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Research Progress on *MTHFR* C677T and A1298C Gene Polymorphisms and Gastrointestinal Tumors

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Abstract

Tumours of the digestive system include a number of malignant tumours such as oesophageal, gastric and colorectal cancers, which have the highest incidence and mortality rates in the world. Their occurrence is related to a variety of factors, such as diet, environment and genetics. As a key enzyme in the process of folate metabolism, *MTHFR* gene polymorphism plays an important role in the pathogenesis and development of gastrointestinal tumours. This paper provides a brief review of the relationship between *MTHFR* polymorphisms and digestive tumours, with a view to identifying the genetic effects of *MTHFR*, exploring the pathogenesis of digestive tract tumours and developing more effective prevention and treatment strategies.

Keywords

MTHFR, Polymorphism, Esophageal Cancer, Gastric Cancer, Colorectal Cancer

1. Introduction

Gastrointestinal tumours are the most common type of malignancy in humans and their occurrence is associated with a variety of factors, including the interaction of genetic, epigenetic and environmental factors [1] [2]. Genetic factors, such as single nucleotide polymorphisms in related genes, and non-genetic factors such as obesity, physical inactivity, smoking and alcohol consumption have been shown to play an important role in the development of tumours [1] [2]. Epidemiological studies have shown that digestive tract tumours have a high morbidity and mortality rate worldwide, especially in Asia [3]. According to relevant surveys, those who die from digestive tumours account for about 36.4% of

all cancer deaths in China, much higher than the 5% in Europe and the United States [3]. Pathophysiological studies have found that the occurrence of digestive tract tumours is related to biological processes such as cell proliferation, apoptosis, DNA damage repair, and also to a variety of genetic variants. Methylenetetrahydrofolate reductase (*MTHFR*) is a key enzyme and important regulator of the pathway of folate metabolism, which catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the major circulating form of folate, and generates methyl donors, thereby affecting DNA synthesis, repair and methylation [4], repair and methylation processes [4]. When mutations occur in the *MTHFR* gene, they cause alterations in enzyme activity, leading to decreased plasma folate levels and hyperhomocysteinemia [5] [6], as well as altered levels of DNA methylation and synthesis, which can affect the risk of many GI cancers, including oesophageal and gastric cancers [7]. Although a large number of clinical studies have explored the statistical relationship between *MTHFR* polymorphisms and GI tumour susceptibility, there is still variability between the findings and the important role of such polymorphisms in the development of tumours remains a hot topic of interest. This paper will focus on the progress of research on *MTHFR* polymorphisms and common GI malignancies, with a view to gaining insight into the pathogenesis of digestive tract tumors and developing more effective prevention and treatment strategies in the future.

2. MTHFR

2.1. The *MTHFR* Gene and Its Genetic Polymorphisms

MTHFR is encoded by the THFR gene located on short chromosome 1-1p36.3 [8]. Several mutations in the *MTHFR* gene have previously been identified, of which C677T (RS1801133) and A1298C (RS1801131) are the two most common mutation types and are clinically important. RS1801133 is located in exon 4 and at position 677th nucleotide converts cytosine (C) to thymine (T), prompting the conversion of alanine to valine at position 222, and has three genotypes: CC, CT and TT [9]. Exon 7, RS1801131, converts adenine (A) to cytosine (C) at nucleotide 1298, prompting a mutation from glutamate to alanine with genotypes AA, AC and CC [10]. This series of alterations leads to reduced enzyme activity and abnormal genomic DNA methylation, which in turn promotes the development of cancer [11].

2.2. The Biological Role of *MTHFR* in Folate Metabolism

MTHFR is a key enzyme in folate metabolism and occupies a central position in maintaining the balance between DNA synthesis and methylation, facilitating the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. The substrate 5,10 methylenetetrahydro-folate is used by thymidylate synthase to methylate dUMP to dTMP. The latter is the sole source of thymidine required for DNA synthesis and repair, and its product functions as a

methyl donor required for the remethylation of homocysteine to methionine [4].

Reduced activity of the *MTHFR* pathway inhibits the production of 5-methyltetrahydrofolate and may lead to the accumulation of substrates. Reduced levels of *MTHFR* products lead to increased levels of homocysteine and reduced levels of folate in the blood. The means of folate synthesis and DNA repair are displaced by the decrease in blood folate levels [12]. Circulating folate is a co-substrate for the remethylation of homocysteine to methionine, which is the precursor. Methionine is a precursor of S-adenosylmethionine (SAM), which is the primary methyl donor [13]. Low levels of folate and/or reduced enzymatic activity of the major proteins involved in folate metabolism may lead to reduced activity of the major proteins involved in folate metabolism and may result in limiting the substrate for methionine synthase, thereby affecting the remethylation pathway and resulting in high plasma concentrations of homocysteine. High plasma concentrations of homocysteine are associated with a variety of diseases including cancer [14].

2.3. *MTHFR* Gene Polymorphisms and Abnormal Folate Metabolism as Major Oncogenic Mechanisms

Folic acid is a B vitamin that is essential for human metabolism. Folic acid plays a key role in the formation of SAM, a common methyl donor for DNA methylation, and also plays an important role in the formation of purines and thymidine [13]. Previous studies have shown that uracil is incorporated into DNA molecules in the presence of folate deficiency; during repair, uracil glycosylase may lead to DNA molecular breaks, resulting in damage and chromosomal translocations, a marker of genomic instability that may contribute to tumour progression [15] [16] [17], and as such, some cancer researchers have suggested that the level of *MTHFR* activity, a key enzyme in folate metabolism, is another important factor influencing the risk of developing certain types of cancer.

Polymorphisms in the *MTHFR* gene result in reduced enzyme activity and lead to decreased plasma folate concentrations. Folate deficiency may increase the risk of tumour development through one of the following mechanisms [15]: by causing abnormal DNA methylation, which alters the expression of key oncogenes and proto-oncogenes; or by causing imbalances in the pool of nucleotide precursors, leading to DNA strand breaks and mutations that disrupt DNA integrity and repair. This is further explained by the work of Taioli [12]: DNA hypo methylation and uracil misincorporation into DNA, both mechanisms are implicated in the development of cancer. These mechanisms are shown in **Figure 1**. Deficiency in *MTHFR* enzyme function decreases the utilisation of 5-methyltetrahydrofolate, leading to a subsequent decrease in the conversion of homocysteine to methionine. This folate depletion may lead to DNA hypomethylation, which in turn affects cell development and function. Any aberrations in DNA methylation may be involved in the cancer process. Secondly, due to folic acid deficiency, low levels of 5,10-methylenetetrahydrofolate reduce the

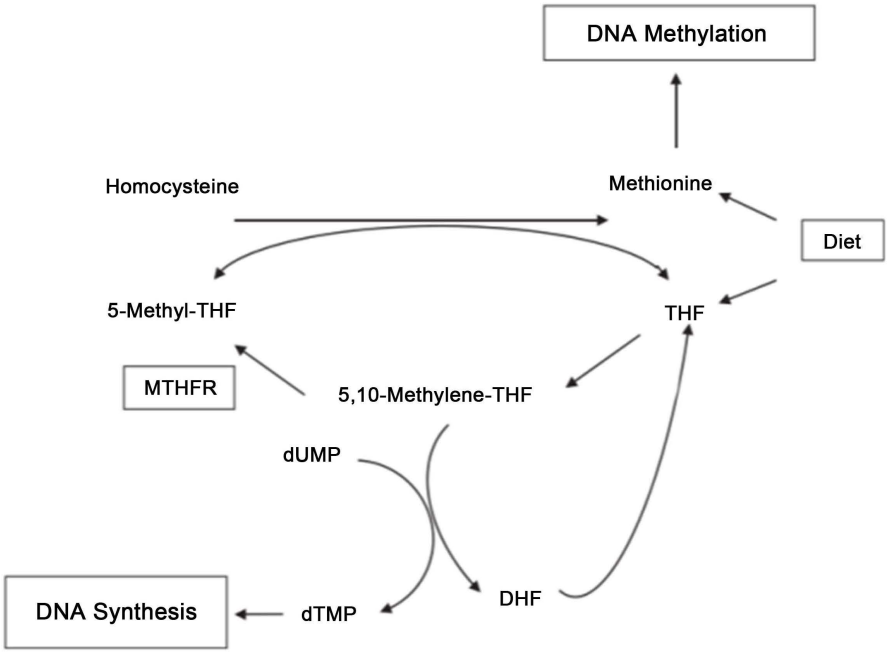

Figure 1. (from Taioli E *et al.* [12]): Schematic diagram of folate metabolism - dihydrofolate (DHF, dihydrofolate); deoxythymidine monophosphate (dTMP, deoxythymidine monophosphate); deoxyuridine monophosphate (deoxyuridylate) (dUMP. deoxyuridine monophosphate (deoxyuridylate)); methylenetetrahydrofolate reductase (MTHFR); tetrahydrofolate (THF, tetrahydrofolate).

synthesis of thymidylic acid deoxythymidine monophosphate and increase the ratio of deoxyuridine monophosphate to deoxythymidine monophosphate, leading to uracil misadulteration. This process leads to DNA damage (e.g. point mutations and/or chromosome breaks), which may be associated with carcinogenesis.

Another study showed two common single nucleotide polymorphisms in *MTHFR*, *MTHFR*C677T and A1298C. Of these, the C677T variant enhances enzyme thermolysis and is associated with reduced *MTHFR* enzyme activity [18] and the A1298C variant is a missense mutation that causes reduced *MTHFR* enzyme activity [19]. *MTHFR*C677T and pure genotypes of A1298C are associated with high homocysteine levels, which may lead to DNA hypomethylation and increased cancer prevalence. However, reduced enzyme activity leads to increased levels of 5,10-methylenetetrahydrofolate and thymidine, which increase DNA synthesis and repair. Therefore, *MTHFR* polymorphisms are considered to be protective factors against tumour development [18] [20].

3. Association of *MTHFR* C677T and A1298C Gene Polymorphisms with Common Gastrointestinal Tumors

3.1. Correlation of *MTHFR* Gene Polymorphisms with Oesophageal Cancer

Esophageal cancer (EC) is the eighth most common cancer worldwide, with a 5-year survival rate of approximately 10%, similar mortality and morbidity, high

lethality and lymph node metastasis, which, together with its rapid progression, explain the poor prognosis of the disease [21] [22]. Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) are the main histological types of oesophageal cancer. In addition, the main types of oesophageal cancer develop differently by ethnicity. In China, the predominant histological subtype is ESCC, whereas in Europe and the United States, the predominant histological subtype is EAC [23]. Low folate diet, high temperature food intake, chronic mucosal irritation and especially alcohol and tobacco consumption have been described as risk factors for oesophageal cancer [24]. However, not all exposure factors lead to oesophageal cancer, suggesting that genetic factors play an important role in the development of oesophageal cancer. Mutations in *MTHFR*, a key enzyme in folate metabolism, lead to reduced plasma folate levels and hypomethylation of genomic DNA, activating oncogenes and leading to DNA strand breaks and chromosome disruption, thereby promoting cancer development [23].

During 2013 a meta-analysis on *MTHFR* showed that the A1298C polymorphism was associated with an increased risk of EC in Asians and Caucasians and may influence the risk of ESCC and EAC [25]. The following year, a case-control study from a region with a high prevalence of EC in China showed that there may be no correlation between the *MTHFR* C677T gene polymorphism and EC pathogenicity, but an association with susceptibility to precancerous oesophageal lesions. This study also found a statistically significant difference in the distribution of the *MTHFR* 677TT genotype in the moderate to severe EC precancerous lesion group compared to the T allele distribution in the moderate group, suggesting that individuals with the *MTHFR* 677TT variant genotype and T allele are at higher risk of developing EC precancerous lesions [26]. However, a study by Tang *et al.* in the same year showed that *MTHFR* RS1801133 C > T SNPs may be genetic modifiers for the development of ESCC in the Chinese Han population [27]. Subsequently, Yang Z *et al.* [28] conducted a meta-analysis of eight studies based on the Chinese Han population with a combined OR of 1.86 and 95% confidence interval of 1.21 - 2.86, indicating a significantly increased risk of oesophageal cancer in patients with TT/CT of the *MTHFR* genotype. In addition, a study exploring the relationship between methylation of genes related to folate metabolism in Kazakhs and the incidence and prognosis of oesophageal cancer found that serum folate levels were significantly lower in the cancer group than in the non-cancer group, and the rate of *MTHFR* methylation was significantly higher in the test group than in the control group. This suggests that low serum folate levels are a risk factor for oesophageal cancer in Kazakhs and that methylation of *MTHFR* is closely associated with oesophageal cancer tumorigenesis [29]. However, a recent study [24] showed no association between the *MTHFR*677C > T and 1298A > C polymorphisms and susceptibility risk for oesophageal cancer, and that the polymorphic pure-hybrid genotype *MTHFR* 677TT was associated with a higher risk of death after surgical treatment of oesophageal cancer. Another study from Turkey [30] showed that carriers of the

1298AC genotype had a 2.98-fold higher risk of EC than carriers of the 1298AA genotype, and that the A1298C polymorphism on the *MTHFR* gene may be a risk factor for oesophageal cancer in eastern Turkey, however, the 677TT genotype was not associated with a significantly different risk of oesophageal cancer compared to the 677CC genotype, and suggested that that these polymorphisms may have no impact on the life expectancy of patients. The discrepancy between these findings reminds us that the carcinogenic effects of *MTHFR* polymorphisms may differ by ethnicity and histological type, and that future basic studies with larger sample sizes and more comprehensive studies are still needed to explore this association.

3.2. Correlation of *MTHFR* Gene Polymorphisms with Gastric Cancer

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related death, with an average five-year survival rate of only 20%, resulting in nearly 800,000 deaths each year [13]. *H. pylori* infection, age, lifestyle habits and diet (e.g. high salt intake, low fruit and vegetables) have been shown to be risk factors for gastric cancer. It has been shown [31] that mutations in the *MTHFR* gene leading to abnormal DNA methylation are an important feature in the early stages of GC development, allowing demethylation and activation of gene expression of GC-associated proto-oncogenes. Similarly, as a risk factor for GC, low folate levels caused by H. pylori interact with *MTHFR* polymorphisms to exacerbate the disruption of gastric mucosal integrity, thereby inducing the development of gastrointestinal malignant disease [32].

In a case-control study [33] of a Chinese Han population, single nucleotide polymorphisms in *MTHFR*RS1801133 were found to increase GC risk in both recessive (OR = 1.31, 95% CI, 1.01 - 1.70; p = 0.042) and log-additive models (OR = 1.19, 95% CI, 1.02 - 1.38; p = 0.025) in terms of GC risk. However, another hospital-based case-control study [34] showed that the RS1801133-TT genotype was associated with a significantly lower risk of gastric cancer in a Han Chinese population and that this association was evident in older patients and in patients who never drank alcohol. a prospective study by Öksüz E [30] showed that the *MTHFR* RS1801131 polymorphism may be a gastric cancer in eastern Turkey risk factor, with individuals with AC and CC genotypes having a 4.13-fold (P = 0.001) and 2.19-fold (P = 0.027) higher risk of GC than those carrying the AA genotype, respectively, however, individuals with the TT genotype with the C677T polymorphism did not have a higher risk of gastric and oesophageal cancer compared to those with the 677CC genotype, and *MTHFR* RS1801133 was not associated with the risk of developing GC. A recent meta-analysis [35] showed that the *MTHFR* C677T polymorphism increased the risk of GC in Asians and Caucasians and was positively associated with cardia, intestinal and diffuse GC, whereas the *MTHFR* A1298C polymorphism was not associated with GC risk, but *MTHFR* A1298C was found to reduce GC risk in a hospital-based subgroup analysis, which is consistent with two other studies [36] [37] results.

However, all these statistical associations were considered as false positive results after credibility assessment. Several baseline experiments reported that supplementation with [38] folic acid reduced GC rates in mice infected with H. pylori, mainly through enhanced DNA methylation and inhibition of the inflammatory response, suggesting that it may be that folate metabolism plays an important role in the development and progression of malignancy. Another study gave a more detailed explanation: altered activity of folate metabolizing enzymes or insufficient folate intake leads to DNA hypomethylation, which affects DNA synthesis and consequently DNA stability and expression of proto-oncogenes and oncogenes, all of which are closely associated with tumour development [39]. Although the association between *MTHFR* polymorphisms and clinical prognosis in GC patients has been established in many populations, however, these results remain somewhat controversial, suggesting that the relationship between *MTHFR* and GC risk is a complex issue, and in addition, factors such as sample source and different SNP detection methods may have had an impact on the results, suggesting that we still need to conduct future multi-centre larger sample size, well-designed studies including gene environment interaction assessment to confirm our findings.

3.3. Correlation of *MTHFR* Gene Polymorphisms with Colorectal Cancer

Globally, more than 1.9 million new cases of colorectal cancer (CRC) were reported in 2020, with a mortality rate of 50%, making CRC the third most common malignancy in adults [40] [41]. It has been shown [42] that colorectal carcinogenesis is a complex multi-step process involving multiple oncogenes and oncogenes alterations induced by the interaction of multiple factors. Also, other factors such as alcohol, low methionine, low folate diet, heavy alcohol consumption, smoking and environmental carcinogens have been suggested as possible risk factors. However, not all individuals exposed to these exogenous risk factors develop CRC, suggesting that individual susceptibility factors may play an important role in the development of tumours.

Several case-control association studies of *MTHFR* gene polymorphisms and CRC have been reported in different populations with contradictory results. Kim [43] *et al.* performed a polymorphism analysis of *MTHFR* (677C > T and 1298A > C) in 477 colorectal cancer cases and 514 controls in Korea, and although no correlation was found in the overall sample, a stratified analysis found that plasma folate ≤ 4.12 ng/ml, *MTHFR* 677CT/1298AC was associated with a significantly increased risk of CRC, suggesting that we can reduce the incidence of CRC to some extent with folic acid supplementation. However, both a case-control study and a meta-analysis conducted by Haerian in an Iranian population showed that RS1801133 was not associated with CRC risk and its characteristics [44]. Furthermore, a study conducted in Han Chinese found that the *MTHFR* RS1801133 polymorphism reduced the risk of CRC [45]. Notably, a meta-analysis [46] that included 91 case-control studies (37,049 cases and 52,444

controls) found that the RS1801133 polymorphism significantly reduced the risk of CRC after excluding 13 studies with greater heterogeneity and HWD, and was significantly associated with Asian ethnicity (OR = 0.94, 95% CI = 0.89 - 1.00), suggesting that the large variability between our current studies may have contributed to the conflicting results. In addition Lin *et al.* [47] found that the variant T allele of *MTHFR* RS1801133 had lower CRC susceptibility than the wild-type C allele, and for gene-lifestyle interactions, the *MTHFR* RS1801133 T allele was significantly protective against CRC risk in non-smokers, former smokers and non-drinkers, but not in drinkers. Panprathip [48] *et al.* similarly found that low folate status was associated with higher CRC risk, particularly in a Thai population with the *MTHFR*677C > T gene polymorphism. However, Baghad *et al.* showed a statistically significant association between the *MTHFR*677T variant and the risk of sporadic colorectal carcinogenesis in a Moroccan population, CT genotype and its combination with TT genotype and allele T were associated with increased risk of CRC, but the pure-hybrid TT was not a protective factor. A recent study [49] showed that the *MTHFR* gene was associated at the genetic level with disease-free survival and CRC-specific survival in CRC patients, and the association of the gene with CRC outcome appeared to be modulated by alcohol consumption and fruit intake. Notably, Teng [42] and Haerian BS [50] studies presented a different view, stating that the *MTHFR* A1298C polymorphism was positively associated with susceptibility to CRC, which may be due to inconsistent genetic modeling. Differences in the association between polymorphisms in genes related to folate metabolism and the risk of CRC in different studies may be explained by genetic heterogeneity in different populations and clinical heterogeneity in different studies [51]. Interestingly, Lathrop *et al.* [52] found that people with the MTHFR677TT genotype had a reduced risk of colorectal cancer when folic acid intake was adequate, but not when folic acid deficiency was present. The reason for this may be that the body has sufficient methyl donors to ensure normal DNA methylation and reduce the risk of DNA damage under adequate folic acid conditions. Meanwhile, other experts have suggested a dual role for folic acid in CRC, whereby a moderate increase in diet before tumour foci are established can inhibit tumor development in normal tissues, while over-supplementation with folic acid can promote tumorigenesis once early lesions are established [53], but extensive basic research is still needed to further validate this claim.

4. Conclusion

Overall, the pathogenic process of cancer is complex and multifactorial, and *MTHFR* gene polymorphisms may be an important genetic risk factor for a variety of health conditions, including digestive tumors. As you can see, although there are significant differences between the results of the studies, there is no denying that *MTHFR* gene polymorphisms play an important role in the development of GI malignancies. These significant differences may be influenced by the type of samples included, the size of the sample, the method of SNP detec-

tion, and in addition, the SNPs of the *MTHFR* gene are highly variable across geographic regions and ethnic groups, so more research is needed to fully understand the genetic effects and pathogenic mechanisms of *MTHFR* gene polymorphisms, and to identify potential prevention and treatment strategies. Future studies should explore the complex interactions between *MTHFR* polymorphisms and other genetic and environmental factors in order to identify high-risk groups and develop personalized prevention and treatment strategies.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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