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·综 述·

淋巴特异性解旋酶与肿瘤关系的研究进展

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[摘 要] 淋巴特异性解旋酶(HELLS)是一种定位于人类染色体10q23-q24区域的DNA解旋酶,在细胞周期进程与基因表达调控中占据着举足轻重的地位。近年来研究发现,HELLS与多种肿瘤的发生、发展密切相关,该基因可促进视网膜母细胞瘤、胶质母细胞瘤、肝细胞癌、胰腺癌和鼻咽癌等多种人类癌症的进展,并影响患者预后。HELLS表达水平的变化可作为潜在的诊断和预后标志物,为这些肿瘤的治疗和预防提供了一定的参考价值。本文就HELLS的分子结构与功能、HELLS与肿瘤的关系作一综述,揭示其作为肿瘤治疗靶点的潜力。

[关键词] 淋巴特异性解旋酶;功能区域;生物学功能;肿瘤
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Research progress on the relationship between helicase, lymphoid specific and tumors

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Abstract: Helicase, lymphoid specific (HELLS), which are DNA helicases located in the 10q23-q24 region of human chromosomes, play a crucial role in cell cycle progression and gene expression regulation. Recent studies have demonstrated that HELLS is significantly associated with the onset and progression of various malignancies. This gene has been shown to facilitate the development of multiple human cancers, including retinoblastoma, glioblastoma, hepatocellular carcinoma, pancreatic carcinoma, and nasopharyngeal carcinoma, and affect the prognosis of patients. Alterations in its expression levels can serve as potential diagnostic and prognostic markers, providing valuable insights for the treatment and prevention of these tumors. This paper reviews the molecular structure and function of HELLS, and the relationship between HELLS and tumors, revealing their potential as therapeutic targets for tumors.

Keywords: helicase, lymphoid specific; functional area; biological function; tumor

近年来,随着分子生物学与基因组学的快速发展,人们对肿瘤分子机制的了解不断深化,其中表观遗传学研究尤为瞩目。该领域不仅成功发掘了一系列新型肿瘤生物标志物,更为临床肿瘤治疗指明了潜在靶点。表观遗传学不改变基因的核苷酸序列,而是通过化学修饰调控基因的表达[1],其核心修饰手段包括DNA甲基化、组蛋白修饰、非编码RNA调控及染色质重塑等[2-8]。研究表明,环境暴露、化学物质刺激等外部因素,可通过干扰表观遗传调控,导致细胞增殖失控,进而诱发恶性肿瘤。而表观遗传变异具有可逆性,也为肿瘤治疗策略的开发提供了新方向。淋巴特异性解旋酶(helicase, lymphoid specific,HELLS)是一种定位于人类染色体10q23~q24区域的DNA解旋酶,隶属于SWI2/SNF2超家族[9],其在细胞周期进程与基因表达调控中占据着举足轻重的地位。以往研究揭示,HELLS的异常表达与视网膜母细胞瘤(retinoblastoma, Rb)[10]、胶质母细胞瘤(glioblastoma, GBM)[11]、肝细胞癌(hepatocellular carcinoma, HCC)[12]、胰腺癌(pancreatic carcinoma, PC)[13]和鼻咽癌(nasopharyngeal carcinoma, NPC)[14]等多种恶性肿瘤的发生密切相关,这一发现进一步强调了HELLS在肿瘤发生发展中的复杂作用机制及其作为潜在治疗靶点的重要性。因此,本文将从HELLS的分子结构与功能、HELLS与肿瘤的关系等方面进行综述,揭示其作为肿瘤治疗靶点的潜力。

1 HELLS的分子结构与功能

HELLS是一种具有解旋酶活性的蛋白,在肿瘤细胞中高表达,并在肿瘤的发生、发展和治疗中发挥重要作用。HELLS主要由以下几个功能区域组成:①SNF2_N结构域,即HELLS的N端区域,含约200个氨基酸残基,该结构域与其他SWI/SNF酶复合物成员共享相似性,可能在调控DNA拓扑结构和解旋酶活性中起着重要作用[15]。②HELICc结构域,为HELLS的核心结构域,也是HELLS解旋酶活性所在[16]。该结构域包含了6个保守的P-loop/相对腺苷三磷酸(adenosine triphosphate, ATP)结合位点,负责HELICc结构域对

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ATP的结合和水解,可提供解旋酶活性所需的能量。同时,该结构域还包含几个高度保守的氨基酸残基,与HELICc结构域的稳定性和功能密切相关[17]。③SANT结构域,即HELLS的C端区域,含约70个氨基酸残基。SANT结构域可以与DNA、蛋白和染色质相互作用,可能在HELLS调控基因转录和染色质重塑中发挥重要的作用[18-19]。④Bromo结构域,HELLS的另一个C端区域,含约160个氨基酸残基。Bromo结构域可以与乙酰化的组蛋白相互作用,参与HELLS对组蛋白修饰的调节。除了这些功能区域外,HELLS还包括低复杂性区、AT-hook结构域和染色质结合结构域等。这些结构域和功能区域共同构成了HELLS蛋白的复杂结构,决定了其在基因转录、DNA甲基化、组蛋白修饰以及DNA复制和修复等过程中的功能和相互作用[20]。在正常情况下,HELLS的表达具有特异性,主要在免疫细胞(如淋巴细胞)中表达[18];但在癌细胞中,HELLS的表达上调。HELLS水平在HCC和PC等多种癌症中异常高表达,通常与肿瘤的恶化相关。HELLS的生物学功能涉及以下几个方面:①DNA修复,HELLS与细胞对DNA损伤的响应有关,可能通过调节染色质结构影响DNA双链断裂的修复[20]。②细胞增殖与分化,由于HELLS参与基因转录的调控和染色质的变化,其对细胞周期的控制和细胞分化过程也有影响。在某些细胞类型(尤其是在造血系统细胞中),HELLS缺失可导致细胞增殖缓慢和分化障碍[21]。③染色质重塑,HELLS参与染色质的重塑,帮助维持染色质开放状态,促进基因转录。HELLS的解旋酶活性可促进DNA解旋,改变染色质结构,从而影响基因的激活或沉默[22]。④DNA甲基化,HELLS与DNA甲基化机制密切相关。HELLS能够影响DNA甲基化模式和DNA甲基转移酶(如DNMT3B)的功能,从而在基因沉默和基因组印迹过程中发挥作用[23-25]。

2 HELLS与肿瘤

HELLS与多种肿瘤相关通路密切相关,涉及细胞增殖信号传导、基因组不稳定性、细胞能量代谢失衡及肿瘤侵袭等多个关键环节。基因组不稳定性(包括基因突变、染色体重排、染色体非整倍体)是近90%的肿瘤共有的显著特征,该特征与肿瘤的异质性、进展、远处转移以及患者低生存率密切相关[26-27]。DNA修复或复制的异常是导致基因组不稳定性的关键途径。染色质重塑是DNA修复效率、基因组稳定性及调控治疗反应的关键环节。HELLS蛋白在维持基因组稳定性、调控肿瘤相关基因表达方面发挥着双向调控作用。

2.1 HELLS与Rb

Rb是由视网膜母细胞瘤1基因(retinoblastoma gene 1, Rb1)双等位基因失活引发的恶性肿瘤,其发病率在婴幼儿眼部恶性肿瘤中居首位,且具有显著遗传倾向性,约60%的患者存在家族史。该病患者多集中于3岁以下婴幼儿,典型临床表现为单侧或双侧眼球“猫眼征”,即瞳孔出现黄白色反光[28]。一项研究报道,在小鼠Rb模型中,HELLS与UHRF1被鉴定为导致肿瘤进展的候选基因,Rb1的失活或缺失可诱导HELLS过表达,促进Rb细胞增殖[10]。Zocchi等[29]通过基因工程小鼠模型探究HELLS在视网膜发育和Rb发生中的作用,结果显示,由于Rb家族基因丧失,在视网膜末端分化过程中未能对HELLS进行转录抑制,从而促进了视网膜肿瘤的发生。此外,视网膜祖细胞中HELLS缺陷不会影响视网膜整体发育,但Rb1/Rbl1双敲除小鼠中HELLS的敲除可显著阻碍肿瘤进展,这进一步证实了Rb家族基因缺失会导致视网膜发育过程中HELLS转录抑制不足,进而导致Rb发生[29]。另有研究表明,Rb1失活后HELLS的上调与脾酪氨酸激酶(人类Rb发生的关键分子)的表观遗传激活相关;同时,HELLS的转录表达受RB/E2F通路调控,HELLS基因是E2F1的直接靶基因,合成的HELLS蛋白与E2F3结合形成蛋白复合物,靶向结合到拥有E2F结合位点、表达产物能启动增殖周期的基因,协同驱动这些靶基因的表达,进一步推动细胞周期进展[30]。在Rb基因工程小鼠模型中,靶向HELLS可有效抑制细胞增殖,降低肿瘤发生率,并提高模型小鼠存活率[31]。综上,HELLS在Rb的发生发展中发挥关键促癌作用,已成为Rb的潜在治疗靶点。

2.2 HELLS与GBM

GBM是一类侵袭性强、增殖迅速的颅内恶性肿瘤,其病理特征与胶质母细胞瘤干细胞(glioblastoma stem cells, GSCs)密切相关,这是由于GSCs具备干细胞特性及活跃的增殖能力,在肿瘤进展中发挥关键驱动作用。HELLS可通过表观遗传调控正常神经干细胞(neural stem cells, NSCs)的关键调节因子,参与NSCs的增殖与自我更新[11]。有研究发现,HELLS可与DNMT3B及PRC1相互作用,在发育过程中介导重复序列的从头DNA甲基化和HOX基因沉默[32-33]。而DNMT1与DNMT3B均被证实与GBM中细胞周期调节因子密切相关。HELLS作为LRP6-GSK3β-E2F1信号通路的下游靶标,与神经胶质瘤生物学行为有关,其还可与E2F3A、E2F3B相互作用,共同促进GBM的发生发展[34]。Zhang等[35]的研究发现,HELLS表达与胶质

瘤进展呈正相关,且其在GBM中呈高表达;HELLS在GSCs中高表达,其可与致癌转录因子E2F3和MYC相互作用,以维持GSCs的特异性增殖;而HELLS敲除后,GSCs中E2F3、MYC表达显著下调,同时诱导复制应激,致使着丝粒、着丝粒周围及端粒重复区域出现DNA双链断裂,最终引发GSCs细胞周期停滞及凋亡;此外,GBM动物模型中,靶向抑制HELLS可有效抑制肿瘤生长,显著提高模型小鼠存活率。综上,HELLS在GBM恶性进展中发挥关键促癌作用,针对HELLS开发潜在的新型分子靶向策略,为GBM的治疗提供了可行方向。

2.3 HELLS与HCC

据报道,HELLS是HCC的主要表观遗传驱动因素。Law等[12]发现,HELLS在HCC中呈显著高表达,其可通过改变无核小体区域及增强子的核小体占有率,介导E-cadherin、FBP1、IGFBP3、XAF1及CREB3L3等多种肿瘤抑制基因的沉默,从而促进HCC进展;与HELLS低表达的患者相比,HELLS过表达会促进肿瘤细胞增殖、迁移,增加其致瘤性,与HCC更具侵袭性的表型相关,尤其是在TP53突变型的HCC中。Schuller等[36]通过实验验证了抑制HELLS表达可阻碍HCC的发生发展。另有研究表明,着丝粒蛋白F(centromeric proteins F,CENPF)作为间期G2期核基质组分,是有丝分裂中着丝粒功能维持及染色体分离的必需分子;HELLS可通过与CENPF的转录起始位点结合,激活并依赖CENPF的转录促进HCC生长[37]。Yan等[38]的研究发现,泛素特异性蛋白酶5可与HELLS相互作用,通过去泛素化修饰增强HELLS蛋白稳定性,并上调溶质载体家族7成员11表达抑制HCC细胞的铁死亡,从而促进HCC的发生。上述研究从表观遗传沉默、信号通路调控、蛋白相互作用及代谢重编程等多个维度,证实了HELLS在HCC发生发展中的促癌作用,使其成为HCC靶向治疗中极具潜力的候选靶点。

2.4 HELLS与PC

HELLS在PC的发生发展中起着促进作用。研究表明,与正常胰腺组织相比,PC组织中的HELLS mRNA及蛋白表达水平均较高,且其过表达与临床分期及不良预后显著相关,下调HELLS可抑制PC细胞增殖和集落形成,并在体外诱导细胞周期停滞[13]。转化生长因子β受体3(transforming growth factor beta receptor 3,TGFBR3)作为转化生长因子β(transforming growth factor beta,TGF-β)信号通路中丰度最高的受体,已在多种肿瘤中被证明是一种特征明确的肿瘤抑制基因[39-40],其可通过促进TGFBR2与特异性配体结合并激活TGFBR1激酶以磷酸化经典或非经典下游介质,增加Caspase-3、Caspase-9和Bax的活性,通过线粒体途径诱导细胞凋亡。在PC细胞中,高表达HELLS使TGFBR3表达显著下调,TGF-β通路促凋亡信号减弱,PC细胞凋亡抵抗、增殖活跃,最终导致肿瘤恶性进展[41]。此外,在PC细胞和PC小鼠模型中下调HELLS表达,促进了细胞DNA的损伤及凋亡,最终显著增加了PC细胞对顺铂化疗的敏感度[41]。因此,HELLS在PC的进展中起着至关重要的促进作用,并且可作为PC化疗过程中的生物标志物以监测化疗敏感性。

2.5 HELLS与NPC

HELLS同样与NPC相关[14]。EB病毒及其产物[如潜伏期膜蛋白1(latent membrane protein 1,LMP1)]所诱导的表观遗传改变,是NPC发生发展中的关键事件[42-43],而染色质重塑因子是表观遗传学的关键因素,在恶性肿瘤的发展中发挥着至关重要的作用[44]。He等[45]的研究表明,HELLS在NPC组织中呈高表达,且其表达受LMP1调控;此外,HELLS可通过调控上皮间质转化相关基因的表达,促进NPC细胞的增殖、迁移、侵袭及体内肿瘤生长和定植,进而增强其恶性表型。其作用机制部分源于HELLS通过调节三羧酸循环的核心成分富马酸水合酶(fumarate hydratase,FH)的表达来促进癌症进展,HELLS与FH启动子结合,募集表观遗传沉默因子G9a以抑制FH转录。FH表达水平降低会导致细胞内琥珀酸盐、富马酸盐和苹果酸盐的减少,α-酮戊二酸(alpha-ketoglutarate,α-KG)与富马酸盐的比值升高。而α-KG、柠檬酸盐等三羧酸循环(tricarboxylic acid cycle,TCA)中间产物可下调E-钙黏蛋白和ZO-1的表达,并上调间质标志物波形蛋白的表达水平。此外,TCA中间产物还能通过调控IKKα依赖性上皮间质转化基因表达,增强NPC细胞的恶性生物学特征。以这种方式,HELLS可通过修饰癌细胞代谢以支持上皮间质转化进程,进而促进NPC的迁移、侵袭及癌症进展[46]。由此可见,抑制HELLS及其下游信号通路有望成为NPC治疗的潜在新靶标。

2.6 HELLS与其他肿瘤

HELLS与肺癌的发生发展也有关。HELLS在肺癌组织中呈上调趋势,且HELLS高表达的肺癌患者生存率较低[47]。Liu等[48]的研究证实,HELLS在结直肠癌的临床样本中显著高表达,在HT29、HCT116结直肠癌细胞系中下调,导致细胞增殖、集落形成和G2/M周期停滞减少,从而抑制肿瘤发生发展。此外,HELLS在人和小鼠髓母细胞瘤组织中也呈高表达,其表达被音猬因子(sonic hedgehog,SHH)通路激活,机制为SHH

通路激活时,平滑蛋白(smoothened,SMO)启动下游信号传导,促进下游的Yes关联蛋白1(Yes-associated protein 1,YAP1)核转位,从而驱动HELLS高表达,参与髓母细胞瘤进展[49]。在头颈部鳞状细胞癌中,致癌性SHH信号通路激活,驱动FOXM1基因转录上调、蛋白表达增加,从而启动并增强HELLS的转录过程,导致HELLS表达上调,介导CDKN2A等肿瘤抑制因子的启动子高甲基化,形成"表观遗传沉默",促进肿瘤进展[50]。据报道,在角质形成细胞中,HELLS通过激活癌基因ΔNp63α来抑制衰老相关基因的表达,促进肿瘤细胞持续增殖;此外,HELLS在头颈部鳞状细胞癌细胞中过表达会上调ΔNp63α,进一步增强肿瘤细胞的增殖能力[51]。

3 总结与展望

HELLS作为一类多功能蛋白,是近年来生物学领域的研究热点,其通过多种机制参与肿瘤的发生发展,已成为癌症生物学及治疗领域的关键调控因子,具有作为新型治疗靶点和生物标志物的潜力。深入探究HELLS在肿瘤中的表达特征、调控机制及其作为治疗靶点的应用潜力,可为肿瘤的研究与治疗提供新的思路和方法。近年来,随着生物信息学与基因编辑技术的快速发展,对于HELLS的研究不断深入并取得了一系列重要进展。然而,关于HELLS的具体生物学功能和作用机制尚未可知,亟待进一步探索。未来可通过基因编辑技术、蛋白质组学分析等对HELLS进行更深入的研究,以揭示其在生物学过程中的更多奥秘;同时还可通过与其他学科相结合开展跨学科研究,以发现更多有意义的生物学现象和规律,为疾病的治疗提供新的思路和方法。

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