Review

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Impact of methylenetetrahydrofolate reductase gene polymorphism on cancer and thalassemia incidence

Arzu Dadashova[A,D], **Mahira Amirova**[B,C], **Gulnara Azizova**[E], **Farah Mammadova**[F]

Azerbaijan Medical University, Baku

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The aim of this study is to assess the risk of cancer and thalassemia development in patients carrying methylenetetrahydrofolate reductase (MTHFR) gene polymorphism. The study emphasizes the role of folate deficiency in methionine metabolism, a process known to affect the immune system and coagulation, potentially influencing tumor development and complications associated with thalassemia.

Material and methods. This review article examines existing research on the association between MTHFR gene polymorphisms and their potential link to cancer and thalassemia. A comprehensive literature search was conducted using databases such as PubMed, Google Scholar, and other reputable scientific sources, with a focus on studies published since 2010. Only those studies that investigated the relationship between MTHFR polymorphisms, hypercoagulability, and immune function, and that provided sufficient statistical data, were included in the analysis.

Results. MTHFR gene polymorphism directly affects all processes related to methionine metabolism. Folate deficiency negatively impacts the synthesis of proteins involved in the anticoagulant system and the synthesis of genetic material for rapidly proliferating cells, leading to anemia, thrombocytopenia, and lymphocytosis. On one hand, a decrease in the activity of actively proliferating cells may seem beneficial in tumor treatment. However, the negative impact of folate deficiency on the immune system, particularly T-cells, creates favorable conditions for tumor escape and immune surveillance failure. The association between MTHFR gene polymorphism and complications related to a hypercoagulable state in patients with thalassemia remains controversial: some scientists report a statistically significant relationship, while others largely refute this claim.

Conclusions. MTHFR gene polymorphism may influence the risk of cancer and thalassemia through its effects on folate metabolism, immune function, and coagulation. Further studies are needed to clarify the relationship between MTHFR gene polymorphism, hypercoagulability, and immune system dysfunction in these conditions.

Ключові слова: рак, гомоцистеїн, метилентетрагідрофолатредуктаза, поліморфізм, таласемія.

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Вплив поліморфізму гена метилентетрагідрофолатредуктази на частоту пухлинного росту та таласемії

Арзу Дадашова, Махіра Амірова, Гульнара Азізова, Фарах Мамадова

Мета роботи – оцінювання ризику розвитку раку та таласемії у пацієнтів із поліморфізмом гена метилентетрагідрофолатредуктази (MTHFR).. У дослідженні наголошено на ролі дефіциту фолієвої кислоти в метаболізмі метіоніну, що, як відомо, впливає на імунну систему та процеси згортання крові, потенційно відіграючи важливу роль у розвитку пухлин та ускладнень, які пов'язані з таласемією.

Матеріали й методи. Проаналізовано наукові праці, присвячені зв'язку між поліморфізмами гена MTHFR та їхнім можливим впливом на розвиток раку й таласемії. Здійснили пошук літератури в наукометричних базах даних PubMed, Google Scholar та інших авторитетних наукових джерелах з акцентом на дослідження, опубліковані після 2010 року. До аналізу залучали лише ті праці, де вивчали зв'язок між поліморфізмами MTHFR, гіперкоагуляцією та функціонуванням імунної системи та які містили достатні статистичні дані.

Результати. Поліморфізм гена MTHFR безпосередньо впливає на всі процеси, пов'язані з метаболізмом метіоніну. Дефіцит фолієвої кислоти негативно впливає на синтез білків, які беруть участь в антикоагулянтній системі, а також на синтез генетичного матеріалу для клітин, що швидко проліферують. Це призводить до анемії, тромбоцитопенії та лімфоцитозу. З одного боку, зменшення активності клітин із високим рівнем проліферації може здаватися позитивним чинником у лікуванні пухлин. Проте негативний вплив дефіциту фолатів на імунну систему, зокрема на Т-клітини, створює сприятливі умови для уникнення пухлиною імунного нагляду та порушення протипухлинної відповіді. Зв'язок між поліморфізмом гена MTHFR та ускладненнями, що пов'язані з гіперкоагуляцією у пацієнтів із таласемією, залишається суперечливим: одні дослідники повідомляють про статистично значущу асоціацію, а інші переважно її заперечують.

Висновки. Поліморфізм гена MTHFR може впливати на ризик розвитку раку та таласемії через зміни у метаболізмі фолатів, роботі імунної системи та процесах згортання крові. Для уточнення зв'язку між поліморфізмом MTHFR, гіперкоагуляцією та порушеннями імунної відповіді за цих станів необхідні подальші дослідження.

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This study advances current understanding of the relationship between methylenetetrahydrofolate reductase (MTHFR) gene polymorphism and the risks associated with cancer and thalassemia. Its novelty lies in comprehensively investigating the impact of folate metabolism on immune function and hypercoagulability within the context of these conditions.

This represents a relatively underexplored area in current biomedical research. The study emphasizes the role of folate deficiency in methionine metabolism, a process known to affect the immune system and coagulation processes, thereby potentially contributing to tumor development and complications associated with thalassemia.

Aim

The aim of this study is to assess the risk of cancer and thalassemia development in patients with methylenetetrahydrofolate reductase gene polymorphism, with particular emphasis on the role of folate deficiency in methionine metabolism, which is known to affect the immune system and coagulation processes, potentially playing an important role in tumor development and complications associated with thalassemia.

Material and methods

This review article examines existing research on the association between MTHFR gene polymorphisms and their potential link to cancer and thalassemia. A comprehensive literature search was conducted using databases such as PubMed, Google Scholar, and other reputable scientific sources, with a focus on studies published since 2010. Only those studies that investigated the relationship between MTHFR polymorphisms, hypercoagulability, and immune function, and that provided sufficient statistical data, were included in the analysis.

This study advances current understanding of the relationship between MTHFR gene polymorphisms and the risks associated with cancer and thalassemia. Its novelty lies in the comprehensive investigation on the impact of folate metabolism on immune functions and hypercoagulability within the context of these conditions, a relatively underexplored intersection in current biomedical research.

Results

Methylenetetrahydrofolate reductase, a folate cycle enzyme, and its polymorphism. MTHFR, methionine synthase, and cystathionine synthase are referred to as folate cycle enzymes; they are directly involved in the synthesis of methionine and reutilization of homocysteine, thereby reducing the manifestations of homocysteinemia. Homocysteine is an amino acid involved in metabolism and interacts with MTHFR, influencing folate metabolism. Thus, homocysteine is one of the methionine methylation cycle metabolites. In this cycle, methionine is methylated under the action of active folate to S-adenosylmethionine *(Fig. 1, (1))*, which then, donating a methyl group in methyltransferase reactions, is converted to homocysteine *(Fig. 1, (2))*. Reverse methylation of homocysteine to methionine closes the cellular methylation cycle catalyzed by methionine synthase *(Fig. 1, (3))* using 5-methyltetrahydrofolate (5-MTHF) as a methyl group donor, as well as vitamin B12 as a folate activator.

In addition, under the action of vitamin B6-dependent cystathionine synthase, part of homocysteine is metabolized to its final product, which is further excreted by the kidneys [1,2]. Homocysteine remethylation decreases with a lack of any component involved in the methylation cycle; the result of such disorders is the accumulation of homocysteine in the body leading to the activation of coagulation, autoimmune diseases, and the weakening of the anticoagulant system, resulting in thrombophilia and vascular damage [3].

MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-MTHF *(Fig. 1, (4))* and thus, is responsible for the activation of folic acid.

Therefore, MTHFR is the main enzyme of the folate cycle. It converts all inactive forms of folate – both those that have entered the body, including synthetic folic acid in tablets, and those that are in cells – into biologically active 5-MTHF. Dysfunction of this enzyme, the activity of which in the heterozygous form of polymorphism is reduced by 30 % from the original, and in the homozygous form – by 60 %, leads to a sharp decrease in the formation of active folates and the development of folate deficiency [4].

The polymorphism of MTHFR gene is accompanied by a violation of the methylation and thus, formation of MTHF necessary for the methionine synthesis from homocysteine [5]. This shifts the methionine cycle towards the breakdown of methionine with the stable formation of homocysteine. The most common violation of the MTHFR enzyme, as in the case of dysfunction of many other proteins, occurs due to congenital polymorphism in its genes. There are 34 known rare deleterious MTHFR mutations and 9 polymorphisms (common variants). The homozygous form of MTHFR mutations is found in 15–20 % of the population, heterozygous – in 40–60 % [2]. A homozygous variant of the C677T has about 30 % wild-type function [4]. A heterozygous variant of MTHFR C677T polymorphism (one normal and one mutated copy, when enzyme activity is reduced by 30–40 % compared to the norm) has about 60 % wild-type function. There are also homozygotes with the A1298C MTHFR polymorphism, in which about 60 % of the wild-type enzyme activity is detected [6]. In individuals with two mutant copies of this gene (homozygous mutation), the activity of MTHFR is practically zero. There are also people with homozygous mutations in one enzyme gene or heterozygous mutations in both enzyme genes.

The 677C→T polymorphism, in position 677 of which the pyrimidine base “C” can be replaced by “T” is the most common genetic cause of hyperhomocysteinemia 6. This single nucleotide polymorphism of the MTHFR gene C677T is also referred to as 677 C>T or 677 C→T. Since each person has two copies of MTHFR gene, one from each parent, MTHFR variants may arise, resulting in the genotypes 677 CC, 677 CT, and 677 TT [7]. Most scientists generally agree that MTHFR polymorphisms, especially C677T, are associated with heart disease, cancer, inflammatory conditions, diabetes, and vascular disease. It is believed to be the most common cause of hyperhomocysteinemia, a risk factor for vascular disease. The C677T polymorphism leads to the substitution of alanine with valine in the MTHFR polypeptide chain, after which the activity of this enzyme decreases at temperatures above 37 °C, but according to

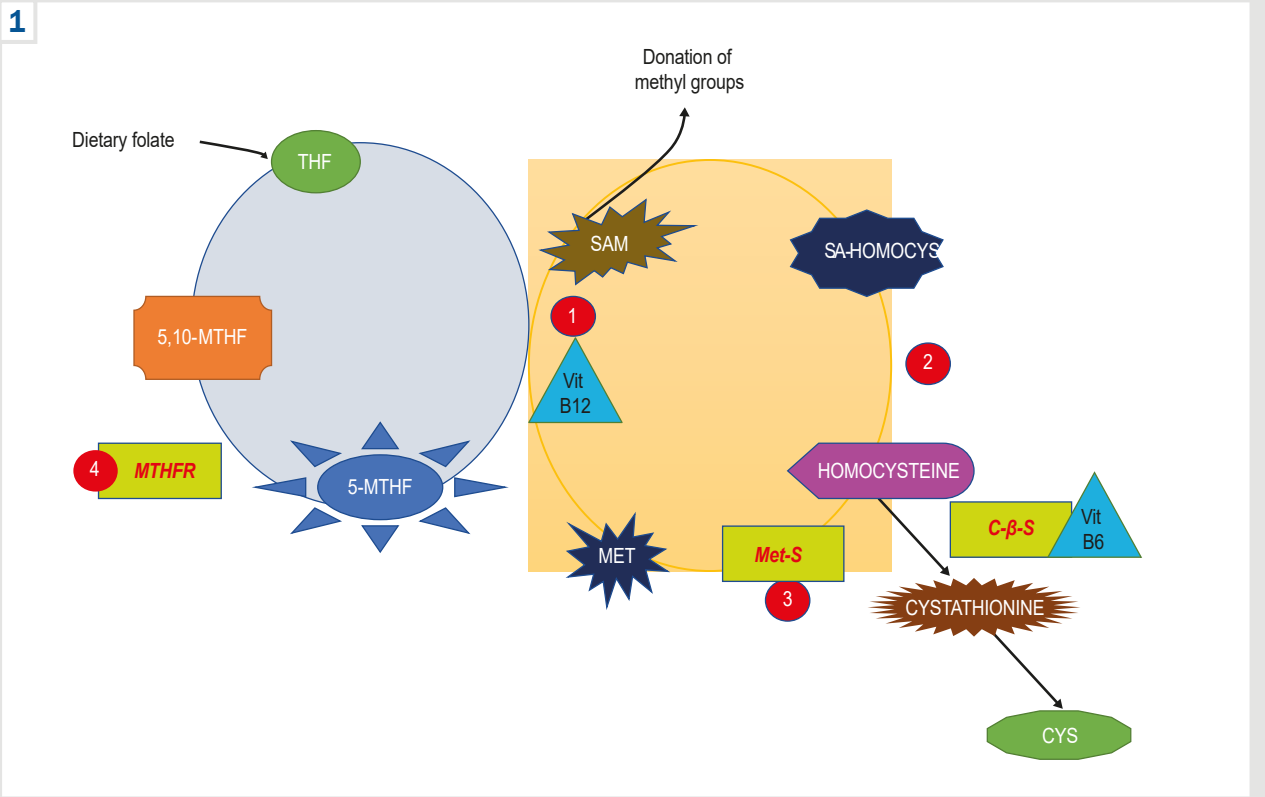

Fig. 1. Enzymes and intermediates of the folate cycle.

Enzymes: MTHFR (4) – methylenetetrahydrofolate reductase, **Met-S (3)** – methionine synthase, **C-β-S** – cystathionine-β-synthase; **intermediates: THF** – tetrahydrofolate, **5,10-MTHF** – 5,10-methylenetetrahydrofolate, **5-MTHF** – 5-methyltetrahydrofolate, **Met** – Methionine, **SAM (1)** – S-adenosylmethionine, **S.A.-Homocys (2)** – S-adenosyl homocysteine, **Cys** – Cysteine. The figure was produced by the authors.

S. Raghubeer and T. E. Matsha, this polymorphism cannot be used to predict the development and progression of cardiovascular diseases [8].

Homocysteinemia as an independent factor in cardiovascular disease development, and vitamin interventions. Homocysteine is now recognized as a pro-atherogenic factor that increases the risk of cardiovascular disease. Homocysteinemia contributes to the formation of atherosclerotic plaques and cardiac ischemia [9,10]. The lack of vitamins B12, B9 and B6 is among the causes of an increase in plasma homocysteine levels. A randomized analysis of 37,485 patients' data has revealed that the complex intake of folic acid with vitamins B6 and B12 reduced the risk of stroke by 18 % [11].

It has been found that supplementation with these vitamins decreased homocysteine by 32 % [12]. Refsum H. et al. state that an increased level of homocysteine above 10 μmol/l leads to an increased risk of coronary heart disease, as well as malignant neoplasms; high homocysteine levels also correlate with early mortality [13]. Folate-dependent methylation is indispensable for the synthesis of myelin, the main component of nerve fibers, which provides their insulation, essential for conducting nerve impulses. So, the coordinated work of the nervous system is impossible without this vitamin [14].

The activity of the folate cycle enzymes methionine synthase and cystathionine synthase depends on the presence of vitamins B12 and B6 in the cell. Therefore, saturating the body with these vitamins can help to quickly eliminate the accumulated pool of homocysteine. However, the situation with hereditary homocysteinemia is much more complicated, when polymorphism of these genes leads to insufficient activity of these enzymes [15].

Folic acid is involved in the process of replication, and therefore the lack of this vitamin adversely affects rapidly proliferating cells, primarily epithelial and blood cells. A decrease in the pool of DNA and RNA in epithelial cells slows down the regeneration, healing of the skin and mucous membranes, a process that sometimes ends with malignant degeneration. The lack of genetic material (impaired replication) forces the body to be content with a small number of cells, which leads to anemia, leukopenia and thrombocytopenia. L-5-methyl-tetrahydrofolate (L-5-methyl-THF) is the only form of folic acid normally found in the bloodstream, and therefore taking L-5-methyl-THF may have advantages over folic acid in reducing hematological symptoms of deficiency. L-5-methyl-THF is especially relevant when prescribing drugs that reduce the activity of dihydrofolate reductase (methotrexate used to treat certain types of cancer, for example, acute lymphoblastic leukemia, non-Hodgkin's lymphoma) [16].

The vast majority of the population is deficient in folic acid, and sometimes this is not due to a lack of intake of folate-containing foods, but to low activity or even the absence of folate cycle enzymes. This is also facilitated by the polymorphism of the enzymes of the folate cycle.

Folate deficiency, MTHFR C677T polymorphism and cancer risk. Recently, it has been found that disorders leading to folate deficiency are associated with breast cancer, as well as cancerous and precancerous conditions in the abdominal organs [17,18]. Physicians state that people with the homozygous mutation of MTHFR have non-standard health problems. The risk of breast cancer has also been found to be approximately two and three times increased in the presence of C677T and A1298C polymorphisms, respectively. As for the A1298C polymorphism, it is associated with an increased risk of breast cancer recurrence with lymph node involvement. Women with the folate reductase gene polymorphism are at high risk of developing malignant diseases [19].

Being rapidly proliferating, malignant cells are the most sensitive to metabolic disorders due to folate deficiency. On the other hand, folate deficiency, by leading to hyperhomocysteinemia, additionally reduces the body's resistance to tumors through the T-cell immune system [20]. Oncological risk increases both with folate deficiency and with an overdose of synthetic folic acid. Thus, the consumption of at least 100 μg/day of folates with the diet significantly reduces the risk of malignant diseases [21], while 400 μg/day of synthetic folic acid, on the contrary, increases the risk of tumors [22,23].

MTHFR C677T polymorphism and thalassemia risk. Due to the development of hypercoagulability, patients with thalassemia major have an increased risk of thromboembolic complications. Mutation of MTHFR, C677T, is considered a possible risk of thrombosis [24]. Data from F. Moreira Neto et al. suggest that the MTHFR C677T polymorphism may be a risk factor for vascular complications resulting in a hypercoagulable state in sickle cell disease, probably due to folate deficiency causing hyperhomocysteinemia [25].

Abd-Elmawla M. A. et al. have found that the prevalence of the MTHFR 677TT genotype was high among patients with β-thalassemia (12 %) compared with the control group. In addition, all patients with β-thalassemia who were found to have the TT genotype suffered from hyperhomocysteinemia and had lower folic acid levels than patients with the CT or CC genotypes. Such patients suffered from oxidative stress, elevated plasma concentrations of MDA and oxidized LDL, as well as decreased HDL.

These data are consistent with the results of studies by El Edel RH and colleagues, according to which the MTHFR 677TT genotype is significantly higher in patients with beta-thalassemia major (23.3 %) compared with the control group (5 %) [26]. However, he results of these investigations are questionable and uncertain. Conversely, according to N. Nigam et al., a meta-analysis of 645 patients' data with severe beta-thalassemia has not shown a significant association between MTHFR C677T gene polymorphism and beta-thalassemia major [27].

According to N. Y. Mustafa et al. natural inhibitors of blood clotting, such as protein C, protein S and antithrombin are significantly reduced in patients with beta-thalassemia major, but hyperhomocysteinemia and the MTHFR C677T mutation are not considered significant risk factors for thromboembolic complications in them [28]. The data coincide with the results of the study by H. Murad et al. When examining patients with thalassemia intermedia, they observed no significant difference in the distribution of heterozygous forms of MTHFR in the control and thalassemic groups (36 % CC, 46 % CT and 18 % TT versus 43.33 % CC, 43.33 % CT and 13.33 % TT) [29].

Generally, there is a relationship between some gene polymorphisms and different diseases, such as CTLA4, TNF-α, and PTPN22 gene polymorphisms and autoimmune thyroiditis [30]. However, the existence of a relationship between thalassemia and MTHFR gene polymorphism is unproven and requires additional research to elucidate the molecular mechanisms leading to serious coagulopathic problems in some thalassemics. Additional studies are needed to elucidate the coupling of the MTHFR gene polymorphism with thalassemia major.

Although a substantial body of data has been reviewed, discrepancies between studies investigating the association between MTHFR polymorphisms and cancer or thalassemia warrant further analysis. For instance, while certain studies report a correlation between MTHFR variants and hypercoagulability in thalassemia patients, others do not demonstrate statistically significant findings. It is essential to investigate the potential sources of these inconsistencies, such as variations in study design, sample size, population genetics, or methodological approaches, and to explore the underlying biological mechanisms that might account for the divergent outcomes.

Conclusions

1. Polymorphism of the MTHFR gene disrupts methionine and folate metabolism, leading to elevated homocysteine levels (hyperhomocysteinemia), impaired DNA methylation, and altered immune function.

2. These changes negatively affect T-cell activity, which plays a vital role in tumor surveillance, thereby increasing the risk of various cancers. A direct association has been observed between elevated homocysteine levels and the development of certain malignancies.

3. Although the link between homocysteinemia and beta-thalassemia major remains inconclusive, some studies suggest a potential role of MTHFR polymorphism in contributing to hypercoagulable states observed in beta-thalassemia patients.

4. Taken together, current evidence indicates that MTHFR gene polymorphism may significantly increase the risk of both cancer and thalassemia through a combination of disrupted folate metabolism, immune dysregulation, and hypercoagulation.

Prospects for further research. However, to fully understand these complex mechanisms, further research is required to consider genetic background, molecular pathways, lifestyle factors, and dietary influences. Future studies should particularly focus on elucidating how MTHFR variants influence T-lymphocyte function and coagulation pathways, especially in beta-thalassemia patients who are predisposed to thrombotic complications.

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Information about the authors:
Dadashova Arzu, Assistant of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0003-4666-9087
Amirova Mahira, Senior Teacher of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0001-5598-6995
Azizova Gulnara, Head of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0002-0754-3839
Mammadova Farah, Senior Laboratory Assistant of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0002-6875-5317

Відомості про авторів:
Дадашова Арзу, асистент каф. біохімії, Азербайджанський медичний університет, м. Баку.
Амірова Махіра, старший викладач каф. біохімії, Азербайджанський медичний університет, м. Баку.
Азізова Гульнара, зав. каф. біохімії, Азербайджанський медичний університет, м. Баку.
Мамадова Фарах, старший лаборант каф. біохімії, Азербайджанський медичний університет, м. Баку.

Arzu Dadashova (Арзу Дадашова)
adadasova1@amu.edu.az

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