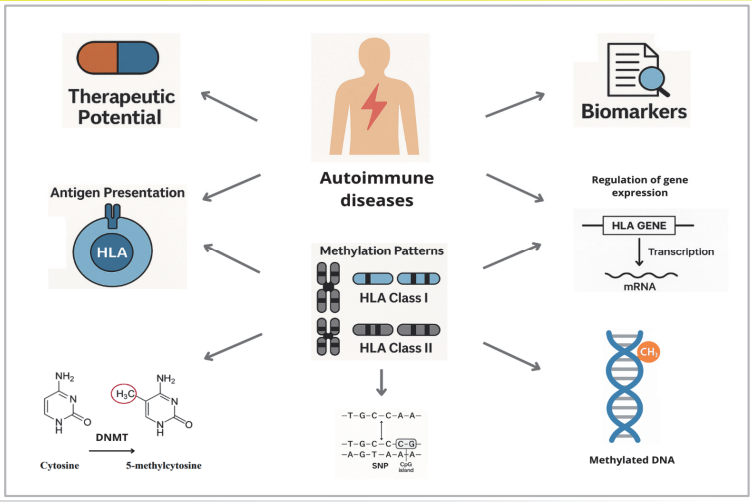
The role of DNA methylation in the regulation of HLA expression

Adam Strnad[1], Martin Petrek[1]

DNA methylation plays a critical role in the regulation of gene expression in the human leukocyte antigen (HLA) system which is a key component of immune function. This article reviews the molecular mechanisms by which DNA methylation influences HLA gene regulation, highlighting its impact on their antigen presentation and immune tolerance functions. We describe how methylation patterns vary in HLA class I and II genes, affecting their expression in a tissue- and allele-specific manner. In addition, we examine the interplay of DNA methylation in shaping immune responses. A focus is on the role of methylation in immune-mediated, namely autoimmune diseases, where aberrant epigenetic modifications at HLA loci contribute to disease susceptibility and progression. We also explore how single nucleotide polymorphisms (SNPs) within CpG sites can alter methylation patterns and gene expression, providing insights into genetic-epigenetic interactions. These findings may contribute to the development of new diagnostic and therapeutic strategies for immune-mediated diseases.



The graphical abstract shows how DNA methylation in HLA genes shapes autoimmune diseases through effects on antigen presentation, gene regulation, and potential biomarker and therapeutic applications.

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Graphical Abstract

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[1]*Department of Pathological Physiology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic*
Corresponding author: Adam Strnad, e-mail: adam.strnad@upol.cz

INTRODUCTION

Epigenetics is a central field of biology that studies how genes are regulated without altering the underlying DNA sequence. These regulatory modifications, known as epigenetic marks, have profound effects on gene expression and consequently on essential biological processes such as development, ageing and disease susceptibility. Among the various epigenetic modifications, DNA methylation has been extensively studied and is known to play a critical role in regulating gene expression[1,2].

Epigenetic mechanisms such as DNA methylation regulate gene expression without altering DNA sequence. Methylation of cytosine to 5-methylcytosine is often associated with gene silencing, but its effects are often context dependent[1,3]. Histone modifications, including acetylation and methylation, affect chromatin structure and thus the

availability of genes for transcription. Non-coding RNAs, which interact with both DNA and histones, also play an important regulatory role[1,4].

The epigenome reflects a number of these modifications and is shaped by both genetic and environmental influences. Its reversibility makes it a promising target for therapeutic intervention and a biomarker in diagnostics[2,5]. Some epigenetic marks can be inherited across generations, although they are often deleted during germ cell development. Transcription factors have been proposed as possible carriers of epigenetic information during early development[5,6].

Epigenetic interplay in autoimmune diseases

Autoimmune diseases result from an immune response against the body's own tissues, and there is increasing evidence that DNA methylation plays a key role in their onset and progression. Aberrant methylation of promoter regions of immunoregulatory genes can lead to their silencing, impairing immune tolerance. Conversely, hypomethylation of promoters of inflammatory genes can increase their expression and contribute to a pro-inflammatory environment and tissue damage[2,3,5]. DNA methylation is also essential for the development of the immune system, including the differentiation of CD4 T helper cells into specific T_h subtypes. This process is controlled by signalling pathways that influence the expression of transcription factors through changes in methylation patterns. Perturbations in this regulation can lead to dysregulated immune responses typical of autoimmune diseases[7,8].

Epigenetics and DNA methylation

DNA methylation is a fundamental epigenetic modification involving the addition of a methyl group at the 5′ position of cytosine, particularly at CpG sites, that are ubiquitous throughout the mammalian genome[9,10]. Within gene promoter regions, CpG dinucleotides often cluster to form CpG islands, which typically remain unmethylated to maintain transcriptional activity. This unmethylated state can be modified by DNA methyltransferases (DNMTs), a family of enzymes responsible for establishing and maintaining DNA methylation patterns. DNMT1 primarily propagates methylation during cell division, whereas DNMT3a and DNMT3b facilitate *de novo* methylation, establishing new methylation marks[4,10,11].

The role of DNA methylation in gene regulation is diverse, but is generally associated with gene repression. This repression occurs either by directly preventing transcription factor binding or by recruiting methyl-CpG-binding proteins that modify chromatin accessibility. Due to its stable and heritable nature, aberrant DNA methylation has been implicated in several human diseases[9,12].

CpG islands and transcriptional regulation

CpG islands are genomic regions enriched in CpG dinucleotides and G+C base pairs that play a critical role in gene regulation. These islands are predominantly associated with human gene promoters, comprising approximately 60–70% of them[13]. While many CpG island promoters regulate housekeeping genes with broad expression across cell types, they also control key developmental regulators such as *HOX* genes[9,14,15].

Unlike the majority of the genome, where CpG sites are often methylated, CpG islands within gene promoters typically remain unmethylated. This state protects against increased mutation rates due to deamination[9,12,16] and facilitates transcription factor binding, thereby supporting active transcription[2,12].

The transcriptional activity of CpG promoters has distinct features compared to non-CpG promoters. CpG promoters initiate transcription over larger regions and often generate transcripts in both sense and antisense orientations, sometimes producing unstable non-coding RNAs (ref.[17-19]). In addition, RNA polymerase II is constitutively recruited to CpG promoters, with its release representing an important regulatory checkpoint[9,15]. CpG promoters are also less dependent on TATA boxes and contain fewer well-defined transcription factor binding sites than their non-CpG counterparts[17,20].

Chromatin architecture further distinguishes CpG promoters from non-CpG promoters. CpG-rich regions preferentially bind CXXC domain proteins, which in turn recruit chromatin-modifying complexes such as the H3K4me3 methyltransferase complex and H3K36me2 demethylase. This results in a chromatin landscape enriched in histone marks associated with transcription initiation, particularly H3K4me3 (ref.[9,12,21]). In addition, CpG promoters exhibit a pronounced nucleosome-depleted region upstream of the transcription start site, distinguishing them from nucleosome-occupied non-CpG promoters[21].

HLA SYSTEM – DNA METHYLATION AND REGULATION

The major histocompatibility complex in humans (HLA) is a central component of the human immune response, mediating self/non-self-recognition and antigen presentation. HLA genes are located on the short arm of chromosome 6 and are grouped into three classes: I, II and III. Class I genes (*HLA-A*, *-B*, *-C*) encode molecules that are expressed on almost all nucleated cells and consist of an α-heavy chain and β2-microglobulin. Class II genes (*HLA-DR*, *-DQ*, *-DP*) encode heterodimeric α and β chains and are expressed primarily on professional antigen-presenting cells such as dendritic cells, macrophages and B-lymphocytes[22]. These molecules present antigens to T-lymphocytes, thereby initiating specific immune responses. The extensive polymorphism of HLA genes allows for broad antigen recognition, which is critical for pathogen defence and immune diversity[23,24]. The expression of HLA genes is tightly regulated, with DNA methylation playing a key role in modulating their transcriptional activity[25,26]. Epigenetic modifications, particularly in promoter regions, can lead to silencing or aberrant overexpression of HLA genes. Hypermethylation can reduce HLA expression and impair immune recognition of pathogens or tumour cells, while hypomethylation has been associated with inappropriate overexpression, potentially contributing to the development of autoimmune

diseases[27]. These methylation-driven changes influence the repertoire of peptides presented to T cells and thus have a direct impact on immune tolerance and immunopathology. The study of methylation patterns at HLA loci provides important insights into the regulation of immune responses[24,27].

Cis- and trans- regulation

The expression of HLA genes is tightly controlled by cis-regulatory elements within their promoters and trans-acting factors that modulate transcription. Conserved cis-elements such as the S-X-Y module, enhancer A and ISRE allow precise regulation by serving as binding sites for key transcription factors such as RFX, NF-Y and CREB/ATF (ref.[28,29]). Trans-activators such as NLRC5 and CIITA enhance MHC I and II transcription, respectively, by interacting with these promoter regions and recruiting chromatin modifying enzymes to ensure transcriptional accessibility[28,29].

Methylation and HLA gene structure

Interestingly, CpG islands in HLA class II genes, particularly within *HLA-DR*, appear to be highly sensitive to methylation changes. These modifications can affect gene expression in several cell types, including antigen-presenting cells. In contrast, HLA class I genes have a high concentration of CpG sites not only in promoter regions, but also in the first exon and intronic sequences, where methylation can affect transcriptional activity and mRNA stability. Methylation levels in these regions vary between tissues and pathological conditions, with some studies suggesting allele-specific differences in methylation patterns[30-33].

HLA class I promoters contain CpG-rich regions that fulfil the main criteria for CpG islands, namely high GC content, increased CpG density, and association with transcription start sites. These islands are typically unmethylated in normal tissues and act as regulatory elements. For HLA class II genes, CpG enrichment is also present, but not all regions strictly meet canonical island definitions, and allele- or tissue-specific differences are reported[34-36].

A key structural factor influencing methylation and gene expression is the presence of single nucleotide polymorphisms (SNPs). SNPs can significantly alter the structure of HLA promoter regions and influence methylation patterns in a variety of ways. SNPs occurring at CpG sites can either create new CpG dinucleotides or remove existing ones, thereby altering potential methylation targets. If a new CpG site is introduced, the region may become susceptible to DNA methyltransferases, increasing methylation. Conversely, the loss of a CpG site due to a SNP can prevent methylation in key regulatory regions, leading to changes in HLA gene expression[27,37].

In addition, SNPs can affect transcription factor binding at unmethylated CpG regions, further modulating the regulatory landscape of HLA genes[33,37,38].

CHARACTERISTICS OF HLA GENES METHYLATION

Class I methylation

The methylation landscape of HLA class I genes plays a crucial role in regulating their transcriptional activity, with different patterns observed at different loci[22] (Table 1). Class I molecules (HLA-A, -B, -C) are expressed on the surface of all nucleated cells, where they present peptides derived from intracellular proteins to $CD8^+$ cytotoxic T cells[11,22].

HLA-A harbours most of its CpG sites in the promoter region, exons 1–3 and introns 1–2. Methylation at these sites, particularly within the promoter, has been shown to correlate negatively with *HLA-A* mRNA expression levels. Notably, the degree of methylation varies between allelic variants, directly influencing gene expression[31,32,42].

For example, *HLA-A*24,* a high expression allele, shows minimal promoter methylation, with only a single CpG site methylated. In contrast, the low expression allele *HLA-A*03* shows increased methylation with multiple CpG sites affected. It has been demonstrated that up to 6% of sequencing reads exhibited methylation at specific CpG sites for *HLA-A*03*, whereas <0.5% of reads were methylated at the single CpG site for *HLA-A*24* (ref.[31,32,42]). These findings highlight the functional impact of allele-specific methylation on *HLA-A* expression and immune responsiveness.

Another HLA class I gene susceptible to DNA methylation is *HLA-C*, which plays a central role in immune responses to bacterial and viral infections, tumour surveillance, allograft rejection and rheumatic autoimmune diseases[40]. Functionally, HLA-C presents peptides to T-lymphocytes and regulates natural killer (NK) cells through interactions with killer cell immunoglobulin-like receptors (KIRs) (ref.[41-43]).

Structurally, *HLA-C* consists of eight exons, with CpG-rich regions concentrated in the first four exons. In particular, exons 1, 2 and 3 contain a high density of CpG sites, making them particularly susceptible to methylation. The α1 and α2 domains encoded by exons 2 and 3 form the peptide-binding groove and their epigenetic regulation directly influences *HLA-C* expression on the cell surface[42,43].

Methylation-mediated silencing of *HLA-C* has been implicated in several autoimmune diseases. For example, hypermethylation can downregulate *HLA-C* expression, potentially impairing antigen presentation and contributing to immune dysregulation[40,44]. Interestingly, allele-specific methylation patterns have been observed in *HLA-C*07*, where higher expression correlates with increased methylation in intron 7, leading to disruption of KIR signalling in NK cells[45]. These findings suggest a complex interplay between DNA methylation, allelic variation and immune function in HLA-C-mediated immunity.

Unlike HLA-A and HLA-C, HLA-G is a non-classical HLA class I molecule and has a distinct expression profile. HLA-G is predominantly expressed in immune-privileged tissues, including the placenta, where it plays

Table 1. Epigenetic regulation of HLA genes: A review of methylation sites and their functional consequences.

HLA	Methylation site	Effect	Ref.
Class I			
HLA-A	Promoter	Low mRNA expression levels	32, 42
	Exons 1–3	Epigenetic regulation of *HLA-A* transcription	32
	Introns 1 & 2	Potential role in alternative splicing and regulatory control	39
	Allele-specific methylation	HLA-A expression varies in an allele-specific manner consistent with DNA methylation levels. SNPs within the high-expressing *HLA-A*24* disrupt a CpG site in the promoter region, while this site is conserved in the low-expressing *HLA-A*03.*	31
HLA-C	Exons 1–3	Epigenetic silencing and hypermethylation negatively affect *HLA-C* expression	43, 44
	Exons 2 & 3	Low mRNA expression levels of α1, α2 domains in the cell membrane	43
	Allele-specific methylation	Disruption of KIR signalling in natural killer cells due to hypermethylation of intron 7 in the *HLA-C*07*.	45
HLA-G	Promoter	Hypomethylation correlates with overexpression, leading to immune evasion in cancer and immune tolerance in pregnancy.	39, 46, 47
	Allele-specific methylation	Methylation variations between alleles modulate *HLA-G* expression, though precise effects remain unclear.	27, 47
Class II			
HLA-DRB1	Exon 2	Allele-specific methylation regulates transcription, influencing antigen presentation.	48, 49
HLA-DQA1	Promoter	Allele-specific methylation patterns observed, but no direct correlation with gene expression.	30
HLA-DQA2	SNP-specific methylation	The SNP rs6906021 (T>C) creates a CpG site; methylation of this site correlates with lower expression.	54
HLA-DQB1	Promoter	Methylation modulates transcription factor binding, affecting gene expression.	29, 59, 56, 57
HLA-DPB1	SNP rs9277534 in 3′UTR	Altered transcript and cell surface expression in B cells, monocytes; G allele → higher expression than A allele	58
CIITA			
CIITA-PIII & PIV	Promoter regions	Hypermethylation silences CIITA expression, inhibiting MHC class II gene transcription.	26, 60, 61
	Chromatin remodeling	Recruitment of DNMTs and transcriptional repressors leads to stable gene silencing.	60, 61

The table summarises key methylation sites in HLA class I (*HLA-A*, *HLA-C*, *HLA-G*) and class II (*HLA-DRB1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*) genes and in the transcriptional regulator CIITA. For each methylation site, its effect on gene expression and possible functional consequences are listed. Special emphasis is placed on allele-specific methylation and its role in the regulation of transcription and immune response. References to relevant literature are given in the last column.

HLA, Major histocompatibility complex in humans; MHC, Major Histocompatibility Complex; CIITA, Class II Transactivator; DNMTs, DNA Methyltransferases; SNP, Single Nucleotide Polymorphism; KIR, Killer-cell Immunoglobulin-like Receptor; mRNA, Messenger RNA; CpG, Cytosine- phosphate-Guanin.

a critical role in immune tolerance, particularly during pregnancy and tumour evasion[27,39].

At the transcriptional level, *HLA-G* expression is tightly regulated by its promoter, with DNA methylation acting as a key modulator. Hypomethylation of the *HLA-G* promoter has been associated with overexpression[36,46,47]. Conversely, hypermethylation of the *HLA-G* promoter results in permanent silencing in most tissues, restricting its expression to specific immunoregulatory environments[47].

In addition to promoter methylation, allele-specific methylation patterns have been identified for *HLA-G*, although their precise functional consequences remain unclear[27,47]. Given its immunosuppressive properties, dysregulated *HLA-G* expression via methylation alterations may have implications in autoimmune diseases, transplantation tolerance and cancer progression[46].

Class II methylation

HLA class II genes play a central role in antigen presentation and $CD4^+$ T cell activation, orchestrating adaptive immune responses. DNA methylation significantly influences the expression of HLA class II molecules, with different patterns observed at different loci. In particular, the *HLA-DRB1*, *HLA-DQA1*, *HLA-DQA2* and *HLA-DQB1* genes exhibit allele-specific methylation patterns that influence their transcriptional activity and immunoregulatory functions (Table 1) (ref.[48,49]).

Among HLA class II genes, *HLA-DRB1* are particularly susceptible to methylation-mediated regulation. DNA methylation patterns in exon 2 have been identified as distinct and functionally relevant beyond conventional genetic influences[48,49].

Analysis of various immune cell types, including $CD14^+$ monocytes, $CD19^+$ B cells, $CD4^+$ T cells and

$CD8^+$ T cells, has revealed consistent differences in DNA methylation near *HLA-DRB1* across multiple cohorts[48,50,51]. These epigenetic modifications align with specific genetic variants, suggesting genotype-dependent regulation of *HLA-DRB1* by DNA methylation[48].

Experimental work has confirmed a causal relationship between CpG methylation in exon 2 and *HLA-DRB1* expression. Using an *in vitro* reporter system, the regulatory properties of exon 2 were shown to be influenced by its methylation status, highlighting the intricate interplay between genetic predisposition and epigenetic modifications in shaping *HLA-DRB1* transcriptional dynamics[48,51].

The HLA-DQ molecules, encoded by *HLA-DQA1*, *-DQA2* and *-DQB1*, are essential for $CD4^+$ T cell activation through presentation of peptides. DNA methylation has been shown to silence *HLA-DQ* expression through epigenetic silencing of regulatory elements. A key mechanism is the loss of transcription factor CTCF binding near the *HLA-DQ* regulatory region, preventing interaction between the promoter and flanking insulators that modulate its transcription. This methylation-driven disruption leads to failure of *HLA-DQ* expression, highlighting a critical epigenetic checkpoint in immune regulation[52,53].

The role of methylation in the expression of *HLA-DQA1* remains complex. While allele-specific promoter methylation has been observed, no significant correlation between methylation levels and gene expression has been found[27].

However, certain *HLA-DQA1* alleles show different methylation patterns. For example, *HLA-DQA1*02:01* and *HLA-DQA1*04:01* have the highest methylation levels, whereas *HLA-DQA1*05:05* has the lowest methylation[30]. These results suggest that although methylation does not directly control *HLA-DQA1* transcription, it may still contribute to allele-specific regulatory differences[30].

In contrast to *HLA-DQA1*, methylation of *HLA-DQA2* directly correlates with gene expression levels. A critical factor in this regulation is the SNP rs6906021 (T>C), that affects DNA methylation and transcription at this locus[54].

Individuals homozygous for the T allele show higher methylation at CpG site cg22933800, leading to reduced *HLA-DQA2* expression. Conversely, heterozygous TC and homozygous CC individuals show lower methylation that correlates with increased gene expression[27,54]. This finding highlights the role of genetic-epigenetic interactions in modulating *HLA-DQA2* transcription[54].

The *HLA-DQB1* gene encodes the MHC class II beta chain which is essential for antigen presentation to $CD4^+$ T cells. The gene consists of six exons, with exons 2 and 3 being are critical for the formation of the peptide-binding groove. The *HLA-DQB1* promoter region contains 19 CpG sites whose methylation modulates transcription factor binding and thus gene expression. SNP rs1063355, located in the 3' untranslated region (3' UTR) of *HLA-DQB1*, plays a key role in this process. The presence of the T allele of rs1063355 is associated with increased methylation at specific CpG sites within the promoter, leading to reduced transcriptional activity and lower mRNA levels[29,55-57]. These findings highlight the interplay between genetic polymorphisms and epigenetic regulation in shaping *HLA-DQB1* expression and influencing immune responses.

In addition to HLA-DR and HLA-DQ, variability in HLA-DPB1 expression significantly influences immunogenicity, particularly in transplantation. A key determinant is the 3′UTR SNP rs9277534, where the G allele is associated with higher, and the A allele with lower HLA-DPB1 expression in B cells and monocytes[58]. These differences contribute to graft-versus-host disease (GvHD) risk and form the basis of expression-based mismatch models for donor selection[33,58]. While direct evidence for DNA methylation in regulating HLA-DPB1 is limited, differential methylation regions downstream of the gene have been described and may correlate with certain alleles, such as *HLA-DPB1*02:01* (ref.[33]). Overall, current data suggest that HLA-DPB1 expression is primarily genetically controlled, with methylation as a potential, but not yet fully defined, modulatory factor[33,58].

Influence of CIITA methylation on HLA class II expression

Class II transactivator (CIITA) is a master regulator of HLA class II gene expression and is essential for the function of antigen presenting cells (APCs) (Table 1). CIITA acts as a transcriptional co-activator and its expression is tightly linked to the transcriptional activity of HLA class II genes. DNA methylation significantly affects CIITA expression, thereby affecting the transcription of MHC class II molecules[29,59]. The *MHC2TA* gene encoding CIITA is regulated by four distinct promoters (PI–PIV), each of which initiates transcription from a unique first exon spliced to a common second exon. This structure allows finely tuned expression of CIITA that is both cell type specific and responsive to immune stimuli such as cytokine signalling[26,60,61]. Of these, PIII and PIV are particularly susceptible to DNA methylation that plays a direct role in the transcriptional silencing of CIITA. Hypermethylation of these promoter regions has been reported in autoimmune conditions, where it correlates with reduced MHC class II expression and impaired antigen presentation[26,60,61]. Genetic studies have identified the rs4774 polymorphism in the *CIITA gene* as a risk factor for autoimmune diseases, especially systemic lupus erythematosus. It is thought that this variant alters CIITA expression and MHC class II pathway activation. This highlights how epigenetic and genetic dysregulation of CIITA can converge to promote immune imbalance and autoimmunity[26,62].

Methylation-mediated silencing of *CIITA*

Hypermethylation of *CIITA* promoter regions induces a chromatin structure that is transcriptionally repressive, resulting in reduced or complete loss of *CIITA* expression. This process is mediated by DNA methyltransferases (DNMTs) that catalyse the addition of methyl groups to CpG dinucleotides within the CIITA-PIII and CIITA-PIV promoters. The functional consequence of *CIITA* methylation is the inhibition of transcription factor binding, in particular STAT1 and IRF1, both of which are essen-

tial for interferon-γ (IFN-γ)-mediated CIITA activation. The failure of these transcriptional activators to bind to the *CIITA* promoter results in the inability to induce HLA class II antigens expression and this significantly impairs antigen presentation to $CD4^+$ T cells[26,63,64]. This epigenetic silencing of CIITA is a key mechanism used by certain tumour cells and pathogens to evade immune detection. By recruiting DNMTs to transcription factor *CIITA* promoters, cells can actively repress *MHC II* gene expression, thereby escaping immune surveillance and promoting immune evasion[26,60,61]. DNMT recruitment is further modulated by chromatin remodelling complexes and transcriptional repressors, highlighting the intricate network of epigenetic and transcriptional regulation governing HLA class II gene expression[26].

THE EFFECT OF DNA METHYLATION IN THE HLA SYSTEM ON AUTOIMMUNE DISEASE

As described above, methylation of HLA genes significantly influences their expression. It has long been recognised that changes in HLA expression disrupt immune regulation and this contributes to the onset and progression of autoimmune diseases. In this section we highlight specific cases where epigenetic modifications within the HLA system have been directly linked to disease pathogenesis (Table 2) (ref.[33,65]).

Regulation of HLA expression by DNA methylation is also critical for establishing central tolerance in the thymus, where self-peptide presentation by HLA molecules on epithelial and dendritic cells determines positive and negative selection of developing T cells. Altered HLA expression – through allele-specific promoter methylation or silencing of regulatory factors – can disturb this balance and permit autoreactive T cells to escape deletion. For example, allele-specific methylation at HLA-A promoters, modulates expression levels in healthy individuals, and higher methylation correlates with reduced expression, a change that may limit peptide presentation required for efficient negative selection[31,66]. Similarly, the class II transactivator CIITA, indispensable for HLA-DR, -DP and -DQ expression, can be epigenetically silenced by CpG methylation, and reduced CIITA activity weakens class II presentation in medullary thymic antigen-presenting cells compromising deletion of autoreactive CD4+ thymocytes. These findings suggest that methylation-dependent regulation of both HLA class I and II expression directly influences thymic selection and the risk of autoimmune disease[31,66].

Table 2. Epigenetic modifications of HLA genes and their association with autoimmune diseases.

HLA locus, genes and antigens	Epigenetic Modification	Effect on Gene Expression	Associated Autoimmune Disease	Ref.
*HLA-A*02:01*	Hypomethylation	Increased expression	Multiple sclerosis (MS)	33
*HLA-C*06:02*	Hypomethylation in promoter and exon 2–3	Increased expression, enhanced autoantigen presentation	Psoriasis	40, 68
HLA-G	Altered promoter methylation	Reduced expression	Systemic lupus erythematosus (SLE), Rheumatoid arthritis (RA)	27, 46, 47
*HLA-DRB1*15:01*	Mixed hyper- and hypomethylation across 10 DMRs	Complex regulation, potential protective effects	Multiple sclerosis (MS)	33, 48
HLA-DRB1	Hypomethylation	Increased responsiveness to interferon signaling	Systemic lupus erythematosus (SLE)	70, 72
HLA-DQB1 (rs1063355 SNP)	SNP-dependent methylation variation at CpG site cg22984282	Decreased expression in pancreatic islets	Type 1 diabetes (T1D)	27,56
HLA-DQB1 (rs9275572 SNP)	Hypomethylation in meQTL-controlled DMRs	Increased expression, enhanced autoantigen presentation	Sjögren's syndrome (SS)	74, 75
HLA-DQA1 (rs9275224 SNP)	Hypomethylation at DMR (position 32 810 706 - 32 810 742 bp, GRCh37)	Increased expression	Sjögren's syndrome (SS)	74
HLA-DQA2 (rs2858332 SNP)	Hypomethylation in regulatory DMRs	Increased expression	Sjögren's syndrome (SS)	74

The table summarises selected epigenetic modifications at HLA loci and their influence on gene expression. It also lists related autoimmune diseases for which the given epigenetic regulation has been demonstrated. Special emphasis is placed on methylation of promoter regions and specific SNPs that influence methylation patterns and subsequent transcription of HLA genes. The last column contains references to relevant literature. HLA, Major histocompatibility complex in humans; DMR, Differentially Methylated Region; SNP, Single Nucleotide Polymorphism; meQTL, Methylation Quantitative Trait Locus; bp, Base Pairs; GRCh37, Genome Reference Consortium Human Build 37; MS, Multiple Sclerosis; SLE, Systemic Lupus Erythematosus; RA, Rheumatoid Arthritis; T1D, Type 1 Diabetes; SS, Sjögren's Syndrome.

Allele-specific methylation is a well-documented feature of the *HLA-A* locus. In multiple sclerosis, the *HLA-A*02:01* allele, known for its moderate protective effect, shows significantly lower levels of methylation[33,67]. This suggests that epigenetic regulation of *HLA-A* expression may contribute to multiple sclerosis susceptibility and progression[33].

DNA methylation in the *HLA-C* region is critical for regulating its expression and influences susceptibility to autoimmune diseases, particularly *psoriasis vulgaris*. Hypomethylation of the *HLA-C* promoter has been associated with increased gene expression, a process that can lead to excessive autoantigen presentation and activation of autoreactive T cells. Specifically, hypomethylation of the *HLA-C*06:02* allele is associated with an increased risk of *psoriasis vulgaris*[40,68,69]. This epigenetic modification is thought to affect the binding of transcription factors to the *HLA-C* promoter, leading to deregulated gene expression and consequently an autoimmune response. Studies have identified specific DNA methylation regions (DMRs) within the first four exons of *HLA-C genes*, particularly in exons 2 and 3 that encode the α1 and α2 peptide-binding HLA-C molecules domains critical for autoantigen presentation. In addition, CpG islands in the promoter region play a key role in epigenetic regulation, and their methylation status can either protect against or predispose to disease, depending on the allelic variant[40,68]. This complex regulation involves transcription factors, microRNAs and histone modifications, all of which collectively influence *HLA-C* genes expression and susceptibility to *psoriasis vulgaris*[40,68,69].

HLA-G, a non-classical HLA class I molecule, has potent immunomodulatory properties and is essential for immune tolerance. Its expression is tightly regulated by DNA methylation within the *HLA-G* promoter region. Alterations to these patterns of methylation may contribute to the development of the autoimmune diseases described in the following sections[27,46,47]. In systemic lupus erythematosus, alterations in *HLA-G* expression have been observed, possibly due to epigenetic modifications. Studies show that SLE patients have reduced *HLA-G* expression on monocytes and dendritic cells, a reaction that may lead to impaired immune tolerance and increased autoimmune responses. Although the exact mechanism remains unclear, DNA methylation within *HLA-G* regulatory regions is thought to be a key determinant of its expression and function[27,46]. Similarly, in rheumatoid arthritis, specific *HLA-G* polymorphisms have been associated with altered gene expression and function, likely influenced by epigenetic modifications such as DNA methylation[46].

HLA-DRB1 plays a critical role in several autoimmune diseases. In systemic lupus erythematosus, $CD8^+$ T cells exhibit epigenetic priming to respond to type I interferon stimuli, accompanied by *HLA-DRB1* hypomethylation. Dysregulated DNMT activity (a key factor in defective DNA methylation) has been implicated in gene transcriptional dysregulation, chromosomal instability and systemic lupus erythematosus pathogenesis. However, conflicting data on DNMT transcript levels highlight the complexity of epigenetic regulation in SLE (ref.[70-73]). In multiple sclerosis, allele-specific methylation of *HLA-DRB1*15:01* – a major risk allele - has been extensively studied. Of ten DMRs within *HLA-DRB1*, eight regions are hypermethylated and two are hypomethylated, suggesting a protective effect that may be mediated by long-range regulatory interactions. In particular, exon 2 of *HLA-DRB1* shows methylation-sensitive regulatory effects that affect gene expression levels. The coexistence of both hyper- and hypomethylated regions within a single gene highlights the complex interplay between genomic and epigenetic factors in multiple sclerosis susceptibility[33,48].

In type 1 diabetes, the SNP rs1063355 regulates *HLA-DQB1* expression through methylation-dependent mechanisms. CC homozygotes show increased methylation at the CpG site cg22984282, whereas CT heterozygotes and TT homozygotes show lower methylation levels – correlating with decreased *HLA-DQB1* expression in pancreatic islets and increased T1D risk[27,56]. Similarly, in Sjögren's syndrome, hypomethylation of *HLA-DQB1* has been identified as a key epigenetic factor modulating disease risk. DMRs within *HLA-DQB1*, controlled by methylation quantitative trait loci (meQTLs), are significantly associated with genetic predisposition to Sjögren's syndrome. In particular, SNP rs9275572, located within the *HLA-DQB1* region, is in strong linkage disequilibrium (LD) with Sjögren's syndrome risk alleles, and its hypomethylation may contribute to *HLA-DQB1* overexpression and increased autoantigen presentation[74,75].

HLA-DQA1 hypomethylation has also been implicated in Sjögren's syndrome as a mediator of genetic susceptibility. One study identified DMRs within *HLA-DQA1* regulated by meQTLs, with SNP rs9275224 significantly affecting methylation levels at position 32 810 706 – 32 810 742 bp (GRCh37) on chromosome 6. These methylation changes may alter transcriptional activity, leading to HLA-DQ antigens overexpression and subsequent autoimmune activation[74,76,77]. Similarly, *HLA-DQA2* hypomethylation has been associated with Sjögren's syndrome risk. A high density of DMRs within *HLA-DQA2* was detected, suggesting a complex regulatory network involving genetic variants and epigenetic modifications. In particular, SNP rs2858332 that is in strong LD with Sjögren's syndrome risk alleles, was identified as a potential regulator of methylation in this region. This supports the hypothesis that epigenetic control of *HLA-DQA2* contributes to SS pathogenesis and may represent a promising therapeutic target[74,76,77].

DISCUSSION

Epigenetic modification of DNA, specifically methylation, plays a crucial role in regulating gene expression in the HLA system and thus influences immune processes that are critical for the development of autoimmune diseases. Changes in the methylation pattern of HLA genes can lead to dysregulation of immunity, with important consequences for the development of various autoimmune diseases[27,78].

In the HLA system, methylation is most prevalent in promoter regions that regulate the expression of both HLA class I (*HLA-A*, *-B*, *-C*) and class II (*HLA-DR*, *-DQ, -DP*) genes. This methylation affects the expression of key molecules involved in antigen presentation, an effect that has a direct impact on T cell activation and the overall immune response[31,57,72]. The finding that CpG islands in gene regions such as *HLA-DR* and *HLA-C* are sensitive to methylation changes underscores the importance of these modifications in regulating gene expression in various cell types, including antigen-presenting cells[79,80].

Of particular interest are SNPs in CpG dinucleotides, which can create new CpG sites or delete existing ones, thereby altering the methylation potential of promoter regions. Research shows that SNPs in these regions can fundamentally alter methylation patterns and thus the expression of HLA genes, with far-reaching consequences for the immune response and the development of autoimmune diseases[27,81]. In some cases, a direct correlation between SNPs, methylation and HLA expression has been identified, suggesting a complex patterned interaction between genetic variants and epigenetic modifications[57,75,82].

One of the most important discoveries in the field of HLA epigenetics is the influence of methylation on the expression of *CIITA*, a transcriptional activator of *MHC II* genes. Hypermethylation of the promoter regions of *CIITA* leads to a strong reduction in the expression of MHC II molecules, a reduction that impairs the ability to present antigens to $CD4^+$ T lymphocytes and may mediate immune escape[28,83,84].

Specific changes in the methylation patterns of *HLA* genes have been shown to correlate with the expression of these genes and are associated with the risk of developing these diseases, such as multiple sclerosis, psoriasis vulgaris, rheumatoid arthritis and lupus erythematosus[75,85-87]. For example, hypomethylation in the *HLA-C* promoter is associated with higher expression of *HLA-C*06:02* and an increased risk of psoriasis vulgaris[27,88]. This methylation pattern may disrupt the interaction with transcription factors, leading to deregulated *HLA-C* expression and subsequent autoimmune responses[57].

In the case of *HLA-DRB1*, which plays an important role in the development of diseases such as multiple sclerosis and systemic lupus erythematosus, specific methylation in exon 2 has been shown to affect antigen expression and may be protective or risky depending on the methylation pattern[33,48,83].

FUTURE PERSPECTIVE

An interesting direction for future research is to explore the mechanisms by which HLA gene methylation influences the development and progression of autoimmune diseases. Given the complexity of these mechanisms, it is essential to improve our understanding of the methylation patterns in individual HLA genes and their interactions with genetic and environmental factors. This understanding could lead to the identification of potential biomarkers for the diagnosis and prediction of autoimmune diseases, as well as the development of therapeutic strategies aimed at modulating methylation patterns in HLA genes as a potential treatment approach[75,89].

This research provides new insights into the regulation of HLA expression at the epigenetic level and offers the possibility of targeted modification of methylation patterns as a therapeutic tool for autoimmune diseases. Given that DNA methylation can be reversible, this area represents a huge potential for the development of potential therapeutic strategies targeting the epigenetic regulation of HLA genes and the immune response[73,86,90,91].

In the future, it will be crucial to further investigate specific methylation markers for individual autoimmune diseases, including their interaction with genetic factors and environmental exposures. This could provide valuable tools for the prediction, diagnosis and personalised treatment of autoimmune diseases, pushing the boundaries of our ability to treat and prevent these disorders[75].

An additional promising avenue is the use of CRISPR-based epigenome editing, where catalytically inactive Cas9 (dCas9) is fused with DNMT or TET enzymes to add or remove methyl groups at specific genomic sites. This approach allows precise and reversible modulation of HLA gene methylation, offering insights into causal mechanisms of autoimmune disease and opening possibilities for highly targeted, personalized therapies, although issues of delivery, stability, and safety remain to be addressed[92-94].

Search strategy and selection criteria:

Our research strategy aimed to identify peer-reviewed studies investigating DNA methylation patterns within the HLA gene region and their relevance to autoimmune diseases. We conducted a thorough literature review using the PubMed, Web of Science and Google Scholar databases, examining publications from 1990 to June 2025. The search terms included combinations of the following keywords: “DNA methylation”, “epigenetics”, “HLA methylation”, “HLA gene regulation”, “HLA and autoimmunity”, “methylation of HLA alleles”, “SNP and methylation”, and specific autoimmune diseases (e.g. “multiple sclerosis”, “type 1 diabetes”, “rheumatoid arthritis”) in conjunction with HLA-related terms. We included original research articles, systematic reviews and meta-analyses published in English in peer-reviewed journals with an impact factor. Studies focusing solely on non-HLA loci or not addressing epigenetic mechanisms were excluded. All searches were updated as of June 2025.

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