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The genetics and epigenetics of autoimmune diseases

Anura Hewagama[a] and **Bruce Richardson**[a,b,*]

[a] Department of Medicine, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA

[b] Department of Medicine, Ann Arbor Veterans Affairs, Medical Center, 2215 Fuller Road, Ann Arbor, MI 48105, USA

Abstract

Self tolerance loss is fundamental to autoimmunity. While understanding of immune regulation is expanding rapidly, the mechanisms causing loss of tolerance in most autoimmune diseases remain elusive. Autoimmunity is believed to develop when genetically predisposed individuals encounter environmental agents that trigger the disease. Recent advances in the genetic and environmental contributions to autoimmunity suggest that interactions between genetic elements and epigenetic changes caused by environmental agents may be responsible for inducing autoimmune disease. Genetic loci predisposing to autoimmunity are being identified through multi-center consortiums, and the number of validated genes is growing rapidly. Recent reports also indicate that the environment can contribute to autoimmunity by modifying gene expression through epigenetic mechanisms. This article will review current understanding of the genetics and epigenetics of lupus, rheumatoid arthritis, multiple sclerosis and type 1 diabetes, using systemic lupus erythematosus as the primary example. Other autoimmune diseases may have a similar foundation.

Keywords

Epigenetics; Genetics; Lupus; Multiple Sclerosis; Rheumatoid Arthritis

1. Introduction

Self tolerance is essential for normal immune function, and loss of self tolerance can result in autoimmunity. Why self tolerance breaks down is incompletely understood. Susceptibility to auto-immunity is associated with multiple risk factors. A generally higher disease concordance rate in monozygotic relative to dizygotic twins or other family members indicates a genetic contribution for some autoimmune diseases [1]. However, autoimmune disease concordance in identical twins is often incomplete, indicating a requirement for additional factors, presumably from the environment [2]. The nature of the environmental component is poorly understood.

*Corresponding author. 3007 BSRB, 109 Zina Pitcher Place, University of Michigan, Ann Arbor, MI 48109-2200, USA. Tel.: +1 734 936 5560; fax: +1 734 936 9220. brichard@umich.edu (B. Richardson).

Recent evidence indicates that environmentally-induced epigenetic changes, and in particular altered patterns of DNA methylation, contribute to the environment–host interaction in some forms of autoimmunity. A failure to maintain epigenetic homeostasis, due to environmental influences, can lead to aberrant gene expression in specific cells causing loss of tolerance, and the modified cells then contribute to the development of autoimmunity in genetically predisposed individuals [3]. Thus a combination of genetic and epigenetic mechanisms appears to be important in understanding causation of some autoimmune diseases.

Many autoimmune diseases occur more frequently in women, and the reason for this female preponderance is also incompletely understood. Functional studies suggest a role for female sex hormones [4,5], with higher Th1-mediated immune responses [6] and altered T cell homing [7] as possible contributors to the female predominance in autoimmune diseases. Others have suggested that women have a genetic predisposition to autoimmunity due to their second X chromosome [8,9]. Since one X chromosome is silenced by epigenetic mechanisms in women, it is possible that epigenetic mechanisms also contribute to the female predisposition to autoimmunity through effects on the inactive X.

This article reviews the current status of genetic contributions to human lupus, rheumatoid arthritis, multiple sclerosis and type 1 diabetes, and how epigenetic mechanisms may contribute to the development of autoimmunity in genetically predisposed hosts. Systemic lupus erythematosus (SLE) is used as an example where some predisposing genes are known, cells affected by epigenetic alterations have been identified, and genetic/epigenetic interactions are reported. Evidence supporting a role for epigenetic mechanisms in the female predisposition to lupus is also discussed. The status of epigenetic research in rheumatoid arthritis (RA), multiple sclerosis (MS) and type 1 diabetes (T1DM) is also summarized, with the goal of stimulating further study in these areas.

2. Genetics and epigenetics

2.1. Genetics

Genetic polymorphisms are heritable alterations in the DNA sequence. Genetic polymorphisms contribute to phenotypic variation, and sometimes to disease susceptibility, through effects on gene expression and function. Identifying predisposing genetic polymorphisms in rheumatic and other autoimmune diseases provides clues to understand the pathogenic mechanisms involved. Recent advances in gene expression analyses, high-throughput single nucleotide polymorphism (SNP) genotyping, and association studies have identified genetic loci or genes that dictate immune abnormalities in autoimmune diseases. Genome wide studies have already identified genes predisposing to human SLE, RA, MS and T1DM (*vide infra*). Further, spontaneous and genetically engineered animal models have been used to characterize the function of some susceptibility genes in autoimmune models. However, as noted above, twin studies demonstrate that genes alone are often insufficient to cause autoimmunity, and other factors are required. Some of these are epigenetic.

2.2. Epigenetics

In contrast to genetic alterations, an epigenetic change is defined as a heritable change in gene expression that does not involve a change in the DNA sequence. Epigenetic mechanisms play an essential role in eukaryotic gene regulation by modifying chromatin structure, which in turn modulates gene expression. How epigenetic mechanisms regulate gene expression is perhaps best explained from an evolutionary standpoint.

Prokaryotic organisms have a limited number of genes, comparatively small amounts of DNA, and no nucleus. Prokaryotic gene transcription is primarily regulated by transcription factors binding to promoter elements in the DNA. In contrast, eukaryotes have multiple cell types,

more genes, and correspondingly more DNA. Eukaryotes also have nuclei, containing the DNA packaged as chromatin. Chromatin serves in part to package the DNA into the nucleus, and in part to regulate gene expression [10].

The basic chromatin subunit is the nucleosome, consisting of two turns of DNA wrapped around a histone octamer made from 2 molecules each of histones H2A, H2B, H3 and H4. The nucleosomes are then arranged into higher order structures to form chromatin fibers. By this mechanism the 2–3 m of human DNA is packaged into the nucleus of each cell. Chromatin in its native form is tightly compacted and inaccessible to transcription factors and the transcription initiation machinery. However, histone "tails" protrude from the nucleosome, and are covalently modified by acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. These modifications serve as signals, referred to as the "histone code", that initiate a number of processes including the localized remodeling of chromatin from a compact, transcriptionally silent configuration to a more open structure accessible to the transcription initiation machinery. One example of this is histone acetylation. N-acetylation of Lys in histone tails prevents the ε-amino group from binding DNA, promoting an open, transcriptionally active chromatin configuration, while deacetylation of Lys permits DNA binding and transcriptional silencing. Other histone modifications are involved in regulating chromatin structure and gene expression as well [11]. Eukaryotic cells use chromatin structure not only as a mechanism to package DNA into the nucleus, but also as a mechanism to prevent expression of genes not essential or detrimental to cellular function, but for which the cell expresses transcription factors which could bind to their recognition elements within the genes, referred to as "transcriptional noise" [10].

Histone acetylation reflects a balance of the histone acetyltransferases and the histone deacetylases, and is thus sensitive to environmental influences that modify these reactions, potentially altering gene expression. For example, acetyl-CoA is the acetyl donor for the histone acetylation process, and acetyl-CoA pools can be influenced by lipid and protein metabolism, and pyruvate dehydrogenase reactions. Similarly, the histone deacetylase inhibitor sulforaphane (SFN), found in cruciferous vegetables such as broccoli and Brussels sprouts, has been shown to promote histone H3 and H4 acetylation in peripheral blood mononuclear cells [12]. The other histone modifications are similarly sensitive to the environment, creating an inherent instability in this mechanism of gene regulation.

Vertebrates, with quantitatively more DNA than the lower eukaryotes, use DNA methylation to provide a more stable epigenetic mark for gene suppression [10]. DNA methylation in vertebrates refers to the methylation of deoxycytosine (dC) bases uniquely in CG pairs, forming deoxymethylcytosine (d^mC). Methylcytosine binding proteins such as MBD1, MBD2 and MeCP2 bind d^mC then attract and tether chromatin inactivation complexes including the histone deacetylases, promoting localized chromatin condensation into a transcriptionally inactive configuration [13]. The effects of DNA methylation and histone acetylation on chromatin structure are illustrated in Fig. 1.

DNA methylation and histone methylation may be functionally linked. Methylated H3-K9 can bind chromodomain-containing proteins such as HP1 and recruit DNA methyltransferases to methylate adjacent CpG sequences and suppress gene expression [14]. However, methylation of H3K4 and arginine residues on H3 and H4 can result in transcriptional activation.

DNA methylation patterns for any given cell type are established during development by the de novo DNA methyltransferases Dnmt3a and Dnmt3b, then replicated during mitosis by the maintenance of methyltransferase Dnmt1. Dnmt1 binds proliferating cell nuclear antigen (PCNA) in the replication fork, and catalyzes the transfer of the methyl group from S-adenosylmethionine (SAM) to dC bases in the newly synthesized DNA only if the parent strand

is methylated at that position, thereby replicating methylation patterns. Importantly, the replication of DNA methylation patterns during mitosis is also sensitive to the environment, and exogenous agents that decrease SAM levels, or decrease Dnmt1 levels or enzymatic activity, will result in failure to replicate the patterns, and errors may accumulate over successive rounds of cell division. This can cause aberrant expression of those genes silenced by DNA methylation, and for which the necessary transcription factors are present in the cell. A list of exogenous agents reported to alter DNA methylation is shown in Table 1.

3. Genetics and epigenetics in autoimmunity: lupus

3.1. Genetics of SLE

Genetic and epigenetic mechanisms interact to cause lupus-like diseases, and possibly other forms of autoimmunity. A genetic contribution to human lupus is well established. A significant difference in disease concordance between monozygotic twins (25–57%) and dizygotic twins (2–9%) supports a genetic basis [15]. Further evidence for a genetic contribution comes from studies of families in which lupus afflicts members at a rate greater than that of the general population [16]. Recent reviews of lupus genetics [17,18] report more than 20 loci containing lupus associated genes. These are listed in Table 2, and their chromosomal locations shown in Fig. 2. Genes identified include components of the complement activation pathway, IgG Fc receptors, and HLA region genes, supporting earlier work demonstrating important roles for complement, Fc receptors and the HLA genes in lupus autoimmunity. Interestingly, the genome wide searches have also shown a high degree of heterogeneity between populations.

Chromosome 1 contains some of the loci most consistently identified in SLE. The linkage interval 1q23 encodes Fcγ receptors FCGR2A and FCGR3A. FCGRs have different affinities for IgG and its subclasses. The Arg variant at amino acid position 131 of FCGR2A (R131) diminishes binding to IgG2. Similarly, a phenylalanine substitution in position 158 (F158) in FCGR3A reduces the IgG1-, IgG3-, and IgG4-binding capacity of the receptor. These variants may result in defective clearance of immune complexes from the circulation, contributing to their deposition in tissues such as the kidney and blood vessels [19,20]. Other disease associated genes on chromosome 1 include PTPN22, IL10, and C1Q. PTPN22 is involved in regulating T cell activation, while a PTPN22 R620W polymorphism is implicated in an increased risk of SLE [21]. IL 10 is an important cytokine with anti-inflammatory and stimulatory activities, and plays a critical role in the regulation of cellular and humoral immune responses. IL-10/TNFα interactions [22] and the IL10 promoter haplotype that produces higher levels of cytokine [23] are all associated with SLE.

The region in chromosome 6 encoding the major histocompatibility complex (MHC) also encodes components of complement pathway (C2, C4) as well as TNFα and TNFβ. TNFα is a multifunctional proinflammatory cytokine involved in regulating a wide spectrum of biological processes including cell proliferation, differentiation, and apoptosis, while TNFβ mediates a variety of inflammatory, immunostimulatory, and antiviral responses. Polymorphisms in these genes have been implicated in SLE susceptibility [24–26]. Deficiencies in complement pathway genes C2 [27,28], C4 [29], C1Q [18] and C3 [30] appear to cause SLE in some people. Polymorphisms in C2, C4A and C4B are in linkage disequilibrium with HLA-B and HLA-DR alleles [31] and may predispose to SLE. In addition, a significant association of the HLA-DRB1 gene with SLE has been established in Latin American populations [32].

Programmed cell death 1 gene (PDCD1), encoded on 2q37, is considered a strong candidate for SLE association. PDCD1 is upregulated in T cells following activation, and inhibits TCR signaling and T/B cell survival. An intronic PDCD SNP alters a binding site for the runt-related transcription factor (RUNX1), suggesting a mechanism through which the SNP may contribute

to SLE development [33]. CTLA4, located on 2q33, is a negative costimulatory molecule that inhibits T cell activation, and may help to limit T cell responses under conditions of inflammation. Genetic variability in CTLA4 has been implicated in the development of several autoimmune diseases including SLE [34–36]. Locus 2q32 encodes the STAT4 transcription factor, essential for mediating responses to IL12 in lymphocytes, and regulates T helper cell differentiation. The risk allele of the SNP rs7582694 in STAT4 is associated with severe disease manifestations of systemic lupus erythematosus [37–39].

Thus, loci in chromosome 1, 2 and 6 encode several functionally significant genes associated with SLE pathogenesis. However, as shown in Fig. 2 and Table 2, the genetic predisposition of SLE is not limited to just these regions of the human genome. PTPN2 (protein tyrosine phosphatase, non-receptor type 2) located at 1p13 is considered to be the strongest common genetic risk factor for human autoimmunity outside the MHC. It encodes a lymphoid-specific phosphatase (Lyp), which inhibits T cell receptor signaling through Csk kinase. The X-linked gene methyl-CpG-binding protein 2 (MECP2), located on Xq28 and encoding a protein that represses transcription from methylated promoters, has also been associated with lupus. Polymorphisms in MECP2 may have relevance to the epigenetic DNA methylation changes found in lupus and discussed below.

3.2. Epigenetics of SLE

While genetic factors clearly influence lupus susceptibility, incomplete disease concordance between identical twins suggests a requirement for non-genetic factors, presumably from the environment [15,40]. Convincing evidence indicates that epigenetic mechanisms, and in particular impaired T cell DNA methylation, provide this additional factor.

Early work revealed that normal, antigen specific CD4 + T cells treated with DNA methylation inhibitors like 5-azacytidine will lose restriction for nominal antigen and respond to self class II MHC molecules presenting inappropriate antigens [41]. These epigenetically modified, autoreactive cells resemble those causing chronic graft-vs-host disease, which presents primarily as lupus in murine models [42]. Injecting demethylated murine CD4 + T cells into syngeneic hosts causes a lupus-like disease [43,44] supporting the association between autoreactive responsiveness to self class II MHC molecules and lupus-like autoimmunity.

The observation that a DNA demethylating drug can cause a lupus-like disease suggests that drugs which cause a lupus-like disease may inhibit DNA methylation. Procainamide and hydralazine, which cause ANA’s in most people and a lupus-like disease in a genetically predisposed subset [45], were subsequently found to inhibit DNA methylation [46], and murine T cells treated with these drugs caused lupus-like autoimmunity in syngeneic mice identical to that caused by 5-azacytidine treated T cells [7]. Procainamide is a competitive inhibitor of Dnmt1, the enzyme responsible for maintaining DNA methylation patterns in differentiated cells [47,48], while hydralazine prevents Dnmt1 upregulation during mitosis by blocking ERK pathway signaling at PKCδ [49]. These reports thus raise the possibility that other agents encountered in the environment may also cause a lupus-like disease in genetically predisposed individuals, either by inhibiting Dnmt1 activity or by decreasing Dnmt1 levels.

Patients with idiopathic lupus have changes in T cell signaling identical to those caused by hydralazine. Initial studies demonstrated that T cells from patients with active lupus have hypomethylated DNA, due to decreased Dnmt1 levels and activity [50,51]. Interestingly, the decrease in Dnmt1 levels is due to impaired ERK pathway signaling [50] caused by a block at PKCδ, also inhibited by hydralazine [49]. Inducing an ERK pathway defect selectively in T cells of adult transgenic mice is sufficient to decrease Dnmt1, demethylate DNA and cause anti-DNA antibodies, persuasively demonstrating that acquired T cell ERK pathway defects are sufficient to cause lupus-like autoimmunity, likely through DNA demethylation [52].

Persuasive evidence also demonstrates that CD4 + T cells from patients with active lupus demethylate the same DNA sequences and overexpress the same genes demethylated by 5-azacytidine in vitro, and that overexpression of the demethylated genes contributes to the development of lupus-like autoimmunity. 5-azacytidine causes T cell autoreactivity by demethylating sequences just upstream of the *ITGAL* promoter, encoding CD11a, leading to overexpression of LFA-1 (CD11a/CD18) [53]. During T cell activation by antigen presenting cells, LFA-1 surrounds the T cell receptor-MHC complex, providing stabilization to the interaction as well as costimulatory signals [54]. Overexpressing LFA-1 may overstabilize the lower affinity interaction between the TCR and self class II MHC molecules as well as increasing costimulatory signals, permitting activation of T cells by the class II MHC molecules without the appropriate antigen. Increasing T cell LFA-1 expression by transfection causes an identical MHC-specific autoreactivity in vitro, and injecting LFA-1 transfected CD4 + T cells into syngeneic mice causes lupus-like autoimmunity [55], demonstrating a causative role for LFA-1 overexpression in T cell autoreactivity and in lupus pathogenesis. Importantly, CD4 + T cells from lupus patients demethylate the same *ITGAL* regulatory sequences and overexpress LFA-1 on an autoreactive T cell subset [56], indicating that the same mechanism contributes to idiopathic lupus and the demethylation lupus model.

The 5-azacytidine T cell DNA demethylation model also predicted other T cell DNA methylation alterations that were subsequently found in lupus T cells. 5-azacytidine was shown to demethylate and cause overexpression of the cytotoxic molecule perforin and the B cell costimulatory molecule CD70 in CD4 + T cells, and CD4 + T cells from lupus patients were found to demethylate the same regulatory sequences and overexpress the same molecules that were affected by 5-azacytidine [57,58]. Perforin contributes to autoreactive macrophage killing by lupus T cells, generating a source of antigenic apoptotic nucleosomes [58], while CD70 overexpression contributes to B cell overstimulation and antibody overproduction [59]. Thus the DNA demethylation model can predict changes in T cell gene expression that contribute to lupus pathogenesis. These studies also demonstrate that demethylated CD4 + T cells are sufficient to cause autoimmunity, indicating that demethylated, autoreactive T cells are the cells responsible for breaking tolerance and activating lupus in genetically predisposed people.

3.3. Epigenetics and X chromosome reactivation in women with lupus

CD40L is another B cell costimulatory molecule overexpressed on lupus T cells and contributing to autoantibody production [60]. Interestingly though, *CD40LG* is on the X chromosome, so men have only one copy while women have 2, and the copy on the inactive X in women is silenced by mechanisms including DNA methylation. Studies similar to those described above demonstrated that 5-azacytidine caused overexpression of CD40L on CD4 + T cells from women but not men, and that the overexpression was associated with demethylation of *CD40LG* on the inactive X [61]. Further, women with active lupus demethylated and overexpressed CD40L, while men with active lupus did not overexpress CD40L [61]. Since CD40L overexpression contributes to the pathogenesis of lupus-like autoimmunity [62], demethylation of genes on the inactive X may predispose women to SLE.

3.4. Genetics and epigenetics in drug induced lupus

Drug induced lupus currently provides the best example of how an environmental agent that affects DNA methylation can cause autoimmunity in a genetically predisposed host. Studies summarized above demonstrate that the lupus-inducing drugs procainamide and hydralazine are DNA methylation inhibitors [46], that human CD4 + T cells treated with these drugs or the DNA methyltransferase inhibitor 5-azacytidine overexpress methylation sensitive genes and become autoreactive, and that murine CD4 + T cells treated with procainamide, hydralazine or 5-azacytidine cause a lupus-like disease in syngeneic mice [7]. These reports suggest that

procainamide and hydralazine may cause a lupus-like disease in humans through similar epigenetic mechanisms.

Interestingly, while a majority of individuals will develop a positive ANA if they receive procainamide or hydralazine long enough, people those genetically metabolize hydralazine or procainamide quickly (rapid acetylators) take longer to develop ANA's than those that metabolize these drugs slowly [45], demonstrating an epigenetic link between "environment" and genetics in the autoantibodies induced by these drugs. Similarly, HLA-DR4 and female sex are reported to predispose individuals to the development of symptomatic hydralazine-induced lupus [63]. It is reasonable to propose that genetic elements will also promote the development of lupus-like autoimmunity in people with hypomethylated DNA caused by other environmental agents affecting DNA methylation.

4. Genetics and epigenetics of rheumatoid arthritis

4.1. Genetics of RA

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting approximately 3% of the population worldwide, and characterized by chronic inflammation and destruction of the synovial joints leading to progressive joint damage and disability. Familial and twin studies suggest a >50% genetic contribution to RA, and a high concordance rate in monozygotic twins (12–30%). RA is also more prevalent in first-degree relatives [64]. A lower prevalence of RA in rural Africans than their counterparts who migrate to the towns suggests the importance of environmental factors in RA [65]. Genes known to be associated with RA are shown in Table 3. The contribution of human leukocyte antigen (HLA) genes at 6p21 shows the strongest linkage to RA. HLA-DRB1 allele variants are well characterized and their predisposition to RA is clear [66]. However, familial risk due to the HLA genes has been estimated to be only ~30%, suggesting that non-HLA genes may play a significant role in RA susceptibility. The PTPN2 1858T variant was found to be associated with RA, T1DM and SLE [67]. However, inconsistent results have been obtained in different populations for the association of CTLA + 49/G SNP to RA [68]. An SNP haplotype marked by rs7574865 of STAT4 is also associated with susceptibility to both RA and SLE.

4.2. Epigenetics of RA

In contrast to lupus where T cell DNA demethylation can be shown to cause autoimmunity, less is known about epigenetics in RA, and the abnormal cell(s) responsible for initiating RA are uncertain. Current models propose that the initiating event is a T cell response to an agent acquired from the environment, but the nature of the environmental trigger is uncertain [69]. Aberrant expression of genes in RA synovial fibroblasts (RASF) lacking specific genetic mutations suggests that epigenetic mechanisms may be involved. Activated RASF demonstrate DNA demethylation and increased expression of normally methylated repetitive DNA elements such as the retrotransposon LINE-1, hypermethylation of regulatory and death-associated proteins, and histone deacetylase induced changes in the posttranslational activation of transcriptional activators and nuclear proteins [70]. T cell DNA is demethylated in RA [51], and may result in the generation of autoreactive T and/or B cell clones in RA as it does in lupus. The CD21 promoter is also demethylated in RA PBMC and synovial fluid cells [71]. Further evidence for an interaction of environmental and genetic factors in RA pathogenesis comes from studies examining cigarette smoking and susceptibility genes in RA patients. The presence of risk factor PTPN22 R620W interacts with heavy cigarette smoking in a multiplicative manner in RA [72]. How and if smoking influences epigenetic mechanisms is unknown.

5. Genetics and epigenetics of multiple sclerosis

5.1. Genetics of MS

Multiple sclerosis is a chronic inflammatory neurodegenerative autoimmune disease also believed to be caused by genetic and environmental factors. A concordance rate of 30% in monozygotic twins compared to 5% for dizygotic indicates a significant genetic component in disease susceptibility. The HLA gene cluster at chromosome 6p21.3 has been established by both candidate gene association and whole genome linkage analysis [73]. HLA-DR2 phenotype, HLA-DRB1*1501, DQAl*0102, and DQB1*0602, are strongly associated with MS susceptibility. HLA-DRB1*1501 is most consistently associated with MS in genome wide linkage studies. T cells recognize antigen presented by molecules of the MHC, and polymorphic HLA-DRB1 residues can affect the shape and charge at the peptide-binding site of the HLA molecule. HLA factors account for 20–60% of the MS genetic risk. Non-MHC loci also associated with MS (Table 4) including cytokines and their receptors which may drive the inflammatory process in an MS plaque. Increased levels of the proinflammatory cytokines IL1, IL4, IL6 and TNFα, and decreased levels of anti-inflammatory cytokines IL10 and IL4 have been reported to correlate with disease progression [74].

5.2. Epigenetics of MS

The discordance rate of 70% among monozygotic twins highlights the importance of environmental factors in disease pathogenesis. Studies of individuals with similar genetic backgrounds but living in different parts of the world have revealed significant differences in disease prevalence [75]. Sunlight exposure appears to have a protective role in MS, possibly mediated by vitamin D3 [76]. Epstein–Barr virus (EBV) infection has also been implicated in the inflammatory response in MS [73]. However, less is known about the epigenetics of MS. Myelin basic protein (MBP) citrullination can result in a loss of myelin stability in MS brains, and the enzyme peptide arginine deiminase 2 (PAD2) catalyzes the MBP citrullination. Increased citrullinated MBP in MS white matter may be due to hypomethylation of the PAD2 promoter and subsequent PAD2 overexpression [77].

6. Genetics and epigenetics of type 1 diabetes mellitus

6.1. Genetics of T1DM

T1DM is another example of an autoimmune disease with genetic and environmental components. A concordance rate of 30–50% in monozygotic compared to 5% in dizygotic twins demonstrates a significant genetic component in disease susceptibility. Common genetic elements appear to contribute to a strikingly higher prevalence of T1DM and MS in the population of Sardinia. Whole genome linkage scans have identified chromosome regions 6q26, 10q21.2, 20p12.3 and 22q11.22 as common to both autoimmune diseases in this population [78]. A comprehensive review reveals several other genetic susceptibility loci [79]. The major locus determining T1DM familial aggregation is the HLA region on chromosome 6p21, and accounts for about 50% of the familial clustering. HLA haplotypes DR4-DQ8, DR3-DQ2 are present in 90% of T1DM patients. DR15- DR6 has a protective association with T1DM [79]. Table 5 shows non-HLA loci associated with T1DM. The insulin gene (INS) locus at 11p15 is the second most important susceptibility locus. A region containing a variable number of tandem repeats (VNTR), located upstream of the insulin gene, is associated with T1DM. Variation in the size of the VNTR correlates with the thymic expression of insulin mRNA. The short form of the insulin VNTR is associated with type 1 diabetes whereas the long form is associated with decreased risk [80].

6.2. Epigenetics of T1DM

Non-genetic factors appear to enhance the autoimmune process causing destruction of islet beta cells in T1DM. Environmental factors proposed include nutrition and viruses [81]. The most persuasive evidence for a viral etiology is provided by the congenital rubella syndrome [82]. However, no direct evidence for epigenetic changes associated with T1DM is available. Since nutrition provides the methyl donors (methionine, choline) and cofactors (folic acid, vitamin B12 and pyridoxal phosphate) essential for DNA and histone methylation [83], it is possible that epigenetic mechanisms contribute to T1DM as well.

7. Summary

Many of the poorly understood autoimmune diseases have a genetic and an environmental component. Understanding of autoimmunity genetics is developing rapidly, but how the environmental contributes to disease development is still largely unknown. Convincing evidence indicates that the environment modifies the immune system through epigenetic mechanisms to cause SLE, raising the possibility that epigenetics may contribute to the development of other forms of autoimmunity. Further study of epigenetic abnormalities in other diseases, such as RA, MS and T1DM, may clarify how the environment alters the immune system in these diseases, and suggest ways to ameliorate these conditions.

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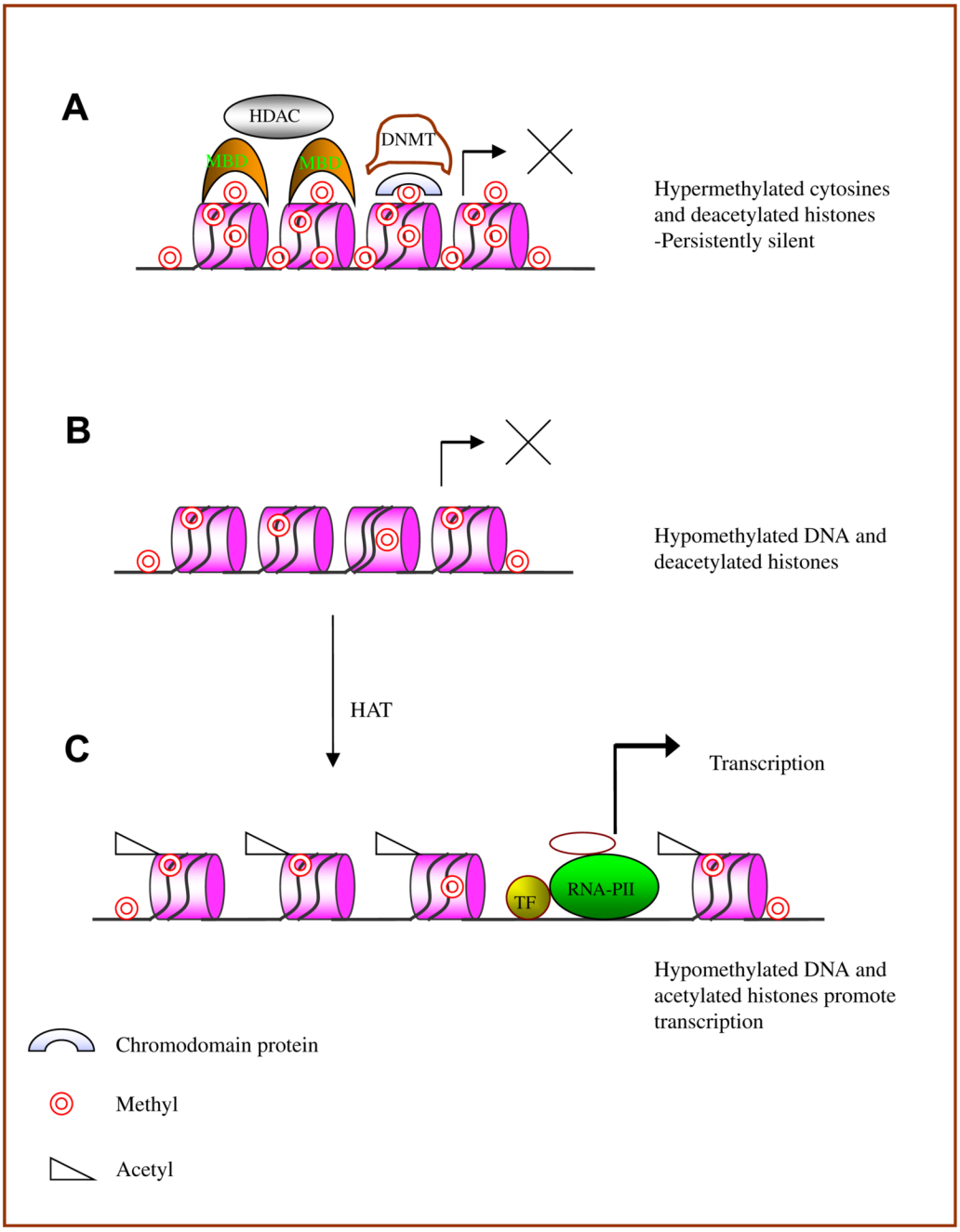

Fig. 1.

Role of DNA methylation and histone modifications in gene regulation. A. Methylation of cytosines in CpG pairs recruits proteins containing a methyl-CpG-binding domain (MBD) such as MeCP2. Once bound, the MDB's form a complex with histone deacetylases (HDAC) or directly block transcription factor binding. In addition, methylated histone tails may recruit DNMTs through chromodomain proteins, to methylate DNA for long term gene silencing. B. MBD cannot bind hypomethylated DNA. Thus the recruitment of HDAC is impaired. C. Acetylation of positively charged lysine amino groups in histones by histone acetyltransferases (HAT) neutralizes the charge and disrupts binding to the negatively charged phosphates in

DNA. The “relaxed” DNA formed facilitates binding of transcription factors and RNA polymerase II promoting active transcription.

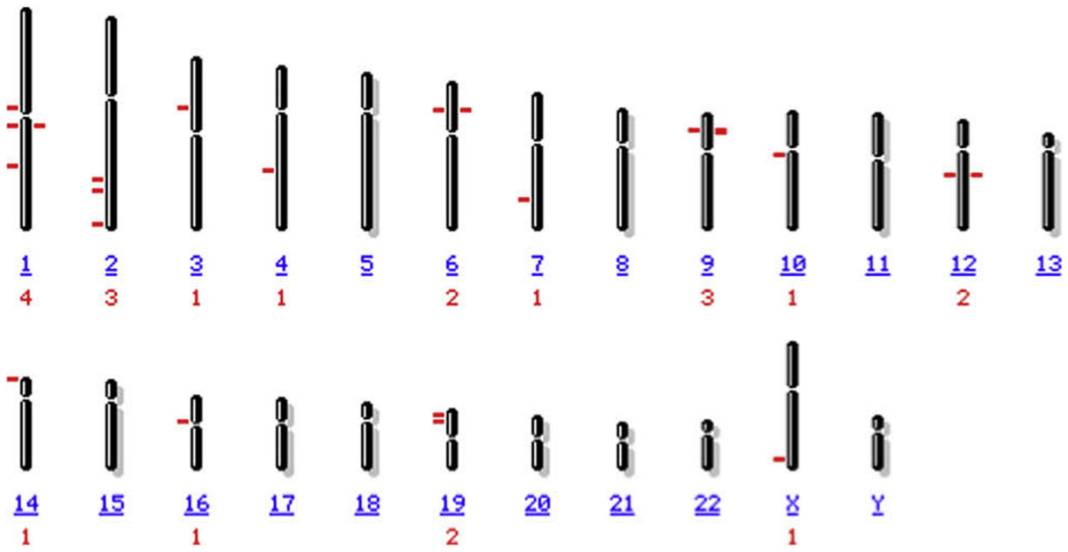

Fig. 2.

Chromosomal location of genes predisposing to SLE. The number or letter beneath each chromosome identifies the chromosome, and the number below that shows the number of lupus associated sites on the chromosome. The locations of lupus predisposing genes are indicated by the lines.

Table 1

Exogenous agents associated with altered DNA methylation.

Agent
Folic acid
Methionine
Choline
Hydralazine
U0126
PD98059
UV light
SP600125
Procainamide
5-azacytidine
Genistein
Lycopene

Table 2

Genes associated with systemic lupus erythematosus.

Chromosome	Locus	Gene	Ref(s)
1	1p13	PTPN22	[84,85]
	1q23	FCGR2A	[20,84,86,87]
	1q23	FCGR3A	[20,84,88]
	1q32	IL10	[22,89,90]
	1p36	C1Q	[18]
2	2q32	STAT4	[38,39,84]
	2q33	CTLA4	[34,35,91–93]
	2q37	PDCD1	[33,94,95]
3	3p14	PXK	[84]
4	4q26	IL21	[96]
6	6p21	C2	[27,28]
	6p21	C4	[27,29,97]
	6p21	TNFA	[22,25,98]
	6p21	TNFB	[26,99,100]
7	7q32	IRF5	[101,102]
9	9p22	IFNA	[103]
	9p21	IFNB	[18]
10	10q11	MBL	[104]
12	12q14	IFNG	[105]
16	16p11	ITGAM	[84]
19	19cen-q13	MAN2B1	[104,106]
	19p13	C3	
X	Xq28	MECP2	[107]

Table 3

Genes associated rheumatoid arthritis.

GeneID	Gene/region	Chromosome	Reference
26191	PTPN22	1p13	[21]
23569	PADI4	1p36	[72]
7133	TNFRSF1B	1p36	[108]
6775	STAT4	2q32	[39]
5133	PDCD1	2q37	[95]
6583	SLC22A4	5q31	[109]
3123	HLA-DRB1	6p21	[110]
861	RUNX1	21q22	[109]

Table 4

Non-MHC genes associated multiple sclerosis.

GeneID	Gene	Region	Reference
3559	IL2RA	10p15	[73]
3575	IL7R	5p13	[73]
7124	TNFA	6p21	[74]
3554	IL1RA	2q12	[74]
348	APOE	19q13	[74]
965	CD58	1p13	[73]
934	CD24	6q21	[74]

Table 5

Non-MHC genes associated with type 1 diabetes.

GeneID	Gene	Region	Reference
3630	INS	11p15	[79]
26191	PTPN22	1p13	[79]
5771	PTPN2	18p11	[79]
3559	IL2RA	10p15	[79]
1493	CTLA4	2q33	[79]
64135	IFIH1	2q24	[79]