Biomedicine & Pharmacotherapy 91 (2017) 526–533

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Review

Epigenetic alterations in chronic disease focusing on Behçet's disease: Review

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ARTICLE INFO

Article history:
Received 19 February 2017
Received in revised form 18 April 2017
Accepted 23 April 2017

Keywords:
Epigenetic
Autoimmune diseases
Behcet's disease
Methylation
microRNAs

ABSTRACT

Objective: 'Epigenetics' is specified as the inheritable changes in gene expression with no alterations in DNA sequences. Epigenetics is a rapidly overspreading scientific field, and the study of epigenetic regulation in chronic disease is emerging. This study aims to evaluate epigenetic changes including DNA methylation, histone modification, and non-coding RNAs (ncRNAs) in inflammatory disease, with focus on Behçet's disease. In this review, first we describe the history and classification of epigenetic changes, and then the role of epigenetic alterations in chronic diseases is explained.
Methods: Systematic search of MEDLINE, Embase, and Cochrane Library was conducted for all comparative studies since 2000 to 2015 with the limitations of the English language.
Results: For a notable period of time, researchers have mainly focused on the epigenetic pathways that are involved in the modulation of inflammatory and anti-inflammatory genes. Recent studies have proposed a central role for chronic inflammation in the pathogenesis of chronic disease, including Behçet's disease.
Conclusion: Studies have been reported on the epigenetic of BD showed the role of alterations in the methylation level of IRS elements; histone modifications such as H3K4me27 and H3K4me3; up regulation of miR-182 and miR-3591-3p; down regulation of miR-155, miR-638 and miR-4488 in the pathogenesis of the disease.

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Contents

Abbreviations: ncRNAs, non-coding RNAs; BD, Behçet's disease; MHC, major histocompatibility complex; HLA, Human Leukocyte Antigen; TNF, Tumor Necrosis Factor; IL-10, interleukin-10; MEFV, Mediterranean fever; TH1, T-helper 1; Me5C, 5-methyl cytosine; DNMTs, DNA methyltransferases enzymes; HATs, Histone acetyltransferases; RA, Rheumatoid arthritis; LPS, Lipopolysaccharide; SLE, Systemic Lupus Erythematosus; pSS, primary Sjögren's syndrome; MS, Multiple sclerosis; T1D, Diabetes type one; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; NFAT2, Nuclear factor of activated T cells 2; PBMCs, Peripheral Blood Mononuclear Cells.

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http://dx.doi.org/10.1016/j.biopha.2017.04.106
0753-3322/© 2017 Published by Elsevier Masson SAS.

1. Introduction

While most cells have the same DNA sequence, the activity of individual genes varies significantly between different cell types and tissues. The cytokine gene is highly compressed in structure and inactive in all tissues except lymphocyte cells, in which it is in an open conformation that simplifies transcription. The word epigenetic includes heritable alterations in gene expression that do not contain changes to the fundamental DNA sequence—a change in phenotype without a change in genotype. Epigenetics was first described in 1924 by Conrad Waddington as the subdivision of biology that researches the causal interactions between genes and their products which bring the phenotype into existence [1]. These mechanisms show a crucial role in the regulation of gene and microRNA (miRNA) expressions, DNA-protein interactions [2], cell differentiation, embryo genesis [3], X-chromosome inactivation [4], genomic imprinting, and cancer and many other medical disorders such as cardiac diseases [5], diseases of the nervous system, and rheumatic diseases [6].

The activity of genes is mostly reliant on whether they are available to transcription factors; this is vastly controlled by the dynamics of chromatin restructuring [7]. Epigenetic modifications to the chromatin play a vital role in regulating the construction of chromatin and thus the availability of DNA for transcription [8]. Some of the sites in the DNA that are transcript can be turned on or off by epigenetic changes. Moreover, it has previously been verified that environmental factors, such as diet, cigarette and alcohol use, stress, exposure to chemical carcinogens and infectious agents, sexuality, and age, affect the epigenome [9,10]. The importance of epigenetic processes has recently motivated many scientists to work in this field of research. Epigenetic changes not only affect physiological mechanisms; the pathophysiology of many diseases is interwoven with them as well [11].

Behçet's is an autoimmune disease that was described by Hulusi Behcet in 1937 as an inflammatory process of indefinite etiology, characterized by recurrent aphthous stomatitis, uveitis, genital ulcers, and skin lesions [12]. Although Behçet's disease (BD) is widespread and universal in different parts of the world, it has significant local differences, with the maximum incidences in the Mediterranean, the Middle East, and the Far East, which was locally called the Silk Road. The highest prevalence of Behçet's disease has been reported in Turkey at 421 people per 10^5 [13]. Also, BD in the Azari population of Iran starts in the third period of their lives and has a male predominance [14].

It seems that the disease is most common in the third decade of age. However, recently there has been an increasing frequency of the disease in children and there is no evidence of hereditary factor. Also, men are affected more than women. The intensity of the disease seems to fade away as they grow older [15]. The exact pathogenesis of Behçet's disease has not clearly been explained. However, many studies reveal that the disease may be initiated by environmental factors such as infective agents and vitamin D deficiency [16] in patients with backgrounds of genetic susceptibility [17]. More lately, researchers have tried to explain the meaning of epigenetics to embrace all that it was supposed to convey [18]. In this paper, we will take a reasonably comprehensive definition of 'epigenetics' as alterations that do not include DNA base changes. It also plays an essential role in regulating tissue and signal-specific gene expression, and these are interchangeably accountable for the determination of gene expression profiles of tissues and cellular subclasses.

2. Genesis of Behcet's disease

The cause of Behcet's disease is still not known. A number of researches have collected proof that HLA-B51 allele, located in the MHC (major histocompatibility complex) locus on chromosome 6p, is directly related with BD in all strata along the Old Silk Road [19]. The HLA-B51 is common in BD patients, with a range of 40–80 percent in racial groups, including Turkish, Asian, and European populations along the ancient Silk Road [20]. Other genes present in the MHC locus have been researched, including MICA (MHC class I related gene) and TNF genes; nevertheless, their contribution is because of the direct disequilibrium linkage with HLA-B51 gene [21]. Also polymorphisms of transporters associated with antigen processing (TAP) loci (TAP1 Val-333/Asp-637) were entirely lacking among Spanish BD patients compared with healthy controls, proposing that the TAP polymorphisms may indicate some importance in BD progress [22]. Some of the genes, located outside the MHC zone, have been suggested to be involved in BD pathogenesis and progression, including genes of interleukin-10 (IL-10) as a potent suppressor of inflammatory cytokines [23], interleukin-1 (IL-1) [24], intercellular adhesion molecule-1 (ICAM-1) [25], and Mediterranean fever gene (MEFV) mutations [26]. Additionally, interleukin-2 (IL-2), interleukin-12 (IL-12), and interferon (IFN-γ) are so intensified in the peripheral blood (PB) and inflammatory tissues in BD that they are produced by T-helper 1 cells as proinflammatory activation of the innate and adaptive immune systems [27,28].

Also IL-23 as a heterodimeric proinflammatory cytokine, has been revealed to activate T-helper cell proliferation and stimulate the production of inflammatory cytokines such as IL-6, IL-17, IL-1, and TNF-α [23,29].

T-lymphocytes of type γδ indicate a vital role in the immune response to microbial infections and in auto-immunity by detecting autologous antigens. Patients with BD have expanded numbers of γδ T-cells in circulation and in mucosal lesions [30]. Therefore, the recognition of expanded levels of γδ T-cells in the peripheral blood of patients with active BD in the studies, proposes that antigens of microbial infections that activate γδ T-cells play an essential role in the pathogenesis of the disease [31]. Also γδ T-lymphocytes express activation markers such as CD25, CD29 and CD69 in BD and then those cells give rise to the production of inflammatory cytokines, including IFN-γ, TNF-α and IL-8 [32]. In addition, antigens of streptococci were indicated to raise the amount of interleukin (IL-6) and interferon (IFN-γ) production by T-cells in peripheral blood from BD patients [33], and then mutually reacted with a 65kD heat shock protein sharing antigenicity with oral mucosal antigens.

3. Mechanisms of epigenetic modifications

The mechanisms of epigenetics are leading to changes in chromatin structure by altering its components. Scientists have found four types of epigenetic mechanisms, which are totally in hand with each other to regulate the expression of genes: DNA methylation, histone modification, non-coding RNAs (ncRNAs) [34], and chromatin remodelling are such epigenetic mechanisms that interact to express the genes. (Fig. 1) Methylation rate plays an important role in physiological conditions, and modifications in methylation can regulate pathological processes [34]. DNA methylation is a main epigenetic modification in autoimmunity disease. Treatment with DNA methylation inhibitors such as 5-azacytidine is proved to control autoimmune disease in experimental animals [35]. In mammals, DNA methylation happens by covalent change of the fifth carbon (C5) in the cytosine base and a greater number of these modifications is present at CpG dinucleotides within the genome [36].

Nonetheless, 5-methyl cytosine (Me5C) accounts for about 1 percent of whole DNA bases and thus is appraised to represent 70–80 percent of all CpG islands in the genome. These CpG islands in gene promoter areas are usually hypo or unmethylated in healthy

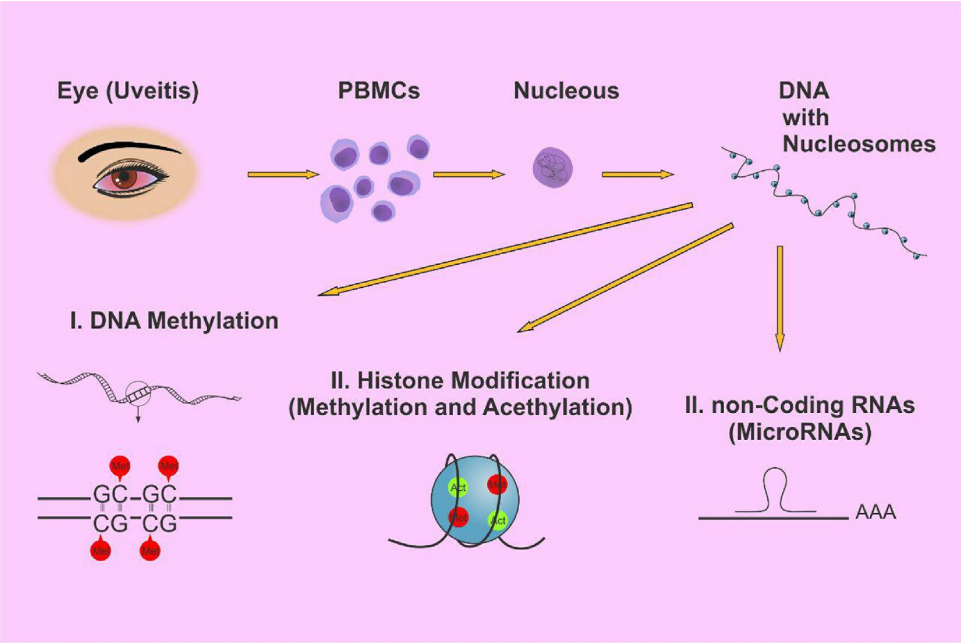

Fig. 1. Epigenetic modifications in Behçet's disease contribute to their destructive phenotype. Behçet's disease is characterized by ocular involvement, leading to eye inflammation with loss of vision. Also peripheral blood mononuclear cells (PBMCs) are important in the pathogenesis processes of BD.

cells and allow for active gene transcription [36]. DNA methylation can decline the affinity for binding of transcription factors. DNA methylation modifications are carried out by a group of enzymes named DNA methyltransferases enzymes (DNMTs). There are four members of the DNMT family—DNMT1, DNMT3A, DNMT3B, and DNMT3L. DNMT1 encodes the conservation methyltransferase enzyme and DNMT3A/DNMT3B encode the de novo methyltransferases required to establish and maintain genomic methylation [37].

During the aging process, total DNA methylation reduces, while some promoters become abnormally hypermethylated [38]. Also, the CpG islands of several tumour suppressor gene promoter sites are usually unmethylated and become methylated with age [39]. Nowadays, it is generally believed that DNA methylation is influenced by genetic and environmental factors, which can vary the DNA methylation status. Given that DNA methylation is influenced by causes such as gender, race/ethnicity, and other environmental factors, researchers during their studies should pay special attention to these factors cautiously [40].

Also, chromatin structure is commonly influenced by varying histone modifications such as acetylation, methylation, sumoylation, and ubiquitination, which also play a critical role in gene regulation. The histone tails consist of a globular C-terminal domain and an N-terminal tail. The N-terminal histone tails are the major sites for epigenetic modifications [41]. Acetylation of the lysine residues at the N-terminus of histone proteins neutralizes positive charges, thus, reducing the affinity between histones and DNA [42]. This makes it easier for RNA polymerase enzyme and transcription factors to contact the promoter region. Consequently, in most cases, histone acetylation increases transcription while histone deacetylation represses it [43]. Histone acetylation and histone methylation are studied intensively for their essential roles in moderating gene transcription. Histone modifications affect the interaction between histone and DNA and regulate the next step of chromatin structure by way of condensation and packaging [44]. Histone acetylation is controlled by histone acetyltransferases (HATs) and histone deacetylation is regulated by histone deacetylases. Histone methylation is essential for appropriate programming of the genome during development, and misregulation of the methylation processes can lead to some diseases such as cancer and autoimmune disorders. Histone methylation generally occurs at lysine and arginine residues of histones H3 and H4, which can be in the form of monomethylated, dimethylated (lysines and arginines) or trimethylated (lysines).

Recently, it was discovered that RNA also has a role as a transcriptional constant repressor in the form of antisense transcripts and non-coding sequences interacting with DNA. The term non-coding RNA is ordinarily employed for RNA that does not translate a protein but this does not mean that such RNAs do not include information nor have any function [45]. Non-coding RNAs contain miRNA, siRNA (short interfering RNA), piRNA (piwi-interacting RNA) and lncRNA (long non-coding RNA). Those ncRNAs that seem to be involved in epigenetic processes can be divided into two central groups—the short ncRNAs (<30nts), and the long ncRNAs (> 200nts) [46]. The three main classes of short non-coding RNAs are miRNAs, siRNAs, and piRNAs [46]. Both major groups are shown to play a role in heterochromatin formation, histone modification, DNA methylation targeting, and gene inactivation. MicroRNAs are short RNA molecules, 19–25 nucleotides in length, which has recently been known to play key roles in regulating gene expression [47]. MicroRNAs usually bind to a definite target messenger RNA with a complementary sequence to induce cleavage, or degradation, or block translation. MiRNAs are emerging as important intermediaries of epigenetic gene regulation in mammals. They obstruct translation and trigger degradation of their target miRNAs. Over the last decade, it has become clear that miRNAs are involved in a multiplicity of epigenetic mechanisms and are recognized as participating in the post-transcriptional gene regulation [34,47].

More than 50 percent of miRNA genes have been confirmed to be situated in cancer associated genomic regions or in fragile sites, proposing that miRNAs may play a more essential role in the pathogenesis of a larger range of human cancers than previously thought [48].

4. Correlation between epigenetics and rheumatic diseases

Rheumatic diseases embrace an extensive range of conditions of incompetently characterized etiopathology, many having both genetic and environmental susceptibility causes. Inflammatory rheumatic disorders, like rheumatoid arthritis (RA) and connective tissue diseases, are accompanied by chronic inflammation that generally can be defeated by constant administration of immunosuppressive therapies [49]. Advances in molecular and genetic techniques have contributed to identification of at-risk genetic patterns in autoimmune and autoinflammatory diseases.

Aging is related with an increased risk of developing a large number of inflammatory rheumatic diseases [50]. Many structures of both the adaptive and innate immune systems vary with aging, leading to a state of increased activity termed inflammageing [51]. Innate immune system alterations include both higher systemic levels of proinflammatory cytokines and intensified lipopolysaccharide (LPS) induced production of tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) by macrophages [52]. These studies propose a multipart pattern of age-related changes in gene expression in different immune cells that may result in an increased risk of inflammatory disorders. (Fig. 2)

The value of epigenetic regulatory processes in controlling the immune and inflammatory responses is appearing. Dietary factors can have intense effects on the expression of particular genes by epigenetic modification; these may be passed on to later generations, with potentially harmful effects.

In association with a disposing genetic history, epigenetic mechanisms play a complementary causal role in the pathogenesis of autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), primary Sjögren's syndrome (pSS), multiple sclerosis (MS), psoriasis and diabetes type one (T1D), and BD. (Table 1)

5. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an enduring autoimmune disorder that predominantly affects joints. The RA fibroblast-like synoviocytes (RASFs) are dominant mediators of tissue damage via the production of a variety of disease-related molecules, containing chemokines, cytokines, and adhesion molecules [53]. Recent researches attempted to show epigenetic alterations with genetic or environmental factors for RA. In addition, global modifications in DNA methylation, promoters of particular genes, were revealed to be hypomethylated or hypermethylated in RA in different cell types [54]. The methylation of CpG islands in the promoter of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in Treg cells of RA patients were displayed due to the damage in binding of the transcription factors such as nuclear factor of activated T-cells 2 (NFAT2), that lead to decline in the expression amount of CTLA-4 in RA patients compared with healthy groups [54,55]. These outcomes illustrate that small epigenetic modifications can control the function of a whole cell type in RA, in this case, Treg.

TLR1 is expressed in leukocyte surface and in other cells, such as astrocytes, fibroblasts, keratinocytes, endothelial, and epithelial cells [56]. It was detected as being expressed also by synovial fibroblasts, including RASF [57]. Recent investigations have revealed that RASF have reduced levels of total DNA methylation, [58] which lead to an improved expression of cell-activating genes and might excite the innate immune response via TLR9.

A single unmethylated CpG site in a promoter of IL-6 in monocytes was also reported, interpreting the expression of IL-6 to be more inducible by LPS (lipopolysaccharides) stimulus [59]. Demethylation of the IL-6 promoter site in peripheral blood mononuclear cells (PBMCs) leads to increase in IL-6 mRNA expression and might play a key role in the progress of RA [59]. On the other hand, the CpG sites in the promoter of death receptor 3 (DR3), a participant of the apoptosis-inducing Fas gene family, was displayed to be specially methylated in first or second passage RA synovial cells and the expression of DR3 was consequently down-regulated [60,61].

Histone modifications also participate in the pathogenesis of RA. For example, MeCP2 (methyl-CpG-binding protein 2) is recognized as a transcriptional repressor that controls gene expression through the processes of DNA methylation and histone modification [62]. In a recent study [62], it was found that MeCP2 expression was increased in synovium from the RA model rats compared with the healthy control rats and this situation may play a role in the pathogenesis of RA.

Expression of mir-146a was increased in PBMCs, macrophages, B cells and $CD3^+$ T cells of RA subjects [63]. Also, MiR-146 production in synovial tissues is intensified by inflammatory moderators. MiR-146 is a down-regulatory element for NF-kB signaling pathway in monocytes. Clear expression of miR-155 and miR-146 was reported in RASFs but not in synovial fibroblast cells in patients with osteoarthritis, that suggesting the responsible roles of these factors in pathogenesis of RA [61].

6. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disorder that can affect nearly any organ and is characterized by overexpression of autoantibodies against nuclear and/or cytoplasmic self-antigens. Some affecting genetic factors have been identified in the emergence of this disease. SLE is also more usual in women in comparison to men [64]. Several researches revealed that the presence of autoantibodies in the SLE process is associated with two major alterations—increased rate of apoptosis in lymphocyte and monocyte cells, and being alien with those self-antigens that are released during apoptosis [65]. Recent studies have indicated a relationship between decrease of DNA methylation in SLE and reduction in the activity

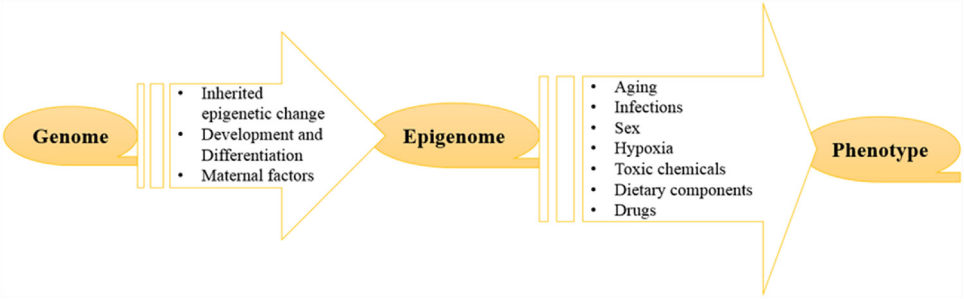

Fig. 2. Environmental factors during life time affect the epigenetic signature of genes resulting in a continuing loss of control of gene expression in different tissues. These changes in immune and inflammatory cells result in the development of inflammageing with improved risk of age-related inflammatory diseases like rheumatic diseases.

Table 1
Aberrant epigenetic patterns in autoimmune diseases.

	DNA methylation	Histone modifications	microRNAs
RA	CTLA-4 in regulatory T cells (Treg) [53]. RASF in synovial fibroblasts [54]. Demethylation of IL-6 in PBMC [55]. DR3 in first or second passage RA synovial cells [56,57].	MeCP2 [58] PIWIL in synovial. Fibroblasts [59] IL-6 promoter region in synovial fibroblasts [60]	Regulation of TNFα production with mir146a in PBMC [61]. Upregulation of mir146a in synovial tissue [57,62]. Downregulation of mir124 in synoviocytes [63]. Repression of MMPs production with mir155 in Synovial fibroblasts [64].
SLE	CD11a (ITGAL) hypomethylation in T cells [65]. Hypomethylation of IL-6 and IL-4 in T cells [66]. Hypomethylation of CD70 (TNFSF7) [67]. enhancer and IL-13 promoter [57,68]	Increasing of histone 3 acetylation and H3K4me2 [69]. increasing of H4 acetylation levels [69].	Down-regulation of mir-146, mir-17-5p, mir-184, mir-141 in PBMC [70,71], miR-142-5p, miR-142-3p, miR-31, miR-186, and miR-197 [72] Up-regulation of mir-21, mir-155, mir-61, mir-78, mir-182, mir-31, mir-189 in PBMC [70,71]
MS	Hypermethylation of HLA-DRB1[73] Hypermethylation of DNHD1 and others [74] Hypermethylation of SHP-1 [75]	Increased histone circulation in animal models of MS [76]	Dysregulated mir-96, mir-18b, mir-599 in PBMC [77] Upregulated miR-21 and miR-106b [78], mir-139a and mir17-5a [57,79]
FMF	Hypermethylation of MEFV gene [80]	–	Dysregulation of miR-4520a [81]
T1D	Hypermethylation of insulin gene by proinflammatory cytokines in NOD mice [82] Elevations in Circulating Methylated and Unmethylated in New-Onset [83] T1D and PDR exhibit altered DNA methylation patterns in blood [84]	Histone H3K9me2 [85]	Downregulated: miR-146a, miR-561 and miR-548a-3p, miR-184 and miR-200a [86] mir-939, mir-720, mir-636 [87] Upregulated: miR-30c and miR-487a [86], mir-338-3p, mir-30b, mir-92a [87] increased expression of miRNA-510, decreased expression of both miRNA-342 and miRNA-191 [88]
BD	Alu sequences in PBMCs [89]	H3K4me27 [90] H3K4me3 [90]	Upregulation of miR-182 [91] Downregulation of miR-155 [92] Downregulated: miR-638 and miR-4488 [93] Upregulated: miR-3591-3p [93]

of DNMTs, signifying a probable mechanism to clarify DNA hypomethylation [66]. The recognition of genes that are disregulated through DNA methylation modifications in SLE contributes to our realization of the pathway of the disease. Recently, specific promoter hypomethylation of several genes have been displayed to involve the atypical overexpression of several genes. These abnormal changes take place in genes such as perforin, whose demethylation could contribute to killing monocytes [67].

Histone acetylation is commonly related with transcriptional activities, but deacetylation of terminal lysine residues contributes to inhibition of transcription. The result of histone methylation depends on the position of lysine; for example, histone H3 lysine 4 (H3K4) methylation increases gene expression, whereas H3K27 trimethylation (H3K27me3) is an inhibitor [68]. CD70, encoded by TNFSF7, is an essential T-cell costimulatory protein that increases expression in lupus. In a recent research, histone modification in the promoter site of TNFSF7 in SLE CD4þ T-cells was measured. The study confirmed increased CD70 mRNA levels in SLE CD4þ T-cells [69]. More remarkably, histone 3 acetylation and H3K4me2 levels were significantly raised in patients with SLE, and both related with the disease activity. Also, Zhang et al. showed that H4 acetylation levels were increased in 179 genes significantly and over expression in SLE patients' monocytes at the genome-wide level study [70].

Signalling processes that take place in local tissue cells reacting to inflammatory cytokines are influenced by specific miRNAs [71]. A recent study discovered that miR-23b was expressed by local fibroblast cells and can restrain activation of NF-κB in response to inflammatory cytokines signalling [71]. Abnormal miRNA expression forms distinguished in SLE include up-regulated miR-21, miR-148a, miR-126, miR-155, miR-31, miR-182, and miR-96-183 cluster; and down-regulated miR-146a and miR-125a. These expression changes are identified to lead to DNA hypomethylation, T-cell activation, failure of T- and B-cell tolerance, and autoantibody production in systemic inflammatory disease [72].

7. Multiple sclerosis

Multiple sclerosis (MS) is a nervous system disease characterized by autoimmune demyelination of the myelin cover of the central nervous system (CNS), affecting about 2.5 million people in general. It damages the myelin sheath, the material that surrounds and defends the nerve cells [73]. MS is driven by dysregulated T-cells that inappropriately respond to myelin and other CNS antigens.

The prominence of epigenetics in the illustration of multiple sclerosis is also proposed by studies of the genetic factors [74], and the increase in female-to-male ratio in diagnosis reported in longitudinal researches [75]. Recent studies have shown an association between CD4+ T-cells, CD8+ T-cells, and whole blood DNA methylation profiles, regardless of disease status. CD4+ T-cells can be greater in acute CNS lesions [76], while CD8+ T-cells can be prevalent in chronic lesions, signifying a vigorous role for these lymphocyte subclasses in MS [77]. Also, vigorous evidence for decreasing methylation in CD8+ T-cell, but not CD4+ T-cell or whole blood DNA in MS patients compared to controls was detected [78]. Genome-wide significant individual CpG-site DNA methylation dissimilarities were not recognized. Moreover, substantial differences in DNA methylation of 148 established MS-associated risk genes were not observed [78]. In the studies of Adam and his participants, they found no significant effect of DNA methylation status across HLA-DRB1* 1501 and HLA-DRB5 on severity of the disease, while they could not rule out time- or tissue-specific effects of DNA methylation [79].

Investigations have recently disclosed the role of miRNAs in the appearance of MS with miRNA profiling techniques [80]. Studies have confirmed that miRNAs play a crucial role in Th-17 polarization and the pathological processes of MS. Some of these miRNAs control the severity of the disease by inducing Th-17 development, which is a significant driver of tissue inflammation [81]. MiRNAs are greatly expressed in immune cells within CNS injuries of patients with MS, and this is consistent with their well-known roles as regulators of T-cell activation and other processes that cause demyelination during MS. Dysregulation of miRNA expression has been detected in patients with MS compared with healthy individuals. Investigations assessing PBMCs from patients with MS have shown that miR-18b and miR-599 levels are correlated with the time of disease relapse but that miR-96 is involved in the stage of disease remission, probably through regulation of cytokines and Wnt signalling [82]. These miRNAs (miR-18b, miR-599, and miR-493) were considerably upregulated in relapsing–remitting MS (RRMS) patients compared with healthy

groups [82]. Also, miRNA expression profiles in serum samples from MS patients and healthy controls were evaluated and it was displayed that miR-21 and miR-106b were upregulated in all types of MS and miR-106b falls into the miR-17–92 cluster class [83]. Overall 365 miRNAs in the lymphocytes of RRMS patients were studied and realized that miR-17-5p, which is correlated with autoimmunity, was increased in the CD4+ cells of MS patients [84].

8. Diabetes mellitus

Type1 diabetes (T1D) is an autoimmune disease which is generated as a result of pancreatic insulin-producing β-cells apoptosis. Genome-wide association studies (GWAS) [85] have connected immune response-related genes with an increased T1D risk, yet the underling mechanisms by which these genes increase T1D susceptibility have not been illustrated [86]. Type 2 diabetes (T2D) is a typical polygenic metabolic disease. GWAS studies have shown that more than 40 genes are associated with increased risk of T2D [86]. These genes are involved in β-cell function, β-cell development, or β-cell mass [87]. Environmental factors and epigenetic modifications are two of the major causes of developing diabetes [18]. DNA methylation, histone post-translational modifications, and non-coding RNA-mediated pathways are most important epigenetic mechanisms that can alter gene expression.

Change in the methylation of some genes, e.g. PDX-1 (pancreatic and duodenal homeobox 1), insulin (Ins1) gene, Ngn3 (neurogenin 3) and MafA (v-maf musculoaponeurotic fibrosarcoma oncogene family, protein A), Arx (aristaless related homeobox), UNC13B gene, have been reported previously [88,89].

DNA methylation happens at cytosines and is generally associated with transcriptional silencing. Regulation of DNA methylation has been related to human diseases including diabetes [90].

Histone acetyltransferases (HATs) catalysed histone acetylation and is associated with regions of actively transcribed chromatin. The removal of the acetyl group is achieved by histone deacetylases (HDACs), which can link with corepressor complexes. The deacetylation of histones makes tighter charge–charge interactions between the DNA and the lysine-rich histone tails. GWAS have involved histone acetylation and especially HDACs in the pathogenesis of both T1D and T2D [91,92].

As well as DNA methylation and histone post-translational modifications, non-coding RNAs, especially microRNAs (miRs), also play important roles in the pathogenesis of diabetes. Previous studies showed that miR-222, miR-27a, miR-195, miR-103, and miR-10b have important roles in the pathophysiology of T2D [93]. Furthermore, increased expression of miRNA-510 and decreased expression of both miRNA-342 and miRNA-191 was established in regulatory T-cells (Tregs) of T1D patients [94]. Overexpression of miR-375 decreases glucose-stimulated insulin release, while its knockdown increases insulin secretion [95]. Another miR (miR-204) that is highly expressed in pancreatic cells is involved in insulin production [96]. In summary, epigenetic modifications have been proved that affect multiple aspects of diabetes and its associated complications.

9. Familial Mediterranean fever

Familial Mediterranean fever (FMF) is an autoinflammatory recessive disease characterized by recurrent attacks of fever, and the inflammation of serosal membranes that usually affects Mediterranean people—mostly Iranians, Turks, Jews, Armenians and Arabs [97]. MEFV gene on the short arm of chromosome 16 is the first identified inflammatory gene which is responsible for FMF [98]. The possible epigenetic factors such as DNA methylation, histone modifications, and non-coding RNAs, may lead to disease phenotype in FMF patients. So researchers decided to analyse MEFV gene expression and evaluate the levels according to DNA methylation.

Recent studies have shown that the MEFV mRNA level is reduced in FMF patients compared to a control group and the reduced MEFV mRNA expression level was correlated with the mutation number [99]. Kirectepe et al. have shown that methylation pattern of exon 2 of MEFV is slightly higher in FMF patients compared to healthy controls. Also, in this study, the expression level of the MEFV was adversely associated with the methylation amount of the CpG islands in both FMF and healthy control groups but more so in the FMF group only [100]. In the other study, methylation pattern at the promoter site was analysed by bisulphite sequencing in different people and may not be the reason of heterogeneity for FMF patients with different clinical phenotype [101].

The relative expression levels of miR-4520a were mutable among FMF patients and not considerably different between the patients and those of the control group [102]. However, when patients who did not harbour any mutations in MEFV were excluded from the analyses, the expression of miR-4520a was statistically dissimilar between FMF patients and control groups ($p < 0.05$), indicating an association between miR-4520a expression and mutations in the MEFV gene [102].

10. Epigenetics and Behçet's disease

More recent studies propose the association of epigenetic variants, predominantly DNA methylation modifications, in the pathogenesis of vasculitis. In some vasculitis, such as Behçet's disease, particular and reversible epigenetic modifications that trigger the disease pathogenesis can vary between active and inactive disease [103]. Also, in a recent study by Yüksel et al., the epigenetic modifications of IRSs (repetitive sequences) in BD were assessed using COBRA-IRS analysis technique. In this study, for Alu sequences, significant differences were detected in the frequency of uCuC (unmethylated cytosine) alleles between the PBMCs of patient and control groups, as well as inactive patients and controls. Thus, alterations in the methylation level of IRS elements might involve the pathogenesis of BD [104] but they found that levels of total methylation were not statistically changed for Alu and LINE-1 among the effective, ineffective, and healthy control groups. In other recent studies, Hughes et al. analysed genome-wide DNA methylation patterns in monocytes and CD4+ T-cells, and found 383 CpG sites in monocytes (129 increased methylation of CpG sites and 254 hypomethylated sites in 228 genes), and 125 in CD4+ T-cells (67 hypomethylated and 58 hypermethylated) in 62 genes, that were differentially methylated between BD patients and controls [103]. In this research, bioinformatics analysis discovered a pattern of unusual DNA methylation modification among genes that regulate cytoskeletal dynamics, proposing that unusual DNA methylation of multiple classes of structural and regulatory proteins of the cytoskeleton might be involved in the pathogenesis of BD.

The histone modifications are associated with DNA methylation by dissimilar, but paired, pathways [105]. Histone acetylation is studied as a definite transcriptional mark, while trimethylation is related with inhibition [106]. The correlation of histone modifications with gene expression is very strong, such as trimethylation of histone 3 lysine 27 (H3K4me27), which may be characteristic of repressed genes, or trimethylation of histone 3 lysine 4 (H3K4me3), which may be present in many active genes [107]. Histone modifications in major rheumatic diseases, such as rheumatoid arthritis, have been considered, while studies on histone modifications in BD are too few. From the functional viewpoint, it is essential to analyse differences of histone

modifications in each functional subtype of the thorough peripheral blood-nucleated cells.

In recent studies, researchers talk about the apparent roles of cellular non-coding RNAs and specific microRNAs in the regulation of autoimmune inflammation diseases. MiRNAs have appeared as a type of gene expression regulators participating in immune regulation processes [108]. MiR-182 plays a main role in the regulation of adaptive immune responses and reacts to a specific site of the 3′ UTR of FoxO1 mRNA and inhibits its expression. The fact that miR-182 is essential for Treg cell maturity may increase our knowledge relating to the role of these cells in the pathogenesis of BD [109]. But the results of recent studies did not disclose an effect of the various rs76481776 genotypes on miR-182 expression. Furthermore, there was no significant relation in the expression of miR-182 by LPS-stimulated peripheral blood mononuclear cells (PBMCs) and the other genotypes [109]. In addition, only miR-155 expression was significantly reduced in PBMCs and dendritic cells (DCs) from BD patients with active uveitis. In this study, overexpression of miR-155 in DCs was revealed to obstruct the production of IL-6 and IL-1b, and to increase the expression of IL-10 by these cells [110]. In the other study, the expression levels of miR-638 and miR-4488 were decreased in patients with stable BD in comparison with healthy groups. In addition, the expression of miR-3591-3p was improved in patients with active BD when compared to patients with BD [111].

11. Conclusion

Research in the last three decades revealed a complex relationship between various epigenetic pathways and pathogenesis of inflammatory diseases. BD is an autoimmune/autoinflammatory disease. Few studies have been reported on the epigenetic of BD showed the role of alterations in the methylation level of IRS elements; histone modifications such as H3K4me27 and H3K4me3; up regulation of miR-182 and miR-3591-3p; down regulation of miR-155, miR-638 and miR-4488 in the pathogenesis of the disease. Identifying the spectrum of epigenetic changes in all cells contributing to the pathogenesis of BD, especially T cells, neutrophils and endothelial cells and translating the relevance of epigenetic changes into cellular and molecular pathways in BD disease is the major way forward for the field.

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