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Chapter

Exploring Epigenetic Drugs in the Regulation of Inflammatory Autoimmune Diseases

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Abstract

During recent years, numerous studies have shown that epigenetics, heritable changes that do not involve alterations in the DNA sequence, play an important role in the development, function, and regulation of the immune system as well as in the onset and progress of autoimmune diseases. For that reason, in the following chapter, we will review some of the most important concepts about epigenetics and how they modulate the development and function of immune cells, specifically macrophages, dendritic cells, and T cells. Moreover, we will review the role of epigenetics on autoimmune diseases, as well as the use of pharmacological modulation of the epigenetic machinery, as an innovative way to approach a potential new treatment or improve the current treatments of autoimmune diseases.

Keywords: epigenetic, DNA methylation, histone modification, autoimmunity, therapy

1. Introduction

Conrad Waddington introduced the epigenetic term in 1942, and it was defined as the causal interactions between genes and their products that allow for phenotypic expression [1]. Currently, this term has been refined to collective heritable changes in phenotype due to processes that arise independent of DNA sequence [2]. The epigenetic information is transferred during cellular division and includes DNA methylation, post-translational modifications of histones such as acetylation and methylation, and non-coding RNA. The transcriptional effects of epigenetic regulation are multidimensional, including on/off gene regulation, maintenance of transcriptional status, and responsiveness or no-responsiveness to external stimuli.

Increasing interest in the study of epigenetic processes has emerged because changes in these mechanisms have been linked to the onset and/or development of several human diseases such as cancer, autoimmune diseases, and systemic metabolic disorders. For that reason, many epigenetic clinical trials are on the horizon. Here, we will examine some of the basic concepts about DNA methylation, post-translational modifications of histones, and their effect on development, differentiation, and effector function in antigen-presenting cells (i.e., dendritic cells and macrophages) and T cells. Finally, we will summarize the epigenetic changes found in immune cell populations and how some of the epigenetic modifications affect the most prevalent autoimmune diseases such as systemic lupus erythematosus (SLE),

rheumatoid arthritis (RA), multiple sclerosis (MS), and inflammatory bowel diseases (IBD). Finally, we will address how "epigenetic drugs" can be used to modulate these immunological changes.

2. A brief introduction to epigenetics

The classical concept of heritable information is that phenotypic characteristics are transmitted from parental cell to their offspring by genetic information [3]. However, several examples of heritable phenotypic variation cannot be fully explained by Mendelian genetics. In this context, epigenetic modifications such as covalent chemical modifications on the DNA, histone posttranslational modifications, and diverse no-coding RNAs can explain the inheritance of specific phenotypes that genetics cannot explain [4]. Those modifications occur in the nucleosome, the fundamental building block of eukaryotic chromatin, that consist of 147 base pairs of DNA wrapped twice around a histone octamer formed by two subunits of each of the core histones H2A, H2B, H3, and H4 [5]. A variety of modifying enzymes are responsible of the generation, maintenance, and removal of DNA methylation and histone modifications. Enzymes involved in the generation of those marks are called "writers," whereas enzymes involved in the removal of them are called "erasers"; the proteins able to bind to the marks are called "readers." Here, will provide a summary of the function and factors involved in these modifications.

2.1 DNA methylation

This modification occurs mostly in CpG dinucleotides and consists of the transfer of a methyl moiety from S-adenosylmethionine (SAM) to the 5 position of cytosines. DNA methylation in a gene regulatory region or in its coding region correlates with repression of gene expression (**Figure 1**). This reaction is catalyzed by DNA methyltransferases (DNMTs) (**Figure 2**). DNMTs comprise two families that are functionally and structurally distinct. Dnmt1 maintains DNA methylation patterns during DNA replication and repair, while Dnmt3a and Dnmt3b establish *de novo* CpG methylation patterns [6]. Methylated DNA is recognized by methyl-CpG-binding proteins (MBPs) (**Figure 2**), which bind to the methylated DNA and

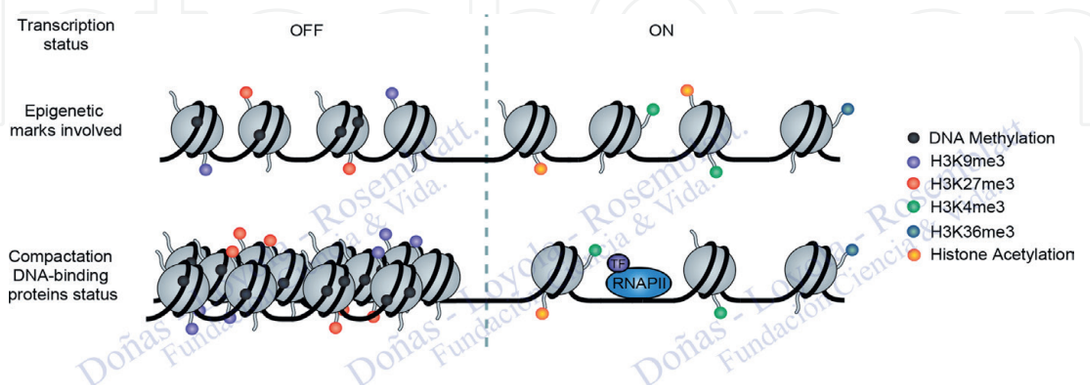

Figure 1.
Epigenetic marks associated to regulation of transcription. DNA methylation and histone modifications induce changes on chromatin structure leading to effects on transcriptional activity. On the left, DNA methylation and histone modifications such as the trimethylation of lysine 9 of H3 (H3K9me3) and the trimethylation of lysine 27 of H3 (H3K27me3) induce the chromatin compaction, making the DNA relatively inaccessible to DNA-binding proteins such as transcription factors (TFs) and RNA polymerase II (RNAPII) causing a transcriptional repression. On the right, histone modifications such as histone acetylation, H3K4me3 and H3K36me3, induce an open chromatin making the DNA to remain accessible to DNA-binding proteins such as TFs and RNAPII generating a state of active transcription.

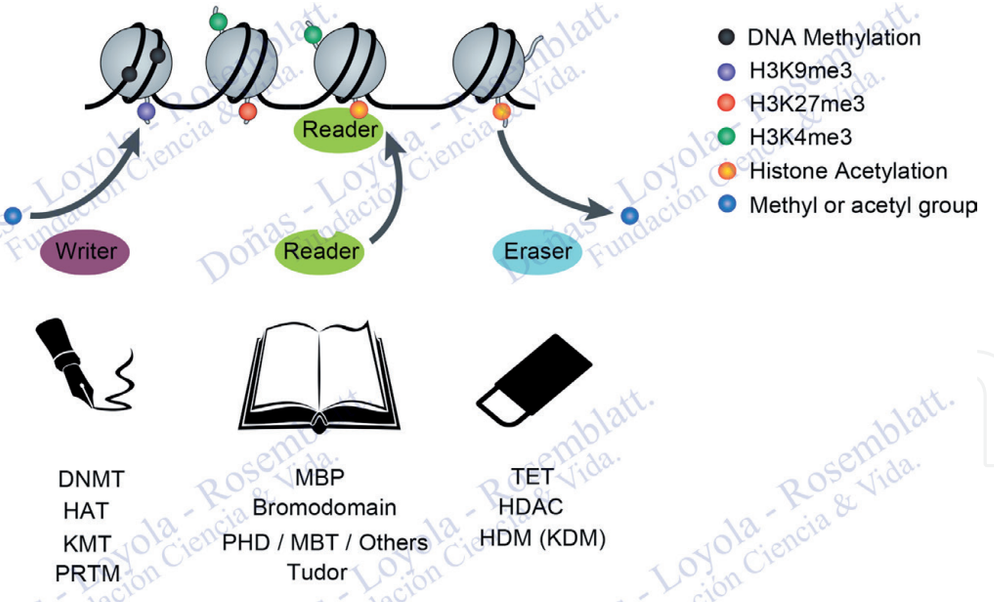

Figure 2.
Writer, readers, and erasers of epigenetic marks. A representative model of epigenetic writers, readers, and erasers and their function. Writers such as DNMT, HAT, KMT, and PRMT carry out the epigenetic modification on DNA and histone tails, while erasers such as TET, HDAC, and KDM remove those modifications. Proteins containing specific domains such as MBP, Bromodomain, PHD, MBT, and Tudor are able to "read" these epigenetic marks and promote either transcriptional activation or repression.

initiate the silencing of chromatin through the recruitment of other factors. These MBP proteins include MeCP2 and MBD1-4 [7]. On the other hand, DNA demethylation is catalyzed by ten-eleven translocation (TET) proteins (**Figure 2**) [8].

2.2 Histone modifications

Over 60 different modifications have been detected on histones. Histone amino-terminal tails are the most frequent target of modifications, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and ADP-ribosylation. These modifications, which regulate a variety of functions, including cell cycle, DNA repair, and transcription, has led to the "histone code hypothesis" that postulates that a combination of different modifications may result in distinct and consistent cellular outcomes [9].

2.3 Acetylation

Histone acetylation consists of the transfer of an acetyl group from acetyl-CoA to the lysine 1-amino groups on the N-terminal tail of histones. Acetylation can occur on specific lysines on H3, H4, H2A, and H2B. Acetylation of histones is considered a hallmark of transcriptionally active regions (**Figure 1**) [9]. Histone acetylation is catalyzed by histone acetyltransferases (HATs) (**Figure 2**), which are also known as lysine acetyltransferases (KATs). They are divided into three families based on sequence conservation: GNAT (GNC5/PCAF), MYST (KAT6-8), and p300/CBP families [10]. In addition to neutralize the positive charge normally present on histones, hence reducing affinity between histone and DNA, lysine acetylation generates binding sites for specific protein-protein interaction domains, such as the bromodomain and tandem PHD domains that facilitate chromatin decompaction (**Figure 2**) [11, 12]. On the other hand, four distinct families of histone deacetylases (HDAC) have been described (**Figure 2**). The classes I, II, and IV are considered classical HDACs and require zinc to catalyze the reaction, whereas

the class III is NAD-dependent enzymes of the Sirtuin family. HDACs are involved in multiple signaling pathways and are present in numerous repressive chromatin complexes [13, 14].

2.4 Methylation

Histone methylation occurs through the covalent addition of methyl group(s) from the donor SAM to arginine and lysine. Arginine can be mono- and dimethylated (symmetrically or asymmetrically), whereas lysine can be mono-, di- and trimethylated. Methylation mark on histones can be related to activation or repression of gene expression, depending on the residue that is modified (**Figure 1**) [9]. For example, methylation of lysine 4 of H3 (H3K4) is linked to the initiation of transcription [15], H3K36 methylation correlates to transcriptional elongation [16], whereas methylation of H3K79 is implicated both in transcriptional activation and elongation [17]. Three lysine methylation sites are correlated to transcriptional repression: H3K9, H3K27, and H4K20 [10, 18].

In the case of arginine methylation, asymmetric and symmetric dimethylations on arginine have an opposite role on gene expression. For example, asymmetric methylation on H4R3 produced by PRMT1 (protein arginine methyltransferase 1) promotes active transcription [19], whereas symmetric methylation on the same residue (H4R3) produced by the enzyme PRMT5 leads to transcriptional repression [20].

In addition, studies have shown that during early development some of the genes that are not expressed have both repressive (H3K27me3) and permissive (H3K4me3) marks on their promoters, forming the so-called bivalent domains. At the time when the differentiation process occurs, bivalent domain genes are resolved by getting rid of either the active or repressive mark. Therefore, these bivalent domains are thought to keep genes repressed at a certain developmental window but poised for activation in another developmental stage [21].

The enzymatic addition of methyl groups to histone lysine residues is mediated by lysine methyltransferases (KMT) (**Figure 2**) [22]. KMTs have a high degree of enzymatic specificity. For example, SUV39H1 and SUV39H2 convert H3K9me1 to H3K9me3, while G9a produces H3K9me2 [23]. In addition, some "writers" are able to produce all of the methylation status on a histone residue such as Ezh2 (Enhancer of zeste homolog 2) on H3K27 [24]. Methylated histone lysine residues can bind to several protein domains, including PHD, Tudor, and WD40 domains (**Figure 2**). Each domain recognizes specific methylated residues. For example, H3K4me3 is recognized by PHD domains, while WD40 domain recognizes several trimethylated lysine residues associated with repressive marks [25]. Histone lysine demethylase (KDM) removes methylation on specific histone lysine residues (**Figure 2**). These enzymes are divided into two families with distinct enzymatic mechanisms: the FAD-dependent amine oxidase family comprises two members, LSD1 and LSD2, while the iron- and α–ketoglutarate-dependent Jumonji C (JmjC) family comprises more than 30 members [26].

In the case of arginine methylation, the addition of methyl groups is mediated by arginine methyltransferases (PRMTs) (**Figure 2**). PRMTs are divided into three types: type I enzymes including PRMT1-4, 6, 8 and CARM1 generate asymmetric dimethylarginine, whereas type II enzymes such as PRMT5 generate symmetric dimethylarginine [27]. Tudor domains are one of the best-characterized domains that recognize methylated arginines (**Figure 2**) [28]. JMJD6 and JMJD1B have proved to serve as arginine demethylases [29].

Notably, DNA methylation cross-talks with histone modifications. In this context, DNA methylation correlates with the absence of activating marks, such as

methylation on H3K4, and the presence of repressive marks, such as H3K9 methylation. H3K4 methylation has been suggested to protect gene promoters from *de novo* DNA methylation. On the other hand, methylated CpG can recruit HDACs to deacetylate histones around the methylated CpG [30].

3. Epigenetic regulation of immune cell development, function, and effector function

3.1 Epigenetic regulation of macrophage development

CCAAT enhancer-binding protein (C/EBP) is a key transcription factor in the development of granulocyte-monocyte progenitors that it is not expressed on hematopoietic stem cells (HSCs). However, the gene promoter that encodes this transcription factor (*Cebpa*) has a "poised" status on HSCs, thus possessing both repressive and activating marks. After the commitment to myeloid cell development, the repressive modification H3K27me3 is removed from the *Cebpa* locus, while the permissive mark H3K4me3 remains, inducing *Cebpa* gene expression [31]. Afterward during myeloid development, the dosage of the transcription factors PU.1 versus C/EBP regulates the macrophage or neutrophil lineage decision, whereas high PU.1 dosage favors macrophage development. PU.1 recruits both DNA demethylases (TET2) and methyltransferases (Dnmt3b) to modulate DNA methylation, facilitating or repressing gene expression, respectively. In contrast, DNA methylation mediated by Dnmt1 is critical for preventing premature differentiation of HSCs [32].

3.2 Epigenetic regulation of macrophage polarization and function

Stimuli and microenvironmental variables induce the polarization of macrophages into M1 or M2 phenotypes. Classical activation is mediated by proinflammatory cytokines such as TNF-α and toll-like receptor (TLR) ligands triggering differentiation to a M1 phenotype. M1 macrophages have host-defense activities that result in pathogen death and are characterized by high expression of proinflammatory cytokines (TNFα, IL-1β, IL-12), antimicrobial molecules, and oxygen reactive species [33]. Studies have shown that regulatory regions of TLR target genes are poised for induction by master transcription factors. Under steady state conditions, those promoters have permissive histone modifications such as H3K4me3 and acetylated H3, and their enhancers are enriched on H3K4me1 [33, 34]. In addition, poised promoters of genes involved in eliminating the infection are primed for a strong and rapid response by IFN-β [35]. However, macrophages under steady state also have the repressive modifications such as H3K9me3, H3K27me3, and H4K20me3 at those loci, limiting effector gene expression in the absence of TLR ligands. Upon TLR activation, repressive histone methylations are removed by inducing histone demethylases such as JMJD3 [36, 37].

The alternative activation of macrophages occurs in the presence of type 2 cytokines, such as IL-4 and IL-13, driving them towards the M2 phenotype that plays an essential role in tissue repair and the resolution of inflammation [33]. In this conversion, the IL-4/Stat6 signaling induces the expression of the histone demethylase JMJD3 that binds to genes required for M2 differentiation [38]. JMJD3 removes the repressive H3K27me3 mark from the regulatory regions of M2-activating genes such as *Irf4* [39]. In contrast, HDAC3, which is a positive regulator of M1 polarization, has been shown to repress M2 programs [40].

3.3 Epigenetic regulation of trained and tolerized macrophages

Trained and tolerized states of macrophages have been recognized as the immunological "memory" of innate immunity. During those states, macrophages have a robust and specific response upon a secondary challenge. Macrophages derived from monocytes treated with β-glucan, called trained macrophages, show an enhanced inflammatory status. β-glucan challenge showed stable changes in H3K4me3 at promoters of proinflammatory cytokines such as *Tnf*, *Il6*, and *Il18*, while no changes were observed in H3K27me3 [41]. In addition, H3K4me1 mark persists at enhancers after a pathogen challenge, contributing to the faster and stronger induction of multiple genes upon restimulation of trained macrophages [42].

In contrast, monocytes-derived macrophages pretreated with LPS produced less proinflammatory mediators such as IL-6 and TNFα upon challenge with certain toll-like receptor agonist(s). At the same time, anti-inflammatory molecules such as IL-10 and TGF-β show an increased expression following a secondary challenge compared to non-tolerized macrophages. H3K4me3 was induced in macrophages at both proinflammatory and anti-inflammatory gene promoters. However, "tolerized" macrophages treated with LPS induce a rapid and selective loss of H3K4me3 at proinflammatory gene promoters maintaining the mark on anti-inflammatory gene promoters. In this context, H4 acetylation was found on both group of genes in naïve macrophages but was reacetylated only on promoters of proinflammatory genes in tolerized macrophages [43, 44].

Additionally, the transcription factor ATF7 controls genes involved on immune response such as *Tnf*, *Ccl3*, and *Cxcl2* in unstimulated macrophages by recruiting the lysine methylase G9a and promoting H3K9me2 on these promoters. LPS treatment in trained macrophages induces phosphorylation of ATF7 via p38, leading to ATF7 release from chromatin with the concomitant removal of G9a and a decrease of the repressive H3K9me2 mark on the promoter of target genes. This partially disrupted chromatin structure leads to enhanced resistance to pathogens in trained macrophages [45].

3.4 Epigenetic regulation of DC development

The permissive mark H3K4me3 is confined to promoters of progenitor genes in multipotent progenitors (MPP) and in common dendritic cell progenitors (CDP), while H3K4me1 is found in their enhancers. H3K27me3 was observed at promoters of progenitor genes in conventional DCs (cDC) and plasmacytoid DCs (pDC). Conversely, H3K4me3 and H3K4me1 in cDCs and pDC were observed at promoter and enhancer of DC-specific genes, while H3K27me3 was seen in progenitors [46, 47].

3.5 Epigenetics and DC function

Few studies have investigated the role of epigenetic modifications on DC function. Genome-wide DNA methylation analysis showed rapid and active demethylation at thousands of loci on DCs exposed to the pathogenic bacterium *Mycobacterium tuberculosis* (MBT) [48].

Our own studies have shown that under steady state conditions *Il6* and *tgfb1* promoters have a bivalent status on splenic DCs and that treatment of DCs with LPS induces H3K4me3, decreasing H3K27me3 on the *Il6* promoter, while it decreases H3K4me3 and increases H3K27me3 on the *tgfb1* promoter. Contrary, the use of GSK-J4, a specific inhibitor of the H3K27me3 histone demethylase JMJD3, reverses this bivalent status and promotes DCs with tolerogenic functions in LPS-treated DCs [49].

Patients who survive sepsis have significant deficiencies in their immune response. One study found that these deficiencies are explained at least in part because post-septic DCs exhibit a significant and chronic suppression of IL-12. Whereas normal

DCs showed a high H3K4me3 and low H3K27me2 at both *Il12p35* and *Il12p40* promoters, suggesting a permissive chromatin structure poised for expression on exposure to stimuli, post-septic DCs showed a significant decreased H3K4me3 and increased H3K27me2 levels. In addition, post-septic DCs fail to recruit histone methyltransferases to *Il12* promoter [50].

Several studies have shown that histone deacetylase inhibitors such as valproic acid and MS-275 inhibit *Cd40, Cd80*, and *Cd86* expression as well as proinflammatory cytokines such as *Il6*, *Il12*, and *Tnf*. All these studies suggest that histone acetylation is a key player in the modulation of DC function [51, 52].

3.6 Epigenetic regulation of B cell development and immunoglobulin gene recombination

The main function of these cells is the production of antibodies. They can also act as APC for T cells. Many epigenetic changes have been described during B cell development, differentiation, and effector function. PAX5 is an essential transcription factor in B-cell differentiation and maintenance as it induces B-cell-specific genes, while repressing genes of other lineages. The permissive marks H3K9ac, H3K4me2, and H3K4me3 are important to mediate PAX5 transactivation [53]. Epigenetic marks also regulate immunoglobulin gene recombination at several levels. For example, H3K4me2 on immunoglobulin genes is correlated with V(D)J recombination, whereas methylation on H3K9 and H3K27 is inversely correlated with the efficiency of V(D)J recombination [54, 55]. DNA methylation and histone acetylation inhibits and enhances the V(D)J recombination, respectively [56, 57]. Furthermore, hypermutation required to produce antibody diversity in V(D)J recombination is mediated by activation-induced cytidine deaminase (AID). DNA methylation as well as hypoacetylation on H3 suppresses *Aicda* gene expression (encoding AID) [58]. Upon activation of B cells, *Aicda* gene is DNA demethylated and the locus becomes enriched in H3K4me3 and H3K9ac/K14ac [58].

3.7 Epigenetic regulation of plasma cell and memory B cell

B cell differentiation into antibody-secreting plasma cells (PC) is initiated by external stimuli. PCs are derived from either germinal center (naïve B cell) or memory B cells. Blimp-1, a key transcription factor required for PC differentiation, inhibits *Bcl6*, *Pax5*, and *Spib* expression by binding to the promoters of these genes and recruiting HDAC to decrease histone acetylation [59] and G9a to induce H3K9me3 [60]. On the other hand, memory B cells quickly react to a second challenge with the same antigen, thereby providing humoral immune protection. Finally, the differentiation of naïve B cells to PC or memory B cells associates with changes in DNA methylation in an DNMT3a-dependent manner [61].

3.8 Epigenetic regulation of early T cell development

Initial commitment of hematopoietic precursors to the T-cell phenotype is triggered by Notch signaling. During this process, B-cell transcription factors *Pax5* and *Ebf1* are repressed by H3K27me3 marks. The myeloid regulatory gene, *Cebpa*, is kept silent by a bivalent status (H3K27me3 and H3K4me3), while the erythroid gene, *EpoR*, is repressed via H3K27me3 [62]. Activation of T-cell-associated genes is strongly and temporally correlated with histone acetylation, although DNA methylation also regulates early T-cell development. DNA demethylation has been observed in many essential T-cell regulators, including genes that encode TCR components such as CD3 molecules and key developmental genes such as *Runx3, Rorc, Ikaros, Rag,* and *Lck* [63].

3.9 Epigenetics on the regulation of terminal differentiation and effector functions of CD4+ and CD8+ T cells

The lineage choice between CD4 and CD8 T cells is defined by the transcription factors ThPOK and Runx. ThPOK activity is necessary and sufficient for CD4 lineage commitment, and its function is abrogated in the presence of the histone deacetylase HDAC1. Runx1 and Runx3 or their common obligatory dimerization partner, Cbfβ, is necessary for the development of CD8 T cells. ThPOK and Runx factors are mutual repressors [64]. After their terminal differentiation, CD4+ T cells exert their function as either helper T cell subsets (Th1, Th2, and Th17) or Treg cells. This section describes the epigenetic regulation of naïve T (Tn) cells to a specific differentiation program upon activation. Genome wide analysis of H3K4me3 (permissive mark) and H3K27me3 (repressive mark) in Tn, Th1, Th2, Th17, and Treg cells demonstrated the enrichment of H3K4me3 in genes that encode signature transcription factors and cytokine production for the corresponding cell subsets, while these genes are enriched in the repressive mark H3K27me3 in the other subsets (**Figure 3**). For example, the permissive mark H3K4me3 is found in the *Tbx21* (encoding Tbet) and *Ifng* loci in Th1 cells, in the *Gata3* and *Il4* loci in Th2 cells, in the *Rorc* (encoding RORγt) and *Il17* loci in Th17 cells, and *Foxp3* in Treg cells. However, these same loci show the repressive mark H3K27me3 in the opposing cell subsets, for example, the *Tbx21* locus in Th2. Most interesting, the master transcription factors for each T cell subset (*Tbx21, Gata3, Rorc*, and *Foxp3*) have a bivalent status (permissive H3K4me3 and repressive H3K27me3) in the opposing cell subsets (i.e., *Tbx21* loci in Treg cells), thus suggesting functional plasticity among Th subsets and Treg cells [65] (**Figure 3**).

Suv39H1, which mediates the repressive H3K9me3 mark, is a key to keep Th1 commitment since disruption of Suv39H1 results in an aberrant induction of IFNγ in Th2 cells after re-culture under Th1 polarizing conditions. However, the absence of Suv39H1 does not disturb Th2 cell differentiation [66]. The histone demethylase JMJD3 has a controversial role in CD4+ T-cell differentiation. One study showed that JMJD3 ablation promotes Th2 and Th17 differentiation, while decreases Th1 cells [67]. However, another study shows that JMJD3 induction is crucial to induce Th17 cells. The same study described that the epigenetic drug GSK-J4, a JMJD3 inhibitor, dramatically suppressed Th17 cell differentiation *in vitro* [68]. Nevertheless, our own studies reveled that GSK-J4 promotes Treg differentiation by DCs. Also, we showed that GSK-J4 treatment decreases the plasticity of Treg to become Th1 or Th17 cells *in vivo* [49]. This is in concordance with another report where the JMJD3 deficiency also restrains plasticity in the conversion of Th2, Th17, or Treg cells into Th1 cells [67].

The vast majority of Foxp3+ Treg cells are generated during thymic development (tTreg). A small portion of Treg cells can also be converted from conventional CD4+ T cells in the periphery. They are called inducible Treg cells (iTreg). This population has specificity towards nonpathogenic foreign antigens, including commensal microbiota, food, and fetal antigens. All Treg cell types (tTreg and iTreg) rely on a proper Foxp3 expression for the acquisition of the immunosuppressive phenotype as well as for the maintenance of their phenotype and function, particularly under inflammatory conditions. Mutations within the Foxp3 gene or deletion of Foxp3 result in the development of autoimmunity [69]. H3 and H4 acetylation as well as H3K4me2 and H3K4me3 are found at the *Foxp3* promoter in Treg cells but not in other CD4+ conventional T cell phenotypes. On the contrary, H3K27me3 (repressive mark) is found in conventional CD4+ T cells, but not in Treg cells [70]. In Treg cells, the polycomb repressor complex is replaced by p300/CREB-binding protein-associated factor (PCAF), a histone acetyltransferase recruited

via the zinc-finger transcription factor Krüppel-like factor 10 (KLF10) to the *Foxp3* promoter, a process that finally results in the opening of the Foxp3 promoter by permissive histone modifications [71]. In addition, our own results showed that treatment with Trichostatin A (TSA), a histone deacetylase inhibitor, increases Treg population as well as H3 acetylation [72]. The data indicate that modulating histone acetylation on Treg might also be a key to improve Treg function and stability.

Foxp3 gene has three conserved noncoding sequences (CNS) that are the primary targets of epigenetic regulation and are necessary to modulate its expression depending on the environmental cues that T cells receive. CNS1, which is a TGF-β-sensitive enhancer element and critical for the generation of Treg cells, does not contain any CpG motifs and thus is solely regulated via histone modifications [70, 73]. Indeed, H3/H4 acetylation and H3K4me2/3 are enriched in both tTreg and iTreg cells compared to other conventional CD4+ T-cell phenotypes [70]. CNS2 is a Treg cell-specific demethylated region (TSDR). Demethylation of this CpG region, mediated by TET2, is mandatory for stable Foxp3 expression. Also, CNS2 contains H3K4 methylation as well as H3/H4 acetylation in Treg cells, suggesting that DNA demethylation and permissive histone modifications generate an open chromatin status at CNS2 that promotes stabilization of *Foxp3* expression [70, 74]. Conversely, DNA methylation

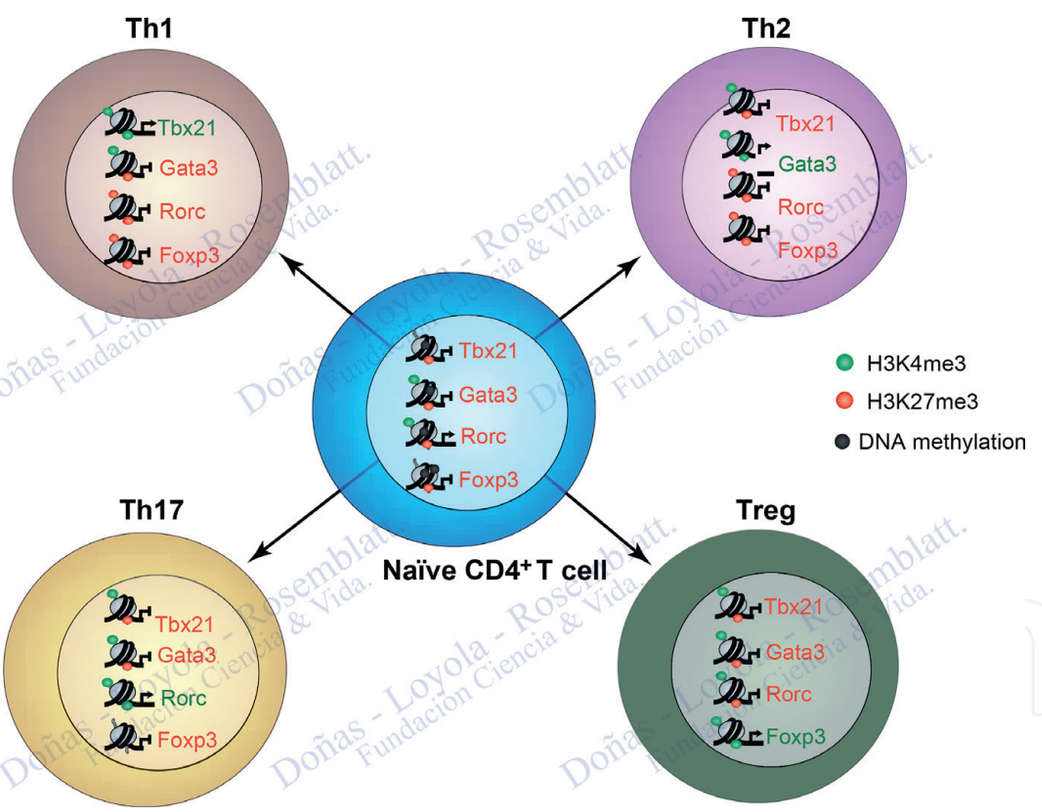

Figure 3.
Epigenetic status of "Master" transcriptional factor gene in CD4+ T cells. DNA methylation and bivalent marks (H3K27me3 repressive and H3K4me3 permissive) present on the promoter of the "master" transcription factors for Th1 (T-bet), Th2 (GATA3), Th17 (Rorγt), and Treg (Foxp3) inhibit their expression on naïve CD4+ T cells (nT cells). Upon TCR stimulation and depending on the cytokines present in the milieu, nT cells will adopt one of those phenotypes. During differentiation of nT cells to Th1, Tbx21 gene promoter (encoding T-bet) is hypomethylated, and repressive marks such as H3K27me3 removed while gaining permissive marks such as H3K4me3, thus allowing Tbx21 expression (in green) while the rest of "master" transcription factors associated to other T subsets are repressed (in red) through the acquisition of bivalent or repressive marks. The same process has been described on the promoters for the master transcription factors critical in the differentiation of the Th2, Th17, and Treg subsets, in which Gata3, Rorc, and Foxp3 are expressed, respectively. The transcription factor expressed on each phenotype is written in green, whereas transcription factors that are not expressed on that particular phenotype are written in red. It should be noted that the acquisition of bivalent marks and the absence of DNA methylation in master transcription factors associated to opposite T subsets are linked to the plasticity described on CD4+ T cells.

of CNS2 can prevent *Foxp3* expression in non-Treg cells [74]. Furthermore, Foxp3 expression cannot be maintained when Treg cells are exposed to inflammatory cytokines such as IL-4 and IL-6 upon deletion of CNS2 [75]. CNS3 has been called "pioneer element," since it plays a critical role for the initiation of Foxp3 expression in Treg cells, but is dispensable once Foxp3 is expressed. It is enriched in the permissive H3K4me1/2 marks, modifications that are increased in the Foxp3-thymocyte subsets, suggesting that CNS3 facilitates the opening of the Foxp3 locus in Treg cell precursors [70].

Epigenetic modifications also play important roles in the regulation of CD8+ T-cell effector functions. For example, H3K27me3 modification at the *Ifng* locus in naive CD8+ T cells is removed upon activation and differentiation to effector cells, whereas the permissive histone modifications H3K9ac and H3K4me3 are deposited in this locus. The *Ifng* locus has reduced levels of total histone H3 in activated CD8+ T cells, suggesting that the depletion of nucleosomes from the locus allows the transcriptional machinery to access the promoter [76]. The *Gzmb* locus, which encodes another CD8+ T-cell effector molecule, granzyme B, also shows similar epigenetic regulation during differentiation from naive to effector cells [77].

4. Epigenetic regulation of autoimmune diseases and the prospect of epigenetic drug as therapeutic agents

Autoimmune diseases are a complex group of diseases in which each one present with a unique epidemiology, pathology, symptoms, and origin. There are intrinsic and extrinsic components that predispose to autoimmunity. The following section describes some important epigenetic changes in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and inflammatory bowel diseases (IBD), and how epigenetic drugs can modulate these changes.

4.1 Systemic lupus erythematosus (SLE)

It is a chronic inflammatory disease with a significant long-term morbidity that affects principally women, with an estimated population frequency in the United States of about 150 for white women to about 400 for African-American women per 100,000. SLE is a systemic multiorgan autoimmune disease characterized by an autoantibody response to nuclear and/or cytoplasmic antigens. Autoreactive T and B cells lead to a gradual loss of self-tolerance leading over time to high levels of autoantibodies.

A global DNA hypomethylation occurs on several promoter regions in CD4+ T cells derived from SLE patients, including genes related to immune response such as *Itgal*, *Cd40l*, *Cd70*, *Ifgnr2*, *Il-4*, and *Il-13*. These hypomethylated regions are correlated with an upregulation in the expression of those genes causing cell hyperactivity and, consequently, perpetuation of inflammatory responses. DNA is hypomethylated on interferon genes in B cells, monocytes, and neutrophils, leading to the upregulation of these genes and a predisposition to produce an increased interferon response, a factor that plays a key role in SLE pathogenesis [78]. Consistently, DNA methyltransferase inhibitors, such as procainamide and hydralazine, induce lupus-like disease in mice [79]. So far, the accumulative evidence show that changes on DNA methylation in immune cells are key during SLE development.

Modified histones, such as H3K4me3, H3K27me3, H4K8ac, H4K16ac, and H2BK12ac, are known to be relevant autoantigens in SLE. These autoantigens trigger NETosis, a phenomenon whereby neutrophils extrude their nuclear material (Neutrophils Extracellular Traps) to kill pathogens [80]. However, very little

attention has been paid to histone modifications in SLE and in the induction or repression of gene expression. In SLE monocytes, H3K4me3 is enriched on type I interferon response genes, which is consistent with the type I interferon effect in lupus [81]. Nevertheless, the histone methyltransferase Ezh2 seems to be important in autoimmune responses of CD4+ T cells. Ezh2 is highly enriched on genes such as *Il-4, Il-10, Il-13, Cd70*, and *Tnf* [82]. Since Ezh2 mRNA levels are decreased in human lupus CD4+ T cells, this leads to an elevated expression of these genes [98]. Gene expression profile of CD4+ T cells generated from Ezh2-deficient mice shows a similar behavior to lupus CD4+ T cells [82]. These results suggest that Ezh2 and histone modifications have a relevant role in SLE.

4.2 Rheumatoid arthritis (RA)

RA is a disease characterized by the progressive destruction of joints by invasive synovial fibroblasts. RA synovial fibroblasts (RASFs) play a major role in this pathology. This disease is characterized by painful joint swelling, cartilage damage, bone erosion, severe joint deformation, disability, and premature mortality.

Global DNA hypomethylation is observed in RASF, T cells, B cells, and monocytes. In RA, Cxcl12 gene is hypomethylated in RASF cells, which allows for overexpression of Cxcl12 and thus promoting infiltration of inflammatory cells in the synovium [83]. The promoter of the transcription factor Tbx5 is also DNA hypomethylated, and its overexpression induces pro-inflammatory cytokines production [84]. In monocytes, DNA methyltransferase expression is reduced leading to a reduction of DNA methylation in inflammatory response promoter genes. For example, hypomethylation in the *Il6* promoter gene causes an overexpression of IL-6, furthering B cell response [85]. In CD4+ T cells, *Cd40l* promoter is DNA demethylated in female patients, leading to the overexpression of this gene and an increased immune response. On the other hand, Tregs responses fail to control the activity of T helper cells in RA. Foxp3 is the master transcription factor for the differentiation of Tregs, and DNA methylation controls its expression (see T cell section above). Methotrexate, a drug that inhibits S-adenosylmethionine (SAM) synthesis (the donor methyl group during methylation reaction), restores the suppressive function of Tregs by demethylating the Foxp3 promoter [86].

Destruction of cartilage on RA synovial tissue is characterized by an imbalance between HAT and HDAC activities (acetylation vs. deacetylation). For example, hyperacetylation on p16 and p21 gene promoters induce their expression with a subsequent decrease in TNFα synthesis leading to an improvement of RA symptoms in a murine RA model [87]. Many studies have described the beneficial effects of HDAC inhibitors *in vitro* and in an *in vivo* mouse model of arthritis. HDAC inhibitors such as Givinostat [NCT00570661] have already started to be used in clinical trials, revealing benefits in patients with systemic-onset juvenile idiopathic arthritis after 12 weeks of treatment. On the other hand, HDAC class III enzymes showed a contradictory function in RA. For example, the levels of the NAD-dependent protein deacetylase SIRT6 are increased in the joint tissues of collagen-induced arthritis (CIA) in mice, and further studies revealed that SIRT6 overexpression attenuates the severity of arthritis by reducing both the inflammatory response and tissue destruction, whereas SIRT1 levels were increased and its overexpression contributed inflammatory cytokine production [88, 89]. Finally, Pan-inhibitors against the BET protein family (acetylation readers) have anti-inflammatory and anti-destructive properties *in vitro* [90] and in CIA mice [91, 92]. The effects of BET inhibitors in CIA are attributed to the suppression of Th17 cell differentiation and function, suggesting that BET inhibitors are potential targets for RA treatment [91].

4.3 Multiple sclerosis (MS)

MS is an autoimmune disease of the central nervous system (CNS) characterized by the abnormal entry of inflammatory cells into the CNS followed by chronic inflammation, myelin destruction, and axonal loss. MS affects more than 2 million people worldwide and has an incidence rate of approximately 5–6 per 100,000 population per year in the United States and 83 per 100,000 in Europe. MS is caused by an autoimmune response against myelin proteins in neurons.

CD44 is an interesting protein in the MS pathophysiology because the signaling induced by its activation modifies DNA methylation patterns in key immune response genes that have been associated to MS in T cells. CD44-ligand interaction leads to hypomethylation of the IFNγ and Il-17 genes and promotes differentiation towards Th1 and Th17 cells [93]. CD44 deficiency decreases Th1 and Th17 differentiation and promotes Th2 differentiation via hypomethylation of the Il-4 promoter. This may explain why CD44-deficient mice are protected against experimental autoimmune encephalomyelitis (EAE) (a mouse model of MS) [94]. Similar effect has been showed in CD4+ T cells from MS patients, where Th17 differentiation and IL-17 expression are increased following DNA hypomethylation of Il-17α gene promoter [95]. On the other hand, the Foxp3 promoter is DNA hypermethylated in CD4+ T cells of relapsing-remitting MS patients leading to a reduction of the Treg population and their control of immune response [96]. Decitabine (5-aza-2′-deoxicytidine), which is a DNMT inhibitor, induces Foxp3 expression in mice exposed to experimental autoimmune encephalomyelitis (EAE, a MS murine model) by demethylating CpG islands in the gene encoding Foxp3. As a result, this drug decreases spinal infiltration and ameliorates disease progression [97]. A crosstalk has been described between DNA methylation and histone acetylation. For example, MeCP2, a reader of methylated DNA, suppresses the brain neurotrophic factor expression, which is necessary for myelin repair, whereas histone acetyltransferase expression and HDAC inhibitors reduce MeCP2 expression and thus favor remyelination [97].

The oligodendrocytes are a key to maintain the central nervous system by providing support and insulation to axons. Stem cell commitment to oligodendrocyte is modulated by histone acetylation levels since deacetylation promotes oligodendrocyte differentiation, while acetylation is associated with inhibition of differentiation. For example, HDAC1 and HDAC2 are needed for oligodendrocyte differentiation, while an increase in H3 acetylation is associated with high levels of oligodendrocyte-differentiation inhibitors such as TCF7 and SOX2 [98]. In PBMCs, high H3K9ac levels correlate with a decrease in the expression of SIRT1, a class III deacetylase (HDAC) during MS relapse when compared to stable MS patients and controls [99]. Therefore, SIRT1 expression has been proposed as an activity marker as well as therapeutic target in MS. Resveratrol, a SIRT1 activator, has shown promising results when tested in EAE mice, preventing neuronal loss during optic neuritis, providing neuroprotection, and a demonstrated secondary benefit in clinical dysfunction [100]. These results have also been shown using other SIRT1 activators. However, these treatments did not prevent inflammatory cell infiltration in these tissues.

Histone acetylation also plays a direct role on immune response. For example, IL-17 expression is regulated by the T cell transcription factor TCF1 through the acetylation of histones. Hyperacetylation on IL-17 promoter was found in TCF1 knockout mice and correlated with more susceptibility to EAE induction [101]. Modification of histone acetylation has emerged as therapeutic treatment for MS. In this context, HDAC inhibitors have potential therapeutic value in MS because of their anti-inflammatory and neuroprotective effects both *in vitro* and

in vivo. For example, sodium phenylacetate (SPA) suppresses neurological damage in mice pretreated with myelin basic protein (MBP)–primed T-cells [102]. Valproic acid reduces the duration and severity of EAE by regulating inflammation through a decrease of macrophage and lymphocyte infiltration into the spinal cord and of proinflammatory cytokines such as IFNγ, TNFα, and IL-17 [103]. Several a histone deacetylase inhibitors have been used in the EAE mouse model as potential drugs for human treatment. Trichostatin A (TSA) treatment after myelin oligodendrocyte glycoprotein (MOG) immunization reduces inflammation, cell infiltration, demyelination, and neuronal loss in the spinal cord and ameliorates the disability of EAE relapse [104]. Likewise, Largazole, another powerful class I histone deacetylase (HDAC) inhibitor, decreases IL-17 and IFNγ production, reduces CNS inflammatory infiltrates, and produces a clinical effect on the incidence, severity, and disability scores in MS murine model [105]. Vorinostat prevents human CD14 monocyte-derived dendritic cell differentiation and reduces Th1 and Th17-mediated inflammation and demyelination in the CNS of EAE mice [106]. Curcumin reduces cytokine synthesis such as IL-17, TGFβ, IL-6, and IL-21 and transcription factors STAT3 and RORγt as well as reduces inflammatory cell infiltration into the spinal cord, thus leading to reduction in clinical severity in EAE mice and MBP-reactive lymphocyte proliferation in a dose-dependent manner [107, 108]. Studies using inhibitors of histone demethylase in EAE model are less extended. However, GSK-J4, a JMJD3 inhibitor, improves EAE disease by the generation of tolerogenic DCs and enhancing Treg function leading to a decrease in CNS inflammatory infiltrates [49]. Histone modifying drugs are promising MS therapies based on their properties to modulate overactive immune system and neuroprotective pathways to prevent CNS damage.

4.4 Inflammatory bowel diseases (IBD)

IBD is the term used to describe disorders that involve chronic inflammation of the digestive tract. Crohn's disease and ulcerative colitis are the main subtypes of IBD. Crohn's disease represents a discontinuous, transmural inflammation that can occur anywhere in the gastrointestinal tract, whereas ulcerative colitis is a continuous inflammation of the mucosal layer of the colon. In addition to the gastrointestinal tract inflammation, so-called extraintestinal symptoms are common, affecting the joints, eyes, skin, and liver.

Active inflamed tissue from ulcerative colitis patients is characterized by global DNA hypomethylation compared to patients with inactive ulcerative colitis or to healthy individuals [109]. The higher turnover of colonic epithelial cells leads to an increase in DNA methylation in tumor-suppressor genes and a decrease on pro-tumorigenic elements which could lead to genome instability and cancer development [110]. A comparison between colonic mucosa from ulcerative colitis patients with dysplasia and/or carcinoma and quiescent mucosa from the same patients showed differential DNA methylation on several genes. For example, the gene encoding cell adhesion molecule E-cadherin (CDH1) is hypermethylated in dysplasia and/or carcinoma samples, a modification that leads to the downregulation of CDH1 expression [111]. In addition, the protein levels of DNA methyltransferases DNMT1 and DNMT3b are increased in inflamed mucosa from ulcerative colitis patients compared with noninflamed paired samples [112].

There are fewer studies regarding histone methylation and acetylation in IBD. Histone acetylations such as H4K8ac and H4K12ac were found in inflamed mucosa compared with non-inflamed mucosa from mice treated with sodium dextran sulfate (DSS) and 2,4-trinitrobenzene sulfonic acid (TNBS). Identical

acetylation pattern is observed in biopsies from patients with Crohn's disease [113]. The administration of HDAC inhibitors in DSS and TNBS-induced experimental colitis reduces the expression of proinflammatory cytokines and, consequently, disease severity [114]. Furthermore, HDAC9 inhibition prevents colitis in mice as a consequence of an increase in both, Treg frequency and its suppressive function [115]. An interesting perspective when talking about IBD is the effect of the gut microbiota. Bacterial metabolites, such as short-chain fatty acids (SCFAs), possess HDAC inhibitory activity [116]. Many bacteria from the Firmicutes and Bacteroides produce SCFAs, such as acetate, propionate, and butyrate, at high concentration, and IBD patients have reported to have a reduced number of those SCFA-producing bacteria [117]. In the same line, ulcerative colitis patients treated with microbiota therapy with *Roseburia*, a bacterium known to produce butyrate, an HDAC inhibitor, showed a positive effect in patient recovery by reducing inflammatory cytokines production [118]. The potential mechanism is through the generation of Tregs from naïve CD4+ T cells. Butyrate increases H3 acetylation on *Foxp3* loci, the master transcription factor required for Treg cell differentiation [116]. In addition, butyrate might modulate the function of intestinal macrophages since macrophages treated with butyrate downregulated LPS induced IL-12 and IL-6 cytokine expressions [119]. Thus, the commensal microbiota may play a beneficial role in IBD treatment via epigenetic regulation of gene expression.

5. Conclusions

During the recent years, several studies have focused on a better understanding of epigenetic processes as well as its connection with biological processes such as immune response and inflammation (**Figure 4**). Currently, many epigenetic studies are being carried out in cells of the immune system related to the inflammasome such as DCs, macrophages, and lymphocytes. Most of those studies are related to the epigenetic mechanisms associated to the development, differentiation, and function of these cells, leading to a better knowledge about how epigenetics of the immune system relates to its function in pathogenesis. However, further studies on the epigenetics of immune cells and/or the associated biological processes are much needed as a means for improving our understanding of the role of epigenetics in inflammation.

The interactions between genetic and epigenetic factors significantly contribute to inflammation and autoimmune diseases. Epigenetic research has grown and is providing new insights into inflammatory autoimmune diseases, insight that will allow us to explain the etiology of these diseases. Furthermore, studies on epigenetic changes could lead us to understand disease progression and to identify future markers for therapy. Although further studies are needed to address the potential of epigenetic factors to act as biomarkers and drug targets, epigenetic enzymes are the current target of drug development and new therapeutic trials.

Epigenetic analyses, including DNA methylation and histone modifications, require a large number of cells making these studies difficult. Recent advances in technologies such as in single-cell analysis provide a new solution to this problem. Nevertheless, an important issue to be addressed is the limited information obtained so far for several cell subsets, specifically those with small representation within the immune system. As conclusion, although some important advances have been achieved in our understanding on the epigenetics of immune cells, inflammation, and autoimmune diseases, new technologies are required to improve our knowledge on these processes.

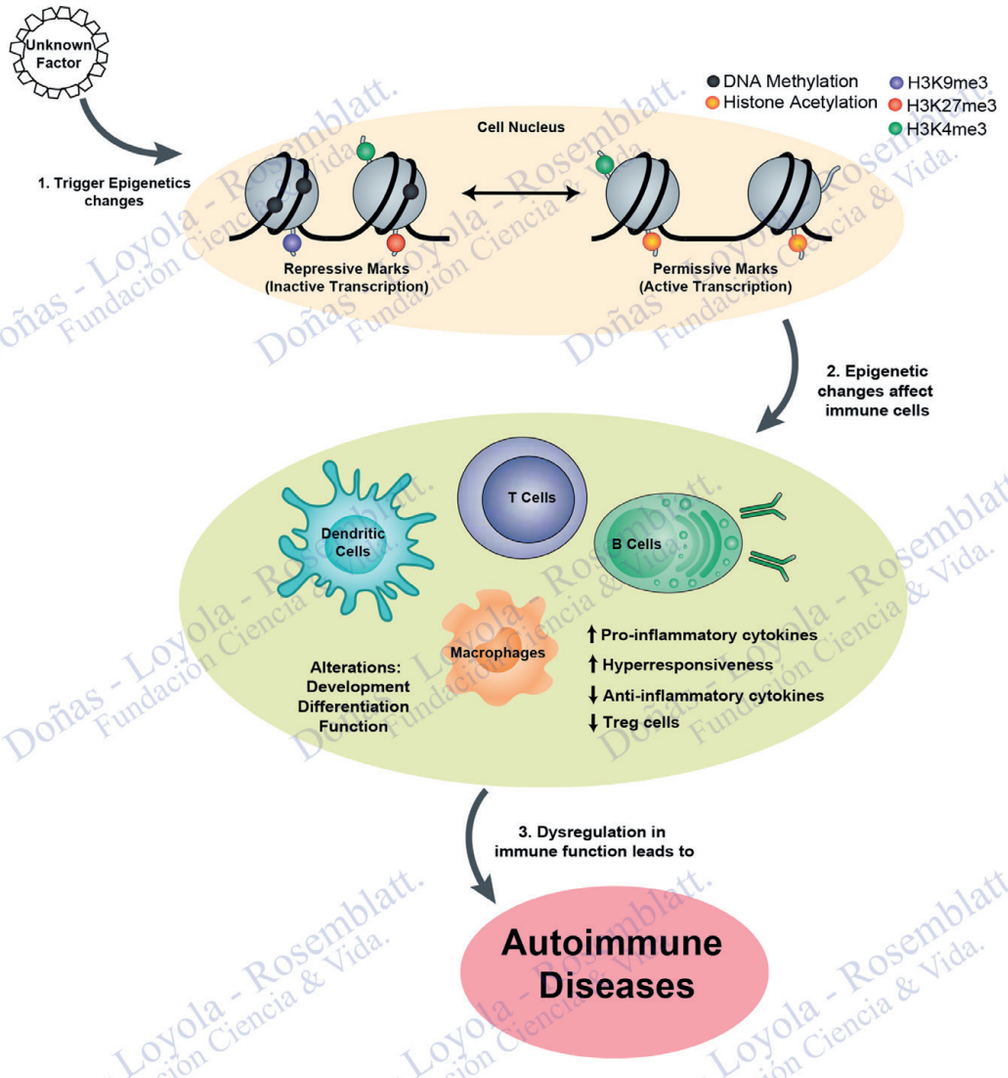

Figure 4.
Epigenetics influences on the development of autoimmune diseases. Epigenetic changes on the promoter of several genes are triggered by yet unknown factors, inducing transcriptional activation or repression. These changes bring up alterations in development, differentiation, and effector function of immune cells. All these changes result in aberrant immune responses, including increased production of proinflammatory cells and cytokines or the reduction of anti-inflammatory cells and cytokines that lead to increased inflammation and autoimmune diseases.

Acknowledgements

Financed by Programa de Apoyo a Centros con Financiamiento Basal AFB 170004, Fundación Ciencia para la Vida and Fondecyt 1160480.

Glossary

AID	activation-induced cytidine deaminase
APC	antigen-presenting cells
ATF	activating transcription factor
BET	bromodomain and extra-terminal motif proteins
Bcl6	B-cell lymphoma 6 protein
Blimp1	B lymphocyte-induced maturation protein-1
cDC	conventional DCs
CDP	common dendritic cell progenitors
CIA	collagen-induced-arthritis

CNS	conserved non-coding sequences
Cxcl12	C-X-C motif chemokine 12
C/EBP	CCAAT enhancer-binding protein
DCs	dendritic cells
DNTMs	DNA methyltransferases
DSS	dextran sulfate sodium
EAE	experimental autoimmune encephalomyelitis
Ezh2	enhancer of zeste homolog 2
Foxp3	forkhead box P3
GATA3	GATA-binding protein 3
Gzmb	granzyme B
H2BK12ac	acetylation of lysine 12 on histone H2B
H3ac	H3 acetylated
H3K4me3	trimethylation of lysine 4 on histone H3
H3K9ac	acetylation of lysine 9 on histone H3
H3K9me3	trimethylation of lysine 9 on histone H3
H3K14ac	acetylation of lysine 14 on histone H3
H3K27me3	trimethylation of lysine 27 on histone H3
H3K36me3	trimethylation of lysine 36 on histone H3
H4ac	H4 acetylated
H4K8ac	acetylation of lysine 18 on histone H4
H4K16ac	acetylation of lysine 16 on histone H4
H4R3	arginine 3 of histone H4
HAT	histone acetyltransferases
HDAC	histone deacetylases
HSCs	hematopoietic stem cells
IBD	inflammatory bowel diseases
Ifgnr	interferon receptor
IRF	interferon regulatory factor
iTreg	inducible Treg cells
JmjC	Jumonji C
KAT	lysine acetyltransferases
KDM	histone lysine demethylase
KLF10	Krüppel-like factor 10
KMT	lysine methyltransferases
MBP	myelin basic protein
MBPs	methyl-CpG-binding proteins
MBT	*Mycobacterium tuberculosis*
MPP	multipotent progenitors
MS	multiple sclerosis
Pax5	paired box gene 5
PC	plasma cells
PCAF	p300/CREB-binding protein-associated factor
pDC	plasmacytoid DCs
PHD	plant homeodomain
PRTM	protein arginine methyltransferase
RA	rheumatoid arthritis
RAG	recombination-activating gene
RASFs	RA synovial fibroblasts
RNAPII	RNA polymerase II
Rorγt	RAR-related orphan receptor gamma t
Runx1	runt-related transcription factor 1
Runx3	runt-related transcription factor 3

SAM	S-adenosylmethionine
SCFAs	short-chain fatty acids
SIRT	sirtuin
SLE	systemic lupus erythematosus
SPA	sodium phenylacetate
Sox	Sry-related HMG box
Tbet	T-box transcription factor
TCF7	transcription factor tau 7
TET	ten-eleven translocation
TGF-β	transforming growth factor beta
Th	T helper
ThPOK	Th-inducing POZ-Kruppel factor
TNBS	2,4-trinitrobenzene sulfonic acid
TSA	trichostatin A
TSDR	Treg cell-specific demethylated region
Treg	regulatory T cell
tTreg	thymic development

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