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The therapeutic potential of epigenetic manipulation during infectious diseases

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ABSTRACT

Epigenetic modifications are increasingly recognized as playing an important role in the pathogenesis of infectious diseases. They represent a critical mechanism regulating transcriptional profiles in the immune system that contributes to the cell-type and stimulus specificity of the transcriptional response. Recent data highlight how epigenetic changes impact macrophage functional responses and polarization, influencing the innate immune system through macrophage tolerance and training. In this review we will explore how post-translational modifications of histone tails influence immune function to specific infectious diseases. We will describe how these may influence outcome, highlighting examples derived from responses to acute bacterial pathogens, models of sepsis, maintenance of viral latency and HIV infection. We will discuss how emerging classes of pharmacological agents, developed for use in oncology and other settings, have been applied to models of infectious diseases and their potential to modulate key aspects of the immune response to bacterial infection and HIV therapy.

1. Transcriptional responses in immune cells

Host defense against infectious pathogens requires a coordinated immune response. Traditionally innate immunity has been viewed as generic and rapid, as lacking immunological memory and occurring with similar magnitude on rechallenge while adaptive immunity is more specific but requires time to mature. Innate immunity is mediated by pattern recognition receptors (PRR, such as Toll-like receptors (TLR), nucleotide-binding oligomerization domain protein like receptors (NLR) and retinoic acid inducible gene 1 like receptors (RLR), that recognize pathogen associated microbial patterns (PAMPs) and mediate an inducible response to micro-organisms (Yoneyama & Fujita, 2007; Chen, Shaw, Kim, & Nuñez, 2009). PRR and the resulting cytokine signals stimulate the production of transcription factors (TFs) that regulate signal transduction and effector responses. Functional specialization is reflected by subsets of monocytes (Schmidl et al., 2014) and different macrophage activation phenotypes (Mosser & Edwards, 2008).

Regulation of the inducible transcriptional program to pathogens includes post-transcriptional control (Medzhitov & Horng, 2009). Transcription of immune genes involves the interaction of promoter regions with distant enhancers that are brought into close spatial alignment through the looping out of interlinking DNA (Smale, 2010). These distant enhancers are particularly important as binding sites for tissue-specific TFs (Lee, Kim, Spilianakis, Fields, & Flavell, 2006). Several DNA-binding proteins act synergistically to integrate the activation of

Abbreviations: AMPK, Adenosine monophosphate activated protein kinase; ART, Antiretroviral therapies; BCG, Bacille Calmette–Guerin; BET, Bromodomain and extra terminal domain family of proteins; cagPAI, Cytotoxin-associated gene A pathogenicity island; C/EBPα, CCAAT/enhancer binding protein-α; Chip-seq, Chromatin immunoprecipitation and sequencing; EZH2, Enhancer of Zeste 2; H3, Histone H3; H3K4me1, Histone 3 lysine 4 monomethylation; H3K4me3, Histone 3 lysine 4 trimethylation; H3K23, Histone lysine 23; H3K27ac, Histone 3 lysine 27 acetylation; H3K9meSe10phosK14ac, Histone 3 lysine 9 methylation, serine 10 phosphorylation and lysine 14 acetylation; HKMT, Histone lysine methyltransferase inhibitors; H3S10, Histone 3 serine 10; H3T3, Histone 3 threonine 3; HDAC, Histone deacetylase; HDACi, Histone deacytelase inhibitor; HAT, Histone acetyl transferase; HIF-1α, Hypoxia-inducible factor; HSP70, Heat shock protein 70; HSPC, Hematopoietic stem cells; IFN, Interferon; IL-10, Interleukin 10; IL-12, Interleukin 12; IL-4, Interleukin 4; IRAK, Interleukin receptor-associated kinase; JMJD, Jumonji domain; LPS, Lipopolysaccharide; TLR, Toll-like receptor; miRNA, microRNA; mTOR, Mammalian target of rapamycin; MBD2, Methyl-CpG binding domain protein 2; NAD, Nicotinamide adenine dinucleotide; NF-κB, Nuclear factor-κB; NK, Natural killer cells; NLR, Nucleotide-binding oligomerization domain protein like receptors; NO, Nitric oxide; PAMPs, Pathogen associated microbial patterns; PRR, Pattern recognition receptor; PTMs, Histone post-translational modifications; RLR, Retinoic acid inducible gene 1 like receptors; RomA, Regulator of methylation A; ROR, Retinoic acid receptor-related orphan receptor; ROS, Reactive oxygen species; SAHA, Suberoylanilide hydroxamic; SET, Suvar3–9, enhancer-of-zeste, trithorax; SIRT, Silent mating type information regulator; TF, Transcription factor; Tfh, Follicular T helper cells; TGF-β, Transforming growth factor beta; TNF, Tumor necrosis factor; Treg, Regulatory T-cells; TSA, Trichostatin A.

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multiple signal transduction pathways and the generation of several distinct TFs (Smale, 2010). The resulting complex of DNA-binding proteins will ensure the acquisition of the chromatin remodeling factors, transcription co-activators, general TFs and RNA polymerase II to activate gene transcription. This results in a relative stimulus and cell specific response. However, a growing body of literature suggests that the configuration of the chromatin structure of immune genes and their regulatory elements is particularly important in determining the specificity of the immune response (Smale, Tarkhovsky, & Natoli, 2014). These chromatin changes are themselves directed in part by the influences of lineage and cell-type specific TFs during cell development, as exemplified by the macrophage responses to the developmental regulator PU-1 (Natoli, Ghisletti, & Barozzi, 2011). These cell-type specific influences then interact with environmental influences to regulate gene transcription in response to infection.

T-cell receptors and immunoglobulin are much more diverse than PRR (Robins et al., 2009; Rothenberg, 2014). The development of specific subsets, aids host defense (Luckheeram, Zhou, Verma, & Xia, 2012) and is regulated by specific TFs e.g. T-bet for T helper (Th) 1 (Lugo-Villarino, Maldonado-Lopez, Possemato, Penaranda, & Glimcher, 2003) and the retinoic acid receptor-related orphan receptor (ROR) γT and RORαT for Th17 (Yang et al., 2008). B-cells can also be separated into functional subsets with distinct transcriptional programs regulating their development (Allman & Pillai, 2008). Other lymphocyte subsets function as having features more typical of innate immune cells e.g. γδT-cells requiring the TF SOX13 for their development (Melichar et al., 2007). Unique TF profiles also define subsets of NK cells (Fu et al., 2014).

A key characteristic of both innate and adaptive effector functions is that functional subsets demonstrate significant plasticity, allowing a more flexible response to pathogens. Regulatory T-cells (Treg) can become Th17, while other conditions allow them to develop into follicular T helper cells (Tfh) (Xu, Kitani, Fuss, & Strober, 2007; Tsuji et al., 2009). Th17 can become Th1 cells when exposed to IL-12 and Th2 cells in the presence of IL-4 (Bending et al., 2009; Lee et al., 2009).

2. Epigenetic regulation of transcription

Epigenetics is defined as a " stably heritable phenotype resulting from changes in a chromosome without changes in the DNA sequence" (Berger, Kouzarides, Shiekhattar, & Shilatifard, 2009). The term epigenetic is, however, increasingly taken to include transient chromatin modifications as long as they result in altered gene transcription (Natoli, 2010). Epigenetic changes play a pivotal role in the adaptation of the transcriptional response (Jenuwein & Allis, 2001). Mechanisms include DNA methylation, histone post-translational modifications (PTMs), long non-coding RNA and microRNA.

Histone PTMs have been the subject of particularly intensive investigation and we will focus on these in this review since these dynamic changes allow modulation of the immune response to infection, even though these are not necessarily inheritable.

Although these modifications may be transient they are more sustained than the transient protein PTMs observed with signaling molecules and thus allow a mechanism for extending the response period to external stimuli (Ivashkiv, 2013). Histone octamers composed of pairs of histone proteins H2A, H2B, H3 and H4 form nucleosomes (Olins & Olins, 2003). Histone PTMs refer to the chemical alteration predominantly of the N-terminal tail of the histones including, but not limited to, acetylation, methylation, phosphorylation, and ubiquitination. These chemical modifications control access of proteins to the underlying DNA or the terminal tail of the histones, and therefore regulate gene transcription (Shahbazian & Grunstein, 2007). The effect on gene transcription of a given PTM can vary, for example methylation of lysine or arginine residues can enhance or inhibit transcription depending on the residue modified and the degree of methylation (Kouzarides, 2007). These histone PTMs are regulated by families of enzymes which have the potential to be therapeutically targeted; histone acetyl transferases (HATs) and histone deacetylases (HDACs) regulate acetylation while lysine or arginine methyltransferases, lysine demethylases, arginine deaminases and arginine demethylases regulate methylation status (Kouzarides, 2007). The concept of the epigenetic landscape has been introduced to reflect the overall influence of DNA methylation status, histone PTMs and proteins pre-bound to promoter and enhancer regions on the accessibility for binding of classic signaling TFs like NF-κB (Ivashkiv, 2013). This mechanism allows gene transcription to respond to the environment, including stimuli from infection (Jenuwein & Allis, 2001) (summarized in Fig. 1). The histone response is therefore a dynamic sensor of the cell's environment. As such epigenetic manipulation makes for an attractive therapeutic target as it allows for a reversible modification in host gene expression.

3. Innate immunity

Many pathogens colonize the host prior to establishing invasive disease, as illustrated by extracellular bacteria (Kadioglu et al., 2008) but similar principles apply for fungi and parasites. The interactions between the innate immune system and the pathogen are a key factor in determining susceptibility to disease and likelihood of clinical infection (Dockrell, Whyte, & Mitchell, 2012). This is clearly dependent on how effective the transcriptional response of innate immune cells is, particularly macrophages as orchestrators of the innate immune response. These early responses are also important for intracellular pathogens such as viruses and bacteria.

3.1. Macrophage activation

Macrophages represent the cornerstone of the innate immune response in tissues (Twigg, 2004; Aberdein, Cole, Bewley, Marriott, & Dockrell, 2013). Resident macrophages, originating from a fetal origin are supplemented by monocyte-derived macrophages recruited to sites of inflammation (Shi & Pamer, 2011). Macrophages have been described as either "classically" activated macrophages (M1 phenotype), that are particularly important for the immune response to intracellular bacteria, and generate increased levels of reactive oxygen species (ROS), nitric oxide (NO) (Dalton et al., 1993), or as "alternatively" activated macrophages (M2 phenotype) that play key roles in wound healing but also immunity to helminths and other parasites (Anthony et al., 2006) (Mosser & Edwards, 2008). In reality every stimulus results in a slightly different transcriptional profile (Murray et al., 2014) and activation states are highly plastic (Daigneault, Preston, Marriott, Whyte, & Dockrell, 2010). Given the different impact on disease processes modulation of the activation-associated transcriptional profile represents a potential therapeutic approach that can promote resolution of inflammation and tissue repair or increase pathogen clearance.

3.2. Epigenetic modification and macrophage differentiation

The differentiation processes driving monocytes to become macrophages or dendritic cells have been extensively studied (Saeed et al., 2014) and comprehensive review of the subject can be found (Álvarez-Errico, Vento-Tormo, Sieweke, & Ballestar, 2014). Myeloid differentiation is characterized by DNA hypomethylation, although it is dynamically regulated (Bocker et al., 2011). It also involves changes in histone PTMs and HDAC7, which represses macrophage specific genes, is repressed by the lineage specific TF CCAAT/enhancer binding protein-α (C/EBPα) that acts in concert with the PU-1 TF to promote macrophage differentiation (Barneda-Zahonero et al., 2013). Recently, mass spectrometry approaches have been utilized to identify histone PTMs occurring during the differentiation process from monocyte to either dendritic cell or macrophage. The results demonstrated that the macrophage differentiation process is associated with the combinatorial modification lysine 9 methylation, serine 10 phosphorylation and lysine