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Interplay Between Cellular Metabolism and Epigenetic Reprogramming in the Pathogenesis of Chronic Inflammatory Disorders: A Translational Perspective

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Abstract

Chronic inflammatory diseases (CIDs), such as rheumatoid arthritis (RA), inflammatory bowel disease, systemic lupus erythematosus and psoriasis represents an enormous global health challenge due to their chronic relapsing-remitting course, high morbidity and lack of therapeutic armament. Although classically viewed as effects of immune deregulation, recent observations reveal a more complex pathogenic scenario involving the crosstalk between cellular metabolism and epigenetic remodeling. The metabolic intermediates including acetyl-CoA, α-ketoglutarate, lactate and NAD^+ not only provide energy supply for the cell but also serve as cofactors for and activators of chromatin-modifying enzymes, connecting bioenergetic status with transcriptional regulation. This reciprocal connection forms a self-propagating feedback loop in immune cells to drive pathological phenotypes and sustain chronic inflammation. Recent evidence indicates that effector T cells and pro-inflammatory macrophages are highly dependent on glycolysis, in contrast to regulatory T cells and anti-inflammatory macrophages which mainly utilize oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO). Such different metabolic requirements mold into epigenetic landscapes with the consequences of being involved in DNA methylation, histone modifications and non-coding RNAs that can ultimately direct pro-inflammatory or tolerogenic programs. Reversed epigenetic memory also adds to the persistence and relapse of abnormal disease.

Clinically, metabolic (e.g., glycolysis inhibitors, AMPK inducers) or epigenetic modifiers (e.g., HDAC, DNMT and BET inhibitors) could restore the immune homoeostasis. Dual approaches targeting metabolic and genetic-epigenetic pathways concurrently may have a synergistic impact, but it will be important to address specificity, toxicity, and heterogeneity of the patient population. Future with single cell multi-omics, precision medicine and integrative modeling Technologically sophisticated developments are necessary to translate pre-clinical results into clinic.

In this review, we amalgamate the recent advances in metabolism–epigenetics axis in CIDs, introducing new mechanistic understanding of immune cell reprogramming and describing potential therapeutic strategies as well as knowledge gaps. Insight into this interaction is the basis for novel, mechanism-based therapies directed at achieving prolonged disease control.

Keywords: Cellular Metabolism, Epigenetic Reprogramming, Chronic Inflammatory Disorders (CIDs), Immune Cell Plasticity, Metabolism–Epigenetics Crosstalk, Translational Therapeutics

Introduction

Chronic inflammatory diseases (CIDs), including rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematous, are a global health problem of pandemic proportion in terms of prevalence, morbidity and complexity underlying the pathogenesis.

Despite great strides made in the understanding of their immunological underpinning, currently available treatments are unsatisfactory for many individuals. An increasing body of evidence indicates that the pathogenesis of CIDs is not purely dependent to altered immune signaling, but a dynamic crosstalk between cellular metabolism and epigenetic regulation (1,2,3).

Cell metabolism, previously considered as only the provider of bioenergetic need, is a master regulator of immune cell destiny and activity. Changes in all three of these pathways, glycolysis, oxidative phosphorylation and lipid metabolism, have been demonstrated to impact the activation, differentiation and survival of immune cells within inflamed tissues. Concomitantly, epigenetic reprogramming–by means of DNA methylation, histone marks and non-coding RNAs—serves as a molecular mediator that deciphers environmental stimuli such as metabolic variations into long-term transcriptional programs (4,5).

Most notably, intermediates of metabolism such as acetyl-CoA, α-ketoglutarate and lactate are cofactors or inhibitors of enzymes that modify chromatin directly connecting metabolic flux to epigenetic states. This is a reciprocal relationship, with metabolic hrewiring not only maintaining inflammattory signalling, but imprinting heritable alterations in immune cell behaviour. This reprogramming drives the enduring pathogenic immune reactions that mediate disease chronicity and relapse (6,7).

On a translational level, targeting the interplay between metabolism and epigenetics now represents an emerging therapeutic strategy. New approaches, such as metabolic modulators and epigenetic-targeting compounds, have potential to reinduce immune tolerance and limit tissue injury. Nevertheless, identification of disease-stratifying mechanisms and accomplishment of cell-type specificity need to be refined as do prevention of unspecific effects (8,9).

This review aims at bridging this gap by giving a comprehensive overview of the mechanistic relationship between cellular metabolism and epigenetic reprogramming in chronic inflammatory disorders and highlight its relevance for new therapeutic approaches. By emphasizing the recent progress and pointing out knowledge gaps, we aim to stimulate a more integrated view on CIDs, which can guide new therapeutic strategies (10,11).

1. Overview of Chronic Inflammatory Disorders (CIDs)

CIDs include a diverse array of diseases that share some common features such as sustained immune activation, organ damage and systemic complications. Unlike acute inflammation that is protective and self-limiting, CIDs result from excessive or lost control of such immune responses, which do not resolve, become chronicissuing and relapsing. They are a major public health burden due to increasing occurrence on global scale and enormous burden of treatment cost, disability and diminished quality of life (12,13).

The following representative diseases exemplify the clinical phenotypic spectrum of CIDs:

Rheumatoid arthritis (RA): A classic autoimmune disease characterized by inflammation of the synovium, joint destruction and systemic features.

Inflammatory bowel disease (IBD): Including Crohn's disease and ulcerative colitis, is a chronic intestinal inflammation, dysbiosis, and extraintestinal manifestations.

Systemic lupus erythematosus (SLE): An autoimmune disease of multiple organs characterized by the presence of high amounts of autoantibodies and organ inflammation (14,15).

Psoriasis: A chronic skin disease characterized by derangement of T-cell function and hyperproliferation of keratinocytes.

A common denominator of these diseases is the interplay between genetic factors, environmental challenges and immune dysregulation. There is an emerging picture that metabolic and epigenetic rewiring in immune cells contribute to the maintenance of inflammation in tissue, thereby connecting cellular biology and disease pathogenesis (16).

Table 1. Representative chronic inflammatory disorders, their key features, and immunopathogenic mechanisms (17,18).

Disorder	Primary Target Tissue/Organ	Key Immunological Features	Clinical Manifestations
Rheumatoid Arthritis (RA)	Joints (synovium)	Autoantibody production (RF, anti-CCP), Th17/Treg imbalance	Synovitis, joint erosion, systemic fatigue
Inflammatory Bowel Disease (IBD)	Gastrointestinal tract	Dysregulated mucosal immunity, defective epithelial barrier, altered microbiota	Abdominal pain, diarrhea, weight loss, extraintestinal inflammation
Systemic Lupus Erythematosus (SLE)	Multisystem (kidneys, skin, CNS, joints)	Autoantibodies (ANA, anti-dsDNA), complement activation	Nephritis, rash, arthritis, neurological symptoms
Psoriasis	Skin	Aberrant Th17/IL-23 axis, keratinocyte activation	Plaques, erythema, pruritus, arthritis (in PsA)

2. Cellular Metabolism in Inflammation

Cell metabolism have traditionally been considered simply as an energy and biosynthetic precursor provider. Nevertheless, it is now firmly established that metabolic reprogramming plays a major role in the control of immune cell activation, differentiation and effector functions. Immune cells undergo dramatic metabolic rewiring during inflammation, allowing for rapid adaptation to micro-environmental signals (19).

2.1 T Cell Metabolism

Resting naïve T cells are largely dependent on oxidative phosphorylation (OXPHOS) and FAO for energy to maintain quiescence. In contrast, once activated T cells rely on aerobic glycolysis — the so-called "Warburg effect" for clonal expansion and effector cytokine production. Different T cell subsets have evolved to engage specific metabolic programs:

Th1 and Th17 effector T cells: These rely on glycolysis and glutaminolysis.

Tregs: Dependent on OXPHOS and lipid oxidation, in line with a suppressive and long lived phenotype (21).

2.2 Macrophage Metabolism

Metabolic plasticity in macrophages that reflects their states of polarization:

M1 macrophages (pro-inflammatory): Favour glycolysis, pentose phosphate pathway (PPP), and incomplete TCA cycle. This promotes the production of ROS and pro-inflammatory cytokines.

M2 macrophages (anti-inflammatory): Rely on OXPHOS and FAO to sustain tissue repair and inflammation resolution (22).

2.3 Other Immune Cells

DC: Activation fosters glycolysis to fuel antigen presentation.

B cells: OXPHOS in naive state to glycolysis in antibody-secreting plasma cell.

ILCs: Have metabolic requirements that are subset specific, which tend to resemble those of their T cell counterparts.

Table 2. Distinct metabolic programs in major immune cell subsets (23).

Immune Cell Type	Resting/Quiescent Metabolism	Activated/Inflammatory Metabolism	Functional Outcome
Naïve T cells	OXPHOS, FAO	Aerobic glycolysis, glutaminolysis	Clonal expansion, effector cytokine secretion
Effector T cells (Th1/Th17)	–	Glycolysis, glutaminolysis	Pro-inflammatory cytokine production
Regulatory T cells (Tregs)	OXPHOS, FAO	Maintain OXPHOS, lipid metabolism	Immune suppression, tolerance
M1 Macrophages	–	Glycolysis, PPP, truncated TCA	ROS, NO, TNF-α, IL-1β production
M2 Macrophages	–	OXPHOS, FAO	Tissue repair, wound healing
Dendritic cells	OXPHOS	Glycolysis	Antigen presentation, T cell priming
B cells	OXPHOS	Glycolysis in plasma cells	Antibody secretion

2.4 Implications for Chronic Inflammation

The persistence of inflammatory signals in CIDs is strongly influenced by these metabolic rewiring events. For example, sustained glycolytic metabolism in Th17 cells and M1 macrophages contributes to chronic tissue inflammation, while impaired FAO in Tregs may weaken tolerance mechanisms. Thus, metabolism not only dictates immune cell fate but also amplifies pathogenic pathways in chronic inflammatory disorders (24).

3. Epigenetic Reprogramming in Immune Cells

Epigenetic modifications play a central role in regulating immune cell identity and function without altering the underlying DNA sequence. In chronic inflammatory disorders (CIDs), persistent environmental cues—including cytokines, microbial metabolites, and metabolic intermediates—reshape the epigenetic landscape of immune cells, resulting in long-lasting changes in gene expression that sustain inflammation (25).

3.1 DNA Methylation

DNA methylation typically occurs at cytosine residues in CpG dinucleotides and is associated with gene silencing. In CIDs:

Rheumatoid arthritis (RA): Aberrant methylation in synovial fibroblasts leads to overexpression of pro-inflammatory mediators.

Systemic lupus erythematosus (SLE): Hypomethylation of genes related to immune activation contributes to autoreactive T and B cell activity (26).

3.2 Histone Modifications

Histone tails undergo diverse modifications, such as acetylation and methylation, which regulate chromatin accessibility:

Histone acetylation (e.g., H3K27ac): Promotes transcription of inflammatory genes.

Histone methylation: Can either activate (H3K4me3) or repress (H3K27me3) gene expression depending on the context.

In macrophages, for example, histone acetylation enhances expression of TNF-α and IL-6, perpetuating inflammation (27).

3.3 Non-coding RNAs

Non-coding RNAs—including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs)—serve as post-transcriptional regulators of gene expression:

miR-155: Upregulated in RA and IBD, driving pro-inflammatory cytokine production.

miR-146a: Functions as a negative regulator of NF-κB signaling but is often dysregulated in CIDs.

lncRNAs: Modulate chromatin remodeling and inflammatory gene networks, representing emerging players in epigenetic regulation (28).

Table 3. Epigenetic mechanisms implicated in chronic inflammatory disorders (30).

Epigenetic Mechanism	Molecular Target	Functional Effect on Immune Cells	Example in CIDs
DNA Methylation	CpG sites in promoters	Gene silencing or activation (context-specific)	Hypomethylation of CD11a in SLE T cells
Histone Acetylation	Lysine residues on histone tails	Enhances chromatin accessibility → ↑ transcription	Increased H3K27ac at TNF-α locus in RA synoviocytes
Histone Methylation	H3K4, H3K27, H3K9, etc.	Activates (H3K4me3) or represses (H3K27me3) genes	Altered H3K4me3 in pro-inflammatory macrophages
microRNAs (miRNAs)	mRNA transcripts	Post-transcriptional silencing or activation	Upregulation of miR-155 in RA, IBD
lncRNAs	Chromatin and transcription factors	Scaffold/regulator of chromatin remodeling	lncRNA NEAT1 dysregulated in SLE

3.4 Epigenetic Memory and Chronicity

One of the most important consequences of epigenetic changes is the generation of **"epigenetic memory"**, whereby immune cells retain a pro-inflammatory phenotype even after the initial stimulus is resolved. This mechanism underlies disease persistence, flares, and the limited efficacy of conventional immunosuppressive therapies (31).

4. Interplay Between Metabolism and Epigenetics

The crosstalk between metabolism and epigenetic control has been regarded as bidirectional and dynamic mechanism that contributes to chronic inflammation. Metabolites act as substrates, cofactors or inhibitors of chromatin-modifying enzymes thereby directly connecting cellular bioenergetics to gene expression programs.

Acetyl-CoA, generated by glycolysis and fatty acid metabolism can directly contribute to histone acetylation by donating the required acetyl groups that increase transcription of pro-inflammatory genes. α-Ketoglutarate (α-KG), also a TCA cycle intermediate, serves as a cofactor for DNA and histone demethylases which are dioxygenases and control DNA accessibility. In contrast, succinate and fumarate derived from the TCA cycle can repress these enzymes and promote a pro-inflammatory epigenetic profile (32,33).

In addition, lactate accumulation in inflamed tissues is also used to power metabolic adaption, as well as promoting histone lactylation, a newly discovered modification that increases the expression of genes required for wound healing and tissue remodelling. Another metabolite, NAD^+, controls sirtuin function and links cellular redox status to histone deacetylation and transcriptional regulation (34).

In CIDs, this cross-talk creates a self-reinforcing crosstalk loop: metabolic reprogramming in immune cells induces epigenetic changes that entrench pathogenic transcriptional programs, which sustain the inflammatory metabolism. This is probably the reason

why CIDs often do not resolve after removing the initial trigger and why therapies addressing metabolic and epigenetic axes may be critical (35).

5. Translational and Therapeutic Perspectives

Understanding the interplay between metabolism and epigenetics and its importance in CIDs is expected to create therapeutic opportunities. Classical immunosuppressive drugs hit inflammatory signaling but they cannot establish control on the metabolic and epigenetic reprogramming that leads to disease chronification. New approaches are being developed to address these underlying causes (36).

5.1 Metabolic Modulators

Cellular metabolic modulating agents A number of agents that target cellular metabolism are being repurposed/investigated, for treatment of CIDs:

Metformin: Stimulates AMPK and oxidative metabolism. In addition to enhancing Treg activity, inhibits Th17 responses (36).

2-Deoxyglucose (2-DG): Suppress glycolysis, decreasing the activation of effector T cells and macrophages.

Enhancers of fatty acid oxidation: These molecules attempt to reprogram a stifled Treg and M2 macrophage anti-inflammatory program (37).

5.2 Epigenetic Therapies

There are also new drugs that target epigenetic changes:

HDAC inhibitors: Inhibit the expression of pro-inflammatory cytokines (e.g.in RA models).

DNMT (DNA methyltransferase) inhibitors: Block abnormal methylation and reactivate normal gene expression (38,39).

Bromodomain and extraterminal (BET) inhibitors: Disrupt transcriptional systems directed by acetylated histones.

5.3 Combination Strategies

Given that metabolism and epigenetics are interconnected, these dual-targeting strategies might have a better therapeutic effect. For instance, glycolysis inhibitors in combination with HDAC inhibitors may deplete energy source for effector cells and erase pro-inflammatory epigenetic marks (40).

5.4 Challenges and Considerations

Selectivity: several metabolic and epigenetic enzymes are widely expressed, which may pose concerns about off-target toxicity.

Patient variation: Both genetic and environmental factors can affect response.

Translation gap: Not all the many promising preclinical results have yet been confirmed in large clinical trials (41).

Table 4. Emerging therapeutic strategies targeting metabolism and epigenetics in chronic inflammatory disorders (42).

Therapeutic Strategy	Target Mechanism	Representative Agents	Potential Application in CIDs
Metabolic Modulation	Glycolysis inhibition	2-Deoxyglucose (2-DG)	RA, IBD, Psoriasis
	AMPK activation, FAO enhancement	Metformin, Bezafibrate	RA, SLE
Epigenetic Modulation	Histone deacetylation (HDACi)	Vorinostat, Trichostatin A	RA, SLE
	DNA demethylation	Azacitidine (DNMTi)	SLE
	BET protein inhibition	JQ1, I-BET151	IBD, Psoriasis
Combination Approaches	Dual targeting of glycolysis + epigenetic enzymes	2-DG + HDACi (experimental)	Multiple CIDs (preclinical)

6. Future Directions and Knowledge Gaps

Despite the remarkable progress in deciphering the crosstalk of cellular metabolism and epigenetic reprogramming in CIDs, important lacunae still exist. Challenges must be met before we can translate basic mechanistic knowledge into effective therapies (43).

6.1 Requirement for integrative multi-omics approaches

The majority of studies in this area have concentrated on single metabolic or epigenetic pathways. Nevertheless, comprehensive high-resolution single-cell multi-omics studies that integrate transcriptomes, epigenomes, proteome and metabolome are necessary to comprehensively profile the dynamic changes within immune cell subtypes of CID patients (44).

6.2 Disease-Specific Mechanisms

Though some metabolic–epigenetic interfaces may be common to all, others might be disease- or tissue-specific. For instance, the contribution of lactate-mediated histone lactylation in cells or tissues is not well defined between IBD and RA. Additional comparative studies are warranted to conclude on generalization or selective approaches of the therapeutic strategies (45).

6.3 Translation from the Bench to the Bedside

Several promising agents (eg, glycolysis inhibitors, HDAC inhibitors) have demonstrated anti-tumor activity in preclinical models, but did not lead to clinically applicable treatments for reasons such as toxic effects, limited specificity or inconsistent responses. Addressing this translational gap will require enhanced biomarkers for patient selection and thoughtful trial design (46).

6.4 Precision Medicine and Stratification of Patients

Future therapeutic approaches should embrace personalized medicine, taking into account genetic background, metabolic position, microbiome makeup and epigenetic marks to predict responses (47,48,49).

6.5 Long-Term Safety Concerns

As metabolism and epigenetics are critical to a wide array of physiological processes, manipulation of these pathways bears risk of off-target effects (e.g. impaired tissue repair, immunosuppression or oncogenesis). Long-term evaluations are needed to determine safety profiles (50,51).

Table 5. Key knowledge gaps and future research directions in metabolism–epigenetics interplay in CIDs (52,53,54).

Research Gap	Current Limitation	Future Direction
Integrative multi-omics	Focus on isolated pathways	Single-cell multi-omics integrating metabolome + epigenome
Disease-specific mechanisms	Limited comparative studies	Identify shared vs unique pathways across CIDs
Translation gap (preclinical → clinical)	Poor predictability of animal models	Develop better biomarkers & patient-derived models
Precision medicine	One-size-fits-all therapeutic approaches	Stratify patients using genetic/epigenetic signatures
Safety and toxicity	Off-target metabolic/epigenetic effects	Long-term monitoring, selective drug design

7. Conclusion

Chronic inflammatory diseases (CIDs) are multifaceted interconnections of immune dysregulation, metabolic adaptation and epigenetic add-ons. Accumulating evidence over the last decade has shown that metabolic intermediates are not only utilized for immune cell function, but also function as key regulators of chromatin

structure and transcriptional programs. This reciprocal interaction creates a self-regenerative inflammatory cycle that is implicated in the perpetuation and recurrence of disease.

From a translational point of view, the focus on metabolism and epigenetics, alone or in combination, provide us with exciting therapeutic options. First-line experimental agents include glycolysis inhibitors, AMPK activators and epigenetic modulators (HDAC, DNMT, BET-inhibitors). Nonetheless, specificity of the treatment remains a major issue together with limiting its toxicity and adapting it to the individual patient.

In the future, integrative multi-omics technologies, advanced disease models and precision medicine could accelerate the next wave of therapies. Finally, a greater appreciation of the metabolism–epigenetics axis may translate new paradigms in the management of CIDs from indiscriminate immunosuppression to mechanism-based, patient-centered interventions that restore immune equilibrium and ensure better long-term prognosis.

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