Chapter 2
Microbial Manipulation Host Dark Matter

Samantha Barichievy, Loretta Magagula, Youtaro Shibayama and Musa M. Mhlanga

Abstract In 2010, Francis Collins, director of the NIH, referenced the transcribed yet untranslated component of the human genome as 'dark matter', a term often used by astrophysicists to describe the vast quantities of invisible hypothetical matter known to make up the majority of our universe. Since then, geneticists have set out to shed light on this matter with remarkable success, in an array of biological contexts ranging from cancer to developmental biology. In recent years, rapid advances have been made towards uncovering the functional biological roles of long noncoding RNAs (lncRNAs), which have been estimated to represent 70–90 % of mammalian genomic dark matter. It has become increasingly evident that the primary function of our noncoding genome is to regulate the coding genome. This makes genomic dark matter an attractive evolutionary target for pathogens, who need to alter the cellular host environment in order to promote their survival and propagation. In this review, we focus on the constituents of the mammalian genomic dark matter that are manipulated by viral and microbial pathogens. We also dive deeper into the involvement of ncRNAs, including enhancer RNAs (eRNAs), in the innate immune response against intracellular pathogens. This commentary further highlights how dark and abstruse our noncoding genome still is, particularly in the context of infection biology.

S. Barichievy (✉) · L. Magagula · Y. Shibayama · M.M. Mhlanga (✉)
Gene Expression and Biophysics Group, CSIR Synthetic Biology ERA, Brummeria, Pretoria, South Africa
e-mail: samantha.barichievy@astrazeneca.com

M.M. Mhlanga
e-mail: musa@mhlangalab.org

S. Barichievy
Discovery Sciences, AstraZeneca, Gothenburg, Sweden

M.M. Mhlanga
Gene Expression and Biophysics Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

L. Magagula · Y. Shibayama · M.M. Mhlanga
Division of Chemical, Systems and Synthetic Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

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2.1 Introduction

The English term ‘orchestrate’ is a verb that means ‘to arrange or direct the elements of a situation to produce a desired effect, especially surreptitiously’. The last part of the definition is intriguing, as it suggests the act of orchestration is clandestine or covert, perhaps even ‘hidden’. It follows then that while the conductor of an orchestra follows a score to guide all of the elements comprising a musical performance to a unified act, the piece is covertly directed according to the personal wishes of the conductor. In truth, conductors make adjustments all of which may not seem obvious to the orchestra members themselves. The ability to furtively direct the elements of a situation to produce a desired effect is also a hallmark of successful pathogenic infection. As obligate parasites, infectious viruses and bacteria need to orchestrate the host cellular response to their very presence, in order to ensure the completion of their life cycles. Numerous strategies exist whereby pathogens engineer the host response to infection, many of which are well characterized and indeed, have led to Nobel Prize winning observations. Notably, the majority of these described host-pathogen interactions involve cellular proteins and microbial manipulation of the coding portions of host cellular genomes. However, with the recent explosion in our understanding of the role noncoding RNAs have in gene regulation, it is unsurprising that pathogens can, and do, manipulate these elementary cellular tools to their own advantage. It seems then that much like the conductor of an orchestra, microbial pathogens use noncoding RNAs akin to a conductor’s baton, to chisel the intracellular environment to their liking.

2.2 Defining Cellular Dark Matter

The central dogma of gene expression has long been taught as the flow of information from DNA to an RNA intermediate and then to protein. The discovery of messenger RNA in 1961 confirmed the intermediate position of RNA within the central dogma (Jacob and Monod 1961). There followed several decades of research confirming the flow of genetic information to proteins via mRNAs, thereby cementing their absolute requirement for protein production, and reinforcing the notion that genetic output is almost completely executed by proteins. The ‘one gene, one enzyme’ paradigm thus helped to obscure our understanding of the human genome, despite being cautioned against by the Nobel laureate Barbara McClintock in a letter she penned in 1950 to Marcus Rhoades. In it she asked ‘Are we letting a philosophy of the protein-coding gene control (our) reasoning? What then is the philosophy of the gene?’ (Mhlanga 2012). Her reservations gained support as observations accumulated showing that cells, in particular eukaryotes, contain large amounts of transcribed RNA that does not code for proteins. While some of these transcripts were shown to comprise the RNA translation machinery (such as rRNAs and tRNAs), and others were shown to be spliced variants of

protein-coding mRNAs, the vast majority remained unexplained (Nickerson et al. 1989; Paul and Duerksen 1975; Salditt-Georgieff and Darnell 1982; Weinberg and Penman 1968). The predominating protein-centric view of the day with its mechanical orientation even led to the term 'junk DNA' being used to describe this unexplained portion of the genome (Mhlanga 2012). However, when the complete sequence of the human genome was published (Lander et al. 2001; Venter et al. 2001), and it became clear just how much non protein-coding RNA is encoded within our own DNA, early proponents of the importance of noncoding RNA gained traction and since then a more nuanced view is emerging regarding our understanding of 'genes'.

Conservatively, only 2 % of the human genome is comprised of protein-coding genes, leaving 98 % of our genome in the dark (Lander et al. 2001; Venter et al. 2001). It is this disproportionate abundance of DNA that we do not comprehend which prompted use of the phrase 'junk DNA' and more recently cellular 'dark matter' when describing the noncoding portion of eukaryotic genomes (Yamada et al. 2003). In astronomical terms, 'dark matter' refers to the matter known to make up perhaps 90 % of the mass of the universe, but which is not directly observable. While studies in prokaryotes neatly supported the idea that genes are generally convertible to proteins via mRNA, comparative genomic studies have revealed that this is not true of eukaryotes. The ratio of coding to noncoding DNA increases as a function of developmental complexity, with fungi and plant genomes comprising 50 % noncoding DNA, and the noncoding proportion in mammalian genomes approaching that of humans at 98 % (Mattick 2004). Without delving deeply into the arena of systems biology, complex organisms obviously require combinations of interrelated gene expression programs in order to layout and maintain the precisely patterned and positionally distinct cell types, body plans and structures of which they are comprised. The fact that typical eukaryotic life cycles span a period of time adds a layer of intricacy, and means that genetic regulation of complex organisms must occur in a four-dimensional space (Buchler et al. 2003; Levine and Tjian 2003). As all of that information must be encoded within the DNA, it is highly suggestive that the abundant cellular dark matter is required to regulate such complex genomes.

The difficulties in understanding noncoding DNA means that noncoding RNAs remain tricky to accurately define and thus quantify. However, a few studies have revealed that noncoding RNAs may be expressed in excess of 20-fold compared to protein-coding RNAs (Nagano and Fraser 2011; Ponting and Belgard 2010). Noncoding RNAs have been segregated into small and long noncoding fractions, based on a somewhat arbitrarily delineated size cutoff of 200 bp. Small noncoding RNAs (<200 bp) are the most abundant transcripts in a cell but are encoded by the lowest number of genes. They include microRNAs, tRNAs, rRNAs and snoRNAs, among others (Nickerson et al. 1989; Paul and Duerksen 1975; Salditt-Georgieff and Darnell 1982; Weinberg and Penman 1968). Long noncoding RNAs (>200 bp) are the least abundant transcripts but are encoded by the highest number of genes comprising nearly 10,000 of the total ~18,000 human genes, and only a handful have been functionally characterized (Cabili et al. 2011; Derrien et al. 2012).

Broadly put, small noncoding RNAs regulate 'how and how much of each gene is made', while long noncoding RNAs regulate 'what genes are expressed when'. These descriptions have been shaped by the burst of long noncoding RNA research within the last decade, which has shown them to be involved in diverse cellular functions regulating nearly all aspects of gene expression from transcription and mRNA degradation, to splicing, translational efficiency, and even regulation of the 3D nuclear architecture via chromatin modification. In addition, long noncoding RNAs have been shown to regulate critical aspects of development, regeneration and disease.

2.3 Cellular Dark Matter Function

Recently the definition of cellular 'dark matter' has been restricted to long noncoding RNAs (lncRNAs) (Derrien et al. 2012). By combining genomic characterisation with chromatin signatures and RNA sequencing across several mammals, consortium-led efforts by ENCODE and FANTOM have identified 15,931 lncRNAs in the human genome (GENCODE version 23). The detailed intricacies of lncRNA definitions are reviewed elsewhere (Guttman and Rinn 2012; Hu et al. 2012; Rinn and Chang 2012; Wang and Chang 2011) but briefly, lncRNAs are typically expressed in a highly tissue-specific manner, their DNA region displays characteristic chromatin signatures (histone 3 lysine 4 tri-methylation, H3K4me3, and histone 3 lysine 36 tri-methylation, H3K36me3), and they are often co-expressed with neighbouring genes (Cabili et al. 2011; Derrien et al. 2012; Guttman and Rinn 2012). In addition, lncRNAs are usually in close proximity to regions of the genome that are rich in protein-coding genes, and they seem to be particularly abundant near transcription factors (Guttman and Rinn 2012; Ponjavic et al. 2009). Early studies showed that certain lncRNAs regulate specific target genes via epigenetic modifications (Pandey et al. 2008; Penny et al. 1996; Sleutels et al. 2002; Wang and Chang 2011). Indeed, it is now appreciated that lncRNAs can alter histone proteins to induce gene activation or repression (Flynn and Chang 2012). Altering the chromatin may also extend to chromosomal looping as certain lncRNAs are transcribed from enhancer regions thereby allowing them to activate genes independently of distance or local genetic context (Orom et al. 2010; Wang et al. 2011). Intriguingly, the functions of lncRNAs are closely tied to their interactions with one or more protein-binding partners, and the associated mechanisms employed during lncRNA-mediated regulation are diverse (Cech and Steitz 2014; Guttman and Rinn 2012; Hu et al. 2012; Kornienko et al. 2013; Rinn and Chang 2012; Wang and Chang 2011).

As more lncRNAs are catalogued and functionally characterised, the assortment of mechanisms by which they regulate their target genes is being refined. At present, they are classed as 'decoys', 'scaffolds', 'guides' and 'enhancers' (Guttman and Rinn 2012; Hu et al. 2012; Rinn and Chang 2012; Wang and Chang 2011). LncRNA decoys bind to and thus titrate away DNA-binding proteins such as

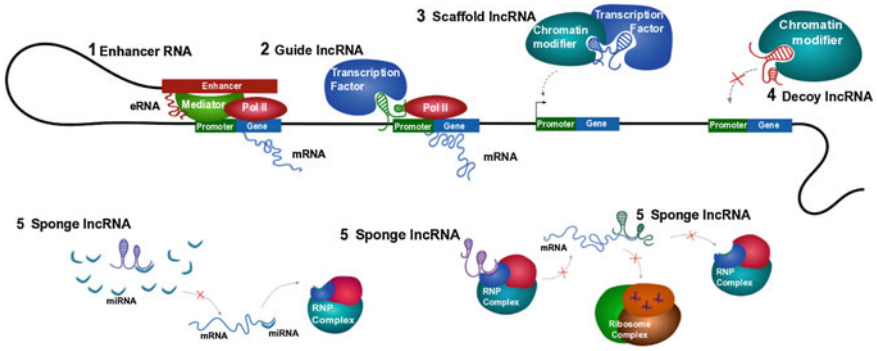


Fig. 2.1 Molecular mechanisms of lncRNAs. 1 Enhancer RNAs (eRNAs) are enhancer-derived transcripts that signal Mediator-directed chromatin looping to form long-range contacts between the parental enhancer sequence and targeted gene promoter thereby activating gene transcription. **2** Guide lncRNAs recruit proteins such as chromatin modifiers and transcription factors to target genes either *in cis* or in *trans*. **3** Scaffold lncRNAs bring multiple proteins within a single complex or spatial proximity. **4** Decoy lncRNAs titrate proteins such as transcription factors and chromatin modifiers away from gene loci. **5** Sponge lncRNAs compete for binding with miRNAs, RNP complexes and/or mRNAs thereby regulating translation

transcriptions factors, or lncRNA decoys can bind miRNAs thereby acting as molecular 'sponges'. Scaffold lncRNAs bring two or more proteins within a single complex or spatial proximity. As a scaffold, lncRNAs can also guide their bound protein(s), such as chromatin modifiers, to a specific DNA or RNA target sequence. Lastly, lncRNA enhancers guide chromosomal looping to exert a *cis* gene regulatory effect (Fig. 2.1). Each of these mechanisms underlies gene expression as they are at the heart of transcriptional control. This is also a critical point of manipulation for pathogens, which are particularly well adapted to altering the host cell in their favour. Historically our understanding of host-pathogen interactions has been informed by how viruses and bacteria manipulate cellular transcription and translation. This allows them to either trigger or suppress the host immune response, as well as to hijack the cellular machinery to ensure production of their own pathogenic components including virulence factors such as toxins. However, when considering that lncRNAs most likely regulate the very proteins that are targeted by pathogens, it is highly likely that host-pathogen interactions extend to the cellular dark matter as well.

2.4 Viruses and Cellular Dark Matter

As obligate intracellular parasites, viruses must exploit host components to complete portions of their life cycle. Typically, viral infection is detected by host cells early on and they mount an innate immune response that often includes inflammation. Unsurprisingly, several lncRNAs have been shown to regulate innate

immunity (reviewed in Atianand and Fitzgerald 2014; Aune and Spurlock 2016; Carpenter 2016; Zhang and Cao 2015). Notably, the identification of lncRNAs involved in innate immunity has typically been based on whole genome lncRNA profiling by RNA-seq or microarrays, and in response to specific stimuli such as toll-like receptor (TLR) agonists. A few of these lncRNAs have also been characterised in response to specific viral infections including the Human Immunodeficiency Virus (HIV), Influenza A Virus (IAV), and the Herpes simplex virus (HSV).

HIV is a retrovirus that begins and ends its infection cycle with two ssRNA copies of the genome, via a critical dsDNA intermediate that must be integrated within the host genome, at a chromatin region that is conducive to integration (Lusic and Giacca 2014; Marini et al. 2015). This action induces DNA damage in the cellular chromatin, alters its 3D structure, and triggers innate immunity, ultimately leading to latency and chronic infection by the virus (Ackerman et al. 2012; Jackson and Bartek 2009; Lilley et al. 2007; Mogensen et al. 2010). The viral integrase protein is responsible for cleaving the host DNA and together with host proteins, enables integration of the proviral genome (Demeulemeester et al. 2015). The generation of a double strand break (DSB) within the cellular chromatin is inherent in this, and because there is no intact sister chromatid to serve as a template, DSBs are the most severe DNA lesions for mammalian cells to endure (Jackson and Bartek 2009). DSBs are so poorly tolerated that a single such lesion within an essential gene can kill a cell (Khanna and Jackson 2001; Rich et al. 2000). As HIV must induce a DSB to complete its life cycle, apoptosis is a likely outcome of infection and indeed continuous decline of CD4 + T cells is used to monitor disease progression. Both viral-mediated integration (Cooper et al. 2013) and abortive infection (Doitsh et al. 2010) drive CD4 + T cell death, but there is also widespread dissemination of the virus throughout the host that is facilitated by infected macrophages. The virus is able to prevent TRAIL-induced apoptosis in macrophages via unknown mechanisms (Swingler et al. 2007) but more intriguingly, HIV is able to selectively impair apoptosis in macrophages by controlling a key apoptosis regulator, namely lncRNA-p21 (Barichievy, personal communication; Barichievy et al. 2015).

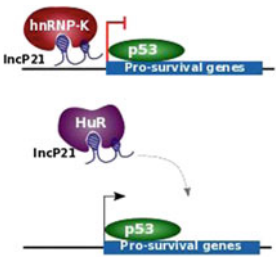
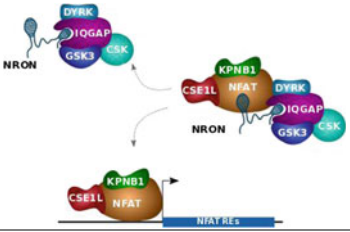
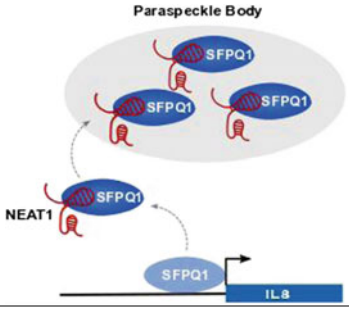
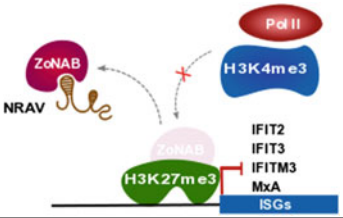
All metazoans have evolved sensitive mechanisms to detect all forms of DNA damage (Hartlerode and Scully 2009) and the tumour suppressor protein p53 is a core transcription factor within the subsequent cellular response to DNA damage (Meek 2004). The activation of p53 initiates various signaling cascades that culminate in either apoptosis, senescence or cell-cycle arrest (Zhou and Elledge 2000). The latter pathway provides time for cells to repair the DNA damage, while senescence and apoptosis are terminal pathways (Riley et al. 2008) and are thus tightly controlled and co-ordinated. Fairly recent data uncovered that the p53-mediated apoptosis response is regulated by an intergenic lncRNA that acts with the nuclear-localised protein hnRNP-K (Huarte et al. 2010). LncRNA-p21 guides hnRNP-K to specific prosurvival p53 target genes *in cis* (Huarte et al. 2010) and *in trans* (Dimitrova et al. 2014). One of these target genes is MAP2K1, which is the primary kinase responsible for phosphorylating ERK2 in healthy cells as part

of the regular survival cycle (Chang and Karin 2001). In healthy cells, both p53 and hnRNP-K are negatively regulated by HDM2 (Enge et al. 2009; Moumen et al. 2005) and therefore p53-transcribed genes, including lncRNA-p21, are not expressed. Concurrently, MAP2K1-activated ERK2 phosphorylates hnRNP-K causing it to accumulate in the cytoplasm (Habelhah et al. 2001) and thus prevent it from complexing with lncRNA-p21 in the nucleus. In addition, healthy cells further negatively regulate lncRNA-p21 by HuR-initiated Ago2/let7-mediated degradation (Yoon et al. 2012). The combined effects of these intersecting pathways ensures cellular survival. In contrast, DNA damage such as DSBs lead to alteRNAtive modifications of p53 thus nullifying HDM2 regulation (Enge et al. 2009). Different upstream signaling cascades prevent ERK2 activation and thus hnRNP-K is able to enter the nucleus (Moumen et al. 2005), interact with lncRNA-p21 and trigger apoptosis (Huarte et al. 2010). The ERK2/lncRNA-p21 intersection is the pivot point manipulated by HIV in order to evade apoptosis in macrophages (Barichievy et al. 2015).

In addition to cellular survival, activated ERK2 is required by HIV during the integration process, and forms part of the pre-integration complex (Bukong et al. 2010). As a consequence of the virus gaining control of this host protein prior to the actual integration event, any subsequent DSBs can be masked. Indeed, our recent unpublished data show that HIV integration does not cause ATM autophosphorylation or downstream activation of apoptosis-specific marks on p53, thus lncRNA-p21 is not transcribed (Barichievy et al. 2015). Central to this is HIV's control of ERK2 and its immediate upstream activator MAP2K1, as inhibition of these host factors leads to apoptosis only in the presence of virus. In addition, by controlling MAP2K1/ERK2, HIV ensures that hnRNP-K remains cytoplasmic and thus unavailable for binding with lncRNA-p21 and subsequent initiation of apoptosis. Intriguingly, integration of the provirus in CD4 + T cells is not facilitated by ERK2 but rather through the actions of JNK and Pin1 (Manganaro et al. 2010). Most likely this is because ERK2 expression is shut down when dual positive CD4 +/CD8 + cells differentiate into CD4 + cells (Chang et al. 2012; Fischer et al. 2005). The intimate tipping point between cellular survival and apoptosis at the intersection of lncRNA-p21 and ERK2 thus possibly only occurs in macrophages, and it seems that HIV has evolved a pivotal mechanism to conduct the cell in favour of viral survival (Table 2.1).

In addition to its manipulation of lncRNA-p21 in macrophages in order to evade apoptosis (Barichievy et al. 2015), HIV modulates the expression of two other lncRNAs in CD4 + T cells in order to enhance viral expression (Imam et al. 2015; Zhang et al. 2013). It has long been known that the nuclear factor of activated T cells (NFAT) transcription factor, which is specifically expressed in primary CD4 + T cells, enhances HIV gene expression by binding to the viral LTR (Cron et al. 2000). Intriguingly, the nuclear import of NFAT is repressed via the interaction of lncRNA NRON with importin-beta family proteins (Sharma et al. 2011; Willingham et al. 2005), thus NRON is a negative regulator of NFAT activity. HIV is able to leverage the gene enhancement function of NFAT by blocking NRON expression early during the infection cycle although the mechanism remains unclear

Table 2.1 LncRNA function during pathogen infection

LncRNA	Species	Stimulus	Type and description	Reference
lncP21	Mouse (human)	HIV	Guide 	Barichievy et al. (2015). Barichievy, submitted
NRON	Mouse (human)	HIV	Decoy, Scaffold 	Willingham et al. (2005), Sharma et al. (2011)
NEAT1	Human (mouse)	IAV HSV HIV	Guide, Scaffold 	Zhang et al. (2013), Imamura et al. (2014)
NRAV	Human	IAV	Decoy 	Ouyang et al. (2014)
VIN	Human	IAV	Unknown	Winterling et al. (2014)

(continued)

Table 2.1 (continued)

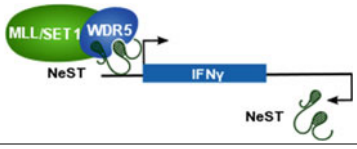
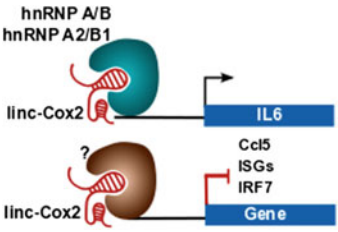
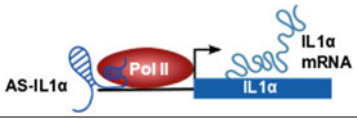
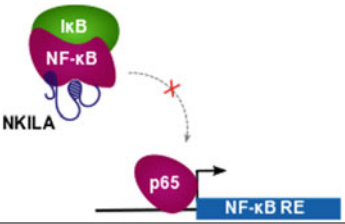
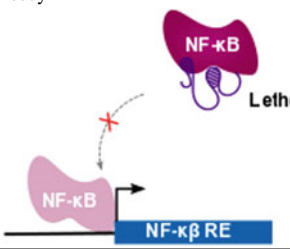
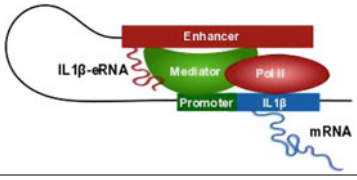
LncRNA	Species	Stimulus	Type and description	Reference
NeST	Mouse	*Salmonella*	Guide, Scaffold 	Gomez et al. (2013)
lincRNA-COX2	Mouse	LPS *Listeria* Pam_3CSK_4	Guide 	Guttman et al. (2009), Carpenter et al. (2013)
AS-IL1α	Mouse	LPS *Listeria* Pam_3CSK_4	Guide 	Chan et al. (2015)
NKILA	Human	LPS TNFα	Scaffold 	Liu et al. (2015)
Lethe	Mouse	TNFα	Decoy 	Rapicavoli et al. (2013)
IL1b-eRNA	Human	LPS	Scaffold, Enhancer 	Ilott et al. (2014)

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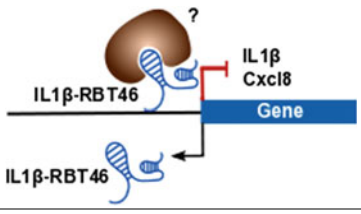
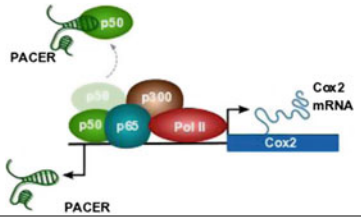
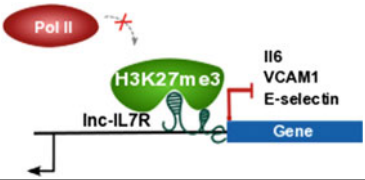
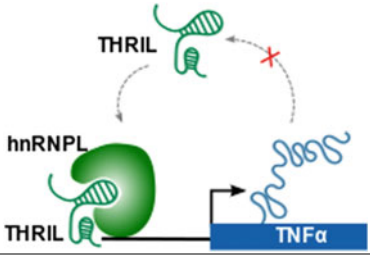
Table 2.1 (continued)

LncRNA	Species	Stimulus	Type and description	Reference
IL1b-RBT46	Human	LPS	Guide 	Ilott et al. (2014)
PACER	Human	LPS	Decoy 	Krawczyk and Emerson (2014)
Lnc-IL7R	Human	LPS Pam_3CSK_4	Guide 	Cui et al. (2014)
THRIL	Human	Pam_3CSK_4	Guide 	Li et al. (2014)

(Imam et al. 2015) (Table 2.1). In addition, the viral accessory proteins Nef and Vpu seem to have contrasting effects on NRON depending on the stage of infection, although they may be acting as 'molecular rheostats' to finely tune T cell activation in favour of viral replication, not cell death.

Within all mammalian cells, the nucleus contains many distinct domains including nuclear bodies known as paraspeckles. Within paraspeckles, the nuclear paraspeckle assembly transcript 1 lncRNA, NEAT1, modulates the cellular response to stress via triage of specific proteins within paraspeckles (Imamura et al. 2014). In HIV-infected CD4 + T cells, NEAT1 increases overall viral expression by enhancing nuclear export of HIV transcripts although the underlying mechanism

remains obscure (Zhang et al. 2013). It may be that as NEAT1 also represses the RNA-specific adenosine deaminase B2 (ADARB2) gene, nucleocytoplasmic transport of all ADARB2-sensitive transcripts, including HIV mRNAs, may be affected (Zhang et al. 2013). Furthermore, as modulation by NEAT1 of the host protein splicing factor proline/glutamine rich (SFPQ) leads to released repression of the interleukin-8 (IL-8) cytokine (Imamura et al. 2014), it may be that NEAT1 is more broadly involved in innate immunity. Indeed, the NEAT1/SFPQ interaction has been noted for IAV and HSV as well (Imamura et al. 2014) (Table 2.1).

In addition to NEAT1, IAV infection has also been linked to two additional functionally characterised lncRNAs, namely NRAV and VIN (Ouyang et al. 2014; Winterling et al. 2014). Mammalian cells respond to infecting viral components via pathogen recognition receptors such as RIG-I, MDA5 and TLR3 (Collins and Mossman 2014). Their activation initiates a signaling cascade that culminates in the expression of hundreds of antiviral proteins encoded by interferon-stimulated genes (ISGs) including MxA (Yan and Chen 2012). Following the activation of this innate immune response, a regulatory cascade is switched on as part of a complex and interconnected network that also includes epigenetic factors, thus ensuring that a rapid antiviral defence is mounted with minimal inflammatory damage (Smale 2012). The lncRNA NRAV (negative regulator of antiviral response) promotes IAV replication by suppressing several ISGs including MxA, probably via modulation of the histone marks on these genes (Ouyang et al. 2014). Thus increased NRAV expression is favourable for IAV infection.The virus inducible lncRNA VIN is also induced during IAV infection but not in response to IBV strains (Winterling et al. 2014). While the nuclear location of VIN suggests a role in gene regulation of IAV specifically, the mechanism has not been at all explored. What is clear is that viruses interact with several mammalian lncRNAs (Table 2.1), and this will only increase as research into host-pathogen interactions expands into the cellular dark matter space.

2.5 Bacteria and Cellular Dark Matter

Analogous to their viral counterparts, the proclivity of bacterial pathogens to hijack their cellular host machinery is driven by their inherent parasitic nature. By commandeering aspects of the cellular regulatory networks, bacteria can subvert host cell responses thus creating a microbially-permissive environment. Similarly to viruses, bacteria have evolved several different mechanisms to control host gene expression and nuclear architecture, all of which promote intracellular bacterial survival and progressive infection (Hamon and Cossart 2008). In recent years, these mechanisms have expanded to include bacterial control of lncRNAs, which allow the pathogens to affect transcriptional control of a cohort of co-regulated genes (Carpenter et al. 2013; Cui et al. 2014; Guttman and Rinn 2012; IIott et al. 2014; Liu et al. 2015; Rapicavoli et al. 2013). Indeed, earlier studies hinted at this via the observation that expression of several innate immunity genes was increased in

response to the microbial cell wall component lipopolysaccharide (LPS) (Arbibe et al. 2007; Levine and Tjian 2003; Saccani et al. 2002; Weinmann et al. 2001).

The first example of bacterial-mediated lncRNA manipulation built upon observations in mice that identified a gene which controlled gamma interferon (IFN-γ) and subsequent susceptibility to persistent Theiler's virus infection (Vigneau et al. 2003). This gene was shown to encode the lncRNA NeST (*Nettoie Salmonella pas Theiler's*) and its increased expression caused extended persistence of Theiler's virus infection but also provided resistance to *Salmonella enterica* pathogenesis in infected mice (Gomez et al. 2013). Functionally, NeST was shown to act in *trans*, as an enhancer RNA by binding to the MLL/SET1 H3K4 methylase WDR5, leading to subsequent induction of IFN-γ (Gomez et al. 2013). Specifically, NeST/WDR5 binding resulted in increased deposition of an H3K4me3 chromatin activation mark at the IFN-γ locus in murine splenic and CD8 + T cells (Gomez et al. 2013). Notably, the observation that a single lncRNA can elicit both pro and anti-pathogenic effects reveals an intricately complex phenomenon for lncRNA functioning that is yet to be understood. Yet NeST is not an isolated case in this regard. LncRNA-Cox2 acts as both an activator and suppressor of innate immune response genes (Carpenter et al. 2013). Initially discovered in LPS-stimulated CD11C + bone marrow derived dendritic cells (BMDCs), the functional involvement of lncRNA-Cox2 in the innate immune response was largely uncharacterised (Carpenter et al. 2013). However, in response to bacterial-derived LPS or a synthetic bacterial lipoprotein Pam_3CSK_4, as well as in response to Listeria infection, lncRNA-Cox2 expression was significantly induced in murine BMDCs and macrophages (Carpenter et al. 2013). Furthermore, lncRNA-Cox2 expression and that of its proximal gene *Cox2* were specifically dependent on the TLR signaling adaptor protein MyD88. Collectively, these findings established the induction of lncRNA-Cox2 as part of the innate immune response.

The underlying complexity of lncRNA-Cox2 function as an activator or repressor of immunity was only revealed by careful dissection of specific immune response genes under different stimulation conditions. RNAi-mediated lncRNA-Cox2 knockdown in unstimulated cells upregulated expression of IRF7, CCL5 and other selected ISGs (Carpenter et al. 2013). In contrast, similar lncRNA-Cox2 knockdown in Pam_3CSK_4 stimulated cells decreased expression of TLR1 and IL6. This suggested that lncRNA-Cox2 represses IRF7, CCL5 and other selected ISGs, while activating TLR1 and IL6, which was supported by transcriptomic analysis of macrophages ectopically expressing lncRNA-Cox2. In addition, by overlaying differential gene expression and RNA polymerase II (RNPII) occupancy profiles for various cell conditions, it was established that lncRNA-Cox2 functions as a repressor in the complex with hnRNP A/B and hnRNP A2/B1 (Carpenter et al. 2013). While a functional mechanism for lncRNA-Cox2's activating state has not yet been characterised, it is likely that a different protein partner will be involved. Furthermore, it would be interesting to decode where the divergence lies in the lncRNA-Cox2 induction cascade to identify how this lncRNA determines its immune-related role.

Several other studies have been published revealing the possibility of additional lncRNA involvement in bacterial infection. Notably, only one of these involved infectious bacteria while the remainder utilised LPS or related innate immunity agonists. However, the lessons remain valuable given the paucity of data that covers host-pathogen interactions in the cellular dark matter space. In the only other study to include bacterial infection, the lncRNA AS-IL1α (which is also a natural antisense transcript) was shown to act as a guide for RNPII II to bind the ILα promoter in response to *Listeria monocytogenes* infection or LPS or Pam_3CSK_4 treatment of murine macrophages (Chan et al. 2015). While AS-IL1α was shown to enhance IL1α expression, the possible manipulation of this interaction by *Listeria* was not explored. In a separate study in the human MCF breast cancer cell line, LPS-mediated activation of innate immunity was related to increased expression of a lncRNA termed NKILA (NF-KappaB Interacting LncRNA) which acts as a scaffold to maintain the inhibitory complex comprising NF-κβ and Iκβ (Liu et al. 2015). In this complexed form, NF-κβ localisation is restricted to the nucleus, which prevents NF-κβ-mediated transcriptional activation of genes typically involved in the innate immune response. Interestingly, LPS stimulation resulted in a 12-fold upregulation of NKILA compared to unstimulated MCFs (Liu et al. 2015). Given that LPS is a well-described and potent NF-κβ activator, and Gram-negative bacterial cell wall component, this suggests that such bacteria may upregulate the expression of NKILA in order to block the host from secreting essential innate immunity cytokines and chemokines.

Acute systemic inflammatory diseases such as Kawasaki disease are characterised by elevated circulating TNFα, which was recently shown to be related to the expression of a lnRNA termed THRIL (TNFα and hnRNPL related immunoregulatory LincRNA) (Li et al. 2014). While neither the study, nor the disease touched on pathogenesis, the involvement of macrophages and TNFα make this data interesting. Indeed, microarray analysis revealed that THRIL expression was significantly downregulated in Pam_3CSK_4 stimulated macrophages, and RNAi-mediated knockdown of THRIL strongly reduced TNFα mRNA and protein expression (Li et al. 2014). Interestingly, the downregulation of THRIL expression resulted in reduced expression of a proximal coding gene, Bri3 bp, which also contributed to a reduction of TNFα transcription. At a molecular level, THRIL was found to directly bind hnRNPL, forming a complex whose occupancy at the TNFα promoter was required to maintain basal levels of TNFα expression (Li et al. 2014). These findings led to the hypothesis that binding of the THRIL-hnRNPL complex at the TNFα promoter is required for basal TNFα transcription, and that under stimulated conditions the high expression of TNFα initiates a negative feedback loop in which both THRIL and TNFα are downregulated. Overall, the involvement of THRIL in an inflammatory disease as well as the ability for bacterial lipoprotein mimic, Pam_3CSK_4, to alter its expression suggests that bacteria may reduce THRIL expression in an attempt to deregulate the innate immune response by targeting TNFα.

The pseudogene lncRNA, Lethe, was also shown to be significantly upregulated upon TNFα stimulation, as well as in response to IL-1β activation or LPS treatment

in mouse embryonic fibroblasts (MEFs) (Rapicavoli et al. 2013). Under these conditions, Lethe functions as a decoy and negative inhibitor of NF-κβ signalling by titrating RelA (p65) away from NF-κβ responsive elements, including the Cox2 promoter (Rapicavoli et al. 2013). By displacing the activating NF-κβ subunit away from its responsive elements, no transcription occurs at these loci. Given the critical role of NF-κβ in the inflammatory response, it is unsurprising that three other lncRNAs, namely IL1β-eRNA, IL1β-RBT46 and PACER (p50-associated COX-2 extragenic RNA) regulate transcription of specific NF-κβ target genes (IIott et al. 2014; Krawczyk and Emerson 2014). Both IL1β-eRNA and IL1β-RBT46 were described in LPS-stimulated monocyte-like ThP1 cells, and their knockdown attenuated transcription of CXCL8 and IL6 although their protein binding partners and molecular functions remain obscure (IIott et al. 2014). PACER (p50-associated Cox2 extragenic RNA) was described in LPS-treated human epithelial cells and shown to act as a decoy for the NF-κβ repressive subunit p50 thus occluding it from the Cox2 promoter (Krawczyk and Emerson 2014). This enabled p300 histone acetyltransferase recruitment and assembly of initiating RNPII complexes thus promoting Cox2 expression.

While none of these studies in bacteria involved complete pathogenic stimulation of NF-κβ, it is tempting to speculate that bacteria may exploit the lncRNA-mediated regulation of NF-κβ to control cellular inflammation. From the host cell perspective, these lncRNAs may also be negatively regulating the sustained NF-κβ stimulation that sometimes follows bacterial infection and which can lead to sepsis. In support of this, the cellular lnc-IL7R was shown to attenuate LPS-induced inflammation in ThP1 cells (Cui et al. 2014). Mechanistically, lnc-IL7R does so by increasing deposition of the epigenetic transcription silencing mark H3K27me3 at promoters of inflammatory mediators such as IL6, VCAM1 and E-selectin (Cui et al. 2014). Collectively, these observations serve to establish a clear role for lncRNAs in innate immunity, and particularly in the inflammatory response that is central to microbial infection. While more examples related to bacterial-lncRNA interactions exist as compared to those for viral infections (Table 2.1), the lack of data generated in the presence of whole microbes does underscore that much remains to be discovered in this dark space.

2.6 Enhancer-Derived Short lncRNAs and Their Involvement in the LPS Response

Nearly all lncRNAs that have been explored above influence transcriptional outcome regardless of mechanism. Another group of lncRNAs that has recently emerged as potential principal regulators of transcription are the enhancer RNAs (eRNAs). Although enhancers are known to be indispensable transcriptional regulatory elements in the genome, the current understanding on the presence, dynamics and function of eRNAs is obscure at best, and their involvement in

inter-kingdom interactions is unexplored. However, studies using LPS as summarised below argue in favour of their participation in the innate immune response specifically in response to bacterial pathogens. In addition, where necessary, studies from other contexts such as cancer also facilitate interpretation of the limited data that is available in current literature. Yet despite the paucity of research in this area, there are strong suggestions that they play a role in host-pathogen interactions, although they do so via different functional mechanisms.

Enhancer elements were first observed when transcription of the beta-globin gene was activated by a piece of SV40 DNA acting in *cis* as far as thousands of bases away from the gene (Banerji et al. 1981). From this remarkable observation, the authors of the study correctly predicted that, given their regulatory potential, similar elements may be widespread throughout the genome. Following decades of research, it has now been established that enhancers outnumber protein-coding genes, and regulate the temporal and spatial expression of genes during development, differentiation and homeostasis (Bulger and Groudine 2010). Transcription at an enhancer was first reported at the beta-globin locus (Collis et al. 1990; Tuan et al. 1992), but more surprisingly enhancers were recently found to be pervasively transcribed bi-directionally by RNAPII to produce a class of lncRNAs called eRNAs (Kim et al. 2010). These are mostly unspliced, non-polyadenylated and have a median length of 346 nt (Andersson et al. 2014). As the levels of eRNA expression correlates with those of mRNA at nearby genes (Kim et al. 2010), the eRNAs have been suggested to be used as a predictor for active enhancers, in addition to the canonical chromatin marks such as H3K4me1, H3K4me2 and H3K27ac as well as transcription factor binding. By using enhancer transcription to delineate active enhancers, a recent enhancer atlas that includes over 43,000 such elements across the majority of human cell types and tissues has been compiled (Andersson et al. 2014).

A number of studies have reported important observations on the dynamics in enhancer landscape during signal-dependent gene activation, including TLR4 signaling. In mouse macrophages stimulated with LPS in the presence of IFNγ, 70 % of extragenic RNAPII peaks along the entire genome were shown to be associated with canonical enhancer marks (De Santa et al. 2010). Enhancer transcription was stimulus-regulated and located nearby the induced protein-coding genes, suggesting eRNAs as an important class of lncRNAs in regulating the LPS response. In another study, KLA-stimulation of TLR4 in mouse macrophages led to the appearance of $\sim$3000 new enhancers as identified by the gain of H3K4me2 chromatin marks and the loss of $\sim$1000 enhancers (Kaikkonen et al. 2013). Inhibition of enhancer transcription by BET inhibitors and flavopiridol reduced H3K4me1 and H3K4me2, suggesting that histone methylation is preceded by enhancer transcription (Kaikkonen et al. 2013). This sequence of events, however, may be stimulus and/or cell type specific, as enhancer transcriptional inhibition in estrogen-stimulated breast cancer cells does not lead to changes in histone modifications and other molecular features of enhancers (Hah et al. 2013). In either case, the presence of eRNAs seems to correlate well with other molecular features of active enhancers, arguing in favor of detection of eRNAs as a good measure of enhancer activity. In

summary, the emergence of new transcribed enhancers during TLR4 signaling and their association with nearby coding genes involved in inflammation have hinted at the importance of eRNAs in regulating the innate immune response.

The study describing IL1β-eRNA and IL1β-RBT46 in LPS-stimulated monocyte-like ThP1 cells (IIott et al. 2014) has also correlated the expression of eRNAs to those of nearby coding genes in a genome-wide fashion, using human macrophages stimulated with LPS. This correlation was stronger than that between canonical lncRNAs and coding genes, particularly for genes involved in monocyte inflammatory responses, confirming the potential importance of eRNAs in regulating the temporal nature of innate immune responses. The regulatory nature of transcribing enhancers was supported by an observation where levels of *IL1β* mRNA were significantly attenuated by the TPCA-1-mediated inhibition of NF-κβ, which binds at the *IL1β* enhancer but not its promoter. This observation suggests a sequence of events that starts with NF-κβ binding to the enhancer in order to promote eRNA transcription, which is then followed by transcription of the target coding gene. Although knocking down rapidly induced eRNAs is not technically trivial, the authors validated a functional role for eRNAs by successfully knocking down those associated with *IL1β* and *CXCL8*, leading to a reduction in the levels of those specific mRNAs (Table 2.1) (IIott et al. 2014).

Super-enhancers, or stretch-enhancers, consist of clusters of enhancers that are densely occupied by key transcription factors. Super-enhancers share most features of regular enhancers, but at a much larger scale. Both their coverage of DNA regions and levels of chromatin marks such as H3K27ac and H3K4me1 are on average an order of magnitude greater than those of regular enhancers (Whyte et al. 2013). Consequently, their ability to activate transcription of coding genes and sensitivity to perturbation are also greater. Like regular enhancers, super-enhancers seem cell type specific and therefore are most likely involved in regulating cellular identity. A few studies thus far have shown involvement of super-enhancers in driving the expression of innate immunity genes. In primary human umbilical vein endothelial cells, stimulation with TNFα causes a recruitment of both p65 and BRD4 to regions nearby pro-inflammatory coding genes, forming de novo super-enhancers (Brown et al. 2014). This recruitment came at the expense of pre-existing basal super-enhancers which were 'decommissioned' upon stimulation. Down-regulated genes nearby these 'lost' super-enhancers were involved in angiogenesis and endothelial barrier function. The gain and loss of these super-enhancers resulted in the largest changes to RNAPII occupancy and expression changes of nearby genes (Brown et al. 2014), implicating these elements as having a crucial role in inflammation.

A similar observation has been made in LPS stimulated mouse macrophages, using eRNAs arising from super-enhancers to identify their active status (Hah et al. 2013). Multiple eRNAs are generally transcribed from super-enhancers, and following stimulation were dynamically induced near most innate immunity genes, but reduced near genes involved in cell metabolism and nuclear organization. Although comprising only 3 % of total enhancers, super-enhancers were strongly enriched near genes that were either induced or repressed in response to TLR4 signaling,

raising the possibility that super-enhancers are potential contributors to not only cellular identity but also functional identity. Using global run-on sequencing (GRO-seq), up to nearly 30 % of total nascent RNAs were identified to be eRNAs, the majority of which were produced at super-enhancers. All of the multiple eRNAs arising from individual super-enhancers were observed to be induced or repressed from a population of cells (Hah et al. 2013), but only single-cell or single-allele analyses will elucidate whether all eRNAs within a super-enhancer coordinately respond to stimuli. Nonetheless, all together, these studies demonstrate that super-enhancers and their transcripts are potentially important regulators of innate immunity and are thus implicated in pathogenesis.

A model of enhancer activity whereby they exert their effect on distal promoters by being in close proximity in three dimensional space, is now widely accepted (Lam et al. 2014). This has raised the possibility that eRNAs are mere transcriptional noise that happen to correlate with the induction of nearby genes. A number of studies, however, suggest their functional contribution to activation of gene transcription. For example, as previously mentioned, enhancer knockdowns have caused a reduction in transcription of specific nearby genes (IIott et al. 2014; Lam et al. 2013; Li et al. 2013; Melo et al. 2013; Mousavi et al. 2013). Additionally, eRNA tethering to reporter genes has shown that the eRNA itself, rather than the act of enhancer transcription, is required for reporter activation (Li et al. 2013; Melo et al. 2013). Moreover, an inversion of enhancer sequence, leading to an eRNA with a completely different sequence, abolished enhancer activity, suggesting that a specific eRNA sequence is necessary for its function (Lam et al. 2013). Furthermore, how eRNAs mechanistically activate nearby genes is currently not very clear. A few studies report the ablation of enhancer-promoter contacts upon knockdown of eRNAs (Lai et al. 2013; Li et al. 2013), whereas others report such contacts being unaffected by eRNA levels (Hah et al. 2013; Schaukowitch et al. 2014). Knocking down subunits of the Integrator complex, which is necessary for 3' cleavage of eRNAs to produce their mature form, leads to accumulation of unprocessed, longer forms of the transcripts, resulting in abrogation of EGF-induced enhancer-promoter chromatin looping in HeLa cells (Lai et al. 2015).

It is possible that eRNA functions depend on context, as the above studies were performed on different loci in various cell types using different stimuli. One mechanism of eRNA function may therefore be to initiate and/or maintain looping between enhancers and promoters. Currently a common observation among all studies is that eRNA knockdown causes a reduction in the transcription of specific nearby target genes. A study using neurons has suggested that, upon membrane depolarization, eRNAs act as a decoy for the NELF complex, which otherwise binds nascent RNAs to cause promoter-proximal pausing of RNAPII, thus facilitating the transition from paused RNAPII to productive elongation (Schaukowitch et al. 2014). It has yet to be established whether this is a widespread mechanism of eRNAs or is specific to the conditions tested in this study. Another potential mechanism of eRNAs that has been proposed is trapping of transcription factors thus leading to a positive feedback loop that contributes to stability of gene expression programs (Sigova et al. 2015). More studies addressing mechanistic

details of eRNA functions are expected in the near future. Furthermore, to our knowledge, there is no study to date that has addressed the status of eRNAs specifically upon infection by a pathogen. It will be interesting to see whether eRNA levels are altered as a means to manipulate downstream gene expression in the host, as the use of LPS to stimulate TLR4 signaling cannot provide this information. Given their transcriptional regulatory capacity however, it will not be surprising to find eRNAs as a target by which pathogens control gene expression in the host.

2.7 Discussion and Outlook

In surveying the landscape of transcriptional regulation in eukaryotes, it is evident that diverse cellular modules are implicated. Transcription in eukaryotic organisms and more specifically in mammals, involves several core molecular players in the nucleus. Though still inchoate, our understanding of lncRNAs has shed light on how lncRNAs interact with a fraction of these core molecular players. However, since lncRNA function is deeply entwined within transcriptional regulation, this introduces the potential for the entire landscape of nuclear and cytoplasmic molecular players involved in transcription to be implicated. This may extend well beyond nuclear architecture associated with transcriptional regulation. Broadly speaking classification of lncRNAs beyond the eRNA and non-eRNA variety is one of the key distinctions. Outside this, the diverse mechanisms of action that they possess as evidenced by this review are indications of how poor our current ability to classify lncRNAs is. In terms of transcriptional regulation by enhancers, eRNAs represent a major class of lncRNAs that could potentially be a target of pathogen manipulation of host transcription. This could potentially link pathogen manipulation of lncRNA to 3D chromatin structure and the disruption of long range chromatin contact. However, to date no evidence of such linkages exist.

In this review we have highlighted several bona fide mechanisms implicating transcriptional regulators in the nucleus that have been experimentally validated in viral and bacterial pathogenesis. Many involve clever adaptations that pathogens have made to prevent lncRNA function; those from the Herpes Simplex Virus and its regulation of innate immune genes come to mind. In surveying the lncRNAs so far identified that are implicated in HIV infection, what is striking is how although lncRNAs are significant targets of pathogenesis, this may occur via rather circumspect interventions, although with devastating effects. Viral manipulation of lncRNAs regulating apoptosis has severe consequences in CD4 + T cells and yet no such effects occur in non-CD4 + T cells where the virus evades apoptosis and uses these cells as a reservoir. Indeed it is conceivable that if HIV gained the capacity to infect CD4 + T cells and not cause their demise, its principal effects in humans would be the cause of lymphomas and associated cancers.

These two examples of how lncRNAs can be co-opted by viral pathogens are highly contrasting. One directly implicates transcriptional regulation (HSV) and the

other (HIV) falls outside the 'traditional' targets of transcription regulation, but the effects are no less severe. Notwithstanding, their investigation is highly revelatory of host cell biology. They are also profound reminders of how viral pathogens have evolved abilities to exploit not only the coding or 'well illuminated' part of the genome, but also its dark matter or noncoding regions. It would be naive to believe that our understanding of transcription and its regulation is anywhere near complete. What generates broad enthusiasm for the study of noncoding RNA biology and its interface with pathogenesis is how such models can be used to uncover poorly understood aspects of host transcriptional regulation.

In bacterial infections the centrality of innate immune signaling and NF-Kappa signal transduction are evident by the large number of lncRNAs that have been implicated in innate immune signaling during bacterial pathogenesis or LPS stimulation. Several lncRNAs have been identified that target the NF-Kappa signal module directly and indirectly. Innate immune signaling is 'ground zero' of pathogenesis and evidently where a great deal of pathogenic ingenuity is expended! Pathogens in general and bacteria in particular devote coding potential in their genomes to either up or downregulate innate immune responses. Many coalesce these efforts around lncRNAs that regulate NF-Kappa. Potentially some of these lncRNAs that have been discovered to be pathogenic targets may also become therapeutic ones in inflammatory bowel disease, colitis, cancer and other maladies of the immune system.

This introduces the nascent field of 'drugging' lncRNA activity to abrogate or augment its activity. As this review has highlighted the numerous ways in which pathogens are able to hijack lncRNAs, so too has it exposed a number of new potential therapeutic targets. Thus techniques that are able to discretely target these lncRNAs may introduce an effective host-directed therapy, particularly as host cells are not mere 'orchestral bystanders' but rather retaliate to infection with a complex suite of responses. This promises to be an intensive area of research in the future with the technologies of RNA interference, genome editing and small molecule inhibitors all playing important roles. Circumventing the abilities of pathogens to control host transcription via lncRNAs may be a robust approach in combating pathogenic infection without the use of antibiotics. It is clear that discoveries in the field of lncRNA and pathogenesis will open new vistas in our understanding of transcriptional regulation of host biology.

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