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

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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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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.\textsuperscript{[9]}

![Figure 1 The metabolism of folate, VB12, VB6, VB2](image)

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\[^{14}\].

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. Abbazadegan et al.\[^{15}\] compared the promoter methylation of P16 in the normal population with esophageal cancer patients, and found that the rate of methylation in the esophageal 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 esophageal 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 esophageal 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 esophageal 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 esophageal 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.\[25\] pointed that there were 64.3% of 42 esophageus 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 esophageus 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 incidence 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 incidence 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 incidence 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 intake of folate and other B-vitamins to prevent the incidence 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


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