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文献综述 REVIEW

*KRAS*基因的突变状态对EGFR单抗治疗结直肠癌的影响

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背景资料
结直肠癌(colorectal cancer, CRC)是常见的恶性肿瘤之一, 其治疗一直备受国内外学者的关注, 靶向治疗被认为是当前治疗转移性CRC最理想的方案, 而*KRAS*基因的突变与CRC的靶向治疗有着密切的关联, 因此, 明确*KRAS*基因的突变状态对EGFR单抗治疗CRC有重要意义.

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Effect of *KRAS* mutation status on efficacy of EGFR monoclonal antibody treatment in colorectal cancer

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Abstract

Colorectal cancer is one of the most common malignant tumors. With the development of economy and the improvement of living standard in China, which have resulted in great changes in lifestyle and eating habits, the incidence of colorectal cancer has increased year by year. Among all treatments currently available, targeted therapy is considered to be the most ideal treatment for metastatic colorectal cancer. *KRAS* mutation is closely related to the efficacy of targeted therapy for colorectal cancer. Thus, it is important to clarify the *KRAS* mutation status before targeted therapy is considered. This paper mainly elaborates the effect of *KRAS* mutation status on the efficacy of epidermal growth factor receptor monoclonal antibody treatment of colorectal cancer with regard to the structure and function of *KRAS* gene, *KRAS* mutations and heterogeneity.

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Key Words: *KRAS* mutation; EGFR monoclonal antibody; Colorectal cancer

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摘要

结直肠癌(colorectal cancer, CRC)是常见的恶性肿瘤之一, 随着我国经济发展和人民生活水平的不断提高, 生活方式及饮食结构的改变, CRC的发病率呈逐年上升趋势. CRC的治疗一直备受国内外学者的关注, 靶向治疗被认为是目前治疗转移CRC最理想的方案, 而*KRAS*基因的突变与CRC的靶向治疗有着密切的关联. 因此, 明确*KRAS*基因的突变对表皮生长因子受体单抗治疗CRC有重要意义. 本文主要从*KRAS*基因结构与功能、*KRAS*基因的突变和异质性对表皮生长因子受体单抗治疗CRC的影响作用进行阐述.

关键词: *KRAS*基因突变; EGFR单抗; 结直肠癌

核心提示: 结直肠癌(colorectal cancer, CRC)的靶向治疗是目前治疗转移性CRC最理想的方案, 而*KRAS*基因的突变与靶向治疗有着密切的关联. 本文主要对*KRAS*基因结构与功能、*KRAS*基因的突变和异质性对EGFR单抗治疗CRC的影响作用进行了较为全面阐述.

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0 前言

结直肠癌(colorectal cancer, CRC)是全球范围内最为常见的恶性肿瘤之一, 2012年CRC新增发病例数分别位列男性和女性的第3、2位[1,2]. 我国随着经济发展和人民生活水平的不断提高, 生活方式及饮食结构的改变, CRC的发病率呈逐年上升趋势, 因而对他的治疗一直受到大家的关注[3]. 随着靶向药物表皮生长因子受体(epidermal growth factor receptor, EGFR)单抗的成功应用[4], CRC的治疗进入了靶向治疗时代, 然而EGFR单抗的有效性受其下游*KRAS*基因状态的影[5-11]. 本文就*KRAS*基因的突变对EGFR单抗治疗CRC效果的影响作一综述.

1 *KRAS*基因的结构与功能

*KRAS*基因是*RAS*基因家族的主要成员之一, 位于EGFR信号通路的下游. *RAS*基因最先发现是在Harvery鼠肉瘤病毒和Kirsten鼠肉瘤病毒中, 随后, 研究人员相继在大鼠、小鼠、人类的基因组上发现了同源的*RAS*基因[12-14]. 目前研究发现RAS家族的主要成员分别为: HRAS、KRAS和NRAS, 其中KRAS与人类肿瘤发生的关系最为密切[15,16]. *KRAS*基因位于人染色体的12p12, 共有5个外显子(包括4个编码外显子和1个非编码外显子), 共同编码189个氨基酸组成的RAS蛋白[17,18], RAS蛋白又名p21蛋白, 分子量为21 kDa.

RAS蛋白在功能上与G蛋白相似, 除了具有与鸟苷酸结合的能力外, 自身还具有弱GTPase活性. RAS蛋白属于膜结合型蛋白, 当其与二磷酸鸟苷结合时为非活性状态, 而当与三磷酸鸟苷结合时为活性状态. *KRAS*基因作为EGFR信号通路的下游基因, 就像体内一个“开关”, 当接受到外界传来的信号时, 可以激活下游的信号通路(主要为RAS/MAPK和RAS/PIK3/AKT通路), 从而调控细胞生长、增殖、分化等重要生理功能[19-21].

2 *KRAS*基因的突变与CRC的EGFR单抗治疗

近年来随着靶向药物逐渐应用于肿瘤的临床治疗, CRC的靶向治疗也向前迈出了重要的一步, 靶向治疗模式被认为是目前治疗转移性CRC最理想的方案(该治疗方案明显延长了转移性CRC患者的生存时间). 治疗转移性CRC的靶向药物: EGFR单抗(如西妥昔单抗和帕尼单抗)的治疗效果与*KRAS*基因的突变状态有重要关系. 突变型的KRAS无需EGFR接收信号能够自动活化该通路并启动下游信号的转导, 因此, 只有野生型*KRAS*基因的患者才能从EGFR单抗中获益, 而突变型的患者则不能. *KRAS*基因的突变发生在CRC恶变的早期, 以点突变为主, 90%以上的突变位于2号外显子的第12、13位密码子和3号外显子的第61位密码子, 也有研究发现在*KRAS*基因的第59、117等密码子有突变存在[22-25].

研发前沿

目前靶向药物治疗转移性CRC被认为最理想的方式, 但*KRAS*基因突变的异质性会影响靶向药物的效果, 如何克服肿瘤异质性防止肿瘤复发, 亟待大家进一步研究.

相关报道

由于CRC在不同组织部位的发展速度不一, 导致*KRAS*基因的突变在CRC原发灶与转移灶、肿瘤内的不同区域之间产生异质性. Baldus等检测了*KRAS*基因在CRC原发灶、转移灶、原发灶瘤内的突变情况, 发现*KRAS*基因在原发灶与转移灶之间*KRAS*基因的异质性为10%, CRC原发灶与淋巴结之间的*KRAS*基因的异质性为31%.

创新盘点

本文主要介绍了*KRAS*基因结构与功能, 较为全面、深入的总结了*KRAS*基因的突变和异质性对EGFR单抗治疗CRC的影响作用.

Karapetis等[26]通过对394例接受西妥昔单抗治疗的转移性CRC患者研究发现有42.3%的患者存在*KRAS*基因突变. 对KRAS野生型和突变型患者同时给予西妥昔单抗治疗后, KRAS野生型患者的无进展, 存活时间明显延长, 而KRAS突变型患者与没有接受西妥昔单抗治疗的患者在存活时间上没有显著. Amado等[27]为了验证*KRAS*基因的状态对帕尼单抗治疗转移性CRC患者的影响, 采用RT-PCR检测了427例CRC患者的第12和13密码子的7个突变位点(Gly12Asp、Gly12Ala、Gly12Val、Gly12Ser、Gly12Arg、Gly12Cys、Gly13Asp), 结果发现43%CRC患者有*KRAS*基因突变. KRAS野生型组在用了帕尼单抗治疗后比KRAS突变型组无进展, 存活时间明显延长. KRAS野生型组中位生存时间为12.3 wk, 但KRAS突变型组的中位生存时间只有7.3 wk, 且该组患者对帕尼单抗治疗后的反应率为0%. 其他学者研究结果显示与上述一致, 当CRC患者*KRAS*基因为野生型时, 对西妥昔单抗治疗敏感, 而当*KRAS*基因发生突时, 则对西妥昔单抗治疗不敏感[27-33]. 因此, *KRAS*基因的状态对EGFR单抗治疗的敏感性有着重要意义, 在决定使用西妥昔单抗靶向治疗之前, 首先应检测*KRAS*基因的突变状态, 以决定患者是否适合使用指针的方能使用抗EGFR抗体治疗[34-38].

3 *KRAS*基因的异质性与CRC的EGFR单抗治疗

由于CRC在不同组织部位的发展速度不一, 导致由*KRAS*基因的突变时产生的CRC原发灶与转移灶、肿瘤不同区域之间的异质性. Baldus等[39]采用测序的方法, 分别检测了*KRAS*基因在CRC原发灶(分别在中心位置和周边的不同空间位置取3个样本)、转移灶、原发灶瘤内的突变情况, 发现*KRAS*基因在CRC原发灶的突变率为41%, CRC原发灶瘤内*KRAS*基因突变的异质性为8%, CRC原发灶与转移灶之间*KRAS*基因的异质性为10%, CRC原发灶与淋巴结之间的*KRAS*基因的异质性为31%. Watanabe等[40]的研究得到了与上述研究一致的结果, *KRAS*基因在原发灶的突变率为34.9%, CRC原发灶与转移灶之间的*KRAS*基因的异质性为11.6%. 为了研究CRC原发灶与不同转移灶之间*KRAS*基因的异质性, Kim等[41]对143位韩国人的*KRAS*基因的第12、13、61密码子在不同突变情况进行了分析, 结果显示CRC原发灶与转移灶之间*KRAS*基因总的异质性为17.5%. 尽管远处转移的器官不同, 但是各个转移灶和CRC原发灶之间的异质性没有差异, CRC原发灶与肝、肺、腹膜、淋巴结、卵巢转移灶之间的异质性分别为10.6%、32.4%、13.3%、11.8%、18.2%. 但也有研究报道CRC原发灶与转移灶之间*KRAS*基因的突变情况一致, 没有*KRAS*基因突变的异质性存在[42,43]. 由于CRC的*KRAS*基因存在原发灶与转移灶之间的异质性, 因此容易导致EGFR单抗的耐药; 同时CRC的*KRAS*基因存在不同空间位置的异质性, CRC某一个区域*KRAS*基因的状态并不能代表整个肿瘤*KRAS*基因的状态, *KRAS*基因突变的检测可能是假阴性, 因此也会影响EGFR单抗对CRC的治疗[44-49].

4 结论

目前CRC可通过手术切除、化疗、放疗、靶向治疗等多种方式进行治疗, EGFR单抗药物的出现对治疗转移性CRC具有里程碑的意义, 相比传统化疗药物有明显优势, 但同时他也存在一些不足之处. 如当CRC患者存在*KRAS*基因的突变时, 对EGFR单抗治疗的反应较差; *KRAS*基因的突变在CRC原发灶与转移灶之间存在异质性时, 采用EGFR单抗治疗易产生耐药和复发. 因而, 提高EGFR单抗的疗效, 减少CRC患者的耐药和复发, 需要我们进一步深入的研究.

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■应用要点

由于CRC的*KRAS*基因存在原发灶与转移灶之间的异质性, 容易导致EGFR单抗耐药. 因此克服CRC的异质性, 对防止肿瘤的复发、延长生存期具有重要意义.

名词解释

EGFR单抗: 即表皮生长因子受体单克隆抗体, 属肿瘤靶向治疗药物, 通过竞争性的抑制内源性配体, 阻断其与胞外受体相关酶的磷酸化, 进而阻断其下游的信号传导通路, 起到直接抑制肿瘤细胞生长作用. 主要用于CRC、非小细胞肺癌等恶性实体瘤的治疗.

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同行评价

本文提出*KRAS*基因的突变与CRC的靶向治疗有着密切的关联, 并就*KRAS*基因的突变状态对EGFR单抗治疗CRC效果的进行了较为深入、详尽的综述. 选题有应用意义, 具有一定的科学性.

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