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· 综述 ·

DNA 甲基化在结直肠癌诊断中的研究进展

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[摘要] 随着表观遗传学中DNA甲基化的深入研究, 人们发现CpG岛(CpG island)DNA甲基化在结直肠癌(colorectal cancer, CRC)的临床诊断中发挥重要作用。目前, 研究证实检测CRC患者组织、粪便和血液中基因的异常甲基化在CRC的早期筛查和诊断中具有很高的敏感性和特异性。本文就胞裂蛋白9(septin 9, SEPT9)、多配体聚糖2前体(syndecan 2 precursor, SDC2)、波形蛋白(vimentin, VIM)、p16和长散布核苷酸元件-1(long interspersed nucleotide element-1, LINE-1)5个基因的甲基化及其在CRC诊断中的相关进展进行了综述。

[关键词] 结直肠癌; 胞裂蛋白9; 多配体聚糖2前体; 波形蛋白; p16; 长散布核苷酸元件-1

Progress in DNA methylation in the diagnosis of colorectal cancer

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Abstract With the development of research on DNA methylation in epigenetics, CpG island DNA methylation has been found to play an important role in the clinical diagnosis of colorectal cancer (CRC). At present, numerous researches have confirmed that the detection of abnormal methylation of genes in tissues, stool and blood of CRC patients has high sensitivity and specificity for early CRC screening and diagnosis. This review summarizes the methylation of five genes which have been investigated clearly, including septin 9 (SEPT9), syndecan 2 precursor (SDC2), vimentin (VIM), p16, and long interspersed nucleotide element-1 (LINE-1), and their progress in diagnosis of CRC.

Keywords colorectal cancer; septin 9; syndecan 2 precursor; vimentin; p16; long interspersed nucleotide element-1

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结直肠癌(colorectal cancer, CRC)是继肺癌、乳腺癌之后全球第3种最常见的癌症类型,也是癌症相关死亡的第二大原因^[1]。由于缺乏有效的早期筛查手段,多数患者确诊时已到中晚期,且大部分发生转移,治疗和预后状况不容乐观。因此,寻找早期筛查和诊断CRC的新途径是降低CRC病死率的关键。近年来,随着表观遗传学的发展,DNA甲基化在CRC中的作用得到了深入的研究,本文就DNA甲基化在CRC诊断中的研究进展进行阐述。

1 表观遗传学、甲基化及其在结直肠的作用

表观遗传学广义上是指在基因的DNA序列不发生改变的情况下,其表达发生了可遗传的变化^[2],是从RNA, DNA, 染色质和蛋白质等多个水平调控基因表达,从而达到基因表型的改变^[3]。因此,我们可以通过调控癌症相关的基因表达来控制癌症。目前已知的在癌症中发挥作用的表观遗传机制包括:1)CG富集序列中胞嘧啶碱基的DNA甲基化,称为CpG岛;2)组蛋白的翻译后修饰;3)microRNAs和非编码RNA;4)核小体定位等^[4]。

DNA甲基化是目前为止研究最多、最清楚的一种生物体内普遍存在的表观遗传学调控机制。DNA甲基化是指在DNA甲基转移酶(DNA methyltransferase, DNMT)的催化作用下,在基因组CpG二核苷酸的胞嘧啶5'碳位共价键结合一个甲基基团^[5]。CpG岛是位于基因启动子区域的一段富含C和G的序列^[6],CRC中CpG岛甲基化可以通过不同机制影响相应基因的表达,从而对肿瘤细胞周期、DNA修复、细胞代谢、信号转导等产生不同作用,在CRC的发生发展中发挥重要作用^[7]。研究^[8]指出:DNA异常甲基化发生在肿瘤的早期,并贯穿肿瘤整个发展过程。因此,DNA甲基化可以作为CRC早期检测的有效生物标志物。

2 与 CRC DNA 甲基化相关的基因

2.1 胞裂蛋白 9

胞裂蛋白9(septin 9, SEPT9)基因普遍存在于人体染色体17q25,是真核生物内一组高度保守的GTP结合蛋白,在细胞分裂、分化过程中提供结构支持^[9]。研究^[10-13]表明:它与乳腺癌、结肠癌、卵巢癌等多种疾病的发生密切相关,其中,SEPT9基因在CRC中的检出率远远高于其他癌症。Su等^[14]检测了172例CRC和62例健康对照组中SEPT9基因甲

基化状态并分析了该基因表达与CRC临床病理特征之间的关系,结果显示: CRC组织中SEPT9基因呈高甲基化,且CRC中SEPT9基因的甲基化状态与患者年龄、性别、Duke's分期、TNM分期、肿瘤分化程度、肿瘤部位等无关。其他临床研究^[15-16]同样证实了CRC中可以检出高甲基化的SEPT9基因。上述研究表明SEPT9基因的高甲基化可以作为CRC早期筛查和诊断的生物标志物。目前,国外已经开展通过监测外周血中游离DNA SEPT9基因甲基化水平来筛查CRC,且有研究者将其与组织检测进行比较^[17]。Tóth等^[18]对26例结直肠腺瘤患者、36例CRC患者和24例无病对照组志愿者分别进行CRC组织和外周血中SEPT9甲基化检测,结果显示:对照组与腺瘤组和CRC组比较,差异均有统计学意义($P < 0.001$),但腺瘤组与CRC组比较,差异无统计学意义,且CRC患者SEPT9甲基化在外周血中的特异性比组织中的高。研究^[16-17]同样证实了血浆游离DNA SEPT9甲基化检测可作为CRC新的筛选方式。Song等^[19]的临床研究进一步证实了血浆DNA SEPT9甲基化水平的检测可作为CRC癌前病变的筛查。上述研究表明外周血DNA SEPT9甲基化检测在CRC早期筛查中具有较高的临床应用价值。

2.2 多配体聚糖 2 前体

Oh等^[20]收集了139例I~IV期的原发性结直肠肿瘤患者的血清DNA,通过CpG微阵列分析和甲基化DNA分离试验发现97.8%的多配体聚糖2前体(syndecan 2 precursor, SDC2)基因存在甲基化。另外一项研究^[21]结果显示: CRC患者的SDC2甲基化的敏感性为87.0%,特异性为95.2%或敏感性为89.4%,特异性为81.1%。Oh等^[22]通过单向线性靶标富集(linear target enrichment, LTE)和甲基化特异性实时PCR(methylation-specific real time PCR, qMSP)进行的基于粪便DNA的SDC2甲基化测试是CRC早期检测的潜在非侵入性诊断工具。Park等^[23]检测190例肠道灌洗液(bowel lavage fluid, BLF)和14例经肠镜切除的息肉标本的SDC2甲基化情况,结果表明SDC2甲基化是CRC癌前病变中的常见事件。Chen等^[24]应用qPCR检测CRC中SEPT9和SDC2甲基化情况,结果显示: SEPT9和SDC2甲基化水平在癌组织中比在其配对的邻近组织中高94.7%和100.0%;单独检测SEPT9和SDC2甲基化在CRC中的敏感性和特异性较联合检测差,表明联合检测CRC患者血清中甲基化SEPT9和SDC2有可能成为CRC筛查的有效方法。Sun等^[25]用收集来的粪便样

本检测SDC2和SFRP2, KRAS的DNA甲基化突变情况显示CRC的敏感性为91.4%, 腺瘤的敏感性为60%, 特异性为86.1%, 比大多数常规血清生物标志物对CRC的检测结果灵敏度高20%, 预示粪便DNA生物标志物将成为CRC早期检测和诊断的新方向。

2.3 波形蛋白

波形蛋白(vimentin, VIM)基因位于人染色体10p13, 属于中间纤维家族, 该基因与细胞增殖、凋亡、黏附、迁移等过程有关^[26]。VIM参与细胞上皮-间充质转化过程, 而该过程是肿瘤细胞侵袭、转移的重要过程^[27]。VIM基因CpG岛甲基化在CRC发生中起重要作用, CRC中检出率约80%, 而正常人结直肠组织中检测不到VIM基因甲基化^[28]。VIM基因甲基化不仅可以特异性地表达在CRC组织中, 而且在粪便DNA检测中具有相当高的特异性(90%)和灵敏度(46%)^[29]。Lu等^[30]研究显示: 粪便DNA中VIM启动子区域的甲基化与CRC相关, 可能作为CRC非侵入性筛查方法。其他研究^[31-32]同样证明了粪便中甲基化的VIM可以作为CRC早期检测的生物标志物。因此, 人们开发了首个通过检测粪便中甲基化的VIM来筛查CRC的商业检测项目。我们不仅可以检测粪便中VIM基因甲基化, 而且有研究^[33]发现尿液中含有来源于循环血液的低分子量DNA, 可以通过检测肿瘤患者尿液中低分子量DNA来发现与癌症相关的特异性突变。Song等^[34]研发了一种检测CRC患者尿液样品中循环衍生的高甲基化VIM试验, 且在CRC患者的尿液样品中检测到了甲基化的VIM, 证实了尿中循环衍生的DNA主要来自低分子量部分的说法。提示粪便和尿液中VIM基因甲基化检测可以代替癌组织用于CRC的早期筛查和诊断。

2.4 p16

p16是由细胞周期蛋白依赖性激酶抑制剂2A(CDKN2A)基因编码的一种抑癌基因, 位于人类染色体9p21^[35-36]。既往研究^[37-40]表明p16基因失活可能通过基因突变、纯合缺失和CpG岛甲基化3种主要机制在人类多种癌症中发挥重要作用。CRC中存在p16基因启动子区域的CpG岛甲基化^[38]。Ye等^[39]收集了30名CRC患者的CRC组织和相应的癌旁正常组织, 评估其p16基因的表达情况, 结果显示: p16基因在CRC组织中呈高表达, 且其表达与CRC患者临床病理分期相关。王爱祥等^[41]采用甲基化特异PCR收集的50例良性结直肠疾病患者、

50例CRC患者和100例对照粪便中p16基因DNA甲基化情况, 结果显示: p16基因DNA甲基化率分别为26%, 70%和14%, 基因甲基化率在CRC组中明显高于对照组和良性组, 差异具有统计学意义($P < 0.05$), p16基因甲基化发生率在CRC粪便中显著增高, 可作为CRC诊断的分子标志物。Karam等^[42]检测了65例CRC和70名健康对照个体的组织和血液中p16基因甲基化水平并分析了该基因与CRC临床病理特征的关系, 结果显示: CRC患者血液中p16基因甲基化显著高于对照组($P = 0.0001$), p16基因甲基化诊断CRC的敏感性和特异性分别为55.38%和98.5%, 诊断准确率为77.7%, 且p16基因甲基化与患者的年龄、性别、Dukes分期、淋巴结受累和癌胚抗原水平显著相关。提示p16基因启动子区域的甲基化可视为CRC诊断的潜在肿瘤标志物。

2.5 长散布核苷酸元件-1

全基因组DNA低甲基化通常发生在重复的转座DNA元件中, 例如散布在包括CRC在内的多种癌症中的长散布核苷酸元件-1(long interspersed nucleotide element-1, LINE-1)和核苷酸元件(SINE或Alu)序列^[43]。全基因组DNA低甲基化通过激活LINE-1等机制在CRC的发病机制中发挥重要作用^[44-45]。Molinari等^[46]研究了343例CRC患者和32个正常结肠组织中LINE-1基因的甲基化状态, 发现在早发性CRC中LINE-1基因甲基化显著降低($P < 0.0001$)。Matsunoki等^[47]指出: 与邻近的正常组织相比, 肿瘤细胞中的LINE1基因甲基化显著降低, 同时肿瘤内异质性很低, 表明其在CRC的分子诊断中具有巨大的潜力。Nagai等^[48]分析了114例CRC患者和53例健康对照者血浆循环无细胞DNA(circulating cell-free DNA, cfDNA)中的LINE-1基因低甲基化水平, 并使用LINE-1低甲基化指数(hypomethylation index, LHI)[未甲基化拷贝数/(甲基化拷贝数+未甲基化拷贝数)]表达, 结果显示: CRC患者的cfDNA LHI明显高于健康对照者, 首次证明了血浆cfDNA LHI作为CRC早期检测的新型生物标志物的潜力。对LINE-1基因低甲基化的深入研究, 为我们理解CRC的发生发展, 寻找CRC早期筛查和诊断的潜在生物标志物提供了新思路。

3 结语

在临床肿瘤研究中, 表观遗传学是一个发展

迅速、前景广阔的研究方向。其中, DNA甲基化可以通过多种机制影响不同基因的表达, 在CRC的早期诊断中发挥重要作用。临床上可以通过检测外周血液、尿液和粪便中基因甲基化的情况来早期筛查和诊断CRC, 这种方法方便、经济、安全、可靠, 同时给患者带来的创伤小, 患者依从性好, 可以大范围筛查CRC, 达到早诊早治的目的, 从而降低CRC的发病率和病死率。此外, 随着DNA甲基化的深入研究, 寻找甲基化相关的基因, 有望发现新的靶向治疗的靶点, 进而研发更多简便、易行的早期筛查和诊断CRC的方法和肿瘤标志物。

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