Review Article

Homocysteine: A Potential Common Route for Cardiovascular Risk and DNA Methylation in Psoriasis

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Abstract

Objective: Homocysteine is a sulfur-containing amino acid with potential clinical significance. Abnormal homocysteine levels have been found in patients with psoriasis. This review summarizes the possible correlations among homocysteine, cardiovascular risk, and DNA methylation in psoriasis.

Data Sources: We retrieved the articles published in English from the PubMed database up to January 2017, using the keywords including "psoriasis," "homocysteine," "cardiovascular risk," "DNA methylation," "methylenetetrahydrofolate reductase," "MTHFR," and "*MTHFR* C677T."

Study Selection: Articles about the roles of homocysteine in the cardiovascular risk and DNA methylation in psoriasis were obtained and reviewed.

Results: Observational studies consistently reported that elevated homocysteine is an independent risk factor for cardiovascular diseases. Several studies also consistently reported an association between psoriasis and increased cardiovascular risk. A substantial body of evidence also suggested that an elevated homocysteine level is related to the demethylation of DNA. Data from clinical trials also demonstrated that *MTHFR* C677T polymorphisms as well as DNA methylation aberrations are associated with psoriasis.

Conclusions: This review highlighted the relationships among homocysteine, cardiovascular risk, and DNA methylation, suggesting that homocysteine may be a biological link between cardiovascular risk and DNA methylation in psoriasis.

Key words: Cardiovascular Disease; DNA Methylation; Homocysteine; Psoriasis

Introduction

Psoriasis is a chronic, genetic, inflammatory disease affecting skin and joints. It features epidermal proliferation and is associated with diabetes mellitus, hypertension, hyperuricemia, and dyslipoproteinemia.[1] Psoriasis has a major effect on the quality of life, without affecting the life span in general. It is also associated with an increased cardiovascular risk.[2] Indeed, patients with psoriasis have nearly twice the risk of cardiovascular disease (CAD) compared with normal controls, although little is understood about the exact reason for this.

DNA methylation has long been recognized as an epigenetic silencing mechanism and plays important roles in many cellular processes, such as gene transcription, genomic imprinting, and X-chromosome inactivation.[3] Homocysteine is an amino acid produced in the liver after the metabolism of methionine. It is also an important intermediate in the one-carbon pathway and plays a crucial role in DNA methylation.[4] Homocysteine has also been implicated in the pathogenesis of a variety of diseases, including CADs and psoriasis,[5] both of which feature an elevated plasma level of total homocysteine.[6] In this review, we provided a brief description of findings on the possible correlations among homocysteine, CADs, DNA methylation, and psoriasis, followed by an assessment of whether homocysteine serves as a bridge between the abnormal DNA methylation and cardiovascular risk in psoriasis.

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Structure and Function of Homocysteine

Homocysteine is a sulfur-containing amino acid that is derived from the metabolism of methionine (Met), which is rapidly oxidized in plasma to the disulfides homocysteine and cysteine-homocysteine.[7] Met can be converted to S-adenosylmethionine (SAM), which is catalyzed by methionine adenosyltransferase. SAM, as a methyl donor, plays an important role in DNA methylation *in vivo*. The loss of the methyl group can result in the transfer of SAM to S-adenosylhomocysteine (SAH), and the hydrolysis of SAH catalyzed by SAH hydrolases yields homocysteine.[8] Homocysteine is metabolized through two biochemical pathways: remethylation and transsulfuration. In remethylation, homocysteine can be remethylated into Met via methionine synthase (MS) or betaine-homocysteine methyltransferase to begin another methyl group transfer cycle. In contrast, in transsulfuration, homocysteine combines with serine and is irreversibly converted to cystathionine via Vitamin B6-dependent enzyme: cystathionine β-synthase. Subsequently, cystathionine is hydrolyzed to yield cysteine, a precursor to the antioxidant glutathione. Deficiencies of folic acid, Vitamin B6, and Vitamin B12, as well as abnormal methylenetetrahydrofolate reductase (MTHFR), cystathionine β-synthase, and MS, can lead to metabolic disturbances of homocysteine.[9]

Plasma total homocysteine consists of free homocysteine, protein-bound homocysteine (S-linked and N-linked), oxidized forms, and homocysteine thiolactone.[9] Hyperhomocysteinemia, involving an elevated plasma total homocysteine concentration (the normal range is 5–15 μmol/L when assessed by high performance liquid chromatography or 5.0–12.0 μmol/L when immunoassay methods used), is classified into mild, moderate, and severe forms. A concentration between 15 μmol/L and 30 μmol/L is considered mildly elevated, between 30 μmol/L and 60 μmol/L is considered moderately elevated, and above 60 μmol/L is considered severely elevated.[10] The factors that cause an increase of homocysteine levels are primarily nutrition and polymorphisms in genes encoding enzymes involved in homocysteine metabolism, such as (1) dietary deficiency of folic acid, Vitamin B6, and Vitamin B12;[11] (2) genetic abnormalities, such as *MTHFR* polymorphism; (3) chronic conditions and diseases (obesity, diabetes mellitus, chronic renal disease, high blood pressure, thyroid dysfunction, cancer, and psoriasis); and (4) certain drugs (fenofibrate and methotrexate).[10]

It was reported that hyperhomocysteinemia is related to the occurrence and development of many diseases, for example, CAD, pregnancy complications, autism, osteoporosis, multiple sclerosis, psoriasis, and Alzheimer's disease.[6,12] Previous studies also highlighted the role of *MTHFR* mutation in hyperhomocysteinemia.[13] MTHFR is involved in folate metabolism, DNA methylation, and DNA stability, among others. Polymorphisms of *MTHFR* C677T are reported to be associated with a moderate increase in homocysteine and many diseases, such as coronary heart disease, stroke, and thrombosis.[14]

Homocysteine, Cardiovascular Diseases, and Psoriasis

Psoriasis is a chronic recurrent inflammatory skin disease affecting approximately 2–3% of the population globally. Many factors, such as genetics, immune system, environmental factors, depression and anxiety disorders, infections, drugs, smoking, and alcohol, are thought to be involved in its pathogenesis. The main clinical feature of psoriasis is sharply demarcated, erythematous, scaling plaques that typically affect the elbows, knees, scalp, and intergluteal cleft.[15]

The skin is constantly exposed to endogenous and environmental pro-oxidant agents, leading to the generation of reactive oxygen species (ROS).[16] An imbalance between ROS and antioxidants can lead to an elevated level of oxidative stress. ROS include nitric oxide (NO), hydrogen peroxide, and malondialdehyde, which may cause DNA modification, lipid peroxidation, modulation of signaling pathways, and secretion of inflammatory cytokines.[17,18] A complex of human antioxidant enzymes consists of superoxide dismutase, catalase, antioxidant potential, and glutathione peroxidase. The T_h1/T_h2 balance is important for psoriasis and dependent on redox events.[19] T_h1 responses occur under oxidative conditions, while T_h2 responses were shown to be supported by antioxidative stress. Thus, an imbalance of T_h1/T_h2 cytokines may be involved in psoriasis.[20] Recently, it has also been reported that an increase of ROS production and deficiency of antioxidant system activities may be involved in the pathogenesis of psoriasis.

Extensive studies, both *in vivo* and *in vitro*, have produced conclusive evidence that high homocysteine levels significantly impair endothelial function.[21,22] Homocysteine has a highly reactive sulfhydryl (-SH) group. The first line of such evidence is that homocysteine increases oxidative stress, which may involve the following mechanism: an increase of nicotinamide adenine dinucleotide phosphate, a decrease of transmembrane L-arginine transport and thus reduced total NO production, and the accumulation of asymmetric dimethylarginine, which is an endogenous NO synthase (NOS) inhibitor that inhibits the activity of endothelial NOS and inducible NOS, among others. The second line of evidence is that homocysteine increases inflammation. Third, homocysteine induces endoplasmic reticulum stress and eventually leads to endothelial cell apoptosis.[23]

CAD is a group of diseases with multiple contributing factors, for which it is difficult to pinpoint a particular factor alone. Increased awareness of the risk of CAD associated with psoriasis has emerged recently.[24] However, guidelines for CAD prevention in the population with psoriasis remain limited to addressing traditional risk factors.[25]

Neimann *et al*.[26] identified 127,706 patients with mild psoriasis and 3854 with severe psoriasis. They found that multiple cardiovascular risk factors (such as diabetes, hypertension, hyperlipidemia, and obesity) are associated with psoriasis. Cardiovascular risk factors that are key components of metabolic syndrome were also revealed to be more strongly associated with severe psoriasis than with mild psoriasis. A meta-analysis about the association between psoriasis and hypertension conducted by Armstrong *et al*.[27] indicated an increased risk for hypertension among patients with psoriasis and psoriatic arthritis compared with that in controls. In addition, in a prospective, population-based cohort study of 130,976 patients with psoriasis and 556,995 controls for myocardial infarction (MI), Gelfand *et al*.[28] demonstrated that psoriasis may be an independent risk factor for MI.

It is known that homocysteine is an independent risk factor for atherosclerosis. A leading hypothesis to explain this is that homocysteine increases oxidative stress and causes endothelial dysfunction, which is a key factor in the pathogenesis of atherosclerosis. Atherosclerosis is the most common pathological event that leads to CADs such as MI, heart failure, and stroke. Previous studies also indicated a relationship between elevated homocysteine levels and the risk of CAD (coronary, heart, cerebrovascular, and peripheral artery diseases).[29] Moreover, individuals with *MTHFR* mutations, namely, genetically mediated hyperhomocysteinemia, have been noted to suffer from premature CADs.

The mechanisms responsible for the associations among homocysteine, CAD, and psoriasis are only partially understood. Erturan *et al*.[30] indicated that plasma homocysteine levels did not differ significantly between patients with psoriasis and healthy controls. Consistent with this, Akcali *et al*.[31] showed that, out of 90 Turkish patients (50 with moderate or severe plaque psoriasis and 40 controls), there was no between-group difference in homocysteine levels. In another study including 56 patients with psoriasis and 33 healthy controls, the serum level of homocysteine showed no significant difference between psoriasis and control groups.[32] An increase of plasma homocysteine levels was also observed by Juzeniene *et al*. in psoriasis patients after exposure to ultraviolet (UV) radiation.[33]

In contrast, Bilgiç *et al*.[34] demonstrated that the mean homocysteine level was significantly higher in chronic plaque psoriasis patients (n = 52) than in controls (n = 48). Moreover, Cakmak *et al*.[35] conducted a cross-sectional study in 70 consecutive outpatients with chronic plaque psoriasis and 70 age- and gender-matched controls. They found that serum homocysteine levels did not differ between patient and control groups, but homocysteine levels correlated directly with psoriasis severity as measured by Psoriasis Area and Severity Index (PASI). A case-control study performed by Tobin *et al*.[36] also revealed significantly raised levels of homocysteine in patients with psoriasis compared with those in controls, but there was no correlation between homocysteine level and disease activity as measured by PASI. Malerba *et al*.[37] also found that psoriasis patients had higher plasma homocysteine levels than controls, and plasma homocysteine levels correlated directly with disease severity (PASI) in patients with psoriasis. In another study, Giannoni *et al*.[38] indicated that there was a significant difference between the serum homocysteine levels of psoriasis patients and a control group, and the mean plasma level of homocysteine was directly correlated with disease severity, but not with disease duration or the presence of arthritis. Finally, in a study of twenty patients with mild or moderate psoriasis and 20 age-matched healthy men, Karabudak *et al*.[39] found that an increased homocysteine concentration may play a role in the atherothrombotic state in psoriasis.

Experimental data have thus shown that homocysteine can be used as a predictive risk factor for cardiovascular risk and is directly correlated with psoriasis severity. Several studies have also confirmed that patients with psoriasis have a higher risk of CADs. However, there is still only a limited understanding of the relationship among CADs, homocysteine, and psoriasis.

Homocysteine, DNA Methylation, and Psoriasis

The term "epigenetic modification" generally refers to heritable traits in gene expression and chromatin organization that are not a consequence of the particular DNA sequence, including DNA methylation, histone modification, and noncoding RNA action.[40] Since epigenetic alterations are reversible, they should be reasonable targets for therapies. DNA methylation is mediated by the DNA methyltransferases and mostly occurs in CpG regions. CpG islands occupy approximately 60% of promoter regions. Hypermethylation in CpG islands within or close to gene promoters is associated with the suppression of transcriptional activity.[41] Global DNA hypomethylation occurs mainly at repetitive sequences, promoting chromosomal instability, translocations, gene disruption, and the reactivation of endoparasitic sequences.[42] Hypermethylation of gene promoters or hypomethylation of the genome may also contribute to the development of autoimmune disease.[43]

Homocysteine plays a key role in the methylation cycle. Homocysteine is methylated to methionine, which undergoes S-adenosylation to form SAM. SAM is the principal methyl donor for most cellular methyltransferase reactions in cells. After transfer of the methyl group, SAM is converted to SAH by methylation.[44,45] The SAM/SAH ratio defines the methylation potential of a cell, and hyperhomocysteinemia decreases this ratio, leading to decreased methylation potential.[46] Several studies support the view that homocysteine can lead to global DNA hypomethylation.[45]

Previous studies have revealed that abnormal DNA methylation is closely associated with the pathogenesis of psoriasis,[47] and strong evidence has shown that

hyperhomocysteinemia can decrease DNA methylation, which prompted us to evaluate the relationship among DNA methylation, hyperhomocysteinemia, and psoriasis.

Human leukocyte antigen (HLA) is one of the most gene-dense regions, and is also the most polymorphic region in the human genome, containing genes with a diverse range of functions. HLA-DRB1 is a transmembrane receptor with α and β chains, belonging to the major histocompatibility complex class II proteins. HLA-DRB1 is important for antigen-presenting cells (APCs), given its key role in the efficient presentation of antigens to T-cells by APCs. Zong *et al*.[48] demonstrated that HLA-DRB1 methylation in psoriatic lesions is significantly lower than in psoriatic nonlesions and is negatively correlated to PASI score; thus, hypomethylation of HLA-DRB1 is associated with the severity of psoriasis. Chen *et al*.[49] also identified that, in psoriatic lesions and psoriatic nonlesions, the proportions of promoter methylation for HLA-C were 14.28% (8/56) and 23.21% (13/56), respectively. However, there was no significant difference in HLA-C methylation between psoriatic lesions and nonlesions. Further studies with a larger sample size are thus needed to ascertain the role of HLA hypomethylation in psoriasis. SHP-1 (protein tyrosine phosphatase, nonreceptor Type 6: PTPN6) is an essential regulatory molecule in many signaling pathways, playing an important role in regulation of the growth and proliferation process depending on the cell type. Ruchusatsawat *et al*.[50] determined that the average methylation level of SHP-1 promoter 2 in normal skin is 94.8%, whereas in psoriasis, it is 68.1%. The demethylation of SHP-1 promoter 2 may thus play an important role in the pathogenesis of psoriatic skin lesions. Using methylation-specific polymerase chain reaction (PCR), Zhang *et al*.[51] revealed significantly lower frequencies of methylation positivity of p15 and p21 gene promoters in high-proliferative-potential colony-forming cells (HPP-CFCs) in psoriasis in comparison with those in normal volunteers. In another study, Zhang *et al*.[52] also indicated that, in comparison with normal controls, there was a downregulated promoter methylation of p16 in HPP-CFCs in psoriasis.

Regarding the pattern of global methylation, Gu *et al*.[53] conducted a study specifically on the epidermal component of psoriasis to obtain a comprehensive DNA methylation signature. They found that there were 3665 methylation-variable positions in an overall state of hypomethylation in samples from psoriasis patients. The DNA methylation pattern was also found to be reversed after narrow-band UVB phototherapy in patients showing excellent clinical improvement. Consistent with this, Roberson *et al*.[54] reported a global CpG methylation study in psoriatic skin. They analyzed the methylation status of more than 27,000 CpG sites in skin samples from psoriatic lesions (12 samples) and nonlesions (8 samples) and skin of healthy controls (10 samples). There was a decrease in methylation at 12 CpG sites mapped to the epidermal differentiation complex. To clarify the genome-wide DNA methylation status in naïve $CD4^+$ T-cells in psoriasis, Han *et al*.[55] compared their profile to that of healthy control T-cells; they found significant hypomethylation in 26 regions mostly around the centromeres on ten different chromosomes, which incidentally coincided with various strong epigenomic signals. In another study on the genome-wide DNA methylation of dermal MSCs in psoriasis, Hou *et al*.[56] found 96 genes that were hypermethylated and 234 that were hypomethylated in six psoriasis patients compared with their levels in six controls. Moreover, using an MeDIP-Seq approach, Park *et al*.[57] showed that the global methylation values of $CD4^+$ T-cells were higher in patients with psoriasis than in healthy controls, particularly in the promoter regions. Elsewhere, using an ELISA-like reaction with 5-methylcytosine antibody, Zhang *et al*.[58] observed a statistically significant increase in global DNA methylation level in psoriatic PBMCs relative to the level in normal controls.

Descriptions have been published of a variety of DNA methylation aberrations, both genome-wide and at particular loci, associated with psoriasis. Regarding our understanding of DNA methylation mechanisms that trigger psoriasis, great progress has been achieved.[59] However, the relationships among DNA methylation, hyperhomocysteinemia, and psoriasis remain unclear.

Methylenetetrahydrofolate Reductase Gene Polymorphisms and Cardiovascular Diseases

The human gene encoding *MTHFR* has been localized to chromosome 1p36.3.[60] MTHFR is a crucial enzyme of one-carbon metabolism as it catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cofactor that directs the folate pool toward the remethylation of homocysteine to methionine.[61] MTHFR deficiency can result in homocysteinemia.[62]

Fourteen rare mutations in the *MTHFR* gene associated with severe enzymatic deficiency and one common polymorphism C677T associated with a milder enzymatic deficiency have been identified, but only the *MTHFR* gene (677C>T) polymorphism, which causes an Ala-to-Val substitution, has been demonstrated to be associated with psoriasis.[63,64] The homozygous form of the *MTHFR* gene at nucleotide 677 (C677T) is prevalent in 10% of the population. The *MTHFR* genotype of T/T has been reported to reduce the homocysteine response to folic acid to a greater extent than C/C or C/T. This genotype has also been shown to correlate with elevated plasma homocysteine levels.[14]

There are consistent reports about the relationship between *MTHFR* C677T polymorphisms and CADs. In a meta-analysis conducted by Li *et al*.,[65] it was shown that there is a significant association between the *MTHFR* C677T polymorphism and congenital heart disease risk. With regard to different ethnic groups, a significant association between *MTHFR* C677T polymorphism

and congenital heart diseases in Egyptian children was also reported.[66] A meta-analysis also suggested a clear association between *MTHFR* C677T polymorphism and hemorrhagic stroke risk.[67] Moreover, Yun *et al*.[68] conducted a study on 379 adult essential hypertensive patients from the Chinese Han population and showed that *MTHFR* C677T gene polymorphism was correlated with early renal damage in hypertension. Furthermore, a meta-analysis of 38 case-control studies including 6310 patients and 8297 controls showed that *MTHFR* C677T polymorphism is a probable risk factor for ischemic stroke.[69] Taking these findings together, *MTHFR* C677T polymorphism is closely related to CADs.

Methylenetetrahydrofolate Reductase Gene Polymorphisms and Psoriasis

Numerous previous studies have reported the association between *MTHFR* C677T polymorphisms and the risk of psoriasis, but the results are inconclusive and inconsistent due to different sample sizes and ethnic populations. Izmirli *et al*.[70] generated a psoriasis-specific gene library to screen for *MTHFR* C677T polymorphism using 96 psoriasis cases and 77 controls from Southern Turkey. They found 34 CC (35.4%), 46 CT (47.9%), and 16 TT (16.7%) genotypes in the psoriasis group, while the respective figures were 39 (50.6%), 35 (45.5%), and 3 (3.9%) in the control group. The proportions of cases heterozygous (CT) or homozygous (TT) at the *MTHFR* C677T polymorphism were significantly higher in the psoriasis cases than in the control group. Karabacak *et al*.[71] further identified a correlation of *MTHFR* gene polymorphism with the severity of psoriasis. They showed that severe involvement (PASI score >12) was present in 38.46% (10/26) of the wild-type cases (CC), 12.50% (1/8) of the homozygote ones (TT), and 7.69% (2/26) of the heterozygote (CT) ones. Hcy levels were also higher in patients with the TT genotype than in those with the CT genotype, and all were higher than in those with the CC genotype. By real-time PCR, Kilic *et al*.[72] also detected a possible association between *MTHFR* C677T and psoriasis risk in a Turkish population. Vasku *et al*.[73] also used PCR to determine the genotypes of *MTHFR* C677T in a sample of 654 Caucasians (Czech), including 410 psoriasis patients (285 plaque psoriasis and 125 other subtypes of psoriasis) and 244 controls. They demonstrated that the incidence of the CC genotype was significantly higher in the psoriatic patients than in the controls.

However, another study suggested that there was no significant difference in the prevalence of the homozygous *MTHFR* 677TT genotype between chronic plaque psoriasis patients and controls among Caucasians. In support of this, a study by Liew *et al*.[74] indicated that there was no significant increase in the proportion of individuals with the *MTHFR* C677T polymorphisms in patients with psoriasis vulgaris (367 patients) compared with the level in controls (84 controls) in the Malaysian population. Moreover, a meta-analysis conducted by Wu *et al*.[75] revealed that, under a random-effects model, there was no association between *MTHFR* C677T polymorphism and susceptibility to psoriasis. However, under a fixed-effects model, CT heterozygotes were found to be at a lower risk of psoriasis than either CC or TT homozygotes. With regard to the effect of ethnicity, there was no association between *MTHFR* C677T polymorphism and both Asian and European psoriatic patients.[75] In another meta-analysis, Qi *et al*.[63] indicated that *MTHFR* C677T polymorphism may not be associated with the risk of psoriasis, and they also found no significant association between *MTHFR* C677T polymorphism and the risk of psoriasis in either Asian or Caucasian populations.

Methotrexate is a systemic therapy for psoriasis, but it has unpredictable efficacy and is associated with significant hepatotoxicity and gastrointestinal symptoms. Warren *et al*.[76] found no significant association between *MTHFR* C677T polymorphism and either the efficacy or the toxicity of methotrexate in a study including 374 chronic plaque psoriasis patients treated with methotrexate. However, in another study of 281 psoriatic arthritis patients, it was shown that the minor allele of *MTHFR* 677C/T (677TT) had more liver toxicity.[77]

Taking these findings together, *MTHFR* C677T polymorphism may not be a factor in the pathogenesis of psoriasis, but could to some extent influence the severity of this disease. However, the relationship between *MTHFR* C677T polymorphism and psoriasis needs to be elucidated in further studies with larger sample sizes.

Conclusions and Future Perspectives

Over the last decade, multiple studies have shown that there are associations between psoriasis on the one hand and cardiovascular risk, homocysteine, and aberrant DNA methylation on the other hand. In addition, the relationships between homocysteine and cardiovascular risk and homocysteine and aberrant DNA methylation have been observed in many studies. As such, understanding the mechanisms by which plasma homocysteine alters the prevalence of CADs and aberrant DNA methylation in psoriasis is essential for us to clarify how homocysteine-induced impairment is the common route to the development of psoriasis and its increased cardiovascular risk and aberrant DNA methylation. While a large number of experimental studies have built a foundation for such understanding, this knowledge remains largely incomplete. New and efficient studies to evaluate whether homocysteine acts as a bridge between cardiovascular risk and aberrant DNA methylation in psoriasis are thus needed.

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Conflicts of interest

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