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One genome, many cell states: epigenetic control of innate immunity

Isabella Fraschilla[1,2,3], **Hajera Amatullah**[1,2], **Kate L. Jeffrey**[1,2,3,4,*]

[1]Division of Gastroenterology and Center for the Study of Inflammatory Bowel Disease, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts 02114, USA

[2]Harvard Medical School, Boston, Massachusetts 02115, USA

[3]Program in Immunology, Harvard Medical School, Boston, Massachusetts 02115, USA

[4]Center for Microbiome Informatics and Therapeutics, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.

Abstract

A hallmark of the innate immune system is its ability to rapidly initiate short-lived or sustained transcriptional programs in a cell- and pathogen-specific manner that is dependent on dynamic chromatin states. Much of the epigenetic landscape is set during cellular differentiation; however, pathogens and other environmental cues also induce changes in chromatin that can either promote tolerance or 'train' innate immune cells for amplified secondary responses. We review chromatin processes that enable innate immune cell differentiation and functional transcriptional responses in naive or experienced cells, in concert with signal transduction and cellular metabolic shifts. We discuss how immune chromatin mechanisms are maladapted in disease and novel therapeutic approaches for cellular reprogramming.

Keywords

innate immunity; epigenetics; chromatin; macrophages; inflammation; metabolism; transcription; histone modifications

Introduction

In addition to adapting to tissue-specific cues, innate immune cells are uniquely programmed to appropriately respond to a diverse array of stimuli that range from pathogen infections to non-threatening microbial ligands and metabolites. Certainly, a key tenet of a successful first line immune defense to pathogens is the induction of a signal-specific, cell lineage-specific, and kinetically precise gene expression program. The products of such synchronized gene expression programs occur following pattern recognition receptor (PRR)

*Correspondence to: KJeffrey@mgh.harvard.edu.

recognition of conserved features of microorganisms that are absent in the host (pathogen-associated molecular patterns or PAMPs) and host-derived molecules only exposed under conditions of excessive cell death and tissue damage (damage-associated molecular patterns or DAMPs). Subsequent signal transduction and cellular metabolic shifts in neutrophils, monocytes, macrophages, natural killer cells, basophils, dendritic cells or epithelial cells leads to the activation of transcription factors that bind to inducible genes -- cytokines, transcription factors, effector proteins, and metabolic regulators - that enable pathogen clearance, aid adaptive immunity, clear cellular debris, and restore damaged tissues. The different PRRs, signaling pathways, and transcription factors involved in cell differentiation and the transmission of information from the cell surface to the nucleus during an innate immune response continue to be explored. How chromatin mechanisms dictate context-appropriate transcription of precise genes from the larger chromatin landscape is an active area of investigation. These mechanisms are not only central to rapid initial responses to first exposure of a pathogen, but chromatin-associated factors also prime innate immune cells for subsequent re-infections and may be disrupted for anti-inflammatory therapies. Moreover, the contribution of tonic or homeostatic PRR signaling in either priming or repressing chromatin remains poorly understood.

In this review, we discuss the epigenetic regulators that instruct innate immune cell state and functional responses to environmental cues, highlighting overlap between these steps of cellular regulation. We describe the differential chromatin regulation of poised LPS primary response genes versus delayed secondary response genes and the signaling cascades that initiate chromatin changes to enable pro-inflammatory gene transcription. Furthermore, recent work has uncovered how pathogen recognition can stably alter chromatin for tolerized or primed responses to subsequent exposures. Finally, we discuss mutations in human epigenetic factors that lead to inflammatory diseases and the advancement of therapeutic strategies that target epigenetic factors. The advent of new chromatin technologies requiring fewer cells, or single cells, will enable further growth of this field within immunology.

Core components of epigenetic regulation

Gene expression requires the binding of transcription factors to promoters and enhancers, resulting in the recruitment of the transcription apparatus that includes RNA polymerase II (RNA Pol II) and permits transcription initiation, elongation, and termination. However, transcriptional machinery first needs access to genes as DNA is condensed into chromatin and epigenetic mechanisms must permit accessibility of underlying DNA. Broadly, the term epigenetics describes the regulatory mechanisms “outside of or above” the cell’s preconceived DNA code that regulate transcription. Four major mechanisms are considered to be involved in the epigenetic regulation of gene expression patterns: covalent modification of DNA; covalent modification of core histones or histone variants; non-protein-coding RNAs (microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) excellently reviewed here [1,2]; and chromatin remodeling machinery.

Modifications of histones

In eukaryotic cells, 2 meters of DNA is tightly packaged in the nucleus. Specifically, 147bp of nucleotides wrap around an octamer of histones (2 copies each of histone H2A, H2B, H3, and H4) to form a nucleosome, and these nucleosomal units repeat throughout the genome and form increasingly higher-order structures that form chromosomes. Importantly, histone tails have an unstructured N-terminus that protrude from the nucleosomes and are subject to covalent modifications. Epigenetic 'writers' catalyze post-translational modifications (e.g. histone methyltransferases, histone acetyltransferases (HATs), kinases), while 'erasers' remove these dynamic modifications (e.g. demethylases, histone deacetylases (HDACs)). Regulatory information stored in modified histones is functionally translated by 'readers', that dock to defined modified histones via distinct protein domains (e.g. bromodomain, PHD, YEATS). Readers recruit other epigenetic or transcriptional machinery to specific loci thereby serving as the chromatin's adaptor molecules. These chromatin readers may have similar structural features to adaptor molecules that transduce PRR signaling upstream of transcription [3]. Overall, the combinatorial 'histone code', first posited more than twenty years ago [4], is a central orchestrator of gene expression in innate immune cells. For example, myeloid cell identity depends on a combination of histone modifications that result in lineage-inappropriate gene silencing and a separate combination that poises chromatin at inflammatory genes for rapid and robust induction in response to microbial recognition.

DNA and RNA methylation

Methylation of the 5′-carbon of the pyrimidine ring at cytosine nucleotides (5-mC), the most widely studied type of DNA methylation, is catalyzed and maintained by the DNA methyltransferase (DNMT) family members. Ten-eleven translocation (TET) cytosine dioxygenase family members mediate oxidation of 5mC into 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), which are critical for active DNA demethylation. In general terms, CpG DNA methylation (DNAme) at promoters inhibits binding of so-called methyl-sensitive transcription factors and recruits repressive DNAme readers (e.g., MeCP2, SETDB1), thus restricting transcription. In contrast, processive oxidation products of DNAme are generally associated with active chromatin and result in loss of DNAme, either passively, through cell division, or actively, via base excision repair. Modifications of RNA have also been shown to regulate gene expression. N6-methyladenosine modification (m6A) on eukaryotic RNA is a common modification which regulates RNA transcript splicing, processing, translation, and decay. In regards to innate immunity, genetic deficiency in METLL3, the methyltransferase catalyzing m6A modification, is associated with reduced NF-κB activity [5] and increased IFN production and viral clearance [6,7].

Chromatin remodeling

Chromatin packaging and topology are important determinants of gene expression. Chromatin undergoes active reorganization of its architecture to permit access of cis-regulatory elements to transcriptional regulators. This is performed by chromatin remodelers, which are ATP dependent translocases that participate in nucleosome sliding, conformational change of the nucleosome, or histone variant exchange. Mammalian

chromatin remodelers fall into four families: SWI/SNF (switch/sucrose non-fermenting, ISWI (imitation switch), IN080 (inositol requiring 80), and CHD (chromodomain helicase domain containing). They associate with large protein complexes and have been shown to both promote or prevent transcription. As discussed later, these proteins have an important role in innate immunity by regulating secondary response genes in macrophages following bacterial and viral challenges.

Epigenomic techniques for immunologists

The advent of high-throughput sequencing technologies and novel biochemical methods that survey genomic regulatory regions, chromatin occupancy, and accessibility has significantly advanced our understanding of chromatin biology in cell development and function (Table 1). Many early techniques, such as chromatin immunoprecipitation (ChIP) and DNase I hypersensitivity assays, to assess chromatin occupancy and accessibility required large amounts of material, had poor signal-to-noise ratios and hence often prohibited use by immunologists examining relatively rare but pure primary immune cells. Recently there has been an influx of technologically improved assays (Table 1), including CUT&Run [8], CUT&Tag [9], ATAC-seq [10] and single cell versions of these, that has enabled many immunologists to embrace epigenetic analyses on limited cells. Moreover, protocols such as MINT-ChIP [11] and MulTI-Tag [12] have enabled multiplexing targets in the same cells. Also, epigenome profiling can now be integrated with bulk- and single cell-transcriptomic data using 10x Genomics Single Cell Multiome, simultaneous high-throughput ATAC and RNA expression with sequencing (SHARE-seq) [13,14], or Paired-seq [15]. In addition, chromatin accessibility or RNA measurements coupled with Cytometry by time of flight (CyTOF) as well as spatial genomic and epigenomic techniques will transform our understanding of chromatin regulation in immune cells.

Regulation of macrophage identity and plasticity by chromatin mechanisms

Diversity and plasticity are fundamental properties of macrophages, and most work examining epigenetic mechanisms in innate immunity have focused on this cell type. To some extent, the properties of macrophages are imprinted through ontogenetic origin (during embryogenesis from yolk-sac progenitor cells vs. hematopoiesis) but are also heavily dependent on chromatin mechanisms that respond to external or tissue-specific environmental cues. Transcriptomic and epigenetic landscapes of human microglia exposed to an *in vitro* culture environment signficantly downregulated microglia-specific genes compared to *ex vivo* microglia, highlighting environment-dependent programming of these macrophages [16]. Similarly, engrafting peritoneal mouse macrophages into the alveolar cavity led to the downregulation of peritoneal-specific gene programs and upregulation of lung macrophage-specific genes [17]. This tissue-specific macrophage identity was shown to be strongly regulated by enhancers [17] and chromatin remodelers, such as BAF/PBAF, to facilitate or prevent transcription factor binding [18,19].

Regulation of silenced facultative heterochromatin, marked by H3K27me3, is also a major orchestrator of macrophage development, polarization, and function. The histone demethylases JMJD3 and UTX specifically facilitate di- and trimethyl H3K27

demethylation and regulate transcription of developmental transcription factors, such as HOX genes [20], and cell fate and patterning proteins, such as Wnt proteins and TGF-β family members [21,22]. JMJD3 is also necessary for expression of IRF4 and the control of macrophage polarization that is required for anti-helminth responses [23]. Similarly, Enhancer of zeste homolog 2 (EZH2), a H3K27 methyltransferase, is required for macrophage cell identity as it mediates Toll-like receptor (TLR)-induced proinflammatory gene expression by directly repressing suppressor of cytokine signaling 3 (SOCS3) expression [24].

Furthermore, work from our group demonstrated a profound role for chromatin reader SP140, associated with inflammatory disease (Table 2), that predominantly occupies heterochromatin marked by H3K27me3 to repress chromatin accessibility and inhibit transcription of lineage-inappropriate genes, including late HOX genes (HOXA7 and HOXA9) [25]. SP140 loss results in severely compromised lineage-defining and microbe-inducible innate transcriptional programs and defective bacterial killing [26]. In addition to histone methylation, histone acetyltransferases and deacetylases serve a role in polarizing macrophages to a pro-inflammatory or alternatively activated state. For example, macrophages that lack HDAC3 become anti-inflammatory [27,28] and polarize towards IL-4 hyperresponsive cells [29]. Inhibition of HDAC3 via butyrate treatment or direct chemical inhibitor alters macrophage metabolism [30], prevents inflammatory responses [31], and enhances anti-microbial responses [30].

Kinetics of Macrophage Transcriptional Programs

Much of what we know about chromatin dynamics that regulate transcription after microbial sensing derives from numerous studies on the effect of LPS or Lipid A stimulation and signaling that stems from TLR4 activation. Response to LPS involves the upregulation of genes that are rapidly induced and others whose transcription is delayed [32]. Following LPS stimulation, primary response genes (PRGs) are rapidly induced in the absence of new protein synthesis whereas secondary response genes (SRGs) require new protein synthesis for activation. The promoters of PRGs, such as *Tnf*, *Fos* and *Nfkbia*, are richer in CpG islands and have higher levels of poised RNA Pol II, H3K4me3, H4ac in naive cells compared to SRG promoters [32–37]. These features are characteristic of actively transcribed genes and are associated with higher levels of H3K9/K14 acetylation and H3K4me3 [32,34]. Thus, naive macrophages have poised chromatin landscapes that enable expression of a defined set of PRGs within minutes of cell activation [34,38]. Transcription of these genes do not require chromatin remodeling complexes, such as the SWI/SNF family, or de novo protein synthesis, as their chromatin state is immediately permissive to transcription factor binding and RNA Pol II elongation [32]. SRGs on the other hand, whose transcription peaks around 4 hours post TLR4 stimulation, display low H3K4me3, H4Ac, and no RNA Pol II occupancy in naive macrophages. SRGs, such as *Il12b*, depend on SWI/SNF remodeling complexes to increase DNA accessibility and transcription [34,38,39]. In addition, PRGs but not SRGs are negatively regulated at baseline by the transcriptional corepressors NCoR/HDAC3 and coREST/HDAC1 to perhaps limit transcription at these poised sites [32].

Signaling to Chromatin: Histone Phosphorylation

Accumulating evidence demonstrates that signal transduction cascades downstream of PRR activation directly regulate histone or DNA modifications or chromatin-interacting proteins [40] (Figure 1). H3S10ph, H3.3S28ph, and H3.3S31ph are examples of histone residue-specific phosphorylation events that occur downstream of TLR4 activation [41]. After LPS stimulation, MSK1 and MSK2 rapidly phosphorylate H3S28 at promoters and enhancers [41]. In addition, H3S10 located at inducible gene promoters is phosphorylated after NFκB activation, although it is not clear which kinases are responsible for this post-translational event [42–45]. IKKα is recruited to inflammatory genes after NFκB activation [45,46] where it mediates phosphorylation of H3.3S31 within LPS induced gene bodies, such as Tnf, Cxcl2, and Il1a [47]. H3.3S31ph correlates with H3K36me3 density, which is exclusively deposited by the histone methyltransferase SETD2 [47]. The SETD2 catalytic domain binds to H3.3S31ph thereby promoting K36 engagement in the active site [47]. Thus, H3.3S31ph augments SETD2 methyltransferase activity. Other epigenetic enzymes that interact with H3.3S31ph include the H3K27me3 demethylase JMJD3 [48,49] while the PHF1 Polycomb group protein family member (H3K27me3 methyltransferase complex) is ejected by H3.3S31ph [50,51]. How these other enzymes orchestrate gene expression after stimulation in regard to H3.3S31ph modification will need further study. However, Armache *et al*. reveal that the K36me3 reader and transcriptional corepressor ZMYND11 is already present at a subset of LPS induced genes at baseline and is ejected by dually modified H3.3S31ph/H3.3K36me3 as – providing a mechanism whereby ZMYND11 ejection allows rapid transcription to occur [47]. Thus, many stimulation-induced genes share distinguishing chromatin features: (1) active chromatin states and pre-existing H3.3K36me3, (2) pre-bound ZMYND11 corepressor, (3) stimulation induced H3.3S31ph, and (4) ejection of ZMYND11. Beyond TLR4 stimulation, histone phosphorylation likely features as a transcriptional inducement mechanism downstream of diverse receptors and in different cell types, including adaptive immune cells [40].

Innate Immune Training and Tolerance

Accumulating evidence demonstrates that innate immune cells have adaptive-like features, such as tolerance and training, that depend on alterations to chromatin state. During innate immune training, epigenetic changes or “scaring” persist even after the cell returns to homeostasis following stimulation [52]. This pattern of exposed enhancers and promoters of host-defense genes results in enhanced transcription in response to homologous or heterologous rechallenge. The opposite of trained immunity, “tolerized” innate immune cells are unable to activate gene transcription following restimulation [53,54]. Both innate immune adaptations are rooted in epigenetic reprogramming.

Tolerized genes include pro-inflammatory genes, such as *Il6* and *Il1b*, whereas non-tolerized genes encode antimicrobial effectors, such as *Cnlp* and *Lcn2* [53]. After stimulation, H4Ac, H3K4me3, and Brg1 associated with promoters of LPS inducible genes then dissociate during resolution [33,53,55]. However, upon secondary exposure to LPS, the promoters of tolerized genes do not exhibit a second increase in H4Ac and Brg1 whereas non-tolerized gene promoters display greater and faster H4Ac accumulation than the initial

response and maintained H3K4me3 deposition [53]. Inhibition of histone deacetylases or H3K4 demethylases rescues transcription at tolerized genes [53] suggesting that epigenetic enzymes negatively regulate transcription of pro-inflammatory genes and limit pathology associated with inflammation while allowing for pathogen defense. While both tolerized and non-tolerized gene transcription is induced by the same upstream PRR signal transduction, the differential epigenome at these distinct gene sets enables selective and fine-tuned transcription for appropriate immune responses. Thus, this level of epigenetic regulation may be leveraged for selective therapies in the clinic that target inflammation versus antimicrobial responses.

Innate immune training has mostly been observed in monocytes exposed to the fungus *C. albicans* or its cell wall component β-glucan for a training period, then allowed to return to steady state, and rechallenged (5,7). *C. albicans*- and β-glucan-induced innate immune training results in a stable increase in H3K4me3 at gene promoters in monocytes and peritoneal macrophages that promotes training [56]. This H3K4me3 deposition is facilitated by lncRNAs [57]. In addition to inflammatory genes, many of the genes with altered promoter H3K4me3 were involved in glycolysis [58] suggesting a metabolic switch accompanies epigenetic reprogramming in innate immune training.

In experimental animal models, the memory of exposure surpasses that of the typical lifespan of innate immune cells. Recent studies have now demonstrated that immune training occurs within the hematopoietic stem cell compartment in bone marrow [59]. Evidence for transmission of trained immunity was also recently demonstrated across generations to murine progeny that survived a sublethal systemic infection with *C. albicans* [60].

Although innate immune training can enhance pathogen responses, maladaptive innate immune training has been proposed to promote chronic immune disease [52]. Furthermore, in addition to peripheral memory, exposure to western diet, exercise, chronic stress, and sleep fragmentation directly alter the chromatin accessibility of the bone marrow progenitor epigenome. Some of these chromatin changes are maintained over time and importantly impact progenitor proliferation, lineage commitment, and functional response to secondary recall challenges [61–63].

Cross-regulation of metabolic and epigenetic pathways in macrophages

As has been thoroughly reviewed previously [64], metabolic and epigenetic pathways are tightly linked (Figure 2). Chromatin regulating proteins rely on available metabolites for their catalytic activity. Thus, when metabolic switches occur following PRR activation or when metabolite availability is altered by the presence of microorganisms, macrophage transcriptional programs adapt or maladapt via epigenetic regulation. For instance, histone acetyltransferases require acetyl coenzyme (acetyl-CoA) for activity, fumarate inhibits the KDM5 family of histone demethylases, and α-ketoglutarate (α-KG) is as cofactor for histone demethylases [65,66]. The tight coupling between metabolism and epigenetic regulation of transcription is also exemplified by recent discoveries of novel epigenetic marks, including histone succinylation [67,68], crotonylation [69], and lactylation [70] that rely on the substrates succinyl-coA, crotonyl-coA and lactate levels, respectively.

The activity of the tricarboxylic acid (TCA) cycle from which these metabolites are produced is thus a major regulator of chromatin state. Accumulated citrate in LPS activated macrophages is used for production of the potent anti-inflammatory metabolite, itaconate, via the LPS and IFN-inducible enzyme immune-responsive gene 1 protein (IRG1) [71]. Itaconate exerts its anti-inflammatory functions through the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2), although how it regulates chromatin modifying enzymes remains to be established.

Succinate acts as a proinflammatory metabolite that directly inhibits histone lysine demethylases (KDM2–7) and the ten-eleven translocation hydroxylases (TET1–3) involved in DNA demethylation. Certainly, in macrophages, an important functional role has been attributed to the αKG/succinate ratio regulating anti-inflammatory versus pro-inflammatory macrophage state. Macrophages polarized with IL4 have increased acetyl-CoA and an increased α-KG:succinate ratio for epigenetic reprogramming via HATS and JMJD3, respectively [72,73]. Conversely, a low α-KG:succinate ratio strengthens the proinflammatory phenotype in LPS activated macrophages. In addition, αKG contributes to endotoxin tolerance after LPS activation [73]. TET2, an LPS inducible DNA demethylase and a target of α-KG was shown to be essential for inflammation resolution [74], and TET2 may be involved in the mechanism by which α-KG promotes LPS tolerance. Thus, pathways involved in α-KG production may be attractive therapeutic targets to reset the epigenome in diseases associated with macrophage malfunction.

Fumarate also has a proinflammatory role in controlling chromatin modifications. Specifically, the accumulation of fumarate in response to pro-inflammatory insults has been shown to be necessary for trained immunity and inflammation by inhibiting KDM5 histone demethylase activity [75]. The inhibition of KDM5 increases the levels of H3K4me3, a marker of active gene transcription at the promoters of *Tnf* and *Il6* cytokines. Notably, fumarate derivatives like dimethyl fumarate (DMF) are currently being used in the clinic to treat autoimmune conditions, including multiple sclerosis (MS) and psoriasis.

In addition to host metabolic pathways, the microbiome serves as the other major source of metabolites in mammals and is emerging as a major influence on host cell epigenetic enzyme activity [76]. Microbiota exclusively metabolize complex carbohydrates derived from dietary fibers in the colonic lumen via fermentative reactions to produce small organic acids, the bulk of which are short chain fatty acids (SCFAs) acetate, propionate, and butyrate – all of which are HDAC inhibitors. Notably, supplementation of SCFAs in germfree mice recapitulated global chromatin states and gene expression patterns observed with complete gut colonization [77]. Other commensal bacteria-derived metabolites, such as inositol-1,4,5-trisphosphate ($InsP_3$), have been shown to stimulate HDAC3 activity in the gut [78]. Recently, butyrate was shown to have a profound impact on macrophage function by promoting antimicrobial transcriptional programs via HDAC3 inhibition [30], but the ability of other microbiota-derived metabolites to dictate innate immune transcription via the epigenome is a fertile area of investigation.

Disease Relevance and Therapeutic Opportunities

The rapid rise in the prevalence of chronic immune diseases that cannot be explained by genetics alone lend support to the critical role of environmental factors and epigenetics in these diseases. Analysis of longitudinal twin cohort studies reveal that by the age of 65, 70% of variance in chromatin modifications can be largely attributed to environmental influences [79]. Genome-wide association studies have identified mutations within genetic loci for chromatin readers, writers, and erasers that are significantly associated with inflammatory disease susceptibility (Table 2). However, in addition to mutations that directly affect expression or function of epigenetic enzymes in immune disease, mutations can lie in non-coding epigenetic regulatory regions, such as enhancers. In fact, 60% of autoimmune disease variants map to active immune cell enhancers, but it is unknown how causal variants affect gene transcription as most mutations do not lie in known transcription factor binding motifs [80]. There is also a gap in knowledge in which epigenetic regulators integrate changes from environmental cues and whether genetic variants in these epigenetic regulators are sufficient for disease pathogenesis or require environmental perturbations as a “second hit”. Furthermore, heterogeneity in clinical phenotypes (penetrance and disease expressivity) commonly observed in different patients with the same mutation could be due to contributions from different environmental cues occurring at critical windows of development.

Epigenetic Therapeutics in Inflammatory Disease

Due to the role of chromatin modifying enzymes in dictating precise gene transcription programs in homeostasis and inflammation, targeting this class of proteins raises the possibility to regulate and reduce the magnitude of entire gene expression programs instead of targeting individual inflammatory mediators. Moreover, many epigenetic modulating drugs have current FDA approval for cancer and can potentially be repurposed to treat epigenetic disruptions in the context of autoimmunity or inflammation.

As outlined in the above sections, H3K27me3 prevents promoter accessibility and suppresses the expression of proinflammatory gene programs in macrophages. GSK-J4, an α-ketoglutarate mimic, binds to the catalytic pocket of the H3K27 demethylases JMJD3 and UTX [48]. Thus, GSK-J4 prevents the demethylation of the repressive H3K27me3 and inhibits LPS-induced inflammation [48]. Recently, GSK-J4 prevented abdominal aortic aneurysms and aortic inflammation in mice that stemmed from monocytes and macrophages [81]. Similarly, pharmacological inhibition of EZH2 specifically resolved H3K27me3 at bivalent gene promoters and attenuated cardiac dysfunction in a mouse model of myocardial infarction [82], ameliorated DSS-induced colitis [83], and alleviated lung injury and fibrosis in the LPS-induced acute respiratory distress syndrome model [84].

Class I and Class II pan HDAC inhibitors have exhibited anti-inflammatory effects *in vitro* and *in vivo* [31,85–87]. Specific HDAC1 or HDAC3 inhibitors also prevent inflammation in animal models of inflammatory diseases and in peripheral blood mononuclear cells (PBMC) from rheumatoid arthritis patients [85,88]. Despite the reasonable success of HDAC inhibitors as anti-inflammatory agents, the details of how such epigenetic alteration prevents inflammation is unclear. Histone acetylation is exclusively “read” by bromodomains, which

have defined lysine acetylation affinities and recruit distinct proteins, such as transcriptional elongation machinery, to the chromatin [32,89,90]. Rather than drugging the enzymes that "write" and "erase" the epigenome, targeting the "readers" of histone modifications may inhibit the function of specific epigenetic modifications without altering the cell's overall epigenetic landscape determined by "writers" and "erasers." By designing small molecules that act as histone mimics and bind to reader domains, such as a bromodomain, this class of therapeutics can disrupt histone binding activity. Most work thus far has focused on targeting the bromodomain and extra-terminal (BET) subfamily. I-BET762 (also known as GSK525762A) specifically interacts with BRD2, 3, and 4 and competitively interacts with the acetylated lysine binding pocket of BET bromodomains, acting as a histone mimic [33]. Inhibition of BET proteins prevents the assembly of chromatin activating and transcription elongation complexes at a subset of LPS-inducible promoters [33]. Importantly, I-BET prevented LPS-induced endotoxic shock and bacteria-induced sepsis in mice [33]. Beyond BET family members, other classes of bromodomains are also predicted to have good druggability [91].

Additional chromatin factors such as topoisomerases (TOP) were recently reported to play key roles in infection-induced gene transcription and leveraged for therapeutic benefit. Certainly, TOP inhibition at low and clinically tolerized doses specifically modulated bacteria and virus-inducible inflammatory gene expression programs and demonstrated pre-clinical efficacy in sepsis and COVID-19 [92,93]. Similarly, TOP inhibition can be utilized to repress aberrant gene expression programs upregulated in immune diseases driven by epigenetic reader SP140 loss-of-function [26]. In addition to TOP inhibitors, inhibitors to the positive transcription elongation factor b (P-TEFb) subunit cyclin-dependent kinase 9 (CDK9), also prevent transcription and are being developed as a new line of therapeutics to alleviate inflammation and autoimmunity [94].

Concluding remarks.

Effective innate immunity depends on the fidelity of immune cell differentiation and rapid adaptability of mature cells to the tissue milieu and other environmental factors, such as pathogen invasion. In these contexts, epigenetic mechanisms allow cells to dynamically initiate or terminate transcriptional programs to appropriately respond to changes in the tissue microenvironment, microbial threats, or the resolution of infection. Failure to fine-tune transcriptional programs to prevent exaggerated responses will cause hyper-inflammatory and autoimmune disorders (Figure 3). As our understanding of innate immune 'training' and innate immune metabolism grows, it is appealing to speculate that epigenetic mechanisms that integrate these signals may contribute to the persistence of disease-associated phenotypes, even in the absence of the initial trigger. Moreover, there are emerging examples of genetic mutations within chromatin modifying enzymes or chromatin regulatory regions that directly contribute to human immune disorders. Thus, resetting metabolic states to alter epigenetic enzyme function or directly epigenetic enzymes may allow resetting of the disease 'epigenetic scar' and restoration of normal transcriptional programs.

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• of special interest

•• of outstanding interest

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Highlights

- Chromatin dynamics regulate pattern, timing and magnitude of gene expression
- Signal transduction downstream of TLR4 regulate histones for inducible gene transcription
- Metabolic shifts and epigenetics of innate immune cells are intimately linked
- Chromatin dynamics enable memory of microbial exposure for tolerance or trained immunity
- Epigenetic therapies demonstrate promise for inflammatory disease

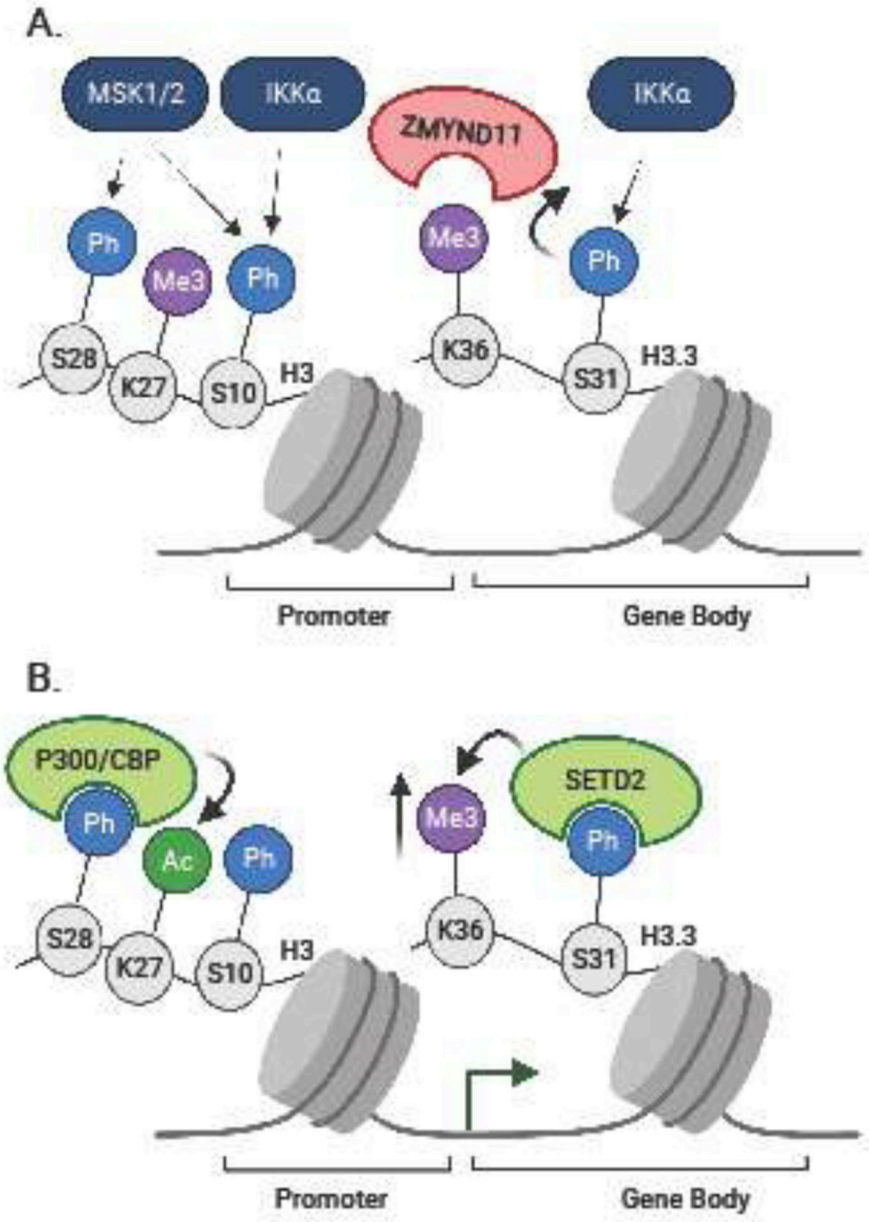

Figure 1. Signaling to chromatin mediates inflammatory responses.

(A) First, kinases, such as MSK1, MSK2, and IKKα, phosphorylate histone modifications, such as H3S28, H3S10, and H3.3S31. Specifically, H3.3S31ph promotes the ejection of ZMYND11 from H3.3K36me3. (B) ZMYND11 ejection allows for increased H3.3K36me3 whereas H3S28ph promotes P300/CBP-mediated acetylation of H3K27 – events that enhance transcription.

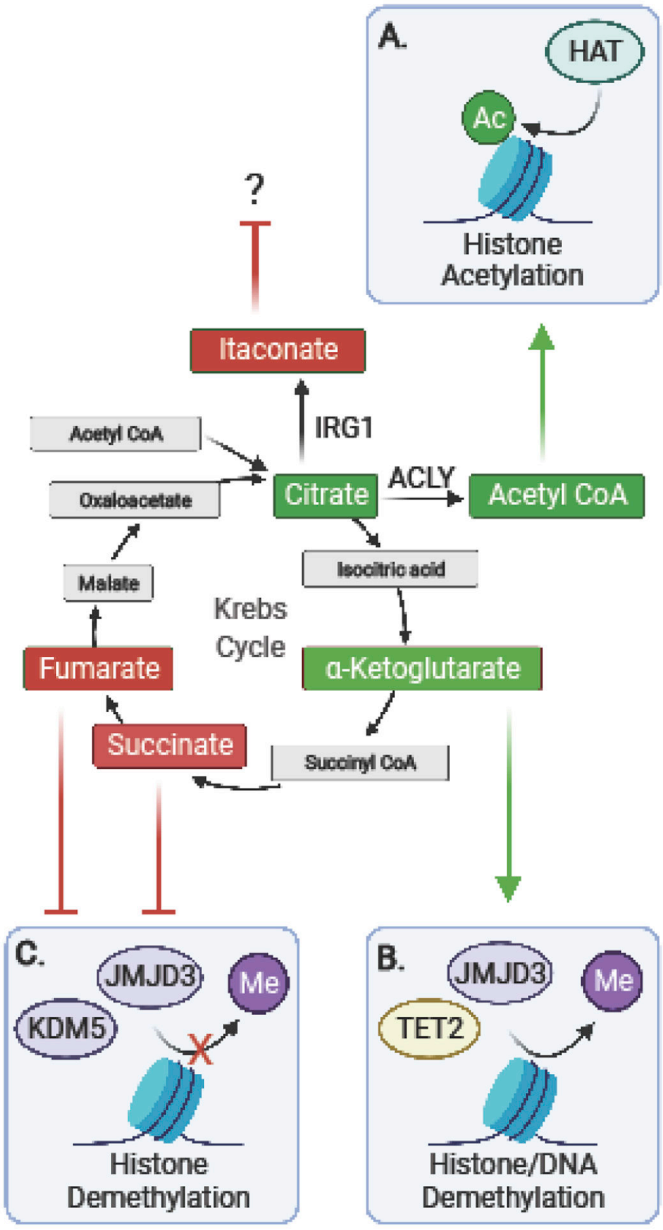

Figure 2. Crosstalk between metabolism and innate immune chromatin architecture.

(A) ATP-citrate lyase (ACLY) synthesizes acetyl coenzyme (acetyl-CoA), a coenzyme for histone acetyltransferases (HATs). However, citrate can also be a source for itaconate, an anti-inflammatory metabolite. (B) α -ketoglutarate (α-KG) promotes the function of histone demethylases, such as JMJD3, and DNA demethylases, such as TET2. (C) Fumarate and succinate inhibit histone demethylases, such as JMJD3 and KDM5.

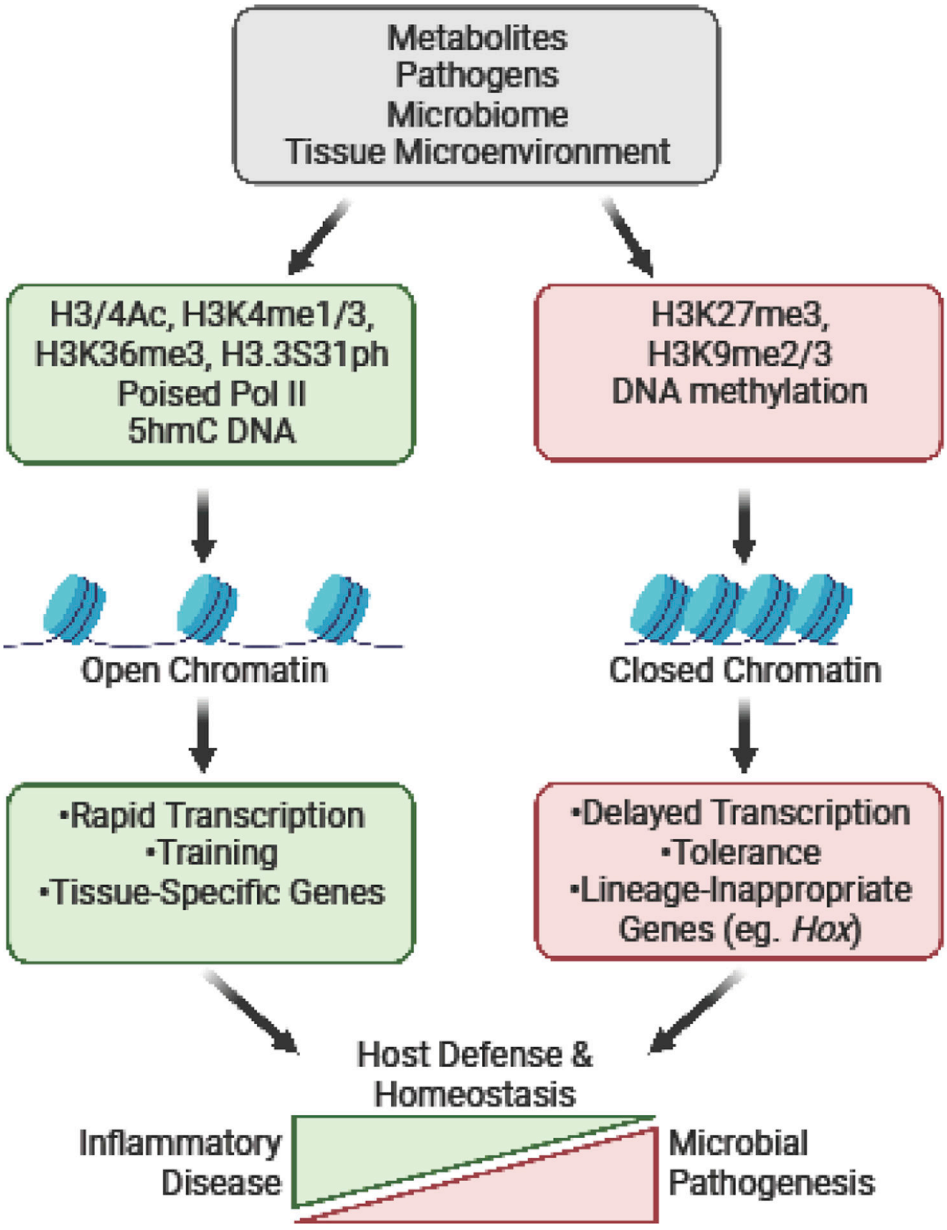

Figure 3.

Environmental factors dictate chromatin modifications and accessibility to determine innate immune cell state and function.

Table 1.

Emerging technologies for immunologists studying chromatin dynamics.

Technique	Information	Cell Numbers	Reference
Bisulfite-seq	DNA methylation	100,000 – 500,000 and single cell	[95,96]
5(h)mC-seq	DNA methylation at 5-methylcytosine	100 – 100,000	[97]
m6A RNA-seq	mRNA methylation	10 million	[98,99]
FAIRE-seq	Chromatin accessibility	10 million	[100]
DNase-seq	Chromatin accessibility	1 – 10 million	[101]
ATAC-seq	Chromatin accessibility	500 – 50,000 and single cell	[10,102]
CUTAC	Chromatin accessibility with the addition of RNA Pol II occupancy	500 – 50,000	[103]
MNase-seq	Chromatin inaccessibility	10,000 – 100,000	[104]
GET-seq	Chromatin accessibility and inaccessibility	5,000 – 20,000 and single cell	[105]
SHARE-seq	Chromatin accessibility in concert with RNA transcript levels	single cell	[13,14]
ChIP-seq	Chromatin occupancy of specific proteins	2 – 10 million	[106]
CUT&Run	Chromatin occupancy of specific proteins, with reduced background	500 – 50,000	[8]
CUT&Tag	Chromatin occupancy of specific proteins, with reduced background	50 – 50,000 and single cell	[9]
Spatial-CUT&Tag	Spatial localization of histone modifications *in situ*	N/A	[107]
MINT ChIP	Chromatin occupancy of up to four histone modifications, multiplexed in the same cell population	50,000 – 100,000	[11]
MulTI-Tag	Chromatin occupancy of multiple histone modifications, multiplexed in the same cell	500 – 50,000	[12]
Hi-C	Three-dimensional chromatin interactions	2 – 5 million and single cell	[108,109]
ChIA-PET	Three-dimensional chromatin interactions bound by a specific protein	100 million	[110]
IGS	Spatial localization of chromatin	100	[111]
CyTOF	Protein abundance	300	[112]

Table 2:

Variants of Epigenetic Regulators that associate with susceptibility of Immune Disease.

Gene	Epigenetic Subclass	Functional Domains	Disease Association
SP100	Reader	SAND, PHD, Bromodomain	Chronic Obstructive Pulmonary Disease [106]
SP110	Reader	SAND, PHD, Bromodomain	Chronic Lymphocytic Leukemia [107]
SP140	Reader	SAND, PHD, Bromodomain	Crohn's Disease [108,109], Multiple Sclerosis [110], Chronic Lymphocytic Leukemia [107]
BRD1	Reader	Bromodo main	Rheumatoid Arthritis [111]
BRD2	Readei	Bromodomain	Crohn's Disease [112], Rheumatoid Arthritis [113]
BRWD2/PHIP	Reader	Bromodomain	Sjögren's Syndrome [114]
BRWD3	Reader	Bromodomain	Pneumonia and COVID19 [115]
UHRF1	Reader	PHD, Tudor, SRA	Type II Diabetes Mellitus [116,117]
UHRF2	Reader	PHD, Tudor, SRA	Asthma [118], Periodontitis [119], Allergy [120], Chronic Sinus Infection [121]
CHD1	Reader	Chromodomain	Type II Diabetes Mellitus [117]
CHD4	Reader	PHD, Chromodomain	Type II Diabetes Mellitus [117]
TRIM66	Reader	PHD, Bromodomain	Type II Diabetes Mellitus [122]
L3MBTL3	Reader	MBT domair	Asthma [123], Multiple Sclerosis [124]
DNMT3A	Writer	DNA methyltransferase	Crohn's Disease [109]
DNMT3B	Writer	DNA methyltransferase	Inflammatory Bowel Disease [108,125,126]
EHMT2/G9a	Writer	Histone methyltransferase	Type II Diabetes Mellitus [127], Chronic Obstructive Pulmonary Disease [128], Asthma [129], Takayasu Arteritis [130]
DOT1L	Writer	Histone methyltransferase	Osteoarthritis [131], Systemic Lupus Erythematosus [132]
SUPT3H	Writer	Histone acetyltransferase	Osteoarthritis [128,133]
KAT2A	Writer	Histone acetyltransferase	Coronary Artery Disease [134,135], Inflammatory Bowel Disease [136]
HDAC4	Eraser	Histone deacetylase	Chronic Obstructive Pulmonary Disease [128]
HDAC7	Eraser	Histone deacetylase	Inflammatory Bowel Disease [137], Allergy [138], Asthma [139]
HDAC9	Eraser	Histone deacetylase	Osteoarthritis [140]
KDM4C	Eraser	Histone demethylase	Systemic Lupus Erythematosus [141], Asthma [142]
KDM5A/JARID1A	Eraser	Histone demethylase	Ankylosing Spondylitis [143]
TET2	Eraser	DNA demethylation	Ulcerative Colitis [137], Multiple Sclerosis [110], Chronic Pulmonary Obstructive Disease [144]
TET3	Eraser	DNA demethylation	Systemic Lupus Erythematosus [145]
SMARCA2	Chromatin remodeler	SNF2 ATPase domain	Asthma [146], Hashimoto's Thyroiditis [147]
SMARCA4/BRG1	Chromatin remodeler	SNF2 ATPase domain	Coronary Artery Disease [148], Multiple Sclerosis [149]