Journal of Clinical and Nursing Research 2017, 1(3): 51-56

BIO-BYWORD SCIENTIFIC PUBLISHING PTY LTD

Journal of Clinical and Nursing Research

Study on the Relationship Between Folate, Dna Methylation and Esophagus Cancer

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ARTICLE INFO

Article history:

Published online: 30th Nov, 2017

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Key words:

Folate

B-vitamins

Esophageal cancer

DNA methylation

Epigenetic mechanism

ABSTRACT

Esophagus cancer is a common malignant tumor in China, and its prevalence rate and fatality rate are the highest in the world whose occurrence is related to multiple factors, including family heredity, race, gender, region, diet and so on. Esophagus cancer is the disease with the most Chinese characteristic. The pathogenesis of esophagus cancer is very complicated, and the epigenetics in the pathogenetic process has become the current research hotspot, and the reversible feature provides a new direction for the early screening, prevention and treatment of esophagus cancer. DNA methylation is the most deep epigenetics in the current study, and the pattern of genome methylation is often abnormal in the cancerization of esophagus cancer. The folate, as the methyl group donor, and B-vitamins related to one-carbon metabolism, shall directly influence the condition of DNA methylation, give rise to the change of epigenetics, affect the occurrence of esophagus cancer. This paper summarizes the relationship among the occurrence of esophagus cancer and folate, several kinds of B-vitamins related to one-carbon metabolism, DNA methylation.

Introduction

Folate is one of the crucial B-vitamins and the essential nutrients of the body, which is mainly ingested through foods, such as fresh vegetables, fruits, animal livers and so on. In the past, folate has been used only as a dietary supplement for pregnant women to prevent children's neural tube abnormalities. However, folate's anti-tumor effect is found in the recent research. The human digestive tract is the vital organ responsible for food intake, digestion and absorption, so the food intake is closely related to the occurrence of digestive tract tumors. The food contains a lot of plant chemicals and nutrients that are found to have anti-tumor effects[1]. Folate, which is involved in DNA methylation, is thought to reduce the incidence of cancer by influencing the change of epigenetics[2]. Food components can selectively activate or inactivate genes[3]. Several studies manifest that dietary folate intake is negatively correlated with the occurrence of esophagus cancer[4], but the underlying mechanism of it and the occurrence of the esophagus cancer is unknown.

Low level of folate may significantly increase the risk of esophagus cancer, and it's probably because: folate is an essential ingredient in DNA synthesis, and the lack of folic acid can affect DNA synthesis and damage DNA repair, resulting in the occurrence of esophagus cancerization. In addition, DNA methylation is an important mechanism of gene expression regulation. When folate is deficient, methionine synthesis is inhibited and DNA methylation levels change. Promoter region DNA methylation disorder

(too high or too low) can selectively result in the improper activation of proto-oncogene and the inactivation of anti-oncogene, thus activating cancerization.

In addition to the DNA methylation, which is researched by many people, the epigenetic mechanism also includes histone modification, chromatin reconstruction and regulated gene expression of microRNA. Because more studies focus on DNA methylation and the DNA methylation is regulated by the B-vitamins related to one-carbon metabolism (such as folate), the less studies will focus on the other epigenetic mechanism and the relationship of them is unclear. This paper only discusses the DNA methylation in detail.

1 The Relation Among Folate, B-vitamins Related to One-Carbon Metabolism and DNA Methylation

The folate and B-vitamins related to one-carbon metabolism are closely related to DNA methylation[6]. The activated form of folate in the body is tetrahydrofolic acid (THF), the THF can carry one carbon unit and then is transformed to 5,10-methylene tetrahydrofolate (5,10-CH2THF) to participate in one carbon unit metabolism and methionine cycle, which is the coenzyme of one carbon unit metabolism[7]. The folate and B-vitamins related to one-carbon metabolism supply methyl through participating in methionine cycle, which plays a crucial role in DNA methylation. In the condition of folate absence, the level of main cyclic form 5-methyl-THF is low[8], which will result in the reduction of the cysteine transforming to methionine, and the available s-adenosine methionine rapidly decreases, the supply of methyl group is insufficient, thus causing DNA hypomethylation.

As shown in Figure 1, the supply of methyl mainly comes from one-carbon metabolism and methionine cycle, and except for folate, the other B-vitamins, including vitamin B12 (VB12), vitamin B6 (VB6) and vitamin B2 (VB2) also indirectly participates in the one-carbon metabolism and methionine circle providing methyl groups for the body's extensive methylation reaction, and thus sustains the normal DNA methylation of the human body.[9]

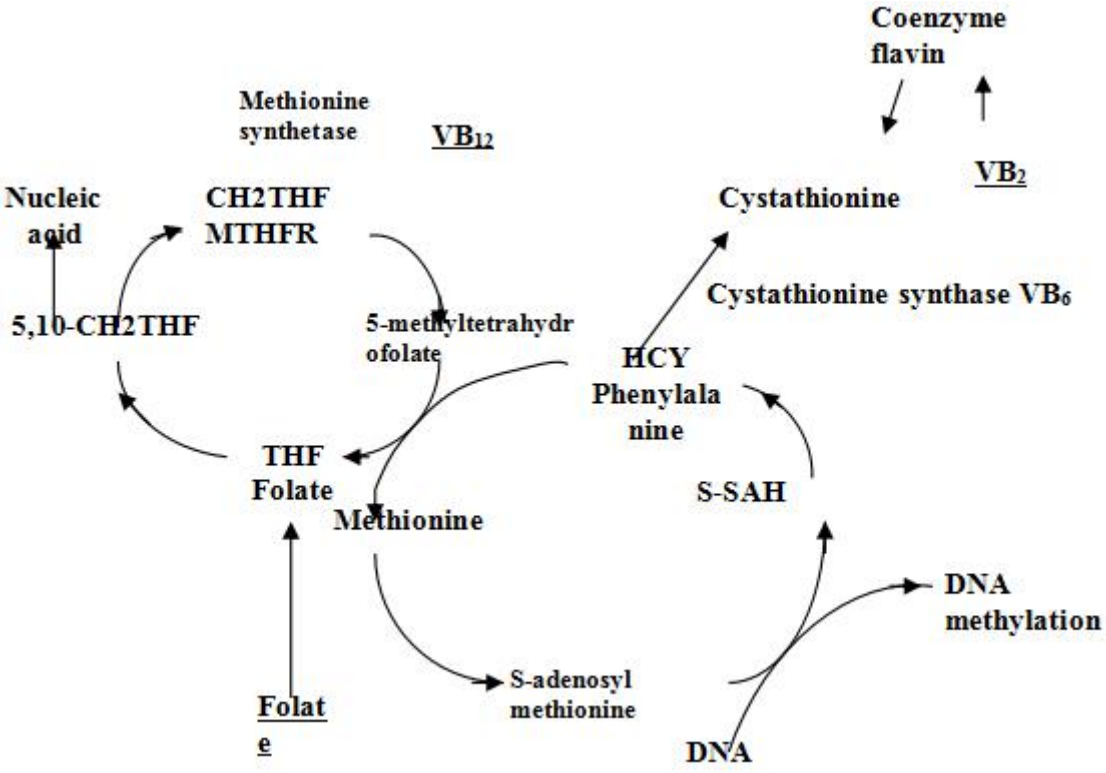

Figure 1 The metabolism of folate,VB_{12},VB_6,VB_2

The above figure shows that folate and B-vitamins related to one-carbon metabolism influence DNA methylation through affecting the supply of the methyl group, and the related process includes one-carbon unit metabolism and methionine cycle. Folate is the donor of methyl, and VitB2, VitB6 and VitB12 play a role regulating the biological activity of methyl groups. As the main coenzyme of the normal reproduction of DNA, B-vitamins promotes methyl tetrahydrofolate to get rid of methyl transforming into tetrahydrofolic acid and methylene tetrahydrofolate to

ensure DNA normal ethylation and sustain the stable essential. DNA methylation is a reversible biological dynamic process, which has many-sided meanings[10]. The normal methylation can sustain biological homeostasis and function, such as gene imprinting, chromosome inactivation, cell differentiation, embryonic development and so on; but the abnormality of the DNA CpG island methylation can cause the tumor suppressor gene to be inactivated and the epigenetics change, which is an important factor in carcinogenesis[11]. Most current studies have focused on folate and cancer, and several B-vitamins and tumors have been focused on other cancers[5] and less studies on esophagus cancer. However, a long-term lack of folate and vitamin B12 may be a factor for the high incidence of esophageal squamous cancer and gastric cardia adenocarcinoma in the Linxian County, according to a study, a high incidence area of esophagus cancer in China[12].

2 The Relationship Between DNA Methylation and Esophagus Cancer

The DNA methylation pattern disorder is common in tumor cells, but the lack of DNA methylation in folate is not consistent with different organs and genes, and the gene methylation associated with esophagus cancer is still being studied. The related gene methylation of esophagus cancer is mainly divided into the following cases: one is the change of hypermethylation of the tumor suppressor genes associated with esophagus cancer, and the other is the change of hypomethylation of the oncogene, or the abnormality of the mismatch repair gene. The detection method of low methylation degree of oncogene is not yet mature and its related research is still in the exploratory stage. This paper mainly summarizes the studies on hypermethylation of the related suppressor genes of esophagus cancer[1].

The CpG island methylation in the promoter region of tumor suppressor gene in the cancerization of esophagus cancer changes gradually, and hypermethylation of CpG island in the promoter region exists in the early stage of esophagus cancer and precancerous stage, which occurs before the change of cell morphology, so the detection of gene methylation is important for early diagnosis of esophageal carcinoma[13]. The current studies on the related gene methylation of esophagus cancer are mainly focused on: P16, FHIT, Rb, secretin 3A1, RUNX3, APC, ER, RASSF1A, OPCML, hMLH1, MGMT and so on[14].

2.1 Tumor Suppressor Gene Methylation and Esophagus Cancer

p16 gene (multiple tumor suppressor 1, MTS) plays a cancer inhibition role through cell cycle regulation. Gene methylation, mutation and deletion of p16 gene exist in many common malignant tumors, such as lung cancer, breast cancer, esophagus cancer, etc., and the p16 gene always as a marker for clinical screening of tumors and prognosis and judgment prognosis. Abbaszadegan et al.[15] compared the promoter methylation of P16 in the normal population with esophagus cancer patients, and found that the rate of methylation in the esophagus cancer group was as high as 64%, but the gene methylation of P16 was not detected in normal people. The hypermethylation of P16 gene may be one of the risk factors for the occurrence of esophagus cancer.

The fragile histidine triad (FHIT) gene achieves the goal of inhibiting cancer incident and development through regulating the cell cycle. FHIT abnormal methylation of genes leads to the inactivation of the gene, which is closely related to the occurrence of esophagus cancer. Xiaoqing Guo et al.[16] studied the methylation of FHIT genes in esophageal epithelial tissue with mild, moderate and severe atypical hyperplasia, squamous cell's carcinoma in situ and invasive carcinoma, found the positive rate was 22.73%, 45.45%, 64.29% and 67.57% respectively, pointed that the gene methylation frequency of FHIT gene was positively correlated with the degree of esophageal epithelial degeneration. The researches of Lee et al.[17] showed that the hypermethylation rate of the FHIT gene in esophageal squamous cell carcinoma was 33%. They pointed that the hypermethylation of the promoter region was the biochemical index of esophageal squamous carcinoma. Guo et al.[18] found that the hypermethylation rate of FHIT gene was 51.58% when detecting esophagus cancer tissue, which could generate 81.63% of expression inactivation rate, and they pointed that the hypermethylation of FHIT gene might be one of the risk factors for the occurrence of esophagus cancer.

Rb gene deletion, rearrangement and hypermethylation change can lead to the occurrence of tumor. Ohtani-Fujita N et al.[19] reported when the Rb gene promoter was in the promoter hypermethylation, the activation activity decreased and the expression was inhibited. Li Huachuan et al.[20] found that in esophagus cancer, Rb gene promoter hypermethylation may cause the Rb gene silencing, and Rb gene deletion, mutation and the inactivation of expression may be one of the risk factors for esophagus cancer.

The secretin-3A1 (secretoglobin23A1, SCGB3A1) is a tumor suppressor gene, and if the gene occurs hypermethylation, the gene will occur gene silencing, the cancer inhibition effect will be deficient and cause the high incidence of cancer. Shuang Liu et al.[21] found that the level of the secretin-3A1 gene promoter methylation in

esophageal squamous carcinoma increased, which caused the expressive inhibition. They pointed that the secretin-3A1 gene promoter hypermethylation might be one of the important factors in esophageal squamous carcinoma.

Human runt-related transcription factor 3 (RUNX3) also is a cancer suppressor gene, and when it occurs hypermethylation, the gene silencing will happen, thus losing cancer inhibition effect. Long et al.[22] pointed that there were 64.3% of 42 esophagus cancer tissues occurring RUNX3 gene promoter hypermethylation, and its promoter hypermethylation and the decreased expression of RUNX3 mRNA had statistical significance ($P < 0.001$).

Adenomatous polyposis coli (APC) gene is the tumor-specific glycoprotein in the wnt signaling pathway. In the detection of esophagus cancer, the universality of APC gene mutation was not high, but the heterozygote frequently losses, which can be concluded that the hypermethylation of the promoter region of this gene is a possible mechanism for the expression of inactivation, therefore, the esophagus cancer occurs. Kim et al.[23] found that in the esophagus cancer that no lymph metastasis existed, the occurrence rate of APC gene promoter hypermethylation was high, pointed that APC gene promoter hypermethylation may be one of the risk factors for the occurrence of esophagus cancer.

Estrogen receptor (ER) is a kind of protein molecule, and it exists more in the cell of target organ, which can combine with hormone to form hormone-receptor compound, make hormone exert a biological effect in the inhibition of the growth and metastasis of tumor. The research shows that the rate of methylation of the ER gene in adenocarcinoma of esophagus is 51%, points that hypermethylation of ER gene is one of the factors for adenocarcinoma of esophagus[24].

RAS association domain family 1A gene (RASSF1A) is a new tumor suppressor gene whose expression losses in multiple malignant tumors, such as lung cancer, breast cancer, ovarian cancer, gastric carcinoma etc., speculating that it is related to RASSF1A gene hypermethylation. Cong et al.[25] compared the condition of RASSF1A gene hypermethylation in esophagus cancer tissues and adjacent normal tissues, found that the methylation rate of esophageal carcinoma was 48.5%, which was significantly higher than that of adjacent tissues (6.1%).

OPCML gene is a molecule on the surface of cells, which belongs to the member of immunoglobulin superfamily. Gui et al.[26] compared esophagus cancer cell line, the primary tumor of esophagus cancer and normal esophageal epithelium OPCML gene promoter region methylation, found that the positive rate is 88%, 66% and 29% respectively, speculated that OPCML gene methylation made the protective effect of normal cell to environmental stress insufficient, thus causing the incurrence of tumor.

2.2 DNA Repair Gene Methylation and Esophagus Cancer

Human mispairing repair gene hMLH1 and hMSH2 are found in multiple cancers, and their expression is silent due to the hypermethylation. Gongyuan Zhang et al.[27] compared the hMSH2 gene promoter methylation status in esophagus cancer tissues and normal mucosal tissue, concluded that the hMSH2 hypermethylation was found in 34.4% of esophagus cancer tissues and no methylation was found in normal mucosal tissue. Vasavi et al.[28] detected the status of hMLH1 gene promoter hypermethylation of esophagus cancer tissue and precancerous lesion issue and the frequency of occurrence of methylation was 63.5% and 53.8% respectively, meant that hMLH1 and hMSH2 gene promoter hypermethylation is the important sign of the incurrence and development of esophagus cancer, and it would increase along with the disease progression.

O6-methylguanine DNA methyltransferase (MGMT) is an enzyme that effectively repairs DNA damage, which can repair the damage of O6-methylguanine (O6-mG) in the DNA sequence. Nakayama K et al.[29] found that MGMT gene promoter hypermethylation could cause the gene express silently in multiple blood malignant cell lines. Lei Zhang et al.[30] compared the status of MGMT gene methylation respectively in esophagus cancer tissues, adjacent tissues and normal esophageal epithelium, and their positive rate was 38.7%, 22.7% and 0.0% respectively. They pointed that there were MGMT gene promoter hypermethylation in esophagus cancer, which might be related to the incurrence of esophagus cancer.

3 Conclusion

The reversible feature of the epigenetics provides new revelations to the cancer preventive medicine of the human race. Daily diet is very closely related to the occurrence of gastrointestinal tumors. People can prevent gastrointestinal tumors such as esophagus cancer by altering their daily diets, adjusting the intake and intake method of nutrients etc.[31]. According to the above review, increasing intake of foods and nutrients such as folate, vitamin B2, vitamin B6, and B12 can prevent esophagus cancer. Ingesting moderate vegetables, fruits, grains and liver, which contain a large amount of B vitamins can prevent the methylation disorders of DNA and has a positive effect on the prevention of esophagus cancer. Although some studies show that the epigenetics can be changed through reasonably regulating diets, increasing intakes of folate and other B-vitamins to prevent the incurrence of esophagus cancer, there is no definite report on this, and the results of the study are contradictory. The

epigenetic mechanisms of esophagus cancer need to be further studied.

References

[1] Guangchang Pang, Qingsen Chen, Zhihe Hu, et,al. The Epigenetic View and Outlook On Food and Nutrition[J]. Food Science, 2011:1-21.

[2] Tiefeng Jin, Meihua Zhang, Zhenhua Lin. Epigenetics of Tumor[J]. Basic & Clinical Medicine, 2011:204-206

[3] Zhendong Hu, Ning Li. The Related Gene Methylation and Nutrient of Esophagus Cancer[J]. *Parenteral & Enteral Nutrition,* 2010:179-185.

[4] Ibiebele TI, Hughes MC, Pandeya N, et,al. High Intake of Folate from Food Sources Is Associated with Reduced Risk of Esophageal Cancer in an Australian Population[J]. Journal of Nutrition, 2011,141:274-283.

[5] Davis CD, Uthus EO. DNA Methylation, Cancer Susceptibility, and Nutrient Interactions[J]. Exp Biol Med (Maywood), 2004,229:988-995.

[6] Lihua Liu, Fangxin Zhang. DNA Methylation Status and Folate in Gastric Precancerous Lesions[J]. World Chinese Journal of Digestology, 2005:2770-2772.

[7] Liang Song. Molecular Epidemiologic Studies on the Relationship Among One-carbon Metabolic Enzyme Gene Polymorphism, Environmental Exposure and Colorectal Cancer[M]. Master Dissertation of Zhejiang University, 2006.

[8] Yurong Wong, Jingyuan Fang, Danfeng Sun, et,al. The Relationship Between Gene Methylation and Expression Related To Tumor in Gastric Cancer Tissue and the Polymorphism of Folate and Metabolic Enzyme MTHFR Gene[J]. World Chinese Journal of Digestology, 2006: 2192-2198.

[9] Guiling Huang. Study on the Relationship among B-vitamins Related to One-carbon Metabolism, Gene Polymorphism and DNA Methylation with Esophagus Cancer and the Precancerous Lesions[D]. Southeast University, 2014.

[10] Robertson KD. DNA methylation and human disease[J]. Nat Rev Genet, 2005,6:597-610

[11] Min Qi, Xianzhao Wei, Aiqun Wu. Study on Epigenetics and Prevention of Esophagus Cancer[J]. Journal of Medical Research, 2009: 20-23.

[12] Stolzenberg-Solomon RZ, Qiao YL, Abnet CC, et,al. Esophageal and Gastric Cardia Cancer Risk and Folate- and Vitamin B(12)-Related Polymorphisms in Linxian, China[J]. Cancer Epidemiol Biomarkers Prev 2003,12:1222-1226.

[13] Huamei Hu. Preliminary Study on the miRNA Gene and DNA Methylation State Related to Esophagus Cancer[D]. Third Military Medical University, 2010

[14] Kuroki T, Trapasso F, Yendamuri S, et,al. Allele Loss and Promoter Hypermethylation of VHL, RAR-beta, RASSF1A, and FHIT Tumor Suppressor Genes on Chromosome 3p in Esophageal Squamous Cell Carcinoma[J]. Cancer Res, 2003,63:3724-3728.

[15] Abbaszadegan MR, Raziee HR, Ghafarzadegan K, et,al. Aberrant p16 Methylation, a Possible Epigenetic Risk Factor in Familial Esophageal Squamous Cell Carcinoma[J]. Int J Gastrointest Cancer, 2005,36:47-54.

[16] Xiaoqing Guo, Shijie Wang, Jianhui Zhang, et,al. Study on the Esophagus Cancer Precancerous Tissue p16 and FHIT Gene Methylation[J]. Chinese Journal of Clinical Oncology, 2005,32,10:554-557.

[17] Lee EJ, Lee BB, Kim JW,et,al. Aberrant Methylation of Fragile Histidine Triad Gene is Associated with Poor Prognosis in Early Stage Esophageal Squamous Cell Carcinoma[J]. Eur J Cancer, 2006,42:972-980.

[18] Guo XQ, Wang SJ, Zhang LW, et,al. DNA Methylation and Loss of Protein Expression in Esophageal Squamous Cell Carcinogenesis of High-Risk Area[J]. J Exp Clin Cancer Res, 2007,26:587-594.

[19] Ohtani-Fujita N, Fujita T, Aoike A, et,al. CpG Methylation Inactivates the Promoter Activity of the Human Retinoblastoma Tumor-Uppressor Gene[J]. Oncogene, 1993,8:1063-1067.

[20] Huachuan Li, Shixin Lu, Luo Feng, et,al. Study on the Effects of Rb Gene Promoter Methylation and Methylbenzyl Nitrosamine to Esophagus Cancer[J]. Chinese Journal of Oncology, 1998: 412-414.

[21] Shuang Liu, Mingzhou Guo, Jiansheng Li, et,al. The Gene Promoter Methylation of Esophageal Squamous Carcinoma Secretin -3a1 Was Abnormal[J]. International Journal of Genetics, 2006: 1-3,19.

[22] Long C, Yin B, Lu Q, et,al. Promoter Hypermethylation of the RUNX3 Gene in Esophageal Squamous Cell Carcinoma[J]. Cancer Invest, 2007,25:685-690.

[23] Kim YT, Park JY, Jeon YK, et,al. Aberrant Promoter CpG Island Hypermethylation of the Adenomatosis Polyposis Coli Gene can Serve as a Good Prognostic Factor by Affecting Lymph Node Metastasis in Squamous Cell Carcinoma of the Esophagus[J]. Dis Esophagus, 2009, 22:143-150.

[24] Brock MV, Gou M, Akiyama Y, et,al. Prognostic Importance of Promoter Hypermethylation of Multiple Genes in Esophageal Adenocarcinoma[J]. Clin Cancer Res, 2003,9:2912-2919.

[25] Cong DG, Wang SF. Hypermethylation of Promoter Region of RAS Association Domain Family Gene1A in Esophageal Squamous Cell Carcinoma and Significance Thereof[J]. Chinese Medical Journal, 2007, 87:2932-2934.

[26] Cui Y, Ying Y, van Hasselt A, et,al. OPCML Is a Broad Tumor Suppressor for Multiple Carcinomas and

Lymphomas with Frequently Epigenetic Inactivation[J]. PLoS One, 2008,3.
[27] Gongyuan Zhang, Chunxiao Ma, Qiuliang Liu, et,al. The hMSH2 Gene Promoter Methylation Detection of Esophagus Cancer Tissue[J]. Chinese Journal of Oncology, 2005:541-543.
[28] Vasavi M, Ponnala S, Gujjari K, et,al. DNA Methylation in Esophageal Diseases Including Cancer: Special Reference to hMLH1 Gene Promoter Status[J]. Tumori, 2006,92:155-162.
[29] Nakayama K, Inokuchi K, Dan K. Hypermethylation of the Putative Tumor-Suppressor Genes DCC, p51/63 and O6-Methylguanine-DNA Methyltransferase (MGMT) and Loss of Their Expressions in Cell Lines of Hematological Malignancies[J]. J Nippon Med Sch, 2005,72:270-277.
[30] Lei Zhang, Deyin Xing, Wen Tan, et,al. MGMT Promoter Methylation of DNA Repair Gene and Esophageal Squamous Cancer[J]. Cancer, 2001: 1335-1338.
[31] Lihong Sun. The Research Progress in the Relationship Between Dietary Factors and Colorectal Cancer[J]. World Chinese Journal of Digestology, 2010:2033-2037.