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文献综述 REVIEW

# 结直肠癌潜在预后标志物的研究进展

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## Recent advances in detection of potential prognostic markers in colorectal cancer

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## Abstract

Colorectal cancer (CRC) is one of the most common malignant tumors. Recent development in molecular biology techniques, gene sequencing and molecular diagnostics has led to the discovery of some new prognostic markers in colorectal cancer. So far, K-ras is a valid prognostic marker that can be used in clinical practice. However, many markers investigated suffer from technical shortcomings, which result mainly from lack of quantitative techniques to capture the impact of molecular alterations. This paper gives an overview of recent advances in research of promising biological prognostic markers in CRC, including RHAMM, FOXP3$^+$ Treg, HSP27, PIK3CA, and PTEN.

Key Words: Colorectal cancer; Prognosis; Molecular marker

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## 摘要

结直肠癌(colorectal cancer, CRC)是世界上最常见的恶性肿瘤之一. 随着分子生物学技术的发展, 基因测序及分子诊断水平的提高, 在CRC分子生物学方面不断有新的预后因素被发现. 目前为止, K-ras被公认为CRC可用于临床实践的有效标志物. 很多分子标志物的研究由于技术上的缺陷, 导致缺乏定量技术来检测分子的改变, 因此不能很好地应用于临床实践. 近年来还发现RHAMM、FOXP3$^+$ Treg、HSP27、PIK3CA、PTEN等对判断CRC的预后具有重要的意义. 本文就CRC潜在预后标志物的研究进展进行综述.

**关键词: 结直肠癌; 预后; 分子标志物**

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**■背景资料**
K-ras是目前被推荐用于结直肠癌(CRC)患者诊断及预后判断的分子标志物, 但其远远不能满足临床需求, 因此亟待寻找更多的CRC预后标志物.

## 0 引言

随着分子生物学技术的迅速发展, 基因测序及分子诊断水平的提高, 不断有新的结直肠癌(colorectal cancer, CRC)预后因子被发现, 但其中许多预后因子尚处于研究阶段, 且结论不一致. 到目前为止, K-ras被公认为CRC可用于临床实践的一个有效标志物[1-3], 可利用K-ras基因突变状态筛选抗表皮生长因子受体(epidermal growth factor receptor, EGFR)靶向药物[4-6]. 对CRC的分子标志物的检测, 有助于其早期诊断、提高疗效及判断预后. 近年来国内外学者对影响CRC预后的分子标志物进行了大量研究, 发现了一些潜在对预后判断有积极意义的分子标志物, 本文将进行简要综述.

## 1 透明质酸介导的细胞游走受体

透明质酸介导的细胞游走受体(receptor for hyaluronan-mediated motility, RHAMM)基因定位

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■研发前沿
对CRC预后标志物的研究是判断肿瘤治疗及预后的热点之一, 近年来国内外学者对影响CRC预后的分子标志物进行了大量的研究, 并取得了一定的进展.

于人染色体5q33.2长臂末端, 并根据其分布特点分为胞内和膜型两种类型, 二者的cDNA序列有高度同源性, 均可通过细胞膜外结合区与透明质酸(hyaluronic acid, HA)结合. RHAMM通过与透明质酸、微管、肌动蛋白、钙调蛋白、细胞外调节激酶信号通路成份相互作用, 在细胞周期、增殖、迁移及粘附过程等信号转导中发挥了关键的作用[7-9]. 研究发现, RHAMM与CD44形成复合物后经Ras-Raf-MEK-ERK通路来发挥其致癌效应[10]. RHAMM与ERK结合并控制其表达水平, ERK通过一连串的磷酸化作用被激活后, 参与细胞的分泌、分化及增殖[11,12]. 有研究表明, RHAMM高表达与肿瘤的演变及转移密切相关[13].

在正常的结肠黏膜, RHAMM在大肠隐窝处的柱状细胞胞浆内呈微弱表达, 而杯状细胞不表达. 郑建建等[14]通过real-time PCR检测了30例结肠癌患者及其相应癌旁组织, 结果表明RHAMM和ERK2在结肠癌中的表达都高于正常组织, 且两者表达有相关性, 并且都与是否发生淋巴结转移有关联, RHAMM可能通过Ras-ERK途径参与了结肠癌的发生、进展及转移. 因此, RHAMM和ERK2可作为患者诊断和预后的参考指标之一. Lugli等[15]将1 420例大肠癌患者分为MMR阳性组、MLH-1阴性组及林奇综合征组, 用组织芯片结合免疫组织化学检测3组中RHAMM的表达水平. 结果发现, MMR阳性组及林奇综合征组的RHAMM表达水平明显高于正常组织, 而且结肠癌中RHAMM阳性的患者较RHAMM阴性患者预后差, 而MLH-1阴性的大肠癌患者中RHAMM的表达与临床病理特征没有关联性. 进一步证实了RHAMM在肠癌组织中的过度表达, 能够诱导肿瘤的发展, 是结肠癌预后不良的一个独立判断指标. Zlobec等[16]研究了587例发生淋巴结转移的大肠癌患者, 发现高表达RHAMM与淋巴结远处转移高度相关, 在结肠癌预后判断因素中, RHAMM的高表达比肿瘤分期及血管浸润更重要.

## 2 FOXP3$^+$ Treg

■相关报道
CRC的一些分子标志物在一定程度上有助于判断其预后, 提高疗效. 有报道*p53*、*bc1-2*、*p21*、*c-myc*、*k-ras*等基因表达与CRC的预后相关.

调节性T细胞(regulatory T cells, Treg)代表一群独特的CD4辅助性T细胞亚群, 通过细胞与细胞直接接触或通过细胞因子的释放, 对效应性CD4/CD8 T细胞活化和增殖发挥抑制作用[17]. CD4、CD25是其主要的分子表型. CD4$^+$CD25$^+$调节性T细胞由Sakaguchi等于1995年首先报道, 是具有免疫调节功能的T淋巴细胞亚群, 约占CD4$^+$T细胞的5%-15%, 可以通过抑制机体自身的免疫反应和对外来抗原或者病原体的过度免疫反应, 来阻止自身免疫性疾病的发生并维持自身免疫耐受[18,19]. 叉状头转录因子(forkhead transcription factor, FOXP3)对调控CD4$^+$CD25$^+$调节性T细胞发育有重要作用, 是CD4$^+$CD25$^+$调节性T细胞的一个特异标志[20,21]. 有研究表明FOXP3在自身免疫性疾病和肿瘤免疫过程中发挥作用[22,23].

Loddenkemper等[24]通过免疫组织化学方法检测40例CRC患者的FOXP3蛋白表达水平, 发现FOXP3$^+$ Treg在大肠癌患者中数量显著增加(肠癌患者中Treg数量平均为12.9/HPF, 而正常的大肠组织中为0.6/HPF). 并且发生淋巴结转移的肠癌患者中Treg的数量会减少为9.9/HPF, 未发生转移的为17.8/HPF. 但是患者的生存期与FOXP3$^+$ Treg的数量没有关联性. Woo等[25]首先报道了Treg表达与肿瘤侵犯局部淋巴细胞有关. 然而, Ling等[26]研究表明, 在肿瘤早期及晚期, Treg的数量没有显著差异. Salama等[27]用组织芯片结合免疫组织化学检测了967例Ⅱ期及Ⅲ期CRC患者, 发现FOXP3$^+$调节性T细胞的表达水平明显提高, CD8$^+$CD45RO$^+$ T淋巴细胞数量反而减少. FOXP3$^+$ Treg的数量增加的患者其生存期得到延长, 相对于CD8$^+$CD45RO$^+$记忆性T淋巴细胞具有更好的预后意义. FOXP3$^+$调节性T细胞的表达水平与组织病理学特征无关, 而与肿瘤的分期密切相关, 可以作为CRC的一个独立的预后指标.

## 3 HSP27

热休克蛋白(heat shock protein, HSP)是生物体内进化保守的蛋白家族, 是重要的分子伴侣, 具有多种生物学功能, 与肿瘤的发生、发展及肿瘤耐药性的产生等都有着密切关系[28,29]. HSP27是sHSP亚家族中的重要一员, 首先在人细胞中发现的一种分子量为27 kDa的HSP, 人类的HSP27又称为HSPB1, 其氨基酸序列具有与αB-晶体蛋白相类似的N末端序列. 在生物体内主要有两种HSP27: 构成型和诱导型. 构成型HSP27在生理状态下低水平表达, 维持细胞的基本活动并与细胞的分化、发育, 特别是神经系统的发育密切相关; 诱导型HSP27主要在外界环境的刺激下表达, 具有保护细胞的功能. HSP27作为caspase抑制剂发挥作用, 这也是最主要的抗凋亡作用

机制[30,31].

HSP27在前列腺癌、卵巢癌、胃癌及肝癌中的高表达提示不良预后, 但在食管及口腔鳞状细胞癌中的高表达则提示预后较好[32,33]. 近年来研究发现, HSP27的异常表达与肠癌的发生及发展有关[34]. Wang等[35]研究表明, HSP27在CRC中的表达明显高于癌旁组织, 而且HSP27高表达患者预后较差, 提示HSP27过度表达是大肠癌不良预后的一个独立相关因素. HSP27还与化疗敏感性和耐药性有关. HSP27是5-FU的反应性(活性)蛋白, 5-FU能够提高肠癌组织中HSP27的表达, 而HSP27表达水平的降低可以使肠癌对5-FU的耐受性下降. 5-FU能使肠癌细胞中的p38 MAPK及HSP27磷酸化, 而p38 MAPK的传导阻滞会抑制5-FU诱导的HSP27磷酸化. 有研究发现, 结肠癌中HSP27与化疗药物伊立替康的耐药性有关, 抑制HSP27的表达能够提高药物对癌细胞的敏感性; 有文献报道HSP27与热疗及放疗有关, HSP27的低表达会促进热诱导的癌细胞发生凋亡, 而HSP27的高表达会提高癌细胞对紫外线辐射的敏感性. 因此, HSP27与肠癌的治疗密切相关, HSP27促进细胞凋亡是其中的一个重要机制. HSP27的表达与肠癌生物学行为的关系错综复杂, 有待于进一步研究.

## 4 PIK3CA

磷脂酰肌醇-3激酶(phosphatidylinositiol 3-kinase, PI3K)是一类特异性磷酸化肌醇磷脂3位羟基的激酶, 称为PI3Ks家族. 根据PI3Ks结构和底物的特异性不同, 可将PI3Ks分为Ⅰ、Ⅱ、Ⅲ型. 其中Ⅰ型PI3Ks研究最多, 是由催化亚基p110和调节亚基p85构成的异二聚体. PIK3CA是PI3Ks家族的关键成员, 与肿瘤形成及细胞的增殖、黏附、存活和迁移等过程相关[36]. PI3K的调节亚基能特异性结合蛋白质因子, 并通过膜受体结合各种信号分子, 进而激活PIK3CA, 活化的PIK3CA能够磷酸化4,5-二磷酸磷脂酰肌醇(4,5-PIP2)生成3,4,5-三磷酸磷脂酰肌醇(PIP3)[37,38]. AKT通过PH区与PIP3结合, 并被蛋白激酶PDK1磷酸化而活化. 磷酸化的AKT可调控一系列下游分子的功能, 从而促进细胞的增殖和存活. 这条信号途径的某些成分包括PIK3CA发生了改变, 会导致肿瘤的发生与发展.

Jehan等[39]发现, 38%的CRC患者出现PIK3CA的扩增, 这与PIK3CA蛋白的高表达密切相关, 而与PIK3CA是否发生基因突变无关. 在接受辅助性化疗或放疗的患者中, PIK3CA发生扩增的患者, 其生存期明显延长. PIK3CA可以作为判断CRC预后的一个独立性标志物, 并能够预测患者能否通过辅助性的放化疗获得更好的治疗效果. 最近的研究表明, 发生PIK3CA基因突变的CRC患者预后不良, 抑制PIK3CA基因突变可能成为新型的肿瘤靶向治疗方法[40,41]. Samuels等[42]的研究发现PIK3CA基因突变主要集中在第9和20外显子(占88%-90%), 分别对应着该酶的螺旋区和激酶区, PIK3CA基因突变可能与在K-ras及Braf基因的致癌突变相似, 是突变激活的. 有研究报道PIK3CA基因突变能够阻碍EGFR抑制剂发挥作用[43,44]. PIK3CA是否在抗-EGFR单克隆抗体的应答中发挥重要作用有待于大量的临床调查研究.

## 5 PTEN

Phosphatase and tensin homolog deleted on chromosome ten(PTEN)是继*p53*基因之后发现的人类肿瘤中最易发生缺失和突变的抑癌基因, 据文献报道, 大多数肿瘤中均存在PTEN缺失和突变[45-47]. PTEN通过去磷酸化作用而负性调节PI3K/AKT信号通路, PTEN的突变或丢失使细胞内PIP3积聚, AKT持续活化, 从而抑制细胞凋亡, 促进肿瘤细胞增殖, 导致肿瘤的发生[48,49].

刘国平等[50]采用链酶亲和素-生物素过氧化物酶(strept avidin biotin complex, SABC)免疫组织化学法检测CRC组织PTEN蛋白的表达, 发现96例CRC组织中50例呈阳性表达, 阳性率52.1%; 46例癌旁组织中37例阳性表达, 阳性率80.4%. 而且PTEN蛋白表达水平降低与CRC细胞分化程度、淋巴结转移、Dukes分期呈正相关, 提示PTEN基因在CRC的发生、发展、侵袭转移过程中起抑制作用. Sawai等研究表明[51], PTEN的缺失在散发性CRC患者中发挥着重要作用, PTEN的低表达可能导致肿瘤复发. 在发生肝脏转移的大肠癌患者中, PTEN缺失的患者预后比PTEN正常表达的差. PTEN很有可能成为K-ras野生型患者抗EGFR治疗的预后标志物[52], PTEN对CRC患者预后的影响仍需要进一步的调查研究.

## 6 结论

CRC的发生、发展是多个基因及蛋白分子相互作用的过程, 寻找判断其预后的分子生物学标志物, 对指导结直肠癌的治疗有着重大意义. 理想的预后指标, 应该能够预测患者预后, 对治疗

**■创新盘点**
本文对RHAMM、FOXP3$^+$ Treg、HSP27、PIK-3CA、PTEN等CRC潜在预后标志物的最新研究进展进行综述, 使读者对CRC的预后标志物研究现状有更加全面的认识.

**■应用要点**
CRC的发生、发展是个复杂的多步骤过程, 有些分子生物学的改变对预后的判断有积极意义, CRC潜在预后标志物对指导治疗、提高疗效有着重大意义.

方案有一定的参考价值, 并且与肿瘤细胞的生物学行为相关, 还要有较高的特异性和灵敏性. 由于缺少检测分子水平的定量技术, 很多分子生物学标志物的检测面临着技术难题. 这些潜在的预后标志物能否用于临床实践, 还需要大量的临床实验进一步证实.

■名词解释
透明质酸介导的细胞游走受体(RHAMM): 该基因定位于人染色体5q33.2长臂末端, 在细胞周期、增殖、迁移及粘附过程等信号转导中发挥了关键的作用, RHAMM的高表达与肿瘤的演变及转移密切相关.

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**■同行评价**
本文对RHAMM、FOXP3$^+$ Treg、HSP27、PIK-3CA、PTEN等CRC潜在预后标志物的研究进展进行综述, 对CRC预后标志物的临床应用与研究有一定意义, 且文章结构合理、叙述有条理, 参考价值较大.

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