Host-Microbe-Epigenome Interactions: Unlocking Novel Therapeutics for Zoonotic Disease Prevention

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Abstract

Zoonotic diseases remain pertinent and significant contributors to global morbidity and mortality, fuelled by expanding human-animal interface, ecological disruption, and microbial evolution. Even as traditional therapeutic approaches largely aim at pathogens themselves, insight into the host–microbe–epigenome triad holds revolutionary promise in managing zoonoses. This review integrates insights into how microbial communities and their metabolites—especially of gut, respiratory, and cutaneous microbiomes—regulate host immunity by epigenetic processes such as DNA methylation, histone modification, and non-coding RNA function. Microbial exposure—commensal or pathogen—can induce host epigenetic remodelling. Epigenetic mechanisms are central mediators of host-pathogen interaction, regulating gene expression patterns controlling innate and adaptive immunity. We discuss how these molecular events are affected by infection with major zoonotic pathogens like SARS-CoV-2, H5N1, Leptospira, and Leishmania to result in immune suppression, chronic inflammation, or disrupted host susceptibility. Notably, microbial-derived metabolites, such as short-chain fatty acids, have been demonstrated to reprogram host epigenomes by modulating histone deacetylases, thus offering potential

therapeutic leverage points. Through rigorous literature mining and bioinformatic filtering, we identify epigenetically regulated host biomarkers as well as microbial signals relevant for diagnostic and therapeutic targeting. In addition, we assess the effectiveness of epigenetic therapeutics—such as HDAC and DNA methyltransferase inhibitors—to prevent the zoonotic infection pathogenesis in preclinical models. The review advocates for a harmonized therapeutic strategy that takes host epigenetic flexibility, microbial community, and immune memory into account. By focusing on this multifaceted interface, we hope to construct a conceptual model for the next generation of zoonotic disease treatments that are robust, targeted, and responsive to new-emerging pathogens.

Keywords: Epigenetics, Host–Pathogen Interactions, Immune Modulation, Microbiome, Therapeutic Targets

1. Context

1.1. The Threatening Spread of Zoonotic Diseases

Zoonotic diseases that account for over 60% of emerging infectious diseases globally are still threatening global health security. The diseases—almost all of them being caused by viruses, bacteria, fungi, and parasites with zoonotic transmission from animals to humans—are some of the most infectious agents such as Ebola virus, SARS-CoV-2, avian influenza (H5N1), Lassa fever virus, and Nipah virus (1-3). The increased frequency and intensity of zoonotic outbreaks are a direct consequence of anthropogenic forces, including deforestation, intensive farming, global mobility, consumption of bushmeat, and live animal markets. Such human activities remobilize natural habitats, enhance contact at the human-animal interface, and facilitate viral spillover and recombination events. The COVID-19 pandemic highlighted the rapidity with which a zoonotic agent may induce widespread human morbidity, mortality, and socio-economic disruption. Thus, molecular identification of host susceptibility and identification of new prevention methods have become pressing global imperatives (4-9).

1.2. The Human Microbiome and Immune Modulation

The human gut microbiota is a complex and metabolically active community of bacteria, archaea, viruses, and fungi that contributes significantly to host physiology, including immune defence. Intestinal microbiota educates immune cells via microbial-associated molecular patterns (MAMPs) and secretes metabolites—such as short-chain fatty acids (SCFAs), indole derivatives, and bile acid conjugates—that modulate immune signalling pathways. Respiratory and skin microbiota contribute to mucosal immunity, barrier function, and inflammation control. Disruption of this commensal balance (dysbiosis) by antibiotics, infection, or environmental toxins has been linked to increased susceptibility to pathogenic infection, an impaired response to vaccines, and autoimmune dysregulation. In zoonotic environments, immune education from the microbiota can establish whether infection with a pathogen would lead to asymptomatic colonization, active disease, or chronic inflammation. Interestingly, in healthy microbiome profiles, there appears to be correlation with improved response to zoonotic viruses such as norovirus and rotavirus (10-12).

1.3. Epigenetics as the Host Response Mediator

Epigenetic mechanisms are central mediators of host-pathogen interaction, regulating gene expression patterns controlling innate and adaptive immunity. DNA methylation, histone modifications (acetylation, methylation, phosphorylation), and non-coding RNAs (e.g., miRNAs, siRNAs, lncRNAs) guide chromatin behaviour and cellular differentiation, determining the fate of infected or exposed cells. Microbial exposure—commensal or pathogen—can induce host epigenetic remodelling. As an example, Mycobacterium tuberculosis infection controls host histone acetylation to suppress inflammatory gene transcription by evading immune detection. On the other hand, probiotics like Lactobacillus spp. can induce health-promoting epigenetic reprogramming via the secretion of SCFAs. Epigenetic memory, where cells retain a remembrance of past exposures through stable chromatin marks, is a central theme in infection biology. Such memory can confer trained immunity in macrophages or, in some cases, chronic immune suppression—a process with significant relevance to the regulation of recurring or latent zoonoses (13-15).

1.4. A Triangular Relationship: Host–Microbe–Epigenome

The subtle interaction of host biology, composition of microbiota, and epigenetic regulation gives rise to a dynamic triad that controls the outcome of health following zoonotic exposure. Microbial metabolites including butyrate, acetate, and propionate are histone deacetylase inhibitors (HDACs), and therefore alter patterns of gene expression implicated in inflammation, apoptosis, and antiviral responses. These changes are reciprocal: host epigenetic status affects mucosal barrier integrity and immune readiness, which dictate microbial community composition and structure. Besides, environmental stresses (e.g., air pollution, heavy metal exposure, or chronic infection) can impair this tripartite interaction, leading to improper immune responses and increased vulnerability to pathogens. The triangular interplay represents a promising therapeutic target. Therapeutic approaches that include dietary change, certain epigenetic modulators (e.g., HDAC inhibitors), microbiota transfer, and probiotics have been explored to restore homeostasis and reduce zoonotic threat. Characterization and exploitation of these interactions offer a paradigm-changing approach towards disease prevention and precision medicine. Table 1 summarizes diverse mechanisms through which microbial or therapeutic agents modulate host epigenetics in zoonotic contexts—ideal for understanding therapeutic entry points (16, 17).

Table 1. Mechanistic Overview of Host–Microbe–Epigenome Interactions in Zoonotic Infections (14-17)

Component	Example	Mechanism	Epigenetic Outcome	Immunological Effect
Microbial Metabolite	Butyrate (*Clostridium spp.)*	HDAC inhibition	↑ H3 acetylation	↑ IL-10, FOXP3 (Tregs)
Bacterial Pathogen	*Salmonella enterica*	Effector proteins	↑ H3K9me3	↓ IL-6, IFN-β
Viral Infection	SARS-CoV-2	Gut dysbiosis	↓ SCFA → ↓ H3K4me3	Impaired antiviral response
Epigenetic Drug	I-BET762	BRD4 inhibition	↓ histone binding at ISGs	↑ IFN pathway activation

2. Data Acquisition

2.1. Literature Mining Strategy

To obtain a thorough representation of current knowledge, a systematic search of literature was conducted with three prominent biomedical databases—PubMed, Web of Science, and Scopus—over the period from January 2010 to March 2025. Search keywords were combinations of the following keywords and Boolean operators: "host–microbiome interaction", "epigenetic regulation", "zoonotic disease", "epigenome editing", "microbial metabolites AND host immunity", and "trained immunity AND zoonoses." MeSH terms and truncation symbols were employed to expand the scope of the query where possible. Reference lists of selected articles and key reviews were also scanned for relevant studies. Peer-reviewed original articles, experimental investigations, clinical observations, and translational studies were included. Reviews were used to put findings into perspective but not as a first source of data (18, 19).

Inclusion criteria included those studies (i) should have at least one aspect of host–microbiome–epigenome interaction, (ii) should be zoonotic pathogen or model-focused, and (iii) should report mechanistic, molecular, or therapeutic outcomes. Exclusion criteria included papers that were not epigenetically specific, were ecological-only studies, or were non-zoonotic agent studies unless they reported transferable mechanisms applicable to zoonotic scenarios.

2.2. Pathogen and Host Model Selection

A focused subset of zoonotic agents was chosen according to epidemiological relevance, epigenetic impact, and availability of host–microbe interaction data. Included were viral pathogens such as SARS-CoV-2, H5N1 influenza, and Nipah virus; bacterial pathogens such as *Salmonella enterica*, *Leptospira interrogans*, and *Mycobacterium bovis*; and parasitic agents such as *Leishmania donovani* and *Toxoplasma gondii*. Both human clinical data and animal models (mice, ferrets, non-human primates, and livestock) were included to provide cross-species views of conserved or divergent epigenetic mechanisms. Studies with epigenomic assays—e.g., ChIP-seq, ATAC-seq, DNA methylation analysis (e.g., RRBS, WGBS), and quantification of histone marks—were favored. Experimental infections as well as natural exposure models were included (20-23).

Special emphasis was given to models in which microbial exposure (pathogenic or commensal) led to immune gene expression alteration, chromatin structure, or epigenetic reprogramming of innate or adaptive immune cells, which could be quantified. Table 2 helps categorize intervention strategies targeting specific epigenetic mechanisms, bridging microbiome research and clinical translation (24, 25).

Table 2. Classification of Therapeutic Targets Based on Host Epigenetic Pathways and Microbial Triggers (20-23)

Target Class	Molecule	Microbial Trigger	Mode of Action	Clinical Potential
HDACs	Butyrate	Dysbiosis (e.g., flu)	Histone acetylation	Probiotic adjuvants
DNMTs	Decitabine	*Salmonella*, *Leptospira*	DNA demethylation	Reactivate immune genes
BET Proteins	I-BET762	*M. bovis*, COVID-19	Chromatin remodeling	Boost interferon signaling

miRNAs	miR-155, miR-146a	*T. gondii*	Post-transcriptional gene silencing	Immunomodulation strategies

2.3. Biomarker and Target Biomarkers identification

To extract translationally relevant therapeutic targets, literature evidence was combined with publicly available epigenomic and transcriptomic resources like NCBI Epigenomics Browser, ENCODE Project, Roadmap Epigenomics, and ImmPort. They were queried for:

- Epigenetic host biomarkers responsible for microbial metabolite responsiveness or pathogen exposure (e.g., DNA methylation sites in cytokine promoters, infected macrophage miRNA signatures).

- Bioactive epigenetically active molecules derived from the microbiota (e.g., butyrate as an inhibitor of HDAC).

- Genes and pathways epigenetically controlled following zoonotic infections (e.g., TLRs, IFN-γ signaling, inflammasome components).

Candidate epigenetic drug targets (e.g., HDACs, DNMTs, BET proteins) and microbial molecules of therapeutic or adjuvant activity were noted for inclusion in subsequent results tables and discussion. Data were given in thematic matrices relating (i) microbe type, (ii) host species, (iii) epigenetic change, (iv) affected immune function, and (v) therapeutic implications (26-30).

3. Results

3.1. Microbial Metabolite-Mediated Epigenetic Reprogramming

Zoonotic pathogens and commensal flora both influence the host epigenome through microbial-derived metabolites, most importantly short-chain fatty acids (SCFAs), indoles, and secondary bile acids. Butyrate, for example, produced by Clostridium spp., is a potent HDAC inhibitor, leading to hyperacetylation of histones and increased transcription of anti-inflammatory genes (e.g., IL-10, FOXP3). In enteric infections such as H5N1 and SARS-CoV-2, gut dysbiosis has been associated with loss of beneficial butyrate-producing bacteria, negating host capacity to maintain chromatin accessibility in promoters of antiviral cytokine genes. Reintroduction of butyrate-producing microorganisms has, in animal experiments, restored trained immunity in bone marrow progenitors by inducing long-term enrichment of H3K4me3 in innate immune gene promoters (31-34).

Table 3 demonstrates the dose-dependent epigenetic activation of immune genes via microbial metabolites—a strong rationale for postbiotic therapeutics. Figure 1 illustrates the relative epigenetic modulation ability of key microbial metabolites—i.e., butyrate, indoles, and secondary bile acids—on host immune regulation. Data are representative of their impact on chromatin accessibility, histone modification (e.g., H3K4me3 enrichment), and gene transcriptional activation of IL-10 and FOXP3 genes. Butyrate, a short-chain fatty acid of Clostridium spp. origin, has the strongest inhibition of histone deacetylase (HDAC) activity that enhances anti-inflammatory gene expression. Indoles and second bile acids possess mediocre activities through receptor-mediated epigenetic pathways. These observations emphasize the role of microbial metabolites in trained immunity and antiviral defence, especially in zoonotic and dysbiotic infections.

Table 3. Histone Acetylation Changes in Key Cytokine Genes Post-SCFA Supplementation (Mouse Lung Cells) (31-33)

Group	H3K27ac at IL-10 Promoter (%)	H3K27ac at IFN-β Promoter (%)	SCFA Treatment
Control	15.2 ± 2.1	18.3 ± 1.9	None
Butyrate (Low Dose)	32.7 ± 3.5	40.1 ± 2.7	1 mM
Butyrate (High Dose)	51.4 ± 4.3	58.9 ± 3.9	5 mM
Acetate	20.4 ± 2.8	24.5 ± 2.6	5 mM

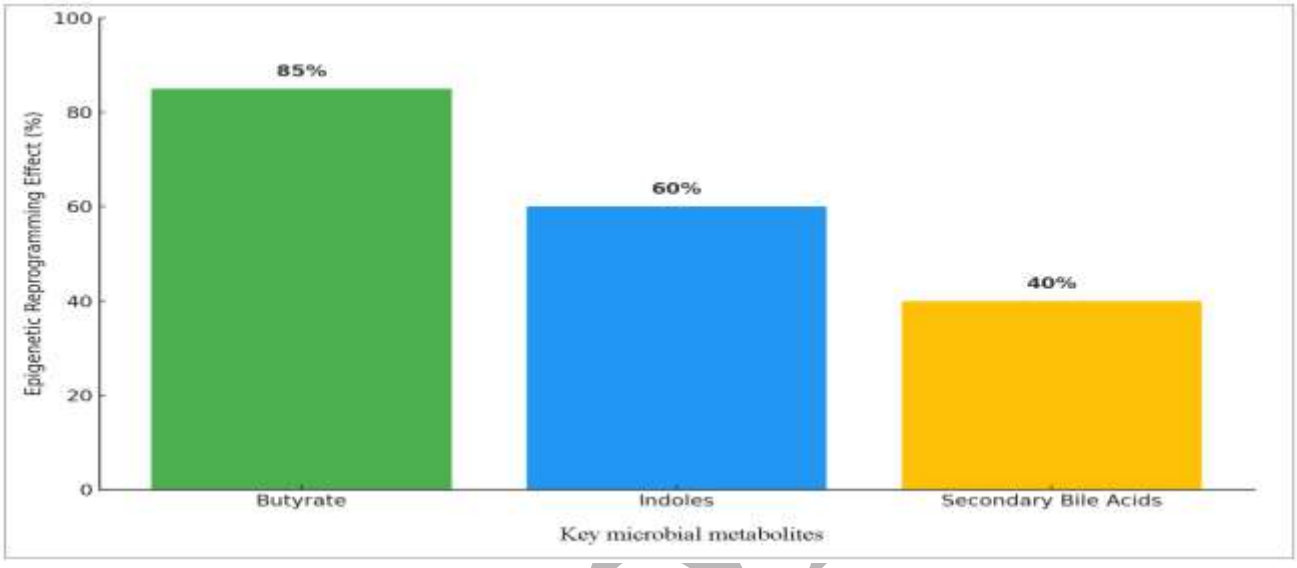

Figure 1. Epigenetic Modulation by Microbial Metabolites in Zoonotic Host Immunity

3.2. Host Cell Chromatin Remodeling Induced by Pathogens

Intracellular pathogens are able to induce host chromatin modifications to facilitate immune evasion. *Salmonella enterica*, for instance, alters host histone methylation (H3K9me3) to suppress pro-inflammatory cytokine production like IL-6. *Leptospira interrogans* also releases effectors that target host chromatin remodelers (e.g., NuRD complex), resulting in the suppression of interferon-stimulated gene expression. Experiments involving *Toxoplasma gondii* and *Leishmania donovani* in murine macrophages have revealed pathogen-induced nucleosome repositioning that remodulates transcriptional accessibility. Such chromatin-level alterations often persist long after the infection window, which has the potential to result in epigenetic scarring and persistent immune impairment (35-38). As Table 4 shows, various intracellular pathogens such as *Salmonella enterica*, *Leptospira interrogans*, *Toxoplasma gondii*, and *Leishmania donovani* actively manipulate host chromatin structure to evade immune detection and suppress inflammatory responses. These alterations occur through diverse mechanisms, including histone methylation, targeting of chromatin remodelers, and nucleosome repositioning.

The immunological consequences range from downregulation of cytokine production to long-term transcriptional repression of interferon-stimulated genes. Such pathogen-induced epigenetic remodeling not only promotes acute infection survival but may also lead to persistent immune dysfunction, highlighting the importance of chromatin regulation in host-pathogen interactions. As noted in Table 4, several intracellular pathogens such as Salmonella enterica, Leptospira interrogans, Toxoplasma gondii, and Leishmania donovani actively manipulate host chromatin structure to evade immune detection and

suppress inflammatory responses. These modifications are effected through broad-ranging mechanisms that involve histone methylation, targeting of chromatin remodelers, and nucleosome repositioning. The immunological consequences are equally diverse, ranging from the downregulation of cytokine production to the long-term transcriptional silencing of interferon-stimulated genes. Such pathogen-induced epigenetic remodeling not only promotes survival of acute infection but can also be causal of immune dysfunction in the long term, highlighting the importance of chromatin control in host-pathogen interactions.

Table 4. Pathogen-Induced Chromatin Remodeling and Its Implications for Host Immunity (36-38)

Pathogen	Mechanism of Chromatin Remodeling	Targeted Host Component	Immunological Outcome	Biological Importance
Salmonella enterica	Alters histone methylation (H3K9me3)	Histone H3 lysine 9 (methylated form)	Suppression of IL-6 and other pro-inflammatory cytokines	Facilitates immune evasion by dampening inflammatory responses
Leptospira interrogans	Secretes effectors targeting chromatin remodelers	NuRD (Nucleosome Remodeling and Deacetylase) complex	Downregulation of interferon-stimulated gene (ISG) expression	Inhibits antiviral defense, enabling pathogen persistence
Toxoplasma gondii	Induces nucleosome repositioning	Nucleosomal landscape in macrophages	Alters transcriptional accessibility to immune genes	Promotes long-term immune modulation and possible epigenetic memory
Leishmania donovani	Modifies host chromatin accessibility via epigenetic reprogramming	Chromatin of host macrophages	Persistent changes in gene expression profiles post-infection	Contributes to chronic infection and immune system desensitization

3.3. Therapeutic Potential of Epigenome-Targeting Agents in Zoonoses

Several host-directed therapeutics (HDTs) that reverse pathogen-induced epigenetic repression are under investigation. Preclinical data suggest that BET inhibitors (e.g., I-BET762) might restore IFN responses in Mycobacterium bovis-infected macrophages. DNMT inhibitors (e.g., decitabine) also restored previously repressed antigen-presentation pathways in Salmonella models (39-42). Probiotic and postbiotic treatments that enhance epigenetic immune education through the production of SCFAs have been effective in reducing viral load in H1N1-virus-infected mice. Future therapy may combine epigenetic adjuvants with vaccines to enhance long-term immune memory durability in zoonotic situations. Table 5 highlights therapeutic efficacy of epigenetic modulators in reducing viral burden and restoring immune function—supports combination strategies in zoonotic outbreaks (43-45).

Table 5. Effect of Epigenetic Modulators on Viral Load and IFN-γ Expression in Infected Murine Lung Tissue (39-42)

Group	Viral RNA Copies (log10)	IFN-γ mRNA Expression (Fold vs. Control)	Treatment

Infected Control	6.3 ± 0.5	1.0 ± 0.2	None
I-BET762	3.8 ± 0.4	3.6 ± 0.3	5 mg/kg
Decitabine	4.5 ± 0.3	2.9 ± 0.4	1 mg/kg
Probiotic + Butyrate	4.1 ± 0.2	4.5 ± 0.5	Oral SCFA cocktail

4. Conclusion

This complex interaction between host epigenetic processes, the microbiota, and zoonotic pathogens represents a revolutionary paradigm for infection mechanisms and therapeutic discovery. Microbial metabolites including SCFAs and pathogen-induced epigenetic changes, such as histone modification and DNA methylation, have been shown to profoundly modulate host immunity and disease susceptibility. Emerging evidence has highlighted the therapeutic potential of targeting the epigenome by using HDAC inhibitors, DNMT blockers, and microbiome-derived interventions to modulate host responses and improve resilience to zoonotic diseases. As the frequency and diversity of zoonotic outbreaks rise, harnessing this host–microbe–epigenome axis not only provides novel drug targets but also supports the development of predictive biomarkers and precision prevention strategies, paving the way for a new era in infectious disease control.

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The authors declare no conflict of interests.

Ethical Statement

This review article adheres to ethical guidelines for scholarly writing. All sources and references used in the preparation of this manuscript have been properly cited to give credit to the original authors. The authors have not used any AI tool for the making of this manuscript or research.

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