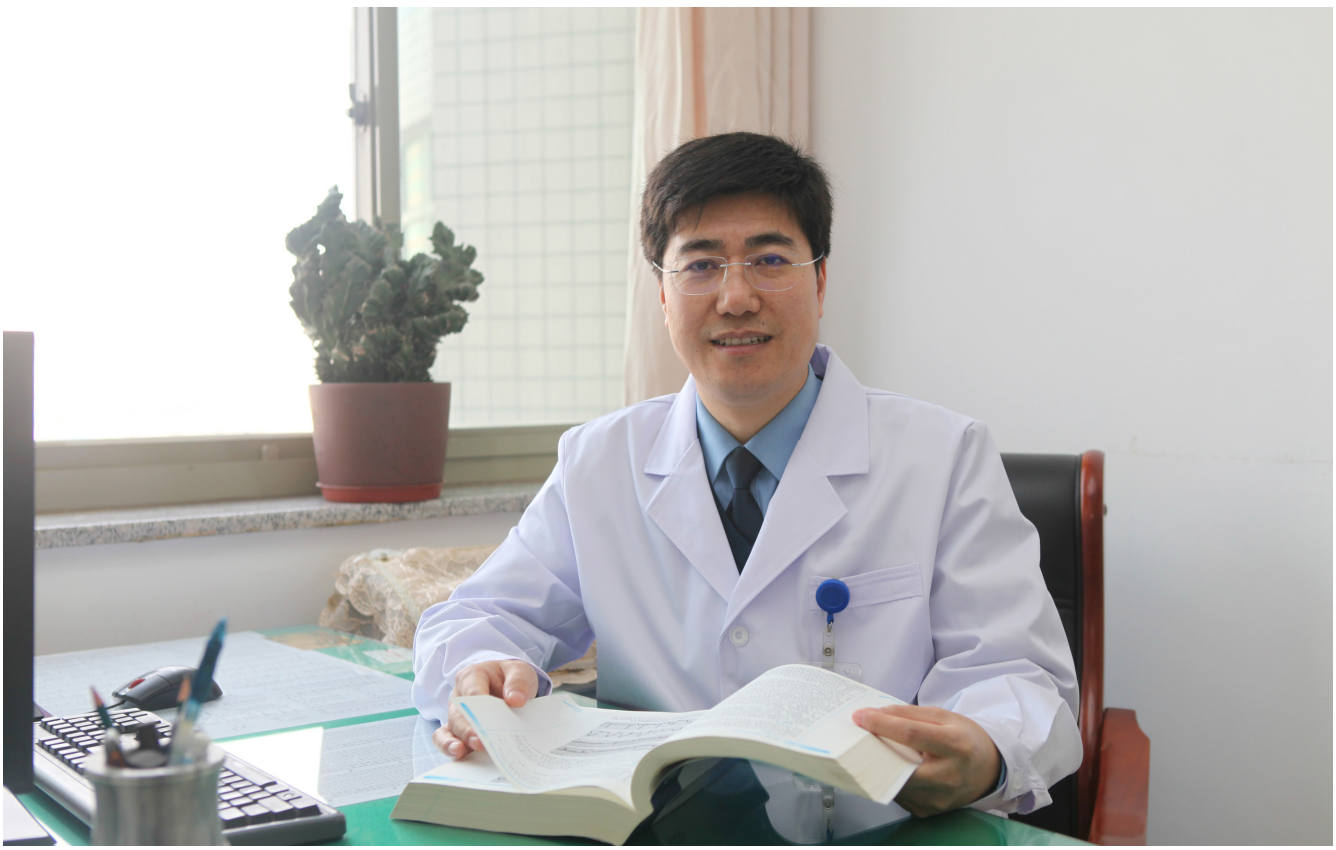
ISSN 1009-3079 (print)
ISSN 2219-2859 (online)

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

Shijie Huaren Xiaohua Zazhi

2023 年 1 月 8 日　　第 31 卷　　第 1 期　　(Volume 31 Number 1)



1/2023

ISSN 1009-3079

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世界华人消化杂志 https://www.wjgnet.com 二零二三年一月八日 第三十一卷 第一期

WCJD 世界华人消化杂志®

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2023年1月8日 第31卷 第1期 (总第717期)

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封面故事

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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 2023-01-08
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)

编辑部
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《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
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
https://www.wjgnet.com

制作
北京百世登生物医学科技有限公司
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《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.

《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

WCJD 世界华人消化杂志®

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Volume 31 Number 1 January 8, 2023

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Indexed/Abstracted by

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

Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993
Renamed on January 25, 1998
Publication date January 8, 2023

NAME OF JOURNAL
World Chinese Journal of Digestology

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

EDITORIAL OFFICE

Jin-Lei Wang, Director
World Chinese Journal of Digestology
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7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@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
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

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.

WCJD 世界华人消化杂志®

在线投稿: https://www.baishideng.com

世界华人消化杂志 2023年1月8日; 31(1): 14-19

DOI: 10.11569/wcjd.v31.i1.14

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

文献综述 REVIEW

Hippo信号通路在结直肠癌中的作用及其机制研究进展

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收稿日期: 2022-09-09
修回日期: 2022-10-27
接受日期: 2022-12-21
在线出版日期: 2023-01-08

Advances in understanding of role and mechanism of Hippo signaling pathway in colorectal cancer

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Received: 2022-09-09
Revised: 2022-10-27
Accepted: 2022-12-21
Published online: 2023-01-08

Abstract

Colorectal cancer (CRC) is one of the most common malignant tumors, and most patients have a poor prognosis. Many studies have shown that the Hippo signaling pathway plays a key role in the occurrence and development of CRC by regulating CRC cell proliferation and apoptosis, tumor invasion and metastasis, autophagy, metabolic reprogramming, drug resistance, and other processes. This article reviews the latest progress in research of the expression of key molecules of the Hippo signaling pathway in CRC as well as the understanding of the mechanism by which this pathway regulates the occurrence and development of CRC.

Key Words: Colorectal cancer; Hippo signaling pathway; Yes-associated protein; Drug resistance; Prognostic markers

Citation: Ma FY, Zhou XH, Liang Q. Advances in understanding of role and mechanism of Hippo signaling pathway in colorectal cancer. Shijie Huaren Xiaohua Zazhi 2023; 31(1): 14-19
URL: https://www.wjgnet.com/1009-3079/full/v31/i1/14.htm
DOI: https://dx.doi.org/10.11569/wcjd.v31.i1.14

摘要

结直肠癌(colorectal cancer, CRC)是最常见的恶性肿瘤之一, 大多数患者预后差. 诸多研究已表明Hippo信号通路在CRC的发生、发展中起关键作用, 调控CRC细胞增殖、凋亡、侵袭、转移、自噬、代谢重编程、耐药性等过程. 现就Hippo信号通路及关键分子在CRC中的表达以及调控CRC的发生发展机制的最新研究进展作一综述.

关键词: 结直肠癌; Hippo信号通路; Yes相关蛋白; 耐药性; 预后标志物

核心提要: 本文就Hippo信号通路对结直肠癌细胞增殖、侵袭、转移、耐药性等的影响, 以及Hippo信号通路作为结直肠癌预后标志、治疗靶点等方面进行阐述, 为结直肠癌的诊治提供思路.

文献来源: 马伏艳, 周喜汉, 梁俏. Hippo信号通路在结直肠癌中的作用及其机制研究进展. 世界华人消化杂志 2023; 31(1): 14-19
URL: https://www.wjgnet.com/1009-3079/full/v31/i1/14.htm
DOI: https://dx.doi.org/10.11569/wcjd.v31.i1.14

0 引言

结直肠癌(colorectal cancer, CRC)的发病率表现出逐年上升趋势, 其致死率高, 预后差, 2020年数据显示, CRC占所有恶性肿瘤的10%, 仅次于乳腺癌、肺癌, 其死亡率在所有恶性肿瘤中排名第2位[1,2]. 结直肠癌的发生发展是一个复杂多级的过程, 从正常肠组织发展到腺瘤再发展为癌组织, 其归因于遗传改变的积累, 包括原癌基因的播散、肿瘤抑制基因的丢失或失活以及多条信号通路的异常激活或者抑制[3,4]. 其中Hippo信号通路与CRC的发生密切相关, 该通路调控失调, 会导致细胞分裂功能失去控制, 最终导致肿瘤的发生, 包括结直肠癌[5-7]. 已有研究表明CRC的增殖、侵袭、转移、复发和耐药等机制均与Hippo信号通路失调密切相关. 本文就Hippo信号通路及关键分子在CRC中的表达以及调控CRC的发生发展机制的最新研究进展作一综述.

1 Hippo通路的概述与癌症

1.1 概述 Hippo信号通路研究始于1995年发现的果蝇Wts抑癌基因, 又称为Salvador/Warts/Hippo(SWH)通路. Hippo途径是进化上保守的信号级联反应, 对器官大小、肿瘤发生、肿瘤代谢、干细胞稳态和间充质转化等方面具有重要调节作用[8]. Hippo信号通路由上游调节分子、核心分子、下游效应分子 3 部分组成, 多种细胞信号如细胞极性、细胞粘附、细胞-细胞接触、压力、机械和激素等, 都可以激活Hippo信号通路[9,10]. 其中核心分子包括Ste20样蛋白激酶1/2(mammalian sterile 20-like 1/2, MSTl/2)、大肿瘤抑制因子1/2(large tumor suppressor 1/2, LATSl/2)、MOB激酶活化因子1A/B(mob kinase activator 1A/1B, MOB1A/1B)、萨尔瓦多蛋白同源物1(salvador homologue 1, SAVl). 各核心分子之间构成蛋白激酶级联反应转导通路. 首先是MST1/2磷酸化, 随后与SAV1形成MST1/2-SAV1复合体, 增强LATS1/2、MOB1的磷酸化, 活化的LATS1/2和MOB1复合体进一步磷酸化下游的效应因子YAP/TAZ. 磷酸化的YAP/TAZ保留在细胞质中或被降解, 未能进入细胞核中, 靶基因的转录受到抑制[11,12]. 然而, 一旦Hippo途径失活, 非磷酸化的YAP就会易位到细胞核中, 与转录因子TEADs相互作用, 驱动靶基因表达, 可导致细胞的无节制增殖和恶性转化[13,14].

1.2 Hippo通路与癌症的发生 许多研究表明, Hippo信号通路的核心组在多种人类癌症中表达异常, 包括CRC、胃癌、乳腺癌和肝癌等. 该通路中相关分子可以促进结直肠癌细胞的增殖和存活, 在结直肠癌的发展中起着重要作用. 有学者研究发现[15]幽门螺杆菌可将致癌蛋白CagA转至胃上皮细胞并促进YAP的表达, 导致上皮间充质转化(epithelial-mesenchymal transition, EMT)及胃癌的发生. T细胞淋巴瘤侵袭转移诱导基因-1(T-lymphoma invasion and metastasis gene 1, TIAM1)是YAP1-TEAD4复合物的靶标, 有证据表明[16,17], YAP1可以促进转录因子TEAD4与TIAM1增强子区域的结合, 从而激活TIAM1表达, 增加RAC1活性并诱导侵袭性母细胞的形成, 另外TAZ有助于增强EMT, 导致乳腺癌的转移. 同时, YAP水平升高也会引起肝细胞过度增殖, 最终导致肝癌的发生[18]. 故当Hippo信号失调时, YAP/TAZ可作为致癌蛋白从而促进癌症的发生.

2 Hippo信号通路在CRC发生发展中的调控作用

2.1 调控增殖 细胞的异常增殖是癌症发生的标志之一. 致癌基因YAP在大多数结肠肿瘤中过表达并促进结肠癌细胞系的增殖. YAP1的激活可以促进CRC细胞的增殖, 而沉默YAP1的表达可以逆转CRC细胞的增殖[19]. YAP和TAZ对结肠癌细胞的增殖具有协同作用. 通过用siRNA转染后YAP和TAZ水平降低, 与对照组相比, 共转染YAP和TAZ siRNA组HCT1116细胞的增殖率显著下降[20]. RASAL2最初被确定为肿瘤抑制因子, 然而有研究发现[21]RASAL2在CRC细胞系和临床标本中表达增加, 并将RASAL2确定为结直肠肿瘤发生中Hippo信号通路中新的调节因子. RASAL2和YAP1之间的相互作用导致YAP1去磷酸化和核易位, 从而阻止YAP1在细胞质中泛素化, 并作为转录共激活剂, 刺激CCND1促增殖基因的表达, 促进CRC进展. Tang等[22]通过qPCR和荧光素酶报告测定表明, TEAD4作为Hippo信号通路下游转录因子, 通过直接结合和转录激活来调节YAP1, 促进结直肠癌细胞增殖.

2.2 调控侵袭、转移 肿瘤转移是癌症患者病情进展的主要原因, 给癌症治疗带来了大难题. Hippo信号通路亦

影响肿瘤的侵袭和转移. Ling等[23]发现来源于HCT116 CRC细胞系的116-LM细胞具有高度侵袭能力, 这与该细胞中YAP及其mRNA水平上调有关.此外, 该研究还发现YAP的表达与EMT基因表达相关, 而抑制YAP表达则降低了EMT基因的表达并抑制肿瘤细胞的迁移和侵袭. 另有研究[24]也指出YAP可以通过抑制E-钙粘蛋白表达和促进CRC中EMT相关转录因子Slug表达来调节EMT, 影响CRC细胞的迁移和侵袭. 另有研究也证实[25], YAP通过调节EMT相关基因的表达促进CRC细胞的迁移, 这可能与Glut3/AMPK信号通路的激活有关.

多种非编码RNA通过直接或以河马途径依赖性的方式靶向YAP/TAZ来调节YAP/TAZ信号通路在结直肠癌侵袭转移中发挥作用. lcnRNA RP11-757G1.5是一种在CRC组织中高度表达的新型lncRNA, 其通过外泌体miR-139-5p调节YAP1的表达并抑制其活性, 从而促进CRC的侵袭和肝、脾转移[26]. YAP1通过诱导lncRNA MALAT1-miR-126-5p轴来促进转移相关分子(如VEGFA、SLUG和TWIST)的表达, 促进CRC的血管生成和EMT[27]. 此外, circPPP1R12A已被阐明通过激活Hippo-YAP信号通路来增强肿瘤进展和转移性扩散, 作为结肠癌的癌基因和不良预后标志物[28]. 总而言之, YAP在CRC的侵袭和转移中起着至关重要的作用, YAP可能是一个有吸引力的治疗靶点.

2.3 调控代谢重编程 代谢重编程是调控肿瘤发生发展的核心, 在各种癌症中观察到代谢途径的失调. YAP/TAZ通常还参与代谢调节, 例如促进糖酵解、脂肪生成和谷氨酸溶解, 这表明YAP/TAZ是为肿瘤细胞活动提供能量和必要合成材料的新兴节点. YAP/TAZ重新编程葡萄糖、核苷酸和氨基酸代谢, 以增加能量和营养的供应, 为癌细胞提供燃料[29]. 研究表明[30], 脂肪酸2-羟化酶(fatty acid 2-hydroxylase, FA2H)在结直肠癌的发展中调节特异性代谢重编程和致癌信号传导, 主要是通过AMPK/YAP途径起作用. 此外, MiR-103a-3p通过直接靶向Hippo通路的核心分子LATS2和SAV1来促进YAP1/TEAD介导的缺氧诱导因子1(hypoxia-inducible factor-1A, HIF1A)表达, 调节CRC糖酵解以促进CRC的发展[31]. 肿瘤细胞主要是通过糖酵解的代谢模式来提供所需能量. 如果肿瘤细胞的糖酵解途径得到有效抑制, 就可以抑制肿瘤细胞的生长. 然而, 目前仍然没有有效的靶向肿瘤细胞代谢的药物. 未来仍需要进一步努力继续研究CRC代谢的具体机制并找到有效的分子诊断和治疗靶点.

2.4 调控自噬 自噬是一种保守的分解代谢过程, 其中聚集的蛋白质或受损的细胞器被双膜自噬体隔离并在自溶体中降解, 其在生理条件下维持细胞稳态[32]. 最近, Hippo-YAP轴被广泛称为调节自噬的病理生理过程[33]. YAP活性的降低与细胞的自噬和分化有关, 已有相关研究证明可通过调节YAP调控CRC自噬[34]. YAP与TEAD相互作用形成复合物以上调细胞凋亡抑制蛋白Bcl-2的转录, 从而促进CRC进展[35]. 另外, 姜黄素可以抑制YAP并激活自噬而发挥抗CRC作用[36]. 毒脂苷G促进了YAP去磷酸化、核定位和下游靶基因表达, 阻断自噬体-溶酶体融合诱导高水平的自噬体积累, 抑制SW480细胞增殖和活力[37].

2.5 介导耐药性 化疗耐药性仍然是癌症治疗中的一个主要挑战. Hippo信号通路的失活已被证明与癌症的化学抗性有关. 据报道[38], YAP参与肿瘤治疗药物的敏感性, YAP可以增加结直肠癌对紫杉醇的耐药性. 在IV期CRC和野生型KRAS患者中, 灭活的YAP1结直肠癌患者在西妥昔单抗单药治疗后具有比活化的YAP1结直肠癌患者更好的疾病控制率和无进展生存期, 对数据的进一步分析显示, YAP1激活与CRC对西妥昔单抗治疗的耐药性密切相关[39]. 此外, 已有研究表明microRNA通过抑制Hippo信号通路介导肿瘤耐药性. Que等人[40]研究发现miR-874-3p通过靶向CRC细胞中的YAP和TAZ使Hippo信号通路失活, 从而促进CRC细胞对5-FU的化疗耐药性. 由此可知, YAP信号传导在结直肠癌的耐药性中发挥了关键作用.

2.6 Hippo通路与其他信号通路的串联与调节 随着肿瘤分子生物学的发展, 结直肠癌变中细胞通路的机制被广泛研究, 如Hippo通路和Wnt/β-连环蛋白信号通路. WNT/β-连环蛋白信号通路是正常肠道干细胞稳态的关键调节因子[41]. Wnt信号通路异常激活在结直肠癌发生中发挥至关重要的作用, 大多数结直肠癌患者至少有一个Wnt信号通路基因发生突变[42]. YAP/TAZ可以是Wnt信号通路的中的一个靶基因, 起负反馈作用, 限制Wnt信号通路的过度激活[43]. Wnt5a通常被认为是一种典型的非规范Wnt配体, 也有数据分析WNT5A是TEAD靶基因, 其两者相互作用促进肿瘤的进展[44]. YAP可以直接与细胞核中的β-连环蛋白相互作用, 并形成转录的YAP/β-连环蛋白/TCF4复合物, 促进CRC的发展[45].

卷曲相关蛋白2(secreted frizzled related protein 2, SFRP2)水平在多种癌症中降低, SFRP2是一种直接与Wnt信号结合的拮抗剂, SFRP2的过表达促进了YAP1和β-连环蛋白的表达, YAP1过表达促进细胞增殖, 而SFRP2过表达抑制细胞增殖并促进细胞凋亡[46]. 肿瘤抑制因子APC作为β-连环蛋白破坏复合物的支架蛋白, 是Wnt/β-连环蛋白信号通路最著名的负调节因子, APC缺乏症通过白细胞介素-6信号传感器的中介增加YAP活性, 使CRC发生[47]. 有证据表明类固醇衍生物促进了YAP与β-

连环蛋白破坏复合物的结合, 抑制了Wnt/β-连环蛋白信号传导, 并加速了CRC细胞中β-连环蛋白的降解, 成为治疗CRC的潜在物质[48]. 这两种信号通路在CRC中发生错综复杂的作用, 进一步探究YAP在Wnt信号传导中的机制是在癌症治疗和预防中的新策略.

2.7 治疗靶点 YAP/TAZ的亚细胞定位是其转录调控和信号转导的关键决定因素, 为癌症治疗提供了有吸引力的靶点. YAP/TAZ由于河马信号通路紊乱, 经常被过度激活.已经证实, YAP/TAZ的活化或过表达与癌症患者的预后不良有关. 能够破坏TAZ/YAP-TEAD之间相互作用的化合物被认为是抑制TAZ/YAP致癌作用的候选药物[49]. 有研究结果表明[50], 二甲双胍降低了YAP1的总蛋白, 诱导了YAP1的磷酸化, 并阻断了YAP1进入细胞核, 以调节人结直肠癌细胞中程序性死亡配体1的表达, 二甲双胍可能成为通过Hippo信号通路治疗CRC的良好选择. 与正常的结直肠组织相比, miR-195-5p在人类CRC组织中显着下调, miR-195-5p的上调通过靶向YAP1 mRNA 3′-UTR抑制结肠癌细胞的增殖, 迁移, 侵袭和EMT, 外泌体miR-195-5p可通过靶向YAP1起抗肿瘤作用[51]. lncRNA kcna3在CRC组织中表达较低, 其低表达与患者TNM等级较高, 淋巴转移和远处转移发生率较高以及总生存期(overall survival, OS)较短密切相关, lncRNA kcna3通过下调YAP1表达在CRC进展中发挥肿瘤抑制作用[52]. PTX耐药性与YAP表达水平呈正相关.

抑制YAP的表达可以诱导细胞凋亡, 降低结肠癌细胞对PTX的耐药性[38,53]. 辛伐他汀通过影响核易位和总YAP表达来抑制YAP生物活性, 增加了西妥昔单抗和吉非替尼对CRC细胞的细胞毒性[54]. 一些直接和间接抑制YAP/TAZ激活的抑制剂已被证明对有效的癌症治疗有显着贡献, 用于Hippo信号通路抑制的肿瘤治疗药物可能对合并症患者造成潜在损害, 因此, 在选择和剂量时应谨慎选择Hippo途径抑制剂[55].

2.8 诊断及预后标志物 在大多数肿瘤中, Hippo/YAP信号通路的异常激活是致癌进展和侵袭性的最重要机制之一, 是被公认为预后不良的预后因素[56-58]. 对YAP1的荟萃分析显示, YAP1的总体和核过表达水平都与包括CRC在内的几种癌症的不良OS和无病生存期密切相关. 有学者对24个正常结直肠组织和81个CRC组织活检进行qRT-PCR和免疫组化, 发现与正常结直肠标本相比, CRC样品中的YAP1上调, YAP1表达与TNM分期、淋巴转移和远处转移有关, 高YAP1表达对CRC患者OS的预后预测具有消极作用[27]. 通过对168名CRC肿瘤组织样品中YAP蛋白的表达进行分析, 发现YAP的表达与结直肠肿瘤的淋巴结状态显著相关(P = 0.001), YAP表达较高的患者往往具有更高的死亡风险[20]. 通过采用免疫组化方法共研究了139例CRC组织中YAP、细胞周期蛋白D1的表达, 发现YAP在52.5%的CRC病例中过度表达, 并且主要表现在细胞核中, 且YAP的表达与淋巴结状态、肿瘤状态和细胞周期蛋白D1过表达显著相关, 重要的是, YAP表达与总生存期短有关[59]. 也有学者通过对Ⅰ-Ⅲ期CRC患者的数据研究了YAP1激活的预后影响, 活化的YAP1结直肠癌患者的生存期比灭活的YAP1结直肠癌患者差得多[39]. Hippo信号通路核心激酶和效应分子具有成为CRC预后的分子标志物的潜力.

3 结论

综上, Hippo信号通路在结直肠癌的发生发展起重要作用. 目前该通路已成为肿瘤学的一个有吸引力的新型治疗靶点, 可能成为CRC患者一个新的治疗选择. 然而关于YAP和TAZ抑制剂的有效性及安全性仍有待进一步明确, 未来仍需要大量研究实验和临床试验去验证.

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科学编辑: 张砚梁 制作编辑: 张砚梁

Published by **Baishideng Publishing Group Inc**
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ISSN 1009-3079