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Nutrigenomics in Clinical Practice: Challenges and Opportunities

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Diet, DNA Methylation, and Systemic Lupus Erythematosus: Evidence and Perspectives Focused on Personalized Nutrition

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Abstract

Background: The pathoetiology of systemic lupus erythematosus (SLE) involves a multifactorial interaction consisting of various genetic, epigenetic, and environmental factors. Considering epigenetic characteristics, notable alterations in DNA methylation, particularly hypomethylation in immune-related pathways, such as T-cell receptor, have been observed. In turn, these alterations are associated with the overexpression of genes related to autoimmunity and a loss of immunological self-tolerance. Furthermore, DNA hypomethylation levels in SLE may contribute to disease progression and also impact disease activity and clinical manifestations. ***Summary:*** It is well established that nutritional epigenetics elucidates the role of nutrition and dietary factors on the interactions of metabolic systems with the molecules that bind to DNA, regulating gene expression. Specific nutritional interventions may reverse initial epigenetic patterns, thereby significantly impacting the chronic disease's treatment and prognosis. In fact, dietary nutrients and bioactive food compounds may influence DNA methylation patterns by inhibiting enzymes related to DNA methylation reactions or by altering the availability of different substrates involved in DNA methylation process (e.g., methyl donor nutrients). ***Key Message:*** The knowledge of how diet plays a role in changing DNA methylation patterns in SLE is in the early stages. While a few studies in the literature have assessed the effects of nutrient intake, supplementation, or treatment on DNA methylation levels and have demonstrated their relevance, further research is imperative to deepen our comprehension of the interactions between epigenetics and nutrients, which is vital for the development of novel precision nutrition approaches.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting thousands of people worldwide [1]. SLE is characterized by autoantibody production and dysregulated immune cell activation [2] which, in turn, leads to an important chronic inflammation marked by an exacerbated level of pro-inflammatory cytokines [3]. This pro-inflammatory state causes damage to tissue and organs, including the skin, joints, kidneys, central nervous system, myocardium, and others [4], resulting in diverse and heterogeneous clinical manifestations such as neurological, renal, hematological, and immunological symptoms [3, 5]. Additionally, patients with SLE face a significantly increased risk of cardiovascular diseases [6]. SLE-related systemic inflammation, use of medications such as glucocorticoids, obesity, insulin resistance, and metabolic syndrome may explain the accelerated risk of atherosclerosis in SLE and are involved in the development of cardiovascular diseases [7, 8]. Impaired insulin action and obesity per se are associated with a heightened inflammatory response, which contributes to the formation of plaques through the accumulation of lipids, calcium, and other elements in the artery walls, causing endothelial damage and, consequently, atherosclerosis [8, 9].

SLE disease pathoetiology involves complex and multifactorial interactions between various genetic, epigenetic, and environmental factors [10]. Genome-wide association studies have identified over 100 susceptibility loci that predispose individuals to SLE [11, 12]. Beyond inherited genetic predisposition, emerging literature shows that epigenetic modifications mediated by sex, hormones, and their interaction with environmental exposures and psychological factors may account for disease susceptibility and clinical manifestations [13, 14] (shown in Fig. 1). Epigenetics encompasses the changes around or above DNA that do not affect the sequence of nucleotides but modulate gene expression [15]. These changes include DNA methylation and non-covalent histone modifications (e.g., methylation, acetylation), as well as microRNA expression [16].

In brief, DNA methylation consists of the addition of methyl (-CH3) groups at the carbon-5 position of cytosine by DNA methyltransferases (DNMTs) enzymes, usually at 5-C-phosphate-G-3 (CpG) sites [17, 18]. These sites are unevenly distributed throughout the genome, forming CpG island [18]. Canonical methylation influences DNA transcription [17] and regulates gene expression of diverse metabolic pathways [19]. Unmethylated CpG sites in gene promoters create a state of "permissive" chromatin, facilitating the recruitment of transcription factors by destabilizing nucleosomes [19]. Moreover, DNA methylation promotes gene silencing by direct inhibition of transcription factors or events mediated by transcriptional methyl-CpG binding domain proteins that recruit methylated DNA mediators of chromatin [20]. In SLE, one of the most common mechanisms related to epigenetic dysregulation involves DNA methylation [20]. Studies in which DNA methylation patterns were examined in SLE patients date back to 1990 and generally show global DNA hypomethylation in both T and B cells [21, 22]. The canonical DNA hypomethylation in hyper-reactive CD4+ T cells may increase pro-inflammatory gene expression and consequently induce immune response, which correlates with disease activity [23, 24]. Additionally, there is some evidence that low expression of DNMTs is a primary cause for the reduced global DNA methylome in SLE [25].

SLE management strategies depend on the organ system involved and disease activity, requiring a multidisciplinary approach. The main medications used include antimalarial drugs in maintenance phases (e.g., hydroxychloroquine) and glucocorticoids in acute phases [26]. Moreover, lifestyle modifications addressing risk factors form the basis of SLE management [27]. In this sense, dietary approaches appear to be an effective tool to control the disease inflammatory profile and the complications derived from per se therapy [14]. In addition, a dietary pattern to prevent/control the increased risk of cardiovascular diseases may be beneficial for these patients [28]. Some nutrients with immunomodulatory and antioxidant capacity, as well as anti-cardiometabolic dietary patterns, could reduce SLE severity and organ damage [29]. Available literature has shown that a diet with high contents of fiber, mono/polyunsaturated fatty acids, vitamins, minerals (especially those with antioxidant activity), and polyphenols can modify disease activity by modulating the inflammation and immune functions of SLE [30]. Several studies showed the positive effects of N-3 PUFA consumption on autoimmune conditions, including improved endothelial function, disease activity, and inflammatory state related to SLE [31–33]. Also, vitamin D status (deficiency or insufficiency) has been related to SLE incidence or exacerbation, and its supplementation may potentially reduce inflammatory and hemostatic markers [34, 35]. Conversely, a cross-sectional study suggested that high consumption of free sugars may have negative impacts on SLE disease activity and its complications [36]. Furthermore, nutrition

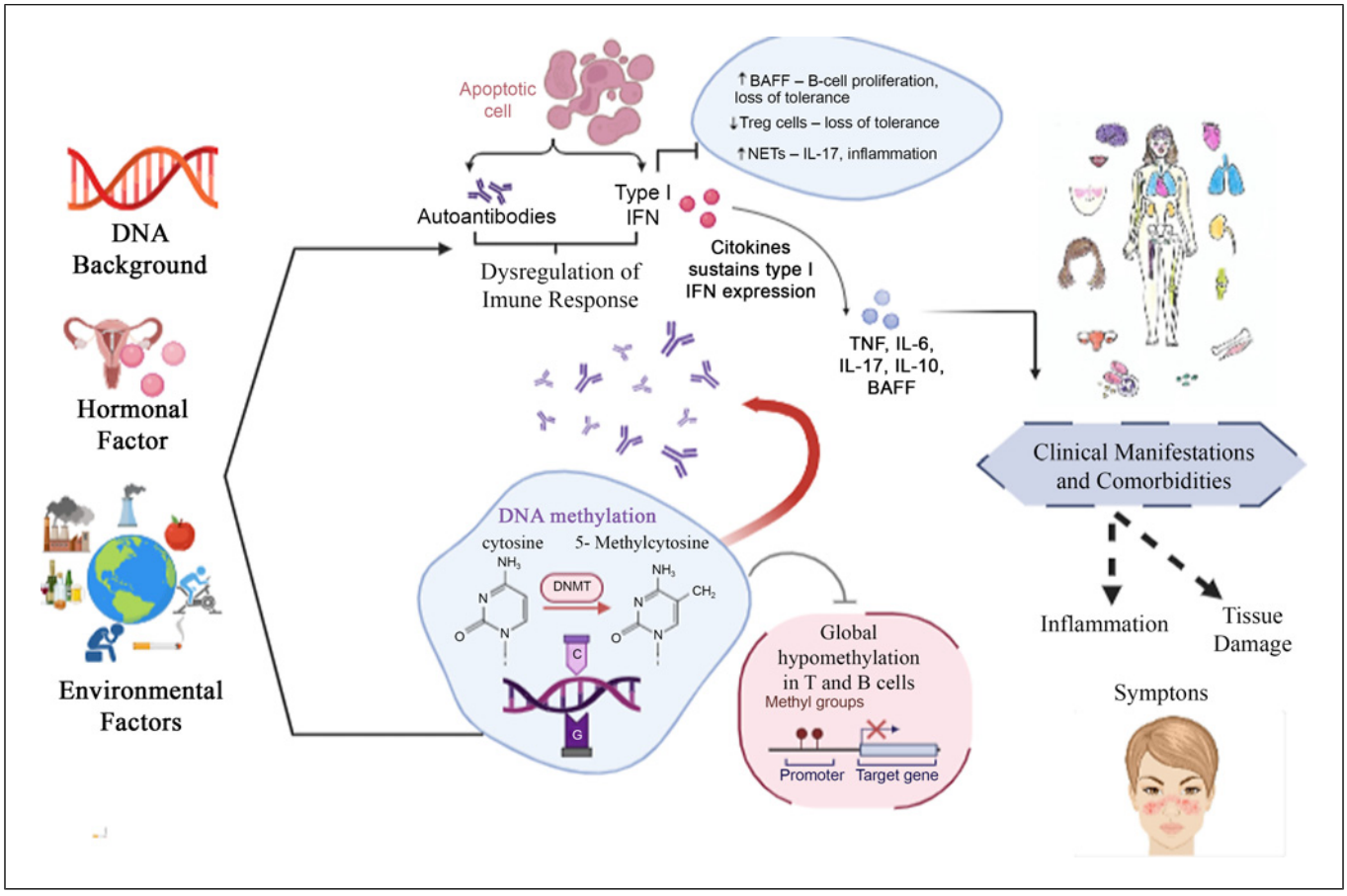

Fig. 1. Epigenetic events and lupus manifestations. DNMT, DNA methyltransferase; INF, interferon; TNF, tumor necrosis factor; IL, interleukin; BAFF, B-cell activating factor; NETs, neutrophil extracellular traps.

is one of the most accessible external factors capable of influencing DNA methylation patterns [37]. Some nutrients and other dietary components may modify epigenetic machinery and, consequently, modulate gene expression and associated metabolic responses [38]. For example, folic acid, vitamin B12, betaine, choline, and methionine are micronutrients involved in one-carbon metabolism acting as methyl donor agents or as coenzymes regulating methyl transfer for DNA methylation reactions [39]. The intake of these micronutrients in the diet (natural and fortified foods) or through supplements is critical to epigenetic remodeling [40].

Despite growing knowledge about the importance of epigenetics in SLE prevention and management and their relation with disease activity, there is an incomplete understanding of nutritional epigenetic moderators in SLE. Based on this perspective, this narrative and descriptive review aimed to summarize the current state of knowledge regarding the role of diet, particularly dietary methyl donor intake, on DNA methylation patterns in SLE disease and suggest future perspectives in SLE management using precision nutrition.

Nutri-Epigenomics

Dietary nutrients and bioactive food compounds may influence DNA methylation patterns, either by directly inhibiting enzymes that catalyze DNA methylation (e.g., DNMT) or by altering the availability of different substrates involved in epigenetic mechanisms, such as methyl groups [41]. Accordingly, nutri-epigenomics aims to understand the role of nutrition and dietary factors in the interactions of metabolic systems with molecules that bind to DNA and control gene expression levels [38]. Previous evidence has indicated that dietary and lifestyle habits can impact human gene expression, and the intake of certain

vitamins and minerals through diet, supplementation, and/or fortification may modulate gene expression at the epigenome level [41].

In this context, the diet provides methyl donor nutrients capable of modifying DNA methylation and, consequently, gene expression [41]. Folic acid, vitamin B12, betaine, choline, and methionine are all involved in one-carbon metabolism, being precursors of the universal methyl donor S-adenosylmethionine (SAM) [41, 42]. The synthesis of SAM is part of the methionine cycle. DNMTs are responsible for transferring methyl groups from SAM to the carbon-5 position of cytosine bases, generating 5-methylcytosine [43, 44], and converting SAM to S-adenosylhomocysteine [45]. S-adenosylhomocysteine is then transformed into homocysteine, and methyl groups may be used for remethylation of homocysteine to produce methionine [45, 46]. Thus, the intake of these nutrients by diet (natural and fortified foods) or through supplements is critical to epigenetic remodeling [42, 47]. Their altered consumption can modify DNA methylation levels both globally and in the promoter regions of disease-related genes [44]. For example, it was observed that folic acid supplementation (400 μg/day during 10 weeks) increased global DNA methylation in human leukocytes [48]. In addition, a long-term supplementation study (400 μg of folic acid and 500 μg of vitamin B12 during 2 years) in elderly subjects evidenced changes in DNA methylation level of *DIRAS3* (distinct subgroup of the ras family member) family genes, *ARMC8* (armadillo repeat containing 8), and *NODAL* (nodal growth differentiation factor) genes, which are implicated in carcinogenesis pathways [47]. Additionally, an experimental study (in Sprague-Dawley rats) that evaluated the effects of maternal betaine supplementation (10 g/kg of chon) showed a hypermethylation on the *Igf-1* (insulin-like growth factor 1) gene in the liver of first-generation offspring [20]. Also, some evidence has indicated that dietary bioactive compounds act as negative regulators of several inflammatory pathways, in which underlying mechanisms by these nutrients affect metabolic traits related to epigenetic modifications [49]. Dietary compounds such as curcumin have been shown to change DNA methylation patterns by altering SAM levels [50] or by inhibiting DNMT activity [51].

Moreover, recent studies have increasingly delineated mechanisms by which dietary patterns play an important role in responses to epigenetic machinery. It is known that a high-fat diet can affect DNA activity through epigenetic modifications that include histone and DNA methylation [52]. Likewise, the Mediterranean diet has been associated with changes in the epigenome through DNA methylation in genes related to immunocompetence and inflammation [53]. In this sense, N-3 PUFA supplementation has been associated with differentially methylated CpG sites related to inflammatory and immune responses [54]. For example, a study conducted by Arpon et al. [55] showed that a Mediterranean diet supplemented with extra virgin olive oil was associated with differential methylation of inflammation-related genes in humans.

Epigenetic Alterations in SLE: Current Evidence

Several studies have provided evidence of potential DNA methylation alterations related to SLE onset, disease activity, and clinical manifestations. Among these changes in the epigenetic machinery, DNA hypomethylation is the most studied [21, 22, 27]. In an effort to establish a link between epigenetic dysregulation and the pathogenic roles of T and B cells in SLE pathoetiology, some studies have demonstrated a dysregulation of DNA methylation profiles related to the overexpression of some key genes in immune pathways [21, 22]. Consequently, many studies evaluated whether DNA methylation levels differ between individuals with SLE compared to healthy controls, leading to the identification of specific genes that may affect SLE risk and disease manifestations [20, 56, 57]. The first study in the context of epigenetics and SLE investigated the DNA methylation profiles of peripheral blood mononuclear cells from genetically identical monozygotic twins discordant for the disease's development and revealed 49 regions exhibiting DNA hypomethylation in SLE patients [58]. Subsequently, important studies have described global DNA hypomethylation in multiple immune cell types, including genes in CD4+ T cells involved in the type I interferon (*IFN*) pathway, autoantibody production, and tissue damage [13, 59]; genes regulating B-cell activation and autoantibody production [60, 61]; and genes in neutrophils [62]. Taking into account that modifications in DNA methylation can influence gene expression, the hypomethylation in immune-related genes may play an important role in SLE. For example, the cluster of differentiation 70 (*CD70*) (encoded by gene TNFSF7) is a cellular ligand for the tumor necrosis factor (TNF) receptor family member CD27 on B cells. Its hypomethylation and consequent overexpression in T cells of SLE patients result in B-cell overstimulation and IgG overexpression and production [63].

In general, some cytokine genes are hypomethylated in CD4+ T cells of SLE patients, resulting in increased protein expression (including *IL-4*, *IL-6*, *IL-10*, *IL-13*, and *IL-17A*), tissue damage, and/or (auto)antibody production [22, 64]. Compared to healthy controls, *IL-10* and *IL-13* genes in CD4+ T cells were hypomethylated in SLE

patients, which led to increased mRNA expression and, consequently, elevated protein levels in serum [65]. Improvement in *IL-10* and *IL-13* expression allows STAT family transcription factor binding (STAT3 and STAT5) recruitment which, in turn, co-recruits the transcriptional coactivator p300. Due to its histone acetylase activity, p300 supports chromatin decompaction through H3K18 acetylation, increasing gene expression [64, 66]. Furthermore, the transcription factor cyclic adenosine-mono-phosphate and response element regulator (*CREM*) are overexpressed in the T cells of SLE patients and contribute to effector T-cell generation and altered cytokine expression. At the same time, CREMa co-recruits DNMT3 to the *IL-2* gene, resulting in DNA hypermethylation and promotion of DNA demethylation of the *IL-17A* gene. This transcription factor is involved in coordinating histone acetylation in effector T cells [67] by inducing H3K18 acetylation in the *IL-17A* gene and decreasing H3K18ac in the IL-2 gene [68]. In addition, other authors demonstrated that interferon genes, including interferon (IFN)-induced protein 44-like (*IFI44L*), myxovirus resistance protein 1 (*MX1*), signal transducer and activator of transcription 1 (*STAT1*), bone marrow stromal cell antigen 2 (*BST2*), and tripartite motif containing 22 (*TRIM22*), are hypomethylated in SLE patients [68].

Moreover, although less studied, global DNA hypomethylation in B cells has been described and associated with autoreactivity [69–71]. Most of the genes are involved in signaling through interferon [67, 72]; however, some authors reported hypomethylation of the *IFI44L*, Programmed Cell Death Protein (*PDCD1*), and sprouty RTK signaling antagonist 2 (*SPRY2*) genes [69]. Specifically, a study comparing patients with SLE and control individuals identified highly significant methylation differences at autosomal CpGs in B cells [23].

Considering disease activity, a study comparing DNA methylome changes in peripheral blood mononuclear cells from patients with SLE demonstrated that those with an Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) >6 had a higher number of hypomethylated CpG sites, specifically in sites associated with IFN-related genes, when compared SLE patients with an SLEDAI ≤6. These results suggest that DNA methylation levels may play a role in the progression of this autoimmune disease [73].

DNA hypomethylation related to SLE can be a consequence of a decrease in methylation or/and an increase in demethylation activity. For example, compared to healthy individuals, significantly lower *DNMT1* and *DNMT3A* expression was observed in SLE patients [74]. As a consequence of these lower levels of *DNMT1*, the DNA methylation patterns are not totally copied from parent to daughter cells during mitosis, resulting in DNA demethylation. Moreover, DNMT1 activity is also controlled by the mitogen-activated protein kinase/ERK (MAPK/ERK) signaling pathway, and an impairment of this pathway may lead to DNA demethylation, contributing to SLE pathoetiology [61, 75]. In addition, many environmental factors have previously been implicated as possible modulators of DNA methylation. It is already evidenced that oxidative stress, smoking, infections, metal exposure, air pollution can reduce DNMT1 levels in T cells and, as a consequence, cause demethylation and overexpression of immune-related genes [76]. Previously, evidence from SLE patients showed increased oxidative stress related to disease condition [77, 78], which may promote a deregulation of the ERK signaling pathway, leading to *DNMT1* downregulation and global DNA hypomethylation in T cells [76, 77]. Additionally, it is important to highlight that SLE medications can alter DNA methylation levels. A study that investigated the effect of prescribed medications for SLE on DNA methylation profiles showed differentially methylated CpG sites associated with glucocorticoid use [57].

Nutri-Epigenomics in SLE: Literature Results Concerning DNA Methylation

Among the environmental factors that modulate the onset and progression of SLE, diet plays a critical role, and nutrients are capable of altering the immune response. The host's metabolic status, which highly depends on diet, can promote or prevent the development of immune abnormalities manifesting with varied symptoms and/or organ involvement that depend on genetic and epigenetic backgrounds and additional factors [64, 67, 72]. In this sense, some studies have demonstrated the role of important micronutrients, mainly methyl donors, in DNA methylation levels across human conditions [79, 80]. However, despite the growing number of studies focusing on the disease and related nutritional aspects in the clinical improvement of patients with SLE, only five studies evaluating DNA methylation levels have been published (Table 1). Three studies were conducted in animal models of lupus and investigated the impact of methyl donor micronutrient [81], high salt concentrations [82], and isoflavone source [83] on DNA methylation levels. Another study conducted an in vitro analysis in CD4+ T cells isolated from lupus patients and examined the effect of different levels of methionine treatment [84]. Finally, another study examined the

Table 1. Dietary components and epigenetic events in SLE

Nutrient/ bioactive compound	Model system	Epigenetic effects	Reference
Methyl donors nutrients	Transgenic mouse model	Low levels of methyl donors and cofactors, together with impaired Erk signaling, instigated a hypomethylation in *Cd40l* gene	Strickland et al. [81], 2013
Methyl-poor diet	In vitro models of CD4+ T cells from SLE patients	Low transmethylation micronutrient levels can increase expression of methylation-sensitive T-cell genes	Ray et al. [84], 2018
High-salt diet	Lupus-prone MRL/lpr mice	Treatment with NaCl promoted DNA hypomethylation and increased DNA hydroxymethylation levels of genes involved in immune responses	Wu et al. [82], 2016
Dietary protein source	Lupus-prone MRL/lpr mice	Type of dietary isoflavone of diet was related to non-condign RNA expression and DNA methylation levels	Edwards et al. [83], 2017
Methyl donor micronutrient intake	Female SLE patients	An increase in methionine, choline, and cysteine intake were associated with methylation levels of the e *CD40L* gene	Vordenbäumen et al. [85], 2021

SLE, systemic lupus erythematosus.

association between dietary methyl donor nutrients and CD40L methylation levels in patients with SLE [85].

A study with a transgenic SLE mouse model showed that dietary micronutrients which affect DNA methylation could exacerbate or ameliorate SLE disease through epigenetic modulation. Mice with a doxycycline-inducible Erk defect bred into lupus-resistant (C57BL/6) or lupus-susceptible (C57BL/6xSJL) strains were fed diets with varying concentrations of methyl donor micronutrients (betaine, methionine, choline, folic acid, vitamin B2, B6, B12, and zinc). As an important result, the authors observed that a diet with low levels of methyl donors and cofactors, in conjunction with impaired Erk signaling, instigated a hypomethylation in the *CD40lg* gene of CD4+ T cells. Moreover, a diet enriched in methyl donors and cofactors prevented DNA demethylation in this region and improved both the autoantibody response and kidney disease. These results underscored that, despite genetic susceptibility, SLE severity can be influenced by nongenetic factors that affect DNA methylation such as methyl donor intake [81].

In another study, it was reported that a high-salt diet was associated with an increased disease activity in lupus-prone MRL/lpr mice. Animals received a sodium-rich chow diet containing 4% NaCl and tap water containing 1% NaCl ad libitum every day. This increase was mediated by an epigenetic mechanism on the pro-inflammatory profile of Th17 and Th1 cells. Treatment with NaCl in CD4+ T cells promoted DNA hypomethylation and increased DNA hydroxymethylation levels of genes involved in immune responses (T-cell activation and differentiation) [82].

Considering bioactive food compounds, genetically lupus-prone MRL/lpr mice were fed with different diets varying in protein source (entirely from casein, entirely from soybean, or from a mix of fish, soybean, and alfalfa) that resulted in altered phytoestrogen (isoflavone) content between diets. The authors observed higher levels of lupus-associated miR-148a and miR-183 in mice fed diets based on soybean. In addition, the authors showed an increase in global DNA methylation levels and in *Dnmt1* expression in those mice fed with diets based on soybean after lipopolysaccharide-induced inflammation [83].

In another study, CD4+ T cells from lupus patients and controls were stimulated with phytohemagglutinin and then cultured in custom media with normal or low methionine levels. The authors reported that decreasing methionine levels promoted a significant increase in the expression of methylation-sensitive genes (e.g., *CD70* and killer cell immunoglobulin-like receptors [*KIR*]) in CD4+ T cells from lupus patients. The authors suggested that the low methionine levels in cell media may inhibit DNA methylation in CD4+ T cells, activating expression of the KIR gene family through demethylation of regulatory elements [84].

A cross-sectional study investigated possible associations of methyl donor micronutrient intake of female SLE patients through the analysis of the food frequency questionnaire and the methylation levels of the *CD40L* promotor in T cells.

Methionine, choline, and cysteine intake were associated with higher methylation levels of the *CD40L* gene. For example, an increase of 168 mg choline per day was associated with a 10% higher methylation level of *CD40L* promotor. Also, daily intake of dietary products with the highest content of methionine (e.g., meat, ice cream, white bread, and cooked potatoes) was associated with an increase in mean *CD40L* methylation or methylation of specific CpG site (CpG17) [85].

Future Perspectives on Precision Nutrition

Despite the therapeutic potential of diet and its involvement in the inflammation process of autoimmune diseases, there is currently no consensus about specific dietary recommendations for the attenuation of clinical manifestation in SLE patients. Precision nutrition is an important part of precision medicine that considers genetic and epigenetic information and environmental conditions [49] and drives nutrition strategies for disease prevention, management, and treatment focused on optimizing health [86]. The primary goal of precision nutrition is to use dietary interventions to preserve or ameliorate health and wellbeing by considering genetic and epigenetic variability [87, 88]. The reversible feature of epigenetic marks has led to the design of specific nutritional interventions aimed at reversing the initial epigenetic patterns, potentially impacting disease treatment and prognosis. Nowadays, the knowledge of how diet plays a role in changing DNA methylation, histone patterns, and miRNA expression and how this may translate to disease pathology is still in its early stages.

As observed above and considering the DNA hypomethylation profile related to SLE, most studies evaluating epigenetic, diet/nutrient, and SLE focus on the role of methyl donor nutrients in DNA methylation levels [83–85]. In line with this, some authors have observed that specific metabolites such as methionine, cysteine, choline, and vitamin B6 were reduced in SLE patients when compared to healthy individuals [89]. Folate depletion may lead to a decrease in SAM production which results in DNA hypomethylation [90]. Therefore, the intake of adequate amounts of methyl donor nutrients according to Dietary Reference Intake (DRI) deserves important attention in the nutritional recommendations to SLE patients. Common food sources of methyl donor nutrients including green vegetables, eggs, red meat, milk, cheese, and yogurts should be included daily in the diet of patients with SLE. Also, taking account of the lack of clinical trials on methyl donor dietary supplementation in SLE, nutrient intake according to recommendations should be encouraged [29].

The commonly used "one-size-fits-all" diet approach often leads to treatment failures. Nutri-epigenomic science may help in the identification of biomarkers that could stratify patients into clusters according to their response to a dietary intervention (e.g., responder/non-responder groups) or also identify whether a given intervention can modulate the epigenome and consequently gene expression. Thus, a better understanding of epigenetic and nutrient interactions could assist in designing new personalized nutrition approaches to more efficiently prevent and reduce the incidence of SLE, thereby improving a patient's quality of life.

Conclusion

A significant body of evidence links SLE onset with DNA methylation patterns, mainly DNA hypomethylation in immune-related genes. However, despite the promising use of diet/nutrients as potential therapeutic tools in SLE management, altering DNA methylation machinery, and subsequently disease development, only a few studies have evaluated these aspects. To date, there is a gap in the literature, and further clinical and longitudinal studies focusing on diet as a therapeutic mediator of SLE considering epigenetics should be encouraged, helping the future establishment of personalized dietary interventions.

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Conflict of Interest Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

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Author Contributions

Carolina Ferreira Nicoletti conceived the idea for the manuscript. Amanda Alves Ribeiro, Lucas Moura Carvalho, Jhulia Caroline Nunes Leal da Mota, and Carolina Ferreira Nicolettia performed the literature review and wrote the manuscript. Carla Barbosa Nonino, Juan A.V. Nuñez, Bruno Gualano, and J. Alfredo Martinez edited and critically reviewed the manuscript. All authors approved the final version of the manuscript.

References

1 Barber MRW, Drenkard C, Falasinnu T, Hoi A, Mak A, Kow NY, et al. Global epidemiology of systemic lupus erythematosus. Nat Rev Rheumatol. 2021;17(9):515–32.
2 Trentin F, Zucchi D, Signorini V, Elefante E, Bortoluzzi A, Tani C. One year in review 2021: systemic lupus erythematosus. Clin Exp Rheumatol. 2021;39(2):231–41.
3 Muñoz LE, Janko C, Schulze C, Schorn C, Sarter K, Schett G, et al. Autoimmunity and chronic inflammation: two clearance-related steps in the etiopathogenesis of SLE. Autoimmun Rev. 2010;10(1):38–42.
4 Das S, Padhan P. An overview of the extra-articular involvement in rheumatoid arthritis and its management. J Pharmacol Pharmacother. 2017;8(3):81–6.
5 Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78(9):1151–9.
6 Oliveira CB, Kaplan MJ. Cardiovascular disease risk and pathogenesis in systemic lupus erythematosus. Semin Immunopathol. 2022;44(3):309–24.
7 Mok CC. Metabolic syndrome and systemic lupus erythematosus: the connection. Expert Rev Clin Immunol. 2019;15(7):765–75.
8 Liu Y, Yu X, Zhang W, Zhang X, Wang M, Ji F. Mechanistic insight into premature atherosclerosis and cardiovascular complications in systemic lupus erythematosus. J Autoimmun. 2022;132:102863.
9 García-Carrasco M, Mendoza-Pinto C, Munguía-Realpozo P, Etchegaray-Morales I, Vélez-Pelcastre SK, Méndez-Martínez S, et al. Insulin resistance and diabetes mellitus in patients with systemic lupus erythematosus. Endocr Metab Immune Disord Drug Targets. 2023;23(4):503–14.
10 Woo JMP, Parks CG, Jacobsen S, Costenbader KH, Bernatsky S. The role of environmental exposures and gene-environment interactions in the etiology of systemic lupus erythematous. J Intern Med. 2022;291(6):755–78.
11 Kwon YC, Chun S, Kim K, Mak A. Update on the genetics of systemic lupus erythematosus: genome-wide association studies and beyond. Cells. 2019;8(10):1180.
12 Chen L, Morris DL, Vyse TJ. Genetic advances in systemic lupus erythematosus: an update. Curr Opin Rheumatol. 2017;29(5):423–33.
13 Adams DE, Shao WH. Epigenetic alterations in immune cells of systemic lupus erythematosus and therapeutic implications. Cells. 2022;11(3):506.
14 Zhan Y, Guo Y, Lu Q. Aberrant epigenetic regulation in the pathogenesis of systemic lupus erythematosus and its implication in precision medicine. Cytogenet Genome Res. 2016;149(3):141–55.
15 Bird A. Perceptions of epigenetics. Nature. 2007;447(7143):396–8.
16 Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications. Nat Rev Genet. 2012;13(2):97–109.
17 Fan S, Zhang X. CpG island methylation pattern in different human tissues and its correlation with gene expression. Biochem Biophys Res Commun. 2009;383(4):421–5.
18 Trerotola M, Relli V, Simeone P, Alberti S. Epigenetic inheritance and the missing heritability. Hum Genomics. 2015;9(1):17.
19 Deaton AM, Bird A. CpG islands and the regulation of transcription. Genes Dev. 2011;25(10):1010–22.
20 Ehtesham N, Habibi Kavashkohie MR, Mazhari SA, Azhdari S, Ranjbar H, Mosallaei M, et al. DNA methylation alterations in systemic lupus erythematosus: a systematic review of case-control studies. Lupus. 2023;32(3):363–79.
21 Ulff-Møller CJ, Asmar F, Liu Y, Svendsen AJ, Busato F, Grønbæk K, et al. Twin DNA methylation profiling reveals flare-dependent interferon signature and B cell promoter hypermethylation in systemic lupus erythematosus. Arthritis Rheumatol. 2018;70(6):878–90.
22 Hedrich CM. Epigenetics in SLE. Curr Rheumatol Rep. 2017;19(9):58.
23 Absher DM, Li X, Waite LL, Gibson A, Roberts K, Edberg J, et al. Genome-wide DNA methylation analysis of systemic lupus erythematosus reveals persistent hypomethylation of interferon genes and compositional changes to CD4+ T-cell populations. PLoS Genet. 2013;9(8):e1003678.
24 Zhang Y, Zhao M, Sawalha AH, Richardson B, Lu Q. Impaired DNA methylation and its mechanisms in CD4(+)T cells of systemic lupus erythematosus. J Autoimmun. 2013;41:92–9.
25 Zhu X, Liang J, Li F, Yang Y, Xiang L, Xu J. Analysis of associations between the patterns of global DNA hypomethylation and expression of DNA methyltransferase in patients with systemic lupus erythematosus. Int J Dermatol. 2011;50(6):697–704.
26 Tunnicliffe DJ, Singh-Grewal D, Kim S, Craig JC, Tong A. Diagnosis, monitoring, and treatment of systemic lupus erythematosus: a systematic review of clinical practice guidelines. Arthritis Care Res. 2015;67(10):1440–52.
27 Chen J, Liao S, Pang W, Guo F, Yang L, Liu HF, et al. Life factors acting on systemic lupus erythematosus. Front Immunol. 2022;13:986239.
28 Alunno A, Carubbi F, Bartoloni E, Grassi D, Ferri C, Gerli R. Diet in rheumatoid arthritis versus systemic lupus erythematosus: any differences? Nutrients. 2021;13(3):772.
29 Pesqueda-Cendejas K, Rivera-Escoto M, Meza-Meza MR, Campos-López B, Parra-Rojas I, Montoya-Buelna M, et al. Nutritional approaches to modulate cardiovascular disease risk in systemic lupus erythematosus: a literature review. Nutrients. 2023;15(4):1036.
30 Islam MA, Khandker SS, Kotyla PJ, Hassan R. Immunomodulatory effects of diet and nutrients in systemic lupus erythematosus (SLE): a systematic review. Front Immunol. 2020;11:1477.
31 Ramessar N, Borad A, Schlesinger N. The effect of Omega-3 fatty acid supplementation in systemic lupus erythematosus patients: a systematic review. Lupus. 2022;31(3):287–96.
32 Duarte-García A, Myasoedova E, Karmacharya P, Hocaoğlu M, Murad MH, Warrington KJ, et al. Effect of omega-3 fatty acids on systemic lupus erythematosus disease activity: a systematic review and meta-analysis. Autoimmun Rev. 2020;19(12):102688.
33 Li X, Bi X, Wang S, Zhang Z, Li F, Zhao AZ. Therapeutic potential of ω-3 polyunsaturated fatty acids in human autoimmune diseases. Front Immunol. 2019;10:2241.
34 Islam MA, Khandker SS, Alam SS, Kotyla P, Hassan R. Vitamin D status in patients with systemic lupus erythematosus (SLE): a systematic review and meta-analysis. Autoimmun Rev. 2019;18(11):102392.
35 Magro R, Saliba C, Camilleri L, Scerri C, Borg AA. Vitamin D supplementation in systemic lupus erythematosus: relationship to disease activity, fatigue and the interferon signature gene expression. BMC Rheumatol. 2021;5(1):53.
36 Correa-Rodríguez M, Pocovi-Gerardino G, Callejas-Rubio JL, Ríos Fernández R, Martín-Amada M, Cruz-Caparros MG, et al. Dietary intake of free sugars is associated with disease activity and dyslipidemia in systemic lupus erythematosus patients. Nutrients. 2020;12(4):1094.

37 Montoya T, Castejón ML, Muñoz-García R, Alarcón-de-la-Lastra C. Epigenetic linkage of systemic lupus erythematosus and nutrition. Nutr Res Rev. 2023;36(1):39–59.
38 González-Becerra K, Ramos-Lopez O, Barrón-Cabrera E, Riezu-Boj JI, Milagro FI, Martínez-López E, et al. Fatty acids, epigenetic mechanisms and chronic diseases: a systematic review. Lipids Health Dis. 2019;18(1):178.
39 Mahmoud AM, Ali MM. Methyl donor micronutrients that modify DNA methylation and cancer outcome. Nutrients. 2019;11(3):608.
40 Niculescu MD, Zeisel SH. Diet, methyl donors and DNA methylation: interactions between dietary folate, methionine and choline. J Nutr. 2002;132(8 Suppl):2333S–5S.
41 Friso S, Udali S, De Santis D, Choi SW. One-carbon metabolism and epigenetics. Mol Aspects Med. 2017;54:28–36.
42 Korsmo HW, Jiang X. One carbon metabolism and early development: a diet-dependent destiny. Trends Endocrinol Metab. 2021;32(8):579–93.
43 Chen CC, Wang KY, Shen CK. DNA 5-methylcytosine demethylation activities of the mammalian DNA methyltransferases. J Biol Chem. 2013;288(13):9084–91.
44 Anderson OS, Sant KE, Dolinoy DC. Nutrition and epigenetics: an interplay of dietary methyl donors, one-carbon metabolism and DNA methylation. J Nutr Biochem. 2012;23(8):853–9.
45 Tibbetts AS, Appling DR. Compartmentalization of Mammalian folate-mediated one-carbon metabolism. Annu Rev Nutr. 2010;30:57–81.
46 Friso S, Choi SW. Gene-nutrient interactions and DNA methylation. J Nutr. 2002;132(8 Suppl):2382S–7S.
47 Kok DE, Dhonukshe-Rutten RA, Lute C, Heil SG, Uitterlinden AG, van der Velde N, et al. The effects of long-term daily folic acid and vitamin B12 supplementation on genome-wide DNA methylation in elderly subjects. Clin Epigenetics. 2015;7:121.
48 Pufulete M, Al-Ghnaniem R, Khushal A, Appleby P, Harris N, Gout S, et al. Effect of folic acid supplementation on genomic DNA methylation in patients with colorectal adenoma. Gut. 2005;54(5):648–53.
49 Ramos-Lopez O, Milagro FI, Riezu-Boj JI, Martinez JA. Epigenetic signatures underlying inflammation: an interplay of nutrition, physical activity, metabolic diseases, and environmental factors for personalized nutrition. Inflamm Res. 2021;70(1):29–49.
50 Chatterjee B, Ghosh K, Kanade SR. Resveratrol modulates epigenetic regulators of promoter histone methylation and acetylation that restores BRCA1, p53, p21CIP1 in human breast cancer cell lines. Biofactors. 2019;45(5):818–29.
51 Fabianowska-Majewska K, Kaufman-Szymczyk A, Szymanska-Kolba A, Jakubik J, Majewski G, Lubecka K. Curcumin from turmeric rhizome: a potential modulator of DNA methylation machinery in breast cancer inhibition. Nutrients. 2021;13(2):332.
52 Zwamborn RA, Slieker RC, Mulder PC, Zoetemelk I, Verschuren L, Suchiman HE, et al. Prolonged high-fat diet induces gradual and fat depot-specific DNA methylation changes in adult mice. Sci Rep. 2017;7:43261.
53 Arpón A, Riezu-Boj JI, Milagro FI, Marti A, Razquin C, Martínez-González MA, et al. Adherence to Mediterranean diet is associated with methylation changes in inflammation-related genes in peripheral blood cells. J Physiol Biochem. 2016;73(3):445–55.
54 Tremblay BL, Guénard F, Rudkowska I, Lemieux S, Couture P, Vohl MC. Epigenetic changes in blood leukocytes following an omega-3 fatty acid supplementation. Clin Epigenetics. 2017;9:43.
55 Arpón A, Milagro FI, Razquin C, Corella D, Estruch R, Fitó M, et al. Impact of consuming extra-virgin olive oil or nuts within a mediterranean diet on DNA methylation in peripheral white blood cells within the PREDIMED-navarra randomized controlled trial: a role for dietary lipids. Nutrients. 2017;10(1):15.
56 Renauer P, Coit P, Jeffries MA, Merrill JT, McCune WJ, Maksimowicz-McKinnon K, et al. DNA methylation patterns in naïve CD4+ T cells identify epigenetic susceptibility loci for malar rash and discoid rash in systemic lupus erythematosus. Lupus Sci Med. 2015;2(1):e000101.
57 Imgenberg-Kreuz J, Carlsson Almlöf J, Leonard D, Alexsson A, Nordmark G, Eloranta ML, et al. DNA methylation mapping identifies gene regulatory effects in patients with systemic lupus erythematosus. Ann Rheum Dis. 2018;77(5):736–43.
58 Javierre BM, Fernandez AF, Richter J, Al-Shahrour F, Martin-Subero JI, Rodriguez-Ubreva J, et al. Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. Genome Res. 2010;20(2):170–9.
59 Karimifar M, Pakzad B, Karimzadeh H, Mousavi M, Kazemi M, Salehi A, et al. Interferon-induced protein 44-like gene promoter is differentially methylated in peripheral blood mononuclear cells of systemic lupus erythematosus patients. J Res Med Sci. 2019;24:99.
60 Garaud S, Le Dantec C, Jousse-Joulin S, Hanrotel-Saliou C, Saraux A, Mageed RA, et al. IL-6 modulates CD5 expression in B cells from patients with lupus by regulating DNA methylation. J Immunol. 2009;182(9):5623–32.
61 Fali T, Le Dantec C, Thabet Y, Jousse S, Hanrotel C, Youinou P, et al. DNA methylation modulates HRES1/p28 expression in B cells from patients with Lupus. Autoimmunity. 2014;47(4):265–71.
62 Coit P, Yalavarthi S, Ognenovski M, Zhao W, Hasni S, Wren JD, et al. Epigenome profiling reveals significant DNA demethylation of interferon signature genes in lupus neutrophils. J Autoimmun. 2015;58:59–66.
63 Patel DR, Richardson BC. Epigenetic mechanisms in lupus. Curr Opin Rheumatol. 2010;22(5):478–82.
64 Hedrich CM, Crispin JC, Tsokos GC. Epigenetic regulation of cytokine expression in systemic lupus erythematosus with special focus on T cells. Autoimmunity. 2014;47(4):234–41.
65 Surace AEA, Hedrich CM. The role of epigenetics in autoimmune/inflammatory disease. Front Immunol. 2019;10:1525.
66 Ngalamika O, Zhang Y, Yin H, Zhao M, Gershwin ME, Lu Q. Epigenetics, autoimmunity and hematologic malignancies: a comprehensive review. J Autoimmun. 2012;39(4):451–65.
67 Rauen T, Hedrich CM, Juang YT, Tenbrock K, Tsokos GC. cAMP-responsive element modulator (CREM)α protein induces interleukin 17A expression and mediates epigenetic alterations at the interleukin-17A gene locus in patients with systemic lupus erythematosus. J Biol Chem. 2011;286(50):43437–46.
68 Long H, Yin H, Wang L, Gershwin ME, Lu Q. The critical role of epigenetics in systemic lupus erythematosus and autoimmunity. J Autoimmun. 2016;74:118–38.
69 Scharer CD, Blalock EL, Mi T, Barwick BG, Jenks SA, Deguchi T, et al. Epigenetic programming underpins B cell dysfunction in human SLE. Nat Immunol. 2019;20(8):1071–82.
70 Hurtado C, Acevedo Sáenz LY, Vásquez Trespalacios EM, Urrego R, Jenks S, Sanz I, et al. DNA methylation changes on immune cells in Systemic Lupus Erythematosus. Autoimmunity. 2020;53(3):114–21.
71 Zouali M. DNA methylation signatures of autoimmune diseases in human B lymphocytes. Clin Immunol. 2021;222:108622.
72 Crispín JC, Oukka M, Bayliss G, Cohen RA, Van Beek CA, Stillman IE, et al. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. J Immunol. 2008;181(12):8761–6.
73 Joseph S, George NI, Green-Knox B, Treadwell EL, Word B, Yim S, et al. Epigenome-wide association study of peripheral blood mononuclear cells in systemic lupus erythematosus: identifying DNA methylation signatures associated with interferon-related genes based on ethnicity and SLEDAI. J Autoimmun. 2019;96:147–57.
74 Nawrocki MJ, Majewski D, Puszczewicz M, Jagodziński PP. Decreased mRNA expression levels of DNA methyltransferases type 1 and 3A in systemic lupus erythematosus. Rheumatol Int. 2017;37(5):775–83.
75 Gorelik G, Richardson B. Key role of ERK pathway signaling in lupus. Autoimmunity. 2010;43(1):17–22.

76 Somers EC, Richardson BC. Environmental exposures, epigenetic changes and the risk of lupus. Lupus. 2014;23(6):568–76.
77 Park JK, Kim JY, Moon JY, Ahn EY, Lee EY, Lee EB, et al. Altered lipoproteins in patients with systemic lupus erythematosus are associated with augmented oxidative stress: a potential role in atherosclerosis. Arthritis Res Ther. 2016;18(1):306.
78 Li Y, Gorelik G, Strickland FM, Richardson BC. Oxidative stress, T Cell DNA methylation and lupus. Arthritis Rheumatol. 2014;66(6):1574–82.
79 Pauwels S, Duca RC, Devlieger R, Freson K, Straetmans D, Van Herck E, et al. Maternal methyl-group donor intake and global DNA [Hydroxy] Methylation before and during pregnancy. Nutrients. 2016;8(8):474.
80 Sarabi MM, Naghibalhossaini F. The impact of polyunsaturated fatty acids on DNA methylation and expression of DNMTs in human colorectal cancer cells. Biomed Pharmacother. 2018;101:94–9.
81 Strickland FM, Hewagama A, Wu A, Sawalha AH, Delaney C, Hoeltzel MF, et al. Diet influences expression of autoimmune-associated genes and disease severity by epigenetic mechanisms in a transgenic mouse model of lupus. Arthritis Rheum. 2013;65(7):1872–81.
82 Wu H, Huang X, Qiu H, Zhao M, Liao W, Yuan S, et al. High salt promotes autoimmunity by TET2-induced DNA demethylation and driving the differentiation of Tfh cells. Sci Rep. 2016;6:28065.
83 Edwards MR, Dai R, Heid B, Cecere TE, Khan D, Mu Q, et al. Commercial rodent diets differentially regulate autoimmune glomerulonephritis, epigenetics and microbiota in MRL/lpr mice. Int Immunol. 2017;29(6):263–76.
84 Ray D, Strickland FM, Richardson BC. Oxidative stress and dietary micronutrient deficiencies contribute to overexpression of epigenetically regulated genes by lupus T cells. Clin Immunol. 2018;196:97–102.
85 Vordenbäumen S, Sokolowski A, Rosenbaum A, Gebhard C, Raithel J, Düsing C, et al. Methyl donor micronutrients, CD40-ligand methylation and disease activity in systemic lupus erythematosus: a cross-sectional association study. Lupus. 2021;30(11):1773–80.
86 Bush CL, Blumberg JB, El-Sohemy A, Minich DM, Ordovás JM, Reed DG, et al. Toward the definition of personalized nutrition: a proposal by the American nutrition association. J Am Coll Nutr. 2020;39(1):5–15.
87 Ferguson LR, De Caterina R, Görman U, Allayee H, Kohlmeier M, Prasad C, et al. Guide and position of the International Society of Nutrigenetics/Nutrigenomics on personalised nutrition: Part 1: fields of precision nutrition. J Nutrigenet Nutrigenomics. 2016;9(1):12–27.
88 Ordovas JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. BMJ. 2018;361:k2173.
89 Wu T, Xie C, Han J, Ye Y, Weiel J, Li Q, et al. Metabolic disturbances associated with systemic lupus erythematosus. PLoS One. 2012;7(6):e37210.
90 Li Y, Liu Y, Strickland FM, Richardson B. Age-dependent decreases in DNA methyltransferase levels and low transmethylation micronutrient levels synergize to promote overexpression of genes implicated in autoimmunity and acute coronary syndromes. Exp Gerontol. 2010;45(4):312–22.