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Review

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

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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.

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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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