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细胞分裂周期相关蛋白5的功能及其在癌症发生中作用的研究进展

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摘　要

细胞分裂周期相关蛋白5 (CDCA5)又名Sororin，最初作为一种调控细胞周期的蛋白被发现，它在姐妹染色单体粘连、细胞周期调控、DNA损伤修复中具有重要作用。近年来CDCA5在癌症发生发展中的作用被逐渐发现，CDCA5在包括肝细胞癌、肺癌、前列腺癌、卵巢癌、膀胱癌、乳腺癌、胃癌、口腔鳞状细胞癌和食管鳞状细胞癌在内的多种癌症中具有肿瘤促进因子的作用。CDCA5参与癌症发生发展的机制主要有：AKT通路、ERK通路、细胞周期调控、蛋白互作等。CDCA5具有作为多种癌症诊断、预后分子标志物及治疗靶点的应用前景。

关键词

细胞分裂周期相关蛋白5，癌症，姐妹染色单体粘连，肿瘤促进因子

Research Progress of the Function of CDCA5 and Its Role in Cancer Progression

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Abstract

Cell division cycle-associated protein 5 (CDCA5), also called Sororin, was first identified as a regulator of the cell cycle. It plays important roles in sister chromatid cohesion, cell cycle regulation

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and DNA damage repair. Recently it has been discovered that CDCA5 plays a part in the progression of various types of cancer, it promotes the progression of different types of cancer including hepatocellular carcinoma, lung cancer, prostate cancer, ovarian cancer, bladder cancer, breast cancer, gastric cancer, oral squamous cell carcinoma and esophageal squamous cancer. CDCA5 exerts its cancer promoting functions through several mechanisms, such as the AKT pathway, ERK pathway, cell cycle regulation and protein interactions. CDCA5 has potential to become diagnosis/prognostic marker and target for treatment in many cancer types.

Keywords

Cell Division Cycle-Associated Protein 5, Cancer, Cohesion of Sister Chromatids, Tumor Promoting Factor

1. 引言

CDCA5 (Cell division cycle associated protein 5，细胞周期相关蛋白 5，别名 Sororin)是在 2005 年的一项对于细胞周期调控蛋白的筛选中作为 APC 复合物(anaphase-promoting complex，后期促进复合物)的底物被发现的[1]。CDCA5 蛋白由 252 个氨基酸组成，分子质量为 27 kD，CDCA5 可以和 PDS5A (PDS5 Cohesin Associated Factor A, PDS5 相关因子 A)和 PDS5B (PDS5 cohesin associated factor B, PDS5 相关因子 B)相互作用。CDCA5 在分裂间期分布于细胞核内，而在分裂期散布在细胞质中。HeLa 细胞中，CDCA5 的敲低可导致有丝分裂停滞及姐妹染色单体间距增加[2]。CDCA5 对于哺乳动物早期发育是必需的，纯合子基因敲除小鼠胚胎致死[3]。CDCA5 最初被发现参与姐妹染色单体粘连和细胞周期调控，而从 2018 年[4]至今 CDCA5 参与各种癌症发生发展逐渐成为研究热点。截至目前，CDCA5 被发现与多种癌症的发生或发展相关，CDCA5 影响多种癌细胞的生长、迁移、凋亡和细胞周期调控，在体内移植瘤实验种被证明与多种肿瘤的生长相关。CDCA5 作为诊断和预后分子标志物以及治疗靶点的潜力需要更加深入的机制探究。

2. CDCA5 在细胞周期中的作用

2.1. CDCA5 在姐妹染色单体偶联中的作用

真核细胞有丝分裂过程中经过 S 期的 DNA 复制形成两条姐妹染色单体，两条姐妹染色单体在黏连蛋白(cohesin)的作用下粘连在一起，随后在有丝分裂后期两个姐妹染色单体分别进入两个子代细胞。姐妹染色单体的粘连对于有丝分裂顺利进行至关重要，两条 DNA 链空间上的靠近为 DNA 同源重组修复提供了结构基础，为姐妹染色单体间的交叉互换提供了结构基础。姐妹染色单体在细胞进入有丝分裂核膜降解时变成显微镜下可见的棒状结构，然而在细胞进入有丝分裂前的几小时内已经可以用 FISH (fluorescence in situ hybridization，荧光原位杂交)观测到成对的基因位点[5]。

黏连蛋白作用周期分为：黏连蛋白装载、建立姐妹染色单体的粘连、粘连的维持以及黏连蛋白卸载。在 DNA 复制前，黏连蛋白短暂地与染色体结合[6]，WAPL (Wings apart-like protein homolog)促进其动态解离[7]。在 S 期，CDCA5 通过抑制 WAPL 的作用使得部分黏连蛋白与染色体稳定结合[8]。CDCA5 可

以维持从 S 期到分裂期姐妹染色单体之间的粘连。CDCA5 参与粘连的维持和黏连蛋白的卸载等过程，在姐妹染色单体的粘连过程具有重要作用[9]。若 CDCA5 被敲除，则姐妹染色单体间的粘连无法维持，在显微镜下观察时可以看到明显的缝隙。

人类细胞有丝分裂中粘连的解除分为两个阶段：分裂前期染色体臂粘连解除和分裂后期着丝粒粘连解除[10]。CDCA5 在这两个阶段中都具有重要作用[11]。CDK1 (Cyclin-dependent kinase 1，细胞周期蛋白依赖性激酶 1)对于 CDCA5 的磷酸化以及 PLK1 (Polo like kinase 1)对于黏连蛋白 SA2 亚基的磷酸化介导了黏连蛋白从染色体臂上的卸载[12] [13]。CDCA5 羧基端 12 个氨基酸可以与黏连蛋白相互作用[14]。

2.2. CDCA5 在 DNA 损伤修复中的作用

CDCA5 对于 G2 期正常的 DNA 双链断裂修复是必需的[8]。使用胸腺嘧啶核苷双阻断法将 Hela 细胞同步在 G1/S 期，加入依托泊苷诱发 DNA 双链断裂，使用咖啡因失活 DNA 损伤检查点，使得 DNA 双链断裂存在的情况下也可进入分裂期，使用纺锤体毒素诺考达唑将细胞阻断在分裂期，后用染色体分散方法检查 DNA 双链断裂情况[7]。发现在对照组细胞中，只有约 35%的细胞含有染色体断裂，然而约有 88%CDCA5 敲低的细胞含有染色体断裂。证明 CDCA5 在 DNA 双链断裂修复中具有重要作用。

2.3. CDCA5 在减数分裂中的作用

哺乳动物卵细胞中 CDCA5 含量降低导致 CDK1 活性降低，细胞被阻滞在 G2/M 期[15]。CDCA5 对于减数分裂中纺锤体组装是必需的。CDCA5 可以保护 Cyclin B2 (细胞周期蛋白 B2)不被泛素化途径降解。

3. CDCA5 在癌症发生中的作用

3.1. CDCA5 影响多种癌症发生发展

利用生物信息学方法筛选与肺腺癌[16] [17] [18] [19]、肝细胞癌[20] [21] [22] [23] [24]、前列腺癌[25]、结直肠癌[26]、乳腺癌[27]、卵巢上皮癌[28] [29]、胰腺癌[30]发展和预后相关的基因中都发现了 CDCA5。多项研究表明 CDCA5 在多种癌症中过表达，起到肿瘤促进因子的作用，如：食管鳞状细胞癌[31]，肺癌[32]，膀胱癌[33]，前列腺癌[34] [35]，肾透明细胞癌[36]，口腔鳞状细胞癌[37]，胃癌[38]，胸膜间皮瘤[39]，乳腺癌[40] [41]，和肝细胞癌[4] [42] [43] [44]。

其中大多数研究从表型上描述了 CDCA5 对不同种类癌细胞生长、凋亡、移植瘤生长的影响，然而机制尚不明确。部分研究对于 CDCA5 参与癌症发生的机制进行了深入的探究，主要发现的机制有：AKT 通路[45]，ERK (extracellular regulated protein kinases，细胞外调节蛋白激酶)通路。

CDCA5 在多种癌症中有着相似的肿瘤促进因子作用。这种作用表现在几个方面[4] [33] [41] [46] [47]：癌组织中 CDCA5 表达量高于癌旁组织；患者中 CDCA5 的高表达和较低存活率相关；在癌细胞系中敲低 CDCA5 使得细胞增殖降低，细胞凋亡增加；在小鼠移植瘤实验中，敲低 CDCA5 可以抑制癌细胞的生长(表 1)。

Table 1. Summary of cancer types and mechanism affected by CDCA5
表 1. CDCA5 影响的癌症种类及机制总结

癌症种类	参考文献	机制
肺癌	[32] [48]	P53-p21 通路、细胞周期[48]
肝细胞癌	[4] [42] [43] [44]	AKT 通路、细胞周期[44] [45]
前列腺癌	[34] [49]	ERK 通路、细胞周期[34]，AKT 通路[49]

Continued

胃癌	[38] [50]	细胞周期[50]
卵巢癌	[51] [52]	N/A
鼻咽癌	[53]	N/A
膀胱癌	[33]	PI3K/AKT 通路[33]
膀胱尿路上皮癌	[54]	细胞周期[54]
食管鳞状细胞癌	[31]	细胞周期[31]
结直肠癌	[46]	ERK 通路[46]
乳腺癌	[40] [41]	PI3K/AKT/mTOR 通路[55]
口腔鳞状细胞癌	[37]	N/A
胸膜间皮瘤	[39]	细胞周期[39]
肾透明细胞癌	[36]	AKT 通路、DNA 损伤及修复、细胞周期[36]
头颈部鳞状细胞癌	[56]	N/A

3.2. CDCA5 参与癌症发生的相关机制

3.2.1. PI3K/AKT 通路

PI3K/AKT (phosphatidylinositide 3-kinase 磷脂酰肌醇激酶－丝氨酸/苏氨酸激酶 AKT)通路参与包括蛋白合成、细胞增殖、细胞凋亡等重要的细胞过程。通路可以被多种信号激活，如：激素，生长因子及细胞外基质成分等。PI3K/AKT 通路参与多种癌症发生发展，在抗癌治疗的研究中备受关注。PI3K 可以被多种上游信号通路激活，包括胰岛素受体，受体酪氨酸激酶，G 蛋白偶联受体，细胞因子受体等。被激活的 PI3K 进一步激活 AKT，AKT 激活后可以通过磷酸化和形成复合体等方式改变下游分子的活性。AKT 激活可以造成细胞凋亡抑制，细胞增殖加快等。AKT 通过与 BAX (BCL-2 associated X protein, BCL-2 相关 X 蛋白)结合，抑制其在线粒体外膜穿孔的功能，从而抑制细胞凋亡。AKT 激活 mTOR (mammalian target of rapamycin，哺乳动物雷帕霉素靶蛋白)信号通路，通过 S6K (Ribosomal protein S6 kinase 1，核糖体蛋白 S6 激酶 1 基因)翻译因子激活 mRNA 向蛋白质的翻译过程，从而促进细胞增殖。FOXO (Forkhead box protein O，叉头框蛋白 O)可以通过抑制细胞增殖起到肿瘤抑制因子的作用，AKT 通过磷酸化 FOXO，使其通过泛素化途径降解，从而抑制 FOXO 的作用。

CDCA5 敲低的肾透明细胞癌、肝细胞癌和前列腺癌细胞中，p-AKT (磷酸化的 AKT)含量降低[36] [45] [49]。CDCA5 敲低对于肝细胞癌及膀胱癌细胞增殖的抑制可以通过加入 AKT 的激活剂 SC79 部分缓解[33] [45]。

CDCA5 通过上调 CDC2 和 cyclin B1 (细胞周期蛋白 B1)以及激活 PI3K/AKT/mTOR 通路促进膀胱癌细胞增殖[33]。当 CDCA5 在乳腺癌细胞中被过表达时，p-mTOR (磷酸化的 mTOR)的水平有超过 2 倍的上调，而 p-PI3K (磷酸化的 PI3K)、p-AKT、以及上皮细胞间充质转化相关标记物也有不同程度的轻微上调[55]。

在肝细胞癌细胞系 MHCC97-H 和 Huh7 中敲低 CDCA5 后，p-AKT 含量降低，皮下肿瘤中敲低 CDCA5 后，p-AKT 含量降低[44]，以上结果提示敲低 CDCA5 对肝细胞癌细胞系细胞增殖的抑制可能是通过 AKT 通路。

3.2.2. ERK 通路

ERK 通路可以被包括生长因子和激素在内的多种细胞外因子激活，最终影响细胞增殖和分化、细胞

凋亡等多种细胞过程。首先，受体酪氨酸激酶，G 蛋白偶联受体或整合素激活 GTP 酶 Ras (rat sarcoma，大鼠肉瘤)。随后 Raf (Rapidly accelerated Fibrosarcoma，快速进展纤维肉瘤)、MEK-1/2 (meiosis-specific serine/threonine-protein kinase 1/2，丝裂原活化蛋白激酶激酶 1/2)和 ERK 依次被激活。激活的 ERK 可以磷酸化一系列核内转录因子，包括：c-fos，c-jun，Elk-1，c-myc 和 ATF2 (activating transcription factor 2，激活转录因子 2)，这些转录因子可以通过调节相关基因表达参与细胞增殖和分化调控。

在结直肠癌细胞系中敲低 CDCA5 导致 p-ERK1/2 (磷酸化的 ERK1/2)及 c-jun 含量降低，表明 ERK 信号通路被抑制[46]。敲低 CDCA5 的前列腺癌细胞系中磷酸化的 ERK 含量降低，而高表达 CDCA5 的前列腺癌患者 ERK 磷酸化水平也较高[34]。

3.2.3. p53-p21 通路

在人类非小细胞肺癌细胞系 A549 和 HCC827 中敲低 CDCA5 后，p53 和 p21 的含量也降低，表明 CDCA5 可能通过 p53-p21 通路影响非小细胞肺癌的细胞周期[48]。

3.2.4. 细胞周期

处于正常细胞周期中的细胞需要受到一系列细胞周期检查点的调控，以保证 DNA 复制和细胞分裂的正常进行。细胞周期检查点主要包括 G1 期、G2 期、M 期检查点。G1 检查点控制细胞能否通过 G1 期进入 DNA 合成的 S 期。G1 检查点检测细胞内是否含有 DNA 损伤，并确认环境中含有足够的营养物质和生长因子以完成 DNA 复制。G1 检查点由 CDK4/6-Cyclin D (周期蛋白依赖性激酶 4/6-周期蛋白 D)和 CDK2-CyclinE (周期蛋白依赖性激酶 2-周期蛋白 E)调控。G2 检查点确保所有 DNA 都已准确复制，并且没有 DNA 损伤。G2 检查点通过 CyclinB/CDK1 复合物调控，若基因中存在 DNA 损伤，则会通过包括 P53、ATM/ATR 等各种信号通路失活 Cyclin B/CDK1 复合物，细胞周期阻滞在 G2/M 期。

在一些种类的癌细胞中敲低 CDCA5 会造成 G2/M 期阻滞。在肾细胞癌细胞系中敲低 CDCA5 导致 G0/G1 期细胞比例降低，G2/M 期细胞比例增加[36]。敲低 CDCA5 的稳转前列腺癌细胞系也有相似表型[34]，表明细胞周期被阻滞在 G2/M 期。Cyclin B1 含量降低，这与细胞周期被阻断在分裂期之前相关。G2/M 期阻滞抑制了肿瘤细胞的增殖。肝细胞癌细胞系中敲低 CDCA5 导致 G2/M 期阻滞[4] [44] [57] [58]。

在另一些种类的癌细胞中 CDCA5 与 G1/S 期阻滞相关。CDCA5 过表达和膀胱尿路上皮癌细胞 G1/S 期阻滞相关[54]。胃癌细胞系中敲低 CDCA5 导致 G1 期细胞比例升高，即 G1/S 期阻滞[50]。在非小细胞肺癌细胞系中敲低 CDCA5 引起 G1 期阻滞[48]。

在细胞周期通路中起到重要作用的 Cyclin A2 (周期蛋白 A2)，cyclin B1，MPIP1 (M-phase inducer phosphatase 1，M 期诱导磷酸酶 1)和 PCNA (proliferating cell nuclear antigen，增值细胞核抗原)，都与 CDCA5 在食管鳞状细胞癌细胞系中有共表达关系。在 CDCA5 敲低的细胞系中，以上几种蛋白的表达量降低。提示 CDCA5 可能通过激活细胞周期通路蛋白促进食管鳞状细胞癌的发展[31]。

3.2.5. DNA 损伤及修复

在肾细胞癌细胞系中敲低 CDCA5 后，利用免疫荧光染色及 WesternBlot 方法发现磷酸化的组蛋白 H2AX 焦点增加，表明 DNA 双链断裂增多[36]。同时，DNA 损伤修复基因 BRCA1 (breast cancer 1，乳腺癌一号基因)和 p-BRCA1 (磷酸化的 BRCA1)表达量降低，提示 DNA 损伤修复能力降低。

3.3. CDCA5 与其他蛋白的互作

3.3.1. 细胞周期相关蛋白

在胃癌组织中 CDK1 和 CDCA5 的表达都上调，且在胃癌细胞系 MGC-803 中 CDK1 和 CDCA5 的表达呈正相关，CDK1 或 CDCA5 抑制会抑制胃癌细胞增殖、克隆形成、迁移能力[59]。以上现象提示 CDCA5

可能通过调节 CDK1 蛋白促进胃癌发展。

CDCA5 敲低的细胞中周期蛋白 E1 (CCNE1) mRNA 和蛋白含量均降低[50]。在 CDCA5 敲低的细胞中过表达 CCNE1 可以使得细胞增殖能力部分恢复，而且可以部分恢复 G1 期阻滞的表型。以上结果提示 CDCA5 可能通过调节 CCNE1 促进胃癌细胞增殖[50]。

CDK1 和 CCNB1 都是 G2/M 细胞周期检查点的核心调节蛋白[60] [61]。肝细胞癌细胞系中敲低 CDCA5 导致 CDK1 和 CCNB1 的表达量降低，这可能与 CDCA5 敲低导致的 G2/M 期阻滞相关[4]。

3.3.2. 黏连蛋白相关蛋白

PDS5 (Precocious dissociation of sisters 5)是一种黏连蛋白结合蛋白，对于黏连蛋白复合体具有重要的调节作用，参与姐妹染色单体粘连、DNA 损伤修复等过程。脊椎动物中 PDS5 有两个旁系同源蛋白：PDS5A (PDS5 cohesin-associated factor A)和 PDS5B (PDS5 cohesin-associated factor B)。PDS5A 在多种癌症中表达量发生变化，如：乳腺癌，肾癌，胃癌，肝癌和结肠癌[62]。PDS5A 的表达量和世界卫生组织神经胶质瘤级别正相关[63]。

乳腺癌细胞中敲低 CDCA5 使得 PDS5A 表达量降低[64]。PDS5A 过表达可以回复 CDCA5 敲低对于乳腺癌细胞增殖和迁移的影响。CDCA5 敲低通过调节 PDS5A 的含量抑制乳腺癌细胞的恶性进展。

3.3.3. 其他上游作用因子

目前已经发现了几个 CDCA5 的上游作用因子，包括：E3 泛素连接酶接头蛋白 SPOP (Speckle-type POZ protein，斑点型锌指结构蛋白) [49]，转录因子 E2F1 [45]，剪接体复合物互作蛋白 SUN2 (SUN domain-containing protein 2，含 SUN 结构域蛋白 2) [65]，miR-326 [51]，MIR4435-2HG [66]，miR-326 [51]，LINC01515 [53]，长非编码 RNA RHPN1-AS1 [67]等。

4. CDCA5 作为预后标志物或治疗靶点的应用前景

一些研究指出了 CDCA5 作为诊断和预后标志物及治疗靶点的价值，如在乳腺癌[27] [68]、卵巢癌[52]、肢端黑色素瘤[69]、非小细胞肺癌[70]、肝细胞癌中[4] [23] [42] [44] [57] [58] [71] [72] [73]。

CDCA5 敲低后提高了食管鳞状细胞癌细胞对于顺氯氨铂化疗敏感性[31]。CDCA5 敲低的细胞相比于未敲低细胞对于顺氯氨铂处理更加敏感，且 CDCA5 敲低的使用顺氯氨铂处理的细胞活力比单独 CDCA5 敲低或单独顺氯氨铂处理的细胞低。

5. 结语

CDCA5 在多种癌症中的肿瘤促进因子作用在近些年被发现，而对于 CDCA5 对癌细胞生长、凋亡、细胞周期的调控作用的机制尚不明确。例如，已经在多种癌症细胞中发现敲低 CDCA5 导致细胞周期阻滞，然而该现象的分子机制尚不明确，即 CDCA5 通过哪个信号通路或哪种蛋白调节细胞周期调控蛋白，目前研究尚缺乏。在未来的研究中，CDCA5 可能会被发现在其他种类的癌症中也起到肿瘤促进因子的作用，但更多的研究应当逐步揭示 CDCA5 参与癌症发生发展的机制，从而推进其作为诊断、预后标志物及治疗靶点的转化研究。

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