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MINI REVIEW

The epigenetics of PBC: The link between genetic susceptibility and environment

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Summary Primary biliary cholangitis (PBC) previously known as primary biliary cirrhosis is an autoimmune disease-associated with progressive cholestasis, the presence of autoreactive T cell and characteristic serological autoantibodies. Genetic and genome-wide association studies (GWAS) have recently shed light on the genetic background of PBC. Besides that some causal nucleotide changes and mechanisms remain largely unknown as suggested for example, by the observation that monozygotic twins have an identical DNA sequence even if presents some phenotypic differences that may be consequences of different exposures to environmental stressors. For this reason, it is believed that epigenetic mechanisms may be involved in PBC pathogenesis, as already demonstrated in many autoimmune diseases and can eventually provide an understanding that has been missed from genetics alone. This review will focus on the most commonly studied epigenetic modifications already demonstrated in PBC; special attention will be paid also to other epigenetic mechanisms so far not demonstrated in PBC patients, but that could increase our understanding in PBC pathogenesis.
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Abbreviations: PBC, primary biliary cholangitis; GWAS, genome-wide association studies; AIDs, autoimmune diseases; TFs, transcription factors; eRNA, enhancer RNAs; TSSs, transcription start sites; NF-κB, nuclear factor kappa-B; CTCF, CCCTC-binding factor; Dnmts, DNA methyl transferases; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; UC, ulcerative colitis; forkhead box P3, transcription factors FoxP3; CNV, copy number variations; DMR, differentially methylated regions; HMT, histone methyltransferases; HDM, demethylases; HAT, histone acetyltransferases; HDAC, deacetylases; ncRNAs, non-coding RNAs; siRNAs, small interfering RNAs; miRNA, MicroRNAs; SNPs, single-nucleotide polymorphisms; lncRNAs, long non-coding RNAs; lincRNAs, large intergenic non-coding RNAs; Xist, X-inactive-specific transcript; HDACIs, deacetylase inhibitors; HDACi, HDAC inhibitors; EWAS, epigenome-wide association studies.

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Introduction

Primary biliary cholangitis (PBC) previously known as primary biliary cirrhosis (PBC) [1—8] is a complex idiopathic autoimmune chronic liver disease characterized by an immune driven biliary injury and cholestasis [9,10]. In PBC like other inflammatory autoimmune diseases (AIDs), the decisive role of genetic factors has been widely demonstrated, as well as the exposure to certain environmental factors that could lead to immune tolerance breakdown [11—15].

The importance of the genetic factor in PBC is supported by numerous studies, principally by the fact that share association with numerous genes or gene complex [16—18]. Thanks to genome-wide association studies (GWAS) numerous genetic loci underlying PBC have already been identified (mainly intronic and intergenic). Besides that, some mechanisms remain largely unknown, such as causal nucleotide changes, rare genetic variants or the missing heritability sequencing [19—21]. Indeed, the use of GWAS have been very disappointing, i.e., it is likely that there are loci that have not been identified due to a lack of statistical significance; this is true not only of PBC, but also for a variety of other AIDs, many of which have been recently reviewed [22—33]. As a consequence, progress towards understanding disease mechanisms has been limited by difficulties in assigning a molecular function to the vast majority of GWAS hits that do not affect protein-coding sequences.

As observed for other AIDs, GWAS have identified hundreds of risk loci [34,35], but most risk variants have subtle effects on disease susceptibility, providing unbiased support for possible etiological pathways [34]. Identified associated loci are enriched for immune cell-specific enhancers [36—38] or for enhancer clusters [39,40] that are implicated in gene regulatory processes that are themselves implicated in disease etiology. However, as is typical of GWAS analyses, the implicated loci comprise multiple variants in linkage disequilibrium and rarely alter protein-coding sequences, which complicates their interpretation. In direct contrast to several AIDs, where concordance rates in monozygotic twins are significantly below 50%, PBC has the highest concordance rate (63%) [41].

Current models suggest the importance of environmental factors (virus, hormones, nutrition, and chemicals) [42—44] but these events are not sufficient to explain certain deficiencies of the genetic basis of PBC to date (such as female predominance) [45]. Supposedly, other mechanisms should be involved in the pathogenesis of this disease. As suggested for other AIDs, epigenetic modifications could represent the link between genetic and environmental factors influencing the onset and evolution of PBC disease (Fig. 1). Intrinsic and extrinsic components (mutations, polymorphisms, and environmental factors) have already been demonstrated to correlate with predisposition to autoimmunity and epigenetic can help to understand several of the mechanisms that may cause autoimmunity. In the mid-1990s, the number of epigenetics-based articles related to AIDs gradually began to grow and by 2007 this number was growing precipitously (Fig. 2). Parallel to what has been observed for other AIDs, a growing attention in the literature to the possible involvement of epigenetic defects in PBC has been observed since 2011 (Fig. 2). Recent studies have shown how epigenetic

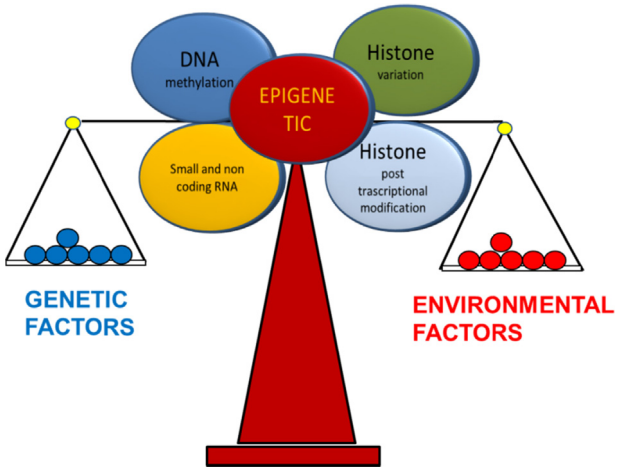

Figure 1 A schematic illustration of the relationship between epigenetic and genetic and environment factors.

dysregulation results in the overexpression of certain genes in several key immune cells. In addition to this evidence, is important to underline that epigenetics is not the only determinant of gene function as demonstrated by the fact that intrinsic components are stable over time and are the same in each cell type. Each cell type is controlled by a unique set of master transcription factors (TFs) that directly shape cell type-specific gene expression programmes, which include genes implicated in AIDs [46—48]. Immune subsets also have characteristic *cis*-regulatory landscapes, including distinct sets of enhancers that may be distinguished by their chromatin states [48] and associated enhancer RNAs (eRNA). Familial clustering of different AIDs suggests that heritable factors underlie common disease pathways, although disparate clinical presentations and paradoxical effects of drugs in different diseases support key distinctions. Hence, epigenetic mechanisms could represent a window to understanding the possible mechanisms involved in the pathogenesis of PBC and the identification of cell-specific targets of epigenetic deregulation could serve as clinical markers for diagnosis, disease progression, and therapeutic approaches.

Adaptive and innate immunity have been proposed as co-players in immune-mediated liver damage. For this reason, in PBC assumes the same importance as the immune system the effector of the autoimmune damage the target organ (i.e. liver-cholangiocytes); for this reason, epigenetic modifications that involve either the immune system or the target organ could play a role in disease development and they should be considered. This review summarises recent findings concerning the main epigenetic mechanisms involved in PBC either related to the immune system that to the target organ. Some epigenetic defects that are already known to be involved in X chromosome inactivation, or in immune cells known to be involved in PBC patients, will also be introduced and discussed.

Chromatine architecture

Chromatin is the combination of DNA and proteins (histones and non-histones) that collectively make up the contents of a cell nucleus; chromatin's function is connected to

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