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Epigenetic Rewiring of Innate Immune Memory: Molecular Mechanisms and Implications for Chronic Inflammatory Diseases

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ABSTRACT
Innate immune memory, also known as trained immunity, is characterized by long-term epigenetic reprogramming of innate immune cells, leading to enhanced or altered responses upon secondary stimulation. This phenomenon has significant implications for chronic inflammatory diseases such as atherosclerosis, rheumatoid arthritis, and inflammatory bowel disease. This review explores the molecular mechanisms underlying the epigenetic rewiring of innate immune memory, focusing on histone modifications, DNA methylation, and non-coding RNA regulation. Additionally, we discuss the potential of targeting epigenetic pathways for therapeutic interventions in chronic inflammation.

1. INTRODUCTION

Chronic inflammatory diseases are driven by persistent activation of the immune system, often independent of persistent infections. Traditionally, adaptive immunity was believed to be the primary driver of immunological memory; however, emerging evidence suggests that innate immune cells, including monocytes and macrophages, can also develop memory-like properties through epigenetic modifications. This phenomenon, termed trained immunity, allows innate immune cells to exhibit heightened responses upon secondary encounters with pathogens or inflammatory stimuli. Understanding the epigenetic basis of innate immune memory provides new avenues for therapeutic intervention in chronic inflammatory disorders.

2. Molecular Mechanisms of Epigenetic Rewiring in Innate Immunity

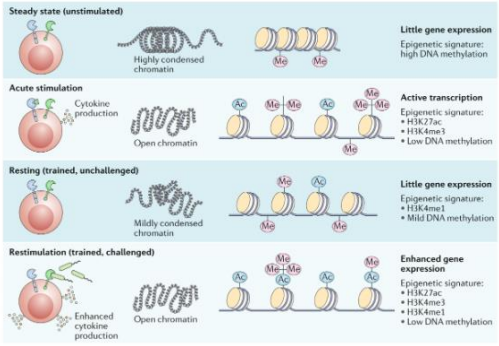

Fig. Molecular Mechanisms of Epigenetic Rewiring

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2.1 Histone Modifications and Chromatin Accessibility

Histone modifications play a central role in modulating chromatin accessibility and gene expression during innate immune training. Key histone marks associated with trained immunity include:

- **H3K4me3 (Histone 3 Lysine 4 Trimethylation):** Enhances transcription at pro-inflammatory gene loci.
- **H3K27ac (Histone 3 Lysine 27 Acetylation):** Promotes active enhancer states in trained monocytes.
- **H3K9me3 (Histone 3 Lysine 9 Trimethylation):** Associated with repression of anti-inflammatory pathways.

Table 1: Key Histone Modifications in Trained Immunity

Histone Mark	Function	Effect on Immunity
H3K4me3	Active promoter mark	Enhances pro-inflammatory responses
H3K27ac	Active enhancer mark	Increases gene accessibility
H3K9me3	Repressive mark	Suppresses anti-inflammatory pathways

2.2 DNA Methylation and Its Role in Innate Immune Memory

DNA methylation at CpG islands regulates gene expression by recruiting methyl-binding proteins that repress transcription. Recent studies indicate that:

- **Hypomethylation at pro-inflammatory gene promoters** leads to increased expression of cytokines like IL-6 and TNF-α.
- **Hypermethylation at anti-inflammatory loci** contributes to prolonged inflammation in chronic diseases.

2.3 Non-Coding RNAs in Epigenetic Regulation

Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) regulate immune gene expression by modifying chromatin structure and mRNA stability. For example:

- **miR-155** enhances trained immunity by stabilizing mRNAs encoding pro-inflammatory cytokines.
- **lncRNA-THRIL** modulates TNF-α expression and contributes to chronic inflammation.

3. Epigenetic Rewiring in Chronic Inflammatory Diseases

3.1 Atherosclerosis

Monocytes exposed to hyperlipidemia develop a pro-inflammatory phenotype due to epigenetic modifications. Histone acetylation at IL-1β and TNF-α loci sustains inflammation, leading to plaque formation and cardiovascular disease progression.

3.2 Rheumatoid Arthritis (RA)

Synovial macrophages in RA patients exhibit altered chromatin accessibility and DNA methylation patterns, resulting in excessive production of inflammatory mediators such as IL-1β and IFN-γ.

3.3 Inflammatory Bowel Disease (IBD)

Trained immunity contributes to sustained inflammation in IBD by reprogramming intestinal macrophages. Epigenetic changes in IL-23R and TNF-α pathways exacerbate intestinal inflammation.

Table 2: Epigenetic Alterations in Chronic Inflammatory Diseases

Disease	Key Epigenetic Changes	Impact on Inflammation
Atherosclerosis	H3K4me3 at IL-1β, TNF-α loci	Promotes plaque formation
Rheumatoid Arthritis	DNA hypomethylation at inflammatory genes	Enhances cytokine production
Inflammatory Bowel Disease	Altered miRNA profiles (miR-146a, miR-155)	Sustains gut inflammation

4. Therapeutic Implications of Targeting Epigenetic Mechanisms

4.1 Histone Deacetylase (HDAC) Inhibitors

HDAC inhibitors such as Trichostatin A and Vorinostat have shown promise in reducing inflammatory cytokine production by reversing histone hyperacetylation.

4.2 DNA Methylation Modulators

Targeting DNA methylation with agents like 5-Azacytidine may help restore immune homeostasis by suppressing aberrant pro-inflammatory gene expression.

4.3 RNA-Based Therapeutics

Modulating miRNA expression using synthetic mimics or inhibitors (e.g., miR-146a mimics) holds potential in dampening trained immune responses in chronic inflammation.

5. CONCLUSION

Epigenetic rewiring of innate immune memory plays a pivotal role in shaping immune responses in chronic inflammatory diseases. Understanding histone modifications, DNA methylation, and non-coding RNA regulation in trained immunity can lead to novel therapeutic strategies targeting inflammation at the epigenetic level. Future research should focus on developing precise epigenetic modulators to mitigate chronic inflammation without compromising host defense.

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