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文献综述 REVIEW

脂代谢与结直肠肿瘤关系的研究进展

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■背景资料
脂类是脂肪及类脂的总称, 是一类不溶于水而易溶于有机溶剂并能为机体利用的有机化合物. 脂肪或称甘油三酯(TG), 生理功能是储存及氧化供能. 类脂包括胆固醇(TC)及其酯, 磷脂及糖脂等, 是细胞膜结构的重要组成部分.

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Advances in understanding the relationship between lipid metabolism and colorectal carcinoma

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Abstract
In recent years, the morbidity and mortality of colorectal carcinoma (CRC) have been increasing and it has become a serious threat to human health. In the research of the development of CRC, more and more researchers are concerned about the relationship between lipid metabolism and CRC. High-fat diets are more likely to cause CRC. Different types of lipids may play an opposite role in the formation and development of CRC. There are various hypotheses explaining the effect of lipid metabolism on the pathogenesis of CRC, and further studies are needed to confirm them. Elucidation of the relationship between lipid metabolism and CRC will be beneficial to the diagnosis and therapy of this malignancy.

Key Words: Lipid metabolism; Colorectal carcinoma; Total cholesterol; Triglyceride; High density lipoprotein cholesterol

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摘要
近年来结直肠肿瘤(colorectal carcinoma, CRC)的发病率和死亡率每年呈上升趋势, 严重威胁着人类的健康. 在对CRC的发生发展的研究中, 脂代谢与CRC的关系受到人们的越来越多关注. 目前研究发现高脂饮食更易导致CRC, 而且血脂中的不同成分在CRC的形成和发展中, 可能发挥了完全相反的作用, 对于这些作用发生的机制有多种推测, 还需要进一步的研究证实. 因此, 对于脂代谢异常对结直肠肿瘤的形成和进展中的作用及机制的研究对结直肠癌的诊断和治疗具有重要意义.

关键词: 脂代谢; 结直肠肿瘤; 胆固醇; 甘油三酯; 高密度脂蛋白

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0 引言
脂类是脂肪及类脂的总称, 是一类不溶于水而易溶于有机溶剂并能为机体利用的有机化合物. 脂肪或称甘油三酯(Triglyceride, TG), 生理功能是储存及氧化供能. 类脂包括胆固醇(total cholesterol, TC)及其酯、 磷脂及糖脂等, 是细胞膜结构的重要组成部分. 脂类代谢包括脂肪、磷脂、胆固醇及血浆脂蛋白的代谢. 越来越多的证据表明, 脂质与肿瘤发生有密切的关系, 有文献报道肿瘤患者存在高血脂的倾向[1], 另外许多研究表明肿瘤的发生与脂代谢异常有关[2-4], 那么血脂及其代谢异常与结直肠肿瘤(colorectal carcinoma, CRC)有什么样的关系呢? 本文将对此做一综述报道.

1 高脂饮食与CRC
高脂肪饮食特别是动物脂肪, 同CRC发生危险

度相关[5], Willett等[6]发现, 脂肪摄入量最高比最低五分位的人群CRC的危险性加. Yiu等[7]对日本人群饮食结构的研究表明, 食用肉类和动物脂肪多的人群, 结直肠癌发病率明显增加. Bernstein等[8]进一步研究证实脂肪可能通过生成的氧化物和脂肪酸产生致癌作用.

2 血脂中不同成分在CRC有不同的表现

流行病学的研究表明血脂中不同成分对CRC有着不同的影响. Liu等[9]在加拿大的调查显示: 膳食胆固醇摄入量与CRC的发生风险呈正相关; Liu等[10]问卷调查的结果发现高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)水平和高TG水平是CRC的独立危险因素; Ikeda等[11]认为TG和TC的血清水平与CRC的发生呈正相关; Borena等[12]的研究提供了TG在CRC的发展中发挥作用的证据. van Duijnhoven等[13]通过大型队列前瞻性调查, 确认HDL-C和载脂蛋白A(Apo-a)的浓度与患CRC的风险呈负相关. 亚太地区的研究也有着类似的结果. Kitahara等[14]在韩国进行的一项长达14年的前瞻性研究表明, 当TC≥240 mg/dL时, 其发生CRC的危险比为1∶12. 日本所做的一项大规模的回顾性研究证实, 高TG对于患有结肠腺瘤的男性患者是一个独立的危险因素[15]; 对家族性腺瘤性息肉病(familial adenomatous polyposis, FAP)患者的观察发现, 其高脂血症的患病率是58%, 平均TG水平≥150 mg/dL, 并且, 最终发展为CRC的患者有着较高的血清TG水平[16]. 我国台湾地区的检测表明, 高TG发生结直肠绒毛/管状腺瘤风险较高[17].

由上可见, 大多数的研究结果支持CRC患者血清中TG、TC存在增高的现象, 而HDL-C减少, 但也有一些不同的研究结果. Chung等[18]的病例对照研究表明, TC和TG水平与CRC的风险成反比. 研究者们认为这种反比关系可能是晚期CRC患者代谢或营养变化的二次结果, 需做进一步研究澄清. 国内研究亦发现类似的结果, 詹建民等[19]对92例CRC患者血脂检测表明: 其血清中TC、LDL、TC、ApoAI、ApoB水平降低. 对于这些矛盾的研究结果要有正确的认识. 体外研究已经证实恶性肿瘤细胞为了满足不断的增殖需求, 其胆固醇的合成代谢呈现明显增强的特征. 表现为胆固醇的摄取增加, 合成加速, 胆固醇合成的限速酶HMG-COA活性升高. 这可能是引起CRC患者血清中TC降低的主要原因[20], 而TG水平的降低是否有同样的机制还需要进一步临床研究的证实.

3 脂代谢异常致CRC发生和发展的可能机制

脂类代谢异常是如何影响CRC的发生与恶变, 其机制尚未完全明确, 可能有如下一些机制.

3.1 高脂饮食的影响 核激素受体过氧化物酶体增殖子激活受体(peroxisome proliferatoer-activated receptor, PPAR)分为α、β、γ等3个亚型. 属于配体激活转录因子家族. 被膳食因子如脂肪酸及其相关代谢产物等激活后, PPAR不仅直接影响脂肪酸的摄取、代谢和贮存过程, 是脂肪细胞增殖、分化重要的控制基因, 并通过与其他肿瘤相关基因的复杂的相互作用[21], 调控细胞的增殖、分化和凋亡[22,23]. PPAR在正常结直肠黏膜、结直肠腺瘤以及结肠痛细胞系等多种组织中均高表达, 动物实验和人群研究均提示PPAR的表达与CRC的发生可能有关. 由于PPARγ特异性外显子B密码子12Pro到Ala的突变和外显子6第161位C-T的替换可使PPAR的活性降低、进而影响脂肪的代谢, 故推测该二处多态可能影响CRC的发生[24,25].

3.2 胆固醇及其代谢产物的作用 胆固醇由细胞色素P450酶介导的酶反应氧化生成氧化型胆固醇, 氧化型胆固醇是平衡胆固醇代谢的中间体, 许多研究表明, 氧化型胆固醇与不同类型的癌症, 包括CRC、肺癌、皮肤、乳房及胆管癌的发生相关. Jusakul等[26]的研究发现, 氧化型胆固醇具有亲氧化和亲发炎的特性, 可以促进癌变; 某些具有致突变和遗传毒性, 直接作用于细胞核和线粒体DNA, 诱发癌变. 转化生长因子-β1(transforming growth factor-beta1, TGF-β1)具有抗肿瘤癌变及增殖的作用, TGF-β1及其受体在许多人类癌症包括CRC中减少. Biasi等[27]发现人体摄入的动物脂肪在体内的氧化产物, 如氧化型胆固醇和醛, 一方面可以消除肿瘤对TGF-β1抗增殖作用的敏感性, 同时可以上调TGF-β1抗体的水平, 进一步对抗TGF-β1的作用. 并认为这可能是消化系肿瘤发生及进展的主要机制.

3.3 脂肪细胞因子和脂肪酶的作用 脂肪代谢异常时会分泌大量脂肪细胞因子. 在众多脂肪细胞因子中, 已发现血管内皮生长因子、肝细胞生长因子、肿瘤坏死因子、肝素结合表皮生长因子样因子、脂联素、瘦素等与肿瘤发生发展有较密切的关系. 研究发现, 在结直肠癌患者中脂联素水平低于正常人群[28,29], 而瘦素水平高于

■研发前沿
脂类代谢异常是如何影响CRC的发生与恶变, 其机制尚未完全明确.

■相关报道
Kodach等认为其通过激活CRC中抑制肿瘤的骨形态发生蛋白(bone morphogenetic protein, BMP)的信号, 下调甲基转移酶(DNMT)的活性, 导致BMP2的启动子去甲基化和表达, 导致CRC细胞增殖分化和减少.

正常人群[30-32], 并且发现其通过刺激肿瘤细胞增殖[33,34]、促进肿瘤细胞迁移[35]、参与多种信号途径[36,37]、相关免疫机制[38,39]等途径达到致癌的作用. 此外, 联合检测血浆脂联素与瘦素水平可以判断结直肠癌的预后[32,40]. 此外, 最近的一些研究已经表明, 一些脂肪细胞因子在体外可显著影响恶性细胞的增殖, 体内是否也存在类似的作用呢? Miyamoto等[41]通过17 wk的小鼠实验发现, 脂肪细胞因子氧化偶氮甲烷(AOM)-糖苷脂钠(DSS)诱导CRC的发生, 主要通过升高血清瘦素水平(6倍于对照组)促进CRC的生长. Ye等[42]发现monoacylglycerol lipase(MAGL-单酰基甘油脂酶), 在CRC组织中高度升高, 通过促进2个靶基因: 细胞周期蛋白D1(Cyclin D1)和原癌基因Bcl-2的表达, 达到细胞增殖, 减少凋亡, 促进肿瘤的生长及发展.

4 脂代谢与结直肠肿瘤的预后

Notarnicola等[43]对84例CRC患者的血脂检测发现, 发生远处转移患者的TC, LDL-C和LDL-C/HDL-C比值水平比未转移患者明显增高. Liu等[44]对968例CRC患者血脂分析发现增高的LDL-C水平和LDC-C/HDL-C比值有利于淋巴结转移, 并且认为对于CRC的男性患者的预后, LDL-C/HDL-C比值是一个更有效的生物标志物. 此外李祖国等[45]进行的动物研究发现载脂蛋白A-Ⅳ(apoA-Ⅳ), 载脂蛋白E(apoE)表达水平随CRC转移程度的增加而升高.

5 他汀类药物与结直肠肿瘤

脂类代谢与CRC的关系日益得到证实, 那么降脂类药物在降脂的同时是否会预防或减少CRC的发生呢? 目前研究的比较多的是他汀类药物, 除了单纯的降低胆固醇实现抑癌, 可能也存在一些其他机制. Kodach等[46]认为其通过激活CRC中抑制肿瘤的骨形态发生蛋白(bone morphogenetic protein, BMP)的信号, 下调甲基转移酶(DNMT)的活性, 导致BMP2的启动子去甲基化和表达, 导致CRC细胞增殖分化和减少. Lakshminarayana Reddy等[47]发现其介导下调SATB1的表达, 而达到抑制肿瘤的作用, 而且该机制没有明显的细胞毒性作用. 对于相关药物还需要进一步深入的研究.

6 结论

流行病学研究统计, 在2000年全球范围内共确诊了944 717例结直肠癌的发病病例[48]. 结直肠癌是发达国家常见的恶性肿瘤之一, 在美国其发病率居恶性肿瘤谱的第3位, 死亡率居第2位[49]. 在亚洲地区, 结直肠癌的发病率和死亡率在近十年时间增加了2-4倍, 并且这种上升趋势有增无减. 在中国, 结直肠癌已居恶性肿瘤的第3-5位, 死亡率位居第2-4位[50], 严重威胁着人类的健康. 随着对脂类代谢与CRC关系研究的深入, 我们将越来越了解两者之间的关系, 为CRC的预防和治疗提供更多更有效的方法.

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■同行评价

本文内容全面, 选题新颖, 综述客观, 对临床实践具有一定指导意义.

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• 消息 •

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标. 静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服*po*, 灌胃ig. s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, lcpm(应写为1/min)÷E%(仪器效率)÷60 = Bq, pH不能写PH或P^H, *H pylori*不能写成HP, T1/2不能写成tl/2或$T_{\frac{1}{2}}$, *V*max不能Vmax, μ不写为英文u. 需排斜体的外文字, 用斜体表示. 如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种. 如幽门螺杆菌(*Helicobacter pylori*, *H.pylori*), *Ilex pubescens* Hook, *et* Arn.*var.glaber* Chang(命名者勿划横线); 常数*K*; 一些统计学符号(如样本数*n*, 均数mean, 标准差SD, *F*检验, *t*检验和概率*P*, 相关系数*r*); 化学名中标明取代位的元素、旋光性和构型符号(如*N*, *O*, *P*, *S*, *d*, *l*)如*n*-(normal, 正), *N*-(nitrogen, 氮), *o*-(ortho, 邻), *O*-(oxygen, 氧, 习惯不译), *d*-(dextro, 右旋), *p*-(para, 对), 例如*n*-butyl acetate(醋酸正丁酯), *N*-methylacetanilide(N-甲基乙酰苯胺), *o*-cresol(邻甲酚), 3-*O*-methyl-adrenaline(3-O-甲基肾上腺素), *d*-amphetamine(右旋苯丙胺), *l*-dopa(左旋多巴), *p*-aminosalicylic acid(对氨基水杨酸). 拉丁字及缩写*in vitro*, *in vivo*, *in situ*; Ibid, *et al*, *po*, *vs*; 用外文字母代表的物理量, 如*m*(质量), *V*(体积), *F*(力), *p*(压力), *W*(功), *v*(速度), *Q*(热量), *E*(电场强度), S(面积), *t*(时间), *z*(酶活性, kat), *t*(摄氏温度, ℃), *D*(吸收剂量, Gy), *A*(放射性活度, Bq), ρ(密度, 体积质量, g/L), *c*(浓度, mol/L), φ(体积分数, mL/L), *w*(质量分数, mg/g), *b*(质量摩尔浓度, mol/g), *l*(长度), *b*(宽度), *h*(高度), *d*(厚度), *R*(半径), *D*(直径), T_{max}, C_{max}, *V*d, $T_{1/2}$ *CI*等. 基因符号通常用小写斜体, 如*ras*, *c-myc*; 基因产物用大写正体, 如P16蛋白.