HHS Public Access

Author manuscript

J Autoimmun. Author manuscript; available in PMC 2024 January 01.

Published in final edited form as:

J Autoimmun. 2023 January ; 134: 102982. doi:10.1016/j.jaut.2022.102982.

Non-coding RNAs in immunoregulation and autoimmunity: technological advances and critical limitations

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Abstract

Immune cell function is critically dependent on precise control over transcriptional output from the genome. In this respect, integration of environmental signals that regulate gene expression, specifically by transcription factors, enhancer DNA elements, genome topography and non-coding RNAs (ncRNAs), are key components. The first three have been extensively investigated. Even though non-coding RNAs represent the vast majority of cellular RNA species, this class of RNA remains historically understudied. This is partly because of a lag in technological and bioinformatic innovations specifically capable of identifying and accurately measuring their expression. Nevertheless, recent progress in this domain has enabled a profusion of publications identifying novel sub-types of ncRNAs and studies directly addressing the function of ncRNAs in human health and disease. Many ncRNAs, including circular and enhancer RNAs, have now been demonstrated to play key functions in the regulation of immune cells and to show associations with immune-mediated diseases. Some ncRNAs may function as biomarkers of disease, aiding in diagnostics and in estimating response to treatment, while others may play a direct role in the pathogenesis of disease. Importantly, some are relatively stable and are amenable to therapeutic targeting, for example through gene therapy. Here, we provide an overview of ncRNAs and review technological advances that enable their study and hold substantial promise for the future. We provide context-specific examples by examining the associations of ncRNAs with four prototypical human autoimmune diseases, specifically rheumatoid arthritis, psoriasis, inflammatory bowel disease and multiple sclerosis. We anticipate that the utility and mechanistic roles of these ncRNAs in autoimmunity will be further elucidated in the near future.

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Author contributions

All authors contributed to the curation of studies presented in this review and writing.

The authors have no conflicts of interest to declare.

Keywords

non-coding RNA; circular RNA; enhancer RNA; autoimmunity; single cell RNA-sequencing; rheumatoid arthritis; psoriasis

Introduction

Precise regulation of gene transcription is essential for the normal function of immune cells, balancing the need for appropriate responsiveness to pathogens and danger signals while maintaining tolerance to self-components. Broadly, transcriptional output from the genome can be divided into coding (messenger) ribonucleic acids (mRNAs) and non-coding RNAs (ncRNAs) based on the potential for translation to proteins. Although ncRNAs account for a large fraction of RNA species in most eukaryotic cells, relatively little is known about the roles played by ncRNAs in the context of immune cell differentiation and fate decisions. In fact, current understanding of genome biology in immune cells is mainly centered on the regulation of coding genes by transcription factors (TFs) and non-coding regulatory elements, such as enhancers. Therefore, a major knowledge gap remains in elucidating the functions of ncRNAs in human physiology and immune-related diseases. Nevertheless, recent primary studies have demonstrated a unique role for a variety of ncRNAs in the regulation of immune cell function at multiple levels, including lymphoid development, inflammatory pathway activation, cellular metabolism, antibody repertoire selection and cytokine secretion. Such functions indicate that ncRNAs participate in xeno-responses to provide immunity to pathogens. Moreover, they have also been implicated in anti-self responses, where components of the immune system are dysregulated and harm otherwise healthy tissues, evident as clinical autoimmunity. Importantly, while TFs and enhancers are typically challenging to target therapeutically, non-coding RNAs may provide better alternatives for gene therapy [1–3]. Thus, not only can ncRNAs act as potential biomarkers and enhance our understanding of the basic molecular mechanisms of disease, but they can also be therapeutically leveraged for the treatment of patients. Recent developments in technology required for the broad detection and discrete analysis of ncRNAs could also shed light on their roles in immune cells. Here, we provide an up-to-date review of ncRNAs, specifically discussing advances in technologies for their detection, mechanisms of action and putative roles orchestrated in human autoimmune diseases.

Classes of ncRNAs

Although ncRNAs make up the majority (~90%) [4,5] of transcriptional products, the functions of most ncRNAs remain poorly understood. Pioneering studies of transfer [6] and ribosomal [7] RNA in the 1950s described the function of the first ncRNAs, and were followed by the study of RNAse P [8], RNA granules [9], RNA methylation and processing [10], RNA structure prediction [11], and XIST-mediated X-inactivation [12]. With advancements in RNA sequencing [13], the number of ncRNAs detected amongst human cells has increased exponentially, with ~0.6 million ncRNAs now estimated to exist (Table 1). This compares to approximately 20,000 genes encoding mRNAs. In humans, the true number of ncRNAs and their expression in nature may vary more widely by cell-type

and condition and, like mRNAs, alternative-splicing. Broadly, ncRNAs are divided into small (<200bp in length) and long ncRNAs [14] (variously defined as either >200bp with or without a putative open reading frame (ORF), or >300bp without an ORF) (Figure 1). Small ncRNAs include micro-RNAs (miRs) [15], transfer RNAs (tRNAs) [16], tRNA-derived small RNAs (tsRNAs) [17], piwi-interacting RNAs (piRNAs) [18] and small nucleolar RNAs (snoRNAs) [19]. The long ncRNAs include linear long non-coding RNAs (lncRNAs) [20], long intergenic non coding RNAs (lincRNAs – essentially lncRNAs that do not overlap with protein-coding genes) [21], enhancer RNAs (eRNAs) [22,23] and circular RNAs (circRNAs) [24,25]. The number of ncRNAs in each category is increasing exponentially. Table 1 lists the number of ncRNAs described to date in each category and the databases curated to enable browsing of all those described.

Overall, many mechanisms of function have been ascribed to ncRNAs, including those that are specific to each class. Broadly, ncRNAs may regulate expression of other genes and basic cellular processes of cells. Some of these are generic to all cells, while others are specific to immune cells. These include regulation of cellular metabolism [26], polycomb repression [27], active-chromatin binding [28], gene transcription [29], alternative splicing [30], CTCF-associated class-switch recombination [31], ribosome activity [32,33], signal-transduction[34] and cytokine production [15,35]. Whereas miRs disrupt target molecule mRNA expression via the miR-induced silencing complex (miRISC) that includes argonaute-based nuclease machinery [36], long ncRNAs generally function differently, for example by acting as signals (i.e. transcriptional regulators), decoys (i.e. for miR binding and sponge activity), guides (i.e. directing localization of molecules) and molecular scaffolds (supporting multimeric complexes) [37]. Some ncRNAs integrate multiple functions. For example, *HOTAIR*, a regulator for anatomic specificity in anterior posterior differentiation, binds to the polycomb repressor complex (PRC) 2 and lysine-specific demethylase (LSD)1 complexes as a modular scaffold and targets PRC2 localization toward discrete genomic locales. Thus collectively *HOTAIR* regulates cellular position identity in complex tissues by regulating gene expression through mobilization of chromatin modifiers [37]. The most common mechanisms by which ncRNAs regulate cellular function are shown graphically in Figure 2.

The focus of much of the literature has historically been on the study of lncRNAs and miRs. More recent attention has shifted to circRNAs and eRNAs. circRNAs and eRNAs are critically important ncRNAs increasingly recognized for regulating fundamental cellular processes. circRNAs are abundant and formed by back-splicing events distinguishing them from linear RNAs [38] (Figure 1C). eRNAs are non-coding RNAs transcribed from enhancer regions of DNA and regulate target gene expression [39–41] (Figure 1D–E). Both circRNAs and eRNAs are critical for mammalian gene regulation in *cis* and/or *trans*. Moreover, controlled over-expression or ablation of specific circRNAs and eRNAs can modulate biological functions of cells [42,43], providing a novel means to alter transcriptional activity of target genes. Because some of these, such as circRNAs, are relatively stable and long-lived, they also have the potential to act as biomarkers of disease or to be the targets of gene therapy.

Detection of ncRNAs in immune cells – old challenges and new

Conventionally, a significant portion of the knowledge gap that exists in the study of ncRNAs stemmed from limitations in ncRNA detection. At present, a variety of techniques exist to detect ncRNAs in cells and tissues under diverse immunological states. These range from prior knowledge-based techniques, such as qRT-PCR, to high-throughput methods that include bulk RNA-sequencing (RNAseq). While RNAseq is now standardized, it is important to point out that most experiments 'capture' RNAs that are 3'-polyadenylated. This is desirable to bias capture towards mRNAs and avoid reactions being saturated by rRNAs (the majority of cellular RNAs). However, because a large fraction of cellular ncRNAs is not poly-adenylated, this approach has low efficiency at capturing the non-coding transcriptome. An approach more suitable to whole transcriptome sequencing uses random priming combined with reagents that deplete ribosomal RNAs ('ribo-depletion') or enrich for RNA species of interest (e.g. RNase R treatment for circRNA enrichment). However, this approach is particularly susceptible to inefficiency if the quality of starting RNA is sub-optimal, as ribo-depletion of partially degraded RNA works poorly. It is also worth pointing out that data from whole transcriptome RNAseq still pose significant challenges when trying to discover novel ncRNAs, partly because many of the ncRNAs have low expression and discerning them from "transcriptional noise" requires large numbers of samples, increased sequencing depth and confirmation by orthogonal methods. An additional challenge is identifying the exact transcription start and end coordinates which would be needed for functional studies, such as overexpression or gene-editing. An additional computational challenge for circRNAs is that identifying exact back-splicing junctions requires sufficient sequencing reads through the junction to distinguish it from artifacts introduced during RNA-seq library preparation, such as random template switching [44]. Such depth of coverage can be difficult to achieve for low-expressed transcripts.

Other novel opportunities for identifying ncRNAs comes from the variety of methods now available for sequencing of nascent RNA molecules, such as methods that sequence transcripts without capture or library prep to enable high-throughput characterization of total nucleotides. These include uninterrupted long-range sequencing, global nuclear run-on sequencing (GRO-seq), precision run-on sequencing (PRO-seq), native elongating transcript sequencing (NET-seq), mammalian NET-seq (mNET-seq) and fastGRO [45–49]. Some of these approaches are gaining traction but are still dependent on input bulk RNA derived from multiple cells and generally measure actively transcribing genes rather than steady-state stable RNA levels.

Single cell RNA-seq (scRNAseq) is a contemporary approach to detect and quantify cell-state specific expression without the need of microdissection [50] or laser capture [51]. It theoretically enables the discrete analysis of cellular transcriptomes on a *per cell* basis and the determination of heterogeneity within a given population of cells. However, current scRNAseq methods are less than ideal for the study of ncRNAs principally for two reasons. Firstly, current scRNAseq platforms are susceptible to 'drop-out', a phenomenon by which a transcript is observed in one cell, often at low or moderate level of expression, but is not detected in another cell within the same population. Thus, because many ncRNA species are of low abundance (*NeST*, for example [see below] is estimated to be expressed at one

molecule or less per T cell) or low expression, they are often subject to dropout within a population of identical cells. Secondly, many commercially available scRNAseq kits employ a reverse transcription (RT)-PCR reaction primed by polydT, which predominantly captures 3'-polyadenylated transcripts. This is fine for some lncRNAs that contain 3'polyA tails and can be captured by priming with polydT. For example, Zhou *et al.*, recently conducted polydT-primed single-cell profiling of lncRNAs during hematopoiesis *in vivo* and produced an atlas of such ncRNAs during hematopoiesis [52]. Unfortunately, the lack of 3'polyA tails in many ncRNAs results in most of these species being ignored by the polydT-primed RT-PCR used in most routine scRNAseq techniques. Conversely, techniques that bias capture towards ncRNAs (e.g. RT-PCR primed with random hexamers) are limited by the opposite problem, namely that the majority of the PCR products are unwanted ribosomal RNAs, which saturate and dominate sequencing reactions, resulting in low depth of sequencing reads for detecting and quantifying desired ncRNAs. In theory, combining random priming with techniques that deplete unwanted rRNAs before or after RT-PCR could enable whole transcriptome assessment and more efficient measurement of ncRNAs at the single cell level, as they have in bulk RNAseq. However, protocols to achieve this aim and efficiently deplete rRNAs are not yet available. It is also conceivable that that innovation in methods for sequencing of nascent RNA molecules will capitalize on existing plate-based or oil-immersion approaches to perform nascent identification of RNAs and other molecules in singe cells at longer lengths.

Achieving single cell transcriptomic readout of cells is clearly an important advance in understanding biology in complex tissues. However, there are two clear limitations that need to be acknowledged. Firstly, many studies use cells from surrogate sites, such as cerebrospinal fluid or blood, to identify disturbed ncRNA expression. While hypothesis-generating, this approach most likely only hints at the exact ncRNAs regulating disease within affected tissues. Secondly, most immune reactions in complex diseases are spatially oriented and dependent on cell-to-cell interactions between cells. Examples include the processes occurring in the synovia of patients with rheumatoid arthritis, kidney tissues in lupus nephritis or brains of patients affected by neuro-immunological diseases, such as multiple sclerosis. Tissue disruption required for single cell methods, such as scRNAseq, by intention disrupts this information. This limitation necessitated the development of post-hoc computational methods, such as CellphoneDB [53], that infer and approximate the interactions that might have occurred *in vivo* in that tissue using existing receptor-ligand pair knowledge base. This approach is generally limited and somewhat tangential.

Spatial transcriptomics approaches have overcome some of the limitations of scRNAseq by probing tissue-level events and cell-to-cell contacts experimentally but have their own limitations. "On-slide" first generation spatial transcriptomic methods showed promise in this domain but were generally of low resolution and provided regional, rather than single cell, information. One reason for the low resolution is exemplified by the 10X Genomics Visium platform [54] that integrates existing scRNAseq approaches to capture cellular transcripts by arrays of barcoded mRNA-binding oligonucleotides tiled across glass histology slides. Inefficient capture of transcripts from individual cells, physical limitations of the number of barcoded oligonucleotides that can be tiled and deadspace between capture spots, results in low resolution and loss of spatial information. On the other hand, this

approach is suitable for discovery-led approach as the method is not dependent on a prior knowledge and will sequence all RNAs captured. Recent improvements in spatial transcriptomic methods have pushed the boundaries in this domain. These second-generation methods have largely eschewed RNA-capture and sequencing in favor of probe-based methods that enable higher resolution of capture. Some of these technologies, such as multiplexed error-robust fluorescence in situ hybridization (MERFISH) [55] or the 10X Genomics Xenium [56] platform, now enable mapping of transcript expression at even sub-cellular resolutions. This depth of resolution holds great promise for revealing how expression of ncRNAs in single cells or within sub-cellular compartments of single cells, can influence biological processes in individual cells and across tissues. In fact, a recent paper combined MERFISH with sub-cellular imaging to show enrichment of ~10,000 coding and non-coding RNAs in organelles and nuclei within a given cell [57]. The major drawback of such second-generation spatial approaches is that they currently rely on limited numbers of probes/genes, which requires *a priori* knowledge of the target transcripts. This reduces the ability to make novel discoveries, such as unexpected expression of a ncRNA. A second major limitation is that a given cell type may not be represented, or represented at a very low frequency, within the plane of the tissue slice selected for probing. Thus, spatial transcriptomics are currently especially useful when combined with data from single cell or bulk RNAseq approaches (which have their inherent drawbacks, as discussed above) and for confirmation of data previously obtained using other methods.

Some of the detection techniques could also shed light on ncRNA function. For example, as discussed, one of the mechanisms of function of ncRNAs is RNA-RNA interactions. A number of methods currently exist to detect RNA-RNA interactions (Table 2). Briefly, they can be classified into low-throughput methods that probe specific individual interactions (‘one to one’) or high-throughput methods that identify a compendium of all interactions (‘one to many’ or ‘many to many’). Moreover, based on the method, the detected interactions can be either directly or indirectly inferred, as delineated in Table 2. RNA-FISH (Fluorescent in situ hybridization) [58] is an enhanced resolution low-throughput method to study probed RNA-RNA interactions that relies of Förster resonance energy transfer (FRET) [59]. Some methods, such as hiCLIP (hybrid and individual-nucleotide resolution UV cross-linking and immunoprecipitation) [60], MS2-TRAP (MS2-tagged RNA affinity purification) [61] and CLASH (cross-linking, ligation and sequencing of hybrids) [62], can be utilized to identify many target RNAs interacting with a previously defined RNA molecule of interest. More recent to the field, high-throughput methods, such as RIC-seq (RNA in situ conformation sequencing) [63], RNA proximity sequencing, PARIS (psoralen analysis of RNA interactions and structures) [64], SPLASH (sequencing of psoralen crosslinked, ligated and selected hybrids) [65], Liger-seq (LIGation of interacting RNA followed by high-throughput sequencing) [66] and MARIO (Mapping RNA interactome in vivo) [67], have been devised to map global RNA-RNA interactions. RIC-seq, in particular, has high sensitivity, relatively lower background and better coverage among all available high-throughput methods. Nevertheless, the resolution remains low, and advancements in the computational dissection and high-resolution visualization of RNA interactions *in vitro* and *in vivo* is still required. A relatively new method on the market is MERFISH. Although ostensibly a spatial transcriptomics solution, the enhanced (sub-cellular) resolution

or MERFISH [55,57] enables it to function as a spatial method to probe 100s to 1000s of targets and provide a visual confirmation of interactions or co-localization, even amongst other labeled molecules. Nonetheless all of these methods, with the exception of RNA-FISH, require millions of cells (or tissues) for input, which is a real limitation when studying rare cell populations, such as immune cells derived from tissues of patients. Thus, there is an unmet need for technology development that can utilize low(er) cell numbers.

Known functions of ncRNAs in immune cells

Among early examples of ncRNAs regulating mammalian immunity was the discovery by the Bartel group that miRs regulate mouse hematopoiesis [68]. ncRNAs have since been found to be involved in many immunological processes and participate in the development and function of both innate and adaptive immune cells and are particularly highly expressed in specific cell types. Examples include *GAS5*, which promotes macrophage and microglial polarization [69,70] and inhibits Th17-cell differentiation [71]; *lnc-DC*, which promotes monocyte to dendritic cell differentiation [72]; *NeST*, which regulates IFN-γ production in both Th1 and Natural Killer (NK) cells [73,74]; *linc-MAF-4*, which guides Th1 specification [75]; *lincR-Ccr2-5′-AS*, which regulates T cell development [76];-ncRNAs that direct $CD8^+$ T cell specification [77]; the TAD-associated (topologically-associated domain) enhancer $lncCSR^{IgA}$, which regulates IgA repertoire diversity in B cells [78]; and *MALAT1*, which sponges *miR-155* for polarizing dendritic cells and Tregs [79]. Figure 3 shows some of the well-characterized ncRNAs associated with specificity for hematopoietic cells at different stages of lineage differentiation and maturation and Figure 4 shows some of the molecular functions controlled by these. A more comprehensive list of ncRNAs regulating function in different immune cell types is shown in Table 3. Although eRNAs and circRNAs have, in general, been less studied in immune cells, accumulating evidence indicates that both classes of RNA play a critical role in immune responses, particularly in cells of the myeloid and lymphoid lineages [3,80]. Some are transcribed especially in response to sensing of danger signals, including a number of eRNAs, transcribed from the *IL1B*, *SOCS3*, *TNFSF8, SLC30A4*, *MARCKS*, *AZIN1 and ACSL1* loci in myeloid cells activated by lipopolysaccharide (via, for example, mitogen activated (MAP) kinase and NF-κB signaling)[81,82]. Some of these induce the expression of pro-inflammatory cytokines and chemokines, notably IL-1β and CXCL8 [81]. Likewise, in lymphoid cells, regulation of T cell receptor (TCR) recombination in both αβ- and γδ-T cell development are dependent on eRNAs derived from the *TCRA* and *TCRB* gene loci [83,84]. Similarly, expanding evidence suggests a diverse role played by circRNAs in regulating the differentiation of both adaptive and innate immune cells (*circNUP214*: Th17 cells; *circKcnt2, circTmem241:* ILC3; *circSnx5:* DCs; *circHIPK3:* macrophage) and polarization (M1 and M2 macrophage polarization by *circCdyl* and *has_circ_0005*, respectively) [85–89].

Broadly, ncRNAs have been described as accessory immunoregulatory nodes in the regulation of key processes, including regulation of interferons [90], cellular damage resolution [91], inflammasome regulation [92], viral interaction [93], cell growth [94], wound-healing [95] and tissue-repair [26]. While much informative work can be done by detecting and functionally assessing ncRNAs in sorted cells from non-inflammatory sites, such as understanding hematopoietic or immune cell differentiation [76,96], one of the

challenges facing the ncRNA field in the context of immunity is that multiple cells work in co-operation and are often spatio-temporally organized. As most immunological responses are characterized by the interactions of many cell types and/or pathogens acting in tandem, experiments directly validating cell-type specific ncRNA expression and function amongst multiple cell types and states in the same reaction is limited in the current literature. Single cell identification of ncRNAs (as discussed earlier) or microscopic analysis of ncRNAs in hematopoiesis, thymic development, lymph nodes or in tissues, such as in spleen or in lungs, are largely absent in the literature. This creates a barrier for truly establishing cell-type specific roles of specific ncRNAs in most autoimmune and pathogen related datasets, which, as discussed, mostly opt for bulk tissue instead of isolated cells.

ncRNAs in immune related diseases

ncRNAs have been experimentally described in several autoimmune diseases, including Sjögren's [97], inflammatory bowel disease (IBD) [98], systemic lupus erythematosus (SLE) [99,100], rheumatoid arthritis (RA) [101,102], psoriasis [103], psoriatic arthritis [104], uveitis [105,106], Behçet's [107], multiple sclerosis (MS) [108], lupus nephritis (LN) [109], myasthenia gravis [110], autoimmune hemolytic anemia [111], immune thrombocytopenia [71] and in other immune-related conditions such as hyperinflammatory lung disease [112], and dyskeratosis congenita [113]. Indeed, the role of ncRNAs in human diseases may be much broader than currently thought and possibly context-dependent. For example, alongside their known roles in immune cell development, eRNAs such as *ARIEL* (ARID5B-inducing enhancer associated long noncoding RNA) and *eRNA-IFNG* are also associated with progression of T-cell leukemia in patients with T-ALL and uveitis (Table 3) [114,115]. Moreover, some pathogens produce ncRNAs that assist their propagation and/or evasion of host immunity, for example Epstein-Barr virus-encoded miRs [116]. Some of these studies are, however, primarily based on *in silico* observations, such as the identification of SARS-CoV-2 miRs that are predicted to interact with transcriptional co-activator subunits and STAT1 [117], rather than via validation experiments, such as those that are still required to detect and test these interactions between SARS-CoV-2 predicted ncRNAs and host cells.

Searching PubMed reveals a plethora of human ncRNAs associated with autoimmune diseases, several being associated with multiple diseases including small ncRNAs *miR-21, miR-146a, miR-155*, and lncRNAs *NEAT1, GAS5, MEG3, MALAT1, TUG1, PRINS, HOTAIR, lnc-DC, hsa_circ_0044235*, and *circCAMSAP1*. These are summarized in Tables 4–7. Of these autoimmune disease-associated ncRNAs, most are specifically expressed in immune cells, implying that they are likely to play a role in the etiology or pathogenesis of these diseases [118]. It is possible, of course, that the functions of ncRNAs differ from cell to cell (e.g. between T and B cells) or between cell states (e.g. resting vs activated T cells, or between Th1 and Th2 cells). Of note are three lncRNAs, *NEAT1*, *GAS5*, and *MALAT1* that demonstrate the diversity of immunoregulatory ncRNA circuits acting amongst cell types in autoimmunity. These are further discussed below.

Nuclear enriched assembly transcript (NEAT1)

NEAT1 is associated with multiple autoimmune diseases (Tables 4, 6–7), as well as some human tumors [119] and neurological diseases (Parkinson [120] and Alzheimer [121] diseases). In fact, *NEAT1* expression is reciprocally correlated with age of onset in female patients with MS, and overall *NEAT1* expression is higher in the peripheral blood [122]. In human SLE, *NEAT1* is overexpressed in circulating myeloid cells and is a regulator of TLR4-inflamatory pathways and cytokines, such as IL-6 and CXCL10 [99].

NEAT1 is expressed constitutively in many immune and non-immune cells. It directly binds active chromatin, suggesting a broad modulatory function on gene expression [28]. *NEAT1* promotes the activation of the NLRP3 inflammasome, a key component of mature IL-1β production [123], in at least dendritic cells, monocytes, and lipopolysaccharide (LPS)-activated THP-1 cells [99,124] (Figure 4). Knockdown of *NEAT1* suppresses Th17 polarization by modulation of STAT3-ubiquitination [125,126], which may partially also explain why *NEAT1* is considered by some as a bridge between STAT3 and histone 3 lysine 27 acetylation (H3K27Ac) [121]. Collectively, elevated *NEAT1* appears to promote inflammatory signatures and contribute to autoimmunity. *NEAT1* is expressed in many cell types and is associated with several diseases, and thus there are shared and distinct mechanisms of action amongst cell types in the context of inflammation. Normalizing the expression of *NEAT1* would be an attractive means of ameliorating some of these processes. However, the mechanisms by which *NEAT1* is overexpressed, and can therefore be normalized, remain less clear.

Growth Arrest Specific 5 (GAS5)

GAS5 is a dynamic, alternatively-spliced, ‘inside-out’ lncRNA (i.e. one that contains processed introns that become intermediates for a variety of snoRNAs [126]). It can exert effects on gene transcription as a ncRNA decoy of the glucocorticoid receptor (GR) [127], or as a miR-sponge for a variety of miRs including *miR-495 (32242002)* and *miR-21* [128]. *GAS5* is associated with cellular proliferation, metastasis [129–131] and is downregulated in many cancers [128,132–134], and associated with multiple autoimmune diseases, including rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), allergy, inflammatory bowel disease (IBD) and immune thrombocytopenia (IT) (Tables 4, 6–7). In fact, *GAS5* expression in plasma can act as a biomarker of SLE [135]. In PBMCs from patients with IT, *GAS5* expression is inversely associated with Th17 polarization via promoting STAT3 degradation by ubiquitin-mediated proteolysis. This is consistent with a direct interaction between *GAS5* and STAT3 and *miR-21*-mediated downregulation of *GAS5* driving Th17 differentiation [71]. However, others have reported that $CD4^+$ T cells from patients with SLE have elevated expression of *GAS5*, as well as *miR-21* [136], which suggests that the *miR-21-GAS5* relationship may not hold true in every disease. *GAS5* is also credited as a regulator of Th2 balance via the *miR-495:circHIPK3* axis to upregulate GATA3 expression and promote allergic rhinitis [137], and as a putative driver of demyelination in MS, where it inhibits microglial M2 polarization [70].

Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1)

Besides cancer, *MALAT1* is associated with multiple autoimmune diseases (Tables 4, 7) and widely expressed amongst immune cells. Expression of *MALAT1* is detectable by conventional scRNAseq, as it contains a non-canonical 3' RNAse P cleavage site, revealing a polyadenylation signal that directs the long *MALAT1* (~7.4kb) cleavage product toward nuclear speckles, with the small cleavage product, termed mascRNA (that is a tRNA-like structure), shuttled to the cytoplasm [138]. Thus, for some ncRNA molecules, like *MALAT1*, this adenylation is positively regulatory, directing the molecule to gain functions, whereas adenylation of other ncRNAs, such as rRNA and tRNA influences their degradation [139,140]. *MALAT1* also has a circularized form termed *circ-MALAT1* that is regulated by GDF15 to induce tolerogenic DCs by dampening NFκB signaling during allograft heart transplantation [141]. In airway epithelial cells (AECs) co-cultured with DCs, *MALAT1* levels are increased and modulate AEC cytokine secretion. Here, *MALAT1* inhibition in AECs induces proinflammatory cytokines (IL-6, IFN-γ and TNF) and chemokines (CXCR2 and CXCR4) secreted by the co-cultured DCs and siRNA directed against *MALAT1* in AECs drives IL-6 secretion [142].

In many contexts, *MALAT1* is found to be regulatory. Notably, overexpression of *MALAT1* in dendritic cells induces regulatory T cells by sponging of *miR-155* [79]. Likewise, *MALAT1* is responsible for regulating IL-10 expression by exerting control over expression of MAF [143]. Thus, mice with *MALAT1* deficiency produce more aggressive responses to infections and are protected against experimental leishmaniasis and malaria [143]. This is concordant with human asthma, in which reduced *MALAT1* expression is associated with loss of regulatory and enhanced inflammatory cytokine production [144]. Consistent with these observations, reduced *MALAT1* expression is observed in activated B and T cells and macrophages, and is important for class-switch recombination, Th1 effector function, and M1 polarization [79,143,145]. In the experimental autoimmune encephalomyelitis (EAE) model, a murine model of human MS, *MALAT1* is downregulated in the CNS and the magnitude of the change correlates inversely with the degree of inflammatory change [146].

Collectively, it is evident that dysregulated expression of *NEAT1, GAS5*, and *MALAT1* are associated with multiple autoimmune diseases. While it is not possible to state definitively whether this association is cause or effect, the fact that all three ncRNAs are potent regulators of immune function suggests that they play an active role in the pathogenesis of these diseases. As ncRNAs commonly demonstrate a range of expression among immune cells, they might have shared and unique cell-type specific functions. However, many of these potential facets remain unexplored. By further analyzing specific ncRNAs associated with autoimmunity and dissecting mechanisms of function in studies of autoimmunity, we may be able to further explore common immunopathogenic mechanisms and the dynamic range under which various ncRNAs operate.

ncRNAs and Specific Autoimmune Diseases

Autoimmunity, the targeting of self-antigens by host, involves a heterogeneous set of processes, that are impacted by a number of cellular mechanisms and extrinsic factors. These include cell signaling events [147], soluble factors [148], gene transcription [149],

cellular metabolism [150], regional microbiota [151], circadian rhythms [152], and genetic polymorphisms [153]. In-depth reviews of autoimmunity can be found elsewhere in the literature, for example [154]. According to the current central molecular dogma, all these cellular processes are mediated or modified in part by protein-coding (mRNA) and non-protein coding transcriptional intermediates. Autoimmune-associations with transcriptional products have been investigated since at least the 1960s beginning with the detection of anti-ribosome autoantibodies [155]. Taking cues from this early work, current studies are exploring whether RNA molecules can be useful in the diagnosis of autoimmunity and the design of precision therapies.

As of today, many studies have described expression of autoimmune-associated ncRNAs using high-throughput techniques (such as microarray and RNAseq) in peripheral blood mononuclear cells [101,156], plasma [100], primary immune cell subsets [3,157], tissue biopsies [103,109,158], and cultured human cell lines [157]. The accumulating data suggest that ncRNAs play important roles in the regulation of pathways contributing to autoimmunity and inflammation (Tables 4–7).

Moreover, ncRNAs that are consistently differentially expressed could potentially be used as diagnostic or prognostic biomarkers of specific autoimmune diseases, especially as some ncRNAs (e.g. circRNAs) are far less susceptible to degradation than others (e.g. linear mRNA). Here we review some of the known functions of noncoding ncRNAs in specific named autoimmune diseases and their putative functional significance towards the pathogenesis of the disease.

Rheumatoid Arthritis (RA)

RA is a systemic autoimmune disease exemplified by inflammation of the synovia leading to joint, cartilage and bone erosion [159]. This is a well-studied disease and, not surprisingly, miRs have been a major component of the research effort in ncRNAs. A variety of miRs are dysregulated in RA and affect expression of target mRNAs encoding cytokines, chemokines, and inflammation-related signaling pathways including TLR signaling [160,161]. For example, in the plasma of patients with RA, 33 miRs are differentially expressed compared to healthy controls, amongst which a single one, *miR-9–5p*, positively correlates with plasma IFN-γ, TNF, IL-17A, IL-4 and CXCL9 levels [162]. A comprehensive review about miRs in RA can be found elsewhere [163,164].

Apart from miRs, many lncRNAs have also been suggested as potential biomarkers of RA and some have been shown to regulate inflammatory processes and tissue damage in both patients and mouse models [165]. These are summarized in Table 4. Owing to unbiased high-throughput approaches, the list of disease-associated lncRNAs is growing. For example, one study identified upregulation of *HOTAIR*, together with 83 other lncRNAs, in the PBMCs of RA patients, as well as in serum exosomes. Although this was corroborated by an independent, targeted study, using qRT-PCR from serum [166], the value of *HOTAIR* as a biomarker of RA remains unestablished [167]. Likewise, microarray screening of serum from patients with RA identified 73 up-regulated and 61 down-regulated lncRNAs, including *LncHIX003209*, which correlated with a number of clinical outcomes [168]. A follow-up study from the same group confirmed elevated expression of *LncHIX003209*

in both PBMCs and circulating myeloid cells and correlation with parameters of disease activity [169]. Further functional assessment identified *LncHIX003209* as a facilitator of macrophage activation via the TLR4/NF-κB pathway [169]. Specifically, *LncHIX003209* acts as a competing endogenous RNA sponge for *miR-6089* [169], a miR that targets TLR4 directly to limit IL-6, IL-29, and TNF generation [170]. Although exhibiting some promise, the utility of *LncHIX003209* as a clinical biomarker remains unknown at present. Other studies in RA have taken a more hypothesis-driven approach aimed at testing the role of specific lncRNAs in disease. For example, one group reported that *lncNTT* expression is upregulated in PBMCs of RA patients compared to healthy controls and regulates differentiation of monocytes to macrophages [171]. This is achieved through interaction with the promoter of *PBOV1*, which is required for maturation and secretion of mediators, such as CXCL10, that recruit inflammatory cells [171]. Consequently, a direct correlation is observed between *lncNTT* expression and parameters of disease severity in RA [171]. Another study noted abnormal expression of two out of ten hypothesized lncRNAs, *LOC100652951* and *LOC100506036*, in T cells of patients with RA and demonstrated some correlation with clinical parameters [172]. Although the functionality of these lncRNAs were not fully investigated, silencing of *LOC100506036* in Jurkat cells was associated with decreased IFN-γ expression [172].

With the growing evidence of the importance of circRNAs in immunobiology, attention in RA has recently also shifted to this class of ncRNAs (Table 4). More than 500 differentially expressed circRNAs have been noted in PBMCs of patients from RA from microarray studies, with some (limited) computational prediction of miRs that may be sponged by these circRNAs [101]. This approach is limited because no experimental validation of target miRs was attempted, and because the methodology, in principle, does not consider the possibility that samples from patients and controls could have different cellularities, which may give the impression of differential circRNA usage. Other studies taking a more targeted approach have assessed individual circRNAs and assessed expression of their target miRs directly. For example, Tang *et. al.*, demonstrated increased expression of hsa-*circRNA-ciRS-7* in PBMCs of patients with RA. In this setting, expression of its target, *miR-7* (*ciRS-7* has more than 70 binding sites for *miR-7*), was repressed, which correlated inversely with elevated mRNA expression of the mammalian target of Rapamycin (mTOR) that harbors *miR-7* binding site in its 3' UTR [173,174]. A similar targeted approach focused on *circNUP214*, which functions as a competitive endogenous RNA sponging miRs and has previously been implicated in Hashimoto thyroiditis [175]. Here, the investigators noted elevated expression of *circNUP214* in PMBCs from patients with RA, although no correlation could be identified between its expression and parameters of disease severity or activity [85]. The authors did, however, demonstrate that *circNUP214* indirectly induces expression of *IL23R* mRNA (via sponging of *miR-125a-3p* [176]), which encodes the IL-23 receptor required for efficient generation of pathogenic Th17 subsets [85]. Although the direct relevance of *ciRS-7* and *circNUP214* to RA is still only tangentially demonstrated, both studies did attempt to make a case for their utility as diagnostic biomarkers. Area under the receptor operator characteristic (ROC) curves (AUC) for the expression of these two circRNAs in PBMCs to distinguish patients with RA from healthy controls were remarkably similar,

0.76 for both [85,174], which represents a moderate diagnostic test. Their utility when used together or in combination with other metrics has not been directly tested.

Despite being a systemic autoimmune disease, one could argue that the predominant site of inflammation, synovial tissues, may offer greater insights into the roles played by ncRNAs in directing inflammation. To our knowledge, there are only a few published high-throughput approaches studying ncRNAs in synovium from RA [177–179]. This report suggests that expression of activating transcription factor 2 (ATF2) and inflammatory cytokines are enhanced at this site and that this transcription factor is targeted for repression by *miR-204/211*, which can in turn be sponged by *hsa-circ-0001859* [177]. There are a number of key limitations that should be acknowledged in this report. Firstly, this study is based on historical expression profiling by array (GSE2053) [180] in which multiple samples were pooled from different donors before RNA extraction and expression profiling. Thus, the provenance of dysregulated *ATF2* expression with respect to donor and cell type is not known. Secondly, neither actual expression nor abnormal expression of *hsa-circ-0001859* was demonstrated, so its role in the local pathogenesis of RA is circumspect and inferential at best. The insights gained from this publication remain unconfirmed by others. However, there are some instances of more targeted, hypothesis-driven studies. For example, fibroblast-like synoviocytes derived from patients with RA demonstrate decreased expression of *circ_0008360*, a circRNA that represses synoviocyte proliferation and production of inflammatory cytokines, including IL-1β, IL-6, and TNF, attributable to sponging of *miR-135b-5p*, a miR that represses expression of histone deacetylase 4 [181].

Psoriasis

Psoriasis is a chronic inflammatory skin disease with rapid proliferation of skin cells that leads to the development of red thick scaly patches on the skin. Similar to other autoimmune diseases, psoriasis is mediated by both innate and adaptive arms of the immune system [182]. Several studies have investigated the expression of ncRNAs in psoriatic skin (Table 5).

High throughput and discovery-led methods have identified a number of differentially expressed lncRNAs in psoriatic skin compared to healthy control skin. One relatively sizeable study performed RNA-seq on 99 lesional psoriatic, 27 uninvolved psoriatic and 90 normal skin biopsies and identified 1214 differentially expressed lncRNAs between normal and lesional psoriatic skin samples. Intriguingly, 505 of these were novel lncRNAs [183]. Although the study did not focus on any particular lncRNA, the authors did note that 26 differentially expressed lncRNAs were from known psoriasis susceptibility regions and that 336 of the differentially expressed lncRNAs could be induced or repressed by IL-17 and TNF, cytokines that play key roles in the pathogenesis of psoriasis [183]. Another study found 971 differentially expressed lncRNAs between lesional skin compared to normal healthy donor samples and confirmed 4 of these (*CYP4Z2P*, *HINT1*, *RPSAP58* and *TRHDE-AS1*) by qRT-PCR. Like the previous study, a large proportion of these lncRNAs were normalized after treatment with anti-TNF therapy, indicating that many lncRNAs are responsive to inflammatory signals and may be the effect rather than cause of disease [103]. Collectively, these data implicate lncRNAs as both potential mediators

of psoriasis and as potential bystanders induced by local cytokines. To help resolve these possibilities, a third study analyzed publicly available transcriptomes deposited in the gene expression omnibus (GEO) database and constructed a psoriasis-associated lncRNA-miR-mRNA network based on the hypothesis that lncRNAs act as competitive endogenous RNAs for miRs. This intriguing study identified two key lncRNAs, named *AL035425.3* and *PWAR6*, that interacted with at least 5 different miRs, were downregulated and hypothesized to play a part in a network that may be pathogenic. Although neither of these were experimentally validated, the analysis does provide a hypothetical pathogenic and targetable node for further exploration in psoriatic skin [184], especially since at least *PWAR6* harbors binding sites for *miR-155*, a driver of NLRP3-dependent inflammation in psoriasis [185]. Interestingly, another high-throughput analysis of psoriatic lesions (12 patients and 12 controls) employing a different computational methodology (weighted gene co-expression network analysis, WGNA) did not identify either of these lncRNAs as key components of a pathogenic causative network, but instead suggested *lnc-SPRR2C* as a candidate repressing *miR-300* by sponging, leading to enhanced inflammatory STAT1 and S100A7 signaling [186]. Similarly, potential biomarkers of psoriatic arthritis (a variant of psoriasis that also affects the joints) have been identified using data analyzed from high-throughput methods deployed on PBMCs. Although only 4 subjects with disease were compared to 4 healthy subjects by RNA-seq, confirmation by qRT-PCR in a larger test cohort of >90 subjects per group suggested that some candidates lncRNAs (*lnc-RP11–701H24.7* and *lnc-RNU12*) were upregulated in disease, correlated with clinical parameters and could distinguish patients from healthy subjects with moderate accuracy (AUCs of 0.76 and 0.84, respectively) [187]. These potential biomarkers have yet to be confirmed in a larger, independent cohort as part of a follow-up study.

Hypothesis-led methods have also identified abnormal expression of several lncRNAs in psoriatic skin, such as *AGXT2L1–2:2* [188], *NORAD* [189], *MEG3* [190], *PRINS* [191,192] and *XIST* [193] and experimental work has revealed some of their functions (summarized in Table 5). For example, *MEG3* is downregulated in psoriasis samples compared to healthy controls and regulates the proliferation and apoptosis of keratinocytes via binding to *miR-21*, which in turn regulates Caspase 8[190]. Over-expression of *MEG3* in keratinocytes, on the other hand, suppresses the PI3K-AKT-mTOR pathway and decreases inflammation on TNF treatment [194]. It is interesting to note that few of these studies include lncRNAs identified in the discovery-led approaches discussed above.

Review articles on the subject are largely in agreement about the disposition and diversity of circRNAs in psoriatic skin, indicating that lesional psoriatic skin mostly demonstrates repression of expressed circRNAs. This position, however, may reflect a bias or tendency to investigate the well-known sponging mechanism of circRNAs (Table 5). For example, one (small) study reported that circRNAs are largely depleted, demonstrating that *circiRS-7*, *circCAMSAP1, circTRIM35, circTULP4, circARAP2* are all decreased, without a correlative change in miRs, in lesional skin compared to paired non-lesional skin using RNAseq [195]. The same group subsequently provided additional evidence of this phenomenon and demonstrated that *ciRS-7* is downregulated and could act as a disease biomarker distinguishing psoriasis from atopic dermatitis (AUC of 0.92), a distinction that can sometimes be difficult to make using current clinical tools [196]. The same publication,

however, also noted that *circZRANB1* is actually upregulated and that its performance as a biomarker is comparable to that of *ciRS-7* (AUC of 0.89) [196]. The top 50 most abundant circRNAs annotated in skin of psoriasis patients by these papers [195] were adopted in a subsequent publication from an independent group for designing a targeted NanoString panel to study circRNAs in lesional skin [197]. As expected, the majority of these were found to be repressed in lesional skin and subsequently be normalized following treatment with secukinumab (anti-IL-17 antibodies), suggesting that IL-17, a known driver of the disease, may be a driver of circRNA repression in psoriasis [197]. Hypothesis-led studies also largely follow similar patterns. Notably, *circRAB3B* has been shown to be repressed in psoriatic skin and to regulate *PTEN* by sponging *miR-1228–3p*. Thus, low *circRAB3B* expression enhances cell proliferation and migration [198].

Other studies, in contrast, suggest that circRNAs can be both up- and down-regulated in psoriatic lesional skin. For example, one publication reported 3016 upregulated and 1940 downregulated circRNAs in psoriatic lesions compared to healthy control samples, with many of these, such as *hsa_circ_0061012*, predicted to sponge miRs that regulate T cell function and development [199]. Additional experiments by the same group demonstrated that *circOAS3*, a psoriatic skin induced circRNA, physically interacts with Hsp70 and regulates signaling through the JNK-MAPK, NF-κB and STAT3 pathways to enhance proliferation of keratinocytes [200]. In a further follow-up study, the authors of the original publication [199], found that one of the circRNAs upregulated in lesional skin, termed *circEIF5*, is an activator of the NF-κB and STAT3 pathways (through undetermined mechanisms) and regulates cellular proliferation and chemokine production [201]. Of these circRNAs, *hsa_circ_0061012* has since been independently verified by others as upregulated in psoriatic skin and to regulate proliferation of HaCaT cells, an immortalized human keratinocyte cell line, by upregulating *GAB2* via sponging of *miR-194–5p* [202]. Meanwhile, two other high-throughput analyses reported differentially expressed circRNAs in skin mesenchymal stromal cells (sMSCs) of patients compared to healthy donors [203,204]. The first identified 123 upregulated and only 6 downregulated circRNAs in sMSCs [203]. One of the downregulated circRNAs labeled *chr2:206992521|206994966* was functionally analyzed and its knockdown in sMSCs found to support enhanced T cell proliferation and altered cytokines secretion (higher IL-11 and lower IL-6 and hepatocyte growth factor secretion)[203]. In the second study, 129 circRNAs were differentially expressed; although it is clear that more circRNAs were up rather than down in terms of detected level, the exact number of detected circRNA were not reported [204]. Of these, expressions of three circRNAs, *hsa_circ_0003689*, *chr4:121675708|121732604* and *hsa_circ_0003718*, were also elevated in plasma and correlated with clinical severity index [204]. The performance of these circRNAs as predictors of disease was not evaluated, nor were functional analyses conducted, but a link to the MAPK pathway was computationally suggested [204]. A number of circRNAs in serum from psoriatic patients detected by microarray are differentially expressed (123 upregulated, 9 nine downregulated) compared to healthy donors, of which the topmost induced, *hsa_circ_005685*, shows some promise as a disease biomarker (AUC of 0.853 to distinguish patients over controls) and iss predicted to act as a miR sponge [205].

Psoriasis is a complex disease, with many immune and non-immune cells participating in the pathology. The major drawback of the available data is due to their being generated from bulk RNA inputs derived from biopsy or blood-derived samples. This means that at least some of the highlighted changes in ncRNAs might reflect changes in cellularity rather than changes in transcriptional output in cells that express transcripts of interest. What is striking from reviewing publications using high-throughput methods is the lack of agreement among them. This may represent an inherent problem with the approach (bulk cells instead of single cells), differences in populations, sample size or the effects of treatments on patients in different cohorts. Part of the disparity in the numbers and identities of circRNAs reported in different publications also relates to computational challenges in identifying back-spliced circularized RNA species. There is room for computational innovation in this area and recent evidence points to novel methods that have been deployed in psoriasis to identify additional sets of previously unrecognized differentially expressed circRNAs, including those that may act as competitive endogenous RNAs sponging cellular miRs [206]. The lack of data on eRNAs is also evident and may reflect similar difficulties in correctly identifying eRNA species using simple methods. Coupled with these limitations, the paucity of proof-of-concept experiments renders it difficult to assess whether highlighted transcripts are abnormally expressed as cause or effect of the disease. These studies, are however, hypothesis-generating and are a reasonable starting point for more in-depth studies that address causation and mechanism.

Inflammatory Bowel Diseases (IBD)

IBD, including ulcerative colitis and Crohn disease, characteristically causes inflammation of the gastrointestinal mucosa. These are another group of diseases in which host genetics and cell-intrinsic mediators (e.g. CXCL10 [207]) interact with cell-extrinsic factors, such as the microbiome. As a result, there is considerable heterogeneity in these diseases, resulting in variable presentation to the clinic. Consensus on the role of the roles of ncRNAs may therefore prove to be difficult to achieve in this sphere.

Aberrantly expressed ncRNAs in Crohn disease are of broad groups and including lncRNAs, lincRNAs and circRNAs (Table 6). miRs in IBD are reviewed elsewhere [208]. Multiple groups have assessed ncRNA expression in mucosal biopsies from patients [209–212] and reported dysregulation of a number of lncRNAs. As anticipated, and similar to other diseases reviewed in this article, there is generally low agreement amongst studies, which may reflect biopsies taken at different sites or differences in cellularity or clinical activity between collected samples used in bulk RNAseq. Briefly, one study identified 329 lncRNAs upregulated and 126 downregulated in colitis using a microarray approach on sigmoid colon biopsies [210]. Here, the authors focused on enhanced expression of lncRNA *BC012900*, which could also be induced by treatment of colorectal adenocarcinoma cells (HT29) with pro-inflammatory agents, including TNF, IL1-β, LPS, Flagelin or CpG oligodeoxynucleotide [210]. The increased expression of *BC012900* was positively correlated with apoptosis in HT29 cells and could be reversed using siRNA mediated knockdown of *BC012900* [210]. In another study, lncRNAs *KIF9-AS1, linc01272*, and *DIO3OS* were found to be differentially expressed in colitis and were suggested as potential biomarkers for the disease, with some of them demonstrating reasonable AUCs (generally

0.8–0.9) in differentiating patients from healthy controls [212]. In a third study, differentially expressed lncRNAs identified in Crohn disease and ulcerative colitis were associated with antigen processing and presentation, immune system processes, and NK cell activation [209]. Finally, a fourth group identified between ~300–2000 lncRNAs as differentially expressed between healthy mucosa and mucosa from patients with uncreative colitis [211], amongst which upregulation of *NeST*, a key regulator of IFN-γ expression, was one of the most statistically significant [211]. In blood, targeted approaches (e.g., qRT-PCR) have identified downregulated *lncMIRT2*, which regulates IL-22 production and apoptosis of colonic epithelial cells [213], and upregulated *DQ786243*, a driver of CREB and FOXP3 expression, in patients with IBD [214]. Perhaps importantly, elevated expression of the lncRNA *THRIL* in serum has very high predictive power for distinguishing patients with IBD from healthy individuals (AUC 1.0) [215]. The interested reader is directed to a number of review articles for a more in-depth discussion of the association between many lncRNAs and IBD [98,216].

Relatively less is known about the role of other ncRNAs in IBD. CircRNAs are no exception in this regard. Although circRNAs are known to play an important role in epithelial cell function in the bowels [217,218] and to immune cell function more generally, little is known about their role in inflammatory bowel diseases. In colonic tissues, *circCDKN2B-AS1* has been reported to be downregulated, and to be a negative regulator of colonic epithelial cell proliferation [219]. In blood, a study of PBMCs from Crohn disease identified 155 upregulated and 229 downregulated circRNAs, amongst which *circRNA_0004662* was predicted to sponge mTOR pathway-related miR [220], hinting at dynamic regulation of cellular immunometabolism. The same group proposed another circRNA, named *circRNA_103765*, as a candidate biomarker of IBD. Although *circRNA_103765* was not a strong biomarker (AUC 0.65–0.7), this circRNA was induced by TNF and normalized after therapy with anti-TNF drugs. Functional experiments indicated that *circRNA_103765* functions to protect epithelial cells from TNF-associated apoptosis, possibly through sponging of members of the *miR-30* family, which negatively regulate expression of delta-like ligand 4 [221]. In other studies, expression of another circRNA, *circRNA_103516*, in PBMC has been shown to be elevated in patients and to correlate with disease severity [222] however the utility of this circRNA as a single biomarker appears to be modest (AUC between 0.6 and 0.79). To our knowledge, eRNAs have not been the subject of intense study in IBD, potentially for the same reasons as their understudy in other diseases, namely difficulties in correctly identifying eRNA species using simple methods.

Multiple Sclerosis (MS)

Multiple sclerosis is an inflammatory immune-mediated demyelinating disease of the central nervous system. Inflammation and the loss of myelin disrupt neural signal conduction and lead to a broad spectrum of mild to severe relapsing-remitting and/or progressive symptoms including pain, motor impairment, cognitive deficit and sensory disturbances [223]. Many miRs are associated with MS, and these are reviewed elsewhere [224]. Of the long ncRNAs, the existing data is currently light on mechanistic insights as most published articles have sought to identify lncRNAs that are surrogates or biomarkers of disease occurring in the central nervous system (CNS), a site that is difficult to access routinely in live humans. The

lack of concerted follow-up or overlapping publications from different groups also makes it difficult to obtain consensus on the disposition of ncRNAs in MS. The main findings are summarized in Table 7.

Genomic variants in several lncRNAs including *GAS5*, *MALAT1*, *HOTAIR* and *ANRIL* are associated with MS [225–230] with several other susceptibility loci close to or within lncRNA-encoding regions [231]. Although it is known that *GAS5* can inhibit microglial M2 polarization and exacerbate myelin loss in EAE [70], the mechanisms of these associations remain largely unknown. In the serum, initial studies reported that *lncTUG1*, *NEAT1* and *RN7SK* (7SK small nuclear RNA) [232], plus *MALAT1* and *lnc-DC* [233], are upregulated in MS patients. The ability of these lncRNAs as biomarkers of disease were either not reported, or in the case of *MALAT1* and *lnc-DC* they had modest performance (AUC ~0.65 alone and 0.75 in combination) [233]. There is, however, some biological plausibility to the functional relevance of *MALAT1* in MS as this lncRNA is a regulator of gene splicing and backsplicing events, including those of MS-associated genes [234]. Microarrays conducted on PBMCs have revealed 2353 upregulated and 389 downregulated lncRNAs in patients with MS and enrichment of these in pathways including tight junctions, regulation of axon guidance, axon guidance receptor activity, and regulation of endothelial cell chemotaxis [235]. Separately, RNAseq of PBMCs using a discovery and validation cohort of patients identified four novel lncRNAs that might potentially serve as biomarkers for the disease [236]. However, the strength of these lncRNAs as biomarkers is still not established and their functional relevance to MS, if any, remains unknown. The associations of transcriptional profiles derived from blood with MS is certainly interesting as these cells are remote from the site of CNS injury. One method to systematically classify peripheral blood transcriptional changes involves creation of an MS-associated competing endogenous RNA network, in which lncRNAs are considered as central hubs. Such a network was constructed by Ding *et al.*, who identified three discrete lncRNAs, *XIST*, *OIP5-AS1*, and *CTB-89H12.4* as hub lncRNAs. Of these, *XIST* was proposed as part of an *XIST-miR-326-HNRNPA1* regulatory module that could be pharmacologically targeted [237]. Interestingly, another method to computationally delineate an MS-associated competing endogenous RNA network by weighted gene co-expression network analysis (WGCNA) identified none of these as a key node and instead focused on *FAM13A-AS1* as the central hub [238]. Unfortunately, the validity and utility of the insights from either analysis have not yet been tested.

Hypothesis-driven studies using qRT-PCR have identified that *lncRNA-PVT1*, *FAS-AS1* and *MEG3* expression are downregulated and *THRIL*, *NEAT1*, *lncTUG1*, *PANDA*, *lncGAS8*, *GAS8-AS1* and *PINK1-AS* expression are upregulated in PBMCs from MS patients compared to healthy controls [122,239–242]. Likewise, *APOA1-AS* and *IFNG-AS1* are elevated in PBMCs, especially during relapses [243]. Because the number of subjects in many of these studies are small and there is heterogeneity in severity, disease stage and treatment, it is not surprising that opposing results for some have also been reported. For example, others have reported that *IFNG-AS1*, *MALAT1*, *ANRIL*, *lncTUG1* and *XIST* are actually repressed in PBMCs of patients with MS [244,245]. Furthermore, despite these associations, almost no functional experiments have been conducted to help substantiate a plausible biological link. One exception is the case of *LncDDIT4*, which is more highly

expressed in PBMCs and $CD4^+$ T cells of patients and acts to promote *DDIT4* mRNA in *cis*, thus enhancing differentiation of naïve $CD4^+$ T cells to Th17 cells [246]. Similarly, another group identified enhanced expression of *linc-MAF-4* in patients with MS and, in a series of functional experiments, showed that *linc-MAF-4* regulates MAF expression to promote encephalitogenic Th1 responses [75].

Comparatively fewer data exist with respect to other forms of ncRNAs. Some studies have described a broad distribution of differentially expressed circRNAs in PBMC samples of patients with MS [247–249], including downregulated circRNAs originated from *ANXA2* (*circ_0005402* and *circ_003556*0) as putative markers of disease [247] and circRNA species that potentially sponge interacting miRs [248,249]. Some differentially expressed circRNAs in blood are detectable within extracellular vesicles [250]. Another study examining exosomes isolated from the cerebrospinal fluid of patients with immune-mediated demyelinating disease (MS and Guillain-Barré syndrome) agreed with broadly dysregulated circRNA dynamics (2364 upregulated and 2730 downregulated), suggesting that *exo-hsa_circ_0087862* and *exo-hsa_circ_0012077* in CSF can function as diagnostic biomarkers for immune-mediated demyelinating diseases [251]. Both these circRNAs performed admirably to distinguish patients from controls (AUCs of 1.0 for both when used alone), although it has to be acknowledged that this was a very small study (n=5 patients and controls each) that has not yet been validated in an independent cohort [251]. A recent report indicates the increased expression of *circ_0000518* at multiple sites, including PBMCs and CSF, of patients with MS [252]. Here, experimental work in microglial cell lines showed that knockdown of this circRNA increased M1 and decreased M2 phenotype [252]. Mechanistically, *circ_000518* interacted with the RNA Binding Protein FUS and its knockdown decreased immune cell infiltration in the CNS of mice with EAE [252]. A significant development in obtaining mechanistic insights into the roles of circRNAs in MS was recently published. Here, the authors showed that *circINPP4B* is upregulated in the peripheral blood $CD4^+$ T cells of EAE and that it positively correlates with the clinical score [253]. Knockdown of *circINPP4B* ameliorated clinical severity and decreased Th17 cells *in vivo* and decreased Th17 differentiation *in vitro*. Mechanistically, *circINPP4B* sponged *miR-30a*, although the targets of *miR-30a* were not elucidated. Finally, the authors showed upregulation of *circINPP4B* in peripheral blood lymphocytes of 18 patients with MS compared to 20 healthy controls [253]. Little is currently known about the disposition of enhancer RNAs in MS.

To summarize, there is a broad collection of dysregulated ncRNAs detected in many autoimmune diseases (Tables 4–7). In most autoimmune workflows, the activities, functions, and utility of many of these ncRNAs remain mostly unknown. There are also many other caveats to these studies, such as the collection of plasma, bulk tissue or circulating PBMCs in lieu of affected tissue or single cells. Consistency is lacking, biased by detection techniques, sample handling, and or biological variability in human samples amongst diverse genomic backgrounds. Nevertheless, emerging studies have genuinely expanded the mechanism of pathogenesis of these various autoimmune diseases and are beginning to show how ncRNAs underpin some of the basic molecular mechanisms of autoimmunity.

Exploiting ncRNAs as diagnostic and therapeutic targets

The study of ncRNAs may offer three potential benefits. Firstly, strong associations between disease and a given ncRNA or sets of ncRNAs could point to clinical utility as biomarkers for diagnostic or prognostic purposes. Autoimmunity, especially if sub-clinical, can be difficult to diagnose in patients and to track. Biomarkers for diagnosis, especially early disease detection, and disease activity represent some of the unmet needs in this domain. The accumulating evidence suggests that most autoimmune diseases are associated with abnormal expression of at least some ncRNAs in accessible sites. Indeed, most human tissues and fluids, such as peripheral blood, plasma, cerebrospinal fluid, vitreous and aqueous humors, saliva, urine, nasal washes, tears, sperm, synovial fluid, vomitus, skin, biliary brushings, feces, cerumen, amniotic fluid, and sputum contain ncRNA signatures and can be sampled. Secondly, a strong association between transcriptional products and a given ailment can form the basis for a more detailed mechanistic understanding of the basic processes of disease. This supposition is likely to depend on precise delineation of the site of expression, the cells in which expression occurs and how expression is switched on and off. Finally, greater understanding of how a transcriptional product relates to disease opens the possibility for therapeutic intervention, either by directly targeting the RNA species of interest, a key node in its regulatory pathway or its mechanism of action. RNA is amenable to the design of discretely targeted therapies, using antisense and related technologies targeted toward the exact RNA of interest. For example, antagonizing miR activity can be accomplished with antisense oligonucleotides to decrease active levels of mature miRs or overexpression of miR sponges (synthetically designed or native), or miR activity can be enhanced using miR mimics. Silencing of long ncRNAs can be achieved with antisense (e.g siRNA, shRNA [254]) or CRISPR technologies (e.g. CRISPR-Cas13 [255]) and disruption of context-specific promoter-associated ncRNAs to modulate gene activation or silencing. Some ncRNAs are candidates for targeted therapies, such as anti- *miR-21, MALAT1, MEG3, GAS5*, and *NEAT1*. Expression of these molecules can theoretically be normalized or modulated, however delivery of the intervention to the correct cellular and sub-cellular compartment is likely to be key [256]. Indeed, delivery is the major limiting factor given most tissues are composed of orthogonally stacked cells that form intricate layers. It is likely that a technological evolution will be needed for the optimal delivery of anti-RNA or RNA-decoy lncRNAs to specific subsets of cells. Care must be taken not to alter putatively healthy cells, and to limit off-target behaviors. Some tissues lend themselves to particular routes of local administration, such as lungs (inhaled delivery), skin (topical delivery), eyes (eyedrops and topical ointments) and joints (direct injection), but off-target effects on “healthy” cells in these tissues is a real possibility. Other tissues will most likely require development of novel delivery methods.

There are some clear limitations with respect to the current state of the field that should be acknowledged. Most of the studies reviewed here are limited by small sample size and geographically isolated populations (most are of European descent). Markers associated with disease in such small studies need first to be confirmed in larger, more heterogeneous populations. Second, poor reproducibility across different studies could indicate either differences in cellularity of samples, or in the case of RNAs that track with disease activity,

differences in disease activity/stage at the time of sampling and/or computational challenges. Processing of samples before capture of ncRNAs should also be standardized, given that sample handling and experimental isolation and necrosis of material can alter the expression of RNA and possibly result in a thanatotranscriptome [257].

Concluding Remarks

As this collection of studies demonstrates, ncRNAs are dynamically associated with and/or regulate a plethora of autoimmune diseases. High-throughput methods reveal a complex network of tissue-level and disease associations. Implementation of single cell methods and advances in spatial transcriptomics are enabling finer molecular dissection of the roles of ncRNAs within individual organelles, individual cells and within tissues as a whole. Rigorous computational network modeling is most likely needed to accurately quantify ncRNAs and correlate respective datasets with one another, given the propensity for autoimmune diseases to share common and unique signatures. An *in silico* machine learning approach of all data may well also define unbiased novel ncRNA regulator associations with immune cell function, which can then be experimentally validated. The curation of larger datasets is critical as part of this endeavor. It is possible, of course, that some ncRNAs may be patient-specific and dependent on individual genetics, so coupling of transcriptomes to patient-specific genomes will probably be an important resource in linking ncRNAs to disease across populations. Likewise, ncRNA studies should be performed in the context of mRNAs, proteins, lipids, organelles and other omics and functional assays, establishing gene-set relationships that are integrated between the library of all available molecules. The majority of studies have focused on highly detected ncRNA molecules. It is likely that low expressed, or harder to detect ncRNAs, such as *NeST* (reported as one ncRNA molecule per *IFNG* allele in some conditions) [73], and their subtle differences in expression, are likely critical for properly assessing the regulatory nature of all ncRNAs in the context of immunological function and disease. Nevertheless, by using and regularly curating community-driven ncRNA resources, it is reasonable to be confident that future studies will directly test and find novelty in many of these hypotheses. Finally, because there are too many ncRNAs with unknown function and/or importance to disease, screening of ncRNAs, for example using a CRISPR library or RNAi, may help to uncover potential functions.

Acknowledgments

This work was supported by extramural research programs of the NIH (R35GM138283) and the Showalter Trust (research award to MK). This research was supported (in part) by the Intramural Research Programs of the National Institute of Diabetes and Digestive and Kidney Diseases (project number ZIA/DK075149 to BA). The authors also gratefully acknowledge the support from the Purdue University Center for Cancer Research, P30CA023168.

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Highlights

- Precise regulation over transcriptional output is key for appropriate immune function
- ncRNAs represent the majority of cellular RNAs and perform indispensable functions
- ncRNAs act as biomarkers of autoimmune diseases and are therapeutic targets
- We review novel methods for their detection and known roles in autoimmunity

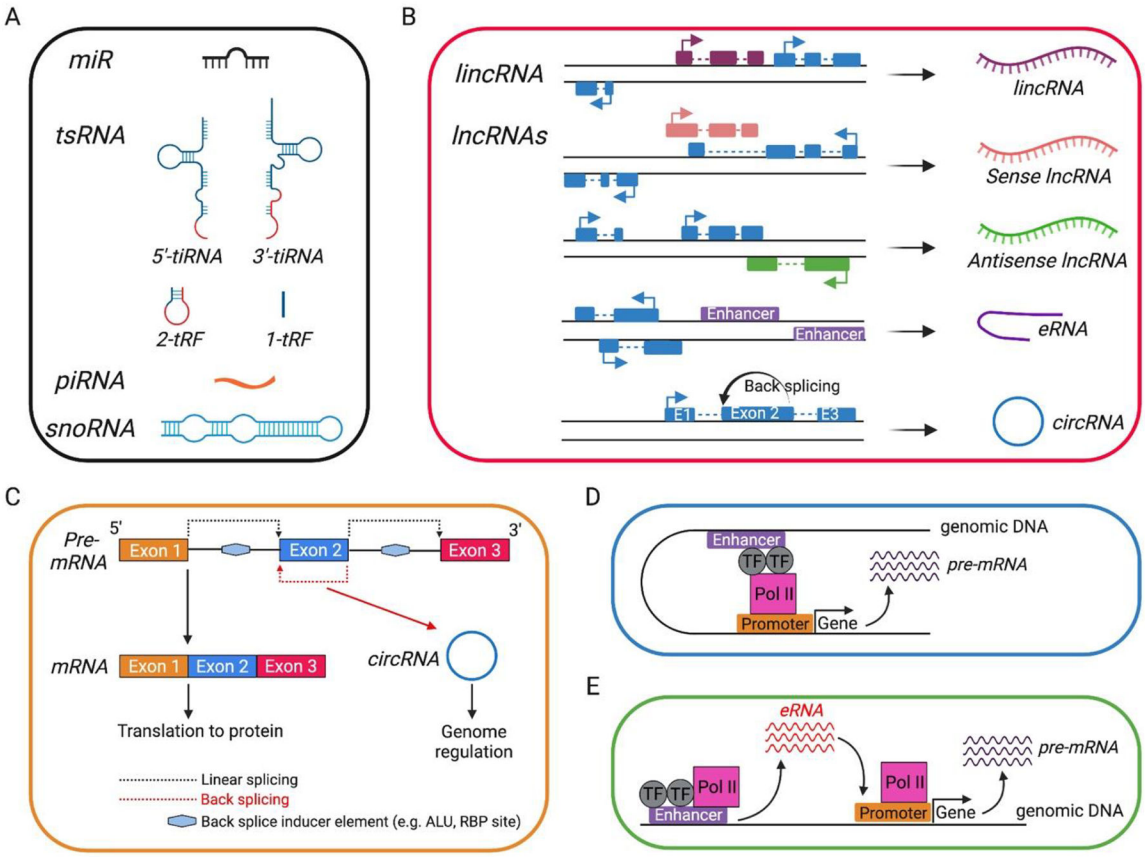

Figure 1. Types of non-coding RNAs and schematic of Circular (circRNAs) and enhancer (eRNAs) RNAs.

A, Small ncRNAs. **B**, Long ncRNAs. In **B**, coding exons are denoted as blue boxes. **C**, pre-mRNA (above) can be spliced in a linear fashion to generate mRNA (below left) or undergo back-splicing to generate circRNA (below right). **D**, conventional enhancers participate in DNA looping bringing transcription factors (TF) and polymerase II (Pol II) together with gene promoters to enhance gene transcription. **E**, some enhancers are themselves transcribed to non-coding RNAs (called eRNAs) that participate in loop formation to enhance gene transcription. For simplicity, loop formation has not been depicted in the cartoon in **E**. miR, micro-RNA; tsRNA, tRNA-derived small RNA (5'-tiRNA/3'-tiRNA, stress induced tRNA-derived RNAs from 5' or 3' ends of tRNA; 2-tRF, anti-codon loop cleaved by unknown ribonuclease; 1-tRF, generated by RNase Z in the 3' trailer of tRNA); piRNA, piwi-interacting RNA, snoRNA, small nucleolar RNAs; lncRNA, linear long non-coding RNA; lincRNA, long intergenic non-coding RNA (lncRNAs that do not overlap with protein-coding genes); eRNA, enhancer RNA; circRNA, circular RNA.

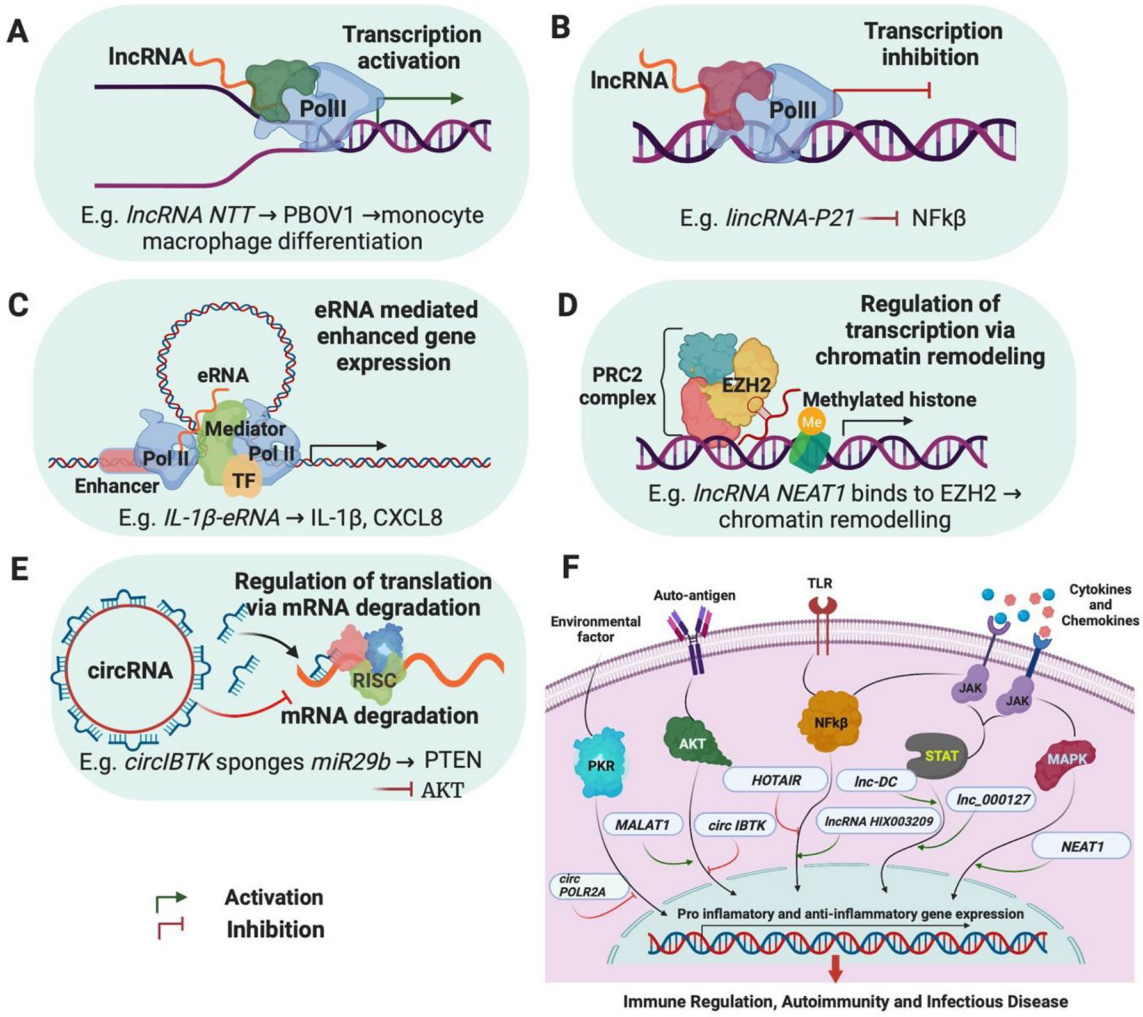

Figure 2. Common mechanisms of action by which ncRNAs regulate cellular function.

Shown in **A-E** are examples of how ncRNAs regulate cellular function, with exemplar genes included. **A**, activation of gene transcription. A common mechanism is physical interactions that facilitate recruitment of the transcriptional machinery to the promotors of target genes to enhance transcription. **B**, inhibition of gene transcription. Here, lncRNAs can act as decoys and bind to transcription factors to alter their recruitment or that of polymerase II to the promoter, resulting in transcriptional suppression. **C**, enhancement of gene transcription. eRNAs transcribed from enhancer elements commonly function to stabilize enhancer-promoter interactions via DNA looping and recruit transcription factors and polymerase II. **D**, chromatin remodeling. ncRNAs, for example lncRNAs, can interact with chromatin remodeling complex proteins, such as EZH2 and PRC2 (promoting polycomb repressor complexes), modulating histone modification and thereby gene expression. **E**, competing endogenous RNAs. Some ncRNAs, such as lncRNAs and circRNAs can act as sponges for miRs, thereby modulating the degradation of mRNAs that are the cognate targets of those miRs. **F**, many of these mechanisms can converge to regulate biological pathways in cells. Shown are just some of the cellular processes implicated in the pathogenesis of autoimmune diseases and how ncRNAs could impact pro- and anti-inflammatory gene expression

programs in those pathways. TLR, Toll Like Receptor; PKR, Protein Kinase RNA; AKT, Protein Kinase B; NFκB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; STAT, Signal Transducer and Activator of Transcription; MAPK, Mitogen-Activated Protein Kinase; JAK, Janus Kinase.

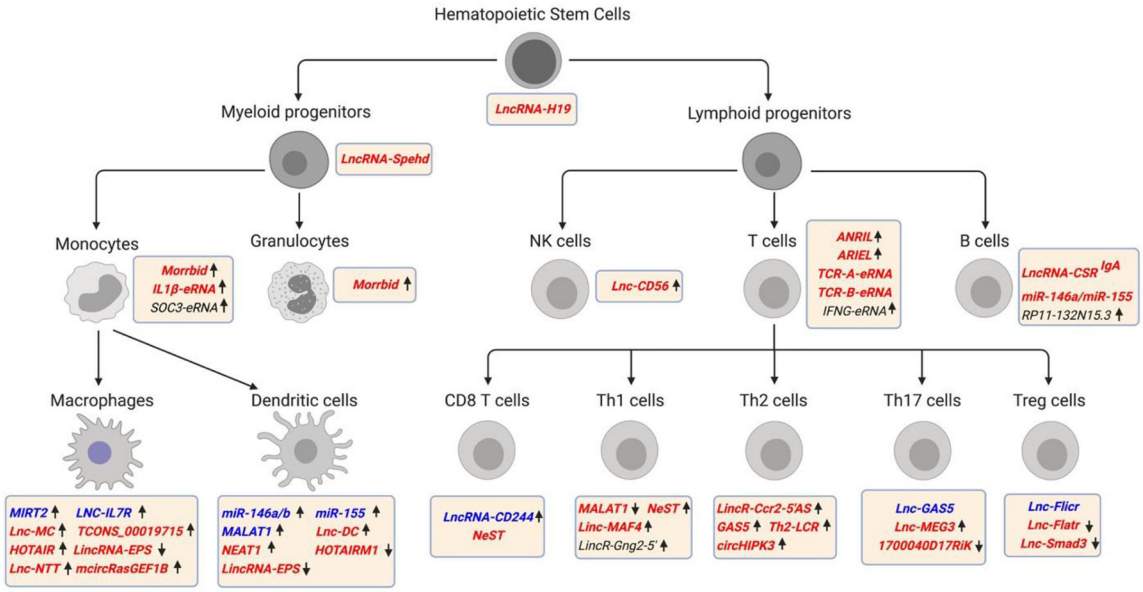

Figure 3. Well-characterized ncRNAs associated with specific hematopoietic lineage cells.

Expression of labeled ncRNAs in different immune cell-types are marked. Arrows indicate expression of ncRNAs in cells: up-arrow, ncRNA upregulated; down-arrow, ncRNA downregulated. Colors represent functions of the indicated ncRNA: blue, impairs cell differentiation and/or function; red, induces cell differentiation and/or function; black, inconclusive effect on differentiation and/or function.

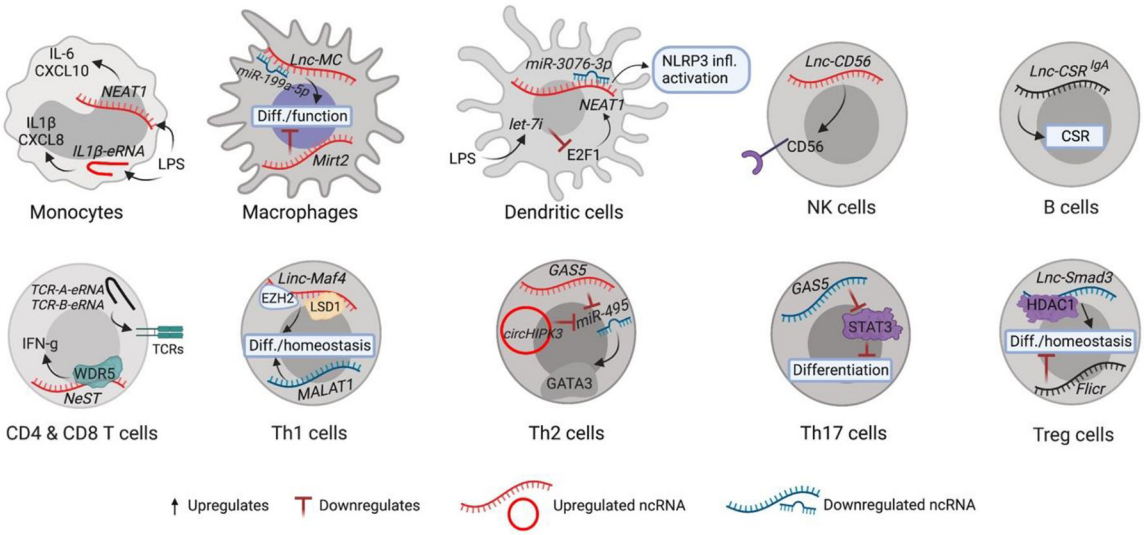

Figure 4. Immune cell ncRNA regulatory circuits.

Examples of known effects of ncRNAs in diverse myeloid and lymphoid cell types. Putative mechanism of regulation is shown for each cell type indicated. Details of these mechanisms (and those of other ncRNAs) are included in Table 3. CSR, class switch recombination; LPS, lipopolysaccharide; Infl., inflammasome; LSD1, lysine-specific demethylase 1; EZH2, enhancer of zeste homolog 2; WDR, tryptophan-aspartic (WD) repeat subunits; Diff., differentiation.

Table 1.

ncRNA types, detection, genomics, databases, and biogenesis.

ncRNAs	Size (bp)		Detection method(s)	Known GRCh38 Coverage	Databases	Biogenesis	Roles in immune cell regulation	Ref
Small to mid-size ncRNAs	*miR*	19–25	Microarray, RNA-seq, Northern blotting, qRT-PCR, ddPCR, SEXPAR, miRacles PCR *In situ stain*	Total # of hairpin precursor: 1917 Total # of mature miRs: 2654 ---- Intronic: 56.44% Intergenic: 23.72% Exonic: 10.38% Other: 13.96%	http://www.mirbase.org http://www.microrna.gr/tarbase (For miR-gene interaction) http://www.microrna.gr/LncBase (For miR-lncRNA interaction)	RNA pol II, RNA pol III, For maturation: Drosha, DGCR8 and Dicer	Target mRNA degradation, translation repression T cells homeostasis, proliferation, plasticity, lineage determination, and functionality (promote and dampen). Regulates B cells development and antibody production	[258–268]
	tRNA	76–90	RNA-seq, Northern blotting PCR *In situ stain*	Total # of tRNAs: 429 # of tRNAs with introns: 28	http://gtrnadb.ucsc.edu	RNA pol III	1/3rd of tRNAs are associated with MHCI on chromosome 6	[269–271]
	tsRNA	14–40	RNA-seq, Northern blotting PCR *In situ stain*	Total # of tRNAs generate tRFs: 321 Total # of tRFs: 28824	http://genome.bioch.virginia.edu/trfdb/ http://cm.jefferson.edu/MINTbase/ (For mitochondrial and nuclear tRNA fragments)	tRNAs cleavage by angiogenin (ANG), Rny1p, Dicer and RNaseZ		[17,272–277]
	piRNA	24–33	RNA-seq followed by piRNApredictor, Piano, Pibomd, piRPred IpiRId PCR *In situ stain*	Total # of piRNAs: 35356 Total 89 clusters	http://resulatorvrna.org/database/piRNA/ http://pirnabank.ibab.ac.in/stats.html https://www.pirnadb.org	Ping-pong amplification	piR30840 (A snoRNA derived piRNA): Binds with IL-4 pre-mRNA intron and inhibit Th2 cells development	[18,278–288]
	snoRNA	60–300	RNA-seq PCR *In situ stain*	Total # of snoRNAs: 2064 Intergenic: 1320 Intronic: 744	http://scottgroup.med.usherbrooke.ca/snoDB/ http://snoatlas.bioinf.uni-leipzig.de http://snoopv.med.mivazaki-u.ac.jp https://www-snorna.biotoul.fr/	RNA pol I, II and III followed by exonuclease activity of RNase III		[288–290]
Long ncRNAs	*rRNA*	121–5070	RNA-seq PCR *In situ stain*		https://www.arb-silva.de http://bioinformatics.psb.ugent.be/webtools/rRNA/	RNA pol I, RNA pol III		[291,292]
	eRNA	200 – 4000	RNA-seq PCR *In situ stain*	Total # of enhancers: 2534123	http://www.enhanceratlas.org https://hanlab.uth.edu/HeRA/ http://gong_lab.hzau.edu.cn/Animal-eRNAdb/	RNA pol II	Regulates chromatin modification, Promotes enhancer-promoter interaction, genes transcription. Releases paused RNA pol II by acting as decoy for NELF. Promotes monocytes activation, TCR recombination.	[23,39,293–296]

ncRNAs	Size (bp)		Detection method(s)	Known GRCh38 Coverage	Databases	Biogenesis	Roles in immune cell regulation	Ref
	circRNA	<100 - >4000	Divergent primer PCR, Northern blotting, Gel trap, 2D Gel electrophoresis, RNaseH, Exonuclease *In situ stain*	Total # of circRNAs: 413657 Exonic: 252494 Intronic: 51291 Intergenic: 22557 5' UTR: 754 3' UTR: 1686 Non-repeat: 24896 Antisense: 39060	http://circatlas.biols.ac.cn/ http://www.circbase.org https://mioncocirc.github.io https://github.com/Xinglab/isoCirc	RNA pol II followed by back splicing	Decoy, promotes autoimmune diseases (SLE, allergic rhinitis, MS, colitis, T1D, RA), Biomarker	[297–302]
	lincRNA/ lncRNA	>200	RNA-seq, RNA-FISH, Microarray, qRT-PCR *In situ stain*	Total # of lncRNAs: 172216 Total # of lncRNA genes: 96308	http://www.noncode.org http://biocc.hrbmu.edu.cn/LNCat/ http://lncrnadb.org/ http://bigd.big.ac.cn/lncbook https://www.monocldb.org/ https://ngdc.cncb.ac.cn/lncrnawiki1/index.php/Main_Page	RNA pol II	Upregulates and downregulates cellular activation and differentiation. Promote and impair immune responses	[71,303–305]

RT-qPCR: Reverse transcription qPCR; ddPCR: droplet digital PCR; SEXPAR: symmetric exponential amplification reaction; miRacles: miR-activated conditional looping of engineered switches. Some databases cover more than one type of ncRNA and are listed here: https://rnacentral.org/; https://nrdr.ncrnadatabases.org/.

Table 2.

Novel and Well-Defined Methods to detect RNA to RNA interactions.

Please note that besides RNA-FISH, all methods here require millions of cells at least.

Type	Method	Direct or indirect?	Advantages	Disadvantages
One to one	RNA-FISH [58,306–309]	Direct	Single cell approach, visualizes target RNA-RNA interactions, can detect nascent and mature transcripts simultaneously.	Low-throughput, fixation req., permeabilization required, difficult to reveal if target sequence is masked by RBPs or any structure.
One to many	hiCLIP (hybrid and individual-nucleotide resolution UV cross-linking and immunoprecipitation) [60,310]	Indirect	Linker addition to make chimeric RNAs improves efficiency and read quality, low background, provides secondary structure of RNAs interacting with target RBPs.	High cell input, antibodies req. against RBPs, two rounds of immunoprecipitation and radiolabeling steps add to complexity, relatively laborious.
	MS2-TRAP (MS2-tagged RNA affinity purification) [61,311]	Indirect	RNA-RBP interactions can be explored, may be utilized to visualize RNA-RNA/RBP interactions *in vivo* by replacing GST tag with fluorescent protein.	Require high cell input, laborious approach, lower coverage, RNA-tagging may interfere with RNAs interactions.
	CLASH (cross-linking, ligation and sequencing of hybrids) [62]	Indirect	One of the earliest established methods for RNA-RNA interactions, UV-cross linking reduces background signal.	High cell input, lower efficiency and quality, limited RNA-RNA interactions, dependency on antibody availability.
Many to many	RIC-seq (RNA in situ conformation sequencing) [63]	Direct	Global mapping of RNA-RNA interactions, pCp-biotin incorporation enhances proximity ligation and read quality, better coverage and accuracy over all existing methods.	High cell inputs needed, formaldehyde crosslinking introduces some background signal and lower nucleotide resolution.
	RNA proximity sequencing [64]	Direct	Global 3D-spatial organization of RNAs *in situ*, can distinguish RNA-dense from sparse regions, reveals nascent and mature RNAs, groups colocalization in sub-nucleolar space, can monitor the speed of RNA-Pol elongation and limits of alternative splicing.	Higher cell inputs needed, requires optimal dilution of single-random barcoded beads and target cells, complex and time-consuming approach.
	PARIS (psoralen analysis of RNA interactions and structures) [65]	Direct	Uses psoralen a nucleotide crosslinker for interacting RNAs, can provide a global map of RNA-RNA interactions.	High cell inputs, complex and laborious method, precise and controlled RNase digestion required, lower coverage and resolution.
	SPLASH (sequencing of psoralen crosslinked, ligated and selected hybrids) [65,312]	Indirect	Biotin-psoralen intercalation in interacting RNAs provides combinatorial method for crosslinking and fragments enrichment, provides inter and intra molecular RNA-RNA interaction map.	High cell inputs, lower yield, relatively large background, low resolution.
	LIGR-seq (LIGation of interacting RNA followed by high-throughput sequencing) [66]	Direct	Crosslinking of interacting RNAs by intercalating psoralen derivative 4'-aminomethyltrioxalen (AMT), followed by interacting RNA circularization and RNaseR treatment enriches target RNAs, can provide global map of RNA interactome.	Requires large numbers of cells, lower coverage, low resolution.
	MARIO (Mapping RNA interactome in vivo) [67]	Indirect	UV-cross linking for reduced background signal, linker enhances proximity ligation, cross-linking can facilitate the study of closely associated RBP-RNA interactions.	High cell input, partially *in vivo* method, complex and laborious.
	MERFISH (Multiplexed error-robust fluorescence in situ hybridization) [55], Xenium [56]	Direct	Single cell resolution identifies broad range of RNAs with subcellular compartmentalization, able to identify cell-cycle stage-associated transcriptional changes.	Requires target RNAs information to design probes (non-discovery led approach), necessitates specific imaging platform, complex and laborious method (probe-design to imaging and decoding)

Table 3.

Described functions of ncRNAs in immune cells.

Immune cells	Type of ncRNA	ncRNA	Expression level	Role	Detection Method	Ref
DCs	miR	*miR-146a, miR-146b*	Upregulated	Promotes apoptosis, impairs pro-inflammatory cytokines production via diminished TRAF6 and IRAK1 expression	Microarray	[313]
	lncRNA	*HOTAIRM1*	Downregulated	Promotes monocytes to dendritic cells differentiation via competitive binding to miR-3960	qRT-PCR, ChIP-chip assay	[314]
		Lnc-DC (LOC645638)	Upregulated	Promotes DCs differentiation via direct interaction with STAT3 through phosphorylation on Tyr-705, prevents SHP1 mediated STAT3 dephosphorylation	Microarray & RNA-seq	[72]
		Malat1	Upregulated	Promotes tolerogenic DCs (via lowered CD80, CD86 and MHCII) by inducing DC-SIGN expression through sponging miR-155, induces Treg expansion	Microarray, qRT-PCR and ChIP assay	[79]
		NEAT1	Upregulated	Promotes DCs maturation, enhances NLRP3 induced inflammasome via direct binding with miR-3076p (a negative regulator of NLRP3)	RNA-seq	[124]
	circRNA	*circSnx5*	N/A	Ectopic expression of circSxn5 induces tolerogenic DCs, impairs T cell response, acts as a sponge for miR-544 to inhibit SOCS1 expression as well as impairs the nuclear translocation of PU.1, negatively regulating DC activation	Overexpression and KO experiments	[315]
DCs and Macrophages	lncRNA	*lincRNA-EPS*	Downregulated	Associated with enhanced pro-inflammatory cytokines (IL1B, IL6 and TNF), iNOS and nitric oxide production	RNA-seq	[316,317]
moDCs	miR	*miR-155*	Upregulated	Dampens pro-inflammatory cytokine production	Microarray	[318]
Macrophages	lncRNA	*HOTAIR*	Upregulated	Promotes proinflammatory responses (enhanced IL-6 and iNOS expression) by NF-kB activation via IkBalpha degradation	qRT-PCR, ChIP assay	[319]
		Lnc-IL7R	Upregulated	Dampens pro-inflammatory responses via association with increased H3K27me3 deposition at promoters of VCAM-1 and E-selectin	Microarray, qRT-PCR	[320]
		Lnc-MC (lnc monocytic RNA)	Upregulated	Sequesters miR-199a-5p and enhances ACVR1B expression promoting monocyte/macrophage differentiation	RNA-seq and PU. 1 ChIP-seq	[321]
		lncRNA-KCNQ1OT1	Downregulated	Polarizes M1 macrophages to M2 macrophages, directly binds miR-21a-5p	qRT-PCR	[322]
		Mirt2	Upregulated	Impairs inflammatory responses, attenuates TRAF6 oligomerization and K63 mediated autoubiquitination inhibiting NF-kB and MAPK pathways to dampen inflammatory molecules (e.g. TNF, IL1B, IL6 and IL12)	Microarray, qRT-PCR	[323]
		TCONS_00019715	Up in M1 and down in M2	Regulates M1/M2 switching, Promotes M1 macrophage differentiation	Microarray	[69]

Immune cells	Type of ncRNA	ncRNA	Expression level	Role	Detection Method	Ref
		PACER	Upregulated	Decoys p50 homodimer, a repressive subunit of NF-kB, promoting COX-2 expression	ChIP assay	[324]
	circRNA	*circCdyl*	Upregulated	Induces the polarization of M1 macrophages by inhibiting the entry of interferon regulatory factor 4 (IRF4) into the nucleus. Sponge for let-7c	Microarray	[88]
		circHIPK3	Upregulated	Induces Macrophage activation via sponging miR-192 and miR-561, in turn upregulating NLRP3 inflammasome and TLR4 expression.	qRT-PCR	[325]
		circRNA-003424, circRNA-001489, circRNA-018127, circRNA-013630	Downregulated	Down in M1 polarized compared to M2 macrophages, mechanism not established	Microarray	[326]
		circRNA-010056, circRNA-003780, circRNA-010231	Upregulated	Up in M1 polarized compared to M2 macrophages, mechanism not established	Microarray	[326]
		circPPM1F	Upregulated	Found to be highly upregulated in type 1 diabetes mellitus patients, associated with LPS-induced M1 macrophage by inducing NF-κB pathway	Microarray	[327]
		hsa_circ_0005567	Downregulated	Ectopic expression of this circRNA induces M2 macrophage polarization, sponge for miR-492 to prevent SOCS2 loss, associated with inhibited osteoarthritis progression	qRT-PCR	[89]
		mcircRasGEF1B	Upregulated	Promotes immune responses via stabilizing ICAM-1 mRNAs	RNA-seq	[328]
Monocytes	lncRNA	*NEAT1*	Upregulated	Promote pro-inflammatory molecules (IL6, CXCL10, CXCL11, CCL2 and CCL8) expression	qRT-PCR	[99]
	eRNA	*IL1B-eRNA*	Upregulated	Enhances pro-inflammatory responses, induces IL1B and CXCL8 expression	RNA-seq	[81]
Monocytic cells (THP1)	eRNA	*SOC3-eRNA, TNFSF8-eRNA, SLC30A4-eRNA, MARCKS-eRNA, AZIN1-eRNA, ACSL1-eRNA*	Upregulated	Upregulated in LPS induced THP1 cells	qRT-PCR, ChIP assay	[82]
Monocytes, macrophages and THP1 cells	lncRNA	*NTT*	Upregulated in RA patients	Upregulates PBOV-1 expression via hnRNP-U binding, NTT overexpression promotes cell cycle arrest, macrophage differentiation and CXCL10 expression	ChIP-PCR, qRT-PCR	[171]
Neutrophils, eosinophils and Monocytes	lncRNA	*Morrbid*	Up: Neu>Eos>Mon	Required for myeloid cell survival by repressing *Bcl2l11* (Bim) expression in *cis*	RNA-seq, Chip-seq, FISH and qRT-PCR studies	[329]
NK cells	lncRNA	*Lnc-CD56 (AB128931)*	Upregulated	Development, positively regulates CD56 expression in human NK cells	Microarray	[330]
ILC3	circRNA	*circKcnt2*	Upregulated	Associated with impaired ILC3 activation during colitis resolution, assembles the nucleosome remodeling deacetylase (NuRD)	Microarray	[86]

Immune cells	Type of ncRNA	ncRNA	Expression level	Role	Detection Method	Ref
				complex onto the *Batf* promoter to reduce *Batf* expression, suppressing IL17 expression and ILC3 activation		
		circTmem241	Upregulated	Induces ILC3 differentiation via recruiting histone methyltransferase ASH1 on *Elk3* promoter to initiate *Elk3* transcription	Microarray, qRT-PCR	[87]
B cells	miR	*miR-146a*	Basal level	Required for marginal zone (MZ) B cells development, directly interacts with Numb (a negative regulator of Notch2) to maintain MZ B cells	RNA-seq, qRT-PCR	[331]
		miR-155	N/A	Regulates IgG class-switched plasma cells development via direct inhibition of transcription factor Pu.1, maintains memory response	Northern blot, microarray and KO studies	[332]
	lncRNA	*lncRNA-CSR* ^{IgA}	N/A	Required for class switch recombination (CSR) to IgA in B cells of the Peyer's patches	High-throughput chromosome capture (Hi-C)	[78]
		RP11–132N15.3	Upregulation	Mechanism and function not established	Microarray	[333]
T cells (Jurkat cells)	eRNA	*ARIEL/XLOC 005968*	Upregulated	Essential in T-cell leukemia cells progression, recruits Mediator Complex proteins to the *ARID5B* enhancer, promotes enhancer-promoter looping and *ARID5B* expression thereby promotes *MYC* oncogene and TAL1-induced transcriptional machinery	RNA-seq, qRT-PCR and ChIP-seq	[115]
T cells	lncRNA	*ANRIL*	Upregulated	Promotes T-cell leukemia cells proliferation, activate NF-kB pathway via ANRIL/EZH2/p65 ternary complex	ChIP-qPCR and KD studies	[334]
		GAS5	N/A	Induces apoptosis and impedes cell cycle	KD and overexpression studies	[335]
		NRON	N/A	Represses NFAT activity via sequestering phosphorylated NFAT in the cytoplasm of unactivated T cells	qRT-PCR, shRNA-based study	[336,337]
		eRNA-IFNG	Upregulated	Promotes Uveitis	qRT-PCR	[114]
	eRNA	*TCR-A eRNA*	Basal level	Required for alphabeta and gammadelta T cells development, promotes V alpha to J alpha rearrangement in alphabeta T cells, required for VdeltaDJdelta and J alpha transcript in gammadelta T cells	Mutation	[84]
		TCR-B eRNA	Basal level	Required for alphabeta T cells development, mediates V(D)J recombination during alphabeta T cells development	Deletion	[83]
CD8 T cells	lncRNA	*lncRNA-CD244 (lncRNA-BC050410)*	Upregulated	Inhibits CD8 T cell responses (reduces IFN-γ and TNF expression) in TB patients via EZH2 recruitment to *ifng* and *tnfa* promoter	Microarray, qRT-PCR, ChIP-qPCR, RIP-qPCR	[338]
		NeST	N/A	Binds with WDR5, a component of H3K4 methyltransferase complex and promotes IFN-γ production	Transgenic expression studies	[339]
	circRNA	*circRNA100783*	Differential exp	Precise role unknown	Microarray	[340]
CD4 T cells	miR	*miR-126a-5p*	Upregulated	Induces Th1 phenotype via promoting Notch-1 signaling in the *Echinococcus granulosus* (a cause of *cystic echinococcosis* disease) infected mice	qRT-PCR	[341]

Immune cells	Type of ncRNA	ncRNA	Expression level	Role	Detection Method	Ref
		miR-181a-5p	Downregulated	miR-181a-5p overexpression in allergic rhinitis (AR) model impedes the binding of RAGE and HMGB1, thereby alleviates Th17/Treg imbalance to block asthma development from AR	qRT-PCR	[342]
	lncRNA	*linc01882*	Downregulated	Downregulated in anti-CD3 and anti-CD28 mediated CD4 T cell activation	RNA-seq, qRT-PCR and KD studies	[343]
		lncSnhg7	Upregulated	Upregulated in the offspring exposed to cadmium during gestation	RNAseq	[344]
		XIST	Upregulated	Induces proliferation and differentiation of CD4 T cells in the PBMCs of primary biliary cholangitis (PBC) patients	qRT-PCR	[345]
	lincRNA	*lincRNA00892*	Upregulated	Promotes CD4 T cell differentiation by inducing CD40L protein expression (minimal impact on mRNA levels), augments B cell activation and IgG secretion	Microarray, qRT-PCR	[346]
	circRNA	*circ003912*	Upregulated	Sponge of miR-31, miR-1231 and miR-647, associated with enhanced expression of miR-146a and Foxp3	Microarray, qRT-PCR	[347]
Th1 cells	lncRNA	*linc-MAF-4*	Upregulated	Maintains Th1 cells homeostasis, recruits chromatin modifiers (EZH2 and LSD1) with MAF, dampens Th2 differentiation	RNA-seq, qRT-PCR	[96]
		lincR-Gng2-5′	Upregulated	Positively regulates STAT4 levels during Th1 differentiation	RNA-seq	[76]
		NeST	Upregulated	Required for IFN-γ production	RNA-seq	[348]
		RP11–552114.1, RP11–37L2.1, linc-MYNN-7, linc-C14orf-up-AS_1, RP11–489018.1, linc-CST7–2, linc-TMEM99–2, linc-LRRC49–4	Upregulated	Precise role unknown	RNA-seq	[96]
		RUNX1-IT1	Upregulated	Promotes Th1 differentiation in the peripheral blood of Graves' disease patients by regulating Tbet	qRT-PCR	[349]
Th1 cells, Th2 cells	lncRNA	*MALAT1*	Downregulated	*MALAT1* downregulation leads to reduced Maf4 expression (a required TF for IL-10 expression) and thereby promotes Th1 and Th2 differentiation by dampening anti-inflammatory cytokines	RNA-seq, qRT-PCR	[143]
Th2 cells	lncRNA	*GAS5*	Upregulated	Promotes Th2 differentiation by inducing GATA3 expression via miR-495 sponging	qRT-PCR	[137]
		GATA3-AS1	Upregulated	Up in effector Th2 cells	qRT-PCR	[137,350]
		lincR-Ccr2-5′ AS	Upregulated	Promotes migration to the target site	RNA-seq	[76]
		lncRNA FR215775	Upregulated	Induces Th2 differentiation in murine allergic rhinitis	qRT-PCR	[351]
		lincR-Epas1-3′ AS	Upregulated	Positively regulated with STAT6 expression in Th2 differentiation	RNA-seq	[76]
	LincRNA	*Th2-LCR (AC004041.2)*	Upregulated	Required for Th2 cytokine production. Interacts with WDR5 and hnRNPs	RNA-seq	[350]
	circRNA	*circHIPK3*	Upregulated	Promotes differentiation by upregulating GATA3 expression via sponging miR-495	qRT-PCR	[137]

Immune cells	Type of ncRNA	ncRNA	Expression level	Role	Detection Method	Ref
		circPVT1	Upregulated	Function and mechanism not established	qRT-PCR	[137]
Th17 cells	lncRNA	*1700040D17Rik*	Downregulated	Promotes differentiation in SLE, biomarker	Microarray, qRT-PCR	[352]
		GAS5	Downregulated	Promotes differentiation in ITP, regulates TRAF6 mediated STAT3 ubiquitination thereby ROR-γt and IL17 production	qRT-PCR	[71]
		GAS5	Downregulated	Reduced expression of GAS5 (act as a sponge for miR-23a) in myasthenia gravis patients induces Th17 phenotype	qRT-PCR	[353]
		MEG3	Upregulated	Sponges miR-17 (a repressing molecule for ROR-γt) thereby promoting Th17 differentiation and function in asthma patients	Microarray	[354,355]
	lincRNA	*LINC01588*	Upregulated	Regulates Treg/Th17 cell balance via peroxisome proliferator-activated receptor (PPAR) signaling pathway	RNA-seq, FISH	[356]
		MIAT	Upregulated	During the development of human Th17 cells STAT3 binds at the promoter of MIAT to induce MIAT expression, ultimately enhanced expression of MIAT induces IL17A expression through PKCa	RNA-seq, qRT-PCR	[357]
	circRNA	*circINPP4B*	Upregulated	Induces Th17 differentiation and EAE progression, sponges miR-30a	Microarray	[253]
		circNUP214	Upregulated	Induces IL-23R and IL-17A expression in RA patients, sponge for miR-125a-3p	qRT-PCR	[85]
Treg cells	lncRNA	*Flatr*	Upregulated	No effect on thymic Treg cells generation, anticipates iTreg cells differentiation	RNA-seq	[358]
		Flicr	N/A	Dampens Foxp3 expression and destabilizes Foxp3 expression, limiting IL-2 concentration	RNA-seq and KO studies	[21]
		lnc-Smad3	Downregulated	Reduced level associated with enhanced iTreg generation, associates with HDAC1 to reduce Smad3 (a required molecule for iTreg conversion) expression	KD and overexpression studies	[359]
HSC	lncRNA	*H19*	N/A	Required for HSC development from endothelium, regulates demethylation of various critical TFs (Runx1 and Spi1) required for hematopoiesis	Single cell RNA-seq, qRT-PCR	[52]
Common myeloid progenitor	lncRNA	*Spehd*	N/A	Maintains oxidative phosphorylation and multi-lineage differentiation	RNA-seq, qRT-PCR, RNA, smRNA-FISH	[360]

DC-SIGN: Dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin; NTT: Noncoding Transcript in T Cells; PACER: P50-Associated COX-2 Extragenic RNA; Lnc-MC: long non-coding; monocytic RNA; Morrbid: myeloid RNA regulator of Bim-induced death; Malat1: metastasis-associated lung adenocarcinoma; transcript 1; ACVR1B: activin A receptor type 1B (ACVR1B; ARIEL: ARID5B-inducing enhancer associated long noncoding RNA; NRON: Non-coding repressor of NFAT; NFAT: nuclear factor of activated T cells; TH2-LCR: Th2 locus control region; ITP: Immune thrombocytopenia; Flicr: Foxp3 long intergenic noncoding RNA.

Table 4.

Discrete ncRNAs associated with rheumatoid arthritis.

Class of ncRNA	ncRNA	Cells/Tissue	Expression (up or down) in disease	Role	Detection method	Refs
lncRNA	*ENST00000572491* *ENST00000563752* *ENST00000569543*	PBMCs, CD4	Up	Biomarkers	Microarray	[361]
	FAM66C	PBMC		Associated in GWAS with RA	GWAS	[362]
	GAS5	T cells	Up	Biomarker	qRT-PCR	[363]
	HIX003209	PBMCs Myeloid cells	Up	Overexpression of *HIX003209* increased THP1 cell proliferation and proinflammatory cytokine secretion	qRT-PCR	[169]
	HOTAIR	PBMCs, Serum exosomes	Up	Forced upregulation of *HOTAIR* in synoviocytes and osteoclasts decreases MMP-2 and MMP-13 activation	Microarray	[167]
		Serum	Up	Biomarker, upregulated in serum of patients	qRT-PCR	[166]
	HOXA3as	Synoviocytes and osteoclasts	Down	Biomarker	Microarray	[167]
	LINC00638	PBMCs	Down	Activation of Nrf2/HO-1 pathway	qRT-PCR	[364]
	lincRNA-p21	PBMCs	Down	Reduced expression of *lincRNA-p21* increases NFκB activity	qRT-PCR	[365]
	LOC100506036 *LOC100652951*	T cells	Up	Knockdown in Jurkat cells linked with decreased IFN-γ and NFAT expression during PMA/Ionomycin treatment	qRT-PCR	[172]
	Lnc-Cox2	Serum	Up	Biomarker, upregulated in serum of patients	qRT-PCR	[166]
	LUST *MEG9* *SNHG4*	Exosomes	Up	Biomarkers	Microarray	[167]
	MALAT1	PBMCs	Down	*MALAT1* SNPs *rs619586* and *rs3200401* were, interestingly, not associated with RA susceptibility	qRT-PCR	[366]
	MEG3	Fibroblast like Synoviocytes (FLS)	Down	*MEG3* knockdown resulted in activation of STAT3, PI3K/AKT pathway, FLS proliferation, IL-6 and IL-8 secretion	qRT-PCR	[367]
	NEAT1	PBMCs	Up	Th17 differentiation	qRT-PCR	[125]
	NTT	PBMCs	Up	Monocyte macrophage differentiation, Cytokine secretion	qRT-PCR	[171]
	PRINS	Exosomes	Down	Biomarkers	Microarray	[167]
	RNA143598 *RNA143596* *HIX003209* *IGHCgamma1* *XLOC_002730*	Serum	Up	Correlation with disease parameters observed. Not functionally assessed	Microarray	[168]

Class of ncRNA	ncRNA	Cells/Tissue	Expression (up or down) in disease	Role	Detection method	Refs
	THRIL	T cells	Up	Biomarker	qRT-PCR	[363]
	TUG1	Exosomes	Up	Biomarker	Microarray	[167]
circRNA	*circHIPK3*	Serum	Up	Sponging of miR-124a	qRT-PCR	[368]
	circNUP214	PBMCs	Up	Biomarker, promotes Th17 cells through IL23R	qRT-PCR	[85]
	circ_000836	Fibroblast like Synoviocytes (FLS)	Down	Represses histone deacetylase 4 by sponging *miR-135b-5p* to limit proliferation and production of IL-1β, IL-6, and TNF	qRT-PCR	[181]
	circRNA_104871 *circRNA 003524* *circRNA 101873* *circRNA_103047*	PBMCs	Up	Biomarkers	Microarray	[369]
	ciRS-7/CDR1as	PBMCs	Up	Biomarker, may inhibit miR-7 and upregulate mTOR	qRT-PCR	[174]
	hsa_circ_0001859	Synovium SW982 cells	Not shown	Competing endogenous RNA for *miR-204/211*. Knockdown of *hsa circ 0001859* decreased expression of ATF2, c-Jun, c-Fos	qRT-PCR	[177]
	hsa_circ_0044235	Peripheral blood	Down	Biomarker	qRT-PCR	[370]
	hsa_circ_0092285 *hsa_circ_0058794* *hsa_circ_0088088* *hsa_circ_0038644*	PBMC	Up Up Down Down	miR sponge	Microarray	[101]

Table 5.

Discrete ncRNAs associated with psoriasis.

Class of ncRNA	ncRNA	Cells/Tissue	Expression (up or down) in disease	Role	Detection method	Refs
lncRNA	*AL035425.3* *PWAR6*	Skin Biopsies	Down	Competing endogenous RNA, candidate regulator of a miR network associated with psoriasis	High-throughput sequencing data from Gene Expression Omnibus (GEO)	[184]
	AGXT2L1–2:2	Keratinocytes	Up	Inhibits apoptosis and promotes proliferation of keratinocytes	qRT-PCR	[188]
	CARD14 *CYP4Z2P* *HINT1* *RPSAP58* *TRHDE-AS1*	Skin Biopsies	Up	Biomarkers	RNAseq	[103]
	lnc-RP11–701H24.7 *lnc-RNU12*	PBMCs	Up	Biomarkers	RNAseq	[187]
	LUCAT1 *TRIM55–1* *LINC00657* *LINC00909*	PBMCs	Up	Decoded to interplay with immune response via pathway analysis	Microarray	[104]
	MEG3	Skin Biopsies	Down	Interacts with miR-21 to regulate caspase-8 levels, implicated in cell proliferation and apoptosis	qRT-PCR	[190]
	NORAD	Keratinocytes	Up	Promotes proliferation of keratinocytes	qRT-PCR	[189]
	PRINS	Keratinocytes	Down in inflammato ry cytokine treated cells	*PRINS* overexpression decreased IL-6 and IL-8 expression	qRT-PCR	[191]
	PRINS	Plasma	Down	Biomarker	qRT-PCR	[192]
	SPRR2C	Keratinocytes and psoriatic lesion	Up	Promotes Inflammation and cell viability, sponges *miR-330* to enhance STAT1 and S1007	RNAseq and qRT-PCR	[186]
	XIST	Serum	Up	Biomarker and miR sponge for miR-338–5p, which targets *IL6* mRNA for silencing	qRT-PCR	[193]
	Many	Skin biopsies	Up and Down	1214 lncRNAs up and down-regulated in lesional psoriasis	RNAseq	[183]
circRNA	*CDR1as* *hsa_circ_0109327* *hsa_skin_05227*	Skin Biopsies	Down	Computationally predicted to act as competitive endogenous RNAs sponging cellular miRs	RNAseq	[206]
	circCAMSAP1 *circTRIM35* *circTULP4* *circARAP2* *ciRS-7/CDR1as*	Skin Biopsies	Down	Genome-wide profiling of circRNAs from paired lesional vs non-lesional skin	RNAseq NanoString CISH	[195]

Class of ncRNA	ncRNA	Cells/Tissue	Expression (up or down) in disease	Role	Detection method	Refs
	circEIF5	Skin Biopsies	Up	Knockdown and overexpression in HaCaT cells inhibited and enhanced proliferation, respectively Activates NF-κB and STAT3	qRT-PCR	[201]
	circOAS3	Skin Biopsies	Up	Interacting with Hsp70 and regulates signaling through the JNK MAPK, NF-κB and STAT3 pathways to enhance proliferation of keratinocytes	Microarray	[200]
	circRAB3B	Skin Biopsies	Down	Downregulated by IL-22 (in HaCaT cells) Inhibits cell proliferation by sponging miR-1228–3p, which targets PTEN	qRT-PCR	[198]
	circRNA chr2:206992521|206994966	Skin Biopsies	Down	Regulation of IL-11, IL-6 and hepatocyte growth factor in skin MSCs; regulation of co-cultured T cell proliferation	RNAseq	[203]
	circTULP4 *circPARD3* *circPTPRA* *ciRS-7*	Skin Biopsies	Down	Repressed circRNAs that normalized after treatment with anti-IL-17	Targeted NanoString panel	[197]
	ciRS-7 *circZRANB1*	Skin Biopsies	Down Up	Biomarkers of disease	RNAseq	[196]
	hsa_circ_0003689 *chr4:121675708|121732604* *hsa_circ_0003718*	Skin Biopsies Plasma	Up	Biomarkers	RNAseq	[204]
	hsa_circ_0056856	Serum samples	Up	Biomarker, predicted to function as a competitive endogenous RNA	Microarray qRT-PCR	[205]
	hsa_circ_0061012	Skin Biopsies	Up	miR sponge	Microarray	[199]
	hsa_circ_0061012	Skin Biopsies	Up	Upregulated in HaCaT cells by IL-22. Silencing reduced proliferation of HaCat cells. Upregulates GAB2 by Sponging miR-194–5p	qRT-PCR	[202]

Table 6.

Discrete ncRNAs associated with inflammatory bowel disease.

Class of ncRNA	ncRNA	Cells/Tissue	Expression (up or down) in disease	Role	Detection method	Refs
lncRNA	*DIO3OS*	Colon tissue and plasma	Down	Biomarkers	qRT-PCR	[212]
	DPP10-AS1 *PDZK1P2* *ANRIL*	Colon tissue	Down	Biomarkers	Microarray	[209]
	DQ786243	PBMCs	Up	Positively corelated with CREB and Foxp3 expression in patient samples	Microarray	[214]
	ENST00000555407 *ENST00000427085 (eRNA)* *TCONS_00027621 (lincRNA)*	Plasma	Down	Biomarkers	Microarray	[371]
	ENST00000569039 *ENST00000422548 (eRNA)* *TCONS_00027580 (lincRNA)*	Plasma	Up	Biomarkers	Microarray	[371]
	GAS5	PBMCs LoVo, HeLa,	No change in PBMC	Affects Glucocorticoid (GC) response	qRT-PCR	[372]
	GAS5	Colon tissue, THP1 cells	Down	*GAS* regulated expression of matrix metalloprotease (MMP) 2 and MMP9	qRT-PCR	[373]
	H19	Colon tissue	Up	*H19* was induced by IL-22 and enhanced proliferation *H19* bound p53 and miRs that normally inhibit cell proliferation	qRT-PCR	[374]
	IFNG-AS1 (NeST or TMEVPG1)	Colon tissue, CD4 cells	Up	Increased expression of *NeST/IFNG-AS1* leads to increased IFN-γ	Microarray	[211]
	LINC01272 *KIF9-AS1*	Colon tissue and plasma	Up	Biomarkers	qRT-PCR	[212]
	lncRNA BC012900	Colon tissue	Up	Apoptosis of colon epithelial cells, knockdown of *lncRNA BC012900* leads to decreased caspase 3/7 activity	Microarray	[210]
	lncRNA Mirt2	Plasma	Down	Positively regulates IL-22 expression	qRT-PCR	[213]
	MMP12 *FAM66D* *SAA2-SAA4*	Colon tissue	Up	Biomarkers	Microarray	[209]
	NEAT1	Colon tissue	Up	*NEAT1* induced *TNFRSF1B* expression, a receptor for TNF, to induce inflammatory signaling. Mechanism not established	qRT-PCR	[375]
	THRIL	Serum	Up	Biomarker.	qRT-PCR	[215]
circRNA	*circCDKN2B-AS1*	Colon tissue	Down	Colonic epithelial cell proliferation	Microarray	[219]
	circGMLC1	Colon tissue	Down	Regulates Inflammation and Autophagy	Microarray	[376]

Class of ncRNA	ncRNA	Cells/Tissue	Expression (up or down) in disease	Role	Detection method	Refs
	circRNA_0001187	Colon tissue	Up	Upregulates Myd88 and TNF	qRT-PCR	[377]
	circRNA_092520 *circRNA_102610* *circRNA_004662* *circRNA_103124*	PBMCs	Up	Biomarkers. *circRNA_004662* has binding potential for miRs related to mTOR	Microarray	[220]
	circRNA_103516	PBMCs	Up	Biomarker. Possible sponge for *miR-19b-1–5p*	qRT-PCR	[222]
	circRNA_103765	PBMC	Up	Biomarker. Induced by TNF. Functions as competitive endogenous RNA to sponge *miR-30* family and impair negative regulation of delta-like ligand 4. Protects epithelial cells from apoptosis	qRT-PCR	[221]

Table 7.

Discrete ncRNAs associated with multiple sclerosis.

Class of ncRNA	ncRNA	Cells/Tissue	Expression (up or down) in disease	Role	Detection method	Refs
lncRNA	*ANRIL*	PBMCs		Significant association between *ANRIL* polymorphisms and MS risk	PCR	[230]
	ENSG00000231898.3 *XLOC_009626* *XLOC_010881*	PBMCs	Up	Biomarker	Microarray	[235]
	ENSG00000233392.1 *ENSG00000259906.1* *XLOC_010931*	PBMCs	Down	Biomarker	Microarray	[235]
	ENSG00000260302 *ENSG00000270972* *ENSG00000272512* *ENSG00000223387*	Whole Blood	Up	Biomarker	RNAseq	[236]
	FAM13A-AS1	Brain		Central hubs in competing endogenous RNA networks in brain tissue	Microarray	[238]
	GAS5	Peripheral blood		Significant association between rs2067079 polymorphisms and MS risk	PCR	[225]
	GAS5	Peripheral blood		Significant association between rs2067079 polymorphisms and MS risk	PCR	[227]
	GAS5	Peripheral blood		Significant association between rs55829688 polymorphisms and MS risk	PCR	[228]
	GAS8 *GAS8-AS1*	PBMC	Up	Biomarker	qRT-PCR	[240]
	HOTAIR	PBMCs	Up	VitD supplementation to MS patients reduced expression of *HOTAIR*	qRT-PCR	[378]
	HOTAIR	PBMCs		Significant association between rs4759314 polymorphisms and MS risk	PCR	[229]
	IFNG-AS1 *APOA1-AS*	PBMCs	Up	Biomarkers. Elevated during disease relapse.	qRT-PCR	[243]
	IFNG-AS1 *GSTT1-AS1*	PBMCs	Down	Biomarkers.	qRT-PCR	[245]
	LncDDIT4	PBMCs, CD4 cells	Up	Regulates *DDIT4* expression in *cis*, to promote Th17 differentiation	Microarray	[246]
	Linc-MAF-4	PBMCS, CD4 cells	Up	Knockdown of *linc-MAF-4* promotes Th2 differentiation and overexpression increases Th1 differentiation	Microarray	[75]

Class of ncRNA	ncRNA	Cells/Tissue	Expression (up or down) in disease	Role	Detection method	Refs
	MALAT1 *Lnc-DC*	Serum	Up	Biomarker	qRT-PCR	[233]
	MALAT1	PBMCs	Up	Biomarker. Contributes to splicing and backsplicing events in cell lines	Microarray	[234]
	MALAT1	Peripheral Blood samples	Up	SNPs were associated with MS risk Biomarker	PCR	[226]
	MALAT1 *ANRIL* *TUG1* *XIST*	PBMCs	Down	Biomarkers	qRT-PCR	[244]
	MEG3	PBMCs	Down	Biomarker (AUC 0.91 to distinguish patients from healthy controls)	qRT-PCR	[241]
	NEAT1	Serum	Up	Biomarker	qRT-PCR	[232]
	NEAT1 *TUG1* *PANDA*	PBMCs	Up	Biomarkers	qRT-PCR	[122]
	PINK1-AS	PBMCs	Up	Biomarker	qRT-PCR	[242]
	PVT1 *FAS-AS1*	PBMCs	Down	Biomarkers	qRT-PCR	[239]
	RN7SK	Serum	Up	Biomarker	qRT-PCR	[232]
	THRIL	PBMCs	Up	Biomarker	qRT-PCR	[239]
	TUG1	Serum	Up	Biomarker	qRT-PCR	[232]
	XIST *OIP5-AS1* *CTB-89H12.4*	PBMCs	Network	Central hubs in competing endogenous RNA networks in peripheral blood, e.g. *XIST-miR-326-HNRNPA1*	Microarray	[237]
circRNA	*circINPP4B*	Peripheral blood lymphocytes	Up	Induces Th17 differentiation in mouse CD4 model of EAE. Sponges *miR-30a*	Microarray	[253]
	hsa_circ_0005402 has_circ_0035560	PBMCs	Down	Biomarkers	Microarray	[247]
	circ_0000518	CSF, PBMCs microglia cells	Up	Induces M1 phenotype and immune cell infiltration to CNS	qRT-PCR	[252]
	hsa_circRNA_001896 *hsa_circRNA_101145*	PBMC	Down	Biomarkers	Microarray qRT-PCR	[249]
	hsa_circRNA_101348 *hsa_circRNA_102611* *hsa_circRNA_104361*	PBMCs	Up	Biomarkers Interacting miRs proposed	Microarray qRT-PCR	[248]