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CHROMATIN AND IMMUNITY: THE ROLE OF INTRACELLULAR PATHOGENS IN MODULATING IMMUNE CELLS

CROMATINA E IMUNIDADE: O PAPEL DOS PATÓGENOS INTRACELULARES NA MODULAÇÃO DAS CÉLULAS IMUNES

CROMATINA E INMUNIDAD: EL PAPEL DE LOS PATÓGENOS INTRACELULARES EN LA MODULACIÓN DE LAS CÉLULAS INMUNITARIAS

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ABSTRACT

This chapter addresses the molecular mechanisms of chromatin remodeling and epigenetic modifications induced by obligate intracellular pathogens, focusing on their effects on the morphology, functionality, and adaptive immune response of lymphocytes. It explores how these pathogens modulate the activation, survival, and function of immune cells, subverting physiological processes to ensure their persistence within the host. The chapter discusses chromatin structure, key epigenetic modifications regulating gene expression, and the temporal dynamics of these changes during infection. Emerging technologies such as ATAC-seq, ChIP-seq, and single-cell sequencing are highlighted for their ability to provide detailed analysis of these processes. Additionally, the interplay between cellular metabolism and epigenetics in immune modulation, as well as the impact of host genetic variability on clinical response heterogeneity, are emphasized. Finally, veterinary pathogens including *Rickettsia*, *Anaplasma*, and *Ehrlichia* are presented as examples illustrating sophisticated epigenetic subversion strategies. Integrating knowledge of these mechanisms lays the groundwork for developing innovative, personalized therapeutic approaches to combat infections by obligate intracellular pathogens.

Keywords: Adaptive immune response. Chromatin remodeling. Epigenetic modifications. Obligate intracellular pathogens.

RESUMO

Este capítulo aborda os mecanismos moleculares da remodelação da cromatina e as modificações epigenéticas induzidas por patógenos intracelulares obrigatórios, com foco em

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seus efeitos sobre a morfologia, funcionalidade e resposta imune adaptativa dos linfócitos. Explora como esses patógenos modulam a ativação, sobrevivência e função das células imunes, subvertendo processos fisiológicos para garantir sua persistência no hospedeiro. São discutidos os aspectos estruturais da cromatina, as principais modificações epigenéticas que regulam a expressão gênica e a dinâmica temporal dessas alterações durante a infecção. O capítulo destaca tecnologias emergentes, como ATAC-seq, ChIP-seq e sequenciamento de célula única, que possibilitam análise detalhada desses processos. Além disso, enfatiza a inter-relação entre metabolismo celular e epigenética na modulação da resposta imune, bem como o impacto da variabilidade genética do hospedeiro na heterogeneidade das respostas clínicas. Por fim, exemplifica com patógenos veterinários como *Rickettsia*, *Anaplasma* e *Ehrlichia*, ilustrando estratégias epigenéticas sofisticadas de subversão imunológica. O conhecimento integrado desses mecanismos fornece base para o desenvolvimento de abordagens terapêuticas personalizadas e inovadoras no enfrentamento das infecções por patógenos intracelulares obrigatórios.

Palavras-chave: Modificações epigenéticas. Patógenos intracelulares obrigatórios. Remodelação da cromatina. Resposta imune adaptativa.

RESUMEN

Este capítulo aborda los mecanismos moleculares de la remodelación de la cromatina y las modificaciones epigenéticas inducidas por patógenos intracelulares obligados, centrándose em sus efectos sobre la morfología, funcionalidad y respuesta inmunitaria adaptativa de los linfocitos. Explora cómo estos patógenos modulan la activación, supervivencia y función de las células inmunitarias, subvirtiendo procesos fisiológicos para asegurar su persistencia en el huésped. Se discuten los aspectos estructurales de la cromatina, las principales modificaciones epigenéticas que regulan la expresión génica y la dinámica temporal de estas alteraciones durante la infección. El capítulo destaca las tecnologías emergentes, como ATAC-seq, ChIP-seq y la secuenciación unicelular, que permiten analizar en detalle estos procesos. También hace hincapié en la interrelación entre el metabolismo celular y la epigenética en la modulación de la respuesta inmunitaria, así como en el impacto de la variabilidad genética del huésped en la heterogeneidad de las respuestas clínicas. Por último, ejemplifica con patógenos veterinarios como Rickettsia, Anaplasma y Ehrlichia, ilustrando sofisticadas estrategias epigenéticas de subversión inmunitaria. El conocimiento integrado de estos mecanismos proporciona una base para el desarrollo de enfoques terapéuticos personalizados e innovadores para hacer frente a las infecciones por patógenos intracelulares obligados.

Palabras clave: Modificaciones epigenéticas. Patógenos intracelulares obligatorios. Remodelación de la cromatina. Respuesta inmunitaria adaptativa.

1 INTRODUCTION

This chapter presents the molecular mechanisms that govern chromatin remodeling and epigenetic modifications triggered by obligate intracellular pathogens, with emphasis on their effects on the morphology, functionality, and adaptive immune response of lymphocytes. It is discussed how these infectious agents modulate the activation, survival and function of immune cells, subverting physiological processes to ensure their persistence in the host.

The structural aspects of chromatin and the main epigenetic modifications that regulate gene expression are addressed, as well as the temporal dynamics of these changes throughout the course of infection. The chapter also examines emerging technologies that allow the analysis of such modifications at high resolution, the complex interactions between lymphocytes and the immune microenvironment, and the role of cellular metabolism in the epigenetic modulation of the immune response. Additionally, the influence of host genetic variability on the regulation of epigenetic remodeling and on the heterogeneity of clinical responses is highlighted. Finally, recent advances in the study of veterinary pathogens, including *Rickettsia*, *Anaplasma,* and *Ehrlichia*, are presented, which illustrate sophisticated epigenetic strategies of subversion and provide relevant comparative models.

This chapter aims to provide an integrated and updated view of the epigenetic processes that regulate adaptive immunity during intracellular infections, contributing to the development of innovative and personalized therapeutic approaches in the fight against these diseases.

2 IMPACT OF BINDING INTRACELLULAR PATHOGENS ON LYMPHOCYTE FUNCTIONALITY AND MODULATION OF ADAPTIVE IMMUNE RESPONSE

Infections caused by obligate intracellular pathogens have a significant impact on the functionality of lymphocytes, central cells in the orchestration of the adaptive immune response (Elemam et al., 2021; Papet et al., 2022). These infectious agents possess the ability to alter the morphofunctionality of host cells, which results in complex and multifaceted changes in the immune response (Vom Werth et al., 2022). In particular, intracellular bacterial infections compromise essential lymphocyte mechanisms such as activation, survival, and effector function, decreasing the immune system's ability to eliminate the pathogen and favoring the chronic persistence of infection (Thakur et al., 2019).

The activation of T and B lymphocytes, which is critical for an effective adaptive immune response, depends directly on the interaction with antigen-presenting cells (APCs), such as macrophages and dendritic cells (Elemam et al., 2021; Thakur et al., 2019).

However, in infections with obligate intracellular pathogens, this interaction is often compromised, leading to important dysfunctions (Cassady-Cain et al., 2018; Thakur et al., 2019). In fact, evidence indicates that such infections impair the expression of essential costimulatory molecules such as CD80 and CD86, resulting in deficient activation of T lymphocytes (Damoiseaux et al., 1998; Moore et al., 2019; Lim, et al., 2012). Specifically, Ehrlichia-infected monocytes exhibit functional changes that compromise antigenic presentation and subsequent activation of lymphocytes (McBride & Walker, 2011; Rikihisa, 2022). In addition, the bacterium interferes with the intracellular signaling pathways of the T cell receptor (TCR), impairing antigenic recognition and activation of the adaptive immune response (McBride & Walker, 2011; Yager et al., 2005).

In addition to these changes, these pathogens modulate intracellular signaling pathways to suppress T and B lymphocyte responses, downregulating the expression of surface proteins, such as gp36 and gp40, involved in cell adhesion and immune evasion (McBride & Walker, 2011). In this context, the activation of the NF-κB pathway, crucial for signal transduction in T lymphocytes, is often inhibited, compromising the ability of these cells to respond appropriately to pathogenic stimuli (Anirudhan et al., 2020; Rahman & McFadden, 2011; Vitiello et al., 2012).

Another relevant mechanism to be considered is the modulation of cell apoptosis. Apoptosis, essential for the elimination of infected cells and for the maintenance of immune homeostasis, can be suppressed in infected host cells, favoring bacterial persistence. During *Ehrlichia canis* infections, resistance to apoptosis is observed in host cells, mediated by signaling pathways such as PI3K/Akt, largely activated by intracellular pathogens to prevent programmed cell death (Lina et al., 2016; Liu et al., 2024; Zhang et al., 2014; Patterson et al., 2022). Such an imbalance between survival and cell death contributes to the chronicity of the infection and to the impairment of inflammatory resolution (Behar & Briken, 2019; Carrero & Unanue, 2006; Labbé & Saleh, 2008; Tolomeo et al., 2003). In addition, pathogens such as *Rickettsia* and *Anaplasma* also induce resistance to apoptosis in immune cells, disrupting the control of cell proliferation and perpetuating the inflammatory state (Alberdi et al., 2016; Ayllón et al., 2013; Behar & Briken, 2019; Clifton et al., 1998; Joshi et al., 2003).

In addition, the influence of these pathogens on the populations of regulatory T lymphocytes (Tregs) is significant, since these lymphocytes modulate the immune response to avoid excessive damage to the host (Belkaid, 2007; Sabbagh et al., 2018). Several intracellular pathogens promote the expansion of Tregs, which in turn suppress the activation of effector T lymphocytes and the production of antibodies by B cells, contributing to immune evasion (Benson et al., 2012; Moyé et al., 2018; Oparaugo et al., 2023; Punkosdy et al.,

2011; So et al., 2023). In experimental models with *Rickettsia*, Tregs-mediated suppression significantly reduces the efficacy of the effector immune response (Fang et al., 2009). This induction of Tregs is attributed to the release of immunosuppressive cytokines, such as interleukin-10 and transforming growth factor beta (TGF-β), which establish a permissive microenvironment for pathogenic survival (Jameel et al., 2024; Komai et al., 2018).

Finally, recent studies show that infections by intracellular bacteria, such as *Chlamydia* and *Mycobacterium*, promote epigenetic modifications in eukaryotic cells, including cells of the immune system, altering their functional capacity in the face of antigenic challenges (Del Rosario et al., 2022; Kylaniemi et al., 2009; Sengupta et al., 2023; Stein & Thompson, 2023; Thomas et al., 2024). In the specific case of *Ehrlichia*, the pathogen directly modifies the nuclear structure and chromatin organization of host cells, affecting gene regulation and, consequently, cellular functionality (Bierne & Cossart., 2012; Green et al., 2020; Kibler et al., 2018). These bacteria secrete effector proteins, such as tandem repeating proteins (TRPs) — TRP47, TRP120, TRP32, and Ank200 — that act as nucleomodulins, capable of remodeling chromatin and modifying host gene expression (Byerly et al., 2021; Farris et al., 2016; Klema et al., 2018).

3 CHROMATINIC REMODELING

Chromatin consists of a macromolecular complex present in the nucleus of eukaryotic cells, formed by DNA associated with proteins, mainly histones, which are essential for the structural organization of the genome (Luger et al., 2012; Tremethick, 2007). This organization occurs in repetitive units called nucleosomes, composed of a protein octamer - formed by the histones H2A, H2B, H3 and H4 - around which the DNA, containing approximately 146 base pairs, is coiled. Thus, chromatin-mediated genome compaction is critical for the efficient storage of genetic material in the cell nucleus (Luger et al., 2012).

In addition to its structural function, chromatin plays a crucial role in regulating vital cellular processes, including gene transcription and DNA damage repair (Kouzarides, 2007). For functional purposes, chromatin can be classified into two main forms: euchromatin, which is less compacted and associated with transcriptionally active regions, and heterochromatin, which has greater compaction and is related to silenced or inactive genomic regions (Tamaru, 2010). It is important to highlight that these forms are dynamic and capable of reciprocally converting in response to intracellular and environmental stimuli (Grunstein et al., 1995; Tamaru, 2010).

In this context, chromatin remodeling refers to biochemical processes that alter the structure of chromatin, modifying the accessibility of DNA and influencing its ability to be

transcribed, replicated, or repaired (Sinha et al., 2017). In mammals, several ATP-dependent remodelling complexes promote the displacement, removal, or replacement of nucleosomes, modulating DNA compaction and accessibility (Centore et al., 2020; Hota & Bruneau, 2016; Becker & Workman, 2013; Feng et al., 2021). Thus, chromatin remodeling is essential for the maintenance of cellular homeostasis and regulates gene expression, especially in responses to external challenges such as infections (Morrison, 2020; Hamon & Cossart, 2008; Rennoll-Bankert & Dumler, 2012).

In addition, intracellular pathogens, such as bacteria and viruses, have developed sophisticated strategies to manipulate host chromatin remodeling, subverting gene expression involved in immune defense (Dong et al., 2024; Hamon & Cossart, 2008; Rennoll-Bankert & Dumler, 2012; Zhong et al., 2013). Through these alterations, pathogens can silence genes essential for the immune response or activate pathways that favor their survival and evasion (Zhong et al., 2013). Classic examples include pathogens such as *Helicobacter pylori*, *Shigella flexneri,* and *Bacteroides vulgatus*, which modulate the expression of inflammatory cytokines and other key molecules of immune signaling (Capparelli & Ianelli, 2022; Gomes et al., 2023; Hamon & Cossart, 2008; Pero et al., 2011).

An extensively studied model of this process is chromatin remodeling associated with gene activation of the immune response during M*. tuberculosis infection*. Detection of the pathogen by the host induces activation of the interferon-gamma-mediated signaling pathway (IFN-γ), which in turn activates the JAK/STAT1 cascade, modulating the transcription of genes crucial for defense, including the transcriptional regulator CIITA (class II transactivator). This regulator controls the expression of molecules of the major histocompatibility complex class II (MHC-II) (Kincaid & Ernst, 2003; Ting et al., 1999; Tur et al., 2021). Therefore, chromatin activation and remodeling in the promoter region of CIITA are fundamental for antigenic presentation and the effectiveness of the adaptive immune response (Włodarczyk et al., 2020; Sengupta et al., 2023; Madden et al., 2023).

4 EPIGENETIC ALTERATIONS AND THEIR IMPLICATIONS FOR CHROMATIN REMODELING

In addition to the remodelling complexes, chromatin is the target of several epigenetic modifications that directly influence its structure and, consequently, the regulation of gene expression (Li et al., 2002; Raleigh, 2021). Among these alterations, DNA methylation and post-translational histone modifications such as acetylation, methylation, phosphorylation, and ubiquitination stand out, which play a crucial role in modulating DNA accessibility and transcriptional activity (Bannister & Kouzarides, 2011; Moore, Le & Fan, 2013)

In the context of bacterial infections, several pathogens have the ability to manipulate these epigenetic marks, silencing genes involved in the immune response or activating pathways that favor their intracellular survival (Fol et al., 2020; Hamon et al., 2011). This emerging mechanism of immune evasion offers new perspectives for the development of innovative therapeutic approaches. Specifically, DNA methylation, characterized by the covalent addition of methyl groups to cytokines (5-methylcytosine), is classically associated with transcriptional silencing (Breiling & Lyko, 2015; Moore, Le & Fan, 2013). This modification is catalyzed by DNA methyltransferase enzymes (DNMTs), which act preferentially in promoter regions, recruiting repressor proteins of the MBD (methyl-CpG-binding domain) family, responsible for inhibiting gene transcription (Philips, 2019). Although this modification is widely studied in cancer and autoimmune diseases (Li et al., 2021), DNA methylation also plays a key role in chronic bacterial infections. For example, in persistent *H. pylori* infections, hypermethylation of immune-related genes contributes to immune evasion and maintenance of chronic gastric inflammation (Denic et al., 2020; Barbachowska & Arimondo, 2023; Qin et al., 2021)

Histones, in turn, undergo multiple post-translational modifications that regulate both chromatin conformation and gene activity (Bannister & Kouzarides, 2011). A classic example of manipulation of these modifications is observed in infections by *Listeria monocytogenes*, whose exotoxin Listeriolysin O (LLO) influences histone acetylation and phosphorylation, resulting in epigenetic alterations that favor the transcription of inflammatory genes and facilitate the subversion of the immune response (Bierne & Hamon, 2020; Eldridge & Hamon, 2021; Hamon & Cossart, 2011; Hamon et al., 2007). Among these modifications, histone acetylation, especially lysine residues in histone tails, neutralizes positive charges, reducing histone-DNA interaction and promoting an open chromatin, permissive to transcription (Grunstein, 1997; Sterner & Berger, 2000). In the scenario of bacterial infections, the manipulation of this modification represents a critical strategy of pathogens: *Shigella flexneri*, for example, secretes the OspF protein, which inhibits histone acetylation, repressing the transcription of crucial genes, such as interleukin-8, a key factor in the inflammatory response (Schator et al., 2021; Zurawski et al., 2006; Ashida & Sasakawa, 2014; Hamon & Cossart, 2008). On the other hand, in *H. pylori* infections, histone acetylation is required for the activation of pro-inflammatory genes, such as IL-6 via NF-κB, suggesting that this modification may exert pro- or anti-inflammatory contextual effects (Ding et al., 2010).

Another important epigenetic mechanism is the phosphorylation of histones, particularly H3 into serine 10 (H3S10), associated with transcriptional activation and recruitment of transcription factors (Komar & Juszczynski, 2020; Sawicka & Seiser, 2012).

Pathogens such as *S. flexneri* manipulate this modification to suppress the activation of inflammatory genes, favoring immune evasion and persistence of infection (Harouz et al., 2015; Fischer, 2020). In addition, specific methylations in histones play a critical role in the regulation of gene expression: H3K9 methylation is associated with gene silencing and condensed chromatin formation, while H3K4 methylation is related to transcriptional activation and uncompressed chromatin (Greer & Shi, 2012; Padeken et al., 2022; Wang et al., 2009). It is relevant to highlight that some pathogens have enzymes capable of mimicking or antagonizing the epigenetic modifications of the host. For example, *M. tuberculosis* recruits histone deacetylase complexes (HDACs) to remove acetyl groups from histones by suppressing the expression of major histocompatibility complex class II genes, which are essential for T cell activation (Jagannath et al., 2022; Poirier & Av-Gay, 2012). Similarly, *Pseudomonas aeruginosa* secretes the exotoxin ExoT, which has ADP-ribosyltransferase activity and modifies cellular proteins, including histones, by altering chromatin structure and suppressing inflammatory responses, favoring its persistence in chronic lung infections (Davies, 2022; Maresso et al., 2007; Jouault et al., 2022).

5 TEMPORAL DYNAMICS OF CHROMATIN REMODELING AND EPIGENETIC MODIFICATIONS DURING INFECTION

The lymphocyte-mediated adaptive immune response is a highly dynamic process, characterized by temporal and specific modifications in chromatin architecture and epigenetic marks that regulate cell activation, proliferation, and differentiation at different phases of infection by obligate intracellular pathogens (Schwartz et al., 2022).

In the early stages of infection, an increase in histone acetylation and DNA hypomethylation in promoter regions of pro-inflammatory and effector genes is observed, which promotes rapid activation of the transcription machinery and mobilization of the immune response (Wang et al., 2018). This chromatin opening facilitates access to transcription factors and regulatory proteins that drive gene expression needed to contain the pathogen.

As infection progresses, there is an increase in epigenetic marks associated with gene silencing, such as repressive histone methylation (e.g., H3K9me3) and DNA hypermethylation, promoting transcriptional repression and resolution of inflammation. This process is essential to prevent tissue damage and contributes to the restoration of immune homeostasis after the acute phase of the response.

However, obligate intracellular pathogens exploit this temporal plasticity of epigenetic modifications to establish states of immune tolerance and evasion of the immune response, thus favoring the persistence and chronicity of the infection (Zhang & Li, 2021). This

phenomenon may manifest through the prolonged maintenance of repressive epigenetic marks in key genes of the immune response or the induction of epigenetic patterns that limit lymphocyte activation.

6 EXPERIMENTAL MODELS AND EMERGING TECHNOLOGIES IN THE STUDY OF CHROMATIN REMODELING AND EPIGENETIC MODIFICATIONS

The advance in the understanding of the molecular mechanisms of chromatin remodeling and epigenetic modifications induced by obligate intracellular pathogens has been largely driven by the development and application of high-resolution experimental technologies, which enable specific and genomic-scale analyses.

One of the most impactful techniques in this context is the ATAC-seq (*Assay for Transposase-Accessible Chromatin using sequencing*), which allows the global mapping of chromatin accessibility. The technique uses a transposase to insert adapters into open and accessible DNA regions, enabling subsequent amplification and sequencing of these regions. In this way, it is possible to identify promoters, *enhancers*, and other regulatory regions that are activated or repressed during infection (Buenrostro et al., 2013; Corces et al., 2017).

Another crucial methodology is ChIP-seq (*Chromatin Immunoprecipitation sequencing*), which combines immunoprecipitation with antibodies specific to post-translational histone modifications, such as H3K27ac or H3K9me3, with large-scale sequencing. This approach allows for detailed mapping of epigenetic profiles along the genome, revealing how pathogens alter the epigenetic landscape of host cells to modulate gene expression (Park, 2004; Barski et al., 2007).

The development of single-cell sequencing (*single-cell RNA-seq and single-cell ATAC-seq*) has revolutionized the understanding of cellular heterogeneity during infections, especially in complex populations such as lymphocytes, whose cell subtypes may present different epigenetic responses. These techniques allow simultaneous analysis of gene expression and chromatin status in individual cells, identifying functional subpopulations and their temporal dynamics during infection (Stuart & Satija, 2019; Satpathy et al., 2019).

In addition, CRISPR/Cas9 gene editing has been shown to be fundamental to investigate the causal function of chromatin-remodeling proteins and epigenetic enzymes in infected cell models. The ability to delete or modify specific genes makes it possible to unravel the precise roles of these molecules in modulating the immune response and evasion mechanisms used by pathogens (Doudna & Charpentier, 2014; Shalem et al., 2014).

Complementing these techniques, proteomic approaches and methods that assess protein-DNA interaction, such as mass spectrometry and Hi-C technology, provide valuable

evidence on the spatial reorganization of the genome and the molecular interaction networks that influence chromatin remodeling during infection (Rao et al., 2014; Méndez et al., 2020).

The experimental models employed range from in vitro systems, using infected immune cell lines that allow strict control of experimental conditions, to animal models that simulate the complexity of the immune system and the tissue microenvironment. The combination of these approaches has enabled the identification of specific epigenetic pathways modulated during infection, contributing to the discovery of new therapeutic targets for the control of diseases caused by obligate intracellular pathogens (Li et al., 2021; Mukherjee et al., 2022).

7 METABOLIC AND IMMUNOMETABOLIC ASPECTS IN EPIGENETIC REMODELING DURING INFECTIONS

Cellular metabolism, especially in immune cells, is closely related to epigenetic regulation and chromatin remodeling, directly influencing the effectiveness of the immune response during infections by obligate intracellular pathogens (O'Neill et al., 2016; Pearce & Pearce, 2013). Lymphocytes in different functional states have distinct metabolic profiles, which impact the availability of essential metabolites for epigenetic modifications. During activation, for example, T lymphocytes transition from a predominantly oxidative metabolism to an accelerated glycolytic metabolism, known as the Warburg effect, increasing the production of intermediates such as acetyl-CoA. The latter serves as a substrate for histone acetylation, promoting chromatin opening and pro-inflammatory gene expression (Buck et al., 2017; Chang et al., 2013).

In addition, metabolites such as α-ketoglutarate and S-adenosylmethionine act as critical cofactors for enzymes that promote DNA and histone methylation, thereby modulating epigenetic patterns (Carey et al., 2015; Lu & Thompson, 2012). On the other hand, intracellular pathogens can induce metabolic reprogramming in host cells, affecting the availability of these epigenetic metabolites and contributing to the suppression of the immune response. Studies have shown that agents such as *M. tuberculosis* and *L. monocytogenes* promote metabolic alterations that limit lymphocyte activation and defense-related gene expression (Shi et al., 2020; Zhang et al., 2014).

In addition, immunometabolic signaling is associated with the induction and maintenance of Tregs, whose expansion is frequently observed in infections by these pathogens. Metabolic pathways that favor fatty acid oxidation and mitochondrial respiration support the regulatory phenotype, facilitating epigenetic remodeling that maintains the immunosuppressive state (Michalek et al., 2011; Angelin et al., 2017). Thus, the

interrelationship between cellular metabolism and epigenetics constitutes a crucial axis in the modulation of the adaptive immune response and represents a strategy potentially exploited by pathogens to subvert the host's defense.

8 HOST GENETIC VARIABILITY AND ITS INFLUENCE ON EPIGENETIC REMODELING AND IMMUNE RESPONSE TO INTRACELLULAR PATHOGENS

Despite advances in the understanding of the molecular mechanisms of chromatin remodeling and epigenetic modifications induced by intracellular pathogens, the clinical heterogeneity observed among individuals infected by similar agents highlights the importance of host genetic variability as a critical determinant of the adaptive immune response. Studies in human populations have shown that genetic polymorphisms modulate the epigenetic plasticity and functional capacity of immune cells, influencing disease severity, infection chronicity, and the effectiveness of the immune response (Brodin & Davis, 2017; Quach & Quintana-Murci, 2017).

In particular, polymorphisms in genes encoding proteins involved in immune signaling, chromatin remodeling, and epigenetic enzymes—such as DNMTs and HDACs—alter the ability of immune cells to modify chromatin in response to infectious stimuli. This genetic variation reflects interindividual differences in resistance or susceptibility to infections (Dawson & Kouzarides, 2012; You & Jones, 2012). In addition, genetic variations in pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), modulate initial immune system activation and subsequent signaling that leads to epigenetic remodeling, directly affecting the activation and functional response of T and B lymphocytes (Kawai & Akira, 2010; Sallusto et al., 2010). Population studies, especially those that analyze responses to infections by *M. tuberculosis* and *C. trachomatis*, have identified associations between specific genetic variants, epigenetic patterns, and differentiated clinical outcomes. This robust evidence indicates that the interaction between genetics and epigenetics shapes the trajectory of infection and the adaptive immune response (Li et al., 2021; Nédélec et al., 2016).

Thus, the integrated understanding of host genetic variability and epigenetic remodeling represents a crucial step towards the development of personalized and effective therapeutic strategies in the management of infections by intracellular pathogens.

9 CHROMATIN REMODELING AND EPIGENETIC MODIFICATIONS IN VETERINARY PATHOGEN INFECTIONS: *RICKETTSIAE*, *ANAPLASMA* AND *EHRLICHIA*

Knowledge about the mechanisms of chromatin remodeling and epigenetic changes induced by intracellular pathogens has been mostly focused on pathogens of human importance. However, pathogens of veterinary relevance, such as bacteria of the genera *Rickettsia*, *Anaplasma,* and *Ehrlichia*, also demonstrate sophisticated strategies to manipulate host chromatin, modulating the immune response and favoring its intracellular survival (Diop et al., 2018; Fol et al., 2020; Garcia-Garcia et al., 2009; Lina et al., 2016a; Londoño et al., 2023; Niller & Minarovits, 2024). *Rickettsiae* are obligate intracellular pathogens that, upon invading the host, activate several cell signaling pathways, including the NF-κB and MAPK cascades, known to promote epigenetic modifications in chromatin (Sahni & Rydkina, 2009; Fol et al., 2020). During *R. rickettsii infection*, an increase in histone phosphorylation, especially H3S10 and H2AX, modifications related to the activation of inflammatory genes, and defense mechanisms is observed (Fol et al., 2020). In addition, *R. conorii* can alter the acetylation and methylation profiles of H3 histones, promoting the downregulation or upregulation of immune genes, which facilitates bacterial persistence in the host organism (Abeykoon et al., 2014; Ribet & Cossart, 2010).

In turn, *A. phagocytophilum* has a significant ability to modify the host's chromatin through epigenetic alterations that impact the activation of immune genes. This bacterium influences signaling pathways such as NF-κB, ERK, and p38 MAPK, which play an important role in histone modifications (Choi et al., 2005; Dumler et al., 2020; Rikihisa, 2011). There is evidence that *A. phagocytophilum* induces changes in DNA methylation, culminating in the silencing of genes crucial for immune defense (Garcia-Garcia et al., 2009; Sinclair et al., 2015). In the case of *Ehrlichiae*, including *E. chaffeensis* and *E. ewingii*, studies reveal that these bacteria reprogram immune cells through sophisticated epigenetic mechanisms. The secretion of effector proteins, such as TRP47, enables direct interaction with specific histones and the modulation of signaling pathways, such as the activation of the NF-κB complex, which regulates the production of inflammatory cytokines (Zhu et al., 2009; Lin & Rikihisa, 2004). For example, the TRP120 protein inhibits the activation of NF-κB, reducing the production of cytokines such as TNF-α and IL-6, contributing to the evasion of the immune response and the persistence of chronic infection (Lina et al., 2016b).

Recent advances in the characterization of bacterial nucleomodulins - proteins capable of translocating to the nucleus of the host cell and directly altering chromatin organization and gene expression - expand the understanding of the epigenetic subversion promoted by these pathogens (Bui et al., 2023; Hanford et al., 2021). These interactions represent a sophisticated coevolutionary mechanism that confers adaptive advantages to

pathogens, especially in immunologically challenging environments, such as persistent infections in domestic and wild animals.

10 CONCLUSION AND FUTURE PROSPECTS

Chromatin remodeling and epigenetic modifications emerge as central mechanisms in the regulation of the adaptive immune response during infections by obligate intracellular pathogens. These microorganisms, through sophisticated strategies, manipulate the immune microenvironment, intracellular signaling pathways, cellular metabolism, and even the epigenome of host cells to ensure their survival and persistence. The ability to alter the activation, proliferation, and function of lymphocytes, as well as induce the expansion of regulatory populations and modulate apoptosis, highlights the complexity of the host-pathogen interaction. Advances in experimental technologies, such as ATAC-seq, ChIP-seq, single-cell sequencing, and CRISPR/Cas9 gene editing, have been instrumental in unraveling the nuances of these processes, providing opportunities for the identification of new therapeutic targets. In addition, the interconnection between cellular metabolism and epigenetic remodeling reinforces the importance of multidisciplinary approaches to understand pathogenic immunomodulation.

Host genetic variability and associated epigenetic diversity are determinant factors of the clinical heterogeneity observed in infections, indicating that personalized and precision medicine strategies will be essential for the effective management of these diseases.
Finally, although much of the current knowledge derives from studies in human pathogens, veterinary pathogens, such as *Rickettsia*, *Anaplasma,* and *Ehrlichia*, offer valuable models to deepen the understanding of epigenetic mechanisms and chromatin remodeling in diverse infectious contexts.

Future prospects include the development of targeted epigenetic therapies capable of reversing the modulation patterns imposed by pathogens, as well as the integration of genomic, epigenomic, and metabolic data to create more effective interventions. The challenge lies in translating these molecular advances into clinical and veterinary applications that can improve the prevention, diagnosis, and treatment of infections caused by obligate intracellular pathogens.

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