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Regulation of chromatin remodeling through RNA polymerase II stalling in the immune system

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ABSTRACT

RNA polymerase II (Pol II) binds to promoter-proximal regions of inducible target genes that are controlled and not transcribed by several negative elongation factors, which is known as Pol II stalling. The occurrence of stalling is due to particular modification signatures and structural conformations of chromatin that affect Pol II elongation. The existence and physiological importance of Pol II stalling implies that there is a dynamic balance in chromatin regulation prior to endogenous or exogenous stimulation. In this review, we discuss the effects of ATP-dependent chromatin remodeling complexes and histone modification via transcriptional machinery Pol II C-terminal domain phosphorylated at serine 5 (S5P RNAPII) initiation and S2P RNAPII elongation on the expression or silence of specific genes after the production of activated or differentiated signals or cytokines. The response occurs immediately during immune cell development and function, and it also includes the generation of immunological memories. This summary suggests that the host immune response genes involve a novel mechanism of selectively regulatory chromatin remodeling, a fundamental and crucial aspect of epigenetic regulation.

1. Introduction

Chromatin exists in various states that play a critical role in physiological and pathological processes, regardless of structure and modification. Chromatin is temporally and spatially dynamic, primarily consisting of DNA, protein and RNA (Wang, 2006). There are 147 base pairs in the nucleosome, a fundamental element of chromatin, which is made up of the core histones, H2A, H2B, H3 and H4, and linker histones, H1, in eukaryotic cells (Richmond, 1999; Bednar et al., 2017). Since information-carrying DNA is organized and condensed in the nucleosome and further compressed into chromatin, the selective expression or silencing of a gene is dominated and controlled by regulation of the chromatin dynamic balance in response to various stimuli.

In recent years, studies focusing on DNA methylation, histone modifications, and noncoding RNAs (Morandini et al., 2016) have demonstrated a critical role of epigenetic regulation in response to both internal and external environmental triggers. Chromatin remodeling, which is mediated through histone modifications and nucleosomal repositioning, determines the gene transcription, cellular fate and developmental processes of an organism (Mostoslavsky et al., 2003). The ability of chromatin to undergo spatiotemporal reprogramming and remodeling leads to the expression of immune response genes. Healthy immune systems ensure that an organism has a normal life and help defend against illnesses and tumors. To target specific antigen signals, the immune response significantly utilizes chromatin remodeling and rapidly initiates selective expression of stalled genes, similar to antibodies and cytokines (Patel et al., 2011).

Recently, genome-wide analysis demonstrated that approximately 30% of genes are controlled by high-concentrations of RNA polymerase II (Pol II) binding to their promoter-proximal regions (Liu and Tao, 2013a; Jiang et al., 2013a). Activation and elongation of these target genes could be prevented through recruitment of several negative elongation factor (NELF) complexes and 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) sensitivity-inducing factor (DSIF), some

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general transcription factors (GTFs) and RNA polymerase II CTD kinase P-TEFb, which collectively block or release Pol II from transcriptional start sites (TSS) (Giraud et al., 2012; Wada et al., 2000). This phenomenon, called RNA polymerase II stalling, is not uncommon. This stalling is caused by the ATP-dependent chromatin remodeling complexes and histones acetylation and transcription factors (Kusch et al., 2014), which make the paused genes transition to activated genes. However, the detailed mechanisms for the release of Pol II from genes are not well known (Toth et al., 2012). The stalling of Pol II often occurs because specific gene responses lead to a dynamic balance state in response to rapid inducers.

A wide variety of infections and cancers can be eliminated and controlled by a healthy host immune response (Nicholson, 2016). In respond to internal stimuli or/and environmental threats, altered chromatin structure after changing modifications and nucleosome density, followed by activated or silenced immunity-associated genes due to immune cell activation, differentiation and immunological memory (Smale and Fisher, 2002). A growing body of knowledge indicates that ATP-dependent chromatin remodeling complexes, such as SWI/SNF, exert a significant influence on human immunodeficiency virus type 1 (HIV-1) (Pisetsky, 2017), autoimmune reactivity (Doe et al., 2014) and hypersensitivity (Sanz et al., 2012). In addition, histone modification via transcription regulatory machinery, such as histone deacetylases (HDACs) and cyclin dependent kinases (CDKs), plays a significant role in immunological disorders and tumor immunology. Therefore, chromatin profiling represents an important and novel approach to study regulatory networks of immune and tumor progression, which depend on inducible immune target genes through Pol II stalling (Winter et al., 2015). Furthermore, the release of Pol II at a tumor suppressor genes locus with H3K9me3 and H3K27me3 causes genetic silencing that is beneficial for breast cancer patients (Tao et al., 2011). In this review, we will discuss histone modifications and chromatin remodeling-dependent regulation of Pol II stalling to control gene elongation properly during the inflammatory response, T cell and B cell activation, differentiation and memory. This can provide information on the interplay between chromatin alteration and paused RNA polymerase II, which elicits changes in immunity to control disease and tumor development.

Chromatin remodeling involves dynamic changes of chromatin architecture and nucleosome remodeling, thereby controlling gene activation and expression (Batugedara et al., 2017), individual physiology and disease. The state of various response genes changed (Davari et al., 2017) transiently and returned (Moores et al., 2017) to normal quickly during immune cell activation and division. Changes to chromatin are mediated through histone modifications by specific enzymes: histone acetyltransferases (HATs) kinases (Singh et al., 2013), protein kinase C (Darieva et al., 2015), and by ATP-dependent chromatin remodeling complexes ATPases, such as SWI/SNF, Mi-2/NuRD, that govern chromatin remodeling in immune cells (Bonnay et al., 2014). Remodeling complexes bind to and reposition nucleosomes, disrupting histone-DNA interactions, and use adenosine triphosphate (ATP) hydrolysis to supply energy and subsequently expose DNA to Pol II and related coactivators (Kadoch and Copeland, 2016). Remodeling of euchromatin could make inducible genes more accessible to transcriptional regulators such as transcription factors, coactivators and basal transcription machinery, including RNA polymerase II, therefore permitting elongation. Conversely, several poised genes could be inhibited by chromatin remodeling complexes, which pack DNA into the nucleosomes to form heterochromatin (Lim et al., 2010).

Prior to Natural Killer (NK) cell activation, a series of poised genes, including *PI3KCA*, *NFATC1* and *TNFSF9*, modified synergistically by both H3K4me3 and H3K27me3 at their promoters, were sensitive to stimulation, as detected using a Chromatin Immunoprecipitation-Sequencing (ChIP-seq) assay (Li et al., 2017a). BRG1 chromatin remodeling of SWI/SNF complexes promotes B cell activation as characterized by inducible gene expression, resulting in accelerated cell proliferation and improved immune efficacy (Holley et al., 2014). Altering chromatin dynamics is a potential mechanism of inducing target gene expression in immune cell activation.

Antigen presentation to specific T cell receptors (TCR) facilitates clonal proliferation of activated native T cells. In the context of T cell activation, rapid histone H3 antibodies have access to epitopes in the decondensed chromatin (Bingham et al., 2015). T cells gain effector functions during the decondensation of nuclear material(chromatin) and the production of macromolecules(RNA) through the SWI/SNF-like Brahma associated factor (BAF) complex in response to Interleukin-2 (*IL-2*). When chromatin is decompacted, *Signal Transducer and Activator of Transcription 5* (*STAT5*) accesses the promoters of target genes required for T cell proliferation; however, no global changes in histone modification occur (Lee et al., 2015a). Under Th1 and Th17 conditions, primary T helper (Th) cell activation opens the *tumor necrosis factor* (*TNF*) transcription start site, enabling transcription factor access (Shebzukhov et al., 2014). Furthermore, activated immune cells constitutively activate many signaling-dependent genes (e.g., cytokines and inflammatory factors) by promoting H3K27ac, repressing H3K27me3, and being involved with their relative transcription factors (TFs) (*NF-κB, Ap-1, IRFs*, and *STATs*) (Winter and Amit, 2014).

Immune cells derived from myeloid and lymphoid progenitor cells express specific genes determined by chromatin remodeling during various stages of cellular differentiation (Redecke et al., 2013). The autorenewal and differentiation of HSC (hematopoietic stem cells) is accompanied by activation of specific genes and the suppressive expression of differentiation factors while preparing the cell to be poised for activation. Surprisingly, after deletion of SNF2-like ATPase chromodomain helicase DNA-bingding protein 4(CHD4/Mi-2β), HSCs readily differentiate into erythroid cells, but not myeloid or lymphoid lineages, due to increased expression of erythroid-specific genes relative to myeloid-specific genes. This indicates that Mi-2β is required for normal HSC differentiation (Yoshida et al., 2008). It is known that naive T cells can differentiate into Th1, Th2, and Th17 cells by controlling the expression of such cytokines as IFN-γ, IL-4, and IL-17 through higher-order chromatin remodeling. Overexpression of SWI3-related gene*(SRG3/BAF155)* in the SWI/SNF complexes, which produces inflammatory cytokines in dendritic cells (DCs) and macrophages, allowing cells to upregulate the differentiation of CD4 + T cells into Th1/Th17 cells and mediating downregulation of Th2 cell division (Lee et al., 2015b). Lipopolysaccharide (LPS) induction of the pro-myeloid cell line HL-60 causes differentiation into monocytes, improves accessibility to the pro-inflammatory cytokine Interleukin (IL)-6 proximal promoter region and enhances its expression (Poplutz et al., 2014). Immune cell activation and differentiation leads to changes in chromatin dynamics due to alterations in histones and remodeling of chromatin complexes.

2. Regulation of inflammatory gene expression by RNA elongation

Inflammation is the first response triggered by infection with viruses, bacteria, or damage to cells. The inflammatory factors may act as mediators between environmental and genetic determinants and may be expressed at specific times and locations via higher-order chromatin regulation. Once the harmful stimulus breaks several surface barriers, inflammation is initiated through cytokines (IL-4, IL-5, and IL-13) and inflammatory factors, such as IFN-γ, IL-4, and IL-17, which are released by infected Th1, Th2, and Th17 cells. Many studies have found that inflammatory cytokines contribute to both medically healthy and unhealthy individuals (Xu et al., 2017; Felger and Lotrich, 2013; Akimzhanov et al., 2007).

In this section, we briefly discuss signal-induced immunity-related genes reactions of Drosophila melanogaster and mammalian cells. Transcription factors of the NF-κB family actively participated in the innate signaling pathways. Less than 50 base pairs transcribed by pol II regulate the balance; expression of the inflammatory gene halts near

the promoter as it is surrounded by two stalling regulators, the 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) sensitivity-inducing factor (DSIF) and negative elongation factor (NELF) (Qiu and Gilmour, 2017; Sebald et al., 2012; Adelman and Lis, 2012). Recruiting Pol II is a key step in determining gene transcription, in addition to the corresponding transcription factors that are involved. Transcriptional initiation is continuously induced by multiple P-TEFbs that are recruited by bromodomain-containing protein BRD4. Transcriptional elongation also depends on the activity of the positive transcription elongation factor P-TEFb. When the complex binds to the transcriptional factors, BRD4 phosphorylates NELF, DSIF, and the Pol II C-terminal domain (CTD) (Patel et al., 2013; Missra and Gilmour, 2010). Several general transcription factors such as *TFIID* and *TFIIB* are necessary for the elongation (Vosnakis et al., 2017). Subsequently, the paused RNA cannot be impeded, and the signal to elongate is given.

BRD4 is a histone acetyltransferase (HAT) that acetylates histone H3 Lys122(H3K122), modulating nucleosomal occupancy and causing chromatin to decompact with a relative increase in transcription. Overexpression of BRD4 indicates that it successfully acetylates H3K4, H3K9, H3K18 and H3K27 and acetylates H4 at K5, K8, K12 and K16 (Devaiah et al., 2016; Hu et al., 2014). For example, after LPS-induced inflammation, macrophages undergo extensive transcriptional changes due to chromatin remodeling (especially acetylation of histone 3, H3Ac) and Pol II phosphorylation at serine 5 (S5P RNAPII) for transcription initiation in the early immune response. Subsequently, the active state shifts toward more Ser-2 phosphorylation during transcription elongation (Davari et al., 2017). These actions jointly determine transcriptional elongation of the inducible gene stalled by Pol II, such as tumor necrosis factor (TNF), and inflammatory mediators such as proinflammatory cytokines and chemokines (Qiao et al., 2013). Similarly, in the macrophage early immune response, LPS-induced responses cause *tumor necrosis factor* (*TNFα*) promoter regions to be poised due to trimethylation of H3K27me3 and to have an open chromatin state when immune cells have H3K4me3 signatures (Bekkering et al., 2016; Iglesias et al., 2012). BRD4 plays a critical role in acetylation of nucleosomal histones via HAT activity and changing chromatin structure and further regulation of transcription via phosphorylation of the Pol II CTD, resulting in the control of inducible inflammatory gene expression. Though there has been extensive research concerning joint regulation of NELF, DSIF, P-TEFb (Fujita et al., 2009) and BRD4 in RNA elongation, the concrete mechanisms of BRD4 recruitment to TSS and initiation of P-TEFb combination have yet to be described. Furthermore, the molecular mechanisms that regulate BRD4 HAT activity and elongation initiation need to be further investigated (Li et al., 2017b).

Although their regulation is complicated, the promoter regions of inflammatory genes and Pol II are always paused by negative elongation factors. Only when the inflammatory responses are initiated are the genes transitioned from stalling of Pol II to elongation.

3. RNA transcription-dependent control of inducible genes in lymphocyte

When the adaptive immune response is triggered by an invading stimulus, in order to differentiate into different cell types, several lymphocytes take measures that induce gene expression by making chromatin accessible (Almuzzaini et al., 2015). Upon activation, B cells secrete specific antibodies, while T lymphocytes differentiate into T helper cells, CD4 + T cells, cytotoxic T cells, or CD8 + T cells (Schirrmacher et al., 1998; Rothe et al., 2017; Mirlekar et al., 2017)

Histone modification, a prominent aspect of an epigenetic mechanism regulating the expression of paused genes, primarily includes acetylation and methylation generated through acetyltransferases and methyltransferases (Chen et al., 2016). Genome-wide studies indicate that inducible genes have high levels of histone3 acetylation (H3K9ac and H3K27ac) and histone4 hyperacetylation at the promoter sites, which may have higher amounts of expression than their counterpart genes in T cells and macrophages. Most histone methylation represses gene expression, but H3K4me3 activates gene expression (Balakrishnan and Milavetz, 2007; Geng et al., 2016). Additionally, the levels of Pol II and the involved transcription factors are low prior to stimulation. For example, we have found that interleukin-10 (*IL-10*) is produced by B cells with active histone modification and Pol II recruitment in a T helper (Th) 2 cytokine dominant environment. Conversely, a reduction of activating histone marks and a corresponding increase of methylation of H3K9me3 and H3K27me3 suppresses the expression of immune genes, such as *Bcl6* and *TNF-α*, via recruitment of Polycomb-repressive complex (PRC) 1 and 2 (Li et al., 2016; Chauhan et al., 2015; Roy and Roeder, 2014; Abou El Hassan et al., 2015). Demethylation of H3K27me3 by demethylases Jmjd3 and Utx is equally important for inducing gene expression in immune cells. Futhermore, with certain stimuli, under the control of chromatin remodeling and Pol II, inducible cytokine gene expression is not only necessary for immune cell differentiation but required for their function. To give a crucial example, interleukin-4 produced by Th2 cells is necessary for their differentiation (Bosselut, 2016; Hwang et al., 2017).

Other than histone modification, regulation of poised immune gene expression is also mediated through ATP-dependent chromatin remodeling complexes (Stockdale et al., 2006). Initially, SWI/SNF-like chromatin-remodeling complexes restructure the nucleosome and reprogram DNA promoter regions where Pol II, transcription factors and coactivators bind. Then, they initiate gene transcription of Th1 cells. Furthermore, SWI/SNF-like BRG1 or BRM encode specific ATPase involved in signaling pathways, such as NF-κB, and recruit CDK9 (PTEF-b subunit). To generate immune responses to interleukin-4 quickly, STAT6-bound receptor gene transcription is facilitated through (Brahma-related gene-1)BRG1 binds to promoter region. During B cell activation, BRG1 regulates the expression of larger quantities of genes than naïve B cells so that they can proliferate rapidly (Bossen et al., 2015; Wu, 2012; Kraus et al., 2010). Furthermore, when Pol II stalling causes a transition to transcriptional elongation on activation induced deaminase(AID) target genes by pol II, diverse antibodies generated by B lymphocytes mount an immune response quickly (Sun et al., 2013).

In addition, the chromatin remodeling Mi2/nucleosome, remodeling deacetylase (Mi-2/NuRD) and the ISWI ATPase components of the SNF2H chromatin remodeling enzyme play a role in gene expression in T and B cells (Precht et al., 2010). Lymphoid-specific helicase (LSH), a crucial epigenetic regulatory factor belonging to the SNF2 family, maintains genome stability and plays a part in the progression of several cancers (He et al., 2016; Xiao et al., 2017; Jia et al., 2017; Jiang et al., 2017; Mao et al., 2018). It has been demonstrated that LSH-mediated modifications enhance nucleosomal occupancy associated with Pol II stalling around the TSS (Tao et al., 2010). This silences some tumor suppressor genes and may involve increased H3K4me3 and reduced H3K27me3 in the development of several tumors (Tao et al., 2011; Liu and Tao, 2013b; Jiang et al., 2015). Additionally, in the absence of LSH, the repressive function of HoxB4 that influences functions of T cells and B cells is lost (Xi et al., 2007; Ruedl et al., 2008).

After deletion of SWI/SNF, nucleosomes could not move, reposition and bind to DNA tightly, which brought about decreased gene silencing in T and B cells. In general, SWI/SNF may have a action that favors activation of H3K4me3 in promoter regions (Nadal-Ribelles et al., 2015). These data imply that remodeling complexes and histone modification may coregulate inducible gene expression. Several transcription factors and environmental factors are also necessary for this process. This finding indicates that T and B cells conduct on genetic reprogramming and expression of cytokines and antibodies through the release of Pol II.

4. Dynamic changes of chromatin in immunological memory

Recent studies have shown that memory T cells can be divided into

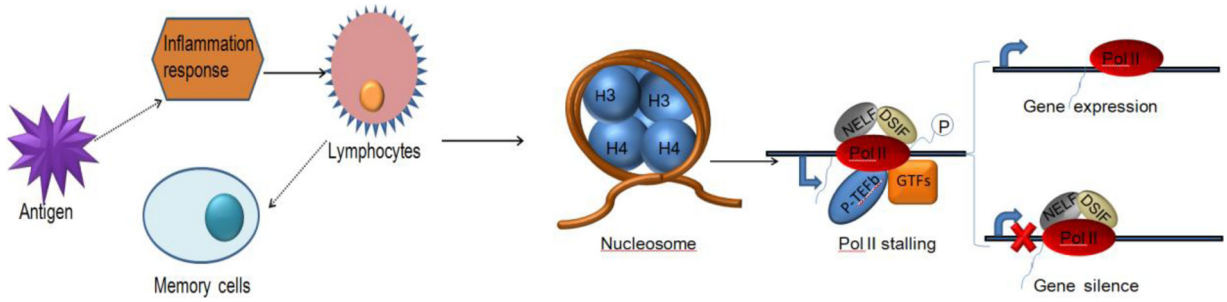

Fig. 1. Histone modification and nucleosome repositioning make RNA polymerase II stall as it is surrounded by two stalling regulators, transcription negative elongation factor (NELF) complexes and 5,6-dichloro-1-β-d-ribofuranosylbenzimidazole (DRB) sensitivity-inducing factor (DSIF). In the abundance of general transcription factors (GTFs) and Pol II CTD kinase P-TEFb, promoter-proximal Pol II was widely halted in quiescent immune cells. Once antigen is present, the immune target genes are activated by RNA polymerase II C-terminal domain phosphorylated at serine 5 (S5P RNAPII) after the enrichment of general transcription factors (GTFs) coactivators. Subsequently, the active state shifts toward more Ser-2 phosphorylation during transcription elongation. Therefore, the inflammatory response will be activated, and prompt lymphocyte and memory cell responses will occur via the stalled gene expression or silencing.

two subsets, central memory (TCM) and effector memory (TEM) T cells, which are prepared to regulate gene expression whenever cells re-encounter the same antigen. Immune cell memory is also an indispensable process of the immune system throughout the whole life of an animal. Formation of immunological memory depends on the development of memory precursor cells into terminally differentiated effector cells which maintain a primed state and develop plasticity and long-term immunity. After the naïve B cells and T cells respond to environmental stimuli, the cells undergo activation and differentiation. For active chromatin maintained by primed DNase I-hypersensitive sites(DHSs), the memory cells can repeat past transcriptional activities and respond more quickly to the same assaulting signal in the future (Bevington et al., 2017, 2016). Chromatin regulation provides immune memory and determines cell function and identity.

Genome-wide analysis of histone H3 lysine residue methylation has indicated a loss of H3K27me3 and gain of H3K4me3 deposited primarily at promoters and enhancers. Such characteristic genes are potentially pro-memory genes in terminally differentiated effector cells and could enhance the function of memory cells, especially memory CD8 + T cells (Gray et al., 2017). Without altering levels of transcription, the islands of chromatin prime nearby enhancers and accelerate the expression of stalled genes rather than activating transcription directly. Similarly, three poised effector genes, *Ifng*, *Gzmb*, and *Prf1*, are mainly characterized by nucleosome occupancy and H3K27 methylation near TSS, which influence memory CD8 + T cell function and memory in spite of deficient Pol II recruitment (Zediak et al., 2011). Above all, it is clear that high levels of H3K4me3, H3K27ac and H3K9ac chromatin modifications are active, and modification of H3K27me3 and H3K9me3 results in the suppression of gene expression in naïve cells and memory CD8 + T cells (Araki et al., 2009). Some of these modifications are associated with a ready-to-respond chromatin state and solely or jointly regulate Pol II poised gene transcription during the secondary immune response. Furthermore, hyperacetylation has been found in many actively expressed genes of memory CD8 + T cells (Northrop et al., 2008).

Due to high levels of acetylation and methylation, memory T cells can express paused target genes rapidly rather than directly regulating activity through the initiation of transcription. Additionally, once antigens are present, immunological memory persists throughout the whole life of the host.

5. Conclusion

To summarize, upon invasion with internal and external immune, various signaling pathways, such as *NF-kB*, are activated quickly (Sanacora et al., 2014). Subsequently, stalled pro-inflammatory factors and cytokine release are controlled by negative elongation factor (NELF) complex and DRB sensitivity-inducing factor (DSIF), with Pol II stimulating an innate immune response (Chen and Ivashkiv, 2010) along with an abundance of general transcription factors and coactivators (Kolev et al., 2017). If the stimuli have not been resolved, encountering released cytokines, T and B cells may rapidly induce and elongate gene transcription synergistically regulated by histone modifications and ATP-dependent chromatin remodeling complexes during the adaptive immune response (Moreira and Holmberg, 1998). No matter which immune response participates, there is a common mechanism for inducible target gene expression, such as proliferation and differentiation of cytokines. Once antigen is present, Pol II-stalling genes necessary for chromatin remodeling modifications and promoter binding of RNA polymerase II C-terminal domain phosphorylated at serine 5 (S5P RNAPII) are activated after the enrichment of GTFs and Pol II CTD kinase P-TEFb. Subsequently, the active state shifts toward more Ser-2 phosphorylation during transcription elongation. Moreover, the immune resolution may involve such transcription factors as the STAT family, coactivators and elongation factors (Lubbert, 2005). Contributing to altered chromatin structure were histone acetylation/deacetylation enzymes and inhibitors that provide hypersensitive sites in the regulatory region. In addition to immune cell activation and differentiation, immune memory plays an equally important role in response to immune stimuli. Transient and rapid expression of stalled immune genes in immune cells is critical so that they can mount a defense against harmful pathogens and prevent tumorigenesis. In addition, to avoid unnecessary inflammation and autoimmune responses, these target genes should be repressed rapidly (Poke et al., 2012) (Fig. 1). However, the concrete mechanisms of how and why chromatin remodeling modulators can be recruited at the proper moment and location remain unclear. We propose that the associated remodeling complexes are recruited when the immune cells received active or repressive signals. The ATP-dependent remodeling complexes utilize hydrolysis-produced ATP to make condensed sites accessible. Simultaneously, the histone modifiers cause activation or silencing of histones. Then, corresponding transcription factors and coactivators bind to a specific locus, which is ready to elongate (Fong et al., 2017; Jiang et al., 2013b).

Based on the data, there seems to be a close interaction between the novel field of chromatin remodeling and the activity of the immune system. Chromatin dynamics can reveal the developmental past, current active mechanisms, and potential responses to an antigenic challenge in a given immune cell. However, the chromatin landscape of all immune cells has not been completely investigated to date, and we can see that chromatin dynamic changes are important for inducible gene expression/silencing at the different immune stages. Furthermore, many immune responses involve the complex and dynamic regulation of DNA methylation and transcription-related factors (Basu et al., 2017). Future research could discover effective and safe inhibitors to target chromatin remodeling pathways. Histone modifying enzymes

(DesJarlais and Tummino, 2016), specific signaling pathways and associated transcription factors may be a good therapeutic choice to treat several diseases and cancers.

Conflict of interest

The authors declare no conflict of interest. This manuscript has been read and approved by all authors and is not submitted or under consideration for publication elsewhere.

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