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抑癌基因 DLC-1 的研究进展 *

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摘要：DLC-1(肝癌缺失基因 1)是近年来被发现的一种重要的抑癌基因，目前研究发现其在多种肿瘤的发生、发展过程中产生了重要的作用。随着基因技术及分子生物技术的飞速发展，关于 DLC-1 基因以及与之相关的上、下游靶基因，DLC-1 基因的甲基化修饰及其相互作用的信号传导通路的研究将更深入、更彻底、更清楚。通过构建肿瘤动物实验模型，我们可以对人类各种肿瘤进行去甲基化药物治疗，分析实验结果，综合评估治疗指征，为临床上对肿瘤的治疗提供理论基础及实践指导。相信在不久的将来，针对 DLC-1 基因在肿瘤分子生物学研究有望成为多种肿瘤诊断、治疗的突破。

关键词：肝癌缺失基因 1；基因甲基化；信号通路；肿瘤治疗

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The Research Progress of DLC-1*

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ABSTRACT: DLC-1 (deleted in liver cancer-1) is discovered as an important tumor suppressor gene in recent years. Present study finds it plays an important role in the occurrence and development of many kinds of tumors. With the rapid development of gene technology and molecular biotechnology, the research to gene methylation modification and interaction of signaling pathways about DLC-1 gene as well as the related upstream or downstream target genes will be deeper, more thoroughly and clearly. It can provide us theoretical basis and practice guidance of clinical treatment to tumor so that we could take various human tumor methylation drug treatment, analyze experimental results and take the comprehensive evaluation of treatment indications by building up tumor animal experimental model. It is believed that the research aiming at DLC-1's molecular biology will be a breakthrough of varieties of tumors in diagnosis and therapy.

Key words: DLC-1; Gene methylation; Signal pathway; Oncotherapy

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随着人们对肿瘤分子生物学机制的深入研究，肿瘤的发生、发展过程以及原癌基因与抑癌基因之间的关系逐渐引起人们的重视[1]。近几年来，较多的研究集中在肿瘤抑癌基因相关的热点问题上，通过对肿瘤抑癌基因相关的遗传学及分子生物学等相关学科的研究，在分子水平上寻找肿瘤特异性的抑制基因并进行相关的干扰，可能对肿瘤的基因诊断、治疗方面产生重大的意义[2-4]。肝癌缺失基因 1(deleted in liver cancer-1，DLC-1)是近年来作为一种重要的抑癌基因被发现的，目前研究发现其在多种肿瘤的发生、发展过程中产生了重要的作用，针对它的分子生物学研究有望成为多种肿瘤诊断、治疗的突破[5,6]。本文将就抑癌基因 DLC-1 相关研究进展及展望做一综述。

1 DLC-1 基因概述

DLC-1 基因最早于 1998 年由 Yuan 等[7]对多种肝癌细胞系的染色体的研究中首次被发现，由于其在基因组染色体片段中呈现低表达而得名。DLC-1 基因位于人染色体 8p21,3-22 区，Yuan 等研究发现，其 cDNA 全长 3850 bp，包含 14 个外显子，表达的蛋白由 1091 个氨基酸组成，相对分子量为 123 kDa。经基因序列测定显示，鼠的 Rho GAP 基因与 DLC-1 基因具有很大的相似性，因而被看作是人的直系同源基因[8]。正常情况下，Rho 蛋白的水解率很低，Rho GAP 基因可通过调整相关氨基酸残基的位置而加速 Rho 蛋白的水解进而发挥相应的生物学作用[9]。

研究发现[10]，DLC-1 基因表达的蛋白含有 3 个结构域：Rho GAP(Rho GTP activating protein)，START(steroidogenic acute regulatory-related lipid transfer)和 SAM(sterile alpha motif)结构域。Rho GAP 结构域能提高内源性 GTP 酶活性，在 DLC-1 基因相关的抑制肿瘤功能方面发挥着重要的作用；START 结构域位于 DLC-1 基因的 C- 端，可能与细胞内部脂质的运输和代谢密切相关；SAM 结构域位于 DLC-1 基因的 N- 端，能抑制自

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身 Rho GAP 结构域的活性,也可结合其他不含有 SAM 结构域的蛋白[11]。近期研究发现[12],在 SAM 结构域和 Rho GAP 结构域之间有一富含丝氨酸的区域,可以引起细胞膜的内陷,可能对 Rho GAP 结构域活性有一定调节作用,具体作用机制尚不清楚。

2 DLC-1 的生物学功能

DLC-1 基因在多种器官和组织如心脏、肺脏、脑组织、肝脏、乳腺、前列腺等均有表达[13]。诸多研究发现[7, 14-16],DLC-1 基因在肝癌、肺癌、前列腺癌中能抑制肿瘤细胞的生长,起到抑癌基因的作用,这或许是此类癌组织中发生基因杂合丢失或者 DNA 甲基化致使 DLC-1 基因的表达出现失衡所致。

2.1 调节细胞骨架的构建

细胞骨架对于维持正常细胞的结构、形态以及细胞的生长、增殖过程和凋亡具有极其重要的作用。Durkin 等[17]运用基因手段对小鼠的 DLC-1 基因进行处理,发现处理后的小鼠的成活能力较未处理组明显下降,这或许提示 DLC-1 基因对小鼠的成活能力具有极其重要的作用。他们通过研究发现,DLC-1 基因的等位基因发生突变后的纯合子胚胎没有存活超过妊娠 10.5 天的。将自 DLC-1 基因突变体胚胎中分离出的成纤维细胞进行培养,发现其肌动蛋白丝呈断裂状态,并且黏着斑的数量也较正常少[10]。Billuart 等[18]运用 RNA 干扰技术使果蝇 Rho GAP 基因失活,通过对果蝇 DLC-1 基因的直系同源基因的等位基因研究发现,DLC-1 基因所表达的蛋白在形态发生中对于肌动蛋白细胞骨架构建的重要作用。

2.2 调节黏着斑的形成

黏着斑主要与细胞和细胞外基质的黏附相关,DLC-1 基因可通过黏着斑的定位序列与张力蛋白 C- 端的 SH2 结构域结合,共同参与黏着斑的形成。SH2 是特异性与磷酸化酪氨酸相结合的基因序列,而目前研究发现 DLC-1 基因与张力蛋白 SH2 的结合不需要酪氨酸的磷酸化,DLC-1 基因阻碍黏着斑形成的机制可能是该基因的过表达引起的相关蛋白的脱磷酸作用所致[19]。DLC-1 基因突变体胚胎中分离所得的成纤维细胞黏着斑的含量减少,说明 DLC-1 基因的丢失能通过反向影响细胞黏着斑的形成而干涉发育过程,这也提示 DLC-1 基因或许与肿瘤的侵袭、迁移有密切的联系[3]。

2.3 调节细胞凋亡及信号通路

DLC-1 基因与张力蛋白均包含与陷穴蛋白 -1(caveolin-1)的结合序列,可与陷穴小泡结合形成复合体,进一步作用于 Rho GTP 蛋白,这是该基因的另一种作用方式[20]。Yuan 等[21]运用免疫组化对正常人肺组织进行染色后发现,DLC-1 基因的核转位出现在细胞凋亡之前,并且该转位对于诱导肿瘤细胞的凋亡发挥了重要的作用,推测 DLC-1 基因可能在核内发挥相关的诱导凋亡活性。近期有研究发现[22],DLC-1 基因与胰岛素相关的一系列信号转导通路密切联系。

3 DLC-1 与肿瘤的关系

相关研究报道[23],Rho GTP 酶参与肿瘤的发生、发展过程并与肿瘤细胞的增殖及凋亡有密切的关系。随着对 DLC-1 基因的深入研究[10],一方面,人们发现 Rho GAP 结构域能够通过某些途径调节 Rho GTP 酶的活性,进一步发挥对肿瘤的抑制作用;另一方面,Rho GAP 结构域可不通过 Rho GTP 酶发挥相应的肿瘤抑制作用。最近通过对多种原发肿瘤以及细胞系的研究发现[24],DLC-1 蛋白表达阳性的组织中无 DLC-1 基因的异常甲基化,而表达阴性的组织则存在启动子区域的异常甲基化出现,并且两组间存在明显的差异性,这提示 DLC-1 基因的甲基化或许与肿瘤的发生、发展具有很大的相关性。

3.1 通过 Rho 蛋白发挥抗肿瘤作用

DLC-1 基因主要作用于 Rho GAP 结构域这一位点,通过下调 Rho GTP 蛋白的活性来抑制肿瘤细胞的生长[25]。Liao 等[26]在研究时发现,DLC-1 蛋白上张力蛋白的结合位点变异会减弱其抑制肿瘤细胞生长的作用。最新研究发现[20],Rho 族蛋白的活化调控开关受 Rho GEF(Rho 鸟嘌呤核苷酸交换因子)和 Rho GAP 的共同调控,二者之间的动态平衡是 Rho 蛋白发挥正常向细胞内传递信号功能的保障,而 DLC-1 蛋白则发挥着负性调控的作用。因此,部分肿瘤的发病机制或许与 DLC-1 基因调控的信号通路的失衡密切相关。

3.2 不通过 Rho 蛋白发挥抗肿瘤作用

近年来发现,DLC-1 蛋白是张力蛋白的结合伴侣,二者之间的结合不但参与黏着斑的局灶性黏附定位,而且与对肿瘤的增值、侵袭的抑制有关。Healy 等[27]最近发现 Rho GAP 蛋白缺乏的 DLC-1 突变体仍能显著抑制肿瘤细胞的生长,并且相似的结果也在基质胶侵袭实验中得到验证。在该实验中 DLC-1 突变体大约减少细胞 1/4 的侵袭。Yam 等[28]推测 DLC-1 可能是细胞膜穴样凹陷的分子靶向位点,它可通过与细胞膜穴样凹陷里丰富的 Rho GTP 酶相结合进而发挥其生物学作用。细胞膜穴样凹陷里 DLC-1 基因和与之结合的伴侣张力蛋白 2 的相互作用可能是 DLC-1 基因的肿瘤抑制作用的分子生物学基础。此外,小窝蛋白 1 近期也被发现具有典型的肿瘤抑制特性[29]。Qian 等[30]发现,Rho GAP 蛋白与张力蛋白结合的活性都涉及对肿瘤细胞迁移、侵袭的抑制。这些结果共同表明 DLC-1 基因的 Rho GAP 酶的活性对其抗肿瘤机制仅起到部分的作用,DLC-1 基因对肿瘤的抑制作用可能涉及张力蛋白对 Rho GAP 酶活性的靶向作用,因而有研究者提出,DLC-1 基因对肿瘤细胞的生长抑制作用可能还存在与 Rho 蛋白无关的机制。

3.3 启动子区域 CpG 岛的异常甲基化

研究证实,在 DLC-1 基因的 5' 端启动子区域有一段 CpG 岛,若该区域发生甲基化改变,则 DLC-1 基因的表达被显著抑制。到目前为止,DLC-1 基因的甲基化修饰已被证实与多种肿瘤组织或细胞系中异常表达相关。Seng 等[31]运用基因技术分析法对 DLC-1 基因的启动子分析后发现,在鼻咽癌、乳腺癌、食道癌以及宫颈癌中均存在启动子的甲基化修饰现象,而在手术边缘区及正常组织中却极少出现,这提示启动子的甲基化修饰是使这些肿瘤中 DLC-1 基因失活的主要机制。

4 小结与展望

DLC-1 基因在肿瘤的发生、发展过程中常发生表达抑制、缺失或甲基化修饰改变。因此,DLC-1 基因表达和甲基化改变的检测可能成为肿瘤早期发现、早期诊断、早期治疗及评估预后的重要指标,并可能为肿瘤治疗效果提供客观的依据[32]。现

阶段相关体内、外实验研究均证实:DLC-1 基因的抗肿瘤作用具有很高的临床应用价值,它作为一种新的抑癌基因,目前已被证实在人体各正常器官、组织中均有表达,且在多数原发肿瘤组织和相关肿瘤细胞系中出现表达抑制或表达缺失[33]。在肿瘤组织中,通过基因手段使 DLC-1 基因高表达可能成为某些肿瘤基因治疗的选择方法之一[34]。另外,除了基因的表达抑制、缺失或突变外, 也与启动子区域的 CpG 岛甲基化修饰而失活相关。相关研究表明[35,36],单独或者联合应用去甲基化药物辅助化疗在预防某些肿瘤,如乳腺癌,可有效地预防肿瘤的转移。

随着基因技术及分子生物技术的飞速发展, 关于 DLC-1 基因以及与之相关的上、下游靶基因,DLC-1 基因的甲基化修饰及其相互作用的信号传导通路的研究将更深入、更彻底、更清楚。通过构建肿瘤动物实验模型,我们可以对人类各种肿瘤进行去甲基化药物治疗,分析实验结果,综合评估治疗指征,为临床上对肿瘤的治疗提供理论基础及实践指导。相信在不久的将来, 针对 DLC-1 基因在肿瘤治疗上开展的应用将有极其广阔的前景。

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