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结直肠癌发病的表观遗传及遗传学机制

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摘　要: 结直肠癌(colorectal cancer,CRC)是全球癌症死亡的主要原因之一,由于早期症状不明显,多发现于晚期,因此针对该病的早期诊断和治疗方法都存在局限性。越来越多的证据表明,肠上皮细胞中各种表观遗传和遗传突变的积累,是CRC癌前病变发生发展的关键途径。表观遗传是影响基因表达但不改变DNA序列的分子修饰过程,在基因的激活或抑制中起重要作用,其中包括DNA甲基化、组蛋白修饰、非编码RNA和染色质重塑,且表观遗传可作为癌症诊断和治疗发展的有效生物标志物。基于表观遗传独有生物特征,本文将以CRC基因突变为切入点,阐述表观遗传机制在CRC发展中的作用,并探讨其在临床应用中的进展,为下一步结直肠癌的早期筛查及治疗提供临床思路。

关键词: 结直肠癌;结直肠腺瘤;基因突变;表观遗传
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The epigenetic and genetic mechanisms of colorectal cancer pathogenesis

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Abstract: Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide. Owing to the lack of obvious early symptoms, CRC is often diagnosed at an advanced stage, highlighting the limitations of current early diagnostic and therapeutic approaches. Accumulating evidence suggests that the accumulation of various epigenetic and genetic mutations in intestinal epithelial cells is a key driver of the occurrence and progression of precancerous lesions in CRC. Epigenetics refers to molecular modifications that influence gene expression without altering the DNA sequence and plays a crucial role in gene activation or repression. Epigenetic mechanisms include DNA methylation, histone modification, non-coding RNAs, and chromatin remodeling. Furthermore, epigenetic alterations can serve as effective biomarkers for the development of diagnostic and therapeutic strategies in cancer. Based on the unique biological characteristics of epigenetics, this review takes CRC-associated genetic mutations as a starting point to elucidate the role of epigenetic mechanisms in CRC progression and to explore their potential in clinical applications, with the aim of providing new insights for the early screening and treatment of colorectal cancer.

Key words: colorectal cancer; colorectal adenoma; gene mutation; epigenetics

结直肠癌(colorectal cancer,CRC)是常见的恶性肿瘤之一,其发病率在全球恶性肿瘤中位列第三,致死率位列第二,已成为严重影响健康的公共卫生问题[1]。研究表明,大约90%的CRC由结直肠腺瘤(colorectal adenoma,CRA)发展而来,CRA是指生长在结肠和直肠黏膜表面并突出到肠腔内的各种隆起病变,被认为是CRC最重要的癌前病变之一,其癌变风险随年龄增长逐步增加[2,3]。CRC的治疗包括手术、放射及化学治疗,但由于该病的临床症状多出现在晚期,传统的治疗预后不理想,目

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前靶向治疗、免疫治疗等新型疗法虽然取得了重大进展[4],但存在免疫治疗耐药、靶向失效等问题,新型治疗方法疗效有限[5]。因此,深入探究CRA向CRC发展的机制,并寻找早期诊疗靶点十分重要。近年来,随着表观遗传学研究的深入,CRC病理生理机制越来越清晰。研究发现,表观遗传修饰积累造成基因组不稳定性增加,诱导正常结肠上皮异型增生,是CRC发病的主要病因,这为寻找CRC生物标志物和治疗靶点提供了新的思路和方向[6]。本文将以CRC基因突变为切入点,阐述DNA甲基化、组蛋白翻译后修饰、非编码RNA(non-coding RNA,ncRNA)及染色质重塑等表观遗传机制在CRC发展中的作用,并讨论其临床应用前景。

1 基因突变与结直肠癌

约85%的腺癌中存在基因突变,其特征是致癌基因*KRAS*和*BRAF*异常激活或抑癌基因*APC*和*TP*53功能丧失,导致突变细胞发生癌变,促进CRC的发生发展[7]。

1.1 *APC*基因

*APC*是一种抑癌基因(tumor suppressor gene,TSG),目前大多数CRA发生的起始步骤是*APC*基因突变,其与Wnt/β-catenin信号通路不受控制的激活密切相关;而β-catenin作为细胞骨架相关蛋白,还可调控APC/Wnt/β-catenin/Oct4信号通路实现肿瘤细胞的自我更新[8]。*APC*功能缺失促进β-catenin积累,导致细胞异常增殖,从而形成CRA[9],是腺瘤-癌症序列转化的触发因素。一项研究显示,与腺瘤相邻的结肠黏膜组织在分子水平发生显著变化,与正常黏膜相比邻近黏膜中*APC*基因表达降低50%,而腺瘤中*APC*基因和蛋白的表达较邻近黏膜更低,活化的β-catenin表达更高,证明经典的Wnt信号通路在结肠癌早期已被激活[10]。

1.2 *TP53*基因

*TP53*作为抑癌基因,参与调控DNA修复、细胞周期、衰老、自噬和细胞凋亡,是人肿瘤上皮细胞中最常见的突变基因之一[11]。*TP53*基因介导的正常细胞凋亡通路缺失是驱动腺瘤癌变的重要决定因素[12]。研究发现,*APC*和*TP53*这两个最常见的突变基因在晚期CRC中经常同时出现。NOTUM是一种细胞外棕榈油酰蛋白羧酸酯酶,可在正常肠上皮中抑制经典Wnt信号转导通路。当仅有*APC*突变时,NOTUM在CRA及CRC中仍具有肿瘤抑制活性;但当*APC*和*TP53*同时突变时,NOTUM将从肿瘤抑制因子转化为促癌因子[13],加速腺瘤向癌的转化。除此之外,*TP53*突变也是肿瘤细胞淋巴结转移的必要因素,其依赖高度表达的TP53RK(TP53调节激酶)和TPRKB(TP53RK结合蛋白)促进CRC的转移[14]。

1.3 *KRAS*/*BRAF*基因

*KRAS*是一种原癌基因,是具有内在鸟苷三磷酸酶(GTPase)活性的膜结合蛋白,属于*RAS*基因家族;该基因突变在CRA中高频率发生,参与调节细胞增殖、分化和存活。*KRAS*突变可导致KRAS蛋白持续处于GTP酶结合的活性状态,持续激活下游增殖信号通路[15]。KRAS/丝裂原活化蛋白激酶(MAPK)通路是主要致癌通路之一,*KRAS*基因突变能够在没有外部信号刺激的情况下激活下游MAPK通路,与丝氨酸/苏氨酸激酶(*BRAF*)基因突变共同驱动细胞异常生长、增殖和存活[16]。在*KRAS*/*BRAF*突变的CRC中,表皮生长因子受体(EGFR)是致癌MAPK信号转导的放大器,在EGFR失活的情况下,癌基因驱动的MAPK信号转导显著受到抑制[17]。研究显示,*KRAS*基因通常与*APC*基因协同作用:在*KRAS*基因突变型CRC中,线粒体谷氨酸转运体通过促进谷氨酰胺分解参与CRC细胞的三羧酸循环,造成三羧酸循环中琥珀酸积累,抑制依赖于α-酮戊二酸的DNA去甲基化酶(ten-eleven translocation,TETs)活性,导致抑癌基因高甲基化,进而诱导Wnt/β-catenin信号通路激活和干细胞标志物(如LGR5)表达增加[18]。除此之外,胆固醇代谢也在*APC*/*KRAS*共同突变的CRC亚群中发挥重要作用。胆固醇代谢的调节因子前蛋白转化酶枯草溶菌素9(PCSK9)能够降低细胞对外源性胆固醇的依赖并促进新生胆固醇合成,促进肿瘤生长,是*APC*/*KRAS*突变型CRC的关键驱动因素[19]。

2 表观遗传与结直肠癌

表观遗传作为一种不改变基因序列而调控基因表达的机制,包括DNA甲基化、组蛋白修饰、非编码RNA及染色质重塑等多种调控模式,参与调控细胞周期、细胞凋亡和DNA修复等。在CRC发生发展过程中,DNA甲基化多发生于CRC早期,而组蛋白翻译后修饰参与肿瘤进展、促进肿瘤细胞增殖,非编码

RNA与染色质重塑多与CRC晚期转移密切相关，因此表观遗传机制贯穿于CRC整个发病过程(图1)。

2.1 DNA甲基化

DNA甲基化是表观遗传调控的重要机制，其动态变化包括高甲基化、低甲基化和去甲基化，在DNA甲基转移酶(DNA methyltransferases，DNMT)和TETs的作用下通过修饰5-甲基胞嘧啶(5-mC)实现DNA甲基化和去甲基化。DNA甲基化在CRC发病过程中通过沉默TSG参与腺瘤-癌症转化过程，而低甲基化作为癌症早期事件，与肿瘤恶性程度密切相关[20]。

2.1.1 DNA高甲基化

DNA高甲基化主要发生在CpG岛，尤其TSG的启动子区域，通常会导致TSG沉默和转录受阻，从而促进肿瘤发展，CRC中已有多个TSG被证明发生了高甲基化[21]。如*PPARGC1A*、*LRBA*和*ATP8A1*基因，作为TSG，其高表达可以抑制肿瘤细胞的增殖和迁移；但在CRC中，其表达水平较CRA病例显著下降，而DNMT的水平却显著升高，提示上述TSG发生甲基化修饰，且其高甲基化能够促进腺瘤向癌症的转化[22]。

2.1.2 DNA低甲基化

DNA低甲基化优先影响DNA重复序列，通过反转录转座子的激活导致基因组不稳定，是CRC发病的早期事件和常见特征[23]。人类基因组中最丰富的反转录转座子是长散在核元件1(LINE-1)。一项研究显示，正常细胞中LINE-1基因发生甲基化修饰，而在早期腺瘤-腺癌-癌症进展过程中，LINE-1甲基化水平逐渐降低，提示低甲基化使LINE-1去抑制，促进突变累积[24]。

2.1.3 DNA去甲基化

DNA去甲基化由TETs 家族(TET1、TET2、TET3)介导，可氧化5-mC生成5-羟甲基胞嘧啶(5hmC)，并在碱基切除修复酶胸腺嘧啶DNA糖基化酶(TDG)的帮助下清除5hmC的转化产物5-甲酰基胞嘧啶(5fC)和5-羧基胞嘧啶(5caC)，从而维持去甲基化状态[25]。在CRC中5hmC水平较低，表明TET参与CRC肿瘤发生，研究显示：TET1会优先与低甲基化的CpG岛结合，清除并阻止附近位点的异常DNA甲基化扩散，来维持其低甲基化状态[26]；TET2和TET3则与CRC预后密切相关，TET2表达水平与肿瘤转移风险呈负相关[27]；而TET3可以促进DNA损伤和细胞周期阻滞，增强CRC对放射治疗的敏感性，靶向TET3-SUMO化通路可增强抗癌效果，提高患者生存率[28]。

2.2 组蛋白翻译后修饰

染色质是由接头组蛋白H1和核心组蛋白H2A、H2B、H3和H4形成的八聚体与DNA共同形成的核小体组成，核小体是表观遗传调控的分子开关，参与基因转录、DNA复制、染色质浓缩和DNA损伤修复等多种生物学过程。组蛋白修饰多发生在核心组蛋白的N端尾部，包括乙酰化、甲基化、磷酸化、泛素化和乳酸化，不同修饰之间常相互作用[29]。

2.2.1 乙酰化

组蛋白的乙酰化依赖于乙酰辅酶A(acetyl-CoA，ac-CoA)，ac-CoA可以通过核孔自由进入细胞核，在组蛋白乙酰转移酶(histone acetyltransferase，HAT)或组蛋白去乙酰化酶(histone deacetylase，HDAC)的作用下影响组蛋白乙酰化修饰，调节基因

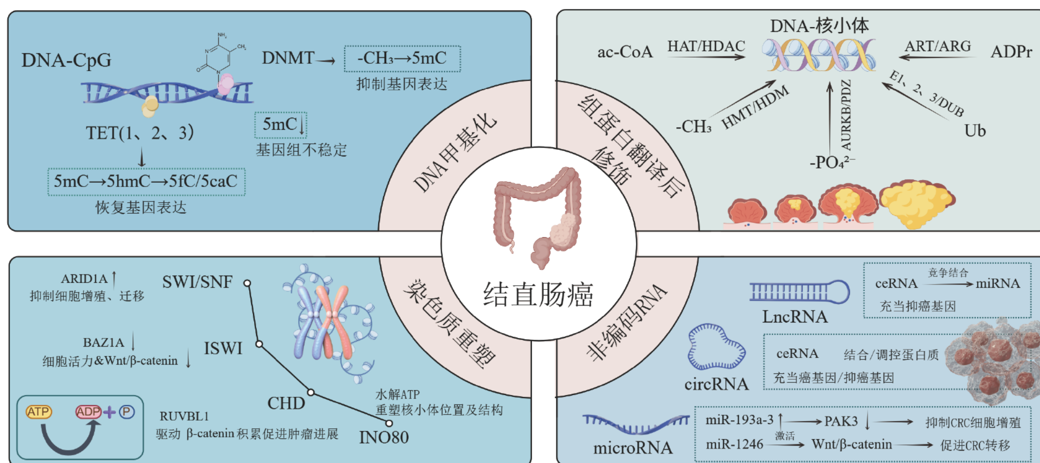

图1 表观遗传与结直肠癌(Figdraw作图)

Figure 1 Epigenetics and colorectal cancer (by Figdraw)

表达[30]。乙酰化通常激活并促进基因表达,*FOXQ1*基因已被证明可以促进CRC细胞增殖、侵袭和转移;p300作为HAT家族成员,能够乙酰化*FOXQ1*的赖氨酸(Lys)190位点并促进其与增强子的结合,加速CRC进展[31];而HDAC能够从组蛋白尾部的N-乙酰化Lys残基中去除乙酰基,导致染色质浓缩并抑制基因表达[32]。研究发现,组蛋白乙酰化和DNA甲基化是拮抗性表观遗传标记,如p300能够促进组蛋白乙酰化并影响TET1活性以共调节*ZNF334*表达,提高*ZNF334*启动子区域的组蛋白乙酰化水平,使其恢复正常表达,从而抑制CRC进展[33]。

2.2.2 甲基化

组蛋白甲基化通常发生在基因启动子区域,通过组蛋白甲基转移酶(histone methyltransferase,HMT)和去甲基化酶(histone demethylase,HDM),有序地调节对Lys和精氨酸(Arg)的特定修饰,使受影响基因组区域基因沉默或激活,是调节TSG和癌基因表达的重要机制。根据甲基化程度,组蛋白甲基化可分为单甲基化 (me1)、二甲基化 (me2) 和三甲基化 (me3)三种形式,从me1到me3的疏水差异会导致特定蛋白质的招募,从而调控基因转录,影响癌前病变、肿瘤发生和转移[34]。Zeste同源物2增强子(EZH2)可充当HMT,特异性催化组蛋白H3中Lys27的me3(H3K27me3)来维持肿瘤关键抑制基因的染色质抑制状态;研究发现,使用EZH2抑制剂(GSK503)可降低肿瘤组织结肠隐窝中H3K27甲基化水平,并上调HDM活性,激活结直肠黏膜免疫反应,减缓CRA进展,抑制CRC转移[35]。

2.2.3 磷酸化

组蛋白磷酸化多发生在组蛋白尾部的丝氨酸(Ser)、苏氨酸(Thr)和酪氨酸(Tyr)残基上,这些位点可被多种蛋白激酶磷酸化,并被磷酸酶去磷酸化[36]。极光激酶B(AURKB)作为一种丝氨酸/苏氨酸激酶,调控细胞周期的各个阶段,在哺乳动物有丝分裂中发挥关键作用;研究发现AURKB能够触发细胞周期蛋白E1(*CCNE1*)基因启动子区域组蛋白H3上Ser 10位点的磷酸化,继而激活*CCNE1*的表达,促进CRC细胞增殖和细胞周期进程[37]。同为丝氨酸/苏氨酸激酶的PDZ结合激酶(PBK),显著提高CRC细胞中磷酸化组蛋白H3的表达,促进肿瘤细胞增殖[38]。除此之外,组蛋白去乙酰化也参与磷酸化过程。HR488B是一种新型HDACs抑制剂,明显降低视网膜母细胞瘤蛋白(retinoblastoma protein,Rb)的磷酸化水平,进而抑制E2F1/Rb/HDAC1复合物释放E2F1并下调其表达,诱导细胞凋亡并导致细胞周期G_0/G_1停滞,抑制CRC细胞生长[39]。

2.2.4 泛素化

组蛋白泛素化通常标志着基因的激活或抑制,依赖泛素(ubiquitin,Ub)末端甘氨酸(Gly)残基与组蛋白Lys残基或Ub本身的Lys残基形成共价键来实现,而Ser和Thr残基也可作为泛素化位点,在Ub和组蛋白之间形成羟基酯键[40]。泛素化较其他组蛋白修饰更为复杂,通过泛素写入器(E1、E2和E3酶)催化实现:E1酶依赖ATP激活Ub,之后Ub被转移到E2酶活性位点,由E3连接酶介导泛素与靶蛋白Lys残基的连接;泛素化酶和去泛素化酶(deubiquitinating enzymes,DUB)共同参与调控基因表达、DNA修复及细胞分裂等多种生物学过程[41]。Ub通常以单体形式在一个或多个位点上与靶蛋白结合,分别称为单泛素化或多单泛素化;也可以通过异肽键相互连接,形成不同长度和结构的聚合链[42]。组蛋白H2A是第一个被发现泛素化修饰的蛋白,也是细胞核中最丰富的泛素化蛋白,Lys119是最常观察到的组蛋白H2A泛素化位点(H2AK119ub1),由RING1A/B组成的E3连接酶催化;研究发现去泛素化金属蛋白酶MYSM1(也称为2A-DUB)可从H2AK119ub1中去除单泛素,并与组蛋白乙酰化协同激活转录,显著抑制细胞周期进程和增殖,并诱导CRC细胞凋亡[43]。

2.2.5 ADP核糖基化

组蛋白ADP核糖基化是由ADP核糖基转移酶(ADP-ribosyl transferase,ART)和ADP核糖基水解酶介导的可逆过程,包含单ADP核糖基化和多聚ADP核糖基化两种形式,发挥促癌作用,并且与其他组蛋白修饰存在互作[44]。ADP核糖来源于烟酰胺腺嘌呤二核苷酸(NAD^+),可在多种ART的催化下被添加到靶蛋白上,其中多聚ADP核糖聚合酶1(poly (ADP-ribose) polymerase-1,PARP1)是主要的组蛋白ART[45]。研究发现,PARP1促进CRA向CRC转化,NUDT13作为具有潜在ADP核糖基水解酶活性的调节因子,能够下调PARP1催化的多聚ADP核糖基化来稳定PKM1蛋白,抑制CRC的启动[46]。同样,单ADP核糖基化在CRC中也发挥关键作用,在未显著分化的人高度恶性结肠癌细胞Lovo细胞中,组蛋白H3的Arg117(H3R117)位点被单ADP核糖基

化，促进癌细胞增殖[44]。

2.3 非编码RNA

ncRNA由基因组非编码序列产生，人类基因组转录产物中大部分是ncRNA，可参与调控表观遗传修饰、基因表达及mRNA稳定性等[47]。根据长度，ncRNA分为小ncRNA和长ncRNA（lncRNA）。小ncRNA长度小于200 nt，包括核糖体RNA（rRNA）、转移RNA（tRNA）、microRNA（miRNA）和piwi相互作用RNA（piRNA）等。lncRNA长度通常超过200 nt，如反义长链非编码RNA（antisense lncRNA）、环状RNA（circRNA）、增强子RNA（enhancer RNA，eRNA）和基因间长链非编码RNA（lincRNA）等。其中，miRNA、lncRNA和circRNAs已被证实在CRC细胞增殖、侵袭和转移中发挥重要作用[48]。

2.3.1 lncRNA

lncRNA作为表观遗传调控因子，参与调控CRC的不同阶段。在CRA到CRC的进展过程中，多个lncRNA被显著上调，发挥促癌或抑癌作用。研究表明，lncRNA在CRC进展中可作为竞争性内源性RNA（ceRNA）或CRC相关通路信号分子发挥作用。ceRNA也称为“miRNA海绵”，通过与内源性mRNA竞争miRNA结合位点来调节基因表达[49]。如*MRPS31P5*作为lncRNA，可以充当miRNA海绵，并调控CRC相关基因*MDM4*和*THBD*的表达[50]。除此之外，CRC中lncRNA的异常甲基化已被广泛研究，*MEF2C-AS1* 作为潜在TSG，其过表达能够显著抑制CRC细胞增殖、迁移和侵袭，而*MEF2C-AS1*高甲基化发生在CRC各个阶段，抑制了该基因的表达，其甲基化水平在非晚期腺瘤、晚期腺瘤和癌的恶性转化过程中依次递增[51]。

2.3.2 miRNA

miRNA可直接靶向mRNA抑制其翻译，也可以与其他miRNA或ncRNA结合调控基因表达[52]。在CRC中，已证实miRNA表达谱随癌症进展而发生改变[53,54]。miR-193a-3过表达通过下调*PAK3*表达来调节CRC细胞凋亡，导致细胞周期停滞，并可在体外抑制CRC转移[55]。在体外和体内CRC模型中，由具核梭杆菌诱导的外泌体miR-1246可通过激活Wnt/β-catenin通路促进CRC细胞迁移[56]。

2.3.3 circRNA

circRNA是一种具有环状结构的非编码RNA，大多数circRNA来源于蛋白质编码基因，通过反向剪接形成，其分子结构高度稳定，主要存在于细胞质中，通过不同的作用机制在癌症发生发展中起关键作用[57,58]。circRNA通过充当miRNA海绵、与RNA结合蛋白相互作用或作为蛋白质翻译模板来充当癌基因或TSG[59]。研究发现，结直肠肿瘤起始细胞（tumor-initiating cell，TIC）富集的circRNA cis-HOX参与TIC活性维持，通过抑制RNA结合蛋白KSRP与*HOXC10* mRNA结合，抑制*HOXC10* mRNA降解，使*HOXC10*在TIC中高表达，驱动*FZD3*的表达继而激活Wnt/β-catenin信号通路，促进TIC自我更新、成瘤及转移[60]。研究还发现，circ_0007379在CRC中显著下调，与KSRP相互作用调节miR-320a生物发生，减弱CRC细胞HT29和HCT116的增殖、迁移和侵袭能力，抑制正常肠上皮细胞转化为异常细胞甚至癌细胞，减缓CRC进展[61]。

2.4 染色质重塑

染色质重塑是指通过ATP依赖性染色质重塑复合物，改变并修饰染色质的结构，调节染色质可及性，导致染色质开放或压缩，继而调控基因表达的表观遗传机制。基于不同的ATP酶催化亚基，染色质重塑复合物可被分为四类，包括SWI/SNF、ISWI、CHD和INO80[62]。大规模癌症基因组测序研究表明，染色质调节因子在肿瘤中经常发生突变，而超过20%的肿瘤存在SWI/SNF染色质重塑复合物亚基基因突变，因此SWI/SNF复合物是人类中最常见的染色质调节因子[63]。SMARCA4是SWI/SNF复合物中两个互斥的催化亚基之一，在多个肿瘤发生发展过程中起促癌作用，但在CRC中的作用尚未明确[64]。研究显示，富含AT的交互结构域蛋白1A（ARID1A）是SWI/SNF染色质重塑复合物的重要亚基，随着TNM分期的进展，*ARID1A*基因丢失比例增加，提示*ARID1A*是CRC的关键TSG，其丢失与CRC进展和转移密切相关[65]；*ARID1A* 过表达可以增加上皮标志物的表达和降低间充质标志物的表达，抑制CRC细胞EMT进程，并抑制CRC细胞迁移[66]。锌指结构域1A相邻的溴结构域（BAZ1A）也是染色质重塑的关键调节因子，*BAZ1A*沉默能够降低CRC细胞活力，并下调Wnt/β-catenin信号通路[67]。RUVBL1也是一种高度保守的ATP酶，是INO80染色质重塑复合物的组成部分，Lyn/RUVBL1复合物能够介导染色质重塑从而调控花生四烯酸代谢重编程，驱动β-catenin易位并积累，促进CRC发生发展[68]。

除此之外,染色质重塑也能够与基因突变或组蛋白修饰相互协作,共同控制基因转录、DNA损伤及修复,发挥肿瘤促进或抑制作用。如*SMARCA4*中的高频热点突变(*R1157W*)可增强SMARCA4与蛋白精氨酸甲基转移酶1(PRMT1)介导的H4R3me2a标记的结合能力,并显著增强SWI/SNF复合物的ATP酶活性,促进染色质重塑,通过促进*EGFR*和*TNS4*的表达加速CRC进展[64]。除此之外,染色质重塑也能与circRNA相互协作。研究显示,circREEP3在侵袭性CRC细胞中高表达,通过招募染色质重塑蛋白CHD7启动*FKBP10*转录,*FKBP10*高表达与患者不良预后相关;同时,circREEP3还抑制RIG-1依赖性抗肿瘤免疫,促进CRC增殖和转移[69]。染色质重塑还可以增强肿瘤细胞耐药性。染色体解旋酶DNA结合蛋白4(CHD4)是染色质重塑复合物的关键亚基,研究表明CHD4过表达会加剧胃肠道癌症患者的化疗耐药并促进肿瘤细胞增殖[70]。以上研究表明,染色质重塑复合物在胃肠道肿瘤的发展、转移和耐药性中起着至关重要的作用,有望成为癌症治疗靶点。

3 基因突变与表观遗传在结直肠癌中的相互作用

CRC中基因突变与表观遗传的相互作用是肿瘤发生发展的核心机制之一,基因突变能够直接或间接影响表观遗传模式,而表观遗传改变亦能影响基因表达,导致癌基因激活或抑癌基因失活[71],驱动肿瘤进展。

3.1 基因突变驱动表观遗传改变

基因突变可直接影响表观遗传调控,如PRMT1是蛋白精氨酸甲基转移酶家族成员,能够催化组蛋白H4R3me2a甲基化,直接募集染色质重塑复合物SWI/SNF的ATP酶亚基SMARCA4,形成表观遗传-染色质重塑协同调控轴。当*PRMT1*基因异常高表达时,H4R3me2a水平随之升高,与SMARCA4相互结合并被募集到*EGFR*启动子区,激活其转录,促进CRC细胞的增殖和迁移[72]。

3.2 表观遗传修饰反馈调控基因突变

TSG启动子区域的高甲基化通常会使基因沉默,*APC*基因是经典的CRC抑癌基因,高甲基化会使*APC*功能丧失,且会迅速产生离散的DNA甲基化,该现象在疾病后期更加普遍[73]。而启动子低甲基化通常导致染色质开放,促进转录因子结合和靶基因表达。*SPRY4*通常作为TSG,在多种癌症中表达下调,但在CRC中,*SPRY4*启动子区低甲基化、编码区高甲基化,二者协同作用最终呈现表观遗传上调,发挥促癌作用,提示表观遗传可能会改变TSG的传统功能[74]。

3.3 基因突变与表观遗传互作影响CRC表征的作用机制

肿瘤的发生发展依赖于一系列癌症标志性特征[75],而基因突变与表观遗传调控相互作用,共同驱动这些特征的形成。如*KRAS*、*BRAF*突变可导致MAPK通路持续激活[18],*TP53*突变可导致细胞丧失周期调控功能[11]。在组蛋白甲基化调控中,*EZH2*过表达可增强H3K27甲基化修饰,抑制抗肿瘤免疫[35]。在ncRNA中,*PAK3*是CRC细胞中miR-193a-3p的靶基因,过表达miR-193a-3p通过抑制*PAK3*表达诱导CRC细胞凋亡;而在CRC中,miR-193a-3p表达降低,对细胞凋亡的抵抗力增强[55]。同样,DNA低甲基化也能够通过激活反转录转座子导致基因组不稳定,促进CRC发展[23]。

4 基因突变与表观遗传在结直肠癌中的临床应用前景

随着高通量测序技术的发展,越来越多的基因突变和表观遗传异常被证实与CRC的发生发展密切相关,不仅为CRC的早期诊断提供了新型分子标志物,而且为精准治疗开辟了新途径,如新型标志物*SEPT9*基因甲基化检测已成功应用于临床CRC筛查[76]。

4.1 早期筛查标志物

CRC早期筛查可以降低发病率和死亡率,目前临床常用的筛查手段分为侵入性及非侵入性两种。侵入性筛查手段多指内镜检查,其中结肠镜检查目前是CRC筛查和诊断的金标准,但受限于前期肠道准备复杂及缺乏早期灵敏度,非侵入性检查能够从一定程度上弥补侵入性检查的不足[77,78]。传统非侵入性检查包括粪便隐血实验、粪便DNA检测、粪便免疫化学检测及血液标志物检测。随着技术的进步,针对早期CRC表观遗传学特征的靶向筛查敏感性和特异性明显提升[79]。目前研究较成熟的标志物主要集中于DNA甲基化及ncRNA领域,且联合标志物的应用能够明显提升早期CRC检出率,如血浆样本中*SEPT9*基因的甲基化,是目前FDA唯一批

准的CRC筛查血浆检测指标[80](表1)。

4.2 潜在治疗靶点

表观遗传调控在CRC免疫逃避和耐药性中至关重要,靶向表观遗传调控分子可能为CRC患者提供更高的生存率,且联合化疗或其他靶向疗法有望逆转耐药或增强免疫[91]。如表观遗传药物EZH2抑制剂可通过抑制H3K27me3修饰激活CRC中去泛素化酶USP22的表达,从而增强PD-L1稳定性,诱导肿瘤细胞免疫逃避,降低抗肿瘤治疗效果;而EZH2抑制剂与抗PD-1免疫检查点阻断疗法联合使用可改善肿瘤微环境,增强对免疫疗法的敏感性,并发挥协同抗癌作用[92]。5-氮杂胞苷为DNMT抑制剂,其与EZH2抑制剂联用有望成为BRAF^{V600E}突变CRC患者的潜在治疗策略[93]。除此之外,基于CRISPR-Cas9的表观遗传编辑技术利用表观遗传学的可遗传性和可逆机制,为修改特定表观遗传标记、改变基因表达提供了更为精确的方法,为CRC治疗带来突破[15,94](表2)。

5 小结与展望

CRC是全球高发的恶性肿瘤,其发生发展涉及复杂的遗传变异和表观遗传调控异常。在遗传变异方面,*APC*、*TP53*和*KRAS*/*BRAF*等经典基因的突变驱动了肿瘤的发生与进展。其中,*APC*基因突变导致Wnt信号通路持续激活,而*KRAS*和*BRAF*突变则促进MAPK通路异常,影响细胞增殖与存活。在表观遗传调控方面,DNA甲基化异常(如启动子高甲基化导致的TSG沉默)、组蛋白修饰失调(如H3K4me3)、ncRNA(如miR-193a-3p、miR-1246)及染色质重塑显著影响基因表达并调控关键信号通路参与CRC的侵袭与转移。早期筛查及早期治疗能够显著提高CRC患者生存率,但确诊时疾病多已进展至晚期。CRA作为最常见的癌前病变,临床多依赖结肠镜检查及病理检查,作为有创诊疗手段,存在一定的局限性。表观遗传依赖其独特的分子特征,不仅为CRC的发生发展提供了依据,还推动了早期筛查、靶向治疗及表观遗传编辑等新技术的发展。未来研究需聚焦多组学技术整合,进一步细分CRC亚型,指导个体化治疗,深入解析表观遗传与遗传突变的协同作用网络,并开发早期体液筛查手段,做到早发现早治疗,降低早癌恶变的概率。此外,表观遗传临床转化药物联合免疫、靶向疗法,能够明显提升疗效并补充免疫治疗和靶向治疗的不足,但仍存在

表1 结直肠癌表观遗传学早期筛查标志物

Table 1 Epigenetic biomarkers for early screening of colorectal cancer

标志物	表观遗传类型	检测样本	灵敏度	特异性	应用阶段	参考文献
miR-92a-1	ncRNA	血清	81.8%	95.6%	临床验证	[80]
miR-21	ncRNA	血清	79.0%	92.0%	临床验证	[81]
miR-223/miR-182	ncRNA	血清	98.0%	97.0%	临床验证	[82]
miR-135b-5p	ncRNA	粪便	96.5%	74.1%	临床验证	[83]
miR-29-3p	ncRNA	粪便	85.0%	61.0%	临床验证	[84]
SFRP2/SDC2	甲基化	粪便	88.5%	89.5%	临床验证	[85]
SDC2/SEPT9/VIM	甲基化	粪便	91.4%	100.0%	临床验证	[86]
SDC2/TFPI2	甲基化	粪便	81.3%	94.3%	临床验证	[87]
NEUROG1	甲基化	血清	33.3%	95.0%	临床验证	[88]
SDC2/NDRG4	甲基化	粪便	85.5%	84.6%	临床验证	[89]
SDC2/ADHFE1/PPP2R5C	甲基化	粪便	84.8%	98.0%	临床验证	[90]

表2 结直肠癌表观遗传治疗靶点的临床试验进展

Table 2 Progress in clinical trials of epigenetic therapeutic targets for colorectal cancer

药物	药物类型	联合治疗	试验阶段	疾病阶段	参考文献
阿扎胞苷	DNMT抑制剂	帕博利珠单抗	Ⅱ期	化疗难治性转移性结直肠癌患者	[95]
瓜地西他滨	DNMT抑制剂	伊立替康与瑞戈非尼或TAS-102	Ⅱ期	伊立替康难治性转移性结直肠癌患者	[96]
Adagrasib (MRTX849)	DNMT抑制剂	\	Ⅰ/ⅠB期	结直肠癌晚期*KRAS*^{G12C}突变实体瘤患者	[97]
西达本胺	HDAC抑制剂	信迪利单抗(PD-1)或贝伐珠单抗(抗VEGF)	Ⅱ期	不可切除的化疗难治性局部晚期或转移性MSS/pMMR结直肠癌患者	[98]
恩科拉非尼	BRAF抑制剂	西妥昔单抗(抗EGFR)	Ⅲ期	既往治疗的BRAF^{V600E}突变转移性结直肠癌	[99]

继发耐药、转移性CRC难治、新型检测技术成本高昂及新药研究周期长等局限性。因此，继续深入探索CRC遗传-表观遗传互作的分子机制，有望为CRC的个体化诊疗提供新思路，做到早期筛查，晚期提升疗效，改善患者预后，最终降低患者死亡率。

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