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The epigenetic mechanism for discordance of autoimmunity in monozygotic twins

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ABSTRACT

Monozygotic twins share an identical DNA sequence but are not truly "identical". In fact, when it comes to health and disease, they may often display some level of phenotypic discordance. The cause of this discordance is often unknown. Epigenetic modifications such as DNA methylation, histone modification, and microRNAs-mediated regulation regulate gene expression and are sensitive to external stimuli. These modifications may be seen to bridge the gap between genetics and the environment. Over the years, the importance of epigenetics as a primary mechanism for the role that the environment plays in defining phenotype has been increasingly appreciated. Mechanisms of epigenetics include DNA methylation, histone modifications and microRNAs. Discordance rates in monozygotic twins vary depending on the specific condition, from 11% in SLE to 64% in psoriasis and 77% in PBC. Other autoimmune diseases in which discordance is found among monozygotic twins has also been studied include type 1 diabetes, multiple sclerosis, rheumatoid arthritis, dermatomyositis and systemic sclerosis. In some cases, the differences in various epigenetic modifications is slight, even though the concordance rate is low, suggesting that epigenetics is not the only factor that needs to be considered. Nonetheless, the study of phenotypic discordance in monozygotic twins may shed light on the pathogenesis of autoimmune diseases and contribute to the development of new methodologies for the diagnosis and treatment of these diseases.

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1. Introduction

Monozygotic (MZ) twins arise from a single cell and therefore share almost all their DNA sequence. However, the concordance rate of the autoimmune diseases in monozygotic twins is considerably below 100% [1]. (Table 1) The reasons for this discordance is unknown. With the emergence of the field of epigenetics, researchers have begun to consider it a critical contributing factor to discordant phenotypes.

Epigenetics was defined by Conrad Waddington in the early 1940s and is now defined as the study of changes in gene function that do not involve a change in DNA sequence. The environment plays a role in determining an individual's phenotype, and the link between environment and genetics is mediated through epigenetic mechanisms [2]. Thus, epigenetics may partially explain the discordant presentation of diseases in monozygotic twin pairs [3–6]. (Fig. 1).

2. Major types of epigenetic alteration

2.1. DNA methylation

DNA methylation is mediated by DNA methyltransferase (DNMT) enzymes. A methyl group from *S*-adenosylmethionine is transferred onto the C5 position of cytosines. There are four general types of DNA methylation according to the target site: the methylation of CpG islands within the promoter region of genes, the methylation of CpG island shores which are located up to 2 Kb from CpG islands, the methylation of gene bodies throughout the gene, and the methylation of repetitive sequences [7]. There are five DNMT enzymes, which can be classified into two classes: de novo DNMTs (DNMT3a, DNMT3b, and DNMT3L) involved particularly in methylation during embryonic development, and maintenance DNMTs (DNMT1 and DNMT2) which methylate the cytosine during DNA replication. Unmethylated DNA has a euchromatin structure that allows transcription factors to easily bind to target sequences, whereas DNA methylation affects the chromatin structure leading to the formation of a corepressor complex, whereby transcription is thus repressed through decreased binding of transcription factors and increased binding of methyl-CpG-binding domain proteins [6].

2.2. Histones modifications

Histones are conserved proteins within the nucleosome structure. Their function is to package and organize DNA. Histones are categorized into two major groups of core (H2A, H2B, H3, and H4) and linker (H1 and H5) proteins. Histone proteins can also undergo a series of posttranslational biochemical modifications such as acetylation, phosphorylation and methylation, deimination, ubiquitylation, ADP ribosylation, and sumoylation. Of these biochemical modifications, histone acetylation is particularly widely studied. Histone acetylation is catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs transfer an acetyl group from acetyl CoA to the amino group of lysine side chains, which neutralizes the positive charge of lysine, and the interaction between the histone and the DNA strand are impaired. These changes lead to a less integrated chromatin structure, which in turns increases gene expression. HDACs, on the other hand, remove an acetyl group from the acetylated lysine tail of histones, which adds a positive charge and leads to a concentrated chromatin structure, which in turn decreases gene expression [8].

Table 1
Concordance rates of monozygotic (MZ) twin pairs in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (T1D), psoriasis, systemic sclerosis (SSc), multiple sclerosis (MS), dermatomyositis (DM), and primary biliary cirrhosis (PBC).

Autoimmune diseases	MZ concordance rate (%)	Reference
SLE	11.1	[22]
RA	12.3	[24]
T1D	27.3	[42]
MS	16.7	[7]
PBC	77	[58]
SSc	4.2	[47,48]
Psoriasis	64	[54]
DM	Only case reports	[36,37,48]

2.3. MicroRNAs-mediated regulation

MicroRNAs(miRNAs) are endogenous noncoding RNAs with 18–23 nucleotides that serve as one of the posttranslational regulators of gene expression. miRNAs play a pivotal role in cell proliferation, development and differentiation, apoptosis. cell metabolism processes, thus affecting the pathogenesis of many human diseases [9–12]. The mechanism by which miRNAs alter gene expression can occur through two pathways. First, miRNAs may induce degradation of target mRNA when the sequence of miRNA and 30 UTR of target mRNA are totally matched. In addition, translation can be depressed when a miRNA strand is incompletely matched with 30 UTR of target mRNA. The second way in which miRNAs affect gene expression is by modulating DNA methylation and histone modifications [13].

2.4. Epigenetics for MZ twin discordance in specific autoimmune diseases

Epigenetic changes have been observed in multiple autoimmune diseases. It is believed that epigenetic modifications of gene expression accounts for the widely varying phenotypes of autoimmune diseases and vasculitides, including type 1 diabetes, systemic lupus erythematosus (SLE), primary biliary cirrhosis (PBC) and even Kawasaki disease [14,15].

3. Epigenetics of SLE discordant MZ twins

SLE is a chronic multiorgan disease characterized by acute and chronic systemic inflammation [10,16,17]. Autoantibodies against nuclear and cytoplasmic antigens have been detected in patients with SLE and are believed to play a role in pathogenesis [18–21]. MZ twin pair concordance for SLE is only 11.1% [22].

A recent study [23] investigated DNA methylation status of 807 CpG-containing promoters of genes in SLE discordant MZ Twins. Forty-nine genes had significant differences in DNA methylation between SLE and healthy MZ twins, including IFNGR2, MMP14, LCN2, CSF3R, PECAM1, CD9, and AIM2, but not PDX1. There are significant differences in genes encoding for immune function, such as defense response, cell activation, immune response, cell proliferation, and cytokine production, all of which are potentially relevant in autoimmune inflammatory diseases. This broad range of associated functions suggests that critical cell types and biological pathways involved in autoimmunity are affected by these aberrant DNA methylation changes.

In addition, aberrant changes in the DNA methylation status of ribosomal genes, particularly in the transcribed region containing the 28S, 18S, and 5.8S that resembles a large CpG island, have been reported to be associated with various disorders. Although no significant differences in DNA methylation were observed in the promoter region, there is a significant decrease in the 18S and 28S segments for the SLE siblings of twin pairs.18S and 28S are hypomethylated in SLE siblings with respect to their corresponding