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述评 EDITORIAL

结直肠癌分子异质性与免疫治疗

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Molecular heterogeneity and immunotherapy of colorectal cancer

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Abstract

Colorectal cancer (CRC) is a common digestive tract malignancy. The complex genetic mechanisms involved in the process of CRC development leads to extensive molecular heterogeneity and various molecular subtypes. As a consequence, there are still about 40% of CRC patients who cannot get more significant survival benefits from comprehensive treatment consisting of surgery, chemotherapy and radiotherapy. Immunotherapy, as one of the emerging strategies of tumor therapy, has become a hot research topic in recent years. Some monoclonal antibodies have shown significant survival benefit in the treatment of CRC. Therefore, understanding molecular heterogeneity of CRC and its relationship with immunotherapy is expected to provide a more reliable treatment strategy which can improve the clinical prognosis of patients with CRC.

Key Words: Colorectal cancer; Heterogeneity; Immunotherapy; Monoclonal antibody

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摘要

结直肠癌(colorectal cancer, CRC)是常见的

背景资料
结直肠癌(colorectal cancer, CRC)是世界上常见的恶性肿瘤之一, 其复杂多变的遗传分子学异质性导致了临床预后的显著差异; 免疫治疗作为肿瘤治疗的新兴策略之一, 已在CRC的治疗中展现出显著的生存效益, 因而有望为改善CRC患者临床预后提供更加丰富可靠的治疗策略.

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研发前沿

本文相关研究领域的热点主要包括微卫星不稳定机制(microsatellite instability, MSI)、CpG岛甲基化表型(CpG island methylator phenotype, CIMP)和染色体不稳定(chromosomal instability, CIN)等在CRC遗传分子异质性形成发展过程中的作用、机制及其意义; 免疫治疗尤其是单克隆抗体(monoclonal antibody, mAb)的在不同分子亚型CRC患者中的应用进展; 如何将免疫治疗与手术、化疗、放疗有机的相结合, 从而为不同分子亚型CRC的治疗提供更加完善高效的治疗策略还亟待大家去解决.

消化系恶性肿瘤, 其形成发展过程中复杂多变的遗传分子学机制导致了他分子亚型的广泛异质性, 以至于目前仍然存在大约40%的CRC患者在以手术结合化疗、放疗的治疗策略中无法获得更加显著的生存效益. 免疫治疗作为肿瘤治疗的新兴策略之一, 已成为近年来的研究热点. 并且部分单克隆抗体在CRC的治疗中已展现出显著的生存效益. 因而深入研究CRC的分子异质性及其与免疫治疗的关系, 有望为改善CRC患者临床预后提供更加可靠地治疗策略.

关键词: 结直肠癌; 异质性; 免疫治疗; 单克隆抗体

核心提要: 本文全面的阐述了结直肠癌(colorectal cancer, CRC)分子异型性的大体类型及其遗传分子学机制, 同时概括了免疫治疗针对于肿瘤患者的具体方法以及单克隆抗体在CRC患者中的应用进展及其意义.

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0 引言

结直肠癌(colorectal cancer, CRC)是世界范围内最为常见的恶性肿瘤之一, 据国际癌症研究中心相关报道显示, 2012年全球新发CRC病例超过130万, 并且因CRC死亡的病例也高达69万, 此数据在各类恶性肿瘤中分别占第3位和第4位[1]. 随着我国经济水平的快速发展, 生活习惯的不断改变以及人口结构老龄化的逐渐加剧, 其发病率和死亡率均呈现不断上升的趋势[2,3]. 多年来, 由于癌胚抗原、粪便隐血检测技术和结肠镜检查手段的不断发展, 加之手术切除结合放疗、化疗的治疗策略的持续广泛实施, 使得非转移性CRC患者的治疗结果获得了稳定的改善[4,5]. 遗憾的是, 仍有超过40%的CRC患者会发生肝、肺等远处转移, 并最终导致其死亡[6].

自2012年Gerlinger等[7]通过对4例肾癌患者的研究有力地证实了肿瘤异质性的存在以来, 越来越多的研究者对其进行了不断深入的探索[8]. 近年来研究者们发现, 肿瘤异质性可能促进肿瘤的进化和适应, 并且阻碍依赖于单个肿瘤活检结果的个体化药物策略, 从而成为影响肿瘤治疗的主要障碍[7,9]. 显然, 作为恶性肿瘤重要组成部分之一的CRC也是一种异质性疾病. Linnekamp等[10]认为, CRC不仅在临床表现和分子特性等方面具有一定的差异, 关键在于他对治疗的反应也存在很大的不同. 相似的, Suzuki等[8]研究也发现, 不同的CRC患者显示出显著多变的瘤内异质性. 这种肿瘤异质性的存在, 不仅可能导致CRC患者的肿瘤进展和治疗抵抗, 而且也可能引发无法预测的肿瘤转移和复发[11]. 因此, 深入分析CRC异质性, 为改善治疗结果提供更加可靠地理论依据显得尤为重要. 本文通过对相关领域的研究结果进行概述, 从而简要的阐述CRC分子异质性的起源和类型以及其对治疗预后的影响.

1 肿瘤异质性的起源、发展与表现

早在19世纪, Virchow[12]就已经观察到肿瘤内癌细胞的多形性, 而随后几十年关于肿瘤异质性的相关研究并无显著的进展. 至20世纪50年代, Makino等[13]通过评估单细胞水平的细胞遗传学特征和致瘤性发现自发性肿瘤中的功能和遗传异质性, 从而开启了肿瘤异质性研究的新篇章. 二十多年后, 相关报道[14,15]进一步表明肿瘤内存在不同的癌细胞亚群, 其在致瘤性, 耐药性和转移能力方面均有所不同. 近年来, 研究者们对肿瘤异质性分子水平及其相关治疗策略的探索也取得了巨大的进展, 其中*KRAS*基因、*BRAF*基因和微卫星不稳定机制(microsatellite instability, MSI)在肿瘤异质性形成过程中作用的发现, 以及贝伐单抗和西妥昔单抗的问世, 不仅使得人们对肿瘤异质性有了更进一步的认识, 也为不同的肿瘤患者提供了更加丰富的免疫治疗策略[16-19].

目前, 对于肿瘤异质性的分类尚不统一. 广义而言, 肿瘤异质性主要分为瘤间异质性和瘤内异质性两种, 而在Almendro等[20]的文献报道中又进一步将瘤内异质性分为了时间异质性、空间异质性、细胞异质性、基因异质性和功能异质性等. 总之, 肿瘤异质性的表现是复杂的多变的, 在肿瘤形成和发展的整个过程中, 几乎都可能产生不同形式的异质性. 重要的是, 应当如何牢牢的抓住异质性产生过程中分子机制的改变与不同功能之间的关系, 从而

表 1 微卫星不稳定结直肠癌的分类比较

类别	Lynch综合征	Lynch样综合征	散发性MSI CRC	CMMRD
胚系突变	*MMR*基因的一个等位基因(*MSH2*、*MLH1*>*MSH6*、*PMS2*、*EPCAM*>*MSH3*)[37-41]	没有报道	没有报道	*MMR*基因的两个等位基因(*PMS2*、*MSH6*>*MSH2*、*MLH1*、*EPCAM*)
体细胞突变	突变的*MMR*基因的2nd等位基因	*MMR*基因的两个等位基因(*MLH1*、*PMS2*、*MSH2*、*MSH6*)	$BRAF^{V600E}$	没有报道
表观遗传突变	EPCAM 3'末端的胚系缺失导致组织中体细胞特异性MSH2甲基化	没有报道	没有报道	没有报道
MMR表型	MMR缺陷(MSI)	MMR缺陷(MSI)	MMR缺陷(MSI)	MMR缺陷(MSI)
终身筛检	是	否	否	否

MSI CRC: 微卫星不稳定结直肠癌; CMMRD: 构成性错配修复缺乏综合征; MMR: 错配修复.

相关报道
近年来, 国内外关于CRC分子异质性形成机制及其意义的研究广泛且深入, 涵盖了CRC分子异质性形成过程的一系列调控机制, 如MSI、CIMP及CIN等; 并且将免疫治疗特别是mAb的应用与不同分子亚型CRC相联系, 为CRC患者的个体化治疗提供了更加丰富的理论基础.

从分子学水平对不同肿瘤患者进行合理有效的靶向治疗.

2 CRC分子异质性的产生机制

随着国内外研究者对CRC分子异质性不断深入的探索并发现, 其复杂多变的分子异质性的产生是多种机制或基因突变相互交织的结果. 本文查阅近年来相关文献报道[21-28], 将其归纳为如下几个方面: (1)MSI表型的产生; (2)CpG岛甲基化表型(CpG island methylator phenotype, CIMP)的出现; (3)染色体不稳定(chromosomal instability, CIN); (4)其他情况: 骨形态发生蛋白信号的异质性等.

2.1 MSI表型与CRC分子异质性 错配修复(mismatch repair, MMR)系统蛋白包含MLH1、MLH3、PMS1、PMS2、MSH2、MSH3、MSH6和Exo1, 他们形成异源二聚体能够修复DNA损伤, 其中与CRC最为相关的异源二聚体包括MLH1/PMS2和MSH2/MSH6[29]. 然而, 当MMR系统蛋白之一的功能缺乏或丧失导致其系统功能不足时, 引起微卫星错误的积累, 如插入或缺失, 进而导致遗传不稳定, 既MSI表型[30].

20世纪90年代, Ionov等[31]就已发现, 大约15%的CRC显示出MMR途径的缺陷, 进而导致MSI. 随着研究者们对MSI相关机制不断深入的研究并发现, MSI的发生率在CRC的不同阶段也有所不同, 其中Ⅱ-Ⅲ期CRC患者MSI发生率为15%, 但又以Ⅱ更为常见, 而Ⅳ期CRC的发生率仅为4%-5%[32-34]. 并且, 研究者根据MSI状态又将CRC分为3种不同的亚型, 既高表达MSI CRC(MSI-High CRC, MSI-H CRC), 其微环境标记不稳定大于30%-40%; 低表达MSI CRC, 其微环境标记不稳定小于30%-40%, 以及没有表现出不稳定标记的微环境稳定(microsatellite stabe, MSS)型CRC[35]. 近年来, Carethers等[36]和Chen等[29]根据胚系突变、体细胞突变以及MSI表型的差异又将MSI CRC进一步细分4大类型[37-41](表1).

MSI-H CRC占全部CRC的15%左右, 其中主要包含上述四大类中的Lynch综合征和散发性MSI CRC[42]. Lynch综合征, 又称遗传性非息肉病性CRC, 主要由MMR系统中*MSH2*、*MLH1*、*MSH6*、*PMS2*和*EPCAM*基因的突变引起, 是最常见的遗传性CRC综合征, 约占全部CRC的3%-5%[43]. Stoffel等[44]研究表明, Lynch综合征受累者发展为CRC的几率较一般人群或息肉病者更高, 其终身风险可达50%-80%. 此外, 与散发肿瘤相比, Lynch综合征受累者在结肠癌中的发病年龄更低, 且在组织学上癌症通常呈黏液性, 分化不全, 有大量的肿瘤浸润淋巴细胞[45]. 显然, Lynch综合征受累者不是其癌症表现为MSI的唯一CRC患者. 目前, 散发性MSI CRC是CRC患者分群中数量最多的一类, 占全部CRC患者的12%左右[42]. 散发性MSI CRC患者具有DNA *MMR*基因*hMLH1*启动子区域的获得性体细胞超甲基化, 且$BRAF^{V600E}$的致癌性突变是其另一个重要特征, 在超过40%-50%的散发性MSI CRC标本中被发现[46-50]. 国外相关研究[49,51]表明, MSI的程度是散发性CRC治疗和预后评估的重要生物学标志, 并已在临床治疗

创新盘点
本文全面的阐述了CRC分子异质性的产生机制及其类型, 并将免疫治疗与之相结合, 不仅盘点了目前主要研究的免疫治疗方法, 而且分析总结了mAb在不同亚型CRC中的应用进展, 从而为临床实践提供有价值的参考.

过程中应用. 此外, MSI-H CRC在组织学上更容易含有黏蛋白, 分化程度较差, 并具有“克隆氏样”亚上皮淋巴集结和上皮内淋巴细胞, 从而能够产生对此类患者有利的免疫应答反应[49]. 然而, 目前研究者对于MSI状态在CRC患者化疗敏感性和预后等方面的看法并不一致[32,52,53]. 总体而言, 通过Guastadisegni等[54]和Webber等[55]的Meta分析可以发现, MSS CRC患者较MSI CRC患者更能从以5-氟尿嘧啶(5-fluorouracil, 5-FU)为基础的化疗方案中获益, 因而在接受5-FU化疗后具有更长的无病生存期和总体生存率.

2.2 CIMP与CRC分子异质性 大量研究[56,57]表明, 人类基因组呈现出高水平的DNA甲基化, 且这种甲基化状态对于维持机体正常功能起着关键的作用. 然而, 除了大量的DNA甲基化基因序列外, 人类基因组中仍然存在较多的以无DNA甲基化或低DNA甲基化为特征的基因组区域, 即CpG岛群(CpGs islands, CGIs)[58,59]. 研究[60]表明, CGIs中胞嘧啶核苷酸的异常甲基化能够引起肿瘤抑制功能的异常沉默, 从而促进癌症的形成. 近年来, 随着对异常DNA甲基化致癌机制探索的不断深入, 发现以多个CGIs的广泛超甲基化为特征的CIMP存在于大约15%的CRC患者中, 并且其可能是CRC发生的主要机制之一[61-63].

目前, 根据CIMP中甲基化标志基因(*CACNA1G*、*IGF2*、*NEUROG1*、*RUNX3*、*MLH1*等)的数量, 研究者们将CIMP进行了粗略的分类, 即CIMP+与CIMP-或CIMP-high(CIMP-H)、CIMP-low(CIMP-L)与CIMP-0等[64,65]. 遗憾的是, 上述分类对于甲基化标志基因的数量并没有统一的规定, 可能少至2个或多达9个, 因而这必然为后续研究结果的综合性对比分析埋下不良的隐患[66-68].

近年来, 研究者们对于CIMP CRC的临床病理特征的认识相对比较一致. 与CIMP-L CRC、CIMP-0 CRC或CIMP- CRC相比, CIMP-H CRC或CIMP+ CRC的临床病理特征主要包括高龄、女性、肿瘤多位于近端结肠、低分化、黏液性、高水平MSI、$BRAF^{V600E}$突变、野生型TP53、染色体稳定以及抑制的WNT/β-catenin信号通路等[69-72]; 而CIMP-L CRC和CIMP-0 CRC分别以KRAS突变和TP53突变为特征[73-75]. 然而, 目前对于CIMP CRC的治疗反应和总体预后情况的相关研究结果却并不一致. 多中心研究[69,75,76]发现, 人群中大约25%-60%的CIMP+ CRC患者表现出高水平的MSI, 这主要是由于MLH1 DNA MMR基因能够通过*MLH1*基启动子区域体细胞DNA甲基化而转录沉默. 与之相对应, 几乎70%-80%的MSI CRC可以归因于CIMP和相关*MLH1*基因的甲基化[77]. 除此以外, KRAS、BRAF等在CIMP CRC患者治疗反应和预后的差异中也扮演着重要的作用[78]. 总之, 通过Juo等[79]的Meta分析发现, 与非CIMP CRC患者相比, CIMP CRC患者的无病生存期和总体生存率显著降低; 可喜的是, 在单纯手术治疗的基础上增加辅助化疗能够潜在的增加CIMP CRC患者的生存获益. 随后, Zong等[80]和Jia等[81]分别纳入29篇和47篇相关研究文献再次进行Meta分析并表明, CIMP-H CRC或CIMP+ CRC患者较CIMP-L CRC、CIMP-0 CRC或CIMP- CRC患者具有更差的生存效益; 上述分析还提出, CIMP状态不统一的划分条件可能是各研究之间结果差异的原因之一. 因而, 进一步深入研究CIMP CRC的相关机制, 并为CIMP状态分类提供更加确切可靠地理论依据, 这在CIMP CRC异质性以及相关治疗策略的研究中显得至关重要.

2.3 CIN与CRC分子异质性 CIN是指从一代细胞到下一代细胞的传代过程中染色体数目或结构的一致性不能有效的维持, 其主要特点为染色体数量的广泛失衡(非整倍体)和杂合性丢失(loss of heterozygosity, LOH)的增加[82,83]. 多中心研究[83-85]发现, CIN不仅是大多数人类癌症的显著标志, 也是肿瘤非整倍体和异质性的重要原因, 在肿瘤适应宿主压力环境并逃避宿主免疫反应的过程中起到了关键的作用. 此外, Grady等[86]报道还表明, CIN是结肠癌中观察到的最常见的基因组不稳定性类型, 发生在大约80%-85%的CRC中, 并且这些CRC的表型主要为非MSI或MSS. 因此, CIN表型不仅在CRC发生机制的研究中具有重要意义, 而且对于CRC异质性及其个体化治疗策略的探索也显得至关重要.

在CRC中, CIN是导致*APC*、*TP53*和*Smad4*等抑癌基因野生型拷贝丢失的一个有效的机制[87], 并且据Fearon等[88]的研究表明, 经典的CIN途径开始于*APC*基因的获得性突变, 随后出现致癌基因*KRAS*的突变激活以及抑

表 2 染色体不稳定结直肠癌表型的产生机制的简要总结

类别	机制	基因位点
非整倍体	有丝分裂检查点的异常表达	hRod、hZwilch、hZw10、Ding、Bub R1、CENP-E、MAD1、CENP-A、CENP-H、AURK和Plk等
DNA损伤途径	碱基切除修复的异常	XRCC1和OGG1、MUTYH等
	双链断裂修复的异常	MRE11
	MMR的异常	-
	核苷酸切除修复的异常	-
LOH	基因位点的丢失	1p、1 q 、4q、5 q、8 p、9 q、11 q、14 q、15 q、17 p、18 p和18 q等
突变类型	基因位点的突变	APC(5q21)、KRAS(12p12)、TP53(17q13)、PIK3CA(3q26)、TGF-β(3p22)、D4S3013(4p15.2)和D4S405(4p14)等

LOH: 杂合性丢失; MMR: 错配修复.

应用要点

本文全面地阐述了CRC分子异质性大体类型及其相应的异常分子学机制, 揭示了CRC分子异质性CRC患者临床预后中的影响, 同时也阐述了免疫治疗的类型及其在CRC患者中应用的相关进展, 为将来免疫治疗在不同分子亚型CRC中运用提供了更有价值的依据.

癌基因*TP53*的失活, 进而可能产生一种致癌性恶性循环. 尽管如此, 目前仍存大约25%的CRC患者并不伴有*APC*基因的突变或LOH, 进而推测在CIN CRC表型的形成过程中必定还存在某些其他的途径[89]. 因此, 本文根据相关研究[89-94]对CIN CRC表型的产生途径进行简要的总结(表2). 然而, 在个体CIN CRC患者中上述机制并不一定孤立存在, 他们相互之间可能交织成网形成杂乱的调控系统, 并诱导复杂多变的CRC分子异质性的产生, 从而导致CRC患者对治疗反应以及预后结果的差异. 多中心研究[95-97]表明, CIN能够促进癌细胞的浸润生长和淋巴组织转移, 增强以5-FU为基础的化疗耐药性, 最终导致CIN CRC患者不良的无病生存期和总体生存率. 然而, 部分研究[98,99]却认为, CIN与CRC患者不良的临床预后没有显著的联系, 因而不能作用CRC患者的预后评估指标, 甚至在Risques等[100]的研究中还发现, CIN CRC患者较非CIN CRC患者具有更好的临床预后. 上述差异产生的原因可能在于: (1)CIN表型形成机制的多样性和复杂性; (2)CIMP、MIS以及其他未知机制导致了诸多的CIN CRC分子亚型; (3)CIN检测手段以及截断值选取的不同等. 但是总体而言, 支持CIN CRC具有更糟的无病生存期和总体生存率的研究报道还是明显较多, 并且通过Walther等[101]的Meta分析发现, CIN的确能够增强以5-FU为基础的化疗耐药性, 并导致CIN CRC患者糟糕临床预后.

3 免疫治疗与CRC分子异质性

3.1 免疫治疗意义与类型 近年来, 基于免疫效应物渗透到结肠肿瘤组织与改善其临床预后有着密切联系的事实表明, 免疫治疗或许能够替代或辅助手术结合化疗、放疗的治疗方案, 成为更加有效的CRC治疗策略[102]. 早期研究[102-104]发现, CRC患者能够通过其体内FasL、转化生长因子-β的表达增多, 白介素-10的表达下降以及肽类运载分子突变, 诱导T淋巴细胞抗原决定簇的表达下调和T淋巴细胞的凋亡增加, 进而抑制免疫应答反应活性, 导致肿瘤细胞的免疫逃逸, 最终促进自身肿瘤的形成和发展. 因而推测, CRC的本质可能就是一种免疫源性疾病, 并且其复杂多变的分子异质性在免疫抑制或免疫逃逸过程中起到了至关重要的作用.

免疫治疗是一种旨在引发免疫系统对肿瘤特异性抗原和肿瘤细胞攻击的积极的治疗方法. 在2011年, 《自然》和《临床肿瘤学杂志》分别刊登题名为“Cancer immunotherapy comes of age”的评论文章, 预测免疫治疗的可能为抗肿瘤策略带来的巨大影响[105,106]. 到2013年, 《科学》杂志里程碑式的将免疫治疗评选为年度科学突破之首和人类肿瘤治疗的新希望[107], 因而开启了人类肿瘤治疗的崭新篇章. 目前, 已有包括肿瘤疫苗、过继性免疫治疗和单克隆抗体(monoclonal antibody, mAb)在内的大量免疫治疗方法(表3)在CRC患者中探索和运用[107], 本文主要对mAb在CRC患者的应用研究进行简要的概述, 旨在总结CRC分子异质性与免疫治疗的潜在联系.

3.2 mAb在不同分子亚型CRC中的应用 据Emmons等[108]的文献报道表明, 全世界首个鼠mAb莫罗单抗-CD3于1986年经美国食品和药

名词解释

肿瘤异质性: 指肿瘤在形成发展过程中, 经过数次分裂增殖, 子细胞表现出不同的分子生物学和基因类型, 从而使其在形态学表现、生长速度、侵袭能力、耐药性和预后等方面产生差异;

微卫星(MS): 指含1-6个碱基的短DNA重复序列, 又称串联序列, 其在编码区和非编码区重复并散在的遍及整个基因组.

表 3 免疫治疗方法的简要对比

类别	治疗方式	作用机制	效应细胞或载体因子	特点
被动免疫	抗体导向细胞毒性杀伤因子	将具有细胞毒性作用的杀伤因子转运到肿瘤病灶杀伤肿瘤细胞.	帕尼单抗、贝伐单抗、^{131}I、阿霉素、氨甲喋呤、白喉毒素、蓖麻毒素等.	优点: 效应快; 缺点: 维持时间短, 且可能产生超敏反应.
	过继性细胞免疫治疗	回输在体外恢复的自身T细胞抗肿瘤活性, 在体内发挥抗肿瘤效应.	CTL细胞、NK细胞、巨噬细胞、和肿瘤浸润性淋巴细胞等.	
	细胞因子疗法	激活免疫系统杀伤肿瘤细胞, 抑制肿瘤细胞转移.	IL-2、IL-4、IL-12、IFN-γ、IFN-α以及GM-CSF等.	
	基因疗法	输送的基因可编码直接针对特定致癌蛋白的抗体	细胞因子基因、抗肿瘤原基因、MHC基因等	
主动免疫	非特异性主动免疫	非特异的增强机体免疫功能, 激活抗肿瘤免疫应答.	卡介苗、短小棒状杆菌菌苗、免疫因子等.	优点: 维持时间长久, 甚至可终生保持; 缺点: 潜伏期长
	特异性主动免疫	具有抗原性的物质刺激机体抗肿瘤免疫机制	细胞、分子和病毒载体疫苗、mAb与多克隆抗体.	

CIN CRC: 染色体不稳定结直肠癌; IL-2/-4/-12: 白介素-2/-4/-1; IFN-γ/-α: 干扰素-γ/-α; GM-CSF: 粒细胞-巨噬细胞刺激因子; CTL细胞: 细胞毒性淋巴细胞; NK细胞: 自然杀伤细胞; mAb: 单克隆抗体.

表 4 经美国食品和药物管理局批准上市且适用于结直肠癌的单克隆抗体

mAb名称	作用靶点	作用机制	适应证	中国上市
西妥昔单抗(cetuximab)	EGFR	与EGFR结合抑制其信号转导通路	EGFR阳性转移性CRC(KRAS野生型)	已上市
贝伐单抗(bevacizumab)	VEGF-A	抑制VEGF与肿瘤血管内皮生长因子受体结合, 阻断肿瘤血管生长	转移性CRC癌(与细胞毒药物联合使用)	已上市
帕尼单抗(panitumumab)	EGFR	与西妥昔单抗相似, 但不诱导抗体依赖细胞介导的细胞毒	EGFR阳性转移性CRC	未上市
阿柏西普 (aflibercept)	VEGF-A、VEGF-B、PGF	减少新生血管的生成并降低血管通透性	与5-FU、亚叶酸、伊立替康联合用于的转移性CRC(奥沙利铂治疗后)	未上市
瑞戈非尼(regorafenib)	VEGFR2、TIE2	抑制肿瘤生成, 肿瘤血管发生和肿瘤微环境信号转导	转移性CRC	未上市
雷莫芦单抗(ramucirumab)	VEGFR2	阻断VEGFR2与其配体结合, 抑制血管内皮细胞的增殖	与5-FU、亚叶酸、伊立替康联合用于的转移性CRC	未上市

FDA: 美国食品和药物管理局; mAb: 单克隆抗体; EGFR: 表皮生长因子受体; VEGF-A/-B: 血管内皮生长因子-A/-B; PGF: 胎盘生长因子; VEGFR2: 血管内皮生长因子受体2; TIE2: 血管生成素受体2; 5-FU: 5-氟尿嘧啶.

物管理局(Food and Drug Administration, FDA)批准适用于器官移植后免疫抑制治疗. 随后30多年里, 研究者们对mAb进行了不断深入的探索. 近年来, 已有超过30个mAb经FAD批准通过后成功上市, 并且分别在白血病、淋巴瘤以及CRC等恶性肿瘤的治疗中取得了可靠地效益[109]. 此外, 据不完全统计还有超过350个mAb处于不同阶段的临床试验中[109]. 截至2016年未, 经FDA批准上市且适用于CRC的mAb已有6种, 其中2种已进入中国市场[110,111](表4). 然而, 遗憾的是仍然只确切的发现表皮生长因子受体(epidermal growth factor receptor, EGFR)和血管内皮生长因子(vascular endothelial growth factor, VEGF)等为数不多的mAb作用靶点.

3.2.1 EGFR与西妥昔单抗: 研究表明, EGFR及其下游信号通路在CRC的发生发展中具有重要的作用[112], 并且西妥昔单抗作为EGFR抑制性mAb, 其单独使用或联合化疗均能在EGFR阳性的转移性CRC患者中取得良好的治疗效益[113,114]. 进一步深入研究[115,116]却发现, 在转移性CRC抗EGFR治疗过程中, KRAS、NRAS、BRAF和PIK3CA等的突变以及KRAS、HER2和EMT的扩增等几种分子遗传学改变重新诱导了西妥昔单抗的抗癌耐药性. 并且Saltz等[117]的报道表明, 目前只有大约10%的CRC患者没有携带上述分子遗传学的改变, 并在西妥昔单抗联合化疗治疗后获得更好的药物的应答、更长的无病生成期以及更佳的生产质量. 因此, 进一步深入研究上述突变在西妥昔单抗耐药性机制中的作用, 对于不同分子亚型的转移性CRC的治疗显得尤为关键.

3.2.2 VEGF与贝伐单抗: VEGF家簇主要包括VEGF-A、VEGF-B、VEGF-C、VEGF-D、VEGF-E和胎盘生长因子, 他们不仅能够上调血管内皮VEGFR的表达水平使新生血管不断生成, 还能通过介导树突细胞导致免疫逃逸[118]. 贝伐单抗是与VEGF结合的重组人源化单克隆IgG1抗体, 由于他能够干扰VEGF与其受体VEGFR-1和VEGFR-2的相互作用, 从而阻断新生血管生成, 因此在CRC等恶性肿瘤的治疗中起到了有效的作用[119,120]. 多中心研究[121,122]表明, 在CRC患者的治疗中, 贝伐单抗联合化疗与单用化疗相比, 无论是一线治疗还是二线治疗均能显著增加治疗有效率, 延长患者生存期. 并且贝伐单抗产生耐药的机会较小, 因而若有病情持续进展可以较长时间使用. 此外, 国内近期的Meta分析也发现, 贝伐单抗联合化疗在转移性CRC的维持治疗中能够提高患者的无病生成期和总体生存率, 但遗憾的是, 在应用贝伐单抗的患者中高血压、出血、血栓以及胃肠道穿孔等并发症明显增加[111,123], 因而对于受伤或手术后患者不推荐使用贝伐单抗[124]. 总体而言, 贝伐单抗在晚期CRC的免疫维持治疗中发挥着重要的意义和价值.

4 结论

免疫治疗作为CRC治疗的4架马车之一, 近年来取得了飞速的进步, 并且部分mAb在晚期CRC的治疗中展现了可喜的生存效益. 然而, 目前仍然存在一些问题迫切的需要我们去探索解决: (1)能否针对每一种CRC分子异质性机制制定一些列单独的、稳定的筛查手段和评判标准; (2)如何将现有的CRC分子异质性机制进行系统的区别于整合, 从而制定一套合理可靠地异质性划分方案; (3)如何根据CRC分子亚型的差异制定出一套涉及免疫治疗的、全面的个体化治疗策略; 尽管还存在诸多问题未能解决, 但我们仍然坚信免疫治疗将为不同分子亚型的CRC患者带来更加光明的未来.

同行评价
本文综述了CRC的分子异质性和免疫治疗的相关性, 文献占有量大, 得出了自己的一些见解, 有一定的意义和价值.

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• 消息 •

《世界华人消化杂志》性质、刊登内容及目标

本刊讯 《世界华人消化杂志》[国际标准刊号ISSN 1009-3079 (print), ISSN 2219-2859 (online), DOI: 10.11569, *Shijie Huaren Xiaohua Zazhi*/*World Chinese Journal of Digestology*], 是一本由来自国内31个省、市、自治区、特别行政区和美国的1040位胃肠病学和肝病学专家支持的开放存取的同行评议的旬刊杂志, 旨在推广国内各地的胃肠病学和肝病学领域临床实践和基础研究相结合的最具有临床意义的原创性及各类评论性的文章, 使其成为一种公众资源, 同时科学家、医生、患者和学生可以通过这样一个不受限制的平台来免费获取全文, 了解其领域的所有的关键的进展, 更重要的是这些进展会为本领域的医务工作者和研究者服务, 为他们的患者及基础研究提供进一步的帮助.

除了公开存取之外, 《世界华人消化杂志》的另一大特色是对普通读者的充分照顾, 即每篇论文都会附带有一组供非专业人士阅读的通俗易懂的介绍大纲, 包括背景资料、研发前沿、相关报道、创新盘点、应用要点、名词解释、同行评价.

《世界华人消化杂志》报道的内容包括食管、胃、肠、肝、胰肿瘤, 食管疾病、胃肠及十二指肠疾病、肝胆疾病、肝脏疾病、胰腺疾病、感染、内镜检查法、流行病学、遗传学、免疫学、微生物学, 以及胃肠道运动对神经的影响、传送、生长因素和受体、营养肥胖、成像及高科技技术.

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