*International Immunology, Vol. 37, No. 12, pp. 733–742*
https://doi.org/10.1093/intimm/dxaf039
Advance Access publication 8 July 2025



REVIEW

# Epigenomic control of immunity: from mechanisms to therapeutic targets in inflammatory bowel diseases

**Han-Yu Shih[1,2], Giuseppe Sciumè[3,4]**, and **Yohei Mikami[5]**

[1]Neuro-Immune Regulome Unit, National Eye Institute, National Institutes of Health, Bethesda, MD 20892, USA
[2]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA
[3]Department of Molecular Medicine, Sapienza University of Rome, Rome 00161, Italy
[4]Laboratory Affiliated to Istituto Pasteur Italia-Fondazione Cenci Bolognetti, Rome 00161, Italy
[5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

*Correspondence to:* H.-Y. Shih, E-mail: han-yu.shih@nih.gov; G. Sciumè, E-mail: giuseppe.sciume@uniroma1.it; Y. Mikami, E-mail: yoheimiakmi@keio.jp

*Received* 22 April 2025, *editorial decision* 23 June 2025, *accepted* 29 June 2025

**Abstract**

**This review presents an overview of the emerging roles of epigenomic regulation in immune cell function, with a particular focus on its relevance in inflammatory bowel diseases (IBD). Epigenetic mechanisms, including DNA methylation, histone modification, chromatin remodeling, and non-coding RNAs, are essential in directing immune cell development, activation, and lineage commitment. Advances in genomics and epigenomics have highlighted the dynamic nature of gene regulation as the cornerstone of immune homeostasis and adaptability. We summarize recent insights into enhancer dynamics, three-dimensional chromatin architecture, transcription factor signaling, and microRNA (miRNA)-mediated regulation that reshape our understanding of immune-mediated diseases. These findings not only deepen our knowledge of disease pathogenesis but also offer promising targets for therapeutic intervention. In this context, miRNAs have emerged as key post-transcriptional regulators with significant diagnostic and therapeutic potential for IBD. The field of immune epigenomics is advancing rapidly, offering powerful tools for dissecting complex immune responses and guiding the development of precise therapies for chronic inflammatory conditions.**

*Keywords:* Crohn's disease, chromatin accessibility, epigenomics, ulcerative colitis

## Introduction

The immune system is a highly complex and intricately regulated network essential for host defense, homeostasis, and tissue repair (1–7). This sophisticated system comprises two primary components: innate immunity, responsible for rapid, non-specific responses; and adaptive immunity, which is characterized by specific antigen recognition and immunological memory. Both arms of immunity involve diverse lymphocyte populations, including T, B, natural killer (NK), and innate lymphoid cells (ILCs). Epigenomic regulation is critical for the development, differentiation, and function of immune cells to orchestrate precise responses (4, 8–13).

Epigenetic regulation encompasses various mechanisms, including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA-mediated post-transcriptional control. These processes collectively govern gene expression patterns without altering the underlying DNA sequence, thereby playing pivotal roles in lineage commitment, functional specialization, and rapid immune responses upon activation. The complexity of these epigenetic mechanisms and their interplay underscores their importance in maintaining immune homeostasis and preventing disease.

The field of genetics was founded in the 19th century by Gregor Mendel, whose experiments with pea plants established the principles of heritable traits transmitted in predictable ratios, now known as Mendelian inheritance. Although initially overlooked, his work was rediscovered around 1900 and became the cornerstone of classical genetics. Over the following decades, the chromosomal theory of inheritance emerged, linking Mendel's "factors" to physical units on chromosomes.

The molecular era of genomics began in the mid-20th century with a series of transformative discoveries. In 1944, Avery and colleagues (14) demonstrated that DNA is a genetic material, and in 1953, Watson and Crick (15) elucidated its double-helix structure, explaining how genetic information is replicated and transmitted. The "central dogma" of molecular biology, proposed by Crick, further defines the flow of information from DNA to RNA and proteins (16, 17). In the 1970s, Susumu Tonegawa revealed that the diversity of antibodies arises from somatic recombination of immunoglobulin gene loci, fundamentally challenging the static view of the genome and introducing the concept of genomic plasticity in immune cells (18, 19). This landmark discovery laid the foundation for understanding adaptive immune specificity. Decades later, the development of genome editing technologies—most notably CRISPR-Cas9 (20, 21)—enabled precise manipulation of genetic sequences, revolutionizing both basic research and the possibility for therapeutic applications.

In 2001, the Human Genome Project produced the first draft of the human genome (22, 23), laying critical groundwork for genomic medicine. More recently, in 2022, the telomere-to-telomere (T2T) consortium announced the first truly complete human genome sequence, including regions that had previously remained unmapped, particularly those near centromeres and telomeres (24) (Table 1). However, it soon became evident that the static genomic sequence alone could not account for the dynamic cell-type-specific gene regulation observed in complex organisms. This has led to an increase in epigenomic research.

In parallel, the field of epigenetics, originally coined by Waddington in 1942 to describe heritable changes in gene expression without altering DNA sequences, evolved rapidly into the modern discipline of epigenomics (27). Landmark discoveries in the 1970s and the 1980s identified DNA methylation and histone modifications as the key regulators of chromatin accessibility and transcriptional activity (28). The concept of a "histone code," introduced in 2000, further highlighted the combinatorial complexity of chromatin regulation (29). By the 2000s, the development of high-throughput sequencing technologies enabled the genome-wide profiling of epigenetic marks, leading to the emergence of epigenomics as a discipline (30). Large-scale consortia such as ENCODE and the NIH Roadmap Epigenomics Project have provided foundational maps of DNA methylation, histone modifications, and chromatin states across diverse human tissues (31) (Table 2).

An additional layer of epigenetic regulation emerged with the discovery of microRNAs (miRNAs) in 1993 and their widespread roles in mammals by the early 2000s (32, 34–37). These small non-coding RNAs act post-transcriptionally to repress gene expression and are epigenetically regulated, forming intricate feedback loops that shape cellular identity and function. miRNAs are incorporated into Argonaute (AGO) proteins within the RNA-induced silencing complex (RISC), inducing sequence-specific binding to target messenger RNAs (mRNAs), leading to translational repression and degradation (42, 43). In parallel, other RNA-binding proteins (RBPs) such as Regnase-1 (ZC3H12A) and Roquin independently regulate mRNA stability by targeting untranslated

**Table 1.** Key milestones in genetics.

| Year | Discovery | Reference |
|---|---|---|
| 1865 | Laws of Inheritance | Mendel (25). |
| 1944 | DNA as genetic material | Avery *et al.* (14) |
| 1953 | DNA double-helix structure | Watson and Crick (15) |
| 1958/1970 | Central dogma of molecular biology | Crick (17); Crick (16) |
| 1976–1979 | Somatic recombination of immunoglobulin genes | Tonegawa *et al.* (18); Tonegawa (19) |
| 2001 | Draft human genome | Lander *et al.* (23); Venter *et al.* (26) |
| 2012 | CRISPR-Cas9 genome editing | Jinek *et al.* (20) |
| 2013 | CRISPR-Cas9 genome editing in mammalian cells | Cong *et al.* (21) |
| 2022 | Complete telomere-to-telomere genome | Nurk *et al.* (24) |

**Table 2.** Key milestones in epigenetics/epigenomics.

| Year | Discovery/concept | Key reference |
|---|---|---|
| 1942 | Epigenetics coined | Waddington (27) |
| 1975 | DNA methylation model | Holliday and Pugh (28) |
| 1993 | First miRNA (lin-4) regulates gene expression | Lee *et al.* (32) |
| 1997 | DNA methylation in cancer | Feinberg and Vogelstein (33) |
| 2000 | Histone code hypothesis | Strahl and Allis (29) |
| 2000 | let-7 miRNA shown to be conserved | Pasquinelli *et al.* (34) |
| 2004 | miRNAs control mammalian development | Chen *et al.* (35) |
| 2005 | miRNA dysregulation in cancer | Lu *et al.* (36) |
| 2006 | miRNAs regulate innate immunity (e.g., miR-146a, miR-155) | Taganov *et al.* (37) |
| 2007 | First methylome map | Weber *et al.* (30) |
| 2009 | Discovery of 5-hydroxymethylcytosine (hmC) | Tahiliani *et al.* (38) |
| 2012 | TADs and 3D genome folding | Dixon *et al.* (39) |
| 2013 | Super-enhancers and gene regulation | Hnisz *et al.* (40) |
| 2015 | NIH Roadmap Epigenomics integrative atlas | Roadmap Epigenomics Consortium (31) |
| 2015 | CRISPR-based epigenome editing | Hilton *et al.* (41) |

regions (UTRs), particularly stem-loop structures of immune-related transcripts (44, 45). Notably, gain-of-function mutations in Regnase-1 have been identified in patients with ulcerative colitis (UC), underscoring its clinical relevance in mucosal inflammation (46, 47). Regnase-1 functions as an anti-inflammatory factor by degrading pro-inflammatory mRNAs, including those encoding transcriptional regulators such as NFKBIZ, which encodes IκBζ, a non-canonical member of the IκB family known to promote IL-6 and IL-17 responses. These protein networks coordinate with miRNAs to fine-tune gene expression programs that are essential for immune cell activation, differentiation, and resolution of inflammation.

In recent years, attention has also shifted toward understanding how higher-order chromatin organization, enhancer accessibility, and three-dimensional (3D) genome architecture influence immune cell fate and function relevant in inflammatory bowel diseases (IBD), where dysregulated immune responses involve both innate and adaptive immune compartments. Aberrations in these regulatory programs have been increasingly implicated in IBD pathogenesis. IBD consists of UC and Crohn's disease (CD), both characterized by relapsing-remitting inflammation affecting specific regions of the gastrointestinal tract. Although genome-wide association studies (GWAS) have identified numerous susceptibility loci, epigenetic dysregulation has emerged as a crucial layer linking genetic risk to environmental cues. For example, histone modification patterns and enhancer landscapes have been shown to shift in mucosal immune cells of IBD patients, contributing to an inappropriate activation of inflammatory pathways (48–50).

In the immune system, epigenomic mechanisms play a crucial role in orchestrating cell fate decisions, maintaining lineage identity, and enabling functional plasticity. Dynamic changes in enhancer landscapes, DNA methylation patterns, histone modifications, and 3D genome architecture underlie the activation, differentiation, and memory formation in both innate and adaptive immune cells (Fig. 1). In this review, we discuss the processes relevant to the pathogenesis of autoimmune diseases and inflammation, where dysregulated epigenomic states contribute to aberrant immune responses.

## Enhancer dynamics in immune regulation

Enhancers are critical cis-regulatory DNA elements that facilitate precise temporal and spatial gene expression by interacting with transcription factors and chromatin remodelers. Enhancers function independently of their distance from gene promoters, with chromatin-looping mechanisms facilitating the long-range interactions necessary for gene transcription. Enhancer activity is governed by transcription factor binding, histone modification, and chromatin accessibility, all contributing to the dynamic regulation of immune responses (51–53).

Activating enhancers in immune cells typically involves specific histone modifications, notably histone H3 lysine 27 acetylation (H3K27ac) and lysine 4 monomethylation (H3K4me1) (52). Studies have demonstrated that enhancers rapidly gain H3K27ac upon immune cell activation, which correlates with increased transcriptional activity of nearby genes. Conversely, enhancer repression often involves the removal of active marks or deposition of repressive histone modifications such as H3K27me3 and H3K9me3, emphasizing the dynamic and reversible nature of enhancer activity in immune cells. These modifications are commonly associated with active enhancer states and are mediated by histone-modifying enzymes such as p300 and CREB-binding protein. In immune cells, the recruitment of these enzymes to enhancer regions is typically driven by a network of transcription factors that includes both lineage-defining transcription factors (LDTFs) and signal-regulated TFs (SRTFs). LDTFs can act as pioneer factors, driving acquisition of chromatin accessibility during differentiation, while SRTFs can rapidly alter the status of the active enhancers upon acute activation, leading to acquisition of an effector phenotype (54–56).

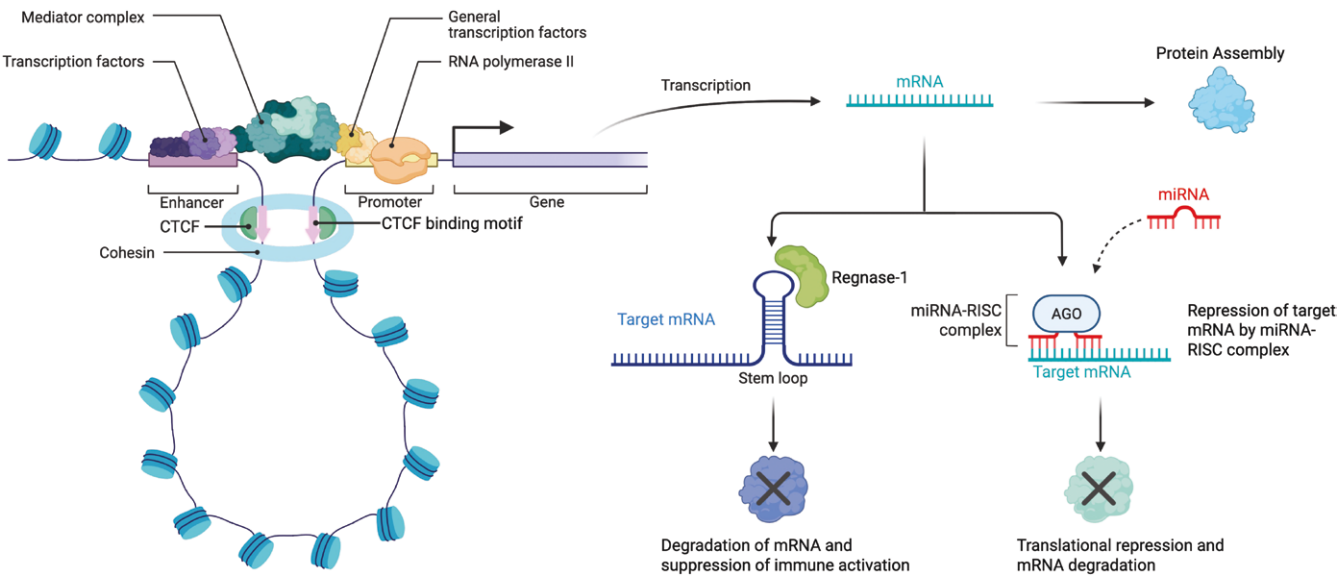


**Figure 1.** Schematic epigenetic transcriptional regulation mechanisms include chromatin structure, TADs, promoters, and enhancers.

Innate and adaptive immune cells deeply differ in the acquisition of their enhancer landscapes during development and activation. For instance, the pre-primed functions of macrophages and innate lymphocytes rely on preexisting accessible chromatin that is acquired during development and before pathogen entry; acute stimulation instead rapidly establishes specific sets of enhancers that are latent in resting cells or formed *de novo* during activation (10, 53, 54, 57–63). On the other hand, T helper (Th) cells acquire their epigenetic landscape only after activation, with LDTFs and the signal transducer and activator of transcription (STAT) family proteins that can both serve as pioneer factors to drive differentiation toward effector populations during infection (52, 64). Since STATs are major regulators of adaptive and innate responses and promising targets in IBD, below, we will review some of the main concepts concerning the role of STATs in the regulation of enhancers during lymphocyte differentiation.

## STAT proteins and enhancers in immune cell differentiation and activation

STAT proteins represent a pivotal family of transcription factors central to the cytokine signaling pathways that influence immune cell differentiation, activation, and function (65). STAT proteins are rapidly activated upon cytokine binding to their respective receptors, leading to their phosphorylation, dimerization, nuclear translocation, and DNA binding. This activation cascade enables STAT proteins to directly modulate gene expression by influencing chromatin accessibility and interacting with enhancer regions, thereby shaping the immune epigenomic landscape. STAT proteins comprise a family of seven distinct members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6), each activated by specific cytokines and responsible for unique biological responses (65–69). STAT1 primarily mediates responses to interferons (IFNs), notably type 1 (IFN-α/β), type 2 (IFN-γ), and type 3 (IFN-λ) interferons. Promoting pro-inflammatory immune responses and host defense mechanisms is crucial, particularly against intracellular pathogens. STAT1 activation leads to transcription of genes involved in antiviral responses, inflammation, and cellular immunity (70). STAT3, which is activated by cytokines such as IL-6, IL-21, and IL-23, is crucial for the differentiation and function of multiple immune cell types, including Th17 cells and regulatory T cells (Tregs). STAT3 signaling pathways critically regulate pro- and anti-inflammatory responses, underscoring their roles in immune homeostasis and tolerance. Dysregulated STAT3 signaling has been implicated in various autoimmune and inflammatory disorders (71–75). STAT4 is predominantly activated by IL-12 and IL-23, and plays a central role in Th1 cell differentiation, NK cell activation, and inflammatory responses. STAT4 facilitates IFN-γ production and enhances cytotoxicity in NK cells, which is essential for effective immune responses against pathogens and tumors (76, 77).

Immune cells, particularly ILCs and T cells, undergo extensive enhancer remodeling during development (from precursor to naïve cells), differentiation toward effector cells, and activation, enabling proper transcriptional responses to environmental stimuli. As discussed above, lineage-specific enhancer landscapes are established during development, priming cells for rapid gene induction upon activation. For instance, lineage-determining transcription factors in NK cells, such as T-bet, establish primed enhancer landscapes critical for subsequent immune responses (78).

Recent studies have highlighted the dynamic nature of enhancer remodeling in NK cells during acute activation and adaptive NK cell responses, revealing that enhancers can be rapidly formed or repurposed to facilitate robust gene expression (53, 79). Such remodeling often involves the redeployment of lineage-defining factors to novel enhancer sites, independent of their canonical DNA motifs, suggesting a high degree of flexibility in enhancer usage (79).

As discussed above, STAT proteins directly influence enhancer dynamics in immune cells. STATs recruit histone acetyltransferases, such as p300, to enhancer regions, inducing localized enhancer activity and chromatin accessibility. STAT-mediated enhancer formation often involves non-canonical mechanisms, with LDTFs redeployed to new enhancer regions without direct sequence-specific DNA interactions. This phenomenon exemplifies the flexibility of enhancer regulation by STAT proteins, which facilitates rapid adaptive responses during infection and inflammation (10).

Innate lymphocytes, including NK cells and various ILC subsets, rely extensively on STAT signaling for their development and functional specialization. In NK cells, STAT4 mediates rapid enhancer formation upon activation, driving the transcriptional induction of effector genes. Moreover, STAT4, together with STAT1 and STAT5, can provide epigenetic control at specific genes early during viral infection and adaptive NK cell responses (53,80). Enhanced remodeling is essential for high-magnitude gene expression responses during acute immune activation. Studies have demonstrated that STAT4 orchestrates rapid enhancer remodeling in NK cells during acute immune responses, forming *de novo* enhancers. These newly formed enhancers drive high-magnitude gene induction, which is critical for an effective immune response. Notably, STAT-mediated enhancer formation involves the redeployment of LDTFs such as T-bet to non-canonical genomic sites, highlighting the flexibility and adaptability of STAT-driven epigenetic regulation (77, 79, 81). Recently, STAT4 has been implicated in the differentiation and effector functions of NK cells and ILC1 subsets during intestinal inflammation. Specifically, STAT4 deficiency impairs NK cell maturation, while paradoxically enhancing cytotoxic ILC1 differentiation by altering the signaling dynamics of cytokines activating STAT5 (81). These findings revealed the complex and divergent roles of STAT proteins in modulating innate lymphocyte differentiation and function.

STAT proteins significantly influence the fate of immune cells by regulating the expression of lineage-specific transcription factors and cytokine profiles. STAT1 and STAT3 exhibit differential regulatory roles downstream of cytokines, such as IL-6 and IL-27. STAT3 broadly enhances transcriptional activity across various cell types, whereas STAT1 confers specificity, particularly to cytokine-mediated signaling pathways. This asymmetric regulation helps determine the balance between inflammation and immune tolerance (82–84). STAT3 activation drives Th17 differentiation, inducing RORγt expression and IL-17 production, which are critical for mucosal immunity and inflammation (85–90).

Similarly, STAT4 activation downstream of IL-12 signaling in T cells promotes Th1 differentiation, characterized by T-bet expression and IFN-γ production. STAT4-deficient models exhibit impaired Th1 responses, underscoring the essential role in cellular immunity (91). STAT4 and STAT6 distinctly shape the chromatin landscape in Th1 and Th2 cells, respectively—STAT4 primarily promotes active histone modifications to induce Th1-specific genes, whereas STAT6 counteracts repressive marks to activate Th2 gene programs, including key Th2 cytokines, and orchestrates broader transcriptional networks (92, 93). STAT5 is a key transcription factor activated downstream of common γ-chain (IL-2Rγ) cytokines such as IL-2, IL-7, and IL-15, through receptors like IL-2R and IL-7R. In Th cells, STAT5—particularly via IL-2 signaling—drives metabolic reprogramming, proliferation, and cytokine expression, promoting Treg and Th2 differentiation while limiting Th17 responses (87, 94). In ILCs, STAT5 is essential for development and survival, with IL-7 supporting ILC1, ILC2, and ILC3, and IL-15 is critical for NK cells. STAT5 activity is finely tuned in a tissue- and subset-specific manner, dictating ILC abundance and function. In NK cells, STAT5 collaborates with factors, such as T-bet, to remodel enhancers and drive effector gene expression, enabling rapid responses to infection (79, 95). Overall, STAT5 integrates cytokine signals to coordinate transcriptional programs across adaptive and innate lymphocytes.

Together, these findings underscore the central role of STATs as signal-regulated transcription factors of immune cell fate and function. By dynamically shaping enhancer landscapes in coordination with LDTFs, STATs ensure precise and timely gene expression programs essential for host defense, immune homeostasis, and adaptation to inflammatory cues.

### 3D chromatin architecture

The 3D chromatin architecture of the cytokine gene loci represents another critical layer of epigenetic regulation within immune cells. Specific loci, such as *Il4-Il13-Il5*, undergo distinct chromatin remodeling events during immune cell activation (96, 97). This chromatin restructuring is differentially regulated across innate lymphoid subsets (such as ILC2) and adaptive lymphocytes (such as Th2 cells), which dictate selective cytokine expression and contribute to functional specificity within immune subsets. Distinct chromatin architectural changes at cytokine gene loci (such as *Il4-Il13-Il5*) occur rapidly upon activation and differ significantly between innate (ILC2) and adaptive (Th2) lymphocytes. This selective remodeling leads to lineage-specific cytokine expression, which is crucial for appropriate immune responses and highlights the intricate regulatory mechanisms underlying cytokine gene expression (98).

In addition to the loci of signature Th2 cytokines, recent studies have highlighted how 3D chromatin architecture ensures lineage-specific cytokine expression during Th1 cell differentiation. A specific 17-bp CTCF-binding site at the *Mdm1-Il22-Ifng* locus anchors a topologically associating domain (TAD) that spatially separates the *Ifng* and *Il22* enhancer landscapes. Deletion of this CTCF site disrupts the TAD, resulting in impaired Th1 polarization with aberrant expression of IL-22, and increased susceptibility to *Toxoplasma gondii* infection (99). Interestingly, this architectural element is dispensable in innate immune cells, such as NK and memory CD8⁺ T cells, which rely on pre-established enhancer accessibility rather than inducible chromatin loops (10, 79). Despite minimal changes in enhancer-associated histone marks, the spatial miswiring of regulatory contacts leads to lineage-inappropriate cytokine expression, emphasizing the importance of chromatin topology in adaptive immunity (100, 101). These findings support a context-dependent model in which CTCF-mediated TADs are essential for Th1 lineage commitment but are dispensable for innate lymphocyte function. These studies broadened our understanding of how genome organization interacts with enhancer dynamics to enforce precise immune responses (102, 103).

### MiRNA regulation in immunity and miRNA involvement in IBD

MiRNAs constitute crucial components of post-transcriptional gene regulation within immune cells, modulating key signaling pathways and cellular differentiation processes. MiRNAs are small (~22 nucleotides) non-coding RNAs that are initially transcribed as primary miRNAs (pri-miRNAs), subsequently processed into precursor miRNAs (pre-miRNAs), and further cleaved into mature miRNAs (42, 104). Mature miRNAs are incorporated into RISCs and regulate gene expression by targeting mRNAs for degradation or translational inhibition by binding complementary sequences within the 3′ UTRs of mRNAs. This precise regulatory mechanism enables miRNAs to fine-tune the immune response, prevent excessive inflammation, and maintain immune homeostasis (43).

### miRNAs in immune cell differentiation

The role of miRNAs in immune cell differentiation, particularly in T cells, is well established. MiRNAs influence the balance between T-cell subsets, such as Th1, Th2, and Th17 cells, andTregs, by regulating LDTFs and cytokines (105). For instance, miR-155 promotes Th1 differentiation and IFN-γ production, whereas miR-146a negatively regulates Th1 responses by targeting key signaling molecules downstream of T-cell receptor activation (106).

The miR-17-92 cluster is another significant example containing multiple miRNAs that differentially regulate T-cell differentiation. MiR-17 and miR-19a within this cluster enhance Th1 differentiation and suppress rTreg formation (107, 108). Conversely, miRNAs such as miR-21 have promoted Th2 differentiation, with potential roles in allergic diseases and asthma (109).

miRNAs also critically regulate Th17 cell differentiation, a particularly relevant subset to inflammatory and autoimmune disorders. MiRNAs such as miR-155, miR-326, miR-301a, miR-183c, and miR-132/212 have been shown to promote Th17 differentiation by targeting negative regulators of the Th17 signaling pathway (110–112). In contrast, miR-15b, miR-17-92, and miR-18a negatively regulate Th17 differentiation by targeting molecules such as *O*-GlcNAc transferase, *Rora*, and *Smad4* (113, 114).

### MiRNAs in IBD

IBD, which encompasses CD and UC, involves dysregulated immune responses that are significantly influenced by

miRNAs. Several miRNAs have been identified as key IBD pathogenesis modulators and serve as biomarkers and potential therapeutic targets (115).

MiRNAs such as miR-21, miR-146a, miR-155, and miR-223 are often upregulated in patients with IBD, correlating with disease severity and inflammatory activity (116, 117). These miRNAs modulate critical pathways including cytokine signaling, autophagy, and epithelial barrier function. For example, miR-223 directly influences NLRP3 inflammasome activity, while miR-146a regulates TLR and NF-κB signaling pathways, contributing to chronic intestinal inflammation (37, 118).

MiR-221 and miR-222 have emerged as important miRNAs regulating Th17 responses in IBD. These miRNAs act as negative feedback regulators downstream of IL-23, targeting the IL-23 receptor (*Il23r*) and transcription factor c-Maf (*Maf*), constraining excessive Th17-mediated inflammation. MiR-221/222-deficient mice exhibit exacerbated colitis symptoms, indicating a protective role against intestinal inflammation (119).

### Clinical implications and therapeutic potential

Enhancer dynamics constitute a fundamental mechanism regulating immune cell differentiation, function, and plasticity. Given the central role of enhancers in regulating immune responses, aberrant enhancer activity has been linked to numerous inflammatory and autoimmune diseases, including IBD, rheumatoid arthritis, and psoriasis. Enhancer-associated genetic variants identified through GWAS have provided insight into disease susceptibility and pathogenesis (120, 121). Therapeutically, modulating enhancer activity is an attractive strategy for treating immune-mediated diseases. Targeting enzymes involved in enhancer activation, such as histone acetyltransferases and Brunauer-Emmett-Teller (BET) bromodomain proteins, has demonstrated potential in preclinical models (122). BET inhibitors, for instance, disrupt enhancer–promoter interactions, reduce the transcription of inflammatory genes, and ameliorate disease symptoms in animal models. The intricate interplay among transcription factors, chromatin remodelers, and signaling pathways underscores the complexity and importance of enhancer regulation in immunity. Further understanding of enhancer biology will advance therapeutic strategies targeting immune-mediated diseases (40, 123). Among transcription factors, dysregulated STAT signaling pathways contribute significantly to autoimmune and inflammatory diseases. For instance, aberrant STAT3 signaling is involved in disorders such as rheumatoid arthritis, psoriasis, and IBD, which are characterized by excessive Th17 responses. Therapeutic strategies targeting STAT pathways have shown promise, with JAK inhibitors such as tofacitinib effectively modulating STAT activity and demonstrating clinical efficacy in treating inflammatory conditions (65). Beyond cytokine signaling, JAK inhibitors also influence the epigenetic landscape by modulating enhancer architecture, thereby altering the expression of enhancer-associated genes implicated in autoimmunity. This dual mechanism—targeting both signal transduction and gene regulatory elements—underscores the therapeutic versatility of JAK-STAT pathway inhibition in chronic inflammatory diseases (123, 124). In summary, STAT proteins serve as central mediators of cytokine signaling, profoundly affecting immune cell differentiation, function, and epigenetic regulation. Their roles in shaping the chromatin landscape and modulating enhancer dynamics underscore their critical involvement in immune responses and pathology. Continued research on STAT-mediated mechanisms promises further insights into immune regulation and novel therapeutic approaches for immune-mediated diseases (Fig. 2).

Another important layer of epigenetic regulation is provided by the function of miRNAs. The stability and detectability of miRNAs in biological fluids, such as blood, make them promising candidates as diagnostic biomarkers for IBD. Circulating miRNAs have shown potential in distinguishing active from inactive disease states, correlating better than traditional inflammatory markers such as C-reactive protein (125, 126).

MiRNA modulation is a novel therapeutic strategy for treating inflammatory and autoimmune conditions. Preclinical studies using miRNA mimics and inhibitors have demonstrated significant therapeutic efficacy in animal models of IBD. For instance, systemic administration of miR-133a reduced inflammation and improved clinical scores in murine models of colitis (127), while miR-141 targeted CXCL12β to regulate leukocyte trafficking into inflamed tissues (128).

ABX464 (obefazimod), an oral drug that boosts anti-inflammatory miR-124 expression, was tested in a phase 2b trial in patients with moderate-to-severe UC who did not respond to prior treatments—in this 8-week placebo-controlled study involving 254 patients, all doses of ABX464 (25, 50, and 100 mg) significantly improved disease severity, as measured by the Modified Mayo Score, compared to the placebo. The most common adverse effect was headache, which occurred more frequently at higher doses. ABX464 showed promising efficacy and manageable safety, supporting its continued development in phase 3 trials (129). ABX464 (50 mg) also showed significantly improved clinical responses (ACR20/50 and DAS28 scores) compared with placebo at 12 weeks (130). These findings highlight that miRNAs are central anti-inflammatory regulators with therapeutic relevance in chronic immune-mediated diseases, positioning ABX464 as one of the most advanced miRNA-based therapies in clinical development.

Although several challenges hinder the clinical translation of miRNA-based therapies, including specificity, efficient tissue-specific delivery, off-target effects, and potential long-term adverse outcomes, ongoing research aims to overcome these barriers by improving the miRNA delivery systems and targeted modulation strategies.

### Conclusions

Understanding the epigenetic regulation of immune cells, including the roles of enhancer dynamics, STAT proteins, and miRNAs, is fundamental to understanding immune system functionality and dysregulation in diseases such as IBD. These epigenetic mechanisms serve as integrative hubs that translate genetic and environmental cues into context-specific immune responses. Notably, JAK inhibitors are thought to exert part of their sustained anti-inflammatory effects by normalizing inflammation-associated enhancer landscapes (123, 124, 131). As our understanding deepens, a new frontier

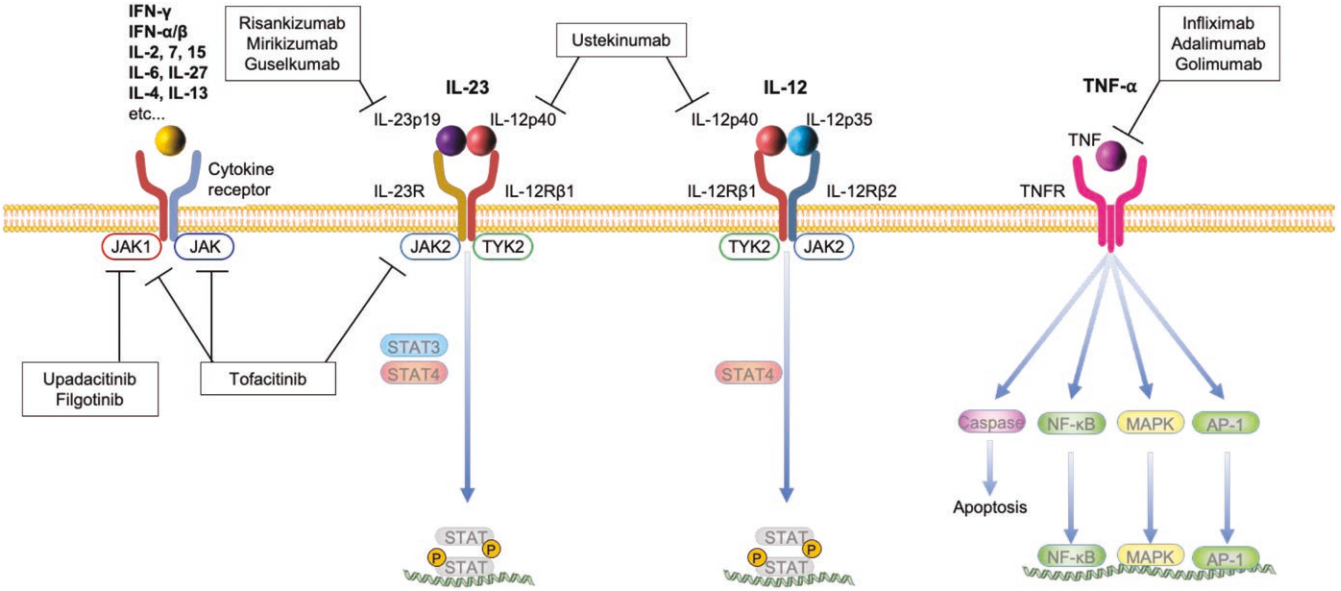


**Figure 2.** Signal transduction pathways mediated by TNF-α, IL-12, IL-23, and other pro-inflammatory cytokines. These cytokines activate downstream signaling cascades including the NF-κB, MAPK, and JAK-STAT pathways. In particular, IL-12 and IL-23 signal mainly through JAK2- and TYK2-dependent mechanisms, leading to STAT4 and STAT3 activation, respectively, while TNF-α predominantly activates NF-κB and MAPK. Targeting TNF-α, IL-12/IL-23, and JAK-STAT signaling has proven effective in the clinical management of IBD.

is emerging in the development of IBD therapies that directly target epigenetic regulators. Small-molecule inhibitors of histone-modifying enzymes, chromatin readers, and RBPs, as well as strategies to modulate enhancer–promoter interactions or miRNA networks, offer promising avenues for precision intervention. Encouragingly, recent advances in nucleic acid-based therapies—such as the clinical success of antisense oligonucleotides in neurological diseases and ongoing trials of miRNA modulators and histone deacetylase inhibitors in IBD—suggest that targeting small and non-coding RNAs may represent a promising therapeutic strategy for IBD and other immune-mediated disorders (132–134). Further research into these epigenetic mechanisms will improve our understanding of immune-mediated diseases and open new avenues for innovative and mechanism-driven therapeutic approaches.

## Acknowledgements

The authors acknowledge help from the site "www.biorender.com" and "bioart.niaid.nih.gov" for the drawing of figures. We used Editage for editing the English text of a draft of this manuscript.

## Conflicts of interest statement

The authors declare no competing interests in this article.

## Funding

This study was funded by the Japan Society for the Promotion of Science (JSPS) KAKENHI (A): 24H00633 and 20H00536 to Y.M.; JSPS Grant-in-Aid for Transformative Research Areas (B): 21H05123 to Y.M.; Grant-in-Aid for Challenging Research (24K2212) to Y.M.; the Japan Science and Technology Agency FOREST (JPMJFR235H) to Y.M.; the Ono Pharma Oncology, Immunology, Neurology Research Foundation; and Keio University Medical Fund; Italian Association for Cancer Research (AIRC): IG 28719 to G.S. NIH: Z IAEY000569-01 to H.-Y.S..

## References

1. Spits H, Artis D, Colonna M, *et al*. Innate lymphoid cells—a proposal for uniform nomenclature. *Nat Rev Immunol* 2013;**13**:145–9. https://doi.org/10.1038/nri3365
2. Henderson NC, Rieder F, Wynn TA. Fibrosis: from mechanisms to medicines. *Nature* 2020;**587**:555–66. https://doi.org/10.1038/s41586-020-2938-9
3. Nakayama T, Hirahara K, Onodera A, *et al*. Th2 cells in health and disease. *Annu Rev Immunol* 2017;**35**:53–84. https://doi.org/10.1146/annurev-immunol-051116-052350
4. Ivanov II, Tuganbaev T, Skelly AN, *et al*. T cell responses to the microbiota. *Annu Rev Immunol* 2022;**40**:559–87. https://doi.org/10.1146/annurev-immunol-101320-011829
5. Gronke K, Diefenbach A. Regenerative biology: innate immunity repairs gut lining. *Nature* 2015;**528**:488–9. https://doi.org/10.1038/nature16325
6. Mikami Y, Takada Y, Hagihara Y, *et al*. Innate lymphoid cells in organ fibrosis. *Cytokine Growth Factor Rev* 2018;**42**:27–36. https://doi.org/10.1016/j.cytogfr.2018.07.002
7. Paul WE. Pleiotropy and redundancy: T cell-derived lymphokines in the immune response. *Cell* 1989;**57**:521–4. https://doi.org/10.1016/0092-8674(89)90121-9
8. Diefenbach A, Colonna M, Koyasu S. Development, differentiation, and diversity of innate lymphoid cells. *Immunity* 2014;**41**:354–65. https://doi.org/10.1016/j.immuni.2014.09.005
9. Vivier E, Artis D, Colonna M, *et al*. Innate lymphoid cells: 10 years on. *Cell* 2018;**174**:1054–66. https://doi.org/10.1016/j.cell.2018.07.017
10. Shih HY, Sciume G, Mikami Y, *et al*. Developmental acquisition of regulomes underlies innate lymphoid cell functionality. *Cell* 2016;**165**:1120–33. https://doi.org/10.1016/j.cell.2016.04.029
11. Klose CS, Artis D. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. *Nat Immunol* 2016;**17**:765–74. https://doi.org/10.1038/ni.3489
12. Neurath MF, Artis D, Becker C. The intestinal barrier: a pivotal role in health, inflammation, and cancer. *Lancet Gastroenterol Hepatol* 2025;**10**:573–92. https://doi.org/10.1016/s2468-1253(24)00390-x
13. Diefenbach A, Colonna M, Romagnani C. The ILC world revisited. *Immunity* 2017;**46**:327–32. https://doi.org/10.1016/j.immuni.2017.03.008

14. Avery OT, Macleod CM, McCarty M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types: induction of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III. *J Exp Med* 1944;**79**:137–58. https://doi.org/10.1084/jem.79.2.137
15. Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* 1953;**171**:737–8. https://doi.org/10.1038/171737a0
16. Crick F. Central dogma of molecular biology. *Nature* 1970;**227**:561–3. https://doi.org/10.1038/227561a0
17. Crick FH. On protein synthesis. *Symp Soc Exp Biol* 1958;**12**:138–63.
18. Tonegawa S, Steinberg C, Dube S, *et al*. Evidence for somatic generation of antibody diversity. *Proc Natl Acad Sci U S A* 1974;**71**:4027–31. https://doi.org/10.1073/pnas.71.10.4027
19. Tonegawa S. Somatic generation of antibody diversity. *Nature* 1983;**302**:575–81. https://doi.org/10.1038/302575a0
20. Jinek M, Chylinski K, Fonfara I, *et al*. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 2012;**337**:816–21. https://doi.org/10.1126/science.1225829
21. Cong L, Ran FA, Cox D, *et al*. Multiplex genome engineering using CRISPR/Cas systems. *Science* 2013;**339**:819–23. https://doi.org/10.1126/science.1231143
22. Istrail S, Sutton GG, Florea L, *et al*. Whole-genome shotgun assembly and comparison of human genome assemblies. *Proc Natl Acad Sci U S A* 2004;**101**:1916–21. https://doi.org/10.1073/pnas.0307971100
23. Lander ES, Linton LM, Birren B, *et al*; International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature* 2001;**409**:860–921. https://doi.org/10.1038/35057062
24. Nurk S, Koren S, Rhie A, *et al*. The complete sequence of a human genome. *Science* 2022;**376**:44–53. https://doi.org/10.1126/science.abj6987
25. Mendel G. Versuche über Pflanzen-Hybriden. In: *Verhandlungen des naturforschenden Vereines in Brünn*, Vol IV (1865). Brünn: Im Verlage des Vereines, 1866, 3–47.
26. Venter JC, Adams MD, Myers EW, *et al*. The sequence of the human genome. *Science* 2001;**291**:1304–51. https://doi.org/10.1126/science.1058040
27. Waddington CH. The epigenotype. *Int J Epidemiol* 2012;**41**:10–3. https://doi.org/10.1093/ije/dyr184
28. Holliday R, Pugh JE. DNA modification mechanisms and gene activity during development. *Science* 1975;**187**:226–32.
29. Strahl BD, Allis CD. The language of covalent histone modifications. *Nature.* 2000;**403**:41–5. https://doi.org/10.1038/47412
30. Weber M, Hellmann I, Stadler MB, *et al*. Distribution, silencing potential and evolutionary impact of promoter DNA methylation in the human genome. *Nat Genet* 2007;**39**:457–66. https://doi.org/10.1038/ng1990
31. Kundaje A, Meuleman W, Ernst J, *et al*.; Roadmap Epigenomics Consortium. Integrative analysis of 111 reference human epigenomes. *Nature* 2015;**518**:317–30. https://doi.org/10.1038/nature14248
32. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993;**75**:843–54. https://doi.org/10.1016/0092-8674(93)90529-y
33. Feinberg AP, Vogelstein B. Hypomethylation distinguishes genes of some human cancers from their normal counterparts. *Nature* 1983;**301**:89–92. https://doi.org/10.1038/301089a0
34. Pasquinelli AE, Reinhart BJ, Slack F, *et al*. Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA. *Nature* 2000;**408**:86–9. https://doi.org/10.1038/35040556
35. Chen CZ, Li L, Lodish HF, *et al*. MicroRNAs modulate hematopoietic lineage differentiation. *Science* 2004;**303**:83–6. https://doi.org/10.1126/science.1091903
36. Lu J, Getz G, Miska EA, *et al*. MicroRNA expression profiles classify human cancers. *Nature* 2005;**435**:834–8. https://doi.org/10.1038/nature03702
37. Taganov KD, Boldin MP, Chang KJ, *et al*. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc Natl Acad Sci U S A* 2006;**103**:12481–6. https://doi.org/10.1073/pnas.0605298103
38. Tahiliani M, Koh KP, Shen Y, *et al*. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. *Science* 2009;**324**:930–5. https://doi.org/10.1126/science.1170116
39. Dixon JR, Selvaraj S, Yue F, *et al*. Topological domains in mammalian genomes identified by analysis of chromatin interactions. *Nature* 2012;**485**:376–80. https://doi.org/10.1038/nature11082
40. Hnisz D, Abraham BJ, Lee TI, *et al*. Super-enhancers in the control of cell identity and disease. *Cell* 2013;**155**:934–47. https://doi.org/10.1016/j.cell.2013.09.053
41. Hilton IB, D'Ippolito AM, Vockley CM, *et al*. Epigenome editing by a CRISPR-Cas9-based acetyltransferase activates genes from promoters and enhancers. *Nat Biotechnol* 2015;**33**:510–7. https://doi.org/10.1038/nbt.3199
42. Bartel DP. Metazoan MicroRNAs. *Cell* 2018;**173**:20–51. https://doi.org/10.1016/j.cell.2018.03.006
43. Mehta A, Baltimore D. MicroRNAs as regulatory elements in immune system logic. *Nat Rev Immunol* 2016;**16**:279–94. https://doi.org/10.1038/nri.2016.40
44. Uehata T, Iwasaki H, Vandenbon A, *et al*. Malt1-induced cleavage of regnase-1 in CD4(+) helper T cells regulates immune activation. *Cell* 2013;**153**:1036–49. https://doi.org/10.1016/j.cell.2013.04.034
45. Iwasaki H, Takeuchi O, Teraguchi S, *et al*. The IκB kinase complex regulates the stability of cytokine-encoding mRNA induced by TLR-IL-1R by controlling degradation of regnase-1. *Nat Immunol* 2011;**12**:1167–75. https://doi.org/10.1038/ni.2137
46. Kakiuchi N, Yoshida K, Uchino M, *et al*. Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis. *Nature* 2020;**577**:260–5. https://doi.org/10.1038/s41586-019-1856-1
47. Nanki K, Fujii M, Shimokawa M, *et al*. Somatic inflammatory gene mutations in human ulcerative colitis epithelium. *Nature* 2020;**577**:254–9. https://doi.org/10.1038/s41586-019-1844-5
48. Stankey CT, Bourges C, Haag LM, *et al*. A disease-associated gene desert directs macrophage inflammation through ETS2. *Nature* 2024;**630**:447–56. https://doi.org/10.1038/s41586-024-07501-1
49. Noble AJ, Nowak JK, Adams AT, *et al*. Defining interactions between the genome, epigenome, and the environment in inflammatory bowel disease: progress and prospects. *Gastroenterology* 2023;**165**:44–60.e2. https://doi.org/10.1053/j.gastro.2023.03.238
50. Awad A, Alcala AJ, Cowles MW, *et al*. Chromatin profiling to identify biomarkers in inflammatory bowel diseases. *Curr Opin Gastroenterol* 2025;**41**:216–22. https://doi.org/10.1097/MOG.0000000000001104
51. Ansel KM, Lee DU, Rao A. An epigenetic view of helper T cell differentiation. *Nat Immunol* 2003;**4**:616–23. https://doi.org/10.1038/ni0703-616
52. Kanno Y, Vahedi G, Hirahara K, *et al*. Transcriptional and epigenetic control of T helper cell specification: molecular mechanisms underlying commitment and plasticity. *Annu Rev Immunol* 2012;**30**:707–31. https://doi.org/10.1146/annurev-immunol-020711-075058
53. Lau CM, Adams NM, Geary CD, *et al*. Epigenetic control of innate and adaptive immune memory. *Nat Immunol* 2018;**19**:963–72. https://doi.org/10.1038/s41590-018-0176-1
54. Glass CK, Natoli G. Molecular control of activation and priming in macrophages. *Nat Immunol* 2016;**17**:26–33. https://doi.org/10.1038/ni.3306
55. Heinz S, Glass CK. Roles of lineage-determining transcription factors in establishing open chromatin: lessons from high-throughput studies. *Curr Top Microbiol Immunol* 2012;**356**:1–15. https://doi.org/10.1007/82_2011_142
56. Zaret KS, Carroll JS. Pioneer transcription factors: establishing competence for gene expression. *Genes Dev* 2011;**25**:2227–41. https://doi.org/10.1101/gad.176826.111
57. Collins PL, Cella M, Porter SI, *et al*. Gene regulatory programs conferring phenotypic identities to human NK cells. *Cell* 2019;**176**:348–60.e12. https://doi.org/10.1016/j.cell.2018.11.045
58. Gury-BenAri M, Thaiss CA, Serafini N, *et al*. The spectrum and regulatory landscape of intestinal innate lymphoid cells are

shaped by the microbiome. *Cell* 2016;**166**:1231–46.e13. https://doi.org/10.1016/j.cell.2016.07.043
59. Kaikkonen MU, Spann NJ, Heinz S, *et al*. Remodeling of the enhancer landscape during macrophage activation is coupled to enhancer transcription. *Mol Cell* 2013;**51**:310–25. https://doi.org/10.1016/j.molcel.2013.07.010
60. Ostuni R, Piccolo V, Barozzi I, *et al*. Latent enhancers activated by stimulation in differentiated cells. *Cell* 2013;**152**:157–71. https://doi.org/10.1016/j.cell.2012.12.018
61. Koues OI, Collins PL, Cella M, *et al*. Distinct gene regulatory pathways for human innate versus adaptive lymphoid cells. *Cell* 2016;**165**:1134–46. https://doi.org/10.1016/j.cell.2016.04.014
62. Sciumè G, Shih H-Y, Mikami Y, O'Shea JJ. Epigenomic views of innate lymphoid cells. *Front Immunol* 2017;**8**:1579. https://doi.org/10.3389/fimmu.2017.01579
63. Hagihara Y, Yoshimatsu Y, Mikami Y, *et al*. Epigenetic regulation of T helper cells and intestinal pathogenicity. *Semin Immunopathol* 2019;**41**:379–99. https://doi.org/10.1007/s00281-019-00732-9
64. Fernando N, Sciume G, O'Shea JJ, *et al*. Multi-dimensional gene regulation in innate and adaptive lymphocytes: a view from regulomes. *Front Immunol* 2021;**12**:655590. https://doi.org/10.3389/fimmu.2021.655590
65. Philips RL, Wang Y, Cheon H, *et al*. The JAK-STAT pathway at 30: Much learned, much more to do. *Cell* 2022;**185**:3857–76. https://doi.org/10.1016/j.cell.2022.09.023
66. Schwartz DM, Kanno Y, Villarino A, *et al*. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov* 2017;**17**:78. https://doi.org/10.1038/nrd.2017.267
67. Villarino AV, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak-STAT signaling in the immune system. *Nat Immunol* 2017;**18**:374–84. https://doi.org/10.1038/ni.3691
68. Bonelli M, Kerschbaumer A, Kastrati K, *et al*. Selectivity, efficacy and safety of JAKinibs: new evidence for a still evolving story. *Ann Rheum Dis* 2024;**83**:139–60. https://doi.org/10.1136/ard-2023-223850
69. Casanova JL, Holland SM, Notarangelo LD. Inborn errors of human JAKs and STATs. *Immunity* 2012;**36**:515–28. https://doi.org/10.1016/j.immuni.2012.03.016
70. Durbin JE, Hackenmiller R, Simon MC, *et al*. Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. *Cell* 1996;**84**:443–50. https://doi.org/10.1016/s0092-8674(00)81289-1
71. Lee C-K, Raz R, Gimeno R, *et al*. STAT3 is a negative regulator of granulopoiesis but is not required for G-CSF-dependent differentiation. *Immunity* 2002;**17**:63–72. https://doi.org/10.1016/s1074-7613(02)00336-9
72. Durant L, Watford WT, Ramos HL, *et al*. Diverse targets of the transcription factor STAT3 contribute to T cell pathogenicity and homeostasis. *Immunity* 2010;**32**:605–15. https://doi.org/10.1016/j.immuni.2010.05.003
73. Laurence A, Amarnath S, Mariotti J, *et al*. STAT3 transcription factor promotes instability of nTreg cells and limits generation of iTreg cells during acute murine graft-versus-host disease. *Immunity* 2012;**37**:209–22. https://doi.org/10.1016/j.immuni.2012.05.027
74. Poholek AC, Villarino AV, Petermann F, *et al*. IL-10 induces a STAT3-dependent autoregulatory loop in TH2 cells that promotes Blimp-1 restriction of cell expansion via antagonism of STAT5 target genes. *Sci Immunol* 2016;**1**:eaaf8612.
75. Steward-Tharp SM, Laurence A, Kanno Y, *et al*. A mouse model of HIES reveals pro- and anti-inflammatory functions of STAT3. *Blood* 2014;**123**:2978–87. https://doi.org/10.1182/blood-2013-09-523167
76. Thierfelder WE, van Deursen JM, Yamamoto K, *et al*. Requirement for Stat4 in interleukin-12-mediated responses of natural killer and T cells. *Nature* 1996;**382**:171–4. https://doi.org/10.1038/382171a0
77. Mikami Y, Scarno G, Zitti B, *et al*. NCR(+) ILC3 maintain larger STAT4 reservoir via T-BET to regulate type 1 features upon IL-23 stimulation in mice. *Eur J Immunol* 2018;**48**:1174–80. https://doi.org/10.1002/eji.201847480
78. Lazarevic V, Glimcher LH, Lord GM. T-bet: a bridge between innate and adaptive immunity. *Nat Rev Immunol* 2013;**13**:777–89. https://doi.org/10.1038/nri3536
79. Sciume G, Mikami Y, Jankovic D, *et al*. Rapid enhancer remodeling and transcription factor repurposing enable high magnitude gene induction upon acute activation of NK cells. *Immunity* 2020;**53**:745–58.e4. https://doi.org/10.1016/j.immuni.2020.09.008
80. Wiedemann GM, Grassmann S, Lau CM, *et al*. Divergent Role for STAT5 in the adaptive responses of natural killer cells. *Cell Rep* 2020;**33**:108498.
81. Scarno G, Mazej J, Laffranchi M, *et al*. Divergent roles for STAT4 in shaping differentiation of cytotoxic ILC1 and NK cells during gut inflammation. *Proc Natl Acad Sci U S A* 2023;**120**:e2306761120. https://doi.org/10.1073/pnas.2306761120
82. Villarino A, Hibbert L, Lieberman L, *et al*. The IL-27R (WSX-1) is required to suppress T cell hyperactivity during infection. *Immunity* 2003;**19**:645–55. https://doi.org/10.1016/s1074-7613(03)00300-5
83. Stumhofer JS, Laurence A, Wilson EH, *et al*. Interleukin 27 negatively regulates the development of interleukin 17-producing T helper cells during chronic inflammation of the central nervous system. *Nat Immunol* 2006;**7**:937–45. https://doi.org/10.1038/ni1376
84. Hirahara K, Onodera A, Villarino AV, *et al*. Asymmetric action of STAT transcription factors drives transcriptional outputs and cytokine specificity. *Immunity* 2015;**42**:877–89. https://doi.org/10.1016/j.immuni.2015.04.014
85. Chen Z, Laurence A, Kanno Y, *et al*. Selective regulatory function of Socs3 in the formation of IL-17-secreting T cells. *Proc Natl Acad Sci U S A* 2006;**103**:8137–42. https://doi.org/10.1073/pnas.0600666103
86. Kimura A, Naka T, Kishimoto T. IL-6-dependent and -independent pathways in the development of interleukin 17-producing T helper cells. *Proc Natl Acad Sci U S A* 2007;**104**:12099–104. https://doi.org/10.1073/pnas.0705268104
87. Laurence A, Tato CM, Davidson TS, *et al*. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity* 2007;**26**:371–81. https://doi.org/10.1016/j.immuni.2007.02.009
88. Nishihara M, Ogura H, Ueda N, *et al*. IL-6-gp130-STAT3 in T cells directs the development of IL-17+ Th with a minimum effect on that of Treg in the steady state. *Int Immunol* 2007;**19**:695–702. https://doi.org/10.1093/intimm/dxm045
89. Zheng Y, Danilenko DM, Valdez P, *et al*. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007;**445**:648–51. https://doi.org/10.1038/nature05505
90. Zhou L, Ivanov II, Spolski R, *et al*. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol* 2007;**8**:967–74. https://doi.org/10.1038/ni1488
91. Kaplan MH, Sun YL, Hoey T, *et al*. Impaired IL-12 responses and enhanced development of Th2 cells in Stat4-deficient mice. *Nature* 1996;**382**:174–7. https://doi.org/10.1038/382174a0
92. Elo LL, Jarvenpaa H, Tuomela S, *et al*. Genome-wide profiling of interleukin-4 and STAT6 transcription factor regulation of human Th2 cell programming. *Immunity* 2010;**32**:852–62. https://doi.org/10.1016/j.immuni.2010.06.011
93. Wei L, Vahedi G, Sun H-w, *et al*. Discrete roles of STAT4 and STAT6 transcription factors in tuning epigenetic modifications and transcription during T helper cell differentiation. *Immunity* 2010;**32**:840–51. https://doi.org/10.1016/j.immuni.2010.06.003
94. Villarino AV, Laurence AD, Davis FP, *et al*. A central role for STAT5 in the transcriptional programing of T helper cell metabolism. *Sci Immunol* 2022;**7**:eabl9467. https://doi.org/10.1126/sciimmunol.abl9467
95. Villarino AV, Sciumè G, Davis FP, *et al*. Subset- and tissue-defined STAT5 thresholds control homeostasis and function of innate lymphoid cells. *J Exp Med* 2017;**214**:2999–3014. https://doi.org/10.1084/jem.20150907
96. Mohrs M, Blankespoor CM, Wang ZE, *et al*. Deletion of a coordinate regulator of type 2 cytokine expression in mice. *Nat Immunol* 2001;**2**:842–7. https://doi.org/10.1038/ni0901-842
97. Lee GR, Fields PE, Griffin TJ, *et al*. Regulation of the Th2 cytokine locus by a locus control region. *Immunity* 2003;**19**:145–53. https://doi.org/10.1016/s1074-7613(03)00179-1

98. Nagashima H, Shayne J, Jiang K, *et al*. Remodeling of Il4-Il13-Il5 locus underlies selective gene expression. *Nat Immunol* 2024;**25**:2220–33. https://doi.org/10.1038/s41590-024-02007-4
99. Liu C, Nagashima H, Fernando N, *et al*. A CTCF-binding site in the Mdm1-Il22-Ifng locus shapes cytokine expression profiles and plays a critical role in early Th1 cell fate specification. *Immunity* 2024;**57**:1005–18.e7. https://doi.org/10.1016/j.immuni.2024.04.007
100. Vahedi G, Takahashi H, Nakayamada S, *et al*. STATs shape the active enhancer landscape of T cell populations. *Cell* 2012;**151**:981–93. https://doi.org/10.1016/j.cell.2012.09.044
101. Petermann F, Pękowska A, Johnson CA, *et al*. The magnitude of IFN-γ responses is fine-tuned by DNA architecture and the non-coding transcript of Ifng-as1. *Mol Cell* 2019;**75**:1229–42.e5. https://doi.org/10.1016/j.molcel.2019.06.025
102. Rowley MJ, Corces VG. Organizational principles of 3D genome architecture. *Nat Rev Genet* 2018;**19**:789–800. https://doi.org/10.1038/s41576-018-0060-8
103. Rao SSP, Huang SC, Glenn St Hilaire B, *et al*. Cohesin loss eliminates all loop domains. *Cell* 2017;**171**:305–20.e24. https://doi.org/10.1016/j.cell.2017.09.026
104. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;**116**:281–97. https://doi.org/10.1016/s0092-8674(04)00045-5
105. Baumjohann D, Ansel KM. MicroRNA-mediated regulation of T helper cell differentiation and plasticity. *Nat Rev Immunol* 2013;**13**:666–78. https://doi.org/10.1038/nri3494
106. Thai T-H, Calado DP, Casola S, *et al*. Regulation of the germinal center response by microRNA-155. *Science* 2007;**316**:604–8. https://doi.org/10.1126/science.1141229
107. Yu D, Rao S, Tsai LM, *et al*. The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. *Immunity* 2009;**31**:457–68. https://doi.org/10.1016/j.immuni.2009.07.002
108. Sasaki K, Kohanbash G, Hoji A, *et al*. miR-17-92 expression in differentiated T cells - implications for cancer immunotherapy. *J Transl Med* 2010;**8**:17. https://doi.org/10.1186/1479-5876-8-17
109. Lu TX, Hartner J, Lim EJ, *et al*. MicroRNA-21 limits in vivo immune response-mediated activation of the IL-12/IFN-gamma pathway, Th1 polarization, and the severity of delayed-type hypersensitivity. *J Immunol* 2011;**187**:3362–73. https://doi.org/10.4049/jimmunol.1101235
110. O'Connell RM, Kahn D, Gibson WS, *et al*. MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development. *Immunity* 2010;**33**:607–19. https://doi.org/10.1016/j.immuni.2010.09.009
111. Ichiyama K, Gonzalez-Martin A, Kim BS, *et al*. The MicroRNA-183-96-182 cluster promotes T helper 17 cell pathogenicity by negatively regulating transcription factor Foxo1 expression. *Immunity* 2016;**44**:1284–98. https://doi.org/10.1016/j.immuni.2016.05.015
112. Nakahama T, Hanieh H, Nguyen NT, *et al*. Aryl hydrocarbon receptor-mediated induction of the microRNA-132/212 cluster promotes interleukin-17-producing T-helper cell differentiation. *Proc Natl Acad Sci U S A* 2013;**110**:11964–9. https://doi.org/10.1073/pnas.1311087110
113. Liu R, Ma X, Chen L, *et al*. MicroRNA-15b suppresses Th17 differentiation and is associated with pathogenesis of multiple sclerosis by targeting O-GlcNAc transferase. *J Immunol* 2017;**198**:2626–39. https://doi.org/10.4049/jimmunol.1601727
114. Montoya MM, Maul J, Singh PB, *et al*. A distinct inhibitory function for miR-18a in Th17 cell differentiation. *J Immunol* 2017;**199**:559–69. https://doi.org/10.4049/jimmunol.1700170
115. Pekow JR, Kwon JH. MicroRNAs in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:187–93. https://doi.org/10.1002/ibd.21691
116. Paraskevi A, Theodoropoulos G, Papaconstantinou I, *et al*. Circulating MicroRNA in inflammatory bowel disease. *J Crohns Colitis* 2012;**6**:900–4. https://doi.org/10.1016/j.crohns.2012.02.006
117. Schönauen K, Le N, von Arnim U, *et al*. Circulating and fecal microRNAs as biomarkers for inflammatory bowel diseases. *Inflamm Bowel Dis* 2018;**24**:1547–57. https://doi.org/10.1093/ibd/izy046
118. Bauernfeind F, Rieger A, Schildberg FA, *et al*. NLRP3 inflammasome activity is negatively controlled by miR-223. *J Immunol* 2012;**189**:4175–81. https://doi.org/10.4049/jimmunol.1201516
119. Mikami Y, Philips RL, Sciumè G, *et al*. MicroRNA-221 and -222 modulate intestinal inflammatory Th17 cell response as negative feedback regulators downstream of interleukin-23. *Immunity* 2021;**54**:514–25.e6. https://doi.org/10.1016/j.immuni.2021.02.015
120. Farh KK, Marson A, Zhu J, *et al*. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* 2015;**518**:337–43. https://doi.org/10.1038/nature13835
121. Mumbach MR, Satpathy AT, Boyle EA, *et al*. Enhancer connectome in primary human cells identifies target genes of disease-associated DNA elements. *Nat Genet* 2017;**49**:1602–12. https://doi.org/10.1038/ng.3963
122. Brown JD, Lin CY, Duan Q, *et al*. NF-kappaB directs dynamic super enhancer formation in inflammation and atherogenesis. *Mol Cell* 2014;**56**:219–31. https://doi.org/10.1016/j.molcel.2014.08.024
123. Vahedi G, Kanno Y, Furumoto Y, *et al*. Super-enhancers delineate disease-associated regulatory nodes in T cells. *Nature* 2015;**520**:558–62. https://doi.org/10.1038/nature14154
124. Tsuchiya H, Ota M, Sumitomo S, *et al*. Parsing multiomics landscape of activated synovial fibroblasts highlights drug targets linked to genetic risk of rheumatoid arthritis. *Ann Rheum Dis* 2020;80:440–50. https://doi.org/10.1136/annrheumdis-2020-218189
125. Fasseu M, Treton X, Guichard C, *et al*. Identification of restricted subsets of mature microRNA abnormally expressed in inactive colonic mucosa of patients with inflammatory bowel disease. *PLoS One* 2010;**5**:e13160. https://doi.org/10.1371/journal.pone.0013160
126. Schaefer JS, Attumi T, Opekun AR, *et al*. MicroRNA signatures differentiate Crohn's disease from ulcerative colitis. *BMC Immunol* 2015;**16**:5. https://doi.org/10.1186/s12865-015-0069-0
127. Jin X, Chen D, Zheng RH, *et al*. miRNA-133a-UCP2 pathway regulates inflammatory bowel disease progress by influencing inflammation, oxidative stress and energy metabolism. *World J Gastroenterol* 2017;**23**:76–86. https://doi.org/10.3748/wjg.v23.i1.76
128. Huang Z, Shi T, Zhou Q, *et al*. miR-141 Regulates colonic leukocytic trafficking by targeting CXCL12β during murine colitis and human Crohn's disease. *Gut* 2014;**63**:1247–57. https://doi.org/10.1136/gutjnl-2012-304213
129. Vermeire S, Solitano V, Peyrin-Biroulet L, *et al*. Obefazimod: a first-in-class drug for the treatment of ulcerative colitis. *J Crohns Colitis* 2023;**17**:1689–97. https://doi.org/10.1093/ecco-jcc/jjad067
130. Daien C, Krogulec M, Gineste P, *et al*. Safety and efficacy of the miR-124 upregulator ABX464 (obefazimod, 50 and 100 mg per day) in patients with active rheumatoid arthritis and inadequate response to methotrexate and/or anti-TNFalpha therapy: a placebo-controlled phase II study. *Ann Rheum Dis* 2022;**81**:1076–84. https://doi.org/10.1136/annrheumdis-2022-222228
131. Tanaka Y, Luo Y, O'Shea JJ, *et al*. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* 2022;**18**:133–45. https://doi.org/10.1038/s41584-021-00726-8
132. Rinaldi C, Wood MJA. Antisense oligonucleotides: the next frontier for treatment of neurological disorders. *Nat Rev Neurol* 2018;**14**:9–21. https://doi.org/10.1038/nrneurol.2017.148
133. Dai W, Qiao X, Fang Y, *et al*. Epigenetics-targeted drugs: current paradigms and future challenges. *Signal Transduct Target Ther* 2024;**9**:332. https://doi.org/10.1038/s41392-024-02039-0
134. Vieujean S, Jairath V, Peyrin-Biroulet L, *et al*. Understanding the therapeutic toolkit for inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2025;**22**:371–94. https://doi.org/10.1038/s41575-024-01035-7