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Review

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lncRNA involvement in immune-related diseases - from SNP association to implication in pathogenesis and therapeutic potential

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Abstract

Development of new high throughput array-based techniques and, more recently, next-generation sequencing (NGS) technologies have revolutionized our capability to accurately characterize single nucleotide polymorphisms (SNPs) throughout the genome. These advances have facilitated large-scale genome-wide association studies (GWAS), which have served as fundamental elements in establishing links between SNPs and the susceptibility to several complex diseases, including those related to the immune system. Nevertheless, the molecular mechanisms underlying the development of most of these disorders are still poorly defined. Decoding the functionality of SNPs becomes increasingly challenging due to the predominant presence of these risk variants in non-coding regions of the genome. Among them, long non-coding RNAs (lncRNAs) are enriched in disease-associated SNPs. lncRNAs are involved in governing the control of gene expression both during transcription and at the post-transcriptional level. The existence of SNPs within the sequences of lncRNAs has the potential to alter their expression, structure, or function. This, in turn, can influence their regulatory roles and consequently contribute to the onset or progression of various diseases. In this review, we describe the implication of SNPs located in lncRNAs in the

development of different immune-related diseases and highlight the potential of these molecules in the development of emerging RNA-based therapies.

Keywords: lncRNA, SNP, immune-related diseases, RNA-based therapies

INTRODUCTION

The development of next-generation sequencing (NGS) techniques has revolutionized the study of biological systems, allowing researchers to sequence entire genomes at an unprecedented speed and scale. These technological advances have presented NGS as an essential tool both in basic and translational research[1], enabling a wide range of scientific applications. NGS, together with recent developments in annotation methods and computational programming[2], have played a critical role in the identification of risk alleles associated with complex diseases through genome-wide association studies (GWAS)[2]. In addition, several high-throughput array-based approaches, such as the Immunochip microarray, have facilitated the analysis of large numbers of single-nucleotide polymorphisms (SNPs) in immune-related loci[3,4].

This genetic mapping has yielded valuable insights into complex diseases, including the identification of immune disease-conferring gene variants that can help in risk prediction. More importantly, this knowledge has guided towards the understanding of the underlying biological mechanisms in these complex diseases[5], which has presented new possible strategies for prevention, diagnosis, and therapeutics. However, this knowledge has remained limited so far, primarily because around 90% of the SNPs identified through GWAS are located in non-coding regions, evenly distributed between intergenic and intronic sequences[6], making it challenging to establish the precise biological functions associated with these variants[7].

Recent studies have shown that disease-associated SNPs are enriched in long non-coding RNAs (lncRNAs)[8]. lncRNAs are a diverse group of non-coding RNAs of more than 200 nucleotides in length[9,10]; their expression is rather cell type-specific in comparison to that of protein-coding genes, and they appear to be predominantly localized in the nucleus[11]. To date, lncRNAs have been implicated in nearly all stages of the gene life cycle, encompassing transcription, mRNA splicing, RNA decay and translation. Given the broad expression of lncRNAs and their participation in fundamental cellular processes, their potential association with various disorders has been explored, particularly in complex diseases, where the signals of association frequently originate from non-coding regions of the genome[12]. Interestingly, increasing studies confirm that the presence of SNPs within lncRNAs can influence diverse aspects of their biogenesis[13,14], and these molecules have shown to be valuable disease-specific biomarkers as well as potential targets for future personalized therapeutic approaches[15,16].

In this review, the implication of immune disease-associated SNPs located in lncRNAs has been studied [Table 1], highlighting the importance of the identification and the functional characterization of these molecules in the context of autoimmune and immune-related disorders (AIDs) to find possible biomarkers and/or therapeutic targets.

GENE REGULATION BY lncRNAs

lncRNAs were initially believed to lack coding capacity and were considered transcriptional by-products or "junk"[17]. However, consortiums such as ENCODE (The Encyclopedia of DNA Elements) and FANTOM (The Functional Annotation of the Mammalian Genome)[2], together with the development of new high throughput sequencing technologies, revealed the presence of an extensive set of non-coding elements with

Table 1. AID-associated lncRNAs and their implication in disease

Autoimmune disease	Associated lncRNA	Associated SNP	Cell type	Function	Refs.
Multiple sclerosis (MS)	*GAS5*	rs2067079	Microglia	SNP located in promoter/enhancer and predicted structure alteration *GAS5* competes with miR-137, which releases its target *Notch1*, resulting in a decrease in neuronal survival	[47-49,51,52]
Celiac disease (CeD)	*Lnc13*	rs917997	Macrophages	SNP disrupts the structure of the lncRNA, decreasing the interaction with hnRNDP and thus leading to the expression of disease-related proinflammatory genes	[13,61]
Type 1 diabetes (T1D)	*Lnc13*	rs917997	Pancreatic β-cells	SNP promotes interaction with PCBP2 and STAT1 mRNA affecting stability	[69]
	ARGI	rs9585056	Pancreatic β-cells	SNP is predicted to change the secondary structure of *ARGI* and it exacerbates type I IFN response	[71]
Psoriasis	*HOTAIR*	rs12826786	Macrophages	SNP increases *HOTAIR* expression, which may induce NFkB activation	[75-79]
Atherosclerosis	*LINC00305*	rs2850711	Monocytes	SNP increases its expression. *LINC00305* modulates NF-κB and promotes monocyte inflammation	[80]
	H19	rs217727	Atherosclerotic plaques	Sponges the miRNAs from the let-7 family	[34,81,82]
	ANRIL	rs10811656 rs10757278 rs10757274 rs2383206 rs2383207 rs10757278 rs7865618	Endothelial cells	It recruits chromatin modifiers to inhibit gene expression in cis and binds to several factors to trans-regulate some genes	[84-86]
Inflammatory bowel disease (IBD)	*IFNG-AS1*	rs7134599	Intestinal cells	Binds to a histone methylation complex and this methylation activates *IFNG* transcription	[87-91]
Rheumatoid arthritis	*FAM211A-AS1*	rs2882581, rs3744281 and rs3760235	Fibroblast-like synoviocytes	SNPs seem to locate in regulatory elements influencing lncRNA transcription and thus nearby genes	[95,99]
Systemic lupus erythematosus	*IL21-AS1*	rs62324212	T cells	SNP located in enhancer regions, which may affect the expression of the lncRNA	[100]

important biological functions, many of them corresponding to lncRNA family[18], which opened a new avenue of research. While protein-coding gene number is similar between highly disparate animal species, the amount of lncRNAs increases with evolutionary complexity. Moreover, these molecules are less conserved than protein-coding genes, present fewer exons, and are more cell-type specifically and less abundantly expressed than coding genes[15,19].

So far, lncRNAs have been defined as non-coding transcripts of more than 200 nt, but recent consensus statement[19] have suggested a more precise categorization of non-coding RNAs into: (1) small RNAs (< 50 nt); (2) Pol III transcripts (i.e., tRNAs, *5S* rRNA, *7SK*, *7SL*, and Alu, vault and Y RNAs) and small Pol II transcripts such as snRNAs or intron-derived snoRNAs (~50-500 nt); and (3) lncRNAs (> 500 nt), which are mostly generated by Pol II. While many lncRNAs are transcribed by Pol II and are spliced and polyadenylated (similarly to mRNAs), there are many other lncRNAs that are not polyadenylated or 5′ capped, are expressed from other RNA polymerases or are processed from introns and repetitive elements. Moreover, regarding their location in the

genome, lncRNAs can be intergenic (referred to as lincRNAs), or intronic when they are transcribed from introns of protein-coding genes[2]. lncRNAs locate on opposite DNA strands of a protein-coding gene[2] and are divergently transcribed[15] or can overlap the DNA strand of a protein-coding gene, and thus, share exons with it[2]. Antisense lncRNAs are transcribed from the antisense strand of protein-coding genes[2], being the most abundant lncRNAs in mice and humans[20].

While significant progress has been made in mapping lncRNAs, elucidating their functional roles has been challenging. There is increasing evidence that specific secondary structure and protein binding motifs of lncRNAs are key for their function; however, we are far from being able to predict the function of a lncRNA from these characteristics[15,16,19]. lncRNAs are able to interact with DNA, multiple proteins, or other RNA molecules, making them good candidates for scaffolding functions and gene regulation[21]. Indeed, lncRNA molecules are involved in various cellular processes and the list of roles that they accomplish is continuously expanding[9].

Most lncRNAs are localized in the nucleus, where they can participate in chromatin regulation, transcription regulation, or the formation of nuclear condensates. Cis-acting and trans-acting lncRNAs can affect interactions with DNA to change chromatin status, both interacting with proteins as transcription factors or chromatin modifiers, as well as forming direct interactions with chromatin, as triplexes or R-loops[15]. Some lncRNAs are able to act locally, silencing genes from the chromosome from which they are transcribed. The most well-known example of this function is *Xist*, which has a vital function in X chromosome inactivation during female development[22]. This lncRNA is transcribed from the X chromosome that has to be inactivated. It acts as a guide for several repressive complexes that bind to the chromatin of the X chromosome, inhibiting the action of RNAPII in the transcription of genes located in the X chromosome[23]. lncRNA *Kcnq1ot1* also generates repressive environments interacting with chromatin and targets repressive histone modifiers in order to silence specific genes[24,25]. Unlike the previous case, it has been reported that some lncRNAs are able to regulate numerous genes throughout the genome. This is the case of the *lincRNA p21*, which is regulated by *p53* and is capable of repressing the transcription of multiple genes in trans[26] [Figure 1A]. Other lncRNAs can bind to regulatory factors, such as chromatin modification complexes or transcription factors, and act as indirect transcriptional repressors or decoys[25,27], preventing these regulatory factors from binding their target genes[2]. An additional group of lncRNAs have been demonstrated to possess the capacity to work as enhancer elements[28] [Figure 1A]. They are usually classified as enhancer-RNAs (eRNAs) and enhancer-associated lncRNAs (elncRNAs), and they are able to promote target gene expression by interacting with scaffold proteins or establishing contacts between enhancers and promoters located far from the genes of interest[15].

Interaction between lncRNAs and splicing factors has been described to be essential for the splicing of different mRNAs, while RNA-RNA duplex formation of some lncRNAs also shows regulation in splicing [Figure 1B][15,29]. Additionally, lncRNAs can also act as physical platforms to enable the assembly of dynamic nuclear structures. For example, lncRNAs such as *NEAT1, MALAT1, or PNCTR*[15,30] participate in the recruitment of proteins to form complexes such as paraspeckles, nuclear paraspeckles or perinucleolar compartments [Figure 1C][31].

The above-mentioned functions occur in the nucleus, but lncRNAs can also perform their roles in the cytoplasm[32], as they may share processing and export pathways with mRNAs[2]. In this compartment, lncRNAs are able to regulate several RNA processes, typically by interacting with mRNA molecules. lncRNAs can stabilize mRNAs by masking the open reading frame (ORF) [Figure 1D][33] or sequester miRNAs due to the presence of complementary sites. This results in a reduced binding of the miRNAs to

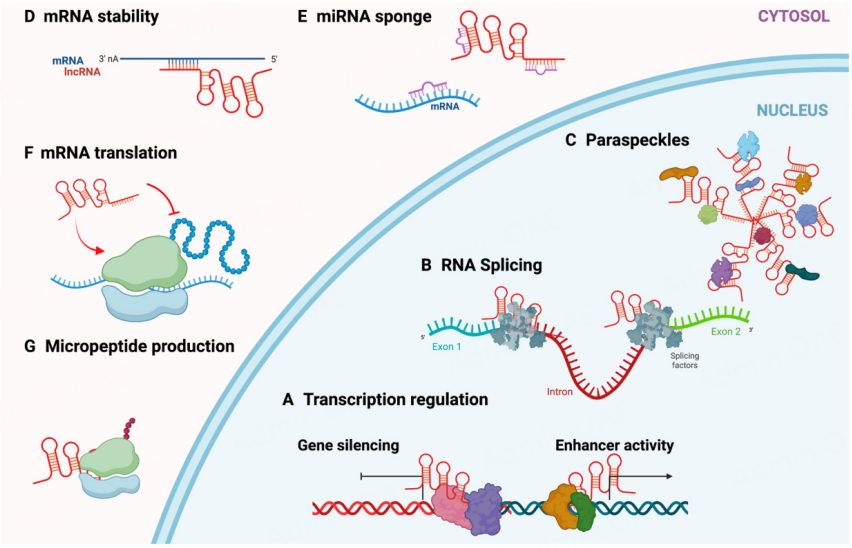

Figure 1. lncRNAs participate in diverse cellular processes. (A) The ability of lncRNAs to bind DNA and protein complexes enables their transcription regulatory function, both inhibiting and enhancing gene transcription. (B) lncRNAs can facilitate the binding of splicing factors to regulate RNA splicing. (C) lncRNAs participate in the formation of nuclear paraspeckles. (D) mRNA stability can be regulated by diverse mechanisms involving lncRNA participation. (E) lncRNAs also bind miRNAs, avoiding the binding of miRNAs to target mRNAs. (F) lncRNAs are able to reduce or activate mRNA translation. (G) Some lncRNAs have small ORFs able to produce functional micropeptides. Created with BioRender.com.

their target mRNAs [Figure 1E][2,15,34]. LncRNAs can also affect the translation process; for example, they are able to bind to the 5′ and 3′ UTR sites and to coding regions, favoring the recruitment of translational repressors that suppress translation[35]. In contrast, some other lncRNAs have been reported to promote translation [Figure 1F][36].

Although lncRNAs are non-coding by definition, they are transcribed by RNAPII, spliced, capped, and polyadenylated[18], similar to mRNAs. According to some novel studies, lncRNAs may also contain small ORFs that encode micropeptides of less than 100 amino acids [Figure 1G][37]. Generally, such small ORFs have been ignored by a length cut-off of 100 amino acids, but computational and ribosome profiling studies have suggested that thousands of these non-annotated ORFs are translated in mammalian cells[38]. However, the biological significance of most of these micropeptides is still being explored.

Cytoplasmic lncRNAs can also be sorted into organelles, such as the mitochondria, for regulating its homeostasis, apoptosis, or communication with the nuclei[39]. Moreover, mitochondrial DNA-encoded lncRNAs have also been described, such as *lncND5, lncND6,* and *lncCytB*, which interact with several mRNA molecules to exert their regulatory functions on their expression and stability[15].

Considering the broadly regulated processes by lncRNA molecules, increasing efforts are being made to gain knowledge on how disease-associated variants can affect these regulatory molecules. Numerous studies have established that the presence of SNPs in lncRNAs can modify their gene expression levels [Figure 2A], structure, or function[13]. These variations have even been suggested to affect the splicing of lncRNAs, as the presence of different alleles would potentially lead to exon skipping [Figure 2B]. Consequently, different isoforms of a certain lncRNA would be transcribed, affecting the regulation of downstream genes[13]. Furthermore, most lncRNAs are known to adopt specific secondary and tertiary structures essential to accomplish their functions. Computational tools have predicted that the presence of SNPs can alter these

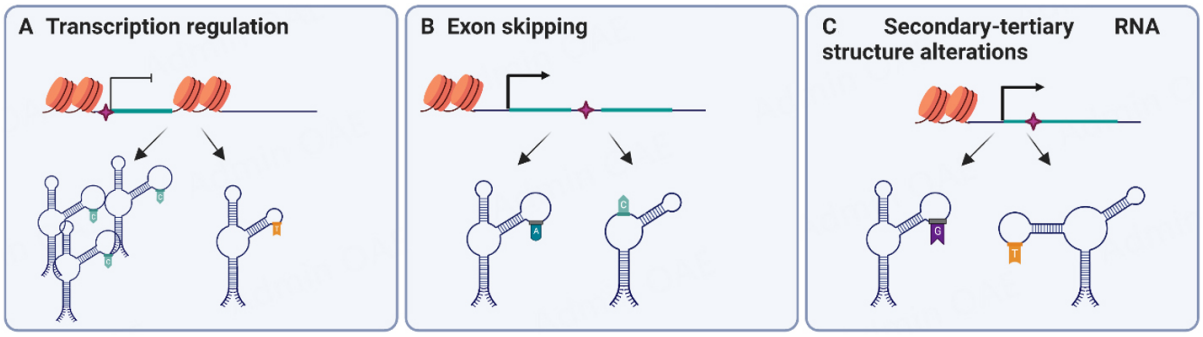

Figure 2. The different effects of SNPs in lncRNAs. Purple stars representing SNPs. (A) If a SNP is present in enhancer/promoter regions of a lncRNA, it can affect the transcription of a lncRNA, changing the transcription factor binding sites or chromatin accessibility. (B) Splicing of a lncRNA can be affected by a SNP enhancing exon skipping. (C) Secondary and tertiary structures of lncRNAs can be modulated by the SNP genotype, mainly when they are located within an exon. Created with BioRender.com.

lncRNA structures[8], and thus, their stability, expression, function, and interactions with other molecules [Figure 2C][40,41]. Hence, the identification of SNPs that disrupt lncRNA function, together with the characterization of the role of these molecules in key cellular processes, makes the study of disease-associated SNPs within lncRNAs an intriguing area of exploration in disease pathogenesis.

IMMUNE-RELATED DISEASE ASSOCIATED SNPs IN incRNAs

The growing evidence demonstrating altered expression of lncRNAs in complex diseases suggests their involvement in a diverse range of disorders, highlighting their significance in preserving cellular homeostasis. AIDs are a diverse group of complex disorders affecting 7% to 9% of individuals worldwide. These diseases are caused by an inappropriate immune response against self-antigens. GWAS and Immunochip mapping have identified numerous AID loci, more than 90% located in non-coding regulatory regions, including lncRNAs[12]. This suggests that lncRNA genes are interesting disease-susceptibility candidate genes. However, the exact molecular mechanisms underlying these associations remain unclear in most cases[42]. Here, we present several disease-specific examples where the effect of an associated variant has been described to affect lncRNA function. Some other studies pointing to possible disease causal effects in interesting lncRNAs are also exposed. The results of these studies point to the potential of these molecules as putative biomarkers and/or therapeutic targets for several inflammatory diseases.

Multiple sclerosis

Multiple sclerosis (MS) is a demyelinating autoimmune disease characterized by the destruction of myelin in the central nervous system (CNS), resulting in various neurological impairments[43]. Although the exact cause of MS remains unclear, a combination of genetic, epigenetic, immune, and environmental factors has been implicated in the development of axonal damage, which contributes to the onset and progression of the disease[44]. Moreover, lncRNA abnormal expression in immune cells and the CNS has been linked to the diagnosis and treatment of MS[45]. Therefore, the discovery of novel genetic and epigenetic markers is crucial for gaining a deeper understanding of the mechanisms driving MS[45,46].

Recently, an Iranian population study demonstrated the association between rs2067079 and susceptibility to MS[47]. Notably, the SNP rs2067079, located in the growth arrest-specific 5 (*GAS5*) gene, has been associated with severe myelosuppression after chemoradiotherapy. This lncRNA has recently emerged as a crucial candidate involved in regulating gene expression[48], and elevated *GAS5* levels have been detected in microglia and macrophages from the brains of MS patients[49]. Increased expression of *GAS5* inhibits the polarization of M2 microglia, which is crucial in innate immune cells from the CNS. Consequently, this

inhibition results in a failure of remyelination and the progression of the disease[49]. The underlying mechanisms by which *GAS5* inhibits the polarization of M2 microglia have not been elucidated yet, but the authors suggest that during the course of MS, mTOR is activated in T-cells, and given that *GAS5* is regulated by this signaling pathway[50], lncRNA expression is increased under these conditions. Another suggested mechanism involves *GAS5* exerting a negative effect on neuronal survival by interacting with miR-137, a critical regulator involved in various aspects of brain function[51]. *GAS5* competes endogenously with this miRNA and inactivates its function, resulting in the release of its target *Notch1*. The modulation of this signaling pathway has been reported to decrease neuronal survival[52].

Moreover, rs2067079 SNP is located within a region that functions as either an active promoter or enhancer and displays a prominent characteristic of expression quantitative trait locus (e-QTL) in multiple tissues, suggesting its potential influence on the expression levels of numerous target genes[53]. Furthermore, this SNP affects *GAS5* secondary structure and stability, potentially affecting its function[53].

Interestingly, another investigation reported elevated levels of circulating *GAS5* in Egyptian MS patients' sera[54]; hence, serum exosomal *GAS5* has been proposed as a potential novel biomarker for MS, showing a correlation with EDSS (expanded disability status scale) scores in most of their patients, indicating its involvement in disease severity[54].

While significant efforts are currently underway within this field, further investigations are required to gain a comprehensive understanding of the mechanism by which *GAS5* is implicated in the development of this disease and the influence exerted by the SNP rs2067079 on its function. Nevertheless, the presence of this lncRNA in non-invasive samples, such as serum, and the fact that it promotes disease progression indicate its potential not only as a biomarker but also as a therapeutic target.

Celiac disease

Celiac disease (CeD) is a chronic immune-mediated disorder characterized by an inappropriate immune response in genetically susceptible individuals due to the consumption of gluten proteins from wheat, barley, and rye. The small intestine is the primary organ affected by this disease[55]. The major genetic factor involved in CeD development is the Major Histocompatibility Complex (MHC) region, which accounts for approximately 40% of the genetic risk associated with the disease[56]. In addition, through various GWAS and Immunochip projects, 39 non-HLA loci have been identified as associated with the genetic risk of CeD. However, only 3 of the CeD-associated SNPs are linked to protein-altering variants located in exonic regions[57], making it difficult to elucidate the role of the associated variants. Within the last years, some lncRNAs have been implicated in CeD pathogenesis[58,59]. However, the precise contribution of these lncRNAs to the disease development remains poorly understood.

Several association studies have linked lncRNAs and CeD risk, for example, the intronic SNP rs6962966 located in *MAGI2*[60] and the SNP rs3130838 in *HCG14*[59], among others. However, there is only one functionally described lncRNA named *lnc13,* which harbors the CeD-associated SNP rs917997. This lncRNA has been observed to be downregulated in small intestinal biopsy samples from CeD patients compared to healthy controls[61]. In basal conditions, *lnc13* interacts with the nuclear RNA binding protein hnRNPD (Heterogeneous Nuclear Ribonucleoprotein D) and HDAC1 (Histone Deacetylase 1) transcriptional repressor[61], repressing the expression of some inflammatory genes, including *STAT1*, *IL1RA*, *TRAF2* and *MYD88*, described to be altered in CeD. Upon exposure to inflammatory stimuli, *lnc13* undergoes degradation, leading to the activation of these proinflammatory genes[61].

In the particular case of rs917997 SNP, the risk allele T[13] disrupts the secondary structure of *lnc13* and reduces the binding to hnRNDP and chromatin, leading to an increased expression of CeD-related proinflammatory genes[61]. This work functionally described how the associated SNP enhances the predisposition to develop CeD.

Moreover, this polymorphism has also been associated with several autoimmune diseases, including inflammatory bowel disease[62] , rheumatoid arthritis[63], and T1D[64]. This suggests that the function of the lncRNA may differ depending on the cell type and the impact of this SNP may vary across different diseases[13].

Type 1 diabetes

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the destruction of insulin-producing pancreatic β-cells by the immune system. The initial stages of the disease involve the infiltration of immune cells into pancreatic islets, resulting in the generation of a proinflammatory microenvironment that facilitates the destruction of β-cells[65]. The reciprocal interaction between β-cells and the infiltrating immune cells induces the production of proinflammatory chemokines and cytokines, resulting in increased inflammation of the pancreatic islets[66]. Multiple studies have implicated lncRNAs in the regulation of innate antiviral immune responses, chemokines associated with innate immunity[67] and other inflammatory genes[68]; hence, it is plausible that lncRNAs are also involved in T1D pathogenesis.

Indeed, while the T allele of rs917997 SNP in the above-mentioned *lnc13* is the risk allele for CeD, the C allele is associated with an increased risk in T1D[69]. The study of this lncRNA in the context of T1D showed a totally different function in pancreatic β-cells. In particular, *lnc13* was described to be a key participant in the activation of the proinflammatory STAT1 pathway. Upon viral infection, which is considered a potential environmental trigger in T1D[70], nuclear export of *lnc13* occurs. Within the cytoplasm, this lncRNA stabilizes the *STAT1* mRNA molecule by facilitating the binding of PCBP2 protein to the 3′-untranslated region of *STAT1*. This stabilization results in an activation of the STAT1 proinflammatory pathway, thereby increasing a proinflammatory environment and consequent β-cell destruction. This critical regulatory role of *lnc13* in T1D-associated dysfunction and death of the pancreatic β-cells highlights its involvement in the disease pathogenesis[69]. Notably, pancreatic islets carrying the T1D risk genotype of rs917997 exhibit increased *STAT1* expression levels compared to the protective genotype. It has been proposed that the secondary structure disruption by the risk allele promotes the formation of the *lnc13*, PCBP2 and *STAT1* mRNA complex[69].

Another example of a T1D-related SNP in a lncRNA that influences disease pathogenesis is illustrated by the SNP rs9585056 located in an exonic region of the lncRNA *ARGI* (Antiviral Response Gene Inducer). This lncRNA is highly expressed in the nuclei of pancreatic β cells after viral infections and is able to bind the transcription factor CCCTC-binding factor (CTCF) to interact with promoter and enhancer regions of the *interferon beta* (IFNβ) and some interferon-stimulated genes (ISGs), promoting their expression[71]. The risk allele of this SNP (G) has been predicted to provoke changes in the secondary structure of *ARGI*, inducing a hyperactivation of the type I IFN response in pancreatic β cells, a common characteristic in pancreatic tissue of T1D patients[71].

The identification of the mentioned SNPs in lncRNAs and their mechanistic association with T1D represents significant advances in understanding the processes in disease development, providing valuable insights into T1D pathogenesis, and suggesting potential therapeutic targets for future approaches.

Psoriasis

Psoriasis is an autoimmune disease[72] in which the interaction between numerous environmental and genetic factors favors the inflammation of skin cells[73,74]. Interestingly, alterations in lncRNA expression have been identified in psoriatic patients, increasing the interest in elucidating their potential role in psoriasis pathogenesis[74].

In this sense, *HOTAIR* harbors several psoriasis-associated SNPs that can alter the expression or function of this lncRNA. Several studies have described an association between the SNP rs12826786 and the risk of developing psoriasis in independent cohorts[75,76]. This lncRNA participates in nuclear factor-kappa B (NF-κB) activation by facilitating the degradation of IκBα inhibitor, resulting in the induction of several of NF-κB downstream genes, including IL-6 and inducible nitric oxide synthases (iNOS)[77]. Interestingly, NF-κB is increased in psoriatic skin, showing an implication of this pathway in the pathogenesis of psoriasis[78]. Furthermore, *HOTAIR* silencing leads to reduced transcription of NF-κB target genes by repressing the binding of NF-κB to target promoter regions. In addition, reduction of *HOTAIR* in macrophages suppresses the induction of diverse NF-κB-related genes[77].

Specifically, the T allele in psoriasis-associated SNP causes increased *HOTAIR* expression and a higher risk of developing the disease[79]. Collectively, association studies point that upregulated *HOTAIR* expression in the presence of rs12826786 risk allele could induce the cytokines and chemokines involved in psoriasis development, explaining the association of this SNP with psoriasis. Nevertheless, a deeper functional study of the effect of the SNP genotype in *HOTAIR*-dependent proinflammatory response in psoriasis is still needed to achieve a more complete understanding of the pathogenesis process.

Atherosclerosis

Atherosclerosis is a chronic vascular inflammatory disorder. It is not considered a disease directly caused by the immune system, but it has a major immune component in all disease stages. For example, the infiltration of leukocytes and the secretion of proinflammatory cytokines by immune cells are among the primary events in early pathogenesis[80].

There is an intronic SNP (rs2850711) in the lncRNA *LINC00305* that shows an association with atherosclerosis[14,80]. *LINC00305* has been demonstrated to have an increased expression in atherosclerotic plaques in comparison to normal arteries. Additionally, these lncRNA levels were higher in monocytes than in endothelial or smooth muscle cells[14,80]. In monocytes, it is in charge of promoting the expression of inflammatory genes[80]. Mechanistic functional analyses have demonstrated that *LINC00305* modulates NF-κB by targeting lipocalin-1 interacting membrane receptor (LIMR) and aryl-hydrocarbon receptor repressor (AHRR). As a result, it is able to enhance monocyte inflammation and phenotypic switch of aortic muscle cells, which are signatures of atherosclerosis[80]. The exact mechanisms that underlie the association between the SNP and the lncRNA in the context of the disease have not been described in detail, but it is known that the risk allele of this SNP increases the expression of the lncRNA[14,80]. As *LINC00305* function consists of increasing inflammation, a higher inflammation is expected in patients with atherosclerosis in the presence of the risk allele.

Several SNPs within the genomic locus of the lncRNA *H19* have also been linked to some cardiovascular-related conditions[14]; for example, rs217727 has been associated with an increased risk of coronary artery disease (CAD)[81]. *H19* has been identified within adult human atherosclerotic plaques, which suggests its implication in this disease[82]. Regarding its mechanism of action, it is a cytoplasmatic sponge for the miRNA family let-7[34]. Interestingly, impaired function of let-7 miRNAs has been linked to cardiovascular diseases[83]. Even if the implication of lncRNA *H19* in different cardiovascular diseases has been widely

described, the contribution of the GWAS-identified SNPs that are thought to confer disease predisposition in the pathogenesis process is unclear[14] and more studies are required.

Some other studies have identified SNPs within the atherosclerosis-related lncRNA antisense non-coding RNA in the *INK4* locus (*ANRIL*). *ANRIL* is located in the gene cluster of the *CDKN2A/B* gene, close to the CAD risk region, and that is why *ANRIL* is known to play an important role in regulating this locus[84]. Mechanistically, *ANRIL* recruits polycomb group proteins that epigenetically modify chromatin, consequently inhibiting gene expression in cis. Moreover, *ANRIL* can also have trans-regulation functions by binding Alu elements, E2F transcription factor 1, or CTCF, among others[84]. It has been identified that the simultaneous presence of the T allele of the rs10811656 SNP and the G allele of rs10757278 increases *ANRIL* expression and disrupts its binding site with STAT1. In addition, carrying the risk allele for the SNPs rs10757274, rs2383206, rs2383207, rs10757278 is linked to more severe atherosclerotic plaques[85]. Another study demonstrated that carrying the A allele for the SNP rs7865618 is strongly associated with a higher expression of a certain transcript of *ANRIL*[86]. Altogether, it has been seen that the expression of diverse *ANRIL* transcripts can be influenced by the SNP genotype, affecting both cis- and trans-gene regulation[86].

In summary, the multiple involvement of lncRNAs in the molecular mechanisms of atherosclerosis pathogenesis emphasizes their promising role as novel targets for potential therapeutic strategies.

Inflammatory bowel disease

Inflammatory Bowel Disease (IBD) comprises a group of disorders characterized by chronic inflammation of the gastrointestinal tract. Typically, it has been classified into two subgroups: Chron's disease (CD), which causes inflammation through the entire gastrointestinal tract, and ulcerative colitis (UC), which exclusively affects the mucosal layer of the colon[87]. The causes of IBD remain unclear, but it has been suggested that it may result from an inappropriate inflammatory response to intestinal microorganisms and foreign antigens in genetically susceptible individuals[88]. Several interleukins and cytokines have been reported to mediate the inflammatory process that takes place in this disorder, including interferon-gamma (IFN-γ). IFN-γ is mainly synthesized by T- and NK-cells and is involved in Th1 responses and bacterial defense[14].

Of interest, there is an intronic SNP (rs7134599) in the genomic sequence of the lncRNA *interferon gamma antisense 1 (IFNG-AS1),* and several GWAS studies have observed a correlation between this SNP and IBD susceptibility[14,87,88]. *IFNG-AS1* overlaps with the locus of *IFN-γ* and is highly expressed in CD4 and CD8 T cells, B cells, and NK cells in the colon. Indeed, it has been demonstrated to be elevated in UC patients, even higher in active UC compared to non-inflamed ones[87]. This lncRNA was demonstrated to promote the expression of *IFN-γ*[87,89] in cis[90]. A mechanism that has been suggested to explain this regulation is that *IFNG-AS* may bind to the MLL/SET1 histone methylation complex and enhance transcription activating methylation on the histones surrounding the gene of *IFN-γ*[87,91].

However, it is unclear how rs7134599 genetically predisposes to IBD[87], nor how it alters the function of *IFNG-AS1* to promote pathogenesis, as there are many association studies but not enough functional studies to clarify the current mechanistic gaps of the SNP implication. One of the strongest hypotheses is that the SNP could regulate the splicing of the lncRNA, which may contribute to its high levels observed in IBD patients[87]. In this way, the expression of *IFN-γ* would be enhanced, creating the characteristic inflammatory environment of this condition. Nevertheless, further studies are of special necessity to establish a mechanistic link between the SNP and the lncRNA functionality, as well as the involvement in the pathogenesis.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disease characterized by erosive and polyarthritis as the main clinical manifestations[92]. The presence or absence of autoantibodies like anti-cyclic citrullinated peptide (CCP) and rheumatoid factor (RF) have been suggested to be adequate to classify different RA subtypes[93]. Due to its complex pathogenesis and subtle clinical features, early diagnosis of RA is challenging to achieve. Hence, there is still a need for early diagnosis, selection of appropriate therapeutic agents, and implementation of effective clinical management strategies[94].

There are various studies describing RA-associated SNPs within lncRNA genes, speculating that they act as genetic regulators in the development of RA. More specifically, the association between several SNPs located within the lncRNA *FAM211A-AS1* and RF-positive RA has been described in a Chinese population[95]. *In silico* analyses have suggested that these polymorphisms are localized in regulatory elements (promoters, enhancers…). Hence, these SNPs could alter the binding of the transcription factors to these regions, potentially altering the expression of *FAM211A-AS1* lncRNA and nearby genes[95]. Indeed, these SNPs were identified to be eQTLs for *FAM211A-AS1* and its nearby genes[95].

Within the last years, many different lncRNAs, including *MALAT1*[96], *UCA1* (urothelial carcinoma associated 1)[97], *ENST00000456270*[98], and the above-mentioned *FAM211A-AS1*[99], have emerged as potential players in the pathogenesis of RA, as they have been found to be dysregulated in RA patients[95]. However, to date, no studies have reported mechanistic evidence between SNPs located within these lncRNAs and the genetic predisposition to RA. Hence, further functional studies are required to progress from association and bioinformatic analyses to the clarification of the precise molecular mechanisms altered by these SNPs in the context of RA pathogenesis.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an immune-related disorder characterized by aberrant immune responses that lead to a loss of self-antigen tolerance and excessive production of autoantibodies. SLE primarily affects females of reproductive age and nearly 50% of SLE patients experience life-threatening complications[100]. Although an imbalance of CD4+ T cells is known to be implicated in the pathogenesis of SLE[100], the exact underlying mechanisms remain unclear as the pathogenesis of SLE involves a complex interplay of genetic, environmental, and hormonal factors.

Dysregulation of some lncRNAs has been reported in SLE patients[101]. In particular, *IL21* antisense RNA 1 (*IL21-AS1*) levels are decreased and positively correlated with *IL-2* gene expression in these patients. Moreover, *IL21-AS1* expression is positively correlated with the proportion of activated T follicular regulatory (Tfr) cells in SLE patients[102]. Interestingly, defective IL-2 production has been observed in SLE patients, resulting in reduced Tfr cell numbers[103]. Additionally, *IL21-AS1* expression is also negatively correlated with disease activity in SLE, suggesting that a reduced expression of this lncRNA may contribute to SLE development[102].

In the context of SLE, around 90% of the associated polymorphisms are located in non-coding regions, too[104]. Notably, a meta-analysis study has identified the SNP rs62324212, situated in the enhancer region of *IL21-AS1*[102], and suggests a potential association between the risk allele of rs62324212 (A) and SLE susceptibility[102]. However, the relationship among rs62324212, *IL21-AS1*, and SLE remains poorly understood. Consequently, more functional studies would shed light on deciphering how the presence of a SNP within the sequence of a lncRNA affects its functionality and how this contributes to the pathogenesis of the disorder.

THE POTENTIAL THERAPEUTIC USE OF lncRNAs

Numerous lncRNAs affected by cancer-associated SNPs have been linked to drug resistance in cancer[14]. Therefore, potential future applications might be incorporating patients' non-coding genome sequence data to significantly improve the selection of appropriate treatment strategies. Nonetheless, a thorough understanding of the link between potential mutations in lncRNAs and the progression of disease or resistance to drugs is still needed[14].

Studying the functional implication of SNPs within lncRNAs reveals diverse molecular mechanisms associated with the progression of complex diseases, opening up new possibilities for targeted therapeutic approaches. Lately, there has been a surge of interest in RNA-based treatments, particularly those focusing on mRNA molecules, such as RNA vaccines[105]. Moreover, the increasing studies relating lncRNAs in diverse complex diseases such as autoimmune disorders have encouraged different research groups to study the therapeutic use of these molecules. Recent clinical studies have opened possibilities for targeting these lncRNAs for therapeutic purposes, emphasizing the importance of further research in this area.

lncRNAs possess characteristics that make them promising diagnostic tools. As they are involved in diverse cellular processes and exhibit cell type-, tissue- and disease status-specific expression patterns, lncRNAs can serve as diagnostic markers for specific diseases. Disease-specific expression levels of lncRNAs have been described; hence, quantification of lncRNA can be used to detect disease presence even before symptoms appear in some patients. Other lncRNAs can be related to disease prognosis or treatment resistance[16]. Interestingly, some lncRNAs have been detected in body fluids such as serum, plasma, or urine, so they can be detected by non-invasive methods, making them attractive candidates as biomarkers for disease diagnosis and prognosis. Additionally, enriched exosome lncRNA expression in plasma has also been identified in esophageal squamous cell carcinoma patients, while circRNAs have also been enriched in exosomes and showed potential diagnostic use[16].

lncRNA features also make them attractive drug targets, as lower doses would potentially minimize off-target toxic effects[105]. The most advanced attempts at therapeutic lncRNA targeting are currently based on the use of antisense oligonucleotides (ASOs), which can form complementary base pairs with their target lncRNAs[105]. ASOs binding to target nascent lncRNAs within the nucleus results in premature transcription termination, hence reducing lncRNA expression levels[106]. Similarly, small interfering RNAs (siRNAs) can trigger post-transcriptional RNA degradation, leading to the knockdown of pathogenic RNAs through a dicer- and argonaute (AGO)-dependent cleavage pathway[107]. Alternatively, lncRNA genes can be modulated through steric blockade of their promoters or by utilizing genome-editing techniques such as CRISPR-Cas9 and its derivatives[107].

Library screenings have already identified small molecules that are capable of specifically binding to lncRNAs and inhibiting their interactions with other molecules. This strategy enhances the stability of the target lncRNA, allowing it to carry out its functions effectively. This is the case of some of the lncRNAs mentioned in this review, such as *GAS5*[108] and *MALAT1*[109].

Rather than modulating their functions, the participation of lncRNAs in diverse cellular pathways underscores their potential as effective therapeutic agents. For example, in order to activate or silence gene expression, lncRNAs can be tethered to the nucleus, where they can regulate target gene expression. Therefore, the design and delivery of lncRNAs to target specific gene loci could enable programmable gene activation or silencing. However, the large size of lncRNAs can pose challenges for delivery and may trigger an immune response. Identification of the functional regions of lncRNAs could facilitate the engineering of

smaller synthetic RNA molecules that function as the lncRNA of interest, evolving as effective drugs. While the sequence of many lncRNAs differs across species, their structures are often conserved, suggesting that structural elements may be a primary determinant of function. Therefore, a comprehensive understanding of how lncRNA domains interact with proteins, mRNAs, or genomic loci is essential for the rational design of lncRNA therapies, enabling the selection of on-target sites while minimizing off-target effects[105].

Although numerous questions and challenges remain to be addressed, the increasing success rate of nucleic acid therapeutics presents an exciting opportunity to explore lncRNAs as viable therapeutic targets in various complex pathologies. Further research in this field holds promise for unlocking the therapeutic potential of lncRNAs[107].

CONCLUSIONS

The understanding of the contribution of genetic variants to immune-mediated diseases has significantly advanced in recent decades. However, the complexity of these variants and the non-coding location of most associated SNPs have posed challenges in deciphering their functional roles in disease development[13]. In this line, lncRNAs, which are enriched with SNPs and participate in the regulation of immune-related processes[8], have opened a new field of studying the involvement of disease-associated SNPs on lncRNA function. Moreover, some lncRNAs have been found to be differentially expressed in patients compared to controls[54,58,61,101], highlighting their potential as biomarkers.

However, the specific functions of lncRNAs themselves and their regulatory mechanisms in disease development remain largely unknown. Most experimental approaches have studied the expression patterns of lncRNAs harboring associated SNPs in disease tissues, while functional studies assessing the effect of associated alleles in lncRNA function and disease development have been limited[13]. Disease-associated SNPs can not only affect the expression of the lncRNAs, but can also influence their splicing, secondary structure, or their ability in transcription of target genes[8,13,40,110]. Additionally, larger-scale studies across diverse ethnic populations are required to validate the roles of genetic polymorphisms within lncRNAs[54,95].

To sum up, identification and functional studies of disease-associated lncRNAs can help to understand the underlying molecular mechanisms and may contribute to a broader image of the disease pathogenesis, opening new diagnostic and therapeutic strategies.

DECLARATIONS

Authors' contributions

Substantially contributed to the conception and design of the article and interpretation of the relevant literature: Bergara-Muguruza L, Olazagoitia-Garmendia A

Drafted the article or revised it critically for important intellectual content: Bergara-Muguruza L, Castellanos-Rubio A, Santin I, Olazagoitia-Garmendia A

Availability of data and materials

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Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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