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饱和脂肪酸的抗癌作用及其机制研究进展

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摘要:饮食中的饱和脂肪酸通常与人体健康的负面影响相关,然而有关各种饱和脂肪酸的生理效应、生物功能等研究结果存在一定的争议。综述了饱和脂肪酸的可能抗癌作用及作用机制,以期为癌症的辅助治疗提供一定的参考。目前对短链饱和脂肪酸、中链饱和脂肪酸、奇数链饱和脂肪酸、支链饱和脂肪酸抗癌作用的报道较多,饱和脂肪酸主要通过阻滞细胞周期、诱导细胞凋亡、抑制细胞迁移和调控细胞生长相关的信号通路,或通过影响相关基因的表达和转录因子的磷酸化水平来发挥抗癌作用。

关键词:饱和脂肪酸;抗癌作用;机制

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Advance in potential anti－cancer effect and mechanism of saturated fatty acids

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Abstract: Dietary saturated fatty acids (SFAs) is usually associated with negative consequences for human health. However, there are some contradictory experimental results on the physiological effects and biological functions of various SFAs. The anti－cancer effects and mechanisms of SFAs were mainly summarized and discussed, so as to provide the way for adjuvant therapy of cancer. At present, there are many reports on the anti－cancer effects of short－chain SFAs, medium－chain SFAs, odd－chain SFAs and branched－chain SFAs, SFAs exert anti－cancer effects mainly by blocking the cell cycle, inducing apoptosis, inhibiting cell migration and regulating cell growth－related signalling pathways, and affecting the expression of related genes and the phosphorylation levels of transcription factors.

Key words: saturated fatty acid; anti－cancer effect; mechanism

饱和脂肪酸(SFAs)的碳链中无不饱和双键,是细胞膜的重要组成成分。研究发现 SFAs 是影响血浆胆固醇水平的主要因素,减少 SFAs 的摄入可降低冠心病风险[1－2]。然而,研究发现并非所有的 SFAs 都能升高血浆胆固醇的水平,同时某些 SFAs 还具有多种有益的生物学功能,如抗癌、抗炎、抗菌等[3－6]。目前,脂肪酸抗癌作用方面的报道大多涉及多不饱和脂肪酸(PUFAs),而有关 SFAs 抗癌作用的报道较少。本文主要介绍了不同碳链长度 SFAs 的抗癌作用及其抗癌机制,以期为癌症的辅助治疗提供参考依据。

1　SFAs 的分类及食物来源

根据碳链的长度,SFAs 可分为短链(4～6 个碳原子)、中链(8～12 个碳原子)、长链(14～20 个碳原子)和超长链(22 个或更多碳原子)脂肪酸。不同碳链长度 SFAs 的食物来源也不同。例如:短链饱和脂肪酸(SC－SFAs)主要存在于牛奶和膳食纤维中;中链饱和脂肪酸(MC－SFAs)和长链饱和脂肪酸(LC－SFAs)主要存在于红肉、乳脂和植物油中[7];超长链饱和脂肪酸(VLC－SFAs)主要存在于芥菜种子油、花生油和菜籽油等油脂中。根据所含碳原子数的奇偶,SFAs 可分为奇数链饱和脂肪酸

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(OC－SFAs)和偶数链饱和脂肪酸(EC－SFAs)。饮食中的OC－SFAs主要存在于乳制品脂肪和一些鱼类及植物中[8],EC－SFAs在常见的食用油脂中含量较高。根据碳链上是否存在甲基支链,SFAs还可以分为直链饱和脂肪酸(DC－SFAs)和支链饱和脂肪酸(BC－SFAs)。饮食中含有的SFAs大部分为DC－SFAs,BC－SFAs主要存在于反刍动物的乳脂和内部组织中,人体中BC－SFAs多存在于皮肤及其分泌物中,内部组织中含量很少[9]。

2 不同碳链长度SFAs的抗癌作用

不同碳链长度的SFAs对于同一种癌细胞可能表现出不同的作用,如SC－SFAs能够抑制结肠癌的生长,而LC－SFAs能促进结肠癌的发展[10]。同一种SFAs对于不同癌细胞的作用也有所不同。有关BC－SFAs与DC－SFAs、OC－SFAs与EC－SFAs抗癌功效的差异,目前还不清楚。关于SFAs抗癌的报道主要列举如表1所示。

表1 不同SFAs对癌细胞的抑制作用

脂肪酸	癌细胞系	抑制效果	参考文献
乙酸(C2:0)	大鼠胃癌细胞RGK－1,人胃癌细胞KATO Ⅲ	0.5%的乙酸对RGK－1细胞的抑制率为70%左右,对KATO III细胞的抑制率几乎为100%	[11]
丙酸(C3:0)	人乳腺癌细胞MCF－7;非小细胞肺癌细胞H1299和H1703;结肠癌细胞HCT116和SW480	丙酸钠对MCF－7细胞的IC_{50}值为4.5 mmol/L。10 mmol/L丙酸钠对H1299细胞的抑制率为50%左右,对H1703细胞的抑制率为40%左右。5 mmol/L丙酸钠对HCT116细胞的抑制率为80%左右,2.5 mmol/L丙酸钠对SW480细胞的抑制率为40%左右	[12－14]
丁酸(C4:0)	人结肠癌细胞HCT116	丁酸处理HCT116细胞48 h时的IC_{50}值为1.3 mmol/L。5 mmol/L丁酸处理HCT116细胞72 h时,细胞抑制率几乎为100%	[15－19]
戊酸(C5:0)	人乳腺癌细胞MCF－7、MDA－MB－231;肝癌细胞HepG2、Hep3B、SNU－449	10 mmol/L戊酸对MCF－7和MDA－MB－231细胞的抑制率为50%左右。戊酸对HepG2、Hep3B、SNU－449细胞的IC_{50}值分别为0.948、1.439、1.612 mmol/L	[20－21]
己酸(C6:0)、辛酸(C8:0)、癸酸(C10:0)	人结肠癌细胞HCT116,皮肤癌细胞A431,乳腺癌细胞MDA－MB－231	与对照相比,C6:0、C8:0和C10:0使结肠癌细胞、皮肤癌细胞和乳腺癌细胞的活力降低60%～90%	[22]
月桂酸(C12:0)	人结肠癌细胞HCT－15,肝癌细胞HepG2;乳腺癌细胞SKBR－3,子宫内膜癌细胞Ishikawa;结肠癌细胞Caco－2	80 μg/mL月桂酸对HCT－15和HepG2细胞的抑制率分别为(97.5±3.22)%和(86.5±3.41)%。100 μmol/L月桂酸对SKBR－3和Ishikawa细胞的抑制率为99%左右。1 mmol/L月桂酸对Caco－2细胞的抑制率为50%左右	[23－25]
12－甲基十四烷酸	人前列腺癌细胞PC3	12－甲基十四烷酸对PC3细胞的IC_{50}值为(20.45±1.05) μg/mL	[26]
13－甲基十四烷酸	T细胞非霍奇金淋巴瘤细胞Jurkat、Hut78、EL4;前列腺癌细胞DU145;膀胱癌细胞T24、5637;乳腺癌细胞SKBR－3	13－甲基十四烷酸对Jurkat、Hut78和EL4细胞的IC_{50}值分别为(25.74±1.50) μg/mL,(31.29±2.27) μg/mL,(31.53±5.18) μg/mL。13－甲基十四烷酸对DU145细胞抑制率为84.6%。13－甲基十四烷酸处理T24、5637细胞12 h的IC_{50}值为70 μg/mL。0.150 mmol/L 13－甲基十四烷酸对SKBR－3细胞的抑制率为40%左右	[27－30]
十五烷酸(C15:0)	人乳腺癌干细胞样细胞MCF－7/SC	200 μmol/L十五烷酸对MCF－7/SC细胞的抑制率为90%	[31]
支链十五烷酸	人乳腺癌细胞MCF－7	400 μmol/L的支链十五烷酸处理MCF－7细胞72 h时的抑制率为99%左右	[32]
棕榈酸(C16:0)	人肝癌细胞HepG2、H4IIE、Hep3B、MHCC97L	0.5 mmol/L的棕榈酸处理HepG2细胞24 h时的抑制率为50%左右。200 μmol/L的棕榈酸处理Hep3B细胞7 d时的抑制率为50%左右,对MHCC97L细胞的抑制率为30%左右	[33－35]
十七烷酸(C17:0)	人肺癌细胞PC－9、PC－9/GR	250 μmol/L的十七烷酸处理PC－9和PC－9/GR细胞48 h时的抑制率分别为90%和70%左右	[36]
硬脂酸(C18:0)	人肺癌细胞A549、NCI－H1688	200 μmol/L的硬脂酸对A549细胞抑制率为40%左右,对NCI－H1688细胞的抑制率为70%左右	[37]
十九烷酸(C19:0)	人原骨髓白血病细胞HL－60	100 μmol/L的十九烷酸能够诱导27.7%的HL－60细胞凋亡	[38]

3　SFAs 的抗癌作用机制

3.1　SFAs 诱导细胞周期阻滞

由于丙酸会影响培养基的酸性,因此选择丙酸的钠盐来评估丙酸对癌细胞的影响。研究表明丙酸钠能够将人乳腺癌细胞 MCF－7 的细胞周期阻滞在 G1 期,而减少处于 S 期的细胞数量,从而抑制细胞增殖[12]。Kim 等[13]发现丙酸钠通过诱导细胞周期停滞来抑制肺癌细胞增殖,尤其是在 G2/M 期。Zeng 等[15]通过细胞周期检测发现丁酸能够诱导人结肠癌细胞 HCT116 的细胞周期阻滞在 G2 期,而 S 期细胞数量减少,从而抑制了细胞增殖。Xu 等[36]发现十七烷酸能够将人肺癌细胞 PC－9 和 PC－9/GR 的细胞周期阻滞在 G2 期,从而抑制细胞的生长。综上,SFAs 可通过诱导细胞周期阻滞从而抑制癌细胞增殖。

3.2　SFAs 诱导癌细胞凋亡

细胞凋亡包括内在途径和外在途径。内在途径是由细胞自身对损伤的响应所触发[39]。外在途径是通过自然杀伤细胞或巨噬细胞产生死亡配体,死亡配体与靶细胞膜中的死亡受体结合后,通过激活 Caspase－8 启动[40]。SFAs 可以同时促进癌细胞内在和外在凋亡。

研究发现丙酸能够诱导人结肠癌细胞 HCT116 的凋亡[14]。Lappano 等[24]发现,月桂酸可以通过 Rho 相关激酶介导的途径促进人乳腺癌细胞 SKBR－3 和子宫内膜癌细胞 Ishikawa 应激纤维的形成,其在细胞凋亡形态变化中具有重要作用。Cai 等[27]发现支链脂肪酸 13－甲基十四烷酸通过激活 Caspase－3 在体内外表现出对 T 细胞淋巴瘤的抗肿瘤活性。Vahmani 等[32]研究发现,支链十五烷酸能够上调促凋亡蛋白 Bax 的表达,同时抑制抗凋亡蛋白 Bcl－2 的表达,从而触发人乳腺癌细胞 MCF－7 凋亡。Salimi 等[41]发现在人乳腺癌细胞 MCF－7 和MDA－MB－231 中,丁酸可以通过诱导活性氧(ROS)的积累和线粒体损伤来促进细胞凋亡。此外,丁酸通过增加对 Caspase－9/8/7/3 和多聚二磷酸腺苷核糖聚合酶(PARP)的切割,同时降低 procaspase－9/8/6/3 的表达从而诱导慢性粒细胞白血病细胞 K562 和阿霉素耐药细胞 K562/ADR 的凋亡,这表明丁酸同时激活了内在和外在细胞凋亡途径[42]。Taylor 等[43]发现丁酸能够促进大鼠胶质瘤细胞 C6 和人胶质母细胞瘤细胞 T98G 的凋亡。以上结果表明,SFAs 能够通过诱导细胞凋亡来发挥抗癌作用。

3.3　SFAs 抑制癌细胞迁移

肿瘤转移,即肿瘤细胞从原发部位向远处器官转移,是导致癌症患者死亡的主要原因[44]。细胞迁移是转移过程中的关键步骤[45],因此评估癌细胞的迁移能力具有重要意义。

Li 等[18]通过划痕实验发现丁酸能够抑制人结肠癌细胞 HCT116、HT29、LOVO 和 HCT8 的迁移。Shi 等[20]研究表明戊酸能够抑制人乳腺癌细胞 MDA－MB－231 和 MCF－7 的迁移。Han 等[21]研究发现戊酸能够抑制人肝癌细胞 Hep3B、SNU－449 和 HepG2 的迁移。To 等[31]发现十五烷酸能够显著抑制人乳腺癌干细胞样细胞 MCF－7/SC 的迁移。Xu 等[36]研究发现十七烷酸能够抑制人肺癌细胞 PC－9 和 PC－9/GR 的迁移。以上研究结果表明抑制癌细胞的迁移是 SFAs 发挥抑癌作用的机制之一。

3.4　SFAs 对转录因子、基因表达和信号通路的调控

SFAs 能够通过抑制细胞生长相关的信号通路,或通过影响相关基因的表达和转录因子的磷酸化水平来发挥抗癌作用。研究表明,丁酸能够抑制 mTOR/S6K1 信号传导从而抑制结肠癌细胞的迁移和增殖[17]。癸酸、辛酸和己酸能够通过下调细胞分裂调控基因来发挥抗癌作用[46]。支链脂肪酸 13－甲基十四烷酸通过下调 p－AKT 在体内外表现出对 T 细胞淋巴瘤的抗肿瘤活性[29]。丁酸通过上调 MAPKs 信号通路和转录因子 NKκB 的磷酸化,从而激活微生物介导的先天性免疫应答,来抑制人结肠癌细胞 SW480 和 CT26 的生长[47]。

除上述几种抗癌机制外,SFAs 还可以通过上调免疫刺激性 NKG2D 配体的表面表达,靶向癌细胞进行免疫识别,从而发挥抗癌作用[48]。棕榈酸可通过调节细胞膜的流动性和葡萄糖代谢来抑制肝癌细胞的发展[35]。丁酸可以通过靶向丙酮酸激酶 M2 来抑制人结肠癌细胞 HCT116 的增殖[49]。

4　结束语

SFAs 主要通过阻滞细胞周期、诱导细胞凋亡、抑制细胞迁移和调控细胞生长相关的信号通路,或通过影响相关基因的表达和转录因子的磷酸化水平等来发挥抗癌作用。目前关于 SFAs 抗癌的报道大多聚焦在细胞水平,体内和临床方面的研究较少,且这些细胞一般为消化系统器官来源的癌细胞及脂代谢较为旺盛的癌细胞。SFAs 抗癌作用的报道大多是关于 SC－SFAs、MC－SFAs、OC－SFAs 和 BC－SFAs。

SFAs 的抗癌活性与其结构有很大的联系。对脂肪酸的结构进行修饰能够进一步提高脂肪酸的抗

癌效果。此外,将脂肪酸与抗肿瘤药物偶联能够更好地发挥药效。SFAs 的抗癌活性将为癌症的辅助治疗提供一个新的策略。

尽管一些 SFAs 具有一定的抗癌功效,然而也有报道 SFAs 能够促进一些癌细胞的增殖和迁移。SFAs 抗癌作用的差异主要是由实验设计的差异、涉及的癌症类型不同以及 SFAs 处理的方式不同造成的。SFAs 抗癌作用的差异表明了深入研究和充分了解 SFAs 在癌症预防和治疗中潜在应用的必要性。

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