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Review

Epigenetic dynamics in immunity and autoimmunity☆

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ABSTRACT

A tightly synchronized and spatial-temporal interaction among regulatory proteins within genomic DNA and chromatin is essential for cellular commitment and differentiation. During development and activation of the immune system, a complex regulatory network that involves induction of lineage instructive transcription factors, installation or removal of histone modifications and changes in DNA methylation patterns locally orchestrate the three-dimensional chromatin structure and determine immune cell fate and immune responses. In autoimmune diseases, disease associated epigenetic marks and dynamic changes control the dysregulated immune system, thus determining the disease development and clinical phenotype. In this review, we introduce the dynamic epigenetic regulation of DNA and histones, summarize the epigenetic regulatory mechanisms in the development and differentiation of some important immune cell subsets and provide new insights for the pathogenesis of autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis and Type 1 diabetes.

This article is part of a Directed Issue entitled: Epigenetics dynamics in development and disease.

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Abbreviations: DNMT, DNA methyltransferase; TET, ten-eleven translocation; AID/AICDA, activation-induced cytidine deaminase; APOBEC, Apolipoprotein B mRNA editing enzyme; BER, base excision repair; MBD4, methyl-CpG binding domain protein 4; HATs, histone acetyltransferases; HDAC, histone deacetylase; HMT, histone methyltransferase; 5mC, 5-methylcytosine; 5hmC, 5-hydroxymethylcytosine; GC, germinal center; DC, dendritic cell; SHM, somatic hypermutation; CSR, class switch recombination; Blimp-1, B lymphocyte-induced maturation protein-1; Treg, regulatory T; NFAT, nuclear factor of activated T-cells; TSDR, Treg-specific demethylated region; PDCD1, programmed cell death 1; Prf1, Perforin; Gzmb, Granzyme B; CTL, cytotoxic T cell; EBF1, early B cell factor1; Pax5, Paired box protein; TSA, Trichostatin A; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MS, multiple sclerosis; T1D, type 1 diabetes mellitus; ERK, extracellular regulated protein kinases; PBMC, peripheral blood mononuclear cell; PAD2, peptidylarginine deiminase 2; IGFBP-1, insulin-like growth factor-binding protein 1; LPS, lipopolysaccharide.

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1. Introduction

Epigenetics refers to chromatin modifications that regulates gene expression without alternating the DNA sequence (Bird, 2007; Wilson, 2008). Two major mechanisms of epigenetic control have been identified that include histone modification and DNA methylation, and both respond to developmental and environmental triggers. Chromatin modification can regulate genomic imprinting, X-chromosome inactivation, heterochromatin formation, transcriptional regulation, and DNA damage repair (Bird, 2002; Goll and Bestor, 2005; Jaenisch and Bird, 2003). Epigenetics can influence numerous biological processes such as cell development and differentiation and therefore play important roles during physiological and pathological conditions.

The immune system is an important barrier for defense against foreign antigens. The development and differentiation of immune cells, as well as innate and adaptive responses, are precisely regulated and is attributed in part by dynamic epigenetic modifications (Allan and Nutt, 2014; Alvarez-Errico et al., 2014; Ansel et al., 2003; Kioussis and Georgopoulos, 2007; Russ et al., 2014; Su and Tarakhovsky, 2005; Won et al., 2014). Here we present a comprehensive review of the epigenetic dynamics related to these processes as well as the role of epigenetics in the pathogenesis of autoimmune diseases.

1.1. DNA methylation/demethylation

DNA methylation occurs on the 5′ carbon position of the pyrimidine ring of the cytosine residues. It is a repressive regulator of genome accessibility to transcriptional factors and RNA polymerases (Wolffe and Matzke, 1999). In mammalian DNA, most CpG dinucleotides are methylated whereas the non-methylated CpGs are often clustered within CpG islands typically located within the promoter region or 5'-end of genes (Bird, 2002; Strichman-Almashanu et al., 2002). Highly methylated areas of the mammalian genome are less transcriptionally active, leading to gene silencing. DNA methyltransferase 1 (DNMT1), together with a methylated cytosine on either strand, is responsible for remethylation of hemimethylated CpGs during cell division and thereby maintains DNA methylation patterns; DNMT3a and DNMT3b produce de novo methylation and result in new methylation patterns during early development (Rountree et al., 2001).

DNA demethylation includes passive and active DNA demethylation (Bhutani et al., 2011). Correlation between active DNA demethylation and ten-eleven translocation (TET) methylcytosine dioxygenases, AID/APOBEC enzymes, BER glycosylases have been reported (Bhutani et al., 2011; Guo et al., 2011). For example, rapid DNA demethylation is caused by the oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and is dependent on regulation by the TET family proteins including TET1, TET2 and TET3 also known as DNA hydroxymethylases (Booth et al., 2012; Tahiliani et al., 2009). Methyl-CpG binding proteins (MBD) serve as essential enzymes for DNA demethylation independent of DNA replication and have potential roles in transcript splicing and chromatin compaction (Young et al., 2005). MBD4 is a DNA glycosylase that works on hemi-methylated CpGs and demethylation occurs through the replacement of 5-methylcytosine with unmethylated cytosine (Zhu, 2009). Rapid and active mechanisms of DNA demethylation have been implicated in cell division (Mayer et al., 2000; Oswald et al., 2000; Paroush et al., 1990; Zhang et al., 2007). Passive demethylation is mostly due to absent or defective DNMTs, which are involved in embryonic development. In such instances, mammals can delete genomic methylation patterns in primordial germ cells (Ohno et al., 2013) or during cellular reprogramming (Guo et al., 2014). In addition, dynamic DNA methylation landscapes within a single cell cycle showed that passive DNA demethylation is induced by cellular replication (Brown et al., 2007).

1.2. Histone modifications

The nucleosome is a repeating subunit that consists of 146 base pairs of chromatin in a double helix wrapped around a protein core composed of histone octamers H2A, H2B, H3 and H4. Accumulating evidence strongly suggests that each histone subtype can be modified by several posttranslational modifications such as acetylation, methylation, ubiquitination, phosphorylation, sumoylation, citrullination, ADP ribosylation and proline isomerization. Among these processes, acetylation and methylation are the most extensively studied and therefore deserve detailed discussion.

1.3. Acetylation/deacetylation

Histone acetylation and deacetylation are of great importance in gene regulation (Berger, 2002). Acetylation relates to transcriptional activity through the loosening of the chromatin structure that prevents chromatin from folding into 30-nm fibers (Shogren-Knaak et al., 2006). Generally, highly acetylated regions are associated with euchromatin and leads to active transcription through increasing chromatin accessibility. Deacetylation, in contrast, contributes to gene silencing by tightening the chromatin structure, which is associated with heterochromatin. Two enzyme families induce these two opposite modifications, namely histone acetyltransferases (HATs) and histone deacetylases (HDACs) respectively. HATs, including p300, CBP and PCAF, acetylate conserved lysine amino acids on histone proteins by transferring an acetyl group from acetyl CoA to form ε-N-acetyllysine. Histone deacetylases (HDACs) are a class of enzymes that remove acetyl groups from a ε-N-acetyl lysine amino acid on a histone, permitting the histones to wrap the DNA more tightly.

1.4. Methylation/demethylation

Histone methylation refers to the addition of methyl groups to lysine residues or arginine residues in the histone tails (Clarke, 1993). Histone methylation, perhaps more than any other chromatin modification, is a major contributor of epigenetic modification and regulates fundamental processes such as gene transcription and DNA repair (Bannister and Kouzarides, 2005). Histone methylation play a critical role in gene expression, genomic stability, stem cell maturation, cell lineage development, genetic imprinting, DNA methylation, and cell mitosis (Cheung et al., 2000; Fischle et al., 2003; Iizuka and Smith, 2003; Kouzarides, 2002). Unlike acetylation, the effects of histone methylation on gene regulation depend on the position of residues modified or the number of methyl groups present (Chen and Li, 2010; Scharf and Imhof, 2011), and thereby, gene transcription may be either activated or suppressed. For instance, methylation of lysine 4 in H3 (H3K4) is related to transcription activation, whereas H3K9 and

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