

世界华人消化杂志®

**WORLD CHINESE
JOURNAL OF DIGESTOLOGY**

Shijie Huaren Xiaohua Zazhi

2020 年 6 月 28 日 第 28 卷 第 12 期 (Volume 28 Number 12)



12/2020

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

- 453 非编码RNA在食管癌中的意义

周苏娜

- 460 超声影像组学在肝脏病变的诊断应用进展

梁梓南, 杨薇

基础研究

- 467 白花丹醌对大鼠肝细胞肝癌自噬活性的影响并机制初探

陈懿, 李雪, 陈金霞, 林文雅, 张友才

- 475 真核起始因子3e亚基与原发性肝细胞癌的发生与发展正相关

张珊, 陈忠伟, 孟诗敏, 丁庆林, 钟自彪, 魏艳红, 叶散发, 胡康洪

文献综述

- 486 调节性B淋巴细胞在消化系统自身免疫性疾病中的作用

霍佳慧, 王小云, 龚镭, 顾馨

- 493 肿瘤微环境对肝细胞癌血管生成的影响

章小珊, 张彩灵, 黄赞松

研究快报

- 501 健康行为能力在初产妇心理弹性和母乳喂养自我效能中的中介作用

楼燕芳

- 506 心理弹性在老年脑卒中合并功能性便秘患者家庭功能与出院准备度的中介作用

蒋元华, 付佳, 方玉华

消 息

- 466 《世界华人消化杂志》参考文献要求
474 《世界华人消化杂志》性质、刊登内容及目标
485 《世界华人消化杂志》2011年开始不再收取审稿费
492 《世界华人消化杂志》消化护理学领域征稿启事

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编务 王栋梅; 送审编辑 张晗; 组版编辑 刘继红; 英文编辑 王天奇;
形式规范审核编辑部主任 吴云晓健; 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 2020-06-28

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)

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Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton,

CA 94588, USA

Telephone: +1-925-3991568

E-mail: wcjd@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

Telephone: +1-925-3991568

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: +86-10-85381892

《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。

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定价

每期136.00元 全年24期3264.00元

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Contents

Volume 28 Number 12 June 28, 2020

EDITORIAL

- 453 Role of non-coding RNAs in esophageal carcinoma
Zhou SN
- 460 Advances in diagnostic application of ultrasomics in liver lesions
Liang ZN, Yang W

BASIC RESEARCH

- 467 Effect of plumbagin on autophagy activity in rat hepatocellular carcinoma and underlying mechanism
Chen Y, Li X, Chen JX, Lin WY, Zhang YC
- 475 Eukaryotic initiation factor 3e subunit is positively associated with tumorigenesis and development of hepatocellular carcinoma
Zhang S, Chen ZW, Meng SM, Ding QL, Zhong ZB, Wei YH, Ye QF, Hu KH

REVIEW

- 486 Role of regulatory B cells in autoimmune diseases of the digestive system
Huo JH, Wang XY, Gong L, Gu X
- 493 Influence of tumor microenvironment on angiogenesis in hepatocellular carcinoma
Qin XS, Zhang CL, Huang ZS

RAPID COMMUNICATION

- 501 Mediating role of healthy behavioral ability in maternal mental resilience and breastfeeding self-efficacy in primiparae
Lou YF
- 506 Mediating effect of mental resilience on family function and discharge readiness in elderly stroke patients with functional constipation
Jiang YH, Fu J, Fang YH

Contents

World Chinese Journal of Digestology
Volume 28 Number 12 June 28, 2020

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Indexed/Abstracted by

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

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Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993

Renamed on January 25, 1998

Publication date June 28, 2020

NAME OF JOURNAL

World Chinese Journal of Digestology

ISSN

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

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World Chinese Journal of Digestology

Baishideng Publishing Group Inc

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

Telephone: +1-925-3991568

E-mail: wjcd@wjgnet.com

<https://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc

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

Telephone: +1-925-3991568

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

PRINT SUBSCRIPTION

RMB 136 Yuan for each issue

RMB 3264 Yuan for one year

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非编码RNA在食管癌中的意义

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基金项目: 国家自然科学基金资助项目, No. 81872458; 浙江省自然科学基金, No. LY19H160017.

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收稿日期: 2020-04-16

修回日期: 2020-05-22

接受日期: 2020-05-28

在线出版日期: 2020-06-28

Role of non-coding RNAs in esophageal carcinoma

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Supported by: National Natural Science Foundation of China, No. 81872458; Zhejiang Provincial Natural Science Foundation of China, No. LY19H160017.

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Received: 2020-04-16

Revised: 2020-05-22

Accepted: 2020-05-28

Published online: 2020-06-28

Abstract

In recent years, the research on the role of non-coding RNAs (ncRNAs) in tumors has received more and more attention. Although research on the role of ncRNAs in the

early diagnosis, disease monitoring, treatment guidance, and prognosis prediction of esophageal carcinoma has been gradually carried out, there are still many problems that need to be addressed. In the current paper, I review the progress in the research of ncRNAs in esophageal carcinoma, with an aim to help provide new strategies for the prevention and treatment of esophageal carcinoma.

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Key Words: Esophageal carcinoma; Non-coding RNAs; Diagnosis and treatment

Citation: Zhou SN. Role of non-coding RNAs in esophageal carcinoma. *Shijie Huaren Xiaohua Zazhi* 2020; 28(12): 453-459
URL: <https://www.wjgnet.com/1009-3079/full/v28/i12/453.htm>
DOI: <https://dx.doi.org/10.11569/wcjd.v28.i12.453>

摘要

近年来, 非编码RNA(non-coding RNAs, ncRNAs)在肿瘤中的研究已受到越来越多的关注. 虽然, 关于ncRNAs在食管癌早期诊断、病情监测、治疗指导及预后判断方面的作用研究已逐步展开, 但仍存在不少亟待解决的问题. 本述评将对食管癌中ncRNAs的研究进展进行简要综述, 期望有助于为食管癌的防治提供新策略.

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关键词: 食管癌; 非编码RNA; 诊治价值

核心提要: 非编码RNA(non-coding RNAs, ncRNAs)在不同疾病中的意义日益受到关注、更新, 成为研究热点. 但食管癌中相关ncRNAs的研究尚处于初始阶段, 讨论及挖掘食管癌中ncRNAs的功能及作用机制, 对于食管癌的防治具有重要的价值及意义.

文献来源: 周苏娜. 非编码RNA在食管癌中的意义. 世界华人消化杂志 2020; 28(12): 453–459

URL: <https://www.wjgnet.com/1009-3079/full/v28/i12/453.htm>

DOI: <https://dx.doi.org/10.11569/wjcd.v28.i12.453>

0 引言

人类基因组绝大部分基因可转录为RNA, 但仅1%-2%具备编码蛋白的能力, 不参与编码蛋白的RNA占绝大多数, 被命名为非编码RNA (non-coding RNAs, ncRNAs)^[1]. ncRNAs主要包括长度小于200 nt的短链ncRNA和长度大于200nt的长链ncRNAs (long non-coding RNAs, lncRNAs). 微小RNA (microRNAs, miRNAs)是目前研究最广泛的短链ncRNA, 通过结合靶基因的mRNA负向调控基因表达, 其失调与多种人类疾病尤其是肿瘤相关^[2]. 同样, lncRNAs参与调控染色质重塑, 转录和转录后加工等细胞生物学过程, 其表达在人类各种疾病包括肿瘤中发挥重要作用^[3]. 环状RNA (circular RNAs, circRNAs)是一类新型ncRNA, 因其价闭环结构具有高度稳定性和保守性, 通过充当miRNA“海绵”, 蛋白质“诱饵”或编码小肽发挥重要的生物学功能. 研究表明许多circRNA在肿瘤中异常表达, 发挥致癌或抑癌基因作用^[4]. 食管癌作为世界第6大致死性恶性肿瘤, 其发生发展过程中同样涉及多种ncRNAs的调控紊乱. 近年来, 随着二代测序技术的日益进步及生物信息学的发展, 关于食管癌中ncRNAs表达差异谱及生物功能学研究日渐受到关注, 本文将对最新的研究进展作一述评, 期望有助于开拓食管癌诊治的新思路.

1 非编码RNA在食管癌诊断中的作用

我国是食管癌的高发区, 2015年新发食管癌477900例, 死亡约375000例^[5]. 绝大部分初次就诊的患者为中晚期, 已失去治愈的机会. 目前临床缺少有效性及特异性高的食管癌筛选肿瘤标记物, 随着消化道内镜早癌筛查的逐步推进及测序技术的发展, 寻找有效、易检测的生物标志物是提高食管癌或癌前病变早期诊断的有效策略.

1.1 miRNAs 食管癌的主要病理类型包括食管腺癌 (esophageal adenocarcinoma, EAC)和食管鳞癌(esophageal squamous cell carcinoma, ESCC). EAC的发生历经肠上皮化生(Barrett食管)→不典型增生→食管腺癌形成的过程. 因此, Barrett食管是EAC的一种癌前病变状态. Barrett食管通常需要通过侵入性的内镜明确诊断. 然而, 许多肿瘤相关性miRNAs不仅稳定存在于组织中, 同时存在于体液如循环血中. 血液中特定miRNAs比值的组合可高效区分EAC与Barrett食管患者、健康者^[6]. Barrett食管或高度不典型增生患者血液中的miR-199a-3p和miR-320c较健康者均显著下降, 是特异性与敏感性较好

的循环标记物^[7]. 肿瘤组织与循环血中的miRNA-95-3p、-136-5p、-194-5p、-451a、-382-5p、-133a-3p和-130a表达谱可有效区分Barrett食管、EAC与健康人^[8,9]. Barrett食管与食管炎可通过组织或血液中的miR-194和miR-215表达差异区分^[10]. 此外, 研究显示血清miR-10a、-22、-100、-148b、-223、-133a、-127-3p、-1246、-25、-92a-3p、-483-5p和组织miR-143、-145、-218-5p、-142-3p、-150-5p、-205-5p、-21、-203单独或联合应用作为食管癌新型的诊断和预后生物标志物应用具有强大的潜力^[11-18].

1.2 lncRNAs 基于TCGA和GEO数据分析, 发现食管癌与良性食管病变之间存在成百上千个差异表达的lncRNAs, 且ESCC与EAC的差异表达谱不同但存在部分重叠^[19-25]. 分析ESCC、食管异型增生及健康人的血液发现Linc00152, CFLAR-AS1和POU3F3是预测ESCC早期发生的潜在生物标志物^[26]. 基于组织中7种lncRNAs联合(BQ376030、ASLNC11164、BF894811、RP11473M20.9、X LOC_00 7869、XLOC_006476、CK327190)构建的危险因素评分预测模型是ESCC独立预后指标^[27]. 基于GEO数据分析提示组织中AC098973、AL133493、RP11-51M24、RP11-317N8、RP11-834C11、RP11-69C17、LINC00471、LINC01193和RP1-124C能高效筛选早期ESCC及预测特定患者群(60岁以下男性, 吸烟喝酒, 分期为N0+N1或T3+T4, 且未接受辅助治疗)的预后^[28]. 而且, 与比常规血清生物标记物(如AFP、CA153和NSE)相比, lncRNAs如CCAT2在食管癌诊断中显示出更高的诊断性能^[29].

1.3 circRNAs circRNAs主要通过充当miRNAs的分子海绵对其下游靶基因进行正向调节从而在肿瘤发生中发挥调控作用, 在肿瘤中提供诊断和预后价值. 多数circRNAs稳定存在于循环血中, 可作为一种微创的肿瘤标记物应用于临床. 越来越多的研究证实食管癌组织或血液中异常表达的circRNAs具有作为食管癌筛查或诊断指标的潜力^[30-34]. 如circ-TTC17在ESCC细胞, 血浆和组织中的表达水平明显高于正常人^[35].

目前关于表达失调的ncRNAs作为食管癌早期诊断的相关证据逐渐增多, 尤其是循环血中稳定表达的ncRNAs与传统肿瘤标记物相比具有微创、敏感性高的优势. 如上所述, ncRNAs无论是单个、两两组合或多个联合用于食管癌的诊断, 通过回归模型评估提示具有显著诊断价值. 但是目前的诊断模型不成熟, 仍需要更大样本量系统全面地训练验证. 此外, 不同病理类型食管癌之间的特异性循环ncRNA也值得进一步探索.

2 非编码RNA在食管癌发生发展中的作用特点

不仅食管癌、食管癌癌前病变、食管良性病变的患者

组织及循环血中的ncRNAs水平存在差异性表达, 不同发展阶段的食管癌之间同样存在ncRNAs表达差异. 不同的ncRNAs在食管发生发展中发挥着癌基因或抑癌基因的功能, 具有促进肿瘤增殖、迁移、侵袭等恶性表型转化功能, 可能提供潜在的食管癌治疗靶点.

2.1 miRNAs 晚期EAC患者血清中的miR-130a和-223-5p明显高于早期患者^[9,17]. ESCC患者血浆中低水平的miR-655、肿瘤组织中miR-92a、-429、-451上调及miR-143、-145表达下调与淋巴转移、TNM分期及预后不良有关^[12,36-38]. 血清miR-331-3p表达下降、miR-652-5p联合-7-2-3p高表达是用于识别高复发风险的EAC患者的有效生物标志物^[39,40]. 机制研究揭示许多miRNAs与靶基因的3'UTR结合, 在mRNA水平上阻断靶基因翻译导致其失活, 从而促进或抑制食管癌细胞的发生和发展^[36,41-47].

2.2 lncRNAs lncRNAs在食管癌中的异常表达预示着肿瘤进展如淋巴结转移、远处转移、更晚的临床分期及更短的生存期^[48-52]. 如食管癌组织中HOTAIR、LINC00152表达与TNM分期、淋巴结转移和组织分化程度显著相关^[49,53]. lncRNA TP73-AS1水平上调与食管癌的肿瘤位置及TNM分期均相关^[54]. 组织中NONHSAT104436、LncH19的过表达与肿瘤大小、远处转移和不良生存预后密切相关^[48,55]. lncRNA Epist在食管组织中高表达, 发挥抑癌基因功能抑制肿瘤转移, 但在食管癌发展过程中表达下调^[56]. 体外实验证实多种lncRNAs促进ESCC细胞的增殖、迁移和侵袭^[23,25,49,53,57-60].

2.3 circRNAs 食管癌中表达异常的circRNAs通过海绵作用抑制miRNAs表达从而激活miRNAs下游靶基因或信号通路发挥癌基因或抑癌基因的功能, 调控食管癌细胞的增殖、迁移和侵袭. 如circUBAP2、circ_0000654、circ_0006168、circ_0006948、circGSK3 β 、cZNF292、circPVT1、circRAD23B、circ_0004370、circ_0000337、circ-TTC17、circRNA_100876、ciRS-7等通过circRNA/miRNA/mRNA轴发挥促进食管癌细胞恶性表型进展^[30-35,61-68]. circLARP4、circ-Foxo3、cZNF292作为抑癌基因竞争性结合相应miRNAs发挥抑制食管癌细胞发展为强侵袭、易迁移的细胞^[69-71]. 此外, 研究证实人工合成的circRNA也可以作为治疗性分子海绵, 有效抑制类似癌基因的miRNAs, 从而阻遏食管癌细胞增殖、迁移^[72]. 血浆高circ-SLC7A5、高circGSK3 β 的ESCC患者与较晚的肿瘤分期及较短的生存期有关^[62,73]. ESCC患者肿瘤组织中circ_0006168表达水平增加与淋巴结转移和TNM分期呈正相关^[63]. 冰冻及石蜡包埋的ESCC组织中的circ_0001946被证实可预测肿瘤复发、总生存期和无病生存期^[74]. ESCC患者血浆中circ-SMAD7表达下调与TNM分期和淋巴结转移呈

高度负相关^[75].

临床中关于食管癌的N分期, 因为诊断性纵隔镜或胸腔镜并非常规开展, 而影像学依据并不是诊断阳性淋巴结的金标准. 综上文献回顾, 关于部分ncRNAs的异常表达对食管癌淋巴转移及TNM分期的预测可能性已被证实, 那么进一步构建有效的分期、预后诊断模型并作为训练验证有助于无法接受手术的食管癌患者准确分期, 有效指导后续治疗.

3 非编码RNA在食管癌抗肿瘤治疗中的作用特点

近年来的研究结果提示ncRNAs在食管癌抗肿瘤治疗疗效及生存预后的预测中也具有很好的临床应用前景. 在接受术前新辅助放化疗或化疗的II期食管癌患者组织中, miR-21水平上调预示着术后预后不良^[76]. 血清miR-339-5p水平与ESCC患者放疗敏感性呈正相关, 且通过miRNAs-mRNA途径调控ESCC细胞的放射敏感性^[77]. miR-125a-5p、miR-455-3p、miR-221、miR-338-5p在ESCC细胞化疗敏感性调控中发挥重要作用^[78-81]. miR-34b/c启动子区域的多态性与局部晚期ESCC患者放化疗疗效密切相关^[82]. 血液中lncRNAs(Linc00152、CFLAR-AS1和POU3F3)表达升高是ESCC患者术后生存期短的预测指标^[26]. 敲除lncRNA TP73-AS1可增强食管癌细胞对5-FU和顺铂的化学敏感性^[54]. lncRNA TUG1通过上调Nrf2促进ESCC细胞对顺铂的耐药性^[83]. 食管癌组织中高表达的lncRNA CCAT2被证实与食管癌患者临床放疗预后负相关, 进一步机制研究发现其异常表达通过对miR-145/p70S6K1的负调控来促进食管癌细胞的放射抵抗性^[84]. circRNA_100367、circRNA_001059、circRNA_000167、circVRK1通过circRNA-miRNA-mRNA途径增强ESCC的放射抵抗性^[77,85,86].

目前关于ncRNAs在食管癌临床抗肿瘤治疗敏感性及其预后预测中的意义处于研究起始阶段, 虽然越来越多的研究发现了与食管癌放化疗敏感性调控相关的各种ncRNAs, 并且对可能涉及的分子调控机制做了初步探索, 但最终如何转化应用于临床诊疗还有漫漫长路需要摸索. 此外, 食管癌患者复查随访过程中尚缺乏敏感性、特异性高的微创肿瘤标记物, 因此发掘能在食管癌抗肿瘤治疗不同阶段进行疗效追踪的循环ncRNAs动态表达谱也是值得探索的方向.

4 食管癌相关非编码RNA的研究难点

ncRNAs在食管癌筛查、早期诊断、监测病情、手术及放化疗疗效评估、预后判断等方面已展示了巨大潜力, 引起广泛关注. 尤其是循环ncRNAs的异常表达不仅存在于组织、细胞中, 还稳定存在于包括血液成分、尿液、唾液等各种体液中, 具有取材方便、微创

等优势. 随着分子生物学技术的发展, 新的检测技术如基因芯片、实时定量逆转录PCR、深度测序等日益更新, 为检测各种组织、体液中的ncRNA提供了技术支持. 目前的研究数据显示有应用潜力的循环ncRNAs成百上千, 但是因为不同研究选择的样本保存条件、质量控制、检测方法等问题, 我们还需要进一步确定统一的样本质检标准及诊断量化标准等. 目前, 现有的食管癌诊断或预测实验模型, 虽然大部分显示了良好的敏感性和特异性, 但是缺少大样本量的验证和训练, 而且缺乏miRNAs、lncRNAs、circRNAs三者的联合诊断模型. 此外, 深入的机制挖掘显示不同ncRNAs在食管癌发生发展中可能通过lncRNA-miRNA-mRNA或circRNA-miRNA-mRNA或circRNAs-lncRNAs的模式参与调控^[31,32,34,52,53,60,61,67-71,84,87-94]. 已有数据显示多种miRNAs、lncRNAs、circRNAs在食管癌的增殖、侵袭、迁移中发挥重要作用, 但是肿瘤进展过程不仅受一个或一种基因的调控, 我们需要进一步探索三者之间的串扰, 明确lncRNA-miRNA-circRNA-mRNA模式在食管癌中的调控机理, 有助于发现决定性的调控基因, 为开发有效的治疗靶点提供重要依据.

5 结论

食管正常上皮经历癌前病变、早期癌及进展期癌的过程中涉及成百上千的非编码RNA表达及功能异常. 非编码RNA相关诊断模型、预测模型的构建及作为治疗靶点应用于食管癌研究中已经有许多的数据结果. 非编码RNA在食管癌中的调节作用涉及复杂精密的机理, 值得进一步深入研究, 有助于为食管癌的防治提供新的机遇.

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科学编辑: 张晗 制作编辑: 刘继红





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ISSN 1009-3079

