

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

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

Shijie Huaren Xiaohua Zazhi

2019 年 1 月 8 日 第 27 卷 第 1 期 (Volume 27 Number 1)



1/2019

ISSN 1009-3079



《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. 本刊被美国国际检索系统《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)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.



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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 2019-01-08

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)

主编

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Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

E-mail: wjgd@wjgnet.com

<http://www.wjgnet.com>

出版

百世登出版集团有限公司

Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

E-mail: 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: 010-85381892

传真: 010-85381893

《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。本刊被美国国际检索系统《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)》和《超星期刊域出版平台(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。

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定价

每期136.00元 全年24期3264.00元

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Editorial Board Member of *World Chinese Journal of Digestology*, Bi-Hui Zhong, Professor, Vice-Director of Gastroenterology, the First Affiliated Hospital of Sun Yat-sen University, NO. 58 Zhongshan Road, Yuexiu District, Guangzhou 510080, Guangdong Province, China

Indexed/Abstracted by

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

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Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993

Renamed on January 25, 1998

Publication date January 8, 2019

NAME OF JOURNAL

World Chinese Journal of Digestology

ISSN

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

EDITOR-IN-CHIEF

Ying-Sheng Cheng, Professor, Department of Radiology, Sixth People's Hospital of Shanghai Jiaotong University, Shanghai 200233, China

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

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EDITORIAL OFFICE

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World Chinese Journal of Digestology

Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

E-mail: wjcd@wjgnet.com

<https://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

E-mail: 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: +86-10-85381892

Fax: +86-10-85381893

PRINT SUBSCRIPTION

RMB 136 Yuan for each issue

RMB 3264 Yuan for one year

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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.

肠道微生物与自身免疫性肝病研究进展与评价

池肇春

池肇春, 山东大学医学院附属医院青岛市市立医院消化内科 山东省青州市 266011

池肇春, 教授, 主任医师, 主要从事肝病的临床研究.

作者贡献分布: 本文由池肇春单独完成.

通讯作者: 池肇春, 教授, 主任医师, 266011, 山东省青州市胶州路1号, 青岛市市立医院消化内科. c.z.chow@163.com

收稿日期: 2018-10-10

修回日期: 2018-10-23

接受日期: 2018-11-15

在线出版日期: 2019-01-08

Intestinal microbiome and autoimmune liver disease

Zhao-Chun Chi

Zhao-Chun Chi, Department of Gastroenterology, Qingdao Municipal Hospital, Affiliated Hospital of Shandong University Medical College, Qingdao 266011, Shandong Province, China

Corresponding author: Zhao-Chun Chi, Professor, Chief Physician, Department of Gastroenterology, Qingdao Municipal Hospital, 1 Jiaozhou Road, Qingdao 266011, Shandong Province, China. c.z.chow@163.com

Received: 2018-10-10

Revised: 2018-10-23

Accepted: 2018-11-15

Published online: 2019-01-08

Abstract

At present, it has been proved that intestinal microbial-related disorders are involved in the development and progression of multi-organ system diseases. Intestinal microflora is the accumulation of microbial antigens and activated immune cells. Changes in the composition of intestinal microflora (biological disorders) can destroy the systemic immune tolerance of intestinal and

symbiotic bacteria. Toll-like receptors in the intestine recognize microbial-related molecular patterns and T helper lymphocyte subpopulations that can cross-react with host antigens (molecular mimics). Activated enterogenous lymphocytes can migrate to lymph nodes, and enterogenous microbial antigens can migrate to extraintestinal sites. Inflammasomes can form in hepatocytes and hepatic stellate cells, which can drive inflammatory, immune-mediated and fibrotic responses. This article reviews and evaluates the role of intestinal microorganisms in the pathogenesis and treatment of autoimmune liver disease.

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Key Words: Autoimmune hepatitis; Primary sclerosing cholangitis; Primary biliary cholangitis; Innate immunity; Intestinal ecological imbalance; Mucosal barrier; Probiotics

Chi ZC. Intestinal microbiome and autoimmune liver disease. *Shijie Huaren Xiaohua Zazhi* 2019; 27(1): 50-62

URL: <https://www.wjgnet.com/1009-3079/full/v27/i1/50.htm>

DOI: <https://dx.doi.org/10.11569/wcjd.v27.i1.50>

摘要

目前, 已被证实与肠道微生物有关的疾病涉及人体的多个器官系统疾病的发生与发展. 肠道微生物群是微生物抗原和活化免疫细胞的蓄积体, 肠道菌群组成的改变(生物障碍)可以破坏肠道和共生菌的系统免疫耐受性. 肠内的Toll样受体可以识别微生物相关的分子模式和T辅助淋巴细胞的形状亚群, 这些亚群可以与宿主抗原(分子模拟)交叉反应. 活化的肠源性淋巴细胞可以迁移到淋巴结, 肠源性微生物抗原可以转移到肠外部位. 炎症小体可以在肝细胞和肝星状细胞中形成, 它们可以驱动促炎、免疫介导和纤维化反应. 本文就肠道微生物在自身免疫性肝病

发病机制和治疗上的作用的研究作一综述和评价。

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关键词: 自身免疫性肝炎; 原发性硬化性胆管炎; 原发性胆汁性胆管炎; 先天免疫; 肠菌生态失衡; 黏膜屏障; 益生菌

核心提要: 肠道微生物是微生物抗原和活化免疫细胞的储存库, 这些细胞参与了多种全身免疫介导的疾病的发生机制。自身免疫性肝炎可能由肠道功能障碍、肠道通透性增加以及微生物和自身抗原之间的分子模拟引起或维持。多种药物、分子、饮食和益生菌干预可以改变肠道微生物群并减弱免疫应答。肠道微生物在自身免疫性肝病(autoimmune liver disease, AILD)中的作用值得进行深入的研究, 并且将寻求新的治疗方法, 如抗生素、益生菌、粪便移植有望成为治疗的新靶点, 以改善AILD的预后。

池肇春. 肠道微生物与自身免疫性肝病研究进展与评价. 世界华人消化杂志 2019; 27(1): 50–62

URL: <https://www.wjgnet.com/1009-3079/full/v27/i1/50.htm>

DOI: <https://dx.doi.org/10.11569/wcjd.v27.i1.50>

0 引言

近年来, 研究发现肠道微生物与许多疾病的发生发展有密切相关, 它被视为人体又一“隐藏的器官”, 携带着人体“第二基因”, 研究发现遗传、环境、饮食、肠道屏障功能的完整性等因素都会影响肠道微生物的结构, 进而引发疾病。

自身免疫性肝病(autoimmune liver disease, AILD)通常包括自身免疫性肝炎(autoimmune hepatitis, AIH)、原发性胆汁性胆管炎(primary biliary cholangitis, PBC)、原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)、IgG4相关性胆管炎和重叠综合征, 是一组以免疫损伤为特征的慢性、进展性、免疫介导的自身免疫性炎症性肝病^[1,2]。近几年的研究证明, 肠道微生物在AILD发病机制中的多个环节均参与作用, 引起了学者们广泛的重视和关注, 成为最热门的研究课题。有关AILD的发病机制错综复杂, 尚未完全澄清。涉及免疫、炎症代谢异常、细胞因子、肠黏膜屏障破坏、和细菌生态失衡等众多机制相关, 目前认为肠道微生物起到关键性作用。在肠道炎症的情况下, 肠道屏障的损伤导致细菌易位, 从而刺激远处器官的免疫反应。或者, 免疫细胞异常失调, 如观察到的Th17极化。Th17细胞在肠道固有层最丰富, 它们分泌促炎细胞因子IL-17A、IL-17F和IL-22, 以增强肠道屏障的完整性和抵抗病原体的能力^[3-6]。

肠源性细菌和细菌产物从肠腔到肝脏、肠系膜淋

巴结和其他肠外部位的迁移可能通过易位发生^[7]。易位意味着肠道通透性增加, 可能是因为肠黏膜内的紧密连接被削弱或肠屏障被细菌过度生长所致。易位的细菌产物, 包括LPS和未甲基化的胞嘧啶-磷酸盐-鸟嘌呤(cytosine-phosphate-guanine, CpG), 然后可以通过门静脉输送到肝脏并激活TLRs和NLRs^[8-11]。

肠道微生物群可通过饮食调整^[11-13]、益生菌制剂^[14-16]、补充维生素A和维甲酸^[17,18]、抗生素^[19]、肠道再定植^[20-23]、降低肠道通透性的药物来控制^[24,25], 或通过阻断TLR信号和产生促炎细胞因子的分子干预, 刺激抗炎反应的分子干预(多糖A), 以及短链脂肪酸调节影响基因表达的信号通路, 应用保持屏障完整性的药物等治疗^[4]。

1 肠道微生物与肝自身免疫

由于70%的肝脏血液供应来自门静脉, 肝脏在生理上暴露于肠道来源的微生物成分和代谢物, 肠道微生物障碍不仅与肝脏疾病有关, 而且与炎症、纤维化或胆汁淤积状态有关^[26]。这种肠-肝轴也与AILD有关, 并且可用PSC和原发性胆管炎作为代表^[5]。

肠道微生物在肝脏自身免疫中的参与模式, 根据肠肝轴、细菌易位、肠道启动淋巴细胞向肝脏迁移、胆汁酸和核受体信号转导等参与了PBC和PSC的发病机制。

1.1 肝脏的细菌易位与免疫激活 肠道黏膜免疫系统, 特别是肠系膜淋巴结, 将共生微生物区隔开。除了系膜淋巴结外, 肝脏还充当第二道防线, 以消除来自肠道的细菌^[27]。值得注意的是, 这种功能在慢性肝病中似乎受到损害, 但是Kupffer细胞在肝病过程中如何不能清除肠道微生物其机制仍然是未知的。在这方面, 肝脏不仅是接受者, 而且是具有Kupffer细胞、肝窦内皮细胞和胆道上皮细胞(BEC)的肠源性药物的一个过滤器。

尽管微生物群与免疫疾病有多种联系, 但它们在自身免疫中的作用却鲜为人知。研究发现, 肠道致病菌, 鸡肠球菌, 转移到肝脏和其他系统组织, 易于导致自身免疫的遗传背景下触发自身免疫应答。在该模型中, 抗生素治疗可预防死亡, 抑制组织中鸡大肠杆菌的生长, 并消除致病性自身抗体和T细胞。肝细胞-鸡胆汁共培养诱导自身免疫促进因子。单克隆和自身免疫倾向小鼠的病原体易位诱导自身抗体并导致死亡, 这个现象可以通过针对病原体的肌肉内注射疫苗来预防。从自身免疫患者的肝活检中回收了鸡大肠杆菌特异性DNA, 并且与人肝细胞共培养复制了鼠的模式, 因此, 在易感的人中明显出现类似的过程。这些发现表明, 肠道病原菌可以在遗传易感宿主中易位和促进自身免疫发生^[28]。

模式识别受体(pattern recognition receptor, PRR), 它们能

够检测微生物相关分子模式(MAMP), 例如细菌L, 肽聚糖, 鞭毛蛋白和细菌DNA, 以及其他配体. 这些MAMP引发的过度免疫应答被认为可导致肝损伤和纤维化发生. 最近的研究描述了控制微生物移位的肠血管屏障(GVB), 研究发现其在不明原因的腹腔疾病患者中受损. 出现血清转氨酶升高^[29]由于这些变化, 细菌易位可能导致肠外炎症, 其中肝细胞和胆管细胞是最脆弱的细胞类型, 容易受到炎症的攻击.

“漏肠”假说已经在NAFLD以及PBC和PSC中得到了证实. 例如, 由于门脉循环中的TLR4和TLR9激动剂, 当缺乏NLRP6和NLRP3炎症小体时可加重肝脏脂肪变性发生^[30]. 敲除小鼠CX3CR1会增加门脉血清中的内毒素, 并促进脂肪性肝炎发展. 在PBC患者中显示胆管受损, 在正常小鼠中慢性细菌暴露后可导致自身抗原产生和随后的类似于PBC的胆管炎发生^[31]. 此外, PSC患者中检测到的核周抗中性粒细胞胞浆抗体(antineutrophil cytoplasmic antibody, p-ANCA)可能以 β -微管蛋白5同种型(Beta tubulin 5 isotype, TBB-5)为自身抗原. 它是基因一种进化的细菌蛋白, 而FtsZ(真核细胞骨架蛋白中的微管蛋白)可引起对肠道微生物的免疫交叉反应^[32]. 在人类中, 损害肠道微生物免疫应答的遗传多态性可能部分会导致肝脏疾病的发生. 事实上, 全基因组关联分析(GWASs)已经建立了PSC与IBD几个遗传易感位点, 包括募集结构域蛋白9(caspase recruitment domain-containing protein 9, CARD-9), 岩藻糖基转移酶2(fucosyl transferase FUT-2)和巨噬细胞刺激蛋白1(macrophage stimulating protein 1, MST-1), 这些基因所编码的蛋白质密切参与了先天免疫和适应性免疫^[33-36]如肠上皮细胞FUT-2的岩藻糖基化, 它还保持宿主-微生物群落共生. CARD9是一种配体蛋白, 它介导模式识别信号, 激活促炎和抗炎细胞因子, 调节炎症和细胞凋亡. PSC患者在胆汁和结肠微生物以不同的模式进行FUT-2变异, 更重要的是, 显示胆道感染和显性狭窄的发生率增加^[37]. CARD9是NOD2与TLR信号通路的一个重要的下游传递者, 与IL-22的产生和肠道完整性相关.

1.2 黏膜淋巴细胞向肝脏的迁移与“肠漏”假说平行的是, 已经提出了“肠淋巴细胞归巢”假说来解释与PSC和PBC相关的肠-肝轴. 黏膜淋巴细胞表达整合素 $\alpha 4\beta 7$ 和趋化因子受体CCR9, 分别与内皮细胞黏附分子MAdCAM-1(黏膜黏连细胞黏附分子-1)和趋化因子配体CCL25结合. 然而, 在炎症性肝病, 包括PSC, 肝窦内皮细胞中检测到MAdCAM-1和CCL25的异常表达^[38]导致肠道启动的T细胞被异常募集到肝脏, 并可能在识别时触发自身免疫反应^[39]实际上, 在卵白蛋白诱导的结肠炎小鼠模型中, 由卵白蛋白引发的GALT中的T细胞在识

别胆管细胞上的相同抗原, 即卵白蛋白时, 迁移到肝脏并引起胆管炎. 他明确了微生物群在IBD发病机制中的作用, 认为黏膜T细胞被共生微生物群异常激活, 进一步迁移到肝脏并与肝脏中存在的抗原发生交叉反应. 根据这一假设, 最近对TCR β 链的测序研究表明, PSC-IBD患者的肠浸润和肝浸润T细胞是克隆相关的, 并且可能识别相同的抗原^[40]. 由于在慢性肝病, 特别是PBC和PSC中经常观察到的血清IgA水平升高, 这一发现进一步突出了肠-肝轴在这些疾病中的潜在参与作用.

然而, 肝内皮细胞表达肠特异性分子的机制仍不清楚, 尽管有人推测肝血管黏附蛋白(VAP)-1在PSC中的上调是肝脏MAdCAM-1异常表达的原因^[41]. 来源于肠道细菌和饮食的半胱胺和其他胺类可以通过门静脉进入肝脏, 并作为VAP-1的底物, VAP-1是一种有效的氨基氧化酶, 导致产生分解代谢物, 在肝窦内皮细胞导致产生分解代谢物^[42].

1.3 肠道微生物、胆汁酸和核受体信号转导 除了与免疫系统直接相互作用外, 微生物与胆汁酸(BA)之间的关系也是肠-肝相互作用的代表^[43]. 胆汁酸主要由肝细胞产生, 然后由肠腔内的细菌代谢成次级胆汁酸. 早期的研究已经报道, GF小鼠的BA组成不同于常规饲养的(CON-R)对应物. Sayin等^[44]通过显示CONV-R小鼠表现出牛磺- β -鼠胆酸(T β MCA)比例降低以及BA池的显著缩小, 提供了对该领域的见解. 更重要的是, 氰尿酸三聚胺(cyanurate melamine, MCA)是强有力的法尼素X受体(farnesyl X receptor, FXR)拮抗剂, 肠道微生物可通过减轻回肠FXR抑制来调节肝脏中BA的合成. 具体地说, 肠内的FXR激活诱导成纤维细胞生长因子15(fibroblast growth factor 15, FGF15)表达, 然后到达肝脏并阻断7- α -羟化酶(7- α -hydroxylase, CYP7A1), 这是BA合成中的限速酶. 通过抗生素或抗氧化剂的微生物重组增加T β -MCA, 抑制肠FXR信号^[45,46]. 相反, BA通过直接激活或间接激活固有免疫系统, 进而通过FXR和G-PR(G蛋白受体偶联胆汁酸受体TGR5)进一步影响宿主生理^[48]. 确实, 宿主胆汁酸的动态导致肠道微生物群的变化^[49]. 应用FXR激动剂胆甾酸对肝硬化大鼠部分地阻止肠屏障功能障碍和减轻肠道炎症, 通过使用GF和FXR-/-小鼠, 减少了细菌易位. 最近的一项研究表明, 由微生物引起的饮食诱导的肥胖和肝脏脂肪变性取决于其对BA谱和FXR信号的调节^[50]. 总之, 证明肠道微生物群、胆汁酸和核受体信号传导通路的作用可影响宿主的代谢和肝脏疾病的发病机制.

2 肠道微生物群与AILD

一些测序研究报告了PSC和PBC中肠道微生物群落的

改变, 尽管特别是在属和种水平上存在差异, 但仍能说明肠道微生物在AILD上的作用. 有报告在UDCA使用之前对PBC群组的粪便微生物进行16s核糖体RNA(rRNA)测序, 以避免胆汁酸的混淆效应. 此外, 还对37例PBC患者在UDCA治疗6 mo前后进行了前瞻性研究^[51]. UDCA对PBC中的肠道微生物群与健康对照组相比, 结果显示体内微生物多样性显著降低, 提出可治疗肠道菌群失调. 这一发现与先前研究不一致, 这可能是由于UDCA治疗的影响有关^[52]. 由12个属定义的PBC的微生物特征可以用来准确区分验证队列中的PBC和对照(AUC为0.84-0.86). 肠杆菌科中增加的一个未知属显示出与PBC的关联最强, 其次是假单胞菌、微囊藻和梭菌, 而在PBC队列中振荡菌和沙特氏菌减少. 值得注意的是, 在这PBC相关细菌属中, 在UDCA治疗6 mo后, 细菌丰度被逆转^[51], 与治疗反应平行, 因此表明肠道微生物群可能是PBC治疗的潜在目标.

由于IBD在PSC病例中高达60%-80%, 肠-肝轴与PSC的发病机制有关. 已发表的样本大小从11到85名患者的研究证实了PSC中独特的微生物分布^[53]—一般来说, PSC中的肠道微生物群与健康对照有显著的偏离, 其特点在不同的研究中, 已经观察到了肠球菌、微囊藻等特异性细菌的丰度变化, 其中一些可以作为PSC的生物标志物. 其中4项研究分析了黏膜活检^[54-66], 而其他研究则集中在粪便微生物群上. Hov等^[53]人的研究是对粪便肠道微生物群在PSC中的评估, 结果在PSC中鉴定出差异较小的微生物群, *Veillonella*是PSC相关属. 然而, 根据Sabino等^[59]的研究, 当排除肝硬化患者时, PSC中*Veillonella*属的差异并不显著. 此外, Sabino等鉴定了PSC中富集的三个菌属, 即肠球菌属、梭菌属和乳杆菌属.

肠道微生物群对于肠道免疫应答的发展是必不可少的, 而肠道免疫应答又维持微生物群的耐受性^[60,61]. 与野生型小鼠相比, 无菌小鼠肠道固有层CD4⁺T淋巴细胞较少, 发育不良的Peyer's斑块较少, IgA产生较少^[62,63]. 通过引入脆杆菌, 纠正了这些免疫缺陷. 定植还可以诱导IL-10分泌的调节性T细胞的产生, 可能是由于细菌分泌多糖A和直接激活Foxp3⁺Treg上的TLR2^[64]. FOXP3(forkhead box P3), 也称为蛇毒精(scurfin), 是转录因子forkhead/winged-helix(叉头样/翼状螺旋)家族的成员. 是一种参与免疫系统应答的蛋白质. FOXP3主要表达在CD4⁺CD25⁺Tregs, 是CD4⁺CD25⁺Tregs发育和功能的决定因素, FOXP3是调节途径的主要调节因子, 可使免疫反应降低. 在自身免疫性疾病中, 调节性T细胞活性的缺乏可允许其他自身免疫细胞攻击身体自身组织^[9,10]. 尽管尚未建立精确的控制

机制, FOX是脊椎动物转录因子的总称, 推测在转录过程中通过类似的DNA结合作用发挥控制作用. 在调节性T细胞模型系统中, FOXP3转录因子占据调节性T细胞功能相关基因的启动子, 在T细胞受体的刺激下可抑制关键基因的转录. 梭菌属的引入也可引起类似的变化^[23]. 逆转录病毒介导转染鼠, FOXP3使传统的CD4⁺T细胞获得调节表型能够抑制体外和体内的免疫反应, 提示异位FOXP3表达使T细胞呈现调节表型, 可用于过继细胞免疫治疗^[65]. 证据表明, 肠道微生物可通过激活Toll样受体(TLR^[66,67])和促进肝脏内炎症小体的形成^[30,68]影响全身免疫应答. TLR受体为表达在巨噬细胞、树突状细胞和上皮细胞表面, 可识别多种类型的病原体相关分子模式(PAMPs)或损伤相关分子模式(DAMPs)的生物分子, 这类模式识别受体可与病原体PAMPs结合, 并启动细胞内信号传导, 导致效应分子表达和分泌的受体. TLR介导的信号传导可导致固有免疫细胞活化, 产生两方面效应, 其一, 表达和分泌多种称之为促固有免疫细胞(proinflammatory cytokine), 如肿瘤坏死因子(tumor necrosis factor, TNF- α), 白细胞介素(IL)-12, IL-6等. 这些细胞因子可诱导炎症发生, 促进抗原提呈, 促进T辅助细胞(T helper cell, Th)发生Th1或Th2的格局变化; 其二, 可诱导共刺激分子(co-stimulatory molecule)表达, 启动特异性免疫应答产生. 由抗生素、遗传因素或疾病(生物障碍)引起的肠道微生物组成的改变可通过克服或回避对共生细菌的正常耐受性反应来维持或增强先天和适应性免疫应答^[69,70]. 细菌成分可充当抗原, 刺激全身免疫应答^[66,67,71]或肠内原代免疫细胞, 随后进入外周淋巴组织^[72]. 微生物和宿主衍生的抗原之间的分子模拟以及抗原致敏的淋巴细胞靶向可能随后启动或加强遗传易感个体的自身反应^[73].

肠道微生物群与肝脏之间的相互作用是多方面的, 肠道微生物失调可以产生微生物相关的分子模式(MAMPs), 激活肠中的Toll样受体(Tlr). 活化的TLR可以刺激巨噬细胞中的转录因子, 核因子- κ B(NF- κ B), 并产生促炎性细胞因子. 它们还可以增加抗原呈递细胞(APC)上主要组织相容性复合物的表达, 并使CD4淋巴细胞对细菌配体敏感. 活化的淋巴细胞可以增殖为T辅助细胞Th1、Th2和Th17细胞. 这种异常微生物还可产生短链脂肪酸、内毒素、脂多糖(LPS)和可作为抗原配体的细菌成分. 肠黏膜内的紧密连接可能随着微生物障碍而减弱, 并允许淋巴细胞、细菌配体和内毒素的细胞旁易位. 这些肠源性元素可以进入门静脉并被输送到肝脏. 肝内的细菌配体可激活肝细胞、肝星状细胞、Kupffer细胞和窦状上皮细胞中的TLR, 并产生促炎性细胞因子和活性氧(ROS), 其可产生激活TLR的

损伤相关分子模式(DAMPs). 肝脏TLR也有助于CD4淋巴细胞对细菌配体和类似细菌配体的自身抗原(分子模拟)的增敏作用. 同时, 细菌配体和肠源性内毒素可激活肝细胞和肝星状细胞中炎性小体的非肥胖型糖尿病样受体(NLR). 半胱氨酸天冬氨酸蛋白酶1的释放可产生白细胞介素(IL)1 β 和IL-18, 促进组织损伤和免疫应答. 净效应是增加肝脏炎症和肝损伤, 并引起自身免疫和肝纤维化^[4,73,74].

3 微生物来源的全身免疫应答的机制

3.1 TLRs的激活 如前所述TLRs是肠内识别微生物相关分子模式、病原体相关分子模式和损伤相关分子模式的关键受体^[67,74,75](表1). 它们有助于产生对病原体和细胞信号的先天免疫应答, 并且它们可以形成T辅助(Th)淋巴细胞的亚群, 这些T辅助(Th)淋巴细胞识别微生物成分并具有与宿主抗原交叉反应的潜力^[60,76,77]. 在人类中已经描述了10种TLR, 并且每种TLR优先对在没有感染的情况下可能是病毒和细菌蛋白或内源性配体的特定配体作出反应^[75]. 除了TLR3之外, 所有受刺激的TLR都激活依赖于髓系分化因子88(MyD88)的信号传导途径^[10,78,79]. 通过MyD88通路的信号转导又激活核因子- κ B(NF- κ B), 并促进促炎细胞因子(TNF- α 、IL-1 β 和IL-6)的转录^[10,79,80].

TLR也能影响适应性免疫应答^[60]. 树突状细胞和巨噬细胞表达的TLRs可上调MHC II类分子并增强CD4⁺辅助性T淋巴细胞的抗原呈递^[81](表1). TLR还可以增加抗原呈递细胞中共刺激分子CD80、CD86和CD40的表达, 从而有利于T淋巴细胞活化和分化^[60,81]. Kupffer细胞表达除TLR5外的所有TLR, 它们是肝内对TLR配体应答的原代细胞^[82]. 通过Kupffer细胞产生促炎性细胞因子、趋化因子和活性氧可促进肝脏炎症和先天性和适应性免疫应答^[60,83]. 肝细胞、胆管上皮细胞(Biliary epithelial cells, BEC)、肝星状细胞(HSC)和窦状上皮细胞也表达TLRs, 但只有HSCs通过TLR9表达TLR1^[67].

细胞因子谱形成构成免疫介导的应答的T淋巴细胞亚群, 并且它受到微环境中配体激活的特定TLR的影响(表1). TLR4和TLR9的激活促进IL-12的释放, 并有利于促炎症的1型细胞因子途径^[84]. TLR4还诱导IL-23的分泌, 促进促炎性Th17淋巴细胞的扩增和存活^[85]. 相反, TLR2的激活有利于IL-10和IL-13的产生, 从而促进抗炎2型细胞因子应答^[86].

革兰阴性细菌的LPS是激活TLR4的主要配体^[10,86]. 细菌和病毒基因组中未甲基化的CpG序列激活TLR9(表1). 革兰阴性细菌的LPS是激活TLR的主要配体^[79], TLR2、TLR5、TLR7和TLR8由CD4⁺T淋巴细胞表达, 激活这些

TLR的配体(病毒蛋白)、鞭毛蛋白和单链核糖核酸可以直接激活记忆淋巴细胞并刺激其增殖. 天然存在的Tregs表达TLR2、TLR5和TLR8, 它们也可以被病毒和细菌成分直接激活^[87]. TLRs还可以通过识别诱导IL-6分泌的微生物产物来阻断Tregs的抑制作用. 病原体特异性适应性免疫应答是有利的, 可以加强防御机制. 因此, 微生物元素可通过TLR调节先天免疫应答和适应性免疫应答, 并通过调节细胞因子谱或直接影响免疫细胞增殖间接的影响免疫稳态.

TLR4是HSCs增加细胞外基质的一个重要信号通路. HSCs中活化的TLR4介导趋化因子和黏附分子的产生, 炎症细胞和免疫细胞对肝脏的化学吸引刺激纤维化过程^[88]. TLR4信号通路还通过下调TGF- β 受体的内源性抑制剂的产生来促进转化生长因子 β (TGF- β)的激活. 此外, TLR4信号还可下调抑制胶原转录的microRNA分子^[89]. TLR4基因的多态性可能影响TLR4对LPS的应答. 因此, LPS诱导的激活NF- κ B的信号通路可能被破坏, 并且促炎细胞因子TNF- α 和干扰素- β 的产生可能减少^[90]. 以这种方式, 遗传变异可能影响TLR4对微生物配体的反应和进行性肝纤维化的倾向.

TLR4信号通路涉及MyD88和NF- κ B在肝病进展中的作用^[91,92]. 肠源性内毒素的浓度在肝纤维化动物模型以及在肝硬化患者的循环系统和门静脉中增加. TLR信号通路尚未在自身免疫性肝炎中得到评价.

3.2 炎性小体刺激 炎性小体是蛋白质复合物, 在多种细胞的胞浆内形成, 包括巨噬细胞、肝细胞和HSC, 以接受与细胞应激、损伤或感染有关的刺激^[68,93,94]. 通过释放促炎细胞因子IL-1 β 和IL-18, 它们驱动对组织损伤的炎症反应, 并影响细胞死亡、炎症活性和纤维化. TLR和炎症小体具有不同的激活途径^[95], 但是它们之间的合作对于促进肠道微生物群与全身免疫应答之间的交流至关重要. 增加炎性小体表达的因素, 如饱和脂肪酸和细菌内毒素, 可增加TLR4的活化, 促进肝纤维化^[96].

炎性小体由非肥胖性糖尿病(NOD)样受体(NLR)家族中的传感器蛋白、适配分子(凋亡相关斑点样CARD结构域包含蛋白)和caspase(半胱氨酸天冬氨酸蛋白酶)1组成^[97]. 炎性小体可以感知微生物产物和代谢应激^[84], 激活caspase1, 触发炎性细胞因子的释放, 并形成先天的^[88]和适应性免疫应答. LPS刺激后肝细胞NLRP3(NOD样受体)表达上调, Kupffer细胞和上皮细胞也表达高水平的NLRP1和NLRP3^[95].

TLR和NLR共同为信号传导途径提供受体, 这些信号传导途径可响应包括微生物成分在内的各种内源性和外源性危险信号, 它们各自可产生促炎症反应, 维持和增强对肝脏的固有和适应性免疫反应^[98]. TLRs也可

表 1 肠微生物驱动全身免疫应答的机制

特征	机制
TLRs的激活	炎症前细胞因子增加 上调Ⅱ类MHC 增加共刺激分子 促进病原体特异性反应 LPS激活TLR4
炎症刺激	细菌激活TLR9序列HSCs TLR4促进肝纤维化 在肝细胞LPS上调 前caspase1激活 促进肝纤维化 固有和适应性免疫
生态失衡的出现	激活TLR, NLR遗传因素影响细菌组成
分子模拟	PANCA与细菌抗原反应 AMA交叉与大肠杆菌反应 靶向表位扩展的渐变同源物
效应物的混杂活性	

AMA: 抗线粒体抗体; BEC: 胆道上皮细胞; DAMPS: 损伤相关分子模式; HSC: 肝星状细胞; IL: 间质细胞; LPS: 脂多糖; MAMPs: 微生物相关分子模式; MHC: 主要组织相容性复合物; MyD88: 髓样分化因子88; NF- κ B: 核因子 κ B; NLR: 非肥胖性糖尿病样病变受体; ANCA: 非典型核周抗中性粒细胞胞浆抗体; TLR: Toll样受体; Tregs: 调节性T细胞。

能对炎性小体有反调节作用。LPS对TLRS的慢性刺激诱导IL-10的产生并降低NLRP3的激活^[99]。此外, 激活TLR2或TLR4可增加肝细胞的自噬、NLRP3的降解和抑制IL-1 β 的产生^[100]。

3.3 肠黏膜屏障作用的产生 生理情况下上皮细胞相互紧密连接形成一个生理屏障, 使细菌和系统循环很少接触。杯状细胞分泌糖蛋白形成黏液层复盖上皮^[101], 这个黏液层由内外两层组成^[101]外层是一个松黏液层, 含有大量细菌, 为共生菌提供一个理想的生存场所, 黏蛋白-2葡聚糖是重要的能量来源, 内层是一个无菌的坚固稠密的黏液层可防止细菌与上皮细胞直接接触^[102]。

共生菌对保持肠屏障完整性可能有益作用, 如艾克曼菌(*Akkermansia muciniphila*)^[103], 这些有益菌黏连至肠细胞, 可保持正常的屏障功能。嗜黏蛋白-艾克曼菌是一种从粪便中分离到的厌氧肠道菌, 可以利用肠道黏蛋白, 其主要功能与是调节肠道内黏液厚度和维持肠道完整性, 它与肥胖、糖尿病、炎症和代谢紊乱呈负相关^[104]。

抗菌分子包括防御素(dofensins)、抗菌肽溶酶体、C型凝集素等可阻止细菌与上皮细胞的相互作用^[105]。抗菌蛋白通过溶酶体或非酶抗菌分子如防御素、抗菌肽等把细菌杀死。

再生胰岛衍生蛋白3 γ (regenerating islet derived protein 3 gamma, REG3g) 是一种C-型凝集素, 在TLR-依存方式和TLR、TLR5配体引起REG3g表达^[106,107]。REG3g缺乏的小鼠肠上皮细胞, 特别是内黏液层的上皮细胞上有细菌定植增加, 揭示REG3g在上皮细胞和肠菌

隔离上的重要作用。

肠道屏障功能破坏后, 细菌和细菌产物从肠腔到达固有层, 其机制是许多细菌易位通过M-细胞(微褶细胞), 细菌蛋白与M-细胞特异的相互作用后经内化、跨细胞转运, 有些病原体可改变紧密连接分子, 因而改变细胞旁渗透性, 有些细菌激活MLCK(肌球蛋白轻链激酶), 引起紧密连接破坏^[108]。

肠道微环境与全身免疫应答之间肠黏膜屏障作用的产生意味着肠道域之间的自然屏障关系(表2)。有充分的证据证明这种假设是正确的, 但实际的机制目前尚不确定。

肠源性细菌和细菌产物从肠腔到肝脏、肠系膜淋巴结和其他肠外部位的迁移可能通过易位发生。易位意味着肠道通透性增加, 可能是因为肠黏膜内的紧密连接被削弱或肠屏障被细菌过度生长所致^[109,110]。易位的细菌产物, 包括LPS和未甲基化的CpG, 可以通过门静脉输送到肝脏并激活TLRS和NLRs^[79]。

细菌产生短链脂肪酸(乙酸、丁酸和丙酸), 这些脂肪酸可以影响肠黏膜内的紧密连接^[14,110](表2)。丁酸诱导肠黏膜中黏蛋白的合成, 加强紧密连接, 并减少细菌穿过应激上皮的传输^[104,111]丁酸还可通过促进外周Tregs的胸腺外分化^[112,113]和抑制NF- κ B和促炎细胞因子的转录而具有抗炎作用。其它短链脂肪酸(丙酸)和细菌副产物(琥珀酸和乙酸)不诱导黏蛋白的产生, 但可能会增加肠的通透性^[11]。

丁酸钠部分通过调节 β -连环蛋白依赖的Wnt信号通路在细胞内起作用。这一途径可影响细胞增殖和分化

表 2 肠道屏障的微生物机制

微生物作用	特征	机制
易位	肠道衍生物迁移	肠源性SCFA对紧密连接的影响
	紧密连接减弱	丁酸盐增强肠屏障
	小肠通透性增加	诱导黏蛋白合成
	细胞旁迁移结果	减少细菌易位增加外周Treg
	LPS和CpG递送到肝脏	抑制NF-κB和炎症
	活化的免疫细胞易位	乳酸强化肠屏障
	微生物抗原的易位激活外周免疫细胞	丁酸发酵
	Toll样受体和NLRs激活	产生低丁酸和乳酸产菌致屏障功能降低
	黏膜通透性增加	TLR影响分子介导
	封闭蛋白主要组成(成分)	信号通路破坏
主动运输	封闭带偶联到细胞骨架	解离紧密结合蛋白
	扣带蛋白接触细胞	细胞旁迁移途径形成
	肌动蛋白和肌球蛋白锚定细胞	大肠杆菌和艰难梭菌关键效应物
	中间丝结合细胞	
	信号通路密封结	
	蛋白激酶C调节闭塞蛋白	
主动运输	细菌抗原主动转运穿过肠屏障	具有主动转运能力的Payer结中的M细胞

CpG: 未甲基化的胞嘧啶磷酸鸟嘌呤寡核苷酸; LPS: 脂多糖; NF-κB: 核因子κB; NLR: 非肥胖糖尿病样受体; SCFA: 短链脂肪酸; TLR: Toll样受体; Tregs: 调节性T细胞。

的基因转录。在结肠癌细胞系中, β-连环蛋白转录复合物在细胞内的水平可影响其对丁酸的生理反应。高水平的转录复合物导致细胞凋亡。丁酸调节细胞增殖和凋亡的能力可能反过来又影响细胞活力和功能, 这些作用可能有助于维持胃肠黏膜屏障的完整性^[114]。

丁酸还可以通过促进细胞的凋亡或通过自噬来保存和调节细胞对内质网应激的反应^[115-117]。丁酸可促进过氧化物酶体增殖物激活受体γ的表达和诱导大肠细胞凋亡的caspases(尤其是caspase3)的激活。它也是一种短链脂肪酸, 包括丙酸酯, 可以诱导受损细胞的自噬, 并通过产生能量和阻滞凋亡的内在途径(线粒体)来保存它们的存活^[117,118]。肠源性短链脂肪酸, 如丁酸和丙酸, 可能是肠黏膜细胞增殖和功能的重要调节因子, 它们可能有助于预防全身性自身免疫反应^[115]。乳酸是碳水化合物发酵的细菌副产物, 也同时可降低肠道的通透性(表2)。乳酸菌主要通过肠道菌群发酵成丁酸酯起作用。乙酰辅酶A途径是乳酸产生丁酸的主要途径, 肠道微生物区系在乳酸的消耗上具有相当大的变异性^[119,120]。

肠上皮细胞与结构蛋白结合在一起^[120]。结构蛋白被组织组成紧密连接、黏附连接和桥粒三部分组成连接复合物。闭塞素是唯一已知的在细胞旁空间具有结构域的跨膜蛋白, 是紧密连接的主要成分。闭塞带1和2和扣带蛋白是在细胞与细胞接触部位紧密连接处发现的非跨膜蛋白。它们可能被封闭, 它们可能将细胞耦合到细胞骨架。肌动蛋白和肌球蛋白丝通过钙依赖性黏附分子

(E-cadherins)在黏附连接处将细胞锚定在一起, 中间丝锚定到桥粒上, 并帮助细胞结合。多种细胞信号通路影响连接点的组装和封闭, 并且它们是蛋白激酶C调节的闭塞蛋白和闭塞带1特异性的细胞类型^[4,5,121,122]。

大肠杆菌和艰难梭菌通过打开细胞旁通路^[11,123], 可解离结合蛋白, 增加肠通透性(表2)。肠上皮细胞上的TLR可以调节肠屏障的完整性, 可能通过影响结合蛋白的结构或功能的分子介质的表达所致^[124]。TLR2的激活增加了蛋白激酶C亚型的磷酸化, 这种作用与增强闭塞带的表达和紧密连接的密封有关。相反, TLR4的激活降低磷酸化闭塞蛋白的表达并增加细胞间的通透性^[124]。来自不同微生物物种的细菌配体可能通过TLR信号来影响肠道通透性, 而微生物产物通过多孔肠屏障的转移可能有助于全身的自身反应的发生^[125]。

微生物体影响全身免疫应答的另一个机制是通过细菌抗原在Peyer结内的M细胞穿过黏膜屏障的活性转运。虽然免疫细胞可以在肠内被激活, 并通过易位迁移到肝脏或外周淋巴组织, 但它们也可以通过易位或主动运输的细菌成分在体内循环中被激活, 这些细菌成分由抗原呈递细胞呈递并识别, 用循环的CD4⁺T辅助淋巴细胞作为外源抗原^[20]。

4 诊断AILD时对肠道菌群检测的评价

传统的粪便培养技术在评估肠道微生物群方面受到限制, 主要是因为厌氧微生物难以培养并且一些微生物种

群可能无法通过常规方法检测^[126,127]。研究肠道菌群多样性的常用方法是测序16S核糖体核糖核酸(rRNA)基因。16S rRNA基因存在于所有原核细胞中, 具有高度可变的区域散布着高度保守的区域, 其序列是原核生物的主要群组所特有的。这些序列可用于重建肠道微生物群的系统发育^[127]。

设计引物以补充可变区域两侧的普遍保守区域, 并确定细菌种类及其在微生物群中的比例。通过聚合酶链反应(PCR)扩增可变区, 并将PCR产物纯化后测序。测序结果与已建立的注释数据集进行比较^[127]。

用于重构人肠道微生物组分的技术的进一步进展包括微阵列技术、指纹技术, 例如末端限制性片段长度多态性的测定和下一代测序(NGS)^[128,129]。脱氧核糖核酸的微阵列杂交提供了一个高通量平台, 它由几千个探针组成, 可以同时检测核酸序列^[130]。

人类肠道芯片有4441个探针, 包括2442个针对已知微生物的探针, 以及1919个针对未知微生物的探针^[130]具有重叠相似性的探针数量较少的微生物物种变得更加敏感, 具有探索性设计的探针正与具有微生物特异性的探针耦合, 以尽力识别具有非特异序列的微生物^[131]。

目前, 肠道生态系统主要通过16S rRNA测序进行研究。该技术在鉴定构成肠道微生物群落的微生物种类、确定微生物群落的进化与变迁(系统发育)以及定量微生物多样性方面是有用的^[128]。

5 治疗策略

肠道微生物群可通过饮食调整、益生菌制剂、补充维生素A和维甲酸、抗生素、肠道再定植、降低肠道通透性的药物来控制 and 调节肠道屏障, 阻断TLR信号和产生促炎细胞因子的分子干预等进行治疗, 也可通过刺激抗炎反应的分子干预(如多糖A), 以及调节短链脂肪酸信号通路来影响基因表达、肠屏障完整性和炎症反应^[129-131]。

含有双歧杆菌的益生菌补充剂促进了Tregs在细胞培养物中的扩展^[15]。鞣酸明胶已被用于小鼠急性结肠炎模型中, 其作用是保护黏膜屏障, 改变微生物组成, 并降低炎症活性^[132]。在LPS刺激的细胞培养中也评价了鞣酸明胶, 它抑制细胞间黏附分子-1的表达, 并以剂量依赖的方式减少IL-8和TNF- α 的产生^[25]。新近报道益生菌可减轻NASH患者的脂肪变性, 此需要进一步验证^[133]。

肠道微生物群的控制动物模型和肝病患者中也显示出了希望。在四氯化碳诱发的肝硬化大鼠中, 抗生素治疗和益生菌补充剂可降低全身内毒素水平并改善了肝功能试验^[134]而在缺血/再灌注性肝损伤大鼠中, 益生菌补充剂乳酸杆菌降低了前体内毒素的产生。炎症、

促纤维化细胞因子和肝功能试验也得到改善^[135]。一个小型随机临床试验表明, 万古霉素或甲硝唑治疗可提高血清碱性磷酸酶和降低胆红素水平, 减少瘙痒^[130]。澄清肠道微生物在自身免疫性肝炎中的作用是必要的, 以指导研究战略, 将有助于制定辅助干预措施, 以改善这种疾病的结局^[136]。

免疫抑制剂皮质类固醇、依那西普、他克莫司、环孢素、硫唑嘌呤、甲氨蝶呤和英夫利昔单抗用于治疗AIH和重叠综合征, 但对PSC患者没有显示出临床效果^[137-139], 因此不推荐使用。最近用布地奈德治疗AIH的效果尚不清楚。

肝移植是PSC患者在斯堪的纳维亚半岛一些国家肝移植的主要适应征。也是美国第五大肝移植最常见的适应症1年和5年生存率分别超过90%和80%, PSC患者是肝移植最成功的患者之一^[140]。

与其他慢性肝病患者相比, PSC患者更容易接受活体供者的肝移植, 自从终末期肝病模型(Model for end-stage liver disease, MELD)评分开始使用以来, 这一趋势有所增加。一项研究并未发现因胆管炎而导致死亡或临床恶化的风险增加^[141]。

6 结论

肠道共生微生物利用多种途径形成黏膜免疫, 从而有助于导致遗传易感个体的系统自身免疫发生。由于肠道微生物随时在变化中, 情况变得非常复杂, 因此观察到的结果是疾病的原因还是结果目前仍不完全了解。从目前研究证据来看, 肠道微生物引起自身免疫进一步导致疾病的发生已得到共识。今后应探索特定微生物的免疫和代谢功能, 并寻求粪便微生物的辅助治疗。粪便移植或益生菌治疗可补充目前的免疫抑制方案, 对于将来临床改善自身免疫性疾病及炎症性疾病有很大的前景。

阻断TLR信号传导或调节信号传导的分子干预可能会减少促炎细胞因子的产生, 限制不利的基因表达, 并增强肠屏障的完整性, 致使减少疾病的发生。

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编辑: 崔丽君 电编: 张砚梁





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ISSN 1009-3079

