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Genetic and epigenetic etiology of autoimmune diseases: lessons from twin studies

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Twin studies have been considered as strong approaches in determining the cause of complex diseases with regard to identifying the involvement of multiple genes, single genes, environmental factors, and a possible relation between genetics and the environment. The concordance observed among monozygotic (MZ) twins suggests the involvement of genetic factors. Nonetheless, MZ twins demonstrate a rate of discordance in different characteristics, like proneness towards diseases, despite virtually identical genetic backgrounds. Discordance has been suggestive of the involvement of the environment alongside genetic factors. As a result, a bulk of studies has supported the hypothesis that environmental factors can impress the epigenetic construction and, therefore, influence disease susceptibility. Twin studies yield data about clinical courses and outcomes of disease, in addition to knowledge of genetics, epigenetics, environmental factors, and risk of disease development. To date, genome-wide association studies (GWASs) have reported that genomic variants are responsible for only a number of cases of autoimmunity in twins and have been unable to explain the disease discordance among MZ twins. With respect to the exploration of epigenetic mechanisms in autoimmunity, discordant MZ twins have been attractive models and have contributed remarkably. It is essential for future studies to evaluate the genetic variants as well as epigenetic changes in large twin populations. The current review discusses the genetic and epigenetic lessons obtained from studies of twin cases.

Keywords: environmental factors, epigenetic changes, genetic factors, monozygotic twins.

Introduction

Twin cases are regarded as precious facilities, which contribute to discriminating the causal mechanisms of disease, mediated by genetic or environmental factors [1, 2]. Twin cases can be applied by comparing the disease concordance/discordance between monozygotic twins (MZ, or identical twins) and dizygotic twins (DZ, or fraternal twins). In MZ twins, it is assumed that both individuals share 100% of their genomic sequences. Moreover, the higher phenotypic concordance rate of MZ twins in comparison to DZ twins implies to predominant influence of the genetic background, while environmental factors are concluded to have a greater role if concordance rates are low.

Oftentimes, the concordance rates are resultant of both genetic and environmental factors, which vary in degrees of influence. Among the environmental factors are microorganisms, chemicals and drugs, and lifestyle-related factors, such as diet and exercise [3]. In combinations of genetic and environmental factors, genetically susceptible individuals are exposed to environmental agents over and over again throughout life, which ultimately eventuates in disease initiation. This scenario occurs in multifactorial disease, such as autoimmune disorders, which are supported through a weak applicability of strong genetic associations obtained from GWASs [4].

It should be noted that MZ twins demonstrate a concordance rate between 5% and 75%, which is 2 to 5 times higher than DZ twins [5]. However, discordance rate is the other side of the coin. In some disorders, a certain mutation is exclusively the cause of the bad outcome, which might occur as somatic mutation during embryonic development. Nonetheless, in case of no mutation is identified in association with the disease, it is suggested that the discordance might be the consequence of epigenetic changes at the locus attributed with the disease pathogenesis. As a result, the discordance observed in the disease occurrence of MZ twins could be explained through the collaboration of external (environmental) factors that impress disease

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predisposition by modifying the epigenome profile that finally determines the function of genes [6].

This review will discuss the current understanding of typical inflammatory autoimmune diseases with respect to genome and epigenome highlights, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Ankylosing Spondylitis (AS), and Psoriasis.

Twin studies in autoimmune diseases

Numerous factors have been implicated in autoimmune disorders, including clinical manifestations, gender, age, genetic predisposing factors, race, geoepidemiology, and etiology. Evaluating the etiopathogeneses of autoimmune disorders in twin cases has shown that there is a contributing genetic component to these diseases with concordance rates varying between 75% to 83% [7, 8]. However, in some other autoimmune conditions like SSc and RA, the role of genetic factors seems to be less significant, and other elements such as environmental factors may be highlighted [9-12]. Although studies may investigate identical populations, they might observe conflicting findings. This may be due to the circumstances of the studies like sample size, limited follow-up or screening of data, a lack of sufficient clinical data, and unsuitable twin determinants. Furthermore, twin studies have largely been case reports with fewer cohort evaluations of twin populations. On the other hand, epigenetic marks seem to be emerging factors affecting the concordance rates of such diseases. In a remarkable proportion of identical twins with autoimmune disorders, one twin remains unaffected, implying that other determinants such as environmental factors and epigenetic modifications may also play a role.

Genetic implications

Rheumatoid arthritis

Genetic association studies of twins with RA have elucidated a lower level of concordance in MZ twins, proposing a lower degree of genetic involvement in RA compared with other autoimmune diseases. Lawrence reported an RA concordance of 30% [13]. However, a broad Finnish cohort study of 4136 MZ and 9162 DZ twins demonstrated an RA concordance of 12.3% among MZ twins, and a DZ twin concordance of 3.5% [9]. A high level of concordance has been shown in a 1980 Australian twin cohort study which included 3808 pairs of twins [14]. Another cohort study of 186 twins conducted in 1990 described an RA prevalence rate of 0.4% among MZ and DZ twins. Pairwise concordance rates were 21% and 0% in MZ and DZ twins, respectively [14]. The exact mechanisms of the concordance rate could not be determined, because there was an 89% false positive proportion of self-reporting RA according to the questionnaire [14]. This indicates that the application of questionnaires in twin studies is limited by the probable lack of clinical verification. Slightly lower rates of twin concordance (3.6% in DZ and 15.4% in MZ twins) were reported in a UK cohort study [11]. However, the sample size of that study included 112 DZ and 91 MZ twins, fewer subjects than the Finnish cohort study. A UK cohort study described that the initial discordance between twins became concordant over time [11]. Furthermore, the risk of developing RA in an initially unaffected twin group was increased over time, implying that overall concordance rates in autoimmune diseases such as RA with obvious clinical manifestations expanded over several years. As a result, it is critical to describe the concordance rate only after prolonged and full follow-up [11]. Such cases provide evidence that the development of RA in pairs may occur with delayed time, implicating the function of non-genetic factors. Some recent studies have presented an incongruous proportion of RA concordance in twins. In the study of Svendsen et al. [12], questionnaires were mailed to 37,338 twins from the Danish twin population. Their results indicated that RA prevalence was confirmed clinically in 36 DZ and 13 MZ twins. Unexpectedly, a 0% MZ and 8.8% DZ concordance was reported [12]. In contrast, the heritability of RA was estimated to be 53% in the UK cohort study and 65% in the Finnish study, highlighting the involvement of a wide spectrum of genetic factors in the RA pathogenesis [15]. Other studies that have investigated the heritability rate of different autoantibodies in RA have highlighted the essential role of genetic components in anti-citrullinated antibodies (ACA)-negative RA patients [16].

Similar to many autoimmune disorders, the prevalence of RA is higher in women than in men, and this has also been reported in many twin studies. In the study of Silman et al., 85.7% of MZ twins [11] versus 82.1% of the DZ twins were female. Moreover, a concordance of 16.7% versus a concordance of 3.8% was demonstrated in female-female MZ twins compared to female-female DZ twins [11]. This trend of high prevalence among females was also indicated by the study of Svendsen et al. [12], in which the prevalence rates of female MZ and DZ twins were 69.2% and 69.4%, respectively. This inclination in the ratio of male/female twins was also shown by the survey of Van Der Woude et al. [16]. The female dominance of RA is revealed in the relative risk of 4:3 in females versus males [14]. The major variable which

influences the concordance rate of RA among twins is gender. In their study, MacGregor et al. [15] estimated concordance rates between male and female twin pairs in Britain and Finland; a 9.5% concordance for RA in Finnish male MZ pairs versus 2.3% in DZ pairs was shown [15]. Furthermore, the concordance rate for female MZ pairs was 13.5%, while this rate was observed to be 3.8% between DZ pairs. Additionally, the concordance rate for British male MZ pairs was 7.7% in comparison to 0% in DZ pairs. In contrast to males, the concordance rates for females in MZ and DZ twins were 16.7% and 3.8%, respectively [15]. There was also a 4.5% opposite-sex pair concordance between British twins [15]. Since the emergence of GWAS studies, more than 30 genes have been identified that demonstrate associations with RA risk [17-24]. Among them, *KAZALD1*, *PRKCQ*, and *TNFAIP2* need further precise investigations, while others such as *IL12RB*, *PTPN22*, *HLA-DQA1*, *HLA-DRA1*, *HLA-DRB1*, and *MICA* have been strongly associated with RA susceptibility [17, 18]. Chromosome 4q27, which had previously been associated with type 1 diabetes mellitus (T1DM), was identified in association with RA risk, proposing that this locus might confer a shared risk for autoimmune disease development [25]. It has been hypothesized that an unaffected twin might be in an intermediate or temporary condition of immune impairment, which could facilitate the development of RA in cases with sufficient and essential environmental factors [26]. Epigenetic modifications as well as other exposures present extra contributing factors for consideration in the initiation and perpetuation of RA and might shed new light on the exploration of the roles of genetic factors in RA and other autoimmune disorders [27]. The emerging epigenetic mechanisms affect the expression of genes by modifying the histone proteins and methylation of DNA CpGs, which could somehow elucidate the disagreement in concordance rates between twins [28]. The implications of the epigenetic involvement observed in twin pairs will be discussed with more detail in upcoming sections.

Systemic lupus erythematosus

SLE is a good example of the potential restrictions associated with variable diagnostic criteria or publication bias over the years to explain concordance rates. One broad literature review [29] evaluated 247 twins who had at least one case of SLE. Of these, 60/151 (40%) MZ twins versus 4/96 (4%) DZ twins were clinically concordant [29]. Moreover, the study of Block et al. [30] described 12 pairs of female-female twins, including 3 DZ, 7 MZ, and 2 of undetermined zygosity, and compared these with 17 previously reported twins. They found that 4 out of 7 MZ twins (57%) were concordant for SLE, whereas there was a 71% concordance for hypergammaglobulinemia and the anti-nuclear factor [30]. Interestingly, Block et al. reported in another study the follow-up results of subsequent concordance in twins that were discordant during initial evaluations [29]. This observation emphasizes that the exact and accurate estimation of concordance rates may require a long follow-up period for twin pairs. It has been revealed that unaffected MZ or DZ twins often have immunological and serological irregularities, including lymphocyte tubuloreticular inclusions (TRIs) and self-reactive antilymphocyte antibodies [31,32]. As is true for other autoimmune diseases, it is possible that epigenetic modifications play a major role in MZ and DZ twin discrepancies and SLE outcomes [33, 34]. A cohort study of MZ twins and HLA identical siblings in Australia described that none of six DZ, one of four MZ, and none of 18 HLA identical siblings displayed concordance for SLE [35], implying that non-HLA genes play a critical role in the pathogenesis of SLE [35]. Up to now, more than 35 genes have been associated with SLE risk, many of which have been near the threshold of genome-wide association significance [36-49]. Significant associations have been demonstrated in complement genes, FCγ receptor genes, and HLA regions [36]. In a GWAS on 1717 SLE patients and 4813 healthy subjects, various genes including *ITGAM*, *STAT4*, *IRF5*, and *HLA* were discovered to be related with the production of anti-dsDNA antibody in SLE [38]. Furthermore, the association of *TNSF4* and *BANK1* with SLE in different populations like Hong Kong, Caucasian, and Chinese have been addressed [39, 50]. The possibility of finding other associations is not far off; however, the study of the importance of gene-gene interaction and its association with the pathogenesis of SLE is still in its infancy [48].

Systemic sclerosis

While the number of twin studies in SSc is limited, those which have been conducted have demonstrated that there is a poor concordance between MZ twins for the clinical manifestation of SSc. On the other hand, a significant concordance for molecular and immunological features of SSc was identified through these studies [51-54]. A study of 703 families in the USA, including 11 SSc families, indicated a 0.026% frequency in the common population compared to a 1.6% frequency of SSc between first-degree relatives [55]. In another large twin study of SSc, including 18 DZ twins (1 male, 13 females, and 4 opposite-sex pairs) and 24 MZ (1 male, 23 females)

twins, the DZ twin concordance was 5.6% versus 4.2% between MZ twins [51]. Furthermore, the concordance rate for anti-nuclear antibody (ANA) was estimated to have a 40% concordance in DZ twins versus 90% concordance between MZ twins [51]. The microarray study of Zhou et al. including 5 DZ discordant, 10 MZ pairs, and 5 healthy subjects also presented a good concordance for molecular mechanisms of SSc in MZ twins [52]. Moreover, the fibroblast gene expression profiles of SSc patients between non-concordant DZ twins and healthy subjects were inconsistent. However, the fibroblast gene expression profile of MZ twins was similar among SSc patients [52]. The upregulation of *CTGF*, *COL1A2*, and *SPARC*, which are SSc signature genes, was observed in a healthy pair of MZ twins [52]. Taken together, while the concordance rate between MZ twins is low, the molecular features of SSc showed a significant concordance, which may not be manifested through the clinical picture of SSc. These findings are supportive of a high genetic susceptibility in the pathogenesis of SSc.

The genetic implications of SSc have also been elucidated in a recent GWAS [56-60]. Prior studies had reported the association of SSc with *CD247*, *STAT4*, *BANK1*, *IRF5*, *BLK*, and *TNFSF4* [56-69], whereas another GWAS showed different results [70]. In the later study which included four cohorts of 5171 healthy individuals and 2296 SSc patients [70], the polymorphisms of *IRF8* were associated with limited cutaneous SSc (lcSSc), while ACA-positive lcSSc was related to the *SOX5* and *GRB10* genes [70]. There was an association between ACA positivity and HLA-DQB1, while the anti-topoisomerase I antibody (ATA) was related to HLA-DPA1/B1 [70]. ATA positivity together with ACA revealed an association with the *NOTCH4* gene [70].

Ankylosing Spondylitis

Genetic studies of AS have provided a deep understanding of the etiopathogenesis of the disease. It has been established that AS predisposition and the intensity of clinical complications are determined mainly through genetic components. Vast advances in exploring the susceptibility alleles in AS have discovered 113 loci with the direct implication that they are responsible for approximately 10% of AS heritability. However, it has been established that the human leukocyte antigen (HLA)-B27 affects roughly 10% of the AS genetic risk. Investigations of familial AS cases have demonstrated that 20% of first-degree relatives with AS probands develop the disease [71-79]. Other than genetics, a few epigenetic studies have also shed new light on the disease etiology and pathogenesis [80].

Although extensive research has revealed a major role of genetic risk factors in the AS etiopathogenesis, fewer twin pair evaluations have addressed this issue. In a cohort study that evaluated 26 pairs of Finnish twins (6 MZ pairs and 20 DZ pairs), it was observed that both individuals in 3 MZ pairs and 3 DZ pairs were affected by AS. Also, 2 MZ pairs were completely discordant for AS characteristics. All the affected cases were HLA-B27 positive. On the contrary, all 5 unaffected DZ twins were B27 negative. This investigation demonstrated that the development of AS lays largely on genetic components, HLA-B27 may play a role in this susceptibility [78]. An evaluation of AS twins from the Royal National Hospital for Rheumatic Diseases database demonstrated that genetics determines a major part of AS susceptibility. Moreover, environmental factors may also contribute to disease proneness, as HLA-B27 was observed to play a minor role in overall AS genetic susceptibility. Other than HLA-B27, HLA-B60 was also associated with AS in probands. Additionally, in the study of Brown et al., 6 out of 8 MZ twins, 4 out of 15 B27-positive DZ twins, and 4 out of all 32 DZ twins were concordant for AS [81]. A Norwegian and two Danish nationwide twin surveys comprising 37,388 and 46,331 Danish twin individuals were determined by questionnaire if they were affected with AS in 1994 and 2002, respectively. After validation, it was observed that 39 probands had AS. This survey disclosed that MZ twins were 40% concordant for AS, while DZ twin pairs were 4% concordant. Although self-reporting AS by questionnaire needs careful confirmation, AS prevalence in a Danish twin population was 0.1%. This cohort twin study assigned, again, a role to genetic factors in AS etiopathogenesis [82]. Although these investigations are few in number, they do demonstrate the strong role of genetics in AS susceptibility.

Psoriasis

Psoriatic disorders are systemic inflammatory settings, which comprise psoriasis and psoriatic arthritis (PsA) and affect both genders similarly [83]. Ranging from 20% to 64%, MZ twins display high concordance rates in patients with skin psoriasis and a higher incidence in male pairs [84-88]. Epidemiological studies have demonstrated that genetic risk factors are responsible for 68% (60-75%) of the psoriasis susceptibility, while the remaining variation is justified through environmental factors and epigenetic modifications [84, 89]. Evidence has proven that psoriasis and PsA are of different genetic backgrounds, as observed by the association between different phenotypes of

psoriasis and HLA-Cw06 or HLA-B27 [90]. Psoriatic cases have rarely been studied in twins; thus, further investigations are required to achieve a clear picture of the role of genetics in psoriasis proneness.

Epigenetics implications

Today, the contributions of both genetic factors and environmental elements to the development of autoimmune diseases have been established. Studies have proven that there is an unaffected twin in most cases of MZ or DZ twins with an autoimmune disorder. While the investigation of concordant twins has recognized genetic risk factors, the concordance rates in most autoimmune disorders are remarkably low, implying to the involvement of other regulatory mechanisms in determining the disease onset and development. While phenotypic concordant twin cases for autoimmune disorders can be employed to investigate the heritability and genetic implications, discordant cases allow the evaluation of the role of non-genetic factors. On the other hand, numerous initially unaffected twins have been observed through follow-up studies to develop the disease in the future. Despite the favorable potential of MZ twins to be exerted in the evaluation of epigenetic implications in the development of autoimmune disorders, little has been investigated within this context. The dysregulation of epigenetic marks has been extensively studied in autoimmune disorders. Of note, aberrancies in the DNA methylation pattern in CpG islands have concentrated mainly on RA, SLE, and SSc. Early abnormal alterations in DNA methylation patterns were noticed in T cells from patients with autoimmune diseases like SLE and RA, supporting a global hypomethylation of DNA [27].

Environmental triggers and autoimmune diseases

Environmental risk factors that are intensely associated with the development of autoimmune disorders are smoking, low serum levels of vitamin D, and infectious agents [91]. Smoking has been reported to affect epigenetic marks such as DNA methylation [92, 93], histone acetylation [94], and the expression profile of miRNAs [93]. Vitamin D has been reported to have an active role in the status of histone modifications such as recruiting histone acetyltransferases or histone deacetylases to the vitamin D target genes, hence regulating the expression circumstances of the related genes [95]. Moreover, the Epstein-Barr virus (EBV) actively employs the epigenetic mechanisms of its host and modulates the expression of viral genes in order to survive within host cells [96-98]. Animal studies have established that various environmental factors, including different physical, chemical, and biological agents, are able to either stimulate the onset of an autoimmune disorder or aggravate disease conditions [99]. Environmental factors are able to break immune tolerance by regulating the posttranslational modifications thereby triggering a span of immune responses [100, 101].

Epigenetic regulatory mechanisms

Epigenetics is commonly characterized as heritable modifications in a gene expression pattern without an alteration in the DNA sequence. During the normal physiology and biology of the cells, epigenetics explains how cells differentiate into diverse types, while they contain a limited number of genes [102]. Epigenetic regulatory mechanisms are evaluated in three levels: first, those that occur in DNA molecules, specifically methylation of the 5^{th} carbon in the cytosine of CpG dinucleotides that causes suppression of gene expression; second, the biochemical alterations in histone proteins, in which the well-studied modification of histone acetylation culminates in the activation of gene transcription (Fig. 1); and third, mRNA regulation through microRNAs, which are small non-coding RNA molecules.

Rheumatoid arthritis

The biostatistical approach, optimized for a small sample size in RA twin studies, discovered aberrant DNA methylation patterns in cases with different autoantibody profiles. It was observed that seven twins discordant for antibodies to citrullinated protein antigens (ACPA)-positive RA disclosed significant differently methylated regions. Further analysis resulted in the identification of the *EXOSC1* gene with a strong, significantly different methylation profile between twins [103]. The *EXOSC1* gene encodes a core component of the exosome, which is vitally involved in innate immunity. Alternately, several members of the exosome family have been observed to be the targets of autoantibodies in autoimmune disorders [104].

An epigenome-wide association study of 28 MZ twin pairs discordant for RA revealed that there were several differentially methylated regions associated with RA. Smoking, as an environmental factor, demonstrated an association with promoter region hypomethylation in the *RNF5* and *AGPAT1* genes, both of which are involved in autoinflammatory conditions. Moreover, disease-modifying antirheumatic drug (DMARD) treatment was observed to play a role in triggering the hypermethylation of these genes. These observations provide an understanding that environmental factors are involved in RA pathogenesis by affecting the epigenome content of the regions involved in pathobiological pathways.

Moreover, the *S100A6* and *EFCAB4B* genes were hypomethylated in the promoter regions. Further gene-set analyses of the results from epigenome-wide data demonstrated the involvement of immunologic signatures in RA pathogenesis [105].

Systemic lupus erythematosus

Evaluation of DNA methylation circumstances in the promoter of genes has led to the identification of perforin DNA demethylation in SLE CD4+ T cells [106], associated with intensified killing of monocytes in such patients. The upregulation of the *CD70* gene, which results in B cell over-stimulation, was associated with its promoter demethylation in SLE CD4+ T cells [107]. Furthermore, the same events have been observed in the promoter of the *ITGAL* (*CD11a*) gene, contributing to the development of SLE [107].

The dysregulation of DNA methylation and gene expression have been elucidated in 10 genes in discordant SLE MZ twins [108]. On the other hand, a cohort study of MZ twins discordant for three autoimmune diseases with shared clinical signs, including SLE, RA, and dermatomyositis, has strengthened the understanding of the functions of epigenetics alterations in autoimmune diseases. In this study, discordant SLE MZ twins demonstrated DNA hypomethylation in numerous genes, mostly related to the immune function as identified through gene ontology analysis. Further evaluations led to the recognition of alterations in both methylation and expression of the loci associated with SLE pathogenesis. It appears that DNA methylation abnormalities play roles in the SLE pathogenesis and may determine its clinical picture; furthermore, they are involved in distinguishing the autoimmune diseases by impressing the clinical manifestations [33].

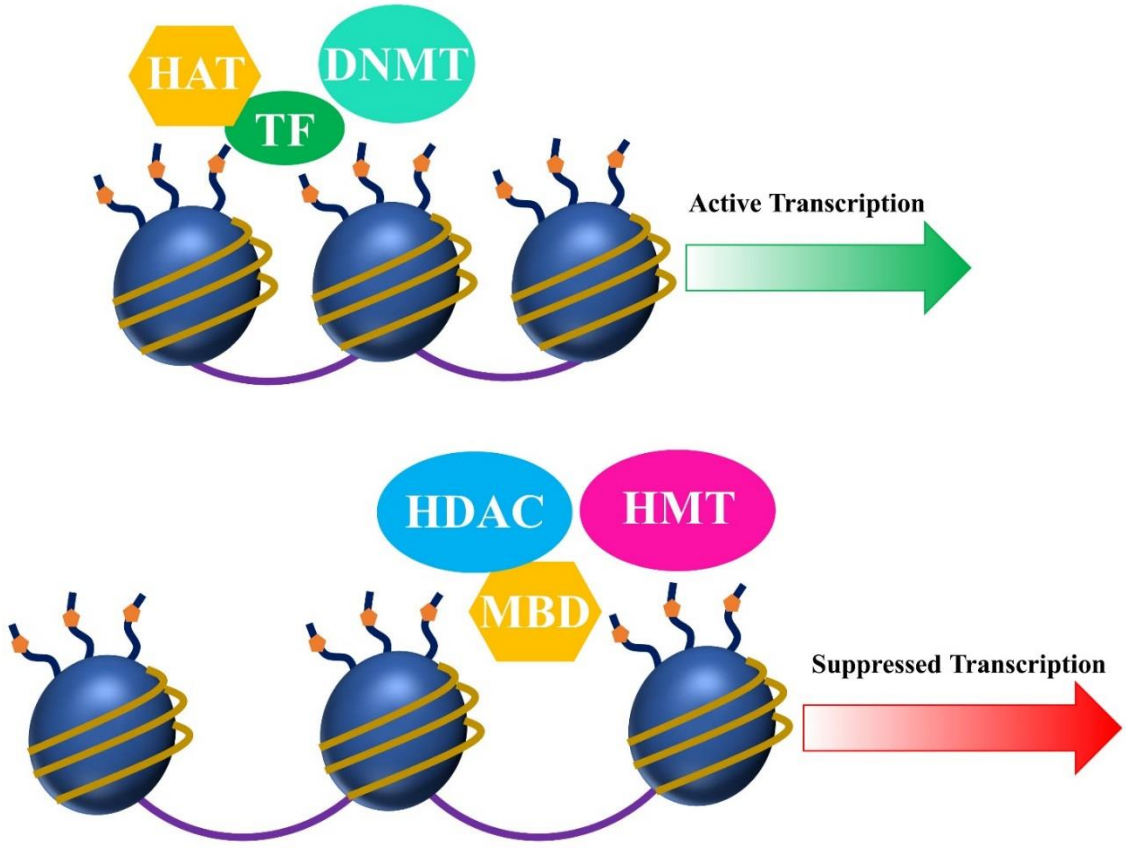

Fig. 1. Various nuclear factors collaborate to establish an epigenetically active (upper) or silenced (lower) configuration. DNA methyltransferases (DNMT) and histone acetyltransferase (HAT), by adding methyl groups to the CpG sites located in the promoter of gene and acetylation of histone tails, cause the suppression of gene expression (heterochromatin conformation). Methyl-CpG-binding domain (MBD) proteins are associated with methylated DNA and recruited by histone deacetylases (HDAC) and histone methyltransferases (HMT) enzymes in order to suppress the transcription of genes (euchromatin conformation).

Systemic sclerosis

Even though discordant MZ twins are potentially favorable prospects for studying the SSc pathogenesis epigenetically, there has been only one investigation in this regard to date. A comparison of methylation profiles was carried out on genes located in the X chromosome in peripheral blood mononuclear cells (PBMCs) from 7 discordant MZ twins and 1 concordant MZ twin for SSc. Differently methylated regions were investigated through biostatistical methods and resulted in the identification of 18 hypermethylated and 25 hypomethylated regions in affected twins. Enrichment analyses demonstrated the involvement of these genes in pathways like apoptosis (*MTM1*), cell proliferation (*SSR4*, *PGK1*, *SMS*, and *UTP14A*), oxidative stress (*ENOX2*), and inflammation (*ARAF*). Among the differently methylated genes were *PGRMC1* and *IL1RAPL2* as well as genes encoding transcription factors such as *HSFX1*, *ZBED1*, *ZNF41*, and *ARX*. The results indicated that the methylation dysregulation of the X chromosome genes is probably involved in SSc pathogenesis [109].

Ankylosing spondylitis

Generally, a few surveys have inspected AS etiopathogenesis under the light of epigenetic aberrations. These studies focused on DNA methylation [110, 111], histone modifications [112], and microRNAs [113-116]. Nonetheless, no study has evaluated the role of epigenetic dysregulation in susceptibility to AS applying twin pairs. As most autoimmune disorders have been evaluated with regard to the disease causality seen in twin cases, a gap exists for AS. Hopefully, the application of such valuable study models in AS will open up new horizons for the study of AS etiopathogenesis.

The application of high-throughput approaches and epigenome-wide studies as well as the evaluation of suitable animal models can provide further understanding of the involvement of epigenetic dysregulations in autoimmune pathogenesis. Discordant MZ twins with virtually identical genetic content can be appropriate tools to exclusively investigate the epigenetic marks, as they decline the chance of interfering elements of genetic heterogeneity like single nucleotide polymorphisms (SNPs).

Psoriasis

The role of environmental factors in the etiopathogenesis of psoriasis is supported by the evidence that shows different onset ages in concordant MZ twins, because early-onset psoriasis is not predominantly genetically determined [117].

Genome-wide evaluations in DNA methylation status and gene expression profiles in CD4+ and CD8+ cells demonstrated no differentially expressed or methylated genes between twins with psoriasis. However, a substantial number of small differences was observed in the players of the immune response, such as cytokines and chemokines [118]. Smoking is an important environmental factor that is assumed to influence the development of psoriatic diseases. Moreover, it has recently been reported that exposure to environmental smoke during childhood is significantly related with the development of psoriasis [119].

A limited number of twin studies performed in PsA patients indicated identical concordance rates for PsA in MZ and DZ twins, suggesting the substantial role of non-genetic players in PsA etiopathogenesis [120]. A deep Koebner phenomenon or repeated joint trauma may accelerate the development of PsA, as was seen in a case report of MZ twins who developed PsA following a trauma [121]. Furthermore, the skin microbiome has been suggested to be a central player in the development of PsA; however, the profiling of the bacterial culture in the psoriatic plaques did not differences at the phylum and genus levels between individuals [122].

Table 1. Summary of epigenetic dysregulation findings in autoimmune twin cases

Disease	Twin type	Modification	Reference
RA	7 twins discordant for RA	Different methylation of *EXOSC1* Gene	[103]
	28 MZ twin pairs discordant for RA	hypomethylation of *RNF5*, *AGPAT1*, *S100A6* and *EFCAB4B*	[105]
SLE	Discordant SLE MZ twins	DNA hypomethylation in several genes, mostly related to immune function	[33]
SSc	7 discordant MZ twins and 1 concordant MZ twin	18 hypermethylated and 25 hypomethylated regions; *PGRMC1*, *IL1RAPL2*, *HSFX1*, *ZBED1*, *ZNF41*, and *ARX*	[109]
Psoriasis	Psoriasis twins	NO differentially expressed or methylated genes in CD4+ and CD8+ cells between twins with psoriasis	[118]

Conclusion

Little is known about the etiopathogenesis of autoimmune disease. Nevertheless, it seems that the close nexus between contributing environmental factors and genetic elements is of great importance in the loss of immunological tolerance. Studies of twins with autoimmune disorders have provided a great deal of data regarding the genetics, epigenetics, and environmental factors related to disease initiation, pathogenesis, and perpetuation. The paucity of twin studies in several autoimmune diseases stems from various conditions, particularly and most challengingly, the infrequency of cases. Other than genetic factors, epigenetic factors and rare variants must be further studied using cases with shared geo-environments, which might be promising in furthering the knowledge of the etiopathogenesis of autoimmune conditions. Furthermore, the utilization of cutting-edge techniques for evaluating the whole genome and epigenome methylation patterns may shed further light on autoimmune diseases, as such studies have rarely been conducted. Gender-associated factors should also be taken into consideration as a female predominance has been highlighted in concordant twins of autoimmune disorders. Hopefully, twin studies will open up new horizons in the acknowledgment and illumination of genetic, epigenetic, and environmental factors engaged in the pathogenesis of autoimmune complications.

Conflicts of interest

The authors declare no conflict of interest.

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