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·综 述·

叶酸与胰腺癌的关系研究进展

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[摘要] 叶酸是一种与肿瘤发生发展关系密切的人体必需微量元素。近年来研究发现叶酸缺乏或代谢障碍可能与胰腺癌的发生有关,其机制至今未明。本文从流行病学角度总结了叶酸与胰腺癌的关系,并就叶酸缺乏可能导致肿瘤的机制等方面对该领域的研究进展情况进行了综述。

[关键词] 叶酸;叶酸缺乏;胰腺肿瘤;危险因素
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Folic acid and pancreatic cancer: an advance

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[**Abstract**] Folic acid, an essential microelement to human, is closely related to tumor development and progression. Recent studies have suggested that a low folate intake and impaired folate metabolism may be involved in the carcinogenesis of pancreatic cancer, but the specific mechanism remains unclear. In this paper we review the progress in the association of folate deficiency with pancreatic cancer from an epidemiological perspective, and introduce the progress in the mechanism by which folate deficiency causes tumor.

[**Key words**] folic acid; folic acid deficiency; pancreatic neoplasms; risk factors
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叶酸是一种广泛存在于蔬菜、水果等食物中的人体必需的水溶性B族维生素,它参与DNA的甲基化及DNA、RNA、蛋白质等主要物质的合成,在细胞的代谢、分化和增殖中发挥重要作用。叶酸与肿瘤的发生、发展关系密切[1-3]。近年来研究发现叶酸缺乏或代谢障碍可能与胰腺癌的发生有关[4]。大量研究结果表明,除年龄和吸烟等因素外,叶酸、$VitB_{12}$、$VitB_6$等营养成分慢性缺乏可能是胰腺癌的危险因素,但研究结果并不完全一致[5-15]。本文对叶酸与胰腺癌关系以及可能机制的最新进展情况进行综述。

1 叶酸与胰腺癌发病关系的流行病学研究

来自很多流行病学的调查结果提示增加饮食中叶酸的摄入量以及提高血浆叶酸水平是预防胰腺癌的保护因素[5-12],而另一些流行病学研究结果持不同意见[13-16]。一项关于叶酸与消化系统肿瘤的meta分析[5]提出了有力的证据证实了对于膳食中含有更多叶酸的人群来说胰腺癌风险更低。在叶酸摄入与胰腺癌发病关系方面包括四项队列研究及一项病例对照研究,结果均表明饮食摄入叶酸的增加是胰腺癌发生的保护因素,在3个研究里这种关联存在明显统计学差异,其中唯一的病例对照研究 *RR* 值为0.36(95%CI:0.18~0.74),其他两个来自芬兰、瑞士的队列研究 *RR* 值分别为0.52 (95%CI:0.31~0.87)和0.25 (95%CI:0.11~0.59)。总体来说,在饮食摄入叶酸最多量人群中的个体罹患胰腺癌的风险比那些在最少量中的低51%。

表1列举了叶酸与胰腺癌发病关系的一些主要的队列研究与病例对照研究。虽然其中相当一部分研究[6-12]认为长期叶酸摄入缺乏或低血浆(清)叶酸水平增加胰腺癌罹患风险,该研究仍存在争议[13-16]。荷兰的队列研究发现,在考虑了年龄、性别、吸烟史、糖份摄入等综合的危险因素,叶酸摄入最高量与最低量人群的胰腺癌发生 *RR* 值为1.37(95%CI:0.97~1.94),该结果表明食物摄入足量叶酸盐或单独的叶酸盐类维生素对胰腺癌的发生风险没有保护作用[13]。同样,在1998年的一个直接调查访问病例-对照研究中,也没有看到两者间的联系[16]。

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从上述研究结果中我们可以看出有 7 篇文献支持叶酸缺乏是胰腺癌的危险因素，4 篇反对。因此，就目前的研究来看，还是倾向于食物来源的叶酸摄入是胰腺癌的保护因素。

表 1　叶酸与胰腺癌发病关系

Tab 1　The relationship between folate and incidence of pancreatic cancer

Study(reference)	Study design	Study panticipants	Follow-up period and number of patients with pancreatic cancer or folate assessment and methods	Result
Oaks et al[6], 2010, America	Cohort	51 988 men and 57 187 women	1998-2006 162 men and 104 women	HR^{a}=0.47(95%CI 0.23-0.94); HR^{ab}=1.20(95%CI 0.70-2.04)
Larsson et al[7], 2006, Switzerland	Cohort	45 306 men and 6 616 women	1998-2004 74 men and 61 women	RR^{a}=0.25(95%CI 0.11-0.59); RR^{c}=0.33(95%CI 0.15-0.72)
Stolzenberg-Solomon et al[8], 2001, Finland	Cohort	27 101 male smokers	1985-1997 157 men	HR^{ab}=0.52(95%CI 0.31-0.87)
Stolzenberg-Solomon et al [9], 1999, Finland	Nested case-control	126 cases, 247 controls	Concentration of serum folate measured with RIA	OR^{d}=0.45(95%CI 0.24-0.82)
Bravi et al[10], 2010, Italy	Case-control	326 cases, 652 controls	Interview based on 78-items FFQs(food-frequency questionnaires)	OR^{a}=0.82 (95%CI 0.70-0.96)
Guo et al [11], 2009, China	Case-control	42 cases, 42 controls	Concentration of plasma folate measured with ELISA	OR^{e}=0.571(95%CI 0.383-0.851)
Gong et al[12], 2009, America	Case-control	532 cases, 1 701 controls	Interview based on 131-items FFQs	OR^{c}=0.67(95%CI 0.48- 0.93)
Keszei et al[13], 2009, Netherland	Cohort	58 279 men, 62 573 women	1986-1999 188 men, 175 women	HR^{a}=1.37(95%CI 0.97-1.94)
Schernhammer et al[14], 2007	Nested case-control	208 cases, 623 controls	Concentration of plasma folate measured with ELISA	OR^{e}=0.55(0.24, 1.55);
Skinner et al[15], 2004, America	Cohort	47 840 men, 77 640 women	1984-1998, 1986-2000 187 men, 139 women	RR^{a}=0.65(95%CI 0.37- 1.35); RR^{ab}=0.66(95%CI 0.37-1.18)
Silverman et al[16], 1998, America	Case-control	436 cases, 2003 controls	Interview based on 131-items FFQs	OR^{f}=0.9, OR^{be}= 1.0

[a]: Relative risk(or Hazard Ratio or Odds Ratio) for highest versus lowest intake category of folate from food. [b]: Folate levels from women. Folate levels from men. [c]: Relative risk(or Hazard Ratio or Odds Ratio) for highest versus lowest intake category of folate from foods and dietary supplements. [d]: Relative risk(or Hazard Ratio or Odds Ratio) for highest versus lowest intake category of serum folate. [e]: Relative risk(or Hazard Ratio or Odds Ratio) for highest versus lowest intake category of plasma folate. [f]: 95%CI was not mentioned

亚甲基四氢叶酸还原酶(MTHFR) 在叶酸的代谢中起着重要的作用，其催化 5,10-甲基四氢叶酸转化为 5-甲基四氢叶酸，从而使叶酸代谢顺利地朝 DNA 甲基化和 DNA 合成通路的方向进行。已发现编码 MTHFR 的基因存在单核苷酸多态性，MTHFR 677C →T 和 1298A →C 多态可导致酶活性的下降[17]。同样在上述 meta 分析表明 MTHFR 677TT 基因型与胰腺癌发生风险有关[5]。2005 年 Li 等[18]通过一个以初诊为胰腺癌的住院患者及健康人群为研究对象的病例-对照试验发现，C667T 基因多态性对胰腺癌的发生有明显作用。拥有 667TT 基因型的个体与那些 CC/CT 基因型相比，罹患胰腺癌的风险增加两倍(OR=2.14；95% CI：1.14～4.01)。此外，在 MTHFR 677TT 基因型与叶酸缺乏、大量吸烟及饮酒间存在正交互作用[17]。

在过去的 30 年里，我们已经知道吸烟是导致胰腺癌最重要的环境因素[19]。同时，吸烟现在已被认识到是一个对人体叶酸吸收状况的负向调节因素[20]。一项巢式病例-对照研究发现，血清叶酸与 5-磷酸吡哆醛浓度表明其与胰腺癌风险在统计学上呈明显负相关[9]。最高浓度组胰腺癌发生风险

几乎是最低组的一半（$OR=0.45$，95% CI：0.24～0.82；$P=0.009$）。增加的罹患风险同样也出现在更多暴露于吸烟因素中（最高四分位数比最低：$OR=2.13$，95% CI：1.13～3.99；$P=0.04$）。这些结果支持了维持足够的叶酸水平减少了胰腺癌的发生，同时稳定了先前就有吸烟因素人群的罹患风险[9]。

2　叶酸影响胰腺癌发病的可能机制

胰腺的外分泌对甲基供体有大量、特别的需求（仅次于肝脏），因此，胰腺可以说是一个对叶酸缺乏非常敏感的器官[21-22]。经过乙硫氨酸抑制细胞内甲基化反应的动物，由于其胰腺外分泌功能损伤，会发生急性胰腺炎[23-24]，而胰腺炎与胰腺癌密切相关[25-27]。另外，饲料缺乏甲基基团的动物，胰腺腺泡细胞的分化会发生异常改变[28-29]。叶酸缺乏的动物比起那些叶酸充足的来说，掺入胰腺细胞 DNA 的放射性胸腺嘧啶较少[29]。同时，S-腺苷蛋氨酸（SAM）/S-腺苷高半胱氨酸（SAH）的比值降低，这主要因为后者的增高[28]。SAM 与 SAH 的比值被认为是甲基化过程的重要调节因素。

来自一些体外实验、动物及人体活体实验的证据支持了叶酸维持 DNA 稳定性及预防癌症的假说。叶酸缺乏可能通过多种分子生物学途径增加胰腺癌发生率。

2.1　*尿嘧啶错掺入 DNA*　叶酸在嘌呤、嘧啶核苷酸的合成中是很关键的，脱氧尿嘧啶核苷酸（dUMP）转化为脱氧胸腺嘧啶核苷酸（dTMP）需要 5，10-甲基四氢叶酸作为 dTMP 合成酶的甲基体。叶酸缺乏时，甲基化的 dUMP 蓄积，导致 dUTP 浓度增加，从而取代 dTTP 位置作为 DNA 合成前体进入 DNA。正常 DNA 切除修复机制可去除错掺入的 dUTP，可在叶酸不足的情况下，导致 DNA 修复进入耗能性无效循环，这种无效循环会带来 DNA 链的断裂[1]及基因组的不稳定性[2]。

在体外实验方面，用叶酸缺乏培养基诱导中国仓鼠卵巢细胞 DNA 链断裂、染色体畸变（断裂、缺失及碎片）、凋亡[30-32]。尿嘧啶在叶酸缺乏培养基里的人淋巴 HL60 细胞、正常人淋巴细胞和修复缺陷中国仓鼠卵巢细胞 DNA 中增多[33-34]。体外实验中的叶酸缺乏改变 DNA 复制、进行性抑制正常人体结肠细胞与活性淋巴细胞的生长[35-36]。更重要的是，叶酸缺乏使得这些细胞尿嘧啶错掺概率增加 2～3 倍[37]。这种叶酸缺乏在 DNA 稳定性上的负面影响是有浓度依赖性的，降低叶酸水平会抑制细胞增殖和进行性诱导尿嘧啶错掺[44]。

在动物实验方面，鼠体内甲基供体缺乏使得肝细胞 dUTP 与 dTTP 比值增加 3 倍，诱导肝细胞 p53 DNA 链、脾淋巴细胞及肝脏细胞基因组 DNA 断裂，同时上调细胞凋亡[38-40]。甲基缺乏或肝脏切除与甲氨蝶呤联合治疗的小鼠肝脏细胞中尿嘧啶错掺增加[41]。Duthie 等[42]的实验中，叶酸缺乏小鼠淋巴细胞尿嘧啶浓度表现出明显增加。在人体实验方面，低但是可以测得的尿嘧啶浓度出现在正常血浆及红细胞叶酸水平的人体细胞 DNA 中，而尿嘧啶错掺率在巨幼红细胞血症患者[43]及叶酸缺乏人群中增加[2,43]。

2.2　*畸形的 DNA 甲基化*　这可能包括了基因组低甲基化、一些导致错误表达的基因启动子区的 CpG 岛的高甲基化[3]。DNA 甲基化在基因表达、DNA 结构稳定和突变中起重要作用，而后者可影响肿瘤的发生。全基因组低甲基化伴随肿瘤基因 CpG 岛区域性的高甲基[44]。目前已发现启动子区 CpG 岛的甲基化与胰腺癌中的一些肿瘤抑制基因及错配修复基因如 p16、ppENK 和 hMLH1 的失活有关[45]。因此，通过甲基供体不足而导致的肿瘤抑制基因的失活可能在胰腺癌组织的生长调节方面起着非常重要的作用。

严重缺乏叶酸或甲硫氨酸和（或）胆碱减少 SAM，改变 SAM/SAH 比率，同时诱导小鼠肝脏 DNA 低甲基化和 mRNA原癌基因的表达[46-47]。相反的，中等程度叶酸缺乏对于肝脏或结肠细胞 DNA 甲基化没有影响，仅仅对一些特定的原癌基因有特殊影响[48-49]。有报道指出叶酸缺乏饮食导致绝经后妇女淋巴细胞全基因组低甲基化[50]。

3　小结和展望

就目前的研究结果来看，提示叶酸缺乏是胰腺癌的危险因素。然而，我们所看到的这方面的流行病学研究相对存在局限性，比如，有些研究的研究对象较少，势必影响到结果的可信度，有些研究存在选择偏倚，而在随访时间较长的研究中容易产生失访偏倚。另外，用于评价人体叶酸营养状况最常用的检测指标是红细胞叶酸及血清或血浆叶酸。目前，叶酸的检测方法已有多种，其中微生物法、核素放射免疫法的使用最为广泛。然而，对目前 20 家研究所或临床实验室用于检测血清及全血叶酸的几种方法进行比较研究[51]，结果表明不同实验室的叶酸检测结果差异较大，不同检测方法的检测结果之间可比性较差。以上这些因素都影响研究结果的准确性及可靠性。鉴于胰腺癌一级预防对减轻胰腺癌疾病负担的重要性，如何证明血清叶酸水平与胰腺癌的关系及研究其对胰腺癌发生、发展的作用机制，将是我们进一步研究的方向与重点。

[参 考 文 献]

[1] Blount B C, Mack M M, Wehr C M, MacGregor J T, Hiatt R A, Wang G, et al. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage[J]. Proc Natl Acad Sci USA, 1997, 94: 3290-3295.

[2] Duthie S J, Mavrommatis Y, Rucklidge G, Reid M, Duncan G, Moyer M P, et al. The response of human colonocytes to folate deficiency *in vitro*: functional and proteomic analyses[J]. J Proteome Res, 2008, 7: 3254-3266.

[3] Kim Y I. Nutritional epigenetics: impact of folate deficiency on DNA methylation and colon cancer susceptibility[J]. J Nutr, 2005, 135: 2703-2709.

[4] Wiseman M. The Second World Cancer Research Fund/American Institute for Cancer Research Expert Report. Food, nutri-

tion, physical activity, and the prevention of cancer: a global perspective[J]. Proc Nutr Soc, 2008, 67: 253-256.

[5] Larsson S C, Giovannucci E, Wolk A. Folate intake, MTHFR polymorphisms, and risk of esophageal, gastric, and pancreatic cancer: a meta-analysis[J]. Gastroenterology, 2006, 131: 1271-1283.

[6] Oaks B M, Dodd K W, Meinhold C L, Jiao L, Church T R, Stolzenberg-Solomon R Z. Folate intake, post-folic acid grain fortification, and pancreatic cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial[J]. Am J Clin Nutr, 2010, 91: 449-455.

[7] Larsson S C, Håkansson N, Giovannucci E, Wolk A. Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men[J]. J Natl Cancer Inst, 2006, 98: 407-413.

[8] Stolzenberg-Solomon R Z, Pietinen P, Barrett M J, Taylor P R, Virtamo J, Albanes D. Dietary and other methyl-group availability factors and pancreatic cancer risk in a cohort of male smokers[J]. Am J Epidemiol, 2001, 153: 680-687.

[9] Stolzenberg-Solomon R Z, Albanes D, Nieto F J, Hartman T J, Tangrea J A, Rautalahti M, et al. Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers[J]. J Natl Cancer Inst, 1999, 91: 535-541.

[10] Bravi F, Polesel J, Bosetti C, Talamini R, Negri E, Dal Maso L, et al. Dietary intake of selected micronutrients and the risk of pancreatic cancer: an Italian case-control study[J]. Ann Oncol, 2011, 22: 202-206.

[11] 郭爱珍，蔡全才，陈　燕，朱　伟，李淑德，李兆申. 叶酸、同型半胱氨酸与胰腺癌关系的病例对照研究[J]. 第二军医大学学报，2009，30：420-423.
Guo A Z, Cai Q C, Chen Y, Zhu W, Li S D, Li Z S. Relationship of folic acid, homcysteine with pancreatic cancer: a case-control study[J]. Acad J Sec Mil Med Univ, 2009, 30: 420-423.

[12] Gong Z, Holly E A, Bracci P M. Intake of folate, vitamins B_6, B_{12} and methionine and risk of pancreatic cancer in a large population-based case-control study[J]. Cancer Causes Control, 2009, 20: 1317-1325.

[13] Keszei A P, Verhage B A, Heinen M M, Goldbohm R A, van den Brandt P A. Dietary folate and folate vitamers and the risk of pancreatic cancer in the Netherlands cohort study[J]. Cancer Epidemiol Biomarkers Prev, 2009, 18: 1785-1791.

[14] Schernhammer E, Wolpin B, Rifai N, Cochrane B, Manson J A, Ma J, et al. Plasma folate, vitamin B_6, vitamin B_{12}, and homocysteine and pancreatic cancer risk in four large cohorts[J]. Cancer Res, 2007, 67: 5553-5560.

[15] Skinner H G, Michaud D S, Giovannucci E L, Rimm E B, Stampfer M J, Willett W C, et al. A prospective study of folate intake and the risk of pancreatic cancer in men and women[J]. Am J Epidemiol, 2004, 160: 248-258.

[16] Silverman D T, Swanson C A, Gridley G, Wacholder S, Greenberg R S, Brown L M, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews[J]. J Natl Cancer Inst, 1998, 90: 1710-1719.

[17] Frosst P, Blom H J, Milos R, Goyette P, Sheppard C A, Matthews R G, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase[J]. Nat Genet, 1995, 10: 111-113.

[18] Li D, Ahmed M, Li Y, Jiao L, Chou T H, Wolff R A, et al. 5, 10-Methylenetetrahydrofolate reductase polymorphisms and the risk of pancreatic cancer[J]. Cancer Epidemiol Biomarkers Prev, 2005, 14: 1470-1476.

[19] Lowenfels A B, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer[J]. Best Pract Res Clin Gastroenterol, 2006, 20: 197-209.

[20] Pilch S M, Senti F R; National Health and Nutrition Examination Survey Ⅱ (U. S.). Assessment of the Nutritional Status of the U. S. Population Based on Data Collected in the Second National Health and Nutrition Examination Survey, 1976-1980 [M]. Bethesda, Md.: Federation of American Societies for Experimental Biology, Life Sciences Research Office. Springfield Va.: Available from NTIS, 1984.

[21] Balaghi M, Wagner C. Methyl group metabolism in the pancreas of folate-deficient rats[J]. J Nutr, 1992, 122: 1391-1396.

[22] Hoover K L, Poirier L A. Hepatocyte-like cells within the pancreas of rats fed methyl-deficient diets[J]. J Nutr, 1986, 116: 1569-1575.

[23] Farber E, Popper H. Production of acute pancreatitis with ethionine and its prevention by methionine[J]. Proc Soc Exp Biol Med, 1950, 74: 838-840.

[24] Govendir M, Canfield P J, Church D B. Effect of d, l-ethionine administration on the histomorphology of canine pancreatic acinar and beta-cells[J]. Exp Toxicol Pathol, 2002, 54: 77-83.

[25] Malka D, Hammel P, Maire F, Rufat P, Madeira I, Pessione F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis [J]. Gut, 2002, 51: 849-852.

[26] Lowenfels A B, Maisonneuve P, Cavallini G, Ammann R W, Lankisch P G, Andersen J R, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group[J]. N Engl J Med, 1993, 328: 1433-1437.

[27] Lowenfels A B, Maisonneuve P, DiMagno E P, Elitsur Y, Gates L K Jr, Perrault J, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group[J]. J Natl Cancer Inst, 1997, 89: 442-446.

[28] Parsa I, Marsh W H, Fitzgerald P J. Pancreas acinar cell differentiation. Ⅵ. Effects of methyl donors and homocysteine[J]. Fed Proc, 1972, 31: 166-175.

[29] Elseweidy M, Singh M. Folate deficiency and pancreatic acinar cell function[J]. Proc Soc Exp Biol Med, 1984, 177: 247-252.

[30] Branda R F, Blickensderfer D B. Folate deficiency increases genetic damage caused by alkylating agents and gamma-irradiation in Chinese hamster ovary cells[J]. Cancer Res, 1993, 53: 5401-5408.

[31] Libbus B L, Borman L S, Ventrone C H, Branda R F. Nutritional folate-deficiency in Chinese hamster ovary cells. Chromosomal abnormalities associated with perturbations in nucleic acid precursors[J]. Cancer Genet Cytogenet, 1990, 46: 231-242.

[32] James S J, Basnakian A G, Miller B J. *In vitro* folate deficiency induces deoxynucleotide pool imbalances, apoptosis and mutagenesis in Chinese hamster ovary cells[J]. Cancer Res, 1994, 54: 5075-5080.

[33] Wickramasinghe S N, Fida S. Misincorporation of uracil into the DNA of folate- and B_{12}-deficient HL60 cells[J]. Eur J Haematol, 1993, 50: 127-132.

[34] Melnyk S, Pogribna M, Miller B J, Basnakian A G, Pogribny I P, James S J. Uracil misincorporation, DNA strand breaks, and gene amplification are associated with tumorigenic cell transformation in folate deficient/repleted Chinese hamster ovary cells [J]. Cancer Lett, 1999, 146: 35-44.

[35] Duthie S J, Hawdon A. DNA instability (strand breakage, uracil misincorporation, and defective repair) is increased by folic acid depletion in human lymphocytes *in vitro*[J]. FASEB J, 1998, 12: 1491-1497.

[36] Duthie S J, Narayanan S, Blum S, Pirie L, Brand G M. Folate deficiency *in vitro* induces uracil misincorporation and DNA hypomethylation and inhibits DNA excision repair in immortalised normal human colon epithelial cells[J]. Nutr Cancer, 2000, 37: 245-251.

[37] Duthie S J, Narayanan S, Brand G M, Pirie L, Grant G. Impact of folate deficiency on DNA stability[J]. J Nutr, 2002, 132(8 Suppl): 2444S-2449S.

[38] Pogribny I P, Basnakian A G, Miller B J, Lopatina N G, Poirier L A, James S J. Breaks in genomic DNA and within the p53 gene are associated with hypomethylation in livers of folate/methyl-deficient rats[J]. Cancer Res, 1995, 55: 1894-1901.

[39] James S J, Yin L. Diet-induced DNA damage and altered nucleotide metabolism in lymphocytes from methyl-deficient rats[J]. Carcinogenesis, 1989, 10: 1209-1214.

[40] James S J, Miller B J, Basnakian A G, Pogribny I P, Pogribna M, Muskhelishvili L. Apoptosis and proliferation under conditions of deoxynucleotide pool imbalance in liver of folate/methyl deficient rats[J]. Carcinogenesis, 1997, 18: 287-293.

[41] Blount B C, Ames B N. Analysis of uracil in DNA by gas chromatography-mass spectrometry[J]. Anal Biochem, 1994, 219: 195-200.

[42] Duthie S J, Grant G, Narayanan S. Increased uracil misincorporation in lymphocytes from folate-deficient rats[J]. Br J Cancer, 2000, 83: 1532-1537.

[43] Wickramasinghe S N, Fida S. Bone marrow cells from vitamin B_{12}- and folate-deficient patients misincorporate uracil into DNA[J]. Blood, 1994, 83: 1656-1661.

[44] Laird P W, Jaenisch R. DNA methylation and cancer[J]. Hum Mol Genet, 1994, 3: 1487-1495.

[45] Ueki T, Toyota M, Skinner H, Walter K M, Yeo C J, Issa J P, et al. Identification and characterization of differentially methylated CpG islands in pancreatic carcinoma[J]. Cancer Res, 2001, 61: 8540-8546.

[46] Wainfan E, Poirier L A. Methyl groups in carcinogenesis: effects on DNA methylation and gene expression[J]. Cancer Res, 1992, 52: 2071s-2077s.

[47] Balaghi M, Wagner C. DNA methylation in folate deficiency: use of CpG methylase[J]. Biochem Biophys Res Commun, 1993, 193: 1184-1190.

[48] Kim Y I, Christman J K, Fleet J C, Cravo M L, Salomon R N, Smith D, Ordovas J, et al. Moderate folate deficiency does not cause global hypomethylation of hepatic and colonic DNA or c-myc-specific hypomethylation of colonic DNA in rats[J]. Am J Clin Nutr, 1995, 61: 1083-1090.

[49] Kim Y I, Pogribny I P, Salomon R N, Choi S W, Smith D E, James S J, et al. Exon-specific DNA hypomethylation of the p53 gene of rat colon induced by dimethylhydrazine. Modulation by dietary folate[J]. Am J Pathol, 1996, 149: 1129-1137.

[50] Jacob R A, Gretz D M, Taylor P C, James S J, Pogribny I P, Miller B J, et al. Moderate folate depletion increases plasma homocysteine and decreases lymphocyte DNA methylation in postmenopausal women[J]. J Nutr, 1998, 128: 1204-1212.

[51] Gunter E W, Bowman B A, Caudill S P, Twite D B, Adams M J, Sampson E J. Results of an international round robin for serum and whole-blood folate[J]. Clin Chem, 1996, 42: 1689-1694.

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