* 2018; 15: 339-351 [PMID: 29511369 DOI: 10.7150/ijms.22927]
- 40 Jiang L, Yang YD, Fu L, Xu W, Liu D, Liang Q, Zhang X, Xu L, Guan XY, Wu B, Sung JJ, Yu J. CLDN3 inhibits cancer aggressiveness via Wnt-EMT signaling and is a potential prognostic biomarker for hepatocellular carcinoma. *Oncotarget* 2014; 5: 7663-7676 [PMID: 25277196 DOI: 10.18632/oncotarget.2288]
- 41 Ren T, Zhu L, Cheng M. CXCL10 accelerates EMT and metastasis by MMP-2 in hepatocellular carcinoma. *Am J Transl Res* 2017; 9: 2824-2837 [PMID: 28670372]
- 42 李娟, 胡晓松, 周方方, 李帅. 肝细胞癌组织中Claudin-3、MMP-2表达观察. *山东医药* 2017; 57: 45-47
- 43 Bodnar M, Szyłberg Ł, Kazmierczak W, Marszałek A. Tumor progression driven by pathways activating matrix

- metalloproteinases and their inhibitors. *J Oral Pathol Med* 2015; 44: 437-443 [PMID: 25244188 DOI: 10.1111/jop.12270]
- 44 Németh Z, Szász AM, Tátrai P, Németh J, Gyorffy H, Somorácz A, Szjártó A, Kupcsulik P, Kiss A, Schaff Z. Claudin-1, -2, -3, -4, -7, -8, and -10 protein expression in biliary tract cancers. *J Histochem Cytochem* 2009; 57: 113-121 [PMID: 18854598 DOI: 10.1369/jhc.2008.952291]
- 45 Ikeda C, Haga H, Makino N, Inuzuka T, Kurimoto A, Ueda T, Matsuda A, Kakizaki Y, Ishizawa T, Kobayashi T, Sugahara S, Tsunoda M, Suda K, Ueno Y. Utility of Claudin-3 in extracellular vesicles from human bile as biomarkers of cholangiocarcinoma. *Sci Rep* 2021; 11: 1195 [PMID: 33441949 DOI: 10.1038/s41598-021-81023-y]
- 46 Lammert F, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, van Erpecum KJ, van Laarhoven CJ, Wang DQ. Gallstones. *Nat Rev Dis Primers* 2016; 2: 16024 [PMID: 27121416 DOI: 10.1038/nrdp.2016.24]
- 47 Tanaka H, Imasato M, Yamazaki Y, Matsumoto K, Kunimoto K, Delpierre J, Meyer K, Zerial M, Kitamura N, Watanabe M, Tamura A, Tsukita S. Claudin-3 regulates bile canalicular paracellular barrier and cholesterol gallstone core formation in mice. *J Hepatol* 2018; 69: 1308-1316 [PMID: 30213590 DOI: 10.1016/j.jhep.2018.08.025]
- 48 D'Souza T, Sherman-Baust CA, Poosala S, Mullin JM, Morin PJ. Age-related changes of claudin expression in mouse liver, kidney, and pancreas. *J Gerontol A Biol Sci Med Sci* 2009; 64: 1146-1153 [PMID: 19692671 DOI: 10.1093/gerona/64.11.1146]
- 49 Yagi S, Hirata M, Miyachi Y, Uemoto S. Liver Regeneration after Hepatectomy and Partial Liver Transplantation. *Int J Mol Sci* 2020; 21 [PMID: 33182515 DOI: 10.3390/ijms21218414]
- 50 Schmelzer E, Wauthier E, Reid LM. The phenotypes of pluripotent human hepatic progenitors. *Stem Cells* 2006; 24: 1852-1858 [PMID: 16627685 DOI: 10.1634/stemcells.2006-0036]
- 51 Zhang S, Sharaf Eldin HE, Gu WL, Li TS. Laminin alpha-3 and thrombospondin-1 differently regulate the survival and differentiation of hepatocytes and hepatic stem cells from neonatal mice. *Am J Transl Res* 2021; 13: 12684-12693 [PMID: 34956483]
- 52 Ando T, Ito H, Kanbe A, Hara A, Seishima M. Deficiency of NALP3 Signaling Impairs Liver Regeneration After Partial Hepatectomy. *Inflammation* 2017; 40: 1717-1725 [PMID: 28656530 DOI: 10.1007/s10753-017-0613-6]
- 53 Sakai Y, Arie H, Ni Y, Zhuge F, Xu L, Chen G, Nagata N, Suzuki T, Kaneko S, Ota T, Nagashimada M. Lactobacillus pentosus strain S-PT84 improves steatohepatitis by maintaining gut permeability. *J Endocrinol* 2020; 247: 169-181 [PMID: 33032263 DOI: 10.1530/JOE-20-0105]
- 54 Garcia-Hernandez V, Quiros M, Nusrat A. Intestinal epithelial claudins: expression and regulation in homeostasis and inflammation. *Ann NY Acad Sci* 2017; 1397: 66-79 [PMID: 28493289 DOI: 10.1111/nyas.13360]
- 55 Assunção R, Alvito P, Kleiveland CR, Lea TE. Characterization of in vitro effects of patulin on intestinal epithelial and immune cells. *Toxicol Lett* 2016; 250-251: 47-56 [PMID: 27067107 DOI: 10.1016/j.toxlet.2016.04.007]
- 56 Typpo KV, Larmonier CB, Deschenes J, Redford D, Kiela PR, Ghishan FK. Clinical characteristics associated with postoperative intestinal epithelial barrier dysfunction in children with congenital heart disease. *Pediatr Crit Care Med* 2015; 16: 37-44 [PMID: 25162512 DOI: 10.1097/PCC.0000000000000256]
- 57 Yuan B, Zhou S, Lu Y, Liu J, Jin X, Wan H, Wang F. Changes in the Expression and Distribution of Claudins, Increased Epithelial Apoptosis, and a Mannan-Binding Lectin-Associated Immune Response Lead to Barrier Dysfunction in Dextran Sodium Sulfate-Induced Rat Colitis. *Gut Liver* 2015; 9: 734-740 [PMID: 25717051 DOI: 10.5009/gnl14155]
- 58 Volynets V, Rings A, Bárdos G, Ostaff MJ, Wehkamp J, Bischoff SC. Intestinal barrier analysis by assessment of mucins, tight junctions, and  $\alpha$ -defensins in healthy C57BL/6J and BALB/cJ mice. *Tissue Barriers* 2016; 4: e1208468 [PMID: 27583194 DOI: 10.1080/21688370.2016.1208468]
- 59 Wang Z, Wang A, Gong Z, Biviano I, Liu H, Hu J. Plasma claudin-3 is associated with tumor necrosis factor- $\alpha$ -induced intestinal endotoxemia in liver disease. *Clin Res Hepatol Gastroenterol* 2019; 43: 410-416 [PMID: 31053499 DOI: 10.1016/j.clinre.2018.11.014]

科学编辑: 张砚梁 制作编辑: 张砚梁





Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton,  
CA 94566, USA  
**Telephone:** +1-925-3991568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**https://**[www.wjgnet.com](https://www.wjgnet.com)



ISSN 1009-3079

