

Review Article

Homocysteine and psoriasis

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Psoriasis is caused by a complex interplay among the immune system, genetic background, autoantigens, and environmental factors. Recent studies have demonstrated that patients with psoriasis have a significantly higher serum homocysteine (Hcy) level and a higher prevalence of hyperhomocysteinaemia (HHcy). Insufficiency of folic acid and vitamin B₁₂ can be a cause of HHcy in psoriasis. Hcy may promote the immuno-inflammatory process in the pathogenesis of psoriasis by activating Th1 and Th17 cells and neutrophils, while suppressing regulatory T cells. Moreover, Hcy can drive the immuno-inflammatory process by enhancing the production of the pro-inflammatory cytokines in related to psoriasis. Hcy can induce nuclear factor kappa B activation, which is critical in the immunopathogenesis of psoriasis. There may be a link between the oxidative stress state in psoriasis and the effect of HHcy. Hydrogen sulfide (H₂S) may play a protective role in the pathogenesis of psoriasis and the deficiency of H₂S in psoriasis may be caused by HHcy. As the role of Hcy in the pathogenesis of psoriasis is most likely established, Hcy can be a potential therapeutic target for the treatment of psoriasis. Systemic folinate calcium, a folic acid derivative, and topical vitamin B12 have found to be effective in treating psoriasis.

Introduction

Psoriasis is a chronic inflammatory disease with a worldwide prevalence of 2–3% [1]. Psoriasis is caused by a complex interplay among the immune system, genetic background, autoantigens, and environmental factors [2]. Notably, psoriasis is associated with increased risk for cardiovascular comorbidities [3], and hyperhomocysteinaemia (HHcy) has been recognized as an independent risk factor for the presence of cardiovascular diseases [4]. Therefore, the relation between psoriasis and homocysteine (Hcy) has attracted attention.

Hcy and Hcy metabolism

Hcy is a sulphur-containing amino acid. The internationally accepted biological reference interval (normal range) of plasma Hcy is 5–15 micromol/l [5]. Of the total plasma Hcy, 80–90% exists in a protein-bound form, approximately 10–20% is in an oxidized form, and only less than 1% exists as a free, reduced amino acid [6,7].

Hcy is produced in all human tissues through the transmethylation of methionine with three steps. S-adenosyl-L-methionine (SAM) synthase catalyzes the reaction of methionine with ATP to form SAM. SAM is converted into S-adenosyl-L-homocysteine (SAH) via a methyltransferase-catalyzed methyl transfer reaction, donating the methyl group to acceptor molecules (DNA, RNA, amino acids, proteins, phospholipids etc.). Finally, SAH is rapidly metabolized by SAH hydrolase to adenosine and Hcy. The disposal of Hcy involves many pathways. In first pathway, approximately 50% of Hcy is re-methylated to form methionine via two distinct mechanisms: folate/vitamin B12-dependent re-methylation and folate/vitamin B12-independent re-methylation. In the folate/vitamin B12-dependent mechanism, folate in the form of 5-methyl tetrahydrofolate, derived from 5,10-methylene tetrahydrofolate reductase catalyzed tetrahydrofolate modification, donates a methyl group to Hcy catalyzed by the vitamin B12-dependent

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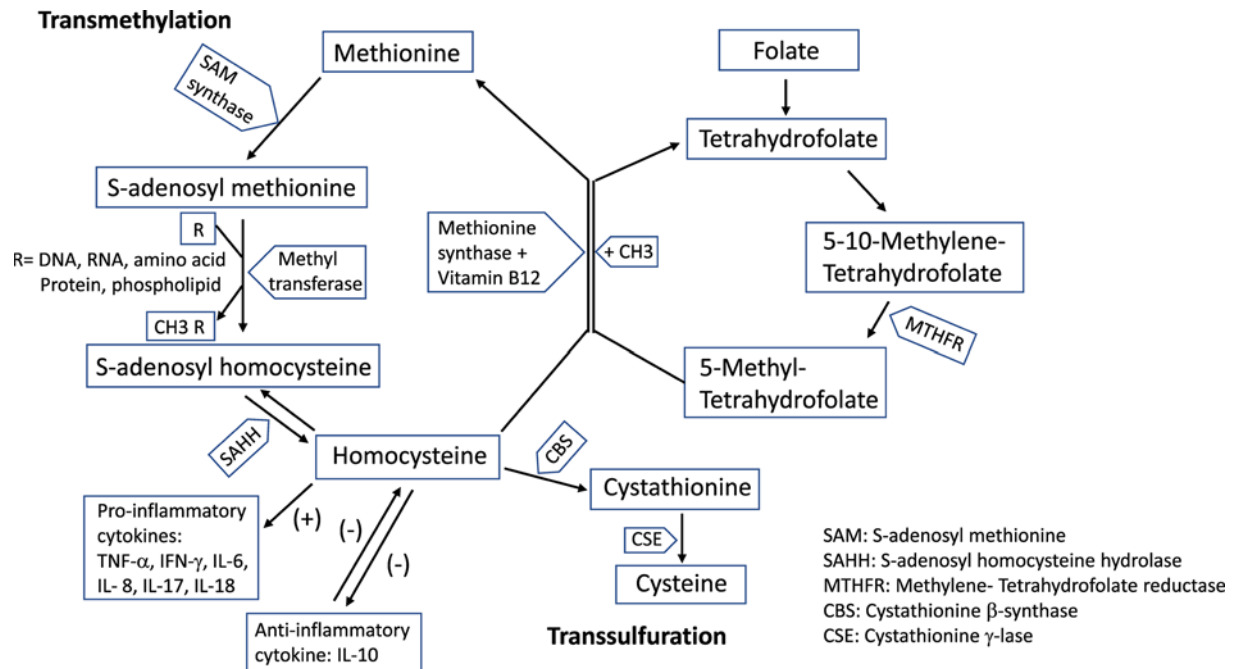


Figure 1. Homocysteine metabolism, role of folic acid and vitamin B₁₂, and interaction with cytokines

Transmethylation of methionine: S-adenosyl-L-methionine (SAM) synthase catalyzes the reaction of methionine to form SAM; SAM is converted into S-adenosyl-L-homocysteine (SAH) via methyltransferase-catalyzed methyl transfer reaction, donating the methyl group to acceptor molecules (DNA, RNA, amino acids, proteins, phospholipids etc.); SAH is metabolized by SAH hydrolase to form Hcy. Hcy can be resynthesized into SAM by SAM synthase; re-methylated to form methionine (folate in the form of 5-methyl tetrahydrofolate, derived from 5,10-methylene tetrahydrofolate reductase catalyzed tetrahydrofolate modification, donating a methyl group to homocysteine catalyzed by vitamin B₁₂-dependent methionine synthase); or metabolized to form cysteine via trans-sulphuration, sequentially catalyzed by cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). Homocysteine up-regulates pro-inflammatory cytokines and negatively interacts with anti-inflammatory cytokine IL-10.

enzyme methionine synthase to form methionine. In second pathway, Hcy is resynthesized into SAM through the reversal of SAH hydrolase activity. In third pathway, Hcy is metabolized to form cysteine via trans-sulphuration, sequentially catalyzed by vitamin B₆-dependent enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). HHcy is the result of increased production and/or decreased disposal of Hcy [6,7] (Figure 1).

Hcy levels in patients with psoriasis

The majority of the studies in the literature demonstrated that patients with psoriasis have plasma/serum Hcy levels significantly higher than controls [8–18]. Among them, some reported that the severity of psoriasis assessed according to psoriasis area and severity index (PASI) directly correlate with plasma/serum Hcy levels [10,15,17,18].

Only a minority of studies reported that Hcy levels do not differ significantly between patients with psoriasis and healthy controls. [19–22]

Very recently, a systematic review and meta-analysis demonstrated that, compared with controls, patients with psoriasis had a significantly higher serum Hcy level and a higher prevalence of HHcy [23]. Therefore, a link between HHcy and psoriasis is established.

Possible causes of high Hcy levels in psoriasis

Generally speaking, deficiencies or genetic polymorphisms in the enzymes taking part in Hcy metabolism and insufficient amounts of cofactors are a major cause of HHcy, and excessive methionine intake, certain diseases, and certain drugs represent additional causes [24]. In psoriasis, lack of folic acid and vitamin B₁₂ can be a cause of HHcy, while smoking, alcohol consumption, and obesity are associated factors.

Folic acid and vitamin B12

In human body, approximately 50% of Hcy is re-methylated to form methionine, and this remethylation reaction requires a folate coenzyme. Thus, folic acid deficiency can result in a buildup of Hcy. Studies have demonstrated that plasma levels of folic acid are lower in psoriatic patients than in controls [9–12], and plasma/serum Hcy levels inversely correlate with serum folic acid levels in psoriatic patients [10,19]. The increase of Hcy can be caused by the decrease of folic acid.

One proposed mechanism of decreased folate in psoriasis may associated with inflammatory changes in intestinal mucosa, which causes reduced absorption of dietary folate [10]. Another rational explanation may be related to rapid skin turn over in psoriasis with subsequent increased consumption of folate leading to low serum folate [13,25,26].

In the conversion of Hcy into methionine, folate in the form of N-5-methyl tetrahydrofolate donates a methyl group to Hcy in the remethylation catalyzed by methionine synthase in concert with vitamin B₁₂ [9]. Lower levels of vitamin B₁₂ were found in patients with HHcy compared with patients with a normal value of Hcy [12]. This suggests that deficiency of vitamin B12 may also contribute to the increase of Hcy in psoriasis.

Smoking and alcohol consumption

Studies have revealed a significant increase in Hcy levels in smokers compared with non-smokers [27–30]. Meanwhile, a systematic literature review and meta-analysis identified significant association between the prevalence of smoking and psoriasis [31].

A number of studies have showed that consumption of alcohol correlates with elevated plasma/serum Hcy [32–40]. According to a systematic literature review, excessive drinking was more prevalent among psoriasis patients than in the general population and psoriasis patients consumed more alcohol than the controls [41]. Therefore, smoking and alcohol consumption can be proposed as common factors between HHcy and psoriasis.

Obesity

The association between psoriasis and obesity has been established [42,43]. A number of studies have demonstrated that Hcy levels are significantly increased in obese individuals when compared with the normal weight population [44–49]. Thus, obesity may also be recognized as one of the associated factors between elevated Hcy levels and psoriasis.

Possible roles of Hcy in the initiation, maintenance, exacerbation, and remission of psoriasis

It is well known that dendritic cells (DCs) play a major role in the initial stages of psoriasis. The activation of plasmacytoid DC is the key in starting the development of the psoriatic lesions, leading to the recruitment and activation of myeloid DCs and T cells that are responsible for lesion maintenance [50,51]. Reactive oxygen species (ROS) may play an important role in activation of DCs [52] and increase the DC ability to activate CD4⁺ T cells [53]. Oxidative stress (OS) has been suggested as a primary mechanism responsible for HHcy-related pathogenesis [54]. Therefore in psoriasis, increased Hcy may facilitate the disease initiation and maintenance via increasing DC activation by ROS.

Many events and factors are associated with the onset and worsening of psoriasis. Among these, some are related to Hcy. For example, it was shown that mental stress elevates the plasma total Hcy level in young men [55]. Smoking increases the risk of psoriasis and its severity. Alcohol use and abuse are also associated with psoriasis [56]. As we mentioned above, smoking and alcohol consumption can be proposed as common factors between HHcy and psoriasis. Some factors contributing to remission of psoriasis are negatively related to Hcy. For example, a majority of psoriatic patients experience improvement during pregnancy [57]. In normal pregnancy, Hcy concentrations fall [58]. Psoriasis severity is negatively correlated with adherence to the Mediterranean diet [59], and adherence to the Mediterranean diet is inversely correlated with Hcy levels [60].

Possible roles of Hcy in the immuno-pathogenesis of psoriasis

Although HHcy has been associated with psoriasis, the role of Hcy in the pathogenesis of psoriasis remains to be elucidated. As psoriasis is considered as an immune-mediated disease, we first review the literature on Hcy's role in various immuno-inflammatory factors relating to the pathogenesis of psoriasis.

Th1 and Th17 cells

Research has unequivocally shown that psoriasis represents a bona fide T-cell mediated disease [2], and Hcy indeed increases the proliferation of lectin stimulated T cells [61]. Psoriasis was originally considered a Th1-mediated skin disease, whereas, in recent years, the focus has been shifted to Th17 cells and to other IL-17-producing cell types [62]. Th1 and Th17 cells may collaboratively interact with each other and contribute to the autoimmune disease pathogenesis [63]. Several lines of evidence have suggested that Hcy may exert a stimulatory effect on T cell functions and induce cytokine secretion, especially Th1-type cytokines, including IFN- γ and IL-2 [64–67]. In lamina propria lymphocytes in colonic mucosa of Wistar rats, Hcy promoted the differentiation of CD4⁺ T cells into Th17 cells in a dose-dependent manner [68]. *In vitro*, Hcy treatment resulted in enhanced IL-17 secretion by T cells [66]. Moreover, *ex vivo* ELISA assay revealed significantly increased IL-2, IFN- γ [66,67], and IL-17 [66] levels in activated splenic T cells from apoE^{-/-} mice with HHcy compared with mice without HHcy. Taken together, above-mentioned studies have demonstrated that Hcy is a activator of Th1 and Th17 cells. HHcy may contribute to the overactivation of Th1 and Th17 cells in the pathogenesis of psoriasis.

Regulatory T cells (Tregs)

The activity of Th1 and Th17 cells is modulated by Tregs, which are able to inhibit the immunological response and to maintain the cutaneous immunological homeostasis, thus preventing autoimmunity against self-antigens. Several studies demonstrate that the function of Tregs is impaired in psoriasis and treatments for psoriasis may increase the number and activity of Treg [69]. Studies showed that HHcy impaired the suppressive function of Tregs *in vitro* and *in vivo*. Feng et al. [66] investigated the role of Tregs in HHcy-accelerated atherosclerosis in apoE^{-/-} mice. Cotransfer of normal Tregs significantly attenuated atherosclerotic lesion size and infiltration of T cells and macrophages into plaque. Furthermore, Treg cotransfer reversed HHcy-accelerated proliferation of T cells. With a clinically relevant level of plasma Hcy (30 μ M), the proportion of Tregs and suppressive activity in splenic T cells were reduced [66]. This was associated with reduced mRNA and protein expression of Foxp3, a factor governing Treg development and function. In addition, Hcy significantly attenuated the proportion and suppressive effects of Tregs *in vitro*. The author concluded that HHcy suppresses the function of Tregs, which may be responsible for HHcy-accelerated atherosclerosis in apoE^{-/-} mice. Of note, psoriasis shares striking similarities with atherosclerosis, such as the histological features and an immunoinflammatory cascade involving Th1, Th17, Tregs, and downstream expression of cytokines [70]. Therefore, HHcy could also suppress the function of Tregs in psoriasis.

Neutrophil

In early phase of psoriasis, neutrophils infiltrate the dermis and subsequently migrate into epidermis to form Munro's microabscesses, a histopathological feature of the disease [71]. Alvarez-Maqueda et al. [72] investigated the role of Hcy in essential functions of human neutrophils and showed that Hcy increases superoxide anion release by neutrophils to the extracellular medium and increases intracellular H₂O₂ production by neutrophils. Hcy enhances the activation and phosphorylation of mitogen-activated protein kinases. The migration of neutrophils is increased by Hcy [72]. Thus, HHcy might contribute to the formation of psoriatic lesions by enhancing the activity and migration of neutrophils.

Cytokines

In psoriasis, a number of pro-inflammatory cytokines including TNF- α , IFN- γ , IL-6, IL-8, IL-12, IL-17, and IL-18 are overexpressed, driving the pathogenesis in the disease. Three cytokines, namely TNF- α , IL-17 and IFN- γ , play the key role in the development of psoriatic lesions [73]. Studies have shown that the production of these pro-inflammatory cytokines may be affected by Hcy (Figure 1).

In a cross-sectional study on healthy men, plasma total Hcy concentration showed positive correlation with IL-1 β , TNF- α , and IL-6 [74]. In experimental rats, moderate exogenous HHcy was associated with increase in TNF- α , IFN- γ , and IL-17 α concentrations in the serum and in mononuclear cells [75]. Acute administration of Hcy and chronic HHcy significantly increased proinflammatory cytokines TNF- α , IL-1 β , and IL-6 in serum of rats [76,77]. Mild HHcy induced in rats increased IL-6 levels in serum [78]. In a mouse model, HHcy elevated plasma levels of TNF- α and IL-6 [79]. Aso et al. [80] found that plasma total Hcy levels were significantly higher in Type 2 diabetic patients with high plasma IL-18 concentration than in those with normal plasma IL-18 concentration. McLachlan et al. [81] reported that Hcy is positively associated with plasma IL-18 concentrations in coronary artery bypass surgery patients. Tso et al. [82] found that plasma concentrations of IL-18 correlated positively and significantly with Hcy in SLE patients. Wang et al. [83] detected increased plasma levels of IL-1 β and IL-18 in HHcy mice as compared

with control mice. *In vitro* studies showed that Hcy can induce IL-1 β [84], TNF- α , IL-6, IL-12 [85], and IL-8 [86,85] production by human peripheral blood monocytes.

The fact of Hcy enhancing the production of pro-inflammatory cytokines which indeed overexpress in psoriasis suggests the role of Hcy in psoriasis pathogenesis.

Treg cells interact with other cells by producing anti-inflammatory cytokines including IL-10, IL-35, and TGF- β [87]. Deficiency of anti-inflammatory cytokines IL-10 [88] and IL-35 [89] in patients with psoriasis are essential factor in pathogenesis. IL-10 has an anti-inflammatory effect, inhibiting the production of pro-inflammatory cytokines [88]. Matrix metalloproteinases (MMPs) are thought to be associated with the pathogenesis and spread of psoriatic disease [90]. Plasma levels of MMP-9 was significantly elevated in psoriasis patients compared with healthy individuals [90]. Hyperhomocysteinemic subjects also had raised serum levels of MMP-9 comparing healthy controls, and although IL-10 markedly suppressed MMP-9 release from PBMCs in controls, no or only minor effect was seen in hyperhomocysteinemic subjects [91]. These findings suggest that Hcy can play a role in psoriasis via attenuating the inhibitory effect of IL-10 on MMP-9 production. Studies in mice showed that administration of IL-10 reduced serum Hcy levels [92], suggesting a negative impact of IL-10 on Hcy (Figure 1). TGF- β is an important regulator in maintaining immune homeostasis. However, the role of TGF- β in psoriasis is still not fully explained [93].

Nuclear factor κ B (NF- κ B)

NF- κ B is a transcription factor that orchestrates inflammation and other complex biological processes. It is a key regulatory element in a variety of immune and inflammatory pathways, in cellular proliferation and differentiation and in apoptosis. NF- κ B is a crucial mediator involved in the pathogenesis of psoriasis which is marked by elevated levels of active, phosphorylated NF- κ B [94].

Studies have observed that Hcy can induce NF- κ B activation. In human aorta vascular smooth-muscle cells, Hcy significantly activated NF- κ B [95]. In human monocytic cell (THP-1)-derived macrophages, Hcy at pathological concentration stimulated NF- κ B activation [96]. In the endothelium of aortas isolated from HHcy rats, activated form of NF- κ B was detected [97]. In a model of heart failure established by high methionine diet treatment, plasmatic Hcy level was elevated and an association between HHcy and activation of NF- κ B was disclosed [98].

Activation of NF- κ B may play a key role in epidermal hyperproliferation in psoriasis [99]. Moreover, NF- κ B is a central mediator of pro-inflammatory gene induction and functions in both innate and adaptive immune cells [100]. Therefore, the effect of Hcy on NF- κ B activation may contribute to the immunopathogenesis of psoriasis.

Hcy and OS in psoriasis

OS is defined as an imbalance between the production of reactive species and antioxidant defences. It can result from increased production of ROS and reduced levels of antioxidants. OS has been suggested as a primary mechanism responsible for HHcy related pathogenesis. ROS are generated during oxidation of the free thiol group of Hcy. Hcy can inhibit the activity of cellular antioxidant enzymes, disrupt extracellular superoxide dismutase, and activate nicotinamide adenine dinucleotide phosphate oxidase [101].

Published studies have provided plenty of evidences that psoriasis is in a state of OS, which may play a critical role in the pathogenesis of the disease [102]. There may be a link between the OS state in psoriasis and the effect of HHcy.

Hcy and hydrogen sulfide (H₂S) in psoriasis

H₂S is a colorless gas with a strong odor that until recently was only considered to be a toxic environmental pollutant with little or no physiological significance. However, in recent years its roles as a major player in many mammalian biological systems have been demonstrated [103]. Under physiological conditions, Hcy metabolizes to produce cysteine, which is a substrate of CBS and CSE for endogenous production of H₂S. Also, endogenous H₂S is generated from Hcy metabolism through trans-sulfuration pathway, catalyzed by CSE and CBS. Hcy and cysteine both are substrates for H₂S generation. In pathological condition, HHcy inhibits CSE enzyme activity and reduces endogenous production of H₂S. Besides, Hcy can compete for binding to CSE with cysteine, thereby decreasing H₂S production from cysteine through substrate inhibition. Therefore, it could be supposed that during HHcy, H₂S production will be diminished [104]. Indeed, in HHcy animal models, decreased H₂S levels [105–107], and decreased CSE activity [105,106] were concomitantly observed. In addition to the generation of H₂S, CSE and CBS can also be considered as Hcy-clearing enzymes. Depletion of both CBS and CSE causes HHcy [108]. H₂S donor may also have a Hcy lowering effect. For example, a H₂S donor—sodium hydrosulfide (NaHS) significantly reduced concentration of Hcy in rats with HHcy [109]. The Hcy lowering effect of H₂S donor could result from the stimulation of the trans-sulphuration pathway by

activating CSE and CBS. For example, administration of NaHS significantly up-regulates the gene expression of CSE and GSH in C₂C₁₂ mouse myotubes. Additionally, it reduces Hcy [110].

Alshorafa et al. [111] investigated the relationship of H₂S with psoriasis and showed that serum H₂S levels in psoriasis patients were significantly lower than those of healthy controls and negatively correlated with clinical disease severity. Exogenous H₂S inhibited the TNF- α -mediated up-regulation of NO, IL-6, and IL-8 in a dose-dependent manner. In addition, H₂S inhibited TNF- α -mediated activation of p38, extracellular-signal-regulated kinase and NF- κ B. The authors concluded that H₂S may play a protective role in the pathogenesis of psoriasis and H₂S-releasing agents may be promising therapeutics for psoriasis. The deficiency of H₂S in psoriasis may be caused by HHcy.

Relationship of psoriasis and psoriatic arthritis (PsA)

PsA is a major comorbidity of psoriasis. The reported proportion of PsA among psoriasis patients ranges from 7% to 26%. Available literature suggests that the highest yield clinical features indicating increased risk for PsA include the following: increased psoriasis severity; positive family history for psoriasis or PsA; patient history of musculoskeletal pain, morning stiffness, fatigue, and difficulty with activities of daily living; presence of scalp, intergluteal, or perianal psoriasis; nail dystrophy; and dactylitis [112]. The frequency of HLA-B27 is reportedly higher among patients with PsA. HLA B27 has been specifically associated with PsA in case-control studies that compared PsA patients with psoriasis patients. HLA-B27 has been shown to be a stronger genetic marker for PsA than for psoriasis. HLA-B27 is an independent risk allele for PsA that is unrelated to skin disease. Recent population case-control studies with adequate patient groups and replication cohorts, as well as confirmation studies in family pedigrees through the use of modern molecular typing methods, have reinforced the aetiological role of this allele in PsA [113]. High levels of Hcy have been documented in a small number of patients with PsA [114].

A potential therapeutic regimen for psoriasis and possible role of methotrexate (MTX) and cyclosporine

Mild-to-moderate psoriasis can be treated topically with a combination of glucocorticoids, vitamin D analogues, and phototherapy. Moderate-to-severe psoriasis often requires systemic treatment. MTX, cyclosporin A, and retinoids are traditional systemic treatment options for psoriasis. Dimethyl fumarate and apremilast are newer drugs that have been approved for psoriasis. Biologics are different from the above-described systemic therapies in that they target specific inflammatory pathways. Biologics presently target two pathways crucial in the development and chronicity of the psoriatic plaque: the IL-23/Th17 axis and TNF- α -signaling. There are currently four drugs in TNF- α inhibitors: etanercept, infliximab, adalimumab, and certolizumab. Ustekinumab is a monoclonal antibody directed against the p40 subunit of IL-23. So far, three human monoclonal antibodies targeting IL-17 are available. Secukinumab and ixekizumab block IL-17A; whereas brodalumab is directed against the IL-17 receptor A [115].

The possible role of MTX in psoriasis is related to its role in inhibiting dihydrofolate reductase (DHFR) and, therefore, in the activation of folic acid. This leads to the inhibition of the synthesis of DNA. By inhibiting DNA synthesis, MTX limits epithelial hyperplasia, reinforces the apoptosis of activated T cells, and inhibits the chemotaxis of neutrophils. In addition, the drug decreases the synthesis of a range of proinflammatory cytokines such as TNF- α and IL-1. Folic acid supplementation may prevent or reduce a range of adverse reactions associated with MTX treatment of psoriasis [116]. In patients with rheumatoid arthritis (RA), during MTX treatment a significant rise in plasma Hcy was seen. In general, this effect could be reversed by folate administration [117]. Presumably, MTX may also increase plasma Hcy in psoriasis patients. It is well established that folic acid supplementation has a role in the treatment of psoriasis in conjunction with MTX treatment [118]. Plasma vitamin B₁₂ levels were not affected by MTX treatment in RA patients [119].

The possible role of cyclosporine is related to its selective action on T cells. Cyclosporine inhibits the activity of calcineurin phosphatase, resulting in failing transportation of nuclear factor of activated T cells to the nucleus for transcription of genes encoding IL-2, which is necessary for full activation of the T-cell pathway. Consequently, cyclosporine depletes lymphocytes and macrophages in the epidermis and dermis and inhibits the activation of T cells. Cyclosporine also inhibits keratinocyte hyperproliferation [120]. Elevated serum Hcy levels were reported in cyclosporine-treated renal transplant recipients. Cyclosporine may interfere with folate-assisted remethylation of Hcy. The HHcy of cyclosporine-treated patients responded to treatment with folic acid [121]. Liver transplant recipients treated with cyclosporine had higher plasma Hcy concentrations. Cyclosporine might interfere with the Hcy clearance [122].

Targeting Hcy as a strategy for treatment of psoriasis

Physical exercise

As obesity may also be one of the factors contributing to elevated Hcy levels in psoriasis and physical exercise can induce changes in protein and amino acid metabolism, the impact of daily physical activity and training programs on the status of Hcy in the body is worth noting. In a systematic review including 34 studies, correlative and comparative studies of Hcy levels revealed lower levels in patients engaged in greater quantities of daily physical activity. Regarding the acute effects of exercise, all studies reported increased Hcy levels. Concerning intervention studies with training programs, aerobic training programs used different methods and analyses that complicate making any conclusion, though resistance training programs induced decreased Hcy levels. In conclusion, this review suggests that greater daily physical activity is associated with lower Hcy levels and that exercise programs could positively affect Hcy control [123].

Folic acid

In the literature, supplementation with folic acid to lower Hcy levels has been studied. However, there is a scarcity of literature describing the effect of folate on psoriasis.

Dawson et al. [124] carried out a double blind trial of folic acid therapy (took one 5 mg tablet of folic acid twice daily) on psoriasis in 21 patients over a period of 6 weeks. The results indicate neither a beneficial nor an adverse effect. Aronson [125] reported that a patient with plaque psoriasis on 10 mg lisinopril did not improve on vitamins B12 and B6 alone. When folic acid (FA) 5 mg daily was added PASI improved by 50%. Three cases of plaque psoriasis flared when given 1–2 mg (FA), 100 mg vitamin B6 and 1000 mcg daily B12. When daily FA was increased to 4–7 mg daily, all three cases were improved.

Gisoni et al. [126] proposed that folic acid appears as a reasonable therapeutic option in patients with moderate-to-severe psoriasis who have concomitant HHcy, low plasma folate and additional cardiovascular risk factors. Folate calcium is a folic acid derivative, a reduced form of folic acid which can be rapidly absorbed after administered orally [127]. Carlesimo et al. [128] treated 30 patients affected by active chronic plaque psoriasis associated with other disorders: hypertension, diabetes, dyslipidemia and obesity, with oral folinate calcium 15 mg once daily for a variable period based on the patient's clinical response. After the therapy a significant reduction of PASI mean values was observed (from 22.78 to 7.92), indicating an improvement of the clinical condition. Simultaneously, a reduction of plasma homocysteine levels and an increase in plasma folic acid levels were observed. The authors concluded that preliminary results support the effectiveness and tolerability of folinate calcium treatment in psoriasis and suggested to continue this study.

Vitamin B12

Deficiency of vitamin B12 may also contribute to the increase of Hcy in psoriasis. Back to 1950s, three published observational reports of systemic vitamin B12 treatment for psoriasis gave inconsistent results [129]. A double-blind controlled trial of unselected cases published in 1962 gave no support to the belief that systemic vitamin B12 is of any value in the treatment of psoriasis, single or combined with a bland ointment, a dithranol regime, or a modified Goeckermann regime [129]. However, it was reported that injection of vitamin B12 into psoriatic lesions showed regression of the lesion in 6 of 8 cases, compared with control group of normal saline. The vitamin B12 was injected into one lesion only in each patient, and no change was noted in other lesions. Where regression took place, a smooth, slightly pink skin resulted [130]. The fact that vitamin B12 level is lower in psoriatic than non-psoriatic skin and active lesions have lower levels than healed lesions [131] may explain the effect of intralesional vitamin B12 on psoriasis.

Since up to 90% of one dose of systemic vitamin B12 is eliminated by the renal pathway within 48 h and is therefore not available at the skin lesions, Stücker et al. [132] considered cutaneous application as the most appropriate way of administration and first carried out a randomized, prospective clinical trial to evaluate the effects of a vitamin B12 cream containing avocado oil in 13 patients against the vitamin D3 analog calcipotriol in an intraindividual right/left-side comparison. After 12 weeks, the PASI score showed no significant differences between the two treatments. While the efficacy of the calcipotriol preparation reached a maximum in the first 4 weeks and then began to subside, the effects of the vitamin B12 cream remained at a constant level over the whole observation period. Moreover, the investigator and patients assessed the tolerability of the vitamin B12 cream as significantly better in comparison with that of calcipotriol. Very recently, Del Duca et al. [133] reported a randomized, controlled, single-blind, intra-patient left- to right-side trial comparing the efficacy and safety of vitamin B₁₂-containing ointment (0.07% cyanocobalamin in a w/o formulation with 20% avocado oil) (M-treatment) with a glycerol-petrolatum-based emollient cream (C-treatment) in 24 patients with mild-to-moderate plaque psoriasis for a period over 12 weeks followed

by a wash-out observation period of 4 weeks. There was a statistically significant difference in PASI reduction between M-treatment side (5.92 ± 2.49) and C-treatment side (1.08 ± 1.0) ($P < 0.001$). The authors concluded that vitamin B₁₂ ointment will represent a new concrete therapy option and should be considered in the update of therapeutic algorithm for the treatment of psoriasis.

Quercetin

Quercetin is one of the important bioflavonoids present in more than 20 plant materials and is known for its anti-inflammatory and antiatherosclerotic activities [134]. Quercetin is effective in decreasing serum Hcy level in high methionine-fed rats and one of possible mechanisms is associated with increased transsulfuration of Hcy [135,136]. The exposure of rats to Hcy leads to OS. Administration of quercetin might attenuate oxidative damage induced by Hcy or have a protective effect against it [137].

Using Perry's scientific mouse tail model, carageenan induced pleurisy in mice and HaCaT cells as experimental models, Vijayalakshmi et al. [138] found that quercetin shows significant orthokeratosis, anti-inflammatory, and maximum antiproliferant activities. The authors concluded that quercetin is promising for further investigations to prove its anti-psoriatic activity. Chen et al. [139] found that quercetin significantly reduces the PASI scores, decrease the temperature of the psoriasis-like lesions, and ameliorates the deteriorating histopathology in imiquimod (IMQ)-induced mice. Moreover, quercetin effectively attenuates the levels of TNF- α , IL-6 and IL-17 in serum and decreases the OS markers in skin tissue in IMQ-induced mice. The mechanism may be associated with the down-regulation of NF- κ B pathway. The authors concluded that quercetin has appreciable anti-psoriasis effects in IMQ-induced mice, and has the potential for further development as a candidate for treatment of psoriasis.

H₂S donors

H₂S may play a protective role in the pathogenesis of psoriasis [111]. In the literature, H₂S may represent an alternative for psoriasis, because it greatly reduced symptoms of a psoriasis-like skin model [140]. H₂S-releasing agents may be promising therapeutics for psoriasis [111].

Recently, many studies have been carried out with the aim of selecting compounds that can deliver H₂S to target tissues. These essentially fall into three categories: sulphide salts, naturally occurring compounds, and synthetic H₂S donors [103]. One possible approach for the therapeutic administration of H₂S is represented by molecules capable of releasing it in a slow and controlled manner, thus mimicking a physiological level [141]. Fast and uncontrollable H₂S release can cause severe problems and sometimes can even be lethal [142]. Studies on some of the H₂S donors regarding their potential use for treatment of psoriasis have been reported.

Sulforaphane (SFN)

SFN is an isothiocyanate compound from broccoli (*Brassica oleracea*). The purported health benefits of isothiocyanates are quite similar to those that are attributed to H₂S or other H₂S-donating drugs [103]. It was found that a large amount of H₂S is released when SFN is added into cell culture medium or mixed with mouse liver homogenates, respectively [143]. It was observed that SFN acts as a slow-releasing H₂S donor supported by several findings [144]. SFN reduced neuropathic pain in mice by releasing H₂S [145]. Yehuda et al. [146] found that SFN contributed to the prevention of inflammation development and reduced ongoing inflammation by downregulating lipopolysaccharide (LPS)-induced mRNA expression of the psoriasis-related cytokines IL-12/23p40, TNF- α , and IL-6 in human macrophage-like cells. Moreover, 3/8 of the SFN-treated psoriasiform severe-combined immunodeficient mice recovered partially or entirely from the psoriasiform process. Results from these models indicate the potential of SFN as biological agent in the therapy of psoriasis.

N-acetyl cysteine (NAC)

The well-known ability of cysteine to mimic H₂S effects, presumably by providing additional H₂S, has led to the evaluation of a number of cysteine analogs as potential substrates for endogenous cysteine-metabolizing enzymes. NAC is one of these molecules [103]. NAC-derived cysteine is desulfurated to generate H₂S [147]. Supplement with NAC can boost endogenous production of H₂S by CSE [148]. Increased neutrophil extracellular trap (NET) formation is seen in psoriasis. In psoriasis, the contents of NETs, namely the antimicrobial peptides and the self-DNA, are able to induce IFN- α production from the plasmacytoid dendritic cells. In addition to anti-IFN- α therapies, other novel agents, such as NAC, target NETs. Treatment of neutrophils with NAC blocks ROS and NET formation *in vitro* [149]. In primary human keratinocytes used as a model of inflammatory skin disease and psoriasis, NAC attenuates the IFN- α -induced production of cytokines, suggesting that NAC should be considered as part of effective therapy for the treatment of inflammatory skin diseases, including psoriasis [150].

GY4137

GY4137 (morpholin-4-ium 4 methoxyphenyl(morpholino) phosphinodithioate) is a synthetic H₂S donor. It releases H₂S when dissolved [103]. GY4137 is generally regarded as a slow-releasing H₂S donor [151]. Injection of GY4137 into rats increases plasma H₂S [103]. Merighi et al. [152] found that application of GY4137 as H₂S donor on human keratinocytes significantly enhances nitric oxide (NO) production. The increment in NO down-regulates extracellular signal-regulated kinase 1/2 activation thereby resulting in the decrease of vascular endothelial growth factor (VEGF) release. The authors suggest that GY4137 may be promising therapeutics for chronic inflammatory disorders of the skin, i.e. psoriasis, in which NO increases as well as anti-VEGF treatments have been suggested to be novel effective approaches.

As we have mentioned above, H₂S donor may also have a Hcy lowering effect. Until recently, the pharmacological treatments for HHcy have primarily focused upon the supplementation of folic acid and other B vitamins. Although these treatments have been effective at decreasing Hcy levels, improving therapeutic options for treatment of HHcy is still an ongoing effort [6]. The evidence that some H₂S donors can lower the levels of Hcy may be of pharmacological interest, connecting to the HHcy status in psoriasis.

Conclusion

According to the literature data including a systematic review and meta-analysis, patients with psoriasis have a significantly higher serum Hcy level and a higher prevalence of HHcy. In psoriasis, insufficient amounts of folic acid and vitamin B₁₂ can be a cause of HHcy, and smoking, alcohol consumption and obesity are associated factors.

Hcy may promote the immuno-inflammatory process in the pathogenesis of psoriasis. As an activator, Hcy can facilitate the overactivation of Th1 and Th17 cells. HHcy can also suppress the function of Tregs. HHcy may contribute to the formation of psoriatic lesions by enhancing the activity and migration of neutrophils. The effect of Hcy enhancing the production of the pro-inflammatory cytokines over-expressed in psoriasis suggests a possible role of Hcy in the development of psoriasis by driving the immuno-inflammatory process. Hcy can induce NF-κB activation. This may contribute to the immunopathogenesis of psoriasis. There may be a link between the OS state in psoriasis and the effect of HHcy. H₂S may play a protective role in the pathogenesis of psoriasis and the deficiency of H₂S in psoriasis may be caused by HHcy.

As folic acid and vitamin B₁₂ can lower Hcy in human body, it is theoretically reasonable to use folic acid and/or vitamin B₁₂ to treat psoriasis as a HHcy-related disease. However, effectiveness of systemic administration of these drugs on psoriasis has not been established. On the other hand, systemic folinate calcium, a folic acid derivative, and topical vitamin B12 have found to be effective in treating psoriasis. Such inconsistency should be further studied. A plant-derived compound quercetin which also can lower Hcy levels has been found to have anti-psoriatic effect in animal models. H₂S donor can increase H₂S and reduce Hcy. Preclinical studies have indicated the potential of some H₂S donors as therapeutic agents for treatment of psoriasis in the future.

Investigation on the role of Hcy in the pathogenesis of psoriasis may shed light on new insight into the pathogenic mechanisms in the disease, opening a path for future researches. Data suggest that Hcy can be a potential therapeutic target for treatment of psoriasis.

Author Contribution

Xiran Lin designed and wrote the manuscript; Xianmin Meng and Zhiqi Song wrote the manuscript.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; DC, dendritic cell; Hcy, homocysteine; HHcy, hyperhomocysteinaemia; MMP, matrix metalloproteinase; MTX, methotrexate; NAC, N-acetyl cysteine; NET, neutrophil extracellular trap; NF-κB, nuclear factor κB; NO, nitric oxide; OS, Oxidative stress; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; RA, rheumatoid arthritis; ROS, reactive oxygen species; SAH, S-adenosyl-L-homocysteine; SAM, S-adenosyl-L-methionine; SFN, Sulforaphane; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

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