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Epigenetic changes: The missing link

Diego Kyburz [a, b, c, *], Emmanuel Karouzakis [c], Caroline Ospelt [c]

[a] Division of Rheumatology, University Hospital of Basel, Basel, Switzerland
[b] Department of Biomedicine, University of Basel, Basel, Switzerland
[c] Center of Experimental Rheumatology, University Hospital of Zurich, Zurich, Switzerland

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A B S T R A C T

The association of rheumatoid arthritis (RA) with a number of genetic risk loci is well established; however, only part of the risk to develop the disease is based on genetics. Environmental factors significantly contribute to the pathogenesis. A gene–environment interaction for smoking and certain major histocompatibility complex (MHC) class II alleles has been shown to promote anti-citrullinated protein antibody (ACPA)-positive RA; however, the molecular mechanisms of interaction remain unclear. In contrast to the genetic background, epigenetic factors are responsive to external stimuli and can modulate gene expression. Therefore, epigenetic mechanisms may function as intermediaries between genetic risk alleles and environmental factors.

In this review, epigenetic mechanisms are explained and the evidence for epigenetic changes relevant for the pathogenesis of RA and potential therapeutic applications are discussed.

Introduction

Sequencing technology has allowed to perform whole genome sequencing approaches to determine the genetic basis of rheumatoid arthritis (RA). A number of new genes were found to be associated with the disease, in addition to the long-known association with HLA-DR genes. However, considering a concordance rate in monocygotic twins of only 15% it follows that only a part of

* Corresponding author. Division of Rheumatology, University Hospital of Basel, Petersgraben 4, 4031 Basel, Switzerland. Tel.: +41 61 265 90 20; fax: +41 61 265 90 21.
E-mail address: diego.kyburz@usb.ch (D. Kyburz).

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the disease risk can be attributed to genetic factors [1]. On the other hand, several environmental factors were identified to impact the disease risk. Among those, smoking is of particular interest, as a gene–environment interaction was demonstrated in anti-citrullinated protein antibody (ACPA)-positive patients with RA. Smoking greatly increased the disease risk when the shared epitope of HLA-DRB1 was present [2]. How smoking and shared epitope are molecularly linked is unknown. In contrast to genetic risk alleles, epigenetic marks are sensitive to external factors. Therefore, environmental exposures may potentially impact the function of the immune system by modulating epigenetic modifications. The term "epigenetics" denotes heritable changes in gene function without alterations of the DNA sequence. These include histone modifications such as methylation and acetylation, as well as DNA methylation. The gene expression profile of a cell is critically dependent on DNA and histone modifications. In a broader sense, also noncoding RNA are included in the definition of epigenetics. In this review, epigenetic changes of cells are described and their role in the disease pathogenesis of RA is discussed, with focus on the implications on gene–environment interactions.

Epigenetic control of gene expression

In the past 10 years, epigenetics research revealed exciting new pathways in the regulation of gene expression. The biochemical modification of DNA and histones was found to have an important role in gene expression and human disease [3].

DNA methylation is often associated with transcriptional repression in CpG-rich genomic regions [4]. Two major mechanisms have been proposed. Firstly, the direct inhibition of transcription factor binding and secondly the recognition of the methylated regions by specific proteins that bind to methylated DNA (MeCP2, MBD1, MBD2, MBD3, MBD4) and inhibit the access of DNA polymerases and transcription factors.

Another field of epigenetics is the study of chromatin biology [5]. Chromatin consists of DNA wrapped around a complex protein network of histone proteins that form the nucleosome. The nucleosome is an octamer consisting of the histones H2A, H2B, H3 and H4 around which DNA is packed in a tight conformation. Posttranslational modification of histones often occurs at specific transcriptionally active or repressed sites in the genome. Histone modifications alter the structural conformation of nucleosomes and allow access of transcriptional activators.

DNA methylation and histone modifications

The addition of a methyl group to the cytosine base pair is known as DNA methylation and is catalysed by DNA methyltransferases. Three DNA methyltransferases, DNMT1, DNMT3A and DNTM3B, have been associated with DNA methylation in humans. DNMT1 is involved in the maintenance of DNA methylation during somatic cell DNA replication. It interacts with the Ubiquitin-like, containing PHD and RING finger domains 1 (UHRF 1) protein and targets hemimethylated 5′CpG 3′ DNA sequences [6]. The DNMT1/UHRF1 complex transfers a methyl group from S-adenosylmethionine to the unmodified cytosine in the opposite DNA strand.

DNMT3A and DNMT3B are called the de novo methyltransferases. During embryonic development, DNA methylation undergoes extensive demethylation [7]. De novo methyltransferases are mainly involved in the restoration of DNA methylation during cell development.

A characteristic of the human genome is the presence of DNA sequences that are CpG rich and remained unmethylated. These are called CpG islands and often associate with promoter and transcriptional starting sites of genes [8]. However, a known feature of DNA methylation is that the CpG islands remain methylated in the inactive X chromosome, imprinted genes and tissue-specific genes [9]. Transposable elements such as LINE-1 have the ability to integrate randomly to the genome and cause genomic instability. DNA methylation is known to silence these elements.

In addition, DNA methylation can actively be reversed by the action of the TET family of DNA dioxygenases that convert 5-methylcytosine (5-mC) to 5-hydroxylmethylcytosine (5-hmC), 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC) [10]. There are three TET genes currently known as TET-1, TET-2 and TET-3.

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