Journal of Clinical Personalized Medicine 临床个性化医学, 2024, 3(4), 1805-1817
Published Online December 2024 in Hans. https://www.hanspub.org/journal/jcpm
https://doi.org/10.12677/jcpm.2024.34257

Hans汉斯

Sirtuins家族对结直肠癌的生物学功能及预后的研究进展

李瑞阳[1]，芦灵军[2*]

[1]成都中医药大学医学与生命科学学院，四川 成都
[2]宜宾市第一人民医院胃肠外科，四川 宜宾

收稿日期：2024年11月16日；录用日期：2024年12月9日；发布日期：2024年12月18日

摘　要

Sirtuins蛋白家族具有ADP-核糖基转移酶活性和NAD+依赖性的组蛋白去乙酰基转移酶等多种酶活性，其家族包括Sirtuin1-7，是有名的长寿蛋白大家族，具有控制能量代谢、DNA修复、细胞活性、组织再生、炎症、神经元信号传递等多种生物学功能，同时在结直肠癌发生发展过程中作为不可替代的调控因素之一。Sirtuin1-7属于同一家族，但Sirtuin1-7表达对结肠癌的发生发展却有不同的影响，与患者预后也存在一定的相关性。本文综述了Sirtuins家族成员概述、在结直肠癌发生发展过程中所表达的生物学功能、作用机制及预后。

关键词

结直肠癌(CRC)，Sirtuins蛋白家族，生物学功能，预后

Research Progress of Biological Function and Prognosis of Colorectal Cancer in Sirtuins Family

Ruiyang Li[1], Lingjun Lu[2*]

[1]School of Medicine and Life Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu Sichuan
[2]Department of Gastrointestinal Surgery, The First People's Hospital of Yibin, Yibin Sichuan

Received: Nov. 16th, 2024; accepted: Dec. 9th, 2024; published: Dec. 18th, 2024

Abstract

Sirtuins protein family has various enzyme activities such as ADP-ribosyl transferase activity and

*通讯作者。

文章引用: 李瑞阳, 芦灵军. Sirtuins 家族对结直肠癌的生物学功能及预后的研究进展[J]. 临床个性化医学, 2024, 3(4): 1805-1817. DOI: 10.12677/jcpm.2024.34257

NAD+ dependent histone deacetyl transferase activity. Its family includes Sirtuin1-7, which is a well-known family of long-lived proteins. It has various biological functions such as controlling energy metabolism, DNA repair, cell activity, tissue regeneration, inflammation, neuronal signal transmission, etc., and serves as one of the irreplaceable regulatory factors in the occurrence and development of colorectal cancer. Sirtuin1-7 belongs to the same family, but the expression of Sirtuin1-7 has different effects on the occurrence and development of colon cancer, and has a certain correlation with the prognosis of patients. In this review, Sirtuins family members, biological functions, mechanisms of action and prognosis of colorectal cancer were summarized.

Keywords

Colorectal Cancer (CRC), Sirtuins Protein Family, Biological Function, Prognosis

Copyright © 2024 by author(s) and Hans Publishers Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/
Open Access

1. 引言

结直肠癌是目前全世界主要的肿瘤之一，也是消化道肿瘤死亡的常见原因。结直肠癌症是全球女性第二常见癌症，是男性第三常见癌症[1]。近年来，结直肠癌的发病率和死亡率逐步得到改善。现阶段治疗方式主要是以通过外科干预为主，并结合放、化疗等治疗手段，从而延长患者的存活率。随着检测技术不断提高，越来越多的研究者们逐渐将研究对象转移到分子水平，通过不断的实验了解到疾病发生发展的机制，通过抑制剂或者激活剂来调节疾病发生发展过程中基因的表达，这对于疾病的预防和治疗都起到了很大作用。Sirtuins 家族是一类具有 ADP-核糖基转移酶活性和乙酰化酶活性的 NAD^+依赖性组蛋白去乙酰化酶，拥有高度保守的结构[2]，其家族包括七种乙酰化酶，即 Sirtuin1 (SIRT1)、Sirtuin2 (SIRT2)、Sirtuin3 (SIRT3)、Sirtuin4 (SIRT4)、Sirtuin5 (SIRT5)、Sirtuin6 (SIRT6)和 Sirtuin7 (SIRT7) [2]。越来越多的研究关注 Sirtuins 家族在结肠癌的发生、发展及预后中的作用，本文旨在阐述 Sirtuins 家族不同成员对结肠癌的生物学功能及临床预后的相关研究。

2. Sirtuins 蛋白家族概述

Sirtuins 蛋白家族占据不同的亚细胞区室：SIRT1、SIRT6 和 SIRT7 主要位于细胞核，SIRT2 位于细胞质和细胞核[3]，SIRT3、SIRT4、SIRT5 位于线粒体[2] (图 1)。从相关研究来看，Sirtuins 蛋白家族涉及许多细胞过程，如衰老、转录、凋亡、能量代谢、炎症[4]和应激，以及低热量情况下的能量效率和警觉性[5]。SIRT1 主要是哺乳动物 NAD^+依赖性脱乙酰酶，它包含至少两个核定位信号和两个核输出信号，在一定条件下可以在细胞核和细胞质之间穿梭[6]。SIRT1 可控制各种细胞的表达和蛋白质活动：细胞增殖、分化、凋亡、代谢、DNA 损伤、氧化应激反应、基因组等过程中的稳定性和复杂环境中细胞存活[7] [8]。SIRT2 参与多种生物学过程包括细胞周期进程、细胞死亡和应激反应[9] [10]等。在多种疾病中体现不同的生物学作用，例如 SIRT2 在肾小管和肝细胞中的抗纤维化作用，也可能作为血管再生的潜在治疗靶点[11]，在小鼠模型中发现阿尔兹海默症(AD)的基因表达过程也受到 SIRT2 的调节[12]，同时使用特异性 SIRT2 抑制剂的体外感染实验表明，特异性靶向 SIRT2 可能为 HIV 感染及其相关神经功能障碍提供新的治疗选择[13]，SIRT2 去乙酰化可以预防并靶向逆转衰老相关的炎症和胰岛素抵抗[14]。SIRT3 是线粒体基质中的一种主要的蛋白质去乙酰化酶[15]，它与 SIRT4、SIRT5 都定位于线粒体，又被称为线粒体

Sirtuins，并且是一个 NAD^+依赖性蛋白二磷酸腺苷(ADP)-核糖基转移酶，它催化 ADP-核糖基转移到目标蛋白上[6]。SIRT3 在多个脏器中发挥细胞保护、细胞增殖及代谢功能，例如在循环系统中，SIRT3 通过激活 AMPK 相关的线粒体生物发生来减少败血症诱导的心肌损伤[16]。有实验证明，小鼠模型中，SIRT3 缺失小鼠出现明显的骨质减少并伴有成骨细胞功能障碍，提示在成骨细胞分化和骨形成中发挥了重要作用[17]。Yogesh 等学者在实验中证明了 SIRT3 表达或活性降低导致数百种线粒体蛋白超乙酰化，这与神经异常、神经兴奋性毒性和神经元细胞死亡有关[18]。SIRT4~7 相关的研究较 Sirtuin1~3 较少，SIRT4 可以确保代谢稳定和生命长寿，例如在果蝇 SIRT4 敲除实验中，SIRT4 过度表达的果蝇寿命长，SIRT4 敲除果蝇分解代谢的途径受损[19]。此外 SIRT4 在消化道肿瘤中，如食管鳞癌、胰腺癌 SIRT4 在体外癌细胞生长过程起抑制作用[20]，在胃癌、结直肠癌、肝癌中低表达，体外实验中也有抑制作用[21] [22]。同时 SIRT5~7 也调控了细胞增殖、分化、代谢等细胞活动，影响肿瘤的发生发展。

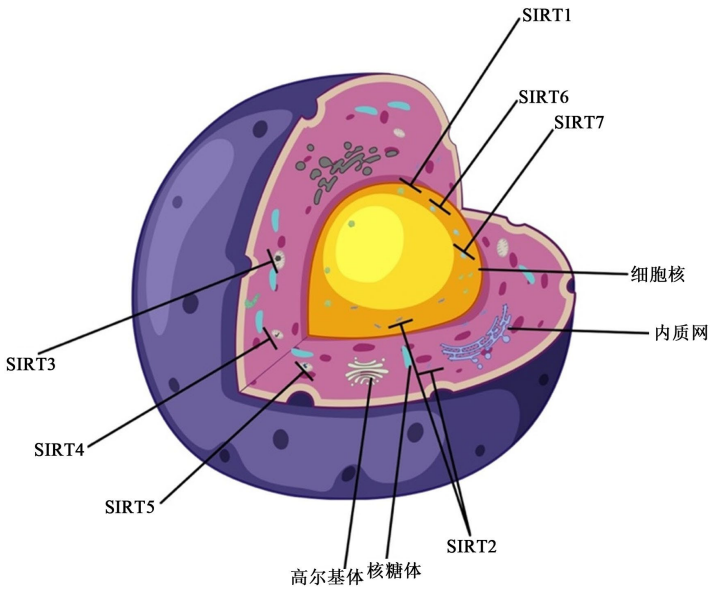

Figure 1. Common locations of the SIRT family in cells
图 1. SIRT 家族在细胞中常见存在位置

3. Sirtuins 蛋白家族成员在结肠癌中的生物学功能

3.1. SIRT1 对结直肠癌进展中的影响及作用机制

Sirtuins 蛋白家族的成员都在不同肿瘤发生发展过程中发挥了一定的生物学功能[23]。SIRT1 其活性通常与健康衰老和长寿有关，但也发现在多种癌症中高表达，包括前列腺癌、急性髓性白血病、结肠癌和一些非黑色素瘤皮肤癌。在小鼠实验中，发现阿司匹林可以直接乙酰化蛋白质中氨基酸侧链，使 SIRT1 乙酰化维持肠道免疫稳定[24]，此外可通过 SIRT-AMPK 通路的相互调节诱导人类结直肠癌细胞衰老，从而发挥抗癌作用[25]。2009 年 Kabra 等学者通过免疫组织化学染色显示正常结肠黏膜和良性腺瘤中存在高水平的 SIRT1。SIRT1 过度表达在大约 25%的 I/II/III 期结直肠腺癌中观察到，但在晚期 IV 期肿瘤中很少发现。此外，大约 30%的癌症表现出低于正常的 SIRT1 表达。所以 SIRT1 对结肠癌的发展可能存在具有双重作用(抗增殖/抗凋亡) [26]。但近几年来，Wang [27]、Wang [28]、Lee [29]等学者通过多种方式证明了 SIRT1 上调可以通过 p53/miR-101/KPNA3 轴、circ-SIRT1/EIF4A3/N-cadherin/vimentin 通路促进结直肠癌细胞的增殖、迁移、侵袭和转化。在结直肠癌的特定背景下，SIRT1 也可被维生素 D 的活性代谢物 1α,25-二羟基维生素

D3 在结直肠癌细胞的自身去乙酰化促进其活化，而 SIRT1 活性的翻译后控制介导 1α,25-二羟基维生素 D3 上调抗增殖作用表达，同时诱导结直肠癌细胞中的促凋亡蛋白表达[30]。炎症因子白细胞介素-1β 诱导的 SIRT1 过表达与恶性肿瘤生长有关[31]。SIRT1 也是细胞应激调节和脂质代谢的主要参与者，在癌症进展中存在错综复杂的关系[32]。总体而言，SIRT1 可通过多种机制影响结直肠癌的进展，对结直肠癌发生进展可能存在双重作用(抗增殖/抗抑制) (图 2)，但抗结直肠癌细胞增殖的证据不充分，有待于进一步研究。

3.2. SIRT2 对结直肠癌进展中的影响及作用机制

SIRT2 是一种 NAD^+ (烟酰胺腺嘌呤二核苷酸)依赖性脱乙酰酶，SIRT2 具有多种调节细胞功能的作用，包括细胞周期调控[32]、代谢作用和肿瘤发生[33]等。SIRT2 在多种器官中都表达，尤其是在大脑组织中[34]。相比于 SIRT1，SIRT2 与结直肠癌的相关性研究要少一些，但 SIRT2 对结直肠癌中的作用仍旧存在争议，在目前的研究中，Wang 等人报道了 SIRT2 过表达可致异柠檬酸脱氢酶 1 (IDH-1)去乙酰化调节细胞代谢，同时抑制结直肠癌细胞增殖、转移[35]。癸基泛醌(Decylubiquinone)和紫草醌(Shikonin)都可通过使 SIRT2 上调从而抑制直肠癌细胞增殖[36] [37]。SIRT2 去乙酰化细胞核中 E-钙粘蛋白加强其与 β-catenin 的相互作用，导致其下游基因表达减少，抑制肿瘤的生长和迁移[38]，除此之外，有研究表明 SIRT2 可促进结直肠癌分化、增殖和转移。Hu 等人报道了 SIRT2 在结直肠癌组织中上调，且与预后不良相关，同时可通过 STAT3/VEGFA 信号通路促进肿瘤血管生成[39]。在免疫细胞中，SIRT2 表达可耗竭 NK 细胞，从而抑制对结直肠癌细胞的肿瘤杀伤活力[40]。有相关文献证明了 SIRT2 可调节 K-RAS 的乙酰化，从而对结肠癌的发生发展产生巨大影响[41]。由上可知，SIRT2 在结直肠癌中也可能存在双重作用(抗增殖/抗抑制) (图 2)，但是作用机制还需要进一步的研究，继续为影响结直肠癌进展提供了相关证据，是可以探究的方向。

3.3. SIRT3 对结直肠癌进展中的影响及作用机制

SIRT3 是线粒体基质中的一种主要的 NAD^+依赖性脱乙酰酶[15]，其功能除了在线粒体中去乙酰化外，还是长寿蛋白[42]、具有心肌细胞保护作用[43]、以及参与线粒体稳态和代谢过程。在结直肠癌中，Li 等学者报道了通过实验对照发现了 SIRT3 稳定表达可能导致 Wnt/β-catenin 级联信号通路失活，可抑制结直肠癌细胞的增殖[44]。此外，体外实验中 MY-13 的新型 SIRT3 小分子激活剂通过 SIRT3/Hsp90/AKT 信号通路促进凋亡和自噬可抑制体内肿瘤的生长[45]，Zuo 证明 GA (甘草酸)通过抑制 SIRT3 导致结直肠癌凋亡[46]。Yong 发现结肠肿瘤形成过程中 SIRT3 与肠道微生物相互作用，但 SIRT3 表达高时肿瘤细胞生长受到抑制[47]。相反，有报道称 SIRT3 调节 Akt/PTEN 通路在结直肠癌应激反应中对抗线粒体裂变同时促进结直肠癌生长/迁移等[48]，同时 Wei 发现 SIRT3 表达增加去乙酰化活性促进丝氨酸羟甲基转移酶 2 (SHMT2)酶活性，推动结直肠癌变发生[49]。在结直肠癌代谢中，PROX1 显著上调募集 EZH2 抑制 SIRT3 启动子活性有助于结直肠癌增殖和葡萄糖代谢[50]。[51]免疫实验发现，SIRT3 可通过去乙酰化所致 T 细胞记忆发育，使其免疫系统功能发挥，SIRT3 也可通过乳酸干扰结肠癌细胞代谢稳态[52]。SIRT3 在线粒体中，SIRT3 沉默会导致线粒体生物合成减少和线粒体功能障碍，最终影响细胞活力[53]，并且可能是一种使细胞对治疗更加敏感的治疗策略。由上可知，SIRT3 在结直肠癌中的表达除了广泛认可的致癌基因外，也存在着抑制癌细胞增殖、转移等抑癌作用(图 2)。目前还需要进一步研究，完善 SIRT3 对结肠癌发生发展的作用机制，便于提供早期干预的证据。

3.4. SIRT4 对结直肠癌进展中的影响及作用机制

SIRT4 是线粒体 Sirtuins 之一[6]，在多种恶性肿瘤中起到抑制作用，同时也调节了脂肪酸氧化、氨基酸分解代谢等多种代谢途径来影响肿瘤的增殖分化，主要通过 NAD^+依赖的 ADP-核糖基转移酶，而不是脱乙酰基酶活性[54]。SIRT4 在结肠癌中的研究较少，在相关文献报道了 SIRT4 在结直肠癌中发挥抗肿

瘤活性可能依赖于抑制谷氨酰胺代谢和上调 E-钙粘蛋白，抑制肿瘤的增殖、转移，同时发现表达越低，预后越差，侵袭性越强[55] [56]。在 Cui 等人的研究中再次确定了 SIRT4 抑制结直肠癌的增殖、分化，可能是谷氨酰胺酶通过 AKT/糖原合酶激酶 3β (GSK3β)/CyclinD1 途径发挥作用[57]。一些 miRNA 也可通过影响靶基因发挥生物学作用，miR-15a-5p 在结直肠癌细胞中调节 STAT3/TWIST1 和 PETN/AKT 信号传导来抑制 SIRT4 的表达，从而加剧恶性表型[58]，也说明了 SIRT4 与结直肠癌的恶性程度呈负相关。5-氟尿嘧啶在结直肠癌化疗上被广泛应用，5-FU (5-氟尿嘧啶)的敏感性受到 SIRT4 表达的影响，SIRT4 不表达结直肠癌对 5-FU 的敏感性降低[59]。目前研究来看 SIRT4 表达对结直肠癌呈抑制(图 2)，但其作用机制还值得进一步讨论和研究，继续研究对结直肠癌的诊断和治疗是有必要的。

3.5. SIRT5 对结直肠癌进展中的影响及作用机制

Sirtuins 蛋白家族主要位于线粒体中表达除了 SIRT3、SIRT4 之外，还有 SIRT5，与其他家族成员不同的是它拥有多种酶活性，包括脱乙酰酶、脱琥珀酰酶和脱丙二酰酶，可通过多种代谢途径影响肿瘤的表达、增殖和侵袭等[54]。首先，SIRT5 脱乙酰酶活性可使乳酸脱氢酶 B (LDHB)的赖氨酸-329 处去乙酰化，提高其酶活性促进自噬和结直肠癌的增殖[60]。在结直肠癌缺少谷氨酰胺时，SIRT5 发挥脱琥珀酰酶活性使线粒体苹果酸酶 2 (ME2)脱琥珀酰化维持线粒体呼吸功能从而促进结直肠癌细胞的增殖，这与 SIRT4 是相反的[61]。同时在三羧酸循环(TCA)中，柠檬酸合酶(CS)由 SIRT5 使 K393 和 K395 处脱琥珀酰化，显著提高了柠檬酸合酶(CS)活性，为结直肠癌细胞增殖和侵袭间接提供了能量[62]。在线粒体结构中，SIRT3 通过去乙酰化酶活性，使丝氨酸羟甲基转移酶 2 (SHMT2)活性提高，SIRT5 直接介导 SHMT2 上赖氨酸 280 的去琥珀酰化，促进 SHMT2 酶活性，都可促进结直肠癌细胞的增殖[63]。SIRT5 除了通过代谢作用影响肿瘤的增殖和侵袭，在免疫微环境中也有调节作用，SIRT5 敲除增强 Th1 (CD^{4+} T 细胞)和 CTL (细胞毒性 T 淋巴细胞)分化，降低 CD^{4+} Treg (CD^{4+}调节性 T 细胞)分化，抑制结直肠癌细胞的增殖和侵袭[64]。综上，在结直肠癌中，SIRT5 的表达起到了抗抑制作用(图 2)，因为酶活性作用的多样，其作用机制仍可以进一步完善，同时，SIRT5 在免疫微环境中的作用和表达也有进一步研究的意义。

3.6. SIRT6 对结直肠癌进展的影响及作用机制

SIRT6 与 SIRT3 类似，是一种同时具有去乙酰化酶和 ADP-核糖基转移酶活性的蛋白，所以除了具有长寿作用外，在免疫和哺乳动物 DNA 修复也能发挥重要作用[65]。SIRT6 可使苹果酸酶 1 (ME1) K337 去乙酰化的方式拮抗磷酸甘油酸变位酶 5 (PGAM5)增强酯酰辅酶 A：胆固醇酰基转移酶 1 (ACAT1)酰基化功能，抑制结直肠癌脂质合成、NADPH 生成、糖酵解，抑制结直肠癌生长[66]。FoxO3a 已被确定为 SIRT6 的直接上游，可上调其表达[67]，SIRT6 可通过靶向抑制致癌磷酸酶细胞分裂周期 25A (CDC25A) [68]，从而抑制干细胞增殖，激活 SIRT6 可介导下游靶向基因细胞色素 P450 家族 24 亚家族 A 成员 1 (CYP24A1)基因位点的组蛋白 H3 去乙酰化，改变其功能，同时 CYP24A1 是维生素 D3 的关键失活酶，可协同抑制结直肠癌细胞增殖和侵袭[69]。此外，Wang 等学者报道了 SIRT6 上游 microR-25 可靶向抑制其表达，促进 SIRT6 介导的 Lin28b/NRP-1 轴表达，促进了结直肠癌的发展和转移[70]。有研究证实 SIRT6 通过调节 PTEN/AKT 信号在结肠癌中发挥抑癌基因的作用[71]。SIRT6 泛素化被肿瘤抑制因子泛素特异性肽酶(USP10)抑制，拮抗 c-Myc 致癌基因转录，从而抑制肿瘤形成和生长[72]。在小鼠免疫实验中，SIRT6 与小鼠 NK 细胞呈负相关，下调 SIRT6 可增强 NK 细胞功能，抑制小鼠结直肠癌进展[73]，值得一提的是，这也与前文中 SIRT6 表达具有抑癌增殖作用相反。在一项 META 分析中 SIRT6 的低表达可能预示着实体瘤患者的良好生存[74]。由上可知，目前大多数证据都证明 SIRT6 上调表达对结直肠癌为抑制作用(图 2)，在免疫系统相反，具体机制仍旧未知，进一步探究有利于为治疗手段提供更好的证据。

3.7. SIRT7 对结直肠癌进展的影响及作用机制

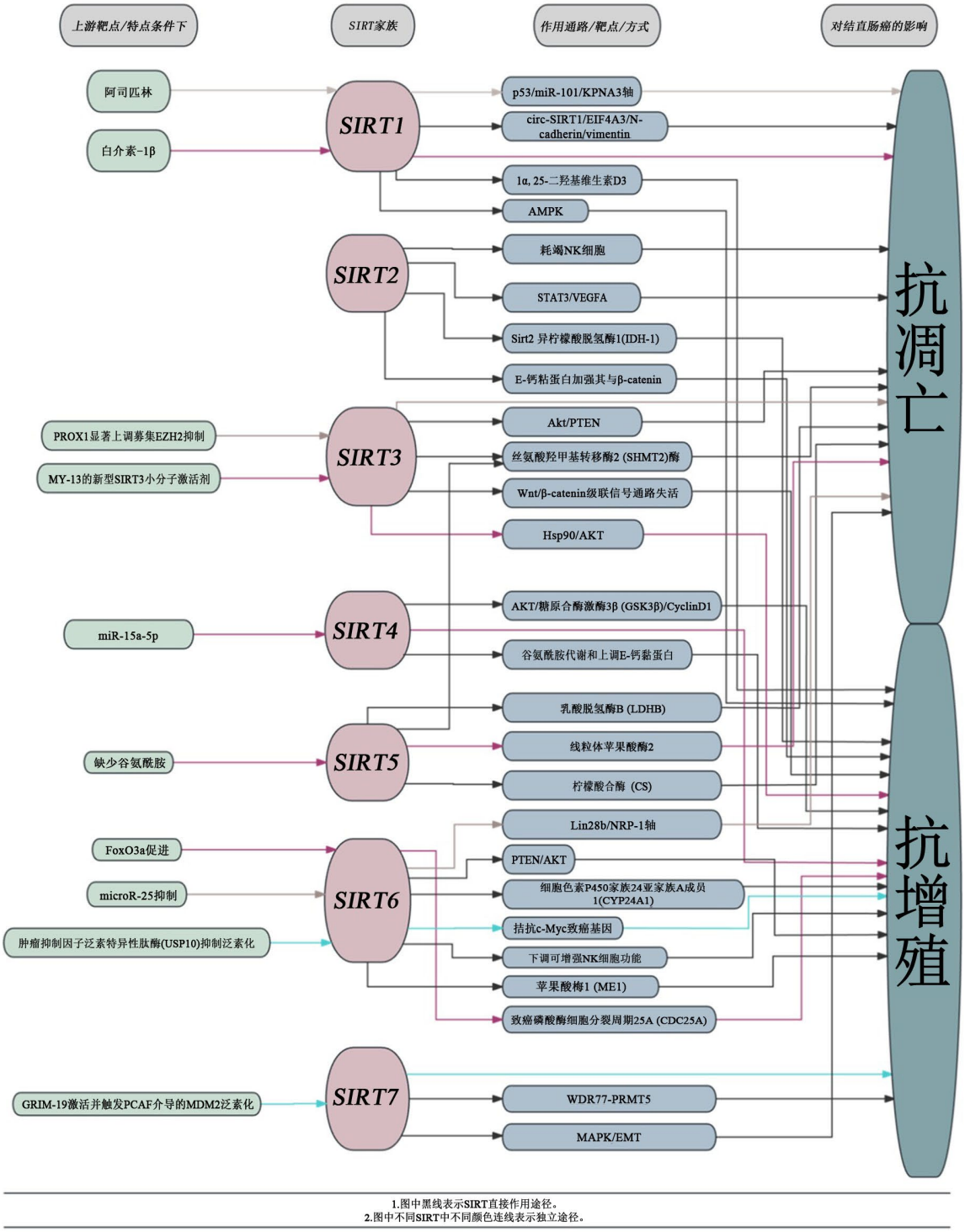

Figure 2. Biological role of the SIRT family in colorectal cancer
图 2. SIRT 家族在结直肠癌中的生物学作用

SIRT7 定位于核仁，对于 DNA 复制有促进作用[75]，同时也有长寿功能，Lagunas-Rangel 指出 SIRT7

缺陷会导致过早衰老[76]，并在肝癌、胃癌、乳腺癌、膀胱癌、结直肠癌等肿瘤中具有重要作用[77]。目前研究中，Qi 等学者指出 SIRT7 介导的 WDR77 在 Lys-3 和 Lys-243 处的去乙酰化会削弱 WDR77-PRMT5 相互作用和活性，从而抑制癌细胞的生长[78]。有关研究表明 SIRT7 缺乏会导致组蛋白乙酰转移酶 1 (AT1) 活性降低，从而降低组蛋白 H4K5 和 H4K12 乙酰化，影响着丝粒处的 CENP-A 和核小体错位，从而进一步影响染色质组装，同时出现细胞衰老，提高了结直肠肿瘤发病率的易感率[79]。此外，SIRT7 可被 GRIM-19 激活并触发 PCAF 介导的 MDM2 泛素化，使其稳定 p53 蛋白，抑制肿瘤进展[80]。5-氟尿嘧啶下调 Sirt7 可诱导结直肠癌细胞的放射敏感性，使其对放射治疗更加敏感[81]。SIRT7 对组蛋白 H3K18 表现出高选择性，并具有维持癌细胞转化表型的功能[6]。Yu 等学者通过 PCR、蛋白质印迹证明 SIRT7 通过 MAPK 信号传导和 EMT (上皮细胞－间充质转化)促进结直肠癌的增殖和转移[82]。总的来说，文献表明 Sirt7 在结直肠癌增殖、转移等生物学过程中起到了抗增殖/抗抑制的重要作用(图 2)。进一步研究 Sirt7 在结直肠癌中功能的分子机制可以为开发这种疾病的新治疗策略提供有价值的见解。

4. Sirtuins 家族成员与结肠癌预后的关系

前文综述了 SIRT 家族概述和对结直肠癌抗增殖或抗抑制的生物学作用，对于与结直肠癌患者预后相关性、能否成为生物标志物仍是近年来值得关注的焦点，这对于结直肠肿瘤的术前诊断、药物干预能提供许多帮助。在 2003 年 Jung 等学者通过免疫组织化学表达实验认为在结直肠癌患者中 SIRT1 的表达与预后良好相关[83]。但 Wu 等学者在 Meta 分析中认为 SIRT1 与结直肠癌患者预后没有相关性[84]。此外，在另一项 META 分析中指明 SIRT1 与肿瘤的浸润深度、淋巴转移和 TMN 分期有一定相关性，以及 SIRT1 过表达可以预测结直肠癌患者预后差[85] [86]，可以作为预后生物标志物[85]。Lee 等学者则认为高 SIRT1 表达作为高龄结直肠癌患者预后不良的因素仍具有统计学意义[87]。现在更多的证据表明 SIRT1 过表达与结直肠癌患者预后不良相关，能否通过干扰 SIRT1 的表达来影响结直肠癌患者的预后还需要进一步研究。对于 SIRT2 而言，Lee 等学者认为在年轻肿瘤患者中 SIRT2 表达预后无差异[87]，但在卵巢癌中存在预后相关[88]。Zhou 等学者提到 SIRT3 表达与总癌症预后之间没有明显关系，SIRT3 表达可能是特定癌症的关键预后因素，包括结直肠癌[89]。有研究表明抗氧化酶在非肿瘤邻近组织和早期结直肠癌肿瘤组织中，都在 I 期和 II 期之间具有显著差异，所以可将 SIRT3 作为新的生物标记物[90]。Liu 等学者在一项临床随访研究中发现 SIRT3 低表达患者的总生存率为 80.2%，SIRT3 高表达患者的总生存率为 55.9% [91]，SIRT3 可能与结直肠癌预后负相关。在 Guo 研究中发现 SIRT4 在人结肠癌中的表达降低与病理分化差、预后差有关[56]。SIRT4 对结直肠癌的抑制作用，也为治疗靶点提供了新思路。目前没有更多的证据表明 SIRT5 与结直肠癌预后具有相关性，但从其生物学功能来看可以猜测 SIRT5 表达与结直肠癌负性预后有一定相关性，并且 SIRT5 可能为结肠癌治疗的新标志物[92]。Geng 等学者的实验中发现 SIRT6 促进结直肠发生、转移，同时与不良预后、总生存率低相关，可作为生物标志物和治疗结肠癌的潜在治疗靶点[93]，与结肠癌具有密切相关性[94]。Yu 等人描述了 SIRT7 的致癌特性，并将其确定为结直肠癌的一个有价值的预后标志物[82]，此外，SIRT7 过表达与各种肿瘤类型的免疫浸润有关，包括结直肠癌，并且患者生产率降低，是预后生物标志物[82] [95]。由上可知，SIRT1、SIR3、SIRT6、SIRT7 高表达与结直肠癌预后不良呈正相关，SIRT2、SIRT4、SIRT5 表达与结直肠癌预后相关性并不明确。所以对于 SIRT 家族对结直肠癌患者预后的影响相关研究还不够全面，能否作为生物学标志物还需要更为全面的分析与探究，进一步全面验证预后相关的同时，也为诊断提供了线索。

5. 未来研究展望

Sirtuins 家族对结直肠癌有不同的影响。就目前证据来看，SIRT1、SIRT2、SIRT3、SIRT6、SIRT7 对

结直肠癌细胞生长、转移、侵袭等具有抗增殖/抗抑制双重作用，SIRT4、SIRT5 结直肠癌细胞生长、转移、侵袭等具有抗增殖的单向作用。SIRT1、SIR3、SIRT6、SIRT7 高表达与结直肠癌预后呈负相关，SIRT2、SIRT4、SIRT5 表达与结直肠癌预后相关性并不明确。对那些不太了解的 Sirtuin 成员，需要进一步完善相关作用机制。同时深入探讨 Sirtuins 家族成员在结直肠癌发生、发展和预后中的作用机制，为结直肠癌的诊断、治疗和预防提供新思路。未来的研究结果不仅将为其生物学功能提供新的见解，研究 Sirtuins 家族成员之间的相互作用，以及与其他信号通路的协同作用，可揭示结直肠癌发生发展的全面机制。同时结合前沿实验方式，筛选与 Sirtuins 家族成员相关的生物标志物，为结肠癌的早期诊断和预后评估提供依据。开发针对 Sirtuins 家族成员的抑制剂或激活剂，为结肠癌的治疗提供新的药物靶点。总之，Sirtuins 家族在结肠癌中的功能及预后研究具有重要的临床意义。随着研究的深入，有望为结肠癌的防治提供新的策略和方法。

参考文献

[1] Dienstmann, R., Vermeulen, L., Guinney, J., Kopetz, S., Tejpar, S. and Tabernero, J. (2017) Consensus Molecular Subtypes and the Evolution of Precision Medicine in Colorectal Cancer. *Nature Reviews Cancer*, **17**, 79-92. https://doi.org/10.1038/nrc.2016.126

[2] Ye, X., Li, M., Hou, T., Gao, T., Zhu, W. and Yang, Y. (2016) Sirtuins in Glucose and Lipid Metabolism. *Oncotarget*, **8**, 1845-1859. https://doi.org/10.18632/oncotarget.12157

[3] Shore, D., Squire, M. and Nasmyth, K.A. (1984) Characterization of Two Genes Required for the Position-Effect Control of Yeast Mating-Type Genes. *The EMBO Journal*, **3**, 2817-2823. https://doi.org/10.1002/j.1460-2075.1984.tb02214.x

[4] Preyat, N. and Leo, O. (2013) Sirtuin Deacylases: A Molecular Link between Metabolism and Immunity. *Journal of Leukocyte Biology*, **93**, 669-680. https://doi.org/10.1189/jlb.1112557

[5] Satoh, A., Brace, C.S., Ben-Josef, G., West, T., Wozniak, D.F., Holtzman, D.M., *et al*. (2010) SIRT1 Promotes the Central Adaptive Response to Diet Restriction through Activation of the Dorsomedial and Lateral Nuclei of the Hypothalamus. *The Journal of Neuroscience*, **30**, 10220-10232. https://doi.org/10.1523/jneurosci.1385-10.2010

[6] Michishita, E., Park, J.Y., Burneskis, J.M., Barrett, J.C. and Horikawa, I. (2005) Evolutionarily Conserved and Nonconserved Cellular Localizations and Functions of Human SIRT Proteins. *Molecular Biology of the Cell*, **16**, 4623-4635. https://doi.org/10.1091/mbc.e05-01-0033

[7] Tanno, M., Sakamoto, J., Miura, T., Shimamoto, K. and Horio, Y. (2007) Nucleocytoplasmic Shuttling of the NAD^+-Dependent Histone Deacetylase SIRT1. *Journal of Biological Chemistry*, **282**, 6823-6832. https://doi.org/10.1074/jbc.m609554200

[8] Alves-Fernandes, D.K. and Jasiulionis, M.G. (2019) The Role of SIRT1 on DNA Damage Response and Epigenetic Alterations in Cancer. *International Journal of Molecular Sciences*, **20**, Article 3153. https://doi.org/10.3390/ijms20133153

[9] Kitada, M., Ogura, Y., Monno, I. and Koya, D. (2019) Sirtuins and Type 2 Diabetes: Role in Inflammation, Oxidative Stress, and Mitochondrial Function. *Frontiers in Endocrinology*, **10**, Article 187. https://doi.org/10.3389/fendo.2019.00187

[10] Fujita, Y. and Yamashita, T. (2018) Sirtuins in Neuroendocrine Regulation and Neurological Diseases. *Frontiers in Neuroscience*, **12**, Article 778. https://doi.org/10.3389/fnins.2018.00778

[11] Yang, S., Yang, G., Wang, X., Xiang, J., Kang, L. and Liang, Z. (2023) SIRT2 Alleviated Renal Fibrosis by Deacetylating SMAD2 and SMAD3 in Renal Tubular Epithelial Cells. *Cell Death & Disease*, **14**, Article No. 646. https://doi.org/10.1038/s41419-023-06169-1

[12] Bai, N., Li, N., Cheng, R., Guan, Y., Zhao, X., Song, Z., *et al*. (2022) Inhibition of SIRT2 Promotes APP Acetylation and Ameliorates Cognitive Impairment in APP/PS1 Transgenic Mice. *Cell Reports*, **40**, Article 111062. https://doi.org/10.1016/j.celrep.2022.111062

[13] Duran-Castells, C., Llano, A., Kawana-Tachikawa, A., Prats, A., Martinez-Zalacain, I., Kobayashi-Ishihara, M., *et al*. (2023) Sirtuin-2, NAD-Dependent Deacetylase, Is a New Potential Therapeutic Target for HIV-1 Infection and HIV-Related Neurological Dysfunction. *Journal of Virology*, **97**, e01655-22. https://doi.org/10.1128/jvi.01655-22

[14] He, M., Chiang, H., Luo, H., Zheng, Z., Qiao, Q., Wang, L., *et al*. (2020) An Acetylation Switch of the NLRP3 Inflammasome Regulates Aging-Associated Chronic Inflammation and Insulin Resistance. *Cell Metabolism*, **31**, 580-591.E5. https://doi.org/10.1016/j.cmet.2020.01.009

[15] Nakamura, Y., Ogura, M., Tanaka, D. and Inagaki, N. (2008) Localization of Mouse Mitochondrial SIRT Proteins: Shift of SIRT3 to Nucleus by Co-Expression with SIRT5. *Biochemical and Biophysical Research Communications*, **366**, 174-179. https://doi.org/10.1016/j.bbrc.2007.11.122

[16] Xin, T. and Lu, C. (2020) SIRT3 Activates AMPK-Related Mitochondrial Biogenesis and Ameliorates Sepsis-Induced Myocardial Injury. *Aging*, **12**, 16224-16237. https://doi.org/10.18632/aging.103644

[17] Gao, J., Feng, Z., Wang, X., Zeng, M., Liu, J., Han, S., *et al*. (2017) SIRT3/SOD2 Maintains Osteoblast Differentiation and Bone Formation by Regulating Mitochondrial Stress. *Cell Death & Differentiation*, **25**, 229-240. https://doi.org/10.1038/cdd.2017.144

[18] Mishra, Y. and Kaundal, R.K. (2023) Role of SIRT3 in Mitochondrial Biology and Its Therapeutic Implications in Neurodegenerative Disorders. *Drug Discovery Today*, **28**, Article 103583. https://doi.org/10.1016/j.drudis.2023.103583

[19] Wood, J.G., Schwer, B., Wickremesinghe, P.C., Hartnett, D.A., Burhenn, L., Garcia, M., *et al*. (2018) SIRT4 Is a Mitochondrial Regulator of Metabolism and Lifespan in *Drosophila melanogaster*. *Proceedings of the National Academy of Sciences*, **115**, 1564-1569. https://doi.org/10.1073/pnas.1720673115

[20] Hu, Q., Qin, Y., Ji, S., Xu, W., Liu, W., Sun, Q., *et al*. (2019) UHRF1 Promotes Aerobic Glycolysis and Proliferation via Suppression of SIRT4 in Pancreatic Cancer. *Cancer Letters*, **452**, 226-236. https://doi.org/10.1016/j.canlet.2019.03.024

[21] Huang, G., Cui, F., Yu, F., Lu, H., Zhang, M., Tang, H., *et al*. (2015) Sirtuin-4 (SIRT4) Is Downregulated and Associated with Some Clinicopathological Features in Gastric Adenocarcinoma. *Biomedicine & Pharmacotherapy*, **72**, 135-139. https://doi.org/10.1016/j.biopha.2015.04.013

[22] Li, J., Zhao, M., Fan, W., *et al*. (2024) SIRT4 Is Associated with Microvascular Infiltration, Immune Cell Infiltration, and Epithelial Mesenchymal Transition in Hepatocellular Carcinoma. *Histology and Histopathology*. https://doi.org/10.14670/HH-18-794

[23] Garber, M.E., Troyanskaya, O.G., Schluens, K., Petersen, S., Thaesler, Z., Pacyna-Gengelbach, M., *et al*. (2001) Diversity of Gene Expression in Adenocarcinoma of the Lung. *Proceedings of the National Academy of Sciences*, **98**, 13784-13789. https://doi.org/10.1073/pnas.241500798

[24] Xie, L., Li, C., Wang, C., Wu, Z., Wang, C., Chen, C., *et al*. (2024) Aspirin-Mediated Acetylation of SIRT1 Maintains Intestinal Immune Homeostasis. *Advanced Science*, **11**, 2306378. https://doi.org/10.1002/advs.202306378

[25] Jung, Y.R., Kim, E.J., Choi, H.J., Park, J., Kim, H., Lee, Y., *et al*. (2015) Aspirin Targets SIRT1 and AMPK to Induce Senescence of Colorectal Carcinoma Cells. *Molecular Pharmacology*, **88**, 708-719. https://doi.org/10.1124/mol.115.098616

[26] Kabra, N., Li, Z., Chen, L., Li, B., Zhang, X., Wang, C., *et al*. (2009) SIRT1 Is an Inhibitor of Proliferation and Tumor Formation in Colon Cancer. *Journal of Biological Chemistry*, **284**, 18210-18217. https://doi.org/10.1074/jbc.m109.000034

[27] Wang, X., Jiang, Y., Ye, W., Shao, C., Xie, J. and Li, X. (2023) SIRT1 Promotes the Progression and Chemoresistance of Colorectal Cancer through the p53/miR-101/KPNA3 Axis. *Cancer Biology & Therapy*, **24**, Article 2235770. https://doi.org/10.1080/15384047.2023.2235770

[28] Wang, X., Liu, S., Xu, B., Liu, Y., Kong, P., Li, C., *et al*. (2021) Circ-SIRT1 Promotes Colorectal Cancer Proliferation and EMT by Recruiting and Binding to eiF4A3. *Analytical Cellular Pathology*, **2021**, Article 5739769. https://doi.org/10.1155/2021/5739769

[29] Lee, Y., Kim, S., Fang, X., Song, N., Kim, D., Suh, J., *et al*. (2022) JNK-Mediated Ser27 Phosphorylation and Stabilization of SIRT1 Promote Growth and Progression of Colon Cancer through Deacetylation-Dependent Activation of Snail. *Molecular Oncology*, **16**, 1555-1571. https://doi.org/10.1002/1878-0261.13143

[30] García-Martínez, J.M., Chocarro-Calvo, A., Martínez-Useros, J., Fernández-Aceñero, M.J., Fiuza, M.C., Cáceres-Rentero, J., *et al*. (2023) Vitamin D Induces SIRT1 Activation through K610 Deacetylation in Colon Cancer. *eLife*, **12**, RP86913. https://doi.org/10.7554/elife.86913

[31] Jung, J., Lee, Y., Fang, X., Kim, S., Kim, S.H., Kim, D., *et al*. (2021) IL-1β Induces Expression of Proinflammatory Cytokines and Migration of Human Colon Cancer Cells through Upregulation of SIRT1. *Archives of Biochemistry and Biophysics*, **703**, Article 108847. https://doi.org/10.1016/j.abb.2021.108847

[32] Simmons, G., Pruitt, W. and Pruitt, K. (2015) Diverse Roles of SIRT1 in Cancer Biology and Lipid Metabolism. *International Journal of Molecular Sciences*, **16**, 950-965. https://doi.org/10.3390/ijms16010950

[33] Kim, H., Vassilopoulos, A., Wang, R., Lahusen, T., Xiao, Z., Xu, X., *et al*. (2011) SIRT2 Maintains Genome Integrity and Suppresses Tumorigenesis through Regulating APC/C Activity. *Cancer Cell*, **20**, 487-499. https://doi.org/10.1016/j.ccr.2011.09.004

[34] Maxwell, M.M., Tomkinson, E.M., Nobles, J., Wizeman, J.W., Amore, A.M., Quinti, L., *et al*. (2011) The Sirtuin 2 Microtubule Deacetylase Is an Abundant Neuronal Protein That Accumulates in the Aging CNS. *Human Molecular*

Genetics, **20**, 3986-3996. https://doi.org/10.1093/hmg/ddr326

[35] Wang, B., Ye, Y., Yang, X., Liu, B., Wang, Z., Chen, S., *et al*. (2020) Sirt2-Dependent IDH1 Deacetylation Inhibits Colorectal Cancer and Liver Metastases. *EMBO reports*, **21**, e48183. https://doi.org/10.15252/embr.201948183

[36] Li, J., Zheng, S., Cheng, T., Li, Y., Mai, X., Jiang, G., *et al*. (2022) Decylubiquinone Inhibits Colorectal Cancer Growth through Upregulating Sirtuin2. *Frontiers in Pharmacology*, **12**, Article 804265. https://doi.org/10.3389/fphar.2021.804265

[37] Zhang, L., Zhan, L., Jin, Y., Min, Z., Wei, C., Wang, Q., *et al*. (2017) SIRT2 Mediated Antitumor Effects of Shikonin on Metastatic Colorectal Cancer. *European Journal of Pharmacology*, **797**, 1-8. https://doi.org/10.1016/j.ejphar.2017.01.008

[38] Zhao, Y., Yu, T., Zhang, N., Chen, J., Zhang, P., Li, S., *et al*. (2019) Nuclear E-Cadherin Acetylation Promotes Colorectal Tumorigenesis via Enhancing *β*-Catenin Activity. *Molecular Cancer Research*, **17**, 655-665. https://doi.org/10.1158/1541-7786.mcr-18-0637

[39] Hu, F., Sun, X., Li, G., Wu, Q., Chen, Y., Yang, X., *et al*. (2018) Inhibition of SIRT2 Limits Tumour Angiogenesis via Inactivation of the STAT3/VEGFA Signalling Pathway. *Cell Death & Disease*, **10**, Article No. 9. https://doi.org/10.1038/s41419-018-1260-z

[40] Jiang, B., Ke, C., Zhou, H., Xia, T., Xie, X. and Xu, H. (2023) Sirtuin 2 Up-Regulation Suppresses the Anti-Tumour Activity of Exhausted Natural Killer Cells in Mesenteric Lymph Nodes in Murine Colorectal Carcinoma. *Scandinavian Journal of Immunology*, **98**, e13317. https://doi.org/10.1111/sji.13317

[41] Yang, M.H., Laurent, G., Bause, A.S., Spang, R., German, N., Haigis, M.C., *et al*. (2013) HDAC6 and SIRT2 Regulate the Acetylation State and Oncogenic Activity of Mutant K-RAS. *Molecular Cancer Research*, **11**, 1072-1077. https://doi.org/10.1158/1541-7786.mcr-13-0040-t

[42] Bellizzi, D., Rose, G., Cavalcante, P., Covello, G., Dato, S., De Rango, F., *et al*. (2005) A Novel VNTR Enhancer within the SIRT3 Gene, a Human Homologue of SIR2, Is Associated with Survival at Oldest Ages. *Genomics*, **85**, 258-263. https://doi.org/10.1016/j.ygeno.2004.11.003

[43] Sundaresan, N.R., Samant, S.A., Pillai, V.B., Rajamohan, S.B. and Gupta, M.P. (2008) SIRT3 Is a Stress-Responsive Deacetylase in Cardiomyocytes That Protects Cells from Stress-Mediated Cell Death by Deacetylation of Ku70. *Molecular and Cellular Biology*, **28**, 6384-6401. https://doi.org/10.1128/mcb.00426-08

[44] Li, T., Fan, L., Jia, Y., Xu, C., Guo, W., Wang, Y., *et al*. (2024) Colorectal Cancer Cells with Stably Expressed *SIRT3* Demonstrate Proliferating Retardation by Wnt/*β*-Catenin Cascade Inactivation. *Clinical and Experimental Pharmacology and Physiology*, **51**, e13856. https://doi.org/10.1111/1440-1681.13856

[45] Mou, Y., Chen, Y., Fan, Z., Ye, L., Hu, B., Han, B., *et al*. (2024) Discovery of a Novel Small-Molecule Activator of SIRT3 That Inhibits Cell Proliferation and Migration by Apoptosis and Autophagy-Dependent Cell Death Pathways in Colorectal Cancer. *Bioorganic Chemistry*, **146**, Article 107327. https://doi.org/10.1016/j.bioorg.2024.107327

[46] Zuo, Z., He, L., Duan, X., Peng, Z. and Han, J. (2022) Glycyrrhizic Acid Exhibits Strong Anticancer Activity in Colorectal Cancer Cells via SIRT3 Inhibition. *Bioengineered*, **13**, 2720-2731. https://doi.org/10.1080/21655979.2021.2001925

[47] Zhang, Y., Wang, X., Zhou, M., Kang, C., Lang, H., Chen, M., *et al*. (2018) Crosstalk between Gut Microbiota and Sirtuin-3 in Colonic Inflammation and Tumorigenesis. *Experimental & Molecular Medicine*, **50**, 1-11. https://doi.org/10.1038/s12276-017-0002-0

[48] Wang, Y., Sun, X., Ji, K., Du, L., Xu, C., He, N., *et al*. (2018) RETRACTED: SIRT3-Mediated Mitochondrial Fission Regulates the Colorectal Cancer Stress Response by Modulating the AKT/PTEN Signalling Pathway. *Biomedicine & Pharmacotherapy*, **105**, 1172-1182. https://doi.org/10.1016/j.biopha.2018.06.071

[49] Wei, Z., Song, J., Wang, G., Cui, X., Zheng, J., Tang, Y., *et al*. (2018) Deacetylation of Serine Hydroxymethyl-Transferase 2 by SIRT3 Promotes Colorectal Carcinogenesis. *Nature Communications*, **9**, Article No. 4468. https://doi.org/10.1038/s41467-018-06812-y

[50] Gan, L., Li, Q., Nie, W., Zhang, Y., Jiang, H., Tan, C., *et al*. (2023) Prox1-Mediated Epigenetic Silencing of *SIRT3* Contributes to Proliferation and Glucose Metabolism in Colorectal Cancer. *International Journal of Biological Sciences*, **19**, 50-65. https://doi.org/10.7150/ijbs.73530

[51] He, J., Shangguan, X., Zhou, W., Cao, Y., Zheng, Q., Tu, J., *et al*. (2021) Glucose Limitation Activates AMPK Coupled SENP1-SIRT3 Signalling in Mitochondria for T Cell Memory Development. *Nature Communications*, **12**, Article No. 4371. https://doi.org/10.1038/s41467-021-24619-2

[52] D'Onofrio, N., Martino, E., Balestrieri, A., Mele, L., Neglia, G., Balestrieri, M.L., *et al*. (2021) SIRT3 and Metabolic Reprogramming Mediate the Antiproliferative Effects of Whey in Human Colon Cancer Cells. *Cancers*, **13**, Article 5196. https://doi.org/10.3390/cancers13205196

[53] Torrens-Mas, M., Hernández-López, R., Pons, D., Roca, P., Oliver, J. and Sastre-Serra, J. (2019) Sirtuin 3 Silencing

Impairs Mitochondrial Biogenesis and Metabolism in Colon Cancer Cells. *American Journal of Physiology-Cell Physiology*, **317**, C398-C404. https://doi.org/10.1152/ajpcell.00112.2019

[54] Kumar, S. and Lombard, D.B. (2015) Mitochondrial Sirtuins and Their Relationships with Metabolic Disease and Cancer. *Antioxidants & Redox Signaling*, **22**, 1060-1077. https://doi.org/10.1089/ars.2014.6213

[55] Miyo, M., Yamamoto, H., Konno, M., Colvin, H., Nishida, N., Koseki, J., *et al*. (2015) Tumour-Suppressive Function of SIRT4 in Human Colorectal Cancer. *British Journal of Cancer*, **113**, 492-499. https://doi.org/10.1038/bjc.2015.226

[56] Huang, G., Cheng, J., Yu, F., Liu, X., Yuan, C., Liu, C., *et al*. (2016) Clinical and Therapeutic Significance of Sirtuin-4 Expression in Colorectal Cancer. *Oncology Reports*, **35**, 2801-2810. https://doi.org/10.3892/or.2016.4685

[57] Cui, Y., Bai, Y., Yang, J., Yao, Y., Zhang, C., Liu, C., *et al*. (2020) SIRT4 Is the Molecular Switch Mediating Cellular Proliferation in Colorectal Cancer through GLS Mediated Activation of AKT/GSK3*β*/CyclinD1 Pathway. *Carcinogenesis*, **42**, 481-492. https://doi.org/10.1093/carcin/bgaa134

[58] Deng, J., Wang, H., Liang, Y., Zhao, L., Li, Y., Yan, Y., *et al*. (2023) MiR-15a-5p Enhances the Malignant Phenotypes of Colorectal Cancer Cells through the STAT3/TWIST1 and PTEN/AKT Signaling Pathways by Targeting SIRT4. *Cellular Signalling*, **101**, Article 110517. https://doi.org/10.1016/j.cellsig.2022.110517

[59] Zhu, Y., Wang, G., Li, X., Wang, T., Weng, M. and Zhang, Y. (2018) Knockout of SIRT4 Decreases Chemosensitivity to 5-FU in Colorectal Cancer Cells. *Oncology Letters*, **16**, 1675-1681. https://doi.org/10.3892/ol.2018.8850

[60] Shi, L., Yan, H., An, S., Shen, M., Jia, W., Zhang, R., *et al*. (2018) SIRT5-Mediated Deacetylation of LDHB Promotes Autophagy and Tumorigenesis in Colorectal Cancer. *Molecular Oncology*, **13**, 358-375. https://doi.org/10.1002/1878-0261.12408

[61] Teng, P., Cui, K., Yao, S., Fei, B., Ling, F., Li, C., *et al*. (2023) SIRT5-Mediated ME2 Desuccinylation Promotes Cancer Growth by Enhancing Mitochondrial Respiration. *Cell Death & Differentiation*, **31**, 65-77. https://doi.org/10.1038/s41418-023-01240-y

[62] Ren, M., Yang, X., Bie, J., Wang, Z., Liu, M., Li, Y., *et al*. (2020) Citrate Synthase Desuccinylation by SIRT5 Promotes Colon Cancer Cell Proliferation and Migration. *Biological Chemistry*, **401**, 1031-1039. https://doi.org/10.1515/hsz-2020-0118

[63] Yang, X., Wang, Z., Li, X., Liu, B., Liu, M., Liu, L., *et al*. (2018) SHMT2 Desuccinylation by SIRT5 Drives Cancer Cell Proliferation. *Cancer Research*, **78**, 372-386. https://doi.org/10.1158/0008-5472.can-17-1912

[64] Wang, K., Hu, Z., Zhang, C., Yang, L., Feng, L., Yang, P., *et al*. (2020) SIRT5 Contributes to Colorectal Cancer Growth by Regulating T Cell Activity. *Journal of Immunology Research*, **2020**, Article 3792409. https://doi.org/10.1155/2020/3792409

[65] Klein, M.A. and Denu, J.M. (2020) Biological and Catalytic Functions of Sirtuin 6 as Targets for Small-Molecule Modulators. *Journal of Biological Chemistry*, **295**, 11021-11041. https://doi.org/10.1074/jbc.rev120.011438

[66] Zhu, Y., Gu, L., Lin, X., Liu, C., Lu, B., Cui, K., *et al*. (2020) Dynamic Regulation of ME1 Phosphorylation and Acetylation Affects Lipid Metabolism and Colorectal Tumorigenesis. *Molecular Cell*, **77**, 138-149.E5. https://doi.org/10.1016/j.molcel.2019.10.015

[67] Zhang, Y., Nie, L., Xu, K., Fu, Y., Zhong, J., Gu, K., *et al*. (2019) SIRT6, a Novel Direct Transcriptional Target of FoxO3a, Mediates Colon Cancer Therapy. *Theranostics*, **9**, 2380-2394. https://doi.org/10.7150/thno.29724

[68] Liu, W., Wu, M., Du, H., Shi, X., Zhang, T. and Li, J. (2018) SIRT6 Inhibits Colorectal Cancer Stem Cell Proliferation by Targeting CDC25A. *Oncology Letters*, **15**, 5368-5374. https://doi.org/10.3892/ol.2018.7989

[69] Shang, J., Zhu, Z., Chen, Y., Song, J., Huang, Y., Song, K., *et al*. (2020) Small-Molecule Activating SIRT6 Elicits Therapeutic Effects and Synergistically Promotes Anti-Tumor Activity of Vitamin D_3 in Colorectal Cancer. *Theranostics*, **10**, 5845-5864. https://doi.org/10.7150/thno.44043

[70] Wang, S., Zhang, Z. and Gao, Q. (2021) Transfer of MicroRNA-25 by Colorectal Cancer Cell-Derived Extracellular Vesicles Facilitates Colorectal Cancer Development and Metastasis. *Molecular Therapy—Nucleic Acids*, **23**, 552-564. https://doi.org/10.1016/j.omtn.2020.11.018

[71] Tian, J. and Yuan, L. (2018) Sirtuin 6 Inhibits Colon Cancer Progression by Modulating PTEN/AKT Signaling. *Biomedicine & Pharmacotherapy*, **106**, 109-116. https://doi.org/10.1016/j.biopha.2018.06.070

[72] Lin, Z., Yang, H., Tan, C., Li, J., Liu, Z., Quan, Q., *et al*. (2013) USP10 Antagonizes c-Myc Transcriptional Activation through SIRT6 Stabilization to Suppress Tumor Formation. *Cell Reports*, **5**, 1639-1649. https://doi.org/10.1016/j.celrep.2013.11.029

[73] Xiao, F., Hu, B., Si, Z., Yang, H. and Xie, J. (2023) Sirtuin 6 Is a Negative Regulator of the Anti-Tumor Function of Natural Killer Cells in Murine Inflammatory Colorectal Cancer. *Molecular Immunology*, **158**, 68-78. https://doi.org/10.1016/j.molimm.2023.04.011

[74] Wu, X., Wang, S., Zhao, X., Lai, S., Yuan, Z., Zhan, Y., *et al*. (2022) Clinicopathological and Prognostic Value of SIRT6

in Patients with Solid Tumors: A Meta-Analysis and TCGA Data Review. *Cancer Cell International*, **22**, Article No. 84. https://doi.org/10.1186/s12935-022-02511-3

[75] Vazquez, B.N., Thackray, J.K., Simonet, N.G., Kane-Goldsmith, N., Martinez-Redondo, P., Nguyen, T., *et al*. (2016) SIRT 7 Promotes Genome Integrity and Modulates Non-Homologous End Joining DNA Repair. *The EMBO Journal*, **35**, 1488-1503. https://doi.org/10.15252/embj.201593499

[76] Lagunas-Rangel, F.A. (2022) SIRT7 in the Aging Process. *Cellular and Molecular Life Sciences*, **79**, Article No. 297. https://doi.org/10.1007/s00018-022-04342-x

[77] Li, L., Dong, Z., Yang, J., *et al*. (2019) Progress in Roles and Mechanisms of Deacetylase SIRT7. *Chinese Journal of Biotechnology*, **35**, 13-26.

[78] Qi, H., Shi, X., Yu, M., Liu, B., Liu, M., Song, S., *et al*. (2018) Sirtuin 7-Mediated Deacetylation of WD Repeat Domain 77 (WDR77) Suppresses Cancer Cell Growth by Reducing WDR77/PRMT5 Transmethylase Complex Activity. *Journal of Biological Chemistry*, **293**, 17769-17779. https://doi.org/10.1074/jbc.ra118.003629

[79] Liu, X., Li, C., Li, Q., Chang, H. and Tang, Y. (2020) SIRT7 Facilitates CENP-A Nucleosome Assembly and Suppresses Intestinal Tumorigenesis. *iScience*, **23**, Article 101461. https://doi.org/10.1016/j.isci.2020.101461

[80] Wang, D., Wei, X., Chen, X., Wang, Q., Zhang, J., Kalvakolanu, D.V., *et al*. (2021) GRIM-19 Inhibits Proliferation and Induces Apoptosis in a P53-Dependent Manner in Colorectal Cancer Cells through the SIRT7/PCAF/MDM2 Axis. *Experimental Cell Research*, **407**, Article 112799. https://doi.org/10.1016/j.yexcr.2021.112799

[81] Tang, M., Lu, X., Zhang, C., Du, C., Cao, L., Hou, T., *et al*. (2017) Downregulation of SIRT7 by 5-Fluorouracil Induces Radiosensitivity in Human Colorectal Cancer. *Theranostics*, **7**, 1346-1359. https://doi.org/10.7150/thno.18804

[82] Yu, H., Ye, W., Wu, J., Meng, X., Liu, R., Ying, X., *et al*. (2014) Overexpression of SIRT7 Exhibits Oncogenic Property and Serves as a Prognostic Factor in Colorectal Cancer. *Clinical Cancer Research*, **20**, 3434-3445. https://doi.org/10.1158/1078-0432.ccr-13-2952

[83] Jung, W., Hong, K.D., Jung, W.Y., Lee, E., Shin, B.K., Kim, H.K., *et al*. (2013) SIRT1 Expression Is Associated with Good Prognosis in Colorectal Cancer. *Korean Journal of Pathology*, **47**, 332-339. https://doi.org/10.4132/koreanjpathol.2013.47.4.332

[84] Wu, S., Jiang, J., Liu, J., Wang, X., Gan, Y. and Tang, Y. (2017) Meta-Analysis of SIRT1 Expression as a Prognostic Marker for Overall Survival in Gastrointestinal Cancer. *Oncotarget*, **8**, 62589-62599. https://doi.org/10.18632/oncotarget.19880

[85] Zu, G., Ji, A., Zhou, T. and Che, N. (2016) Clinicopathological Significance of SIRT1 Expression in Colorectal Cancer: A Systematic Review and Meta Analysis. *International Journal of Surgery*, **26**, 32-37. https://doi.org/10.1016/j.ijsu.2016.01.002

[86] Chen, X., Sun, K., Jiao, S., Cai, N., Zhao, X., Zou, H., *et al*. (2014) High Levels of SIRT1 Expression Enhance Tumorigenesis and Associate with a Poor Prognosis of Colorectal Carcinoma Patients. *Scientific Reports*, **4**, Article No. 7481. https://doi.org/10.1038/srep07481

[87] Lee, G.J., Jung, Y.H., Kim, T., Chong, Y., Jeong, S., Lee, I.K., *et al*. (2021) Surtuin 1 as a Potential Prognostic Biomarker in Very Elderly Patients with Colorectal Cancer. *The Korean Journal of Internal Medicine*, **36**, S235-S244. https://doi.org/10.3904/kjim.2019.249

[88] He, Q., Chen, K., Ye, R., Dai, N., Guo, P. and Wang, L. (2020) Associations of Sirtuins with Clinicopathological Variables and Prognosis in Human Ovarian Cancer. *Oncology Letters*, **19**, 3278-3288. https://doi.org/10.3892/ol.2020.11432

[89] Zhou, Y., Cheng, S., Chen, S. and Zhao, Y. (2018) Prognostic and Clinicopathological Value of SIRT3 Expression in Various Cancers: A Systematic Review and Meta-Analysis. *OncoTargets and Therapy*, **11**, 2157-2167. https://doi.org/10.2147/ott.s157836

[90] Gaya-Bover, A., Hernández-López, R., Alorda-Clara, M., Ibarra de la Rosa, J.M., Falcó, E., Fernández, T., *et al*. (2020) Antioxidant Enzymes Change in Different Non-Metastatic Stages in Tumoral and Peritumoral Tissues of Colorectal Cancer. *The International Journal of Biochemistry & Cell Biology*, **120**, Article 105698. https://doi.org/10.1016/j.biocel.2020.105698

[91] Liu, C., Huang, Z., Jiang, H. and Shi, F. (2014) The Sirtuin 3 Expression Profile Is Associated with Pathological and Clinical Outcomes in Colon Cancer Patients. *BioMed Research International*, **2014**, Article 871263. https://doi.org/10.1155/2014/871263

[92] Ekremoglu, O. and Koc, A. (2021) The Role of SIRT5 and P53 Proteins in the Sensitivity of Colon Cancer Cells to Chemotherapeutic Agent 5-Fluorouracil. *Molecular Biology Reports*, **48**, 5485-5495. https://doi.org/10.1007/s11033-021-06558-9

[93] Geng, C., Zhang, C., Zhang, J., Gao, P., He, M. and Li, Y. (2018) Overexpression of SIRT6 Is a Novel Biomarker of Malignant Human Colon Carcinoma. *Journal of Cellular Biochemistry*, **119**, 3957-3967.

https://doi.org/10.1002/jcb.26539

[94] Li, N., Mao, D., Cao, Y., Li, H., Ren, F. and Li, K. (2018) Downregulation of SIRT6 by miR-34c-5p Is Associated with Poor Prognosis and Promotes Colon Cancer Proliferation through Inhibiting Apoptosis via the JAK2/STAT3 Signaling Pathway. *International Journal of Oncology*, **52**, 1515-1527. https://doi.org/10.3892/ijo.2018.4304

[95] Huo, Q., Li, Z., Cheng, L., Yang, F. and Xie, N. (2020) SIRT7 Is a Prognostic Biomarker Associated with Immune Infiltration in Luminal Breast Cancer. *Frontiers in Oncology*, **10**, Article 621. https://doi.org/10.3389/fonc.2020.00621