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述评 EDITORIAL

丁酸和叶酸预防与治疗肠道疾病及其分子基础

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摘要

丁酸和叶酸是酪酸梭菌的主要代谢产物. 人体内丁酸的血清半衰期仅仅6 min. 肠道菌群合成的叶酸量是人从食物中摄取的叶酸量1.5倍. 产丁酸和叶酸的肠道菌群足以影响人体丁酸和叶酸的供应、吸收及代谢等生理状态. 酪酸梭菌产生的丁酸能抑制去乙酰化酶活性、产生的叶酸参与甲基化和去甲基化, 二者各自起到了调节宿主的基因表达, 预防和治疗肠炎、肠癌等肠道疾病的作用.

关键词: 丁酸; 叶酸; 肠炎; 肠癌; 基因表达; 去乙酰化酶; 甲基化; 表观遗传

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0 引言

联合国粮农组织(FAO)和世界卫生组织(WHO)在2001年定义: 益生菌是“经适量服用后, 有益于其宿主健康的活的微生物[1]. 酪酸梭状芽孢杆菌(Clostridium butyricum, 下简称酪酸梭菌)是1877年就已经开始被人们研究的益生菌[2]. 属于人类肠道正常菌群[3]. 日本国千叶医学院的Miyairi博士1933年分离到酪酸梭菌, 1940年实现其商业化生产. 此后, 酪酸梭菌先后被作为人用处方药、非处方药、 兽药、 饲料添加剂、食品添加剂等广泛应用. 酪酸梭菌的主要代谢产物有丁酸、叶酸和多种维生素等[4]. 本文对丁酸和叶酸预防与治疗肠道疾病及其分子基础作一综述.

1 丁酸和叶酸的吸收与代谢

1.1 丁酸的吸收和代谢 短链脂肪酸(SCFA)一般是食物纤维或聚糖在结肠中经厌氧菌发酵后产生的[5-6], 其速率>100 mmol/d[7-8]. 与甲酸、乙酸、丙酸比较, 丁酸在SCFA中所占比例较高. 结肠内SCFA的浓度因人们食物不同而有差别, 因肠道微生态菌群不同而有变化. 近端结肠内SCFA浓度高达70-140 mmol/L, 而远端结肠内下降到20-70 mmol/L. 结肠上皮细胞优先吸收利用丁酸[9-10]. 肝门循环中, 丁酸浓度较高[11], 汗液和粪便中也含有微量丁酸[6,12]. 一般食物中都不含丁酸, 但牛奶是人类的丁酸来源之一. 反刍动物是唯一的其奶中含有较多丁酸的动物. 全牛奶中含有的乳脂不到4%[13-15]. 100 mol牛乳脂中含有7.5-13.0 mol丁酸[15]. 人乳中的乳脂含量和牛、羊的近似, 但丁酸含量仅为乳脂的0.4%[16], 比牛乳脂中的丁酸含量(3.1%)和羊的(2.6%)低得多[17]. 用小猪体内研究表明, 丁酸只在结肠中合成, 其他内脏组织基本不合成丁酸. 核素示踪法[18]研究SCFA吸收的结果表明, 人结肠中, SCFA的吸收和代谢能力很强, 其中尤以丁酸为快. 正是由于其代谢速度很快, 所以人体内丁酸的血清半衰期仅仅6 min[19-20].

1.2 叶酸的吸收和代谢 叶酸是B族维生素之一, 由蝶啶对氨基苯甲酸和1个或多个谷氨酸结合而成. 人和其他哺乳动物都只能通过肠道吸收外源的叶酸而不能自身合成叶酸. 因此, 肠道在调节和控制叶酸的吸收与代谢、维持人体内叶酸的动态平衡方面起着决定性的作用[21]. 人体内叶酸供应不足是全世界都很常见的现象, 而肠道内叶酸吸收过程发生障碍往往是其主要原因. 志愿者口服生理剂量的^{14}C标记叶酸后, 10 min内就有被标记叶酸在血浆中出现[22], 2 h内达到峰值. 口服剂量的90%被吸收. 42 d后, 口服剂量的75%以上的叶酸仍然保持在体内. 2004年Lin *et al*[23]发现, 叶酸表观吸收系数为0.65到0.97, 均值0.79. 从食物中吸收的叶酸量为248-1762 nmol/d, 均值826 nmol/d. 在口服后4.2 min内受试者血浆中出现^{14}C叶酸. 血浆中标

■背景资料
酪酸梭菌是一种越来越受到重视的益生菌. 其重要代谢产物丁酸和叶酸对于预防和治疗肠道疾病, 特别是肠癌, 显示出好的效果. 随着中国经济的持续发展和生活水平的逐步提高, 肠癌发生率呈日益升高的趋势. 因此, 充分利用益生菌预防和治疗肠道疾病具有重要的现实意义.

■研发前沿
丁酸如何通过抑制组蛋白去乙酰化酶的活性而实现其对基因表达的调控是目前的研究热点之一. 结合病理学、药理学研究, 在分子生物学水平阐明丁酸的作用机制必将推动微生态新药的研究和开发.

记叶酸的峰值在口服后2 h出现并随后开始下降. 红细胞中出现^{14}C标记是在口服标记叶酸后的第6天, 第20天达到峰值, 第80天后进入平台期, 随后由于血液循环中红细胞的老化而不断下降. 对于慢性腹泻或吸收不良的患者, 胆汁中的叶酸分泌很可能导致叶酸缺乏. 一天内胆汁可以给胃肠道供应227 nmol叶酸[24]. 2004年, kim *et al*'发现[25], 婴儿固体排泄物中的叶酸占日摄取叶酸总量的63%. 配方奶粉喂养婴儿(简称奶粉儿)的粪便中, 叶酸的平均含量是完全母乳喂养婴儿(简称母乳儿)的2倍. 这种差异的原因很可能是结肠中的肠道菌群不同, 特别是合成叶酸的肠道菌和消耗叶酸的肠道菌的相对比例不同. 母乳儿的粪便叶酸为47.1±36.9 nmol/d, 其中有13.7-22.8 nmol来源于母乳, 有24.3-33.4 nmol/d来源于肠道菌; 而奶粉儿的粪便叶酸为148.5±109.3 nmol/d, 其中有47.9-79.9 nmol来源于奶粉, 有68.6-100.6 nmol/d来源于肠道菌. 无论母乳儿或奶粉儿, 其肠道菌群合成的叶酸量都大大超过从食物中摄取的叶酸量, 前者大约是后者的1.5倍. 由此可见, 产叶酸的肠道菌群合成叶酸的总量足以影响人体叶酸供应、吸收和代谢等生理状态. 叶酸对于组成核酸的嘌呤和嘧啶的生物合成以及包括高半胱氨酸在内的几种氨基酸的代谢都是必需的. 叶酸作为酶代谢中最活跃的辅酶之一, 参与蛋氨酸的代谢循环. 叶酸还参与肾上腺素、胆碱、肌酸等有机物质的合成. 叶酸在叶酸还原酶、二氢叶酸还原酶和其他酶的作用下, 最终形成甲基四氢叶酸. 甲基四氢叶酸为一碳单位的载体, 参与组成DNA和RNA的嘌呤、嘧啶等重要物质的生物合成[26]. 在一碳代谢中, 叶酸的作用至关重要. 正常情况下, 来自丝氨酸或甘氨酸的一碳单位被转移到四氢叶酸, 形成5, 10-亚甲基四氢叶酸[27]. 5, 10-亚甲基四氢叶酸既可以被用于胸腺嘧啶脱氧核苷的生物合成, 也可以氧化为甲酰四氢叶酸后用于嘌呤的生物合成, 或者还原为5-甲基四氢叶酸后用于蛋氨酸的生物合成[28]. 在依赖于ATP的腺苷转移酶的作用下, 将腺苷转移到蛋氨酸, 形成S-腺苷蛋氨酸(SAM). SAM极其重要, 具有不稳定的甲基, 可以为生物体内近100种甲基化反应提供其甲基. 这些反应中就包括DNA, RNA和蛋白质的甲基化[29].

2 丁酸和叶酸预防与治疗肠道疾病

2.1 丁酸与肠道黏膜和肠炎 大量动物实验和人体临床研究表明, 丁酸在修复肠黏膜和治疗肠炎时发挥重要作用. 经葡聚糖硫酸钠(DSS)处理后, 急性结肠炎小鼠结肠内丁酸吸收减少, 导致黏膜的完整性受到破坏[30]. DSS诱发结肠炎的早期, 黏膜通透性就开始增加, 并伴随细胞存活率的下降和组织学的变化. 而丁酸能够逆转黏膜通透性的增加[31]. 丁酸、乙酸等SCFA促进小鼠空肠[32]和回肠[33]的上皮细胞增殖. 用SCFA滴注法[34]证实了丁酸修复肠道黏膜的作用. 大鼠模型也进一步证实, 丁酸的确能减轻实验性肠炎对黏膜的损伤[4]. 灌肠实验表明, 丁酸对功能失调和萎缩的大鼠黏膜表面有保护作用[35]. 如果肠上皮细胞发生丁酸饥饿, 就可能引发溃疡性结肠炎或者其他炎症[36]. 丁酸和5-氨基水杨协同作用减少炎症因子转谷氨酰胺酶和血栓素的合成[37]. 大鼠结肠炎增加癌变的发生[38], 而丁酸具有很强的防止癌变的作用. 随机双盲双模拟对照实验[39]和临床研究[40]表明, 产丁酸的酪酸梭菌治疗急性慢性腹泻效果很好. 丁酸对远端结肠炎患者有治疗作用[41]. 丁酸显著增加黏蛋白的合成[42], 从而对治疗效果产生很好的影响. 溃疡性肠炎患者的还原性细菌产生硫化物诱导黏膜的上部隐窝过度增殖, 而丁酸能逆转这种硫化物诱导的致病性作用[43]. 丁酸灌肠也被用于有效的治疗顽固性溃疡结肠炎[44]和直肠乙状结肠炎[45]. 膳食纤维作为肠道菌的发酵底物, 在促进肠道菌生长的同时, 产生大量的SCFA, 尤其是大量的丁酸. 丁酸对防止肠炎和癌变有显著作用[46]. 抗性淀粉有利于治疗肠炎, 其原因就是来源于抗性淀粉发酵的丁酸能恢复肠黏膜的完整性[47]. 因此, 丁酸被认为是结肠黏膜的生长诱导剂和炎症抑制剂[16]. 土著东非人和相同环境下生活的欧洲人相比, 罹患肠癌、心脏病等非感染性疾病的比例要低很多, 其原因是土著东非人的膳食中, 高含量膳食纤维有利于丁酸产生[48]. 2005年Ohkawara *et al*[49]用1, 2-二甲肼(1, 2-dimethylhydrazine)诱发小鼠癌前病变, 产生变性隐窝, 再饲喂产丁酸的丁酸菌. 结果发现, 变性隐窝数和含3或4个变性隐窝的病灶数都减少了. 说明产丁酸菌抑制了这种癌前病变. 有趣的是这种菌被匀浆后就不起作用, 提示了对于抑制癌前病变, 完整的活细菌是必须的. 我国吴恺 *et al*[50]和程勇前 *et al*[51]研究表明, 酪酸梭菌能调节肠道菌群平衡, 具有重新建立平衡的微生态环境的功能.

2.2 丁酸与肠癌 大约2千年前就有人猜测炎症是癌症发生的原因[52]. 19世纪, Rudolf Virchow证实

了肿瘤在慢性炎症部位发生[53]. 在肿瘤内或其周围微环境中, 某些细胞分泌促炎症因子TNFα, IL-1, IL-6,和 IL-8等, 还分泌基质降解酶, 生长因子和活性氧. 这些因子和活性氧导致DNA的损伤[54], 最终导致癌症发生. 酪酸梭菌产生大量丁酸, 在防治肠道疾病、特别是防治结肠直肠癌[55-56]和调节基因表达等方面发挥十分重要的作用[57]. 在体外实验或人体研究中, 丁酸都能抑制多种癌细胞的增殖, 因此被认为是一种抗癌剂[16]. 丁酸的防癌作用主要集中于结肠癌[58]. 丁酸对于结肠上皮细胞保持正常的形态和完整的功能十分重要. 丁酸的缺乏是结肠炎的主要原因[59], 也可能导致结肠癌和自发性溃疡性结肠炎. 在丁酸作用下, 结肠蛋白质合成增加, 从而促进肠上皮细胞愈合[60]. 丁酸在肠道中是一种保护剂, 降低肠癌发病风险[61]. 丁酸还能诱导细胞凋亡, 并能抑制肠癌发生[62-63]. 用丁酸治疗实体瘤的动物实验[64]和临床研究[65-66]几年前就已开始并逐步取得了进展[67]. 丁酸抑制癌细胞的增生[68], 也能抑制表皮生长因子诱导的细胞增生, 并通过下调环氧合酶(cyclooxygenase)抑制人肠微血管内皮细胞的血管发生, 从而抑制癌的生长[69]. 丁酸钠能够抑制乳腺癌[70], 在治疗恶性胶质瘤中也发挥作用[71]. Clarke *et al*[72]和 Iacomino *et al*[73]利用结肠癌的模型发现, 丁酸的同型物三丁酸甘油酯(tributyrin)通过活化细胞凋亡蛋白酶(caspase-3)而诱导癌细胞的凋亡. 也有研究表明, 三丁酸甘油酯对人的癌瘤有治疗作用[74-75]. 丁酸抑制结肠癌细胞的生长[76], 还能抑制人体侵袭性结肠癌细胞[77]. 联合应用丁酸和IL-2甚至能使晚期结肠癌发生逆转[78].

2.3 叶酸与肠道疾病 缺乏叶酸可能增加罹患结肠直肠癌、肺癌、胰腺癌、食道癌、胃癌、宫颈癌、乳腺癌以及成神经细胞瘤和白血球过多症的风险[79]. 大量的流行病学和临床研究提示, 从食物中吸收叶酸的量, 血液中叶酸的浓度都与结肠直肠癌发生的风险成反相关[80-84], 叶酸缺乏引起肿瘤发生前的DNA低甲基化[85]. 食物叶酸浓度很低时, 人的淋巴细胞也发生DNA低甲基化现象. 如果补充叶酸, 则DNA低甲基化现象被逆转[86]. Freudenheim *et al*[87]于1991年首先提出叶酸能减少癌症发生的风险. 随后有研究表明, 叶酸缺乏增加了癌症发生的风险[79]. 对428例结肠癌和372例直肠癌进行的病例对照研究表明, 叶酸缺乏与癌症发生有密切关系[87]. 食物叶酸含量低时增加乳腺癌、胰腺癌和结肠癌发生的风险[88]. 对121 000例55-69岁的受试者进行的15 a内长期补充叶酸的研究表明, 叶酸能够减少结肠癌的发生[89]. 溃疡性结肠炎、结肠癌与基因甲基化密切相关[90], 溃疡性结肠炎和结肠癌患者有4个基因比没有肠炎和结肠癌的受试者(对照)的甲基化程度要高得多. 溃疡性肠炎患者容易罹患结肠癌, 而叶酸供应不当可能是发生结肠癌的重要原因. Biasco *et al*[91]给24个溃疡性结肠炎患者服用叶酸(15 mg/d) 或安慰剂, 结果发现, 叶酸有利于直肠细胞增殖, 而安慰剂没有作用. 刘丽华 *et al*[92]用叶酸干预性治疗萎缩性胃炎, 结果发现, 叶酸治疗组临床症状缓解快而持久, 患者血浆叶酸水平升高, 病理改变逆转, 有效率达61.6%.

3 丁酸和叶酸防治疾病的分子基础

3.1 丁酸调节基因表达 丁酸在分子和细胞水平上的作用机制得到了广泛的研究[8,93-95]. 在结肠中, 丁酸能够穿过结肠细胞的细胞质膜和细膜核膜, 再与其受体结合, 从而影响基因的转录, 最终导致结肠细胞的生理状态发生变化. 丁酸调节基因的转录, 下调25种基因、上调88种基因的表达[96]. 在结肠癌细胞HT29中, 丁酸下调*c-myc*的表达, 抑制DNA合成[97]. 在11种分化诱导剂中, 只有丁酸能够增加人结肠癌细胞中的半乳凝素-1的表达[98]. 这种结合半乳糖苷的凝集素与癌细胞的分化相关, 并且参与了细胞黏附. 去氧胆酸是结肠癌的诱发因子. 丁酸能抑制结肠中去氧胆酸诱导的细胞增殖[99-100]. 在肠道黏膜上覆盖着黏液层, 其主要成分是高分子量的黏蛋白. 他们构成了肠腔内抵御有害微生物入侵的第一道防线. 在基因转录水平, 丁酸上调黏蛋白基因的表达[101]. 丁酸盐增加酪氨酸羟化酶和前脑啡肽mRNA的转录水平[102]. 丁酸钠引起Burkitt's淋巴瘤的*c-myc*原癌基因永久性下调[103-104]. 丁酸钠也调控原癌基因*c-jun*的表达[105].

3.2 丁酸是组蛋白去乙酰化酶抑制剂 丁酸通过抑制组蛋白去乙酰化酶(histone deacetylase, HDAC)的活性而实现对基因表达的调控. 通过这种抑制使转录作用受到调节的基因有很多种. 例如: 钙结合蛋白(calbindin), 细胞周期调节蛋白, 也称周期素(cyclin), 周期素依赖性蛋白激酶的抑制剂P21等等. 因为去乙酰化酶不仅在组蛋白的乙酰化中发挥作用, 而且对非组蛋白, 包括多个转录因子和高移动性的一些蛋白质的乙酰化也发挥作用. 因此, 这就造成了

■相关报道

程留芳 *et al*用随机双盲双模拟对照方法. 在临床研究中表明, 酪酸梭菌对急性慢性腹泻的治疗有很好的效果. 丁酸通过抑制组蛋白去乙酰化酶的活性而实现对基因表达的调控、叶酸影响基因表达等基础研究则初步说明了这种临床效果的分子基础. 宏观和微观研究的深入将全面阐明酪酸梭菌的作用机制.

■创新盘点
针对肠道疾病, 特别是急性腹泻和肠炎, 常用的治疗药物是抗生素. 滥用抗生素导致严重的问题已经被医药和科技界甚至一般公众所认识. 因此, 有人用中草药治疗或调理肠道疾病, 然而其效果不能令人满意. 对于肠癌等重大肠道疾病, 人们只能依赖外科手术. 利用益生菌调节肠道菌群的平衡, 既可以避免其他治疗手段的诸多弊端, 又可以安全有效的预防和治疗肠道疾病, 是正在被日益重视的一种新趋势.

基因表达既有上调也有下调的现象[106]. 丁酸调节基因表达, 可能发生在翻译水平, 但更多的是在转录水平. 而转录水平的调节主要在于丁酸抑制去乙酰化酶的活性[95,107-108]. 组蛋白的超乙酰化(hyperacetylation), 特别是H3和H4的超乙酰化, 往往与RNA转录本的积累和蛋白质的从头合成密切相关[109-110]. 用丁酸处理Hela细胞的研究表明, 在转录因子结合到他们位于核小体内的识别部位这一过程中, 组蛋白H4有重要作用[111]. HDAC决定了染色质的乙酰化和去乙酰化状态[112], 保持着二者之间的平衡, 最终调节基因的表达. 由于HDAC的抑制剂能够通过调节转录过程而恢复被沉没了的基因的功能, 所以关于HDAC抑制剂的研究极其重要. 酪酸梭菌产生的丁酸就正是这样一种HDAC抑制剂. 丁酸在人结肠中的浓度为2-12 mmol/L , 具有生理作用[5], 是组蛋白去乙酰化酶抑制剂[113-114]. 用5 mmol/L丁酸处理HeLa细胞时, 被乙酰化的组蛋白H4的含量是对照的3倍[115], 说明丁酸抑制了组蛋白去乙酰化酶的活性. 组蛋白乙酰转移酶(HAT)和HDAC参与了细胞的很多生理过程, 例如DNA复制、基因转录、基因沉默、细胞周期、细胞分化、和遗传毒性反应以及癌瘤的发生等等[116]. 因为丁酸是HDAC的抑制剂, 因此对这些过程也产生影响. 所以在临床上丁酸被作为一种安全的抗癌剂进行深入的研究. 染色质上发生组蛋白去乙酰化的位置可能是其区域划分的位置[117]. 染色质的组蛋白发生乙酰化和去乙酰化, 二者的平衡调节着基因的表达. HDAC决定了二者之间的平衡, 因此, 实际上HDAC在调节基因表达方面起着关键作用[112]. 例如, 丁酸促进某些基因的超乙酰化, 从而增加了这些基因的转录[118].

3.3 叶酸和DNA甲基化 DNA甲基化是DNA上胞嘧啶第5位碳原子和甲基间的共价结合, 胞嘧啶由此被修饰为5甲基胞嘧啶(5-mC). 哺乳动物基因组DNA中5-mC约占胞嘧啶总量的2%-7%, 绝大多数5-mC存在于CpG二联核苷(CpG doublets)中. 结构基因5'端附近富含CpG二联核苷的区域称为CpG岛. 基因调控元件(如启动子)所含CpG岛中的5-mC会阻碍转录因子复合体与DNA的结合, 所以DNA甲基化一般与基因沉默相关联, 非甲基化一般与基因的活化相关联, 去甲基化则往往与一个沉默基因的重新激活相关联.

由于发生甲基化而使基因失活似乎是癌变的极早期事件, 例如在结肠癌的癌前病变组织中就发现过特定基因的甲基化, 并观察到甲基化程度和整个病程演进过程中的相关性. 肿瘤形成中表观遗传修饰的病理作用为我们提供了一种不涉及DNA序列改变的病因研究途径, 也为我们提供了一种肿瘤治疗新手段. 对于医师和药物研发企业来讲, 他比基因治疗具有更大的吸引力. 20多年前就已经发现, 在癌细胞中存在DNA甲基化异常的现象[119]. 在人类癌细胞中, 基因启动子区的超甲基化与基因的转录沉默有关. 这种现象像DNA突变一样普遍, 是一种使抑癌基因失活的机制[120-121]. 有一些候补的抑癌基因在通常情况下不能被突变作用所失活, 但是却可以通过启动子区的超甲基化机制实现转录沉默[120]. 如果那些抑制肿瘤发生的基因被异常地甲基化, 就会导致恶性肿瘤的发生[122-123]. DNA甲基化是基因转录的一种非常重要的调节方式[26]. 在维持细胞正常的生理功能方面, DNA甲基化的作用至关重要. 一旦DNA甲基化的方式发生异常, 就很可能引起癌症的发生. 5-甲基四氢叶酸(MTF)、二氢叶酸(DF)和四氢叶酸(TF)都是叶酸代谢中间产物. 用叶酸(FA)或者上述叶酸代谢中间产物中的一种(10 mg/L)预先处理结肠癌HCT-116细胞株48 h, 再将这些结肠癌细胞在存在或不存在100 mL/L胎牛血清的情况下, 加入FA或者DF, TF, 5-MTF中的一种, 继续培养48 h. 结果表明, 由于叶酸及其代谢中间产物5-MTF增强了甲基化作用, 所以显著抑制了结肠癌细胞的表皮生长因子受体启动子的活性[124]. 因而, 在结肠直肠癌发生发展过程中, 叶酸实际上发挥了抑制癌瘤生长的作用.

3.4 叶酸和亚甲基四氢叶酸还原酶 亚甲基四氢叶酸还原酶(MTHFR)是甲基代谢过程的重要分枝点[26], 他决定了叶酸库中的叶酸是用于从高半胱氨酸合成蛋氨酸还是用于胸苷酸或其他分子的合成. MTHFR基因存在单核苷酸多型性(677C→T). 这个基因的单核苷酸多型性既与丙氨酸-缬氨酸取代有关, 也与这种还原酶的活性有关[125]. 基因型为MTHFR677TT的个体, 其细胞内主要积累5, 10-亚甲基四氢叶酸. 而基因型为MTHFR677CC或者MTHFR677CT的个体, 其细胞内以5-甲基四氢叶酸占优势[126]. 5, 10-亚甲基缺乏时, 一磷酸脱氧尿苷不能足量的形成一磷酸脱氧胸苷, 导致DNA聚合酶错误地将尿苷作为胸苷合成到DNA中. 因此, 如果有丰富的叶酸营养, 因而能够增加5, 10-亚甲基四氢叶酸, 则MTHFR 677TT基因型可能是有益的. 然而, 当

叶酸缺乏时, MTHFR677TT基因型就可能是有害的[127]. 正是由于叶酸缺乏能够引起DNA合成中发生错误, 还能影响DNA的甲基化, 所以, 叶酸与癌症的发生、发展以及预防和治疗有密切的联系. 在4项关于MTHFR677C→T多型性与结肠癌的关系的研究[128-131]中, 结果都表明, MTHFR677TT基因型个体在低风险食物(即叶酸含量高而乙醇含量低)情况下, 癌瘤发生的风险小. 与此相反, 如果食物中叶酸含量低而乙醇含量高, MTHFR677TT基因型个体癌瘤发生的风险就高于其他基因型.

3.5 叶酸和基因表达 大鼠结肠中P53的表达因为叶酸缺乏而减少, 但当补充叶酸时, 其表达又超过了基线水平[132]. P53转录的稳态水平与叶酸的供应呈正相关性. 人鼻咽拟表皮癌细胞中, 叶酸缺乏导致5种基因表达被上调, 3种基因表达被下调[133]. 尽管叶酸缺乏时造成总体DNA低甲基化, 但是在5'CpG岛则被超甲基化, 并且导致H-钙黏蛋白基因表达的下调. 年轻大鼠缺乏叶酸时, 84种基因表达被下调, 52种基因表达被上调; 而老年大鼠缺乏叶酸时, 21种基因表达被下调, 41种基因表达被上调[134]. 由此可见, 年轻的成鼠对于叶酸缺乏似乎有更强烈和宽广的反应. 叶酸供应不足的情况下, 老化诱导几种免疫相关基因表达的下调作用. 如果给叶酸供应不足的大鼠补充叶酸, 则P53和胰岛素样生长因子结合蛋白-3的基因表达就不再发生下调作用. 由此可见, 充足的叶酸供应阻止了老化过程中某些关键基因的有害变化, 从而减少了与老化相关的癌症的发生风险. 生物合成过程中的甲基化反应和核苷酸的生物合成之间存在着一种平衡, 如果这种平衡被打破就导致叶酸相关的癌变发生[29]. 例如, 5, 10-亚甲基缺乏时, 一磷酸脱氧尿苷不能充分足量的形成一磷酸脱氧胸苷, 导致DNA聚合酶错误的将尿苷作为胸苷合成到DNA中[135]. 在叶酸缺乏症患者的白血细胞DNA中, 每个细胞含约4 000 000个尿嘧啶分子. 在患者补充叶酸后, 这个数字下降到200 000[136]. 补充叶酸还降低了染色体断裂的频率. 这种错误地将尿苷合成到DNA中的现象会导致基因组异常, 例如增加自发突变[137], 对破坏DNA的试剂更加敏感[138]、染色体畸变率更高[139-140]、DNA复制中的错误频率也会更高[140-142]. 用动物模型的研究表明, 缺乏叶酸的饲料饲喂大鼠后导致其基因组DNA的断裂, 引起P53基因的破坏[143], 还诱导肠道细胞中P53肿瘤抑制基因的突变[144].

人的肠道内有10^{13}到10^{14}个微生物. 他们的基因组所包括的基因数至少是人基因组所包括的基因数的100倍[145]. 他们极大的增强了多聚糖、氨基酸、外源性化学物质的代谢, 促进了甲烷生成, 有利于维生素和类异戊二烯的生物合成. 而这些代谢产物中有很多被人体直接利用. 实际上, 人体内发生的是人体代谢和微生物代谢交织在一起的混合代谢. 因此, 整体的“人”实际上是一种“超级生物”(superorganism). 或者, 我们也可以把肠道微生物看作人体的“特殊器官”. 深入细致的研究肠道微生物这一“特殊器官”, 不仅会推动人体生理、生化代谢、分子遗传、尤其是表观遗传等方面的基础研究, 而且必将在疾病预防、诊断和治疗以及新药开发方面获得令人满意的进展. 人体内丁酸的血清半衰期极短, 而且60%-70%的丁酸被用于能量代谢. 所以, 直接口服丁酸防治肠道疾病显然不是合适的方法, 而利用在肠道中产生丁酸的益生菌是日益受到重视的选择. 肠道菌群合成的叶酸量大大超过了从食物中摄取的叶酸量. 产叶酸的肠道菌群足以影响人体叶酸供应、吸收和代谢等生理状态. 酪酸梭菌产生大量的丁酸和叶酸, 在调节肠道菌群平衡, 调控基因表达, 阻止肠恶变方面发挥了其他益生菌和药物不可替代的重要作用.

■应用要点

人类正常膳食中的丁酸含量极微, 而丁酸在人体内的血清半衰期又仅仅只有6 min, 所以, 利用能在人肠道中产生丁酸的酪酸梭菌补充防治肠道疾病所需的丁酸, 是安全有效的一种选择.

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■同行评价
本文综述的内容很有参考价值, 立题较新, 基本都是新的研究成果, 资料详实可靠.

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• 消息 •

第五届中国百种杰出学术期刊评选揭晓

本刊讯 第五届中国百种杰出学术期刊评选日前揭晓, 周光召院士任主编的《科学通报》、韩启德院士任主编的《北京大学学报医学版》以及马连生任主编的《World Journal of Gastroenterology》等100种期刊入选“第五届中国百种杰出学术期刊”. 中国科学技术信息研究所每年出版的《中国科技期刊引证报告》, 定期公布《中国科技论文与引文数据库》(CSTPCD)收录的中国科技核心期刊的十余项科学计量指标, 目前该数据库共收录中国科技核心期刊1652种. (记者 潘锋 2006-11-08)