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Emerging Involvement of long non-coding RNAs in gastrointestinal associated inflammatory disorders

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ABSTRACT

Gastrointestinal (GI) disorders including a wide range of infectious, inflammatory, autoimmune, etc. disorders. Inflammatory bowel and celiac disease are non-fatal but overwhelming GI associated disorders. IBD and celiac's complications, besides the great suffering, disturb the normal life of the patients and make them involved in mental and physical problems. The emerging role of genetic content is deniable for GI inflammatory disorders incidence, and long non-coding RNAs (lncRNAs) function is the recent topic for its association. Analyzing of absolute lncRNAs interference in GI inflammatory appearance remains in infancy, and more studies are requested. Here, we concisely performed a systematic review in the last knowledge up to 2020 to identify all of the significant lncRNAs associated with the initiation and progression of GI inflammatory diseases. Accordingly, this assay attempted to refer to the expression of lncRNAs changing from the normal state, discovery of genetic mechanisms, and main effectors that would trigger associated IBD and celiac expression and immune responses would be effective for therapeutic approaches. It could be useful for prognostic and diagnostic purposes of GI associated inflammatory disorders.

1. Introduction

Immune-related disorders such as celiac disease (CeD), inflammatory bowel disease (IBD), type 1 diabetes (T1D), Rheumatoid Arthritis (RAs), Multiple sclerosis (MS), are considered to be a group of heterogeneous diseases stemming from the lack of immune system regulation. Although the general belief is that they grow because of an imbalance in the interaction between the genetic and environmental factors, they share the pathogenic mechanisms that are not entirely understood [1]. Following important information from genome-wide association studies (GWAS), the emergence of a new generation of sequencing techniques has expanded the genetic knowledge of key regulatory mechanisms in immune-related disorders. [2,3]. Over the last decade, thousands of common polymorphisms have been reported in genes associated with 186 types of immune diseases through the use of next-generation sequencing and microarray technology. Although molecular studies aimed at discovering the varieties of polymorphism and disease-related genes provide a great deal of information on the sequence and gene loci, there is limited information on the mechanisms involved in signaling and metabolic pathways. Besides, it was observed that about 90 % of SNPs correlated with these diseases occur in non-coding areas, rendering it challenging to identify their biological function [4–6].

Previous studies focused on the protein-coding gene, ENCODE (Encyclopedia of DNA elements) consortium researches have demonstrated that mammalian genomes are far enriched by a wide variety of non-coding RNA transcripts containing thousands of lncRNAs [7,8].

Inverse to the obsolete belief of ncRNAs as junk, recent studies suggest that ncRNAs are key determinative regulators in physiological and pathological processes, which are of great interest in molecular biology today. LncRNAs form a large portion of non-RNAs that are over 200 nucleotides in length. This type of ncRNA has its expression profiles in each cell line and plays different roles in cellular processes [9,10].

Although lncRNAs have been recognized in the immune cell, their disease-associated mechanistic function mostly unknown. Recent studies revealed that lncRNAs mediated in inflammatory pathways as key

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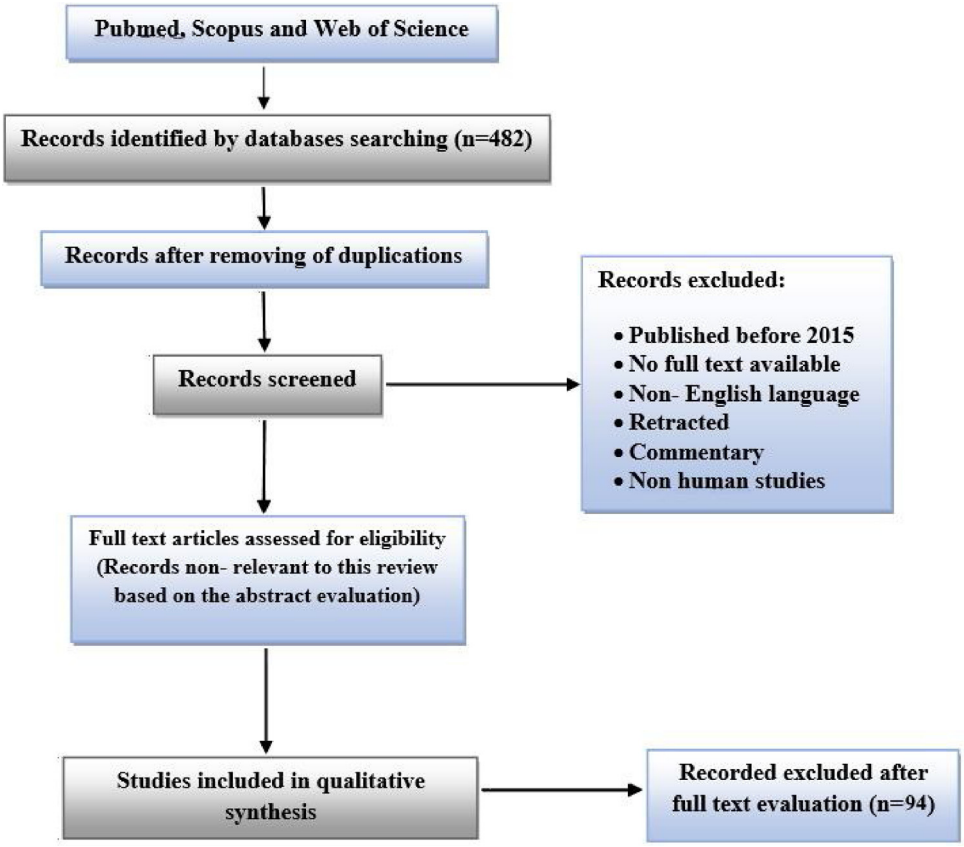

Fig. 1. Investigation map by various searches correlated with subject area.

regulators [11,12]. Increased perception of how lncRNA mechanistic and function details in this manner may influence future therapies for the inflammatory gastrointestinal (GI) disorders [13]. Herein, we tried to exclusively study the last body of present knowledge regarding the lncRNA role in GI associated inflammatory disorders incidence and improvement. We discuss how lncRNAs can impair immunoregulation and drive immune components to promote the onset of epithelial lesions and inflammation cascade. Before starting the study, data were extracted from Pubmed, Scopus, and Web of Science databases. Subsequent reports prior to 2015 were excluded. In addition, incomplete, invalid, and full-text reports were excluded. Keywords used in this search are lncRNA, celiac, polymorphism, autoimmunity, IBD, and genetic profiling. Fig. 1 shows the search and data collection procedures for analysis.

2. lncRNAs and inflammatory diseases

LncRNAs have been involved in multiple diseases such as cancer, cardiovascular disease, and Alzheimer's disease. Evidence suggests that lncRNAs affect the mechanisms involved in inflammatory diseases [14]. In a non-coding antisense locus called INK4 (ANRIL), which is located in the human genome chr9p21, the well-known lncRNA associated with the inflammatory response has been recognized [15]. One of the best markers of genetic susceptibility to coronary artery disease (CAD) is the ANRIL molecule. The ANRIL gene is expressed by a complicated pattern. It is translated into two different isoforms of the ANRIL molecule; Including short isoforms (SANRIL) terminating with exon13 and long isoform (LANRIL) lacking exon13 terminating with exon19 and exon20. The ANRIL molecule is a lncRNA with proven coronary artery disease function that can trigger the cascade of the inflammatory pathway. Evidence suggests that this lncRNA plays an important role in several disorders such as periodontitis, diabetes, cancers, and other inflammatory diseases [14,16,17]. The ANRIL molecule is strongly induced by inflammatory factors and regulates the expression of downstream genes by the NF-κB signaling pathway [18,19].

Moreover, by binding to the YY1 protein, the ANRIL molecule plays a regulatory function in the inflammatory pathway. YY1 is a protein that binds RNA and acts as a bridge between regulatory RNA and target chromatin [20]. The NF-κB pathway is both a central mediator and a major contributor to inflammatory processes, and it has been shown

Table 1
Profile expression of lncRNAs as an emerging factor for inflammatory diseases.

Inflammatory Disease	Regulation state	LNCRNA	Reference
Inflammatory bowel disease	Down-Regulated	ANRIL, MALAT1, BC029135, CDKN2B-AS1, BC062296	[21]
	Up-regulated	BCO12900, AK001903, AK023330, DQ786243, IFNG-AS1, H19, GUSBP2	[22,23]
Eosinophilic-esophagitis inflammatory disease	Up-regulated	BANCER	[24]
Inflammatory liver disease	A allele expression	JAM2-6	[25]
Crohn's disease	DQ786243	Increase in active & inactive CD and affects CREB and Foxp3 expression of T regulatory	[26,27]
	ANRI, DIO3OS, PDZK1P2, DPP10-AS1	Down regulate in inflamed CD	[5]

that lncRNAs control this pathway and thus regulate other inflammatory processes [18,19]. Table 1 presents different types of lncRNAs related to various types of inflammatory disorders.

3. Prevalence of CeD & IBD

The serologic test showed the 1.4 % CeD incidence in population while biopsy test report 0.7 % prevalence. In addition to genetic content, which is the most important cause of the disease, also, CeD incidence depends on age, sex, race, geographical location, and lifestyle [28]. The female and children are more susceptible than the male gender and in adult individuals, respectively [14,29]. Both environmental and genetic factors detect the complexity of the disease and level enteropathy from mild to severe. The most prevalent value for CeD was found in Europe and Oceania with 0.8 %. The disturbance values of 0.4 %, 0.5 %, 0.6 % were reported for South America, Africa, and North America, and Asia, respectively [28,30]. Other investigators believed that CeD is uncommon in sub-Saharan Africa and East Asia [31].

The epidemiological studies reported that 3.1 million (1.3 %) of US adults (age ≥ 18) diagnosed as IBD patients. The studies reported one in 1299 children (aged 2–7) affected by IBD, in 2016. However, IBD prevalence altered remarkably among a number of sociodemographic characteristics containing age, race, ethnicity, education, employment status, nativity, and urbanity [32,33]. These statistics was different in Canada with 0.7 % prevalence, and it was estimated at 725 per 100,000 in population in 2018, and the annual rate was 2.86 % [34,35].

In Asian countries, UC is more frequent than DC. Due to different genetic makeup and environmental factors such as lower rate of urbanization in the Asian population, IBD prevalence is less than the American population and, IBD accomplished by fewer extra intestinal manifestations and familial aggregation, but UC older patients have worse clinical outcomes. The highest annual rate for IBD was observed in East versus Southeast Asian countries with a lower annual rate for IBD [36].

4. LncRNAs and CeD

The patients with active CeD showed various heterogeneous manifestations that contained villous atrophy, hyperplasia crypt, and lymphocytic infiltration of small intestine mucosa [37]. By now, the only available treatment for CeD is a hard, gluten-free diet. While the role of environmental stimuli in CeD's development is well-established, the involvement of genetic factors in CeD's incidence suggests that 87–57 % of genetically susceptible individuals are affected (Fig. 2). So, CeD is considered to be an immuno-genetic disease. The most potent genetic association is associated with heterodimer of HLADQ2 (encoded by HLA-DQA1*05 and HLA-DQB1*02) and HLA DQ8 (HLA-DQA1*03-HLA-DQB1*0302). As a result, 40 % of the genetic risk is the emergence of disease-associated to these genes in the 6P21 position [38].

Of note, this is non-HLA gene sites, which are known to be the genetic risks associated with CeD. Two GWAS studies on CeD identified 26 genomic regions associated with the disease's genetic susceptibility. Also, with the Immunochip genotyping project, 13 additional sensitization sites were identified for CeD. Among these 39 non-lymphocyte human antigens that are associated with the risk of CeD development, non-encoding lncRNA regions can be mentioned [38,39]. Events in CeD drive the inflammatory and immunological pathways. Also, the evidence reported the lncRNAs act in inflammation and autoimmune associated disorders. Therefore, the lncRNAs role in inflammatory and autoimmune diseases were discussed in the following.

CeD pathological studies indicate the prominent role of inflammatory factors in the incidence of autoimmune disease. On the other hand, by acknowledging the role of lncRNAs in the development of inflammatory diseases, it seems that the development of CeD as an inflammatory disorder is predictable as an effective role of lncRNAs.

It seems that approximately 70 % of the human non-coding human genome is transcribed to RNA, and recently the developed RNA sequencing technique helps identify new transcriptional areas (non-coding RNA and RNA), which can be involved in the pathogenesis of the disease. Among these elements, non-coding RNAs are very abundant, and even though the performance of the majority of lncRNAs is unknown, the study of these molecules has recently been considered a lot of attention. Emerging evidence suggests that lncRNAs are important regulators of gene expression and, interestingly, have become increasingly important in recent years [40,41].

LncRNAs are fundamental transcriptional regulators capable of regulating gene expression at each level of transcription and configurable in both Cis and Trans. They are also capable of controlling protein synthesis and RNA maturation, altering the chromatin structure. Subsequently, it affects the transcriptional level of certain genes and thus has a significant role in homeostasis, pathophysiological changes, immune responses, cellular and environmental signals, lymphocyte function regulation, immune cell growth and communication signals through a molecular network Play. Although lncRNAs do not encode any proteins, these molecules have other potentials, such as scaffolding to other proteins and RNAs. As functional protein cofactors, they have an active role in enzymatic and signaling activities. It has also been shown that some lncRNAs are involved in the translocation of other RNAs and proteins [42,43]. A wide range of lncRNA functions is classified into five groups: the first, mechanical approach, which acts as a signal molecule in feedback from specific stimuli. The second function is to function as decoys by way of a competitive regulation and to bind to their targets resulting in target molecule decoys. The third mechanical function of lncRNAs is to direct the ribonucleoprotein complex to specific gene loci and thereby up- or down-regulation. Fourth, as a transient scaffold for assembly of several effector subunits in which transcriptional repression or activation occurs. Lastly, the current

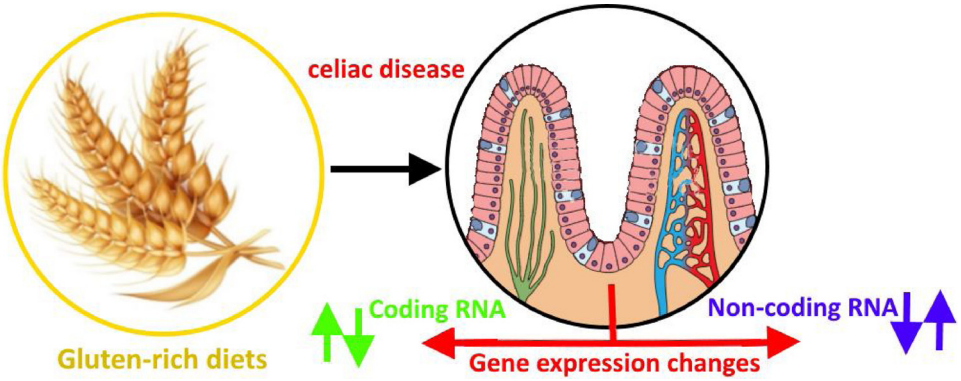

Fig. 2. Different location of lncRNAs classes.

mechanical function for lncRNAs suggests their role in binding to functional gene regulatory sites as enhancer RNA (eRNA) and enhancing their transcription [17].

An interesting example of the role of lncRNA in the regulation of gene expression is the function of lncRNA NKILA, which regulates the formation of NF-κB signaling by forming a complex to prevent IkB degradation and thus maintains NF-κB in the nucleus. There is also evidence that the lncRNA marker coding called Rroid is responsible for the circular interaction that influences gene expression [38].

Some lncRNAs have been associated with a special protective role in inflammatory diseases, while others seem to be susceptible to swelling or inflammation. For instance, LINC MAF4 is associated with MS, and RMRP lncRNA is involved in the progress of cartilage-hair hypoplasia. Analysis of data from RNA-SEQ showed that many gene loci correlated with immune components include lncRNA genes. Of the 9 diseases investigated, including celiac, about 420 lncRNAs and 626 protein-coding genes were found in 11 specific immune cell groups.

Studies show that the frequency ratio of lncRNAs to protein-coding genes in most gene loci is roughly 1:3. As predicted, gene loci involved in autoimmune disorders are common, which implies that the role of most lncRNAs in various diseases is similar [44].

Surprisingly, the highest number of lncRNAs and genes encoding proteins involved in rheumatoid arthritis (RA) and celiac disease were found to be 30 and 31 %, respectively. Moreover, lncRNAs-related loci involved in RA and CeD were 2.5 times greater than the remaining loci in the genome [44].

Based on the available data, genetic linkage and common mechanisms are well established in various diseases, especially autoimmune disorders, therefore, it can be expected that other autoimmune disorders such as CeD occurs with the emergence of an autoimmune disease [45].

Increased expression of AC104820.2 in the intestinal sample of celiac patients was also shown to be directly related to the onset of the disease [44]. In another study in CeD patients, increased expression of Carl's lncRNA was observed in cytoplasm followed by increased expression of NF-κB pathway genes. These findings suggest that the increase in Carl's gene expression and its effect on cytoplasm NF-κB signaling is associated with the development of CeD inflammatory reactions [43].

Throughout one research, LPS activation in animal models resulted in increased expression of early inflammation and late inflammation genes.The research further suggests that lncRNAs have an effective role in the remodeling of chromatin and the prevention of inflammatory reactions. In contrast, NF-κB interacting lncRNA (NKILA) is strongly triggered by IL-1β and TNF-α as two major inflammatory cytokines.

Aune et al. (2017) by studying whole-genome RNA using RNA-seq analysis of leukocytes in autoimmune patients, concluded that lncRNA sites are not randomly distributed throughout the whole genome but are concentrated in small genomic regions called buckets. They suggested that the more buckets in the enhancer sites, the higher the risk of autoimmune disorders [46].

Although the regulating functions of lncRNAs on the enhancer loci of the genes involved in the immune response have been established, the mechanism of its impact on immune function remains unknown [46].

An important LncRNA involved in CeD, called Hotair, has also been identified that interacts with HOX genes (homeobox genes class I) that play essential roles in regulating body program and fetal growth. Hox associated-lncRNA (Hotair) is a non-cRNA located in locus 12q13.13 and between HOXC11 and HOXC12, and over-expression is linked with several diseases such as gastric, liver and colon cancer and CeD. In general, Hotair is vital for transition epithelial-mesenchymal (EMT). Hotair negatively regulates the expression of HOXD interacting with polycomb responsive element (PRE) and silencing of mir-34a. Therefore, HOX genes and Hotair-lnc influence the epithelial cell memory program because of the deregulation of the EMT process. An epigenetically Hotair is capable of developing EMT commonly by using miRNA34a off and reacting with Polycomb-Responsive-Element-2 (PRC2) [47].

Epigenetic regulation of gene expression is an essential event for normal cell homeostasis. Gene expression may be through epigenetic regulation of DNA structure. One of the epigenetic alterations involves well-known mechanisms that use histone replacement RNAs or non-coding RNAs (lncRNA/miRNA) to regulate gene expression. Drugs that can target epigenetic control devices are currently undergoing clinical trials in a wide range of autoimmune and cancerous conditions [42].

SNPs associated with the disease may affect not only their lncRNA expression, but also their splicing, their secondary structure, or their ability to regulate the expression of the downstream genes. Therefore, approaches that evaluate the functional differences of the alleles are necessary to understand how disease-associated lnc cause inflammation.

Studies have shown that 10 percent of SNPs are associated with 11 immune-related diseases in the lncRNA region, which indicates the critical role of lncRNA in regulating gene expression in autoimmune diseases [43,48]. To characterize the function of lncRNA, the combination of genomic, transcriptional, and epigenetic information requires functional experiments based on molecular biology using a comprehensive analytical method.

In 2017, Santin et al. identified a new variant of a CeD variant in a non-coding region of HCG14 using a broad haplotype-based strategy that specifies the particular case of the NOD1 gene expression allele [49]. Although more functional studies are needed to clarify the role of HCG14 in regulating gene expression and determining molecular mechanisms involved in the pathogenesis of CeD.

The fact that it is difficult to understand the exact mechanism of lncRNAs is challenging to detect the presence of SNPs associated with the disease in lncRNAs. These polymorphisms may modify the regulatory function of lncRNA through a variety of mechanisms, such as altering the secondary structure or expression level, increasing or decreasing the supervisory role, amplifying and weakening the affinity binding. Sequence study of autoimmune-related lncRNAs has shown that SNP-rich sites are prevalent in these genes' loci.

Since SNPs in non-coding regions affects the regulation of lncRNA genes and does not affect other adjacent genes, however, since lncRNA can regulate distant and near genes, SNPs on lncRNA function clarify that lncRNA acts as a bridge between non-coding SNPs and expression of protein-coding genes.

The presence of polymorphisms in the lncRNA regions can alter the genomic pattern of the transcription, and thus depending on the allele present in the SNP site; different isoforms may be created for the lncRNA, each of which has a different interaction for the other components. Involved in downstream grafting reactions, and consequently, SNP in lncRNA can affect downstream events. SNPs can modify the secondary and third-order lncRNA structures and change the function of lncRNA.

The second structure analysis using computational tools can predict the structural changes caused by the presence of specific SNPs. For example, GWAS studies concerning IBD and T1D show that SNPs are involved in the pathogenesis of both diseases associated with the BACH2 gene in the lncRNA structure. However, further studies should be carried out on the role of SNPs in the function of lncRNA. Confirming the role of SNPs correlated with autoimmune diseases in lncRNA-related loci, particular attention has been paid to elucidating the function of these polymorphisms in various diseases, including inflammatory diseases.

In a study in CeD, the identification of a new celiac polymorphism called rs3130838 was found in the non-coding region of HCG14. Rs3130838 is located in an intergenic region on both sides of the two genes, TRIM27 and HCG14, a protein-encoding gene and a non-coding protein gene. The TRIM27 gene (or RFP) encodes proteins in triple motifs that are located in the nuclear matrix and involved in regulating

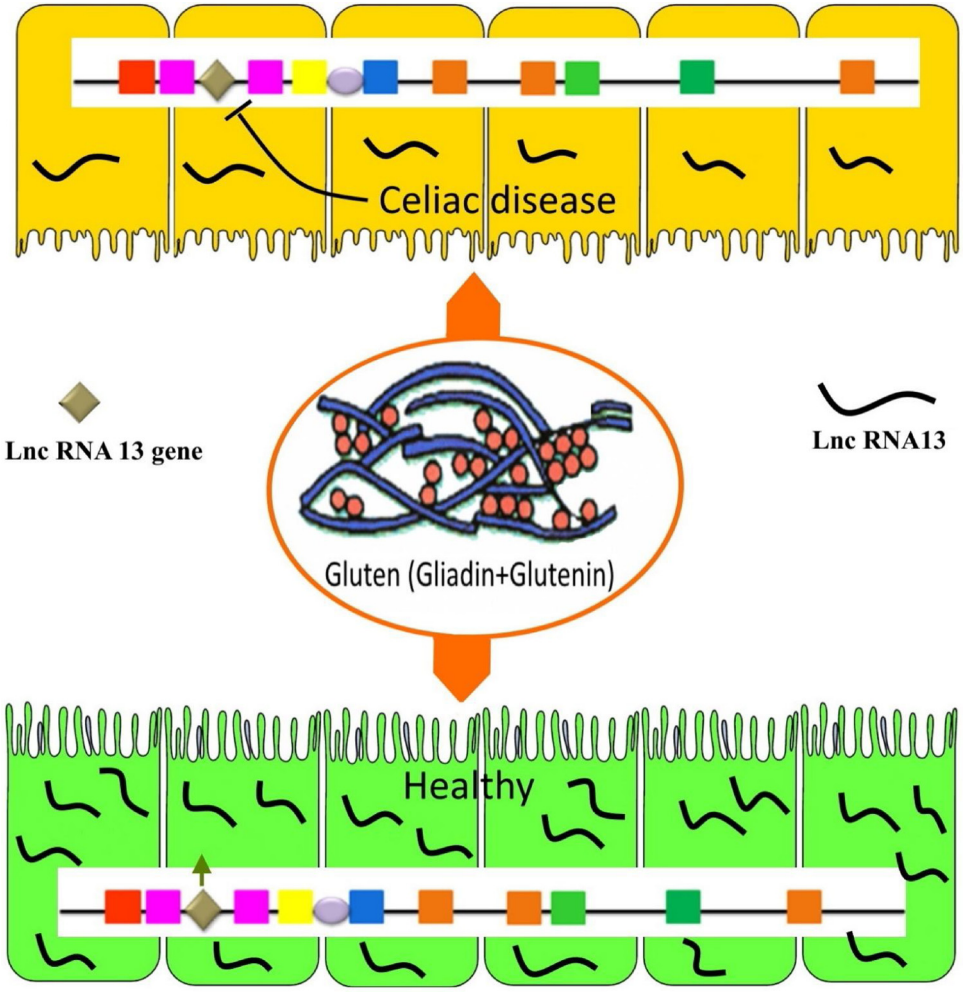

Fig. 3. Comparison of lncRNA13 expression level in healthy individuals and CeD patients.

gene expression and cell proliferation.Interestingly, TRIM27 adjusts the activation of NF-κB negatively and thus plays a role in regulating innate immune responses and inflammatory processes [49]. In general, lncHCG14 seems to play a role in the naming of the nod gene in an allele-specific manner.

One of the most known lncRNAs involved in CeD expression is lnc13, which is rich in endogenous SNPs. Lnc13 has been shown to play an important role in regulating the NF-κB pathway, which is continuously active in the mucosa of celiac patients (Fig. 3). Castellanos-Rubio et al. (2016) observed that lnc13 regulates the expression of inflammatory genes in macrophages and interacts with various regulatory proteins. Studies have shown that NF-κB degrades lnc13 as an important factor in maintaining homeostasis in intestinal mucosal immunity, which is a region carrying CeD-associated single nucleotide polymorphisms. Lnc13 appears to control the expression of a subset of CeD-associated inflammatory genes by interacting with chromatin and the multifunctional protein HNRNPD. The lnc13 binding site to the RNA molecules has specific sequences called AU-rich AREs [39,47].

The amount of lnc13 in small colon biopsy samples was significantly lower in celiac patients than in control subjects. Decreased levels of lnc13 in the intestinal tissue in patients with CeD point to the fact that lnc13 can play a role in CeD. In fact, the mechanism of lnc13 is such that, under the underlying conditions, lnc13 suppresses the expression of celiac associated genes, such as STAT1, MYD88, STAT3, IL1RA, and TRAF2 genes. Lnc13 applies for its role by reacting with HNRNPD and RNA-bound AU1-rich nuclei, and HDAC1 and histone-Deacethylase, which negatively regulates transcription. However, in inflammatory conditions, lnc13 decomposes by DCP2 and allows the expression of a pro-inflammatory gene by releasing a protein complex from chromatin. The nucleotide variants found in lnc13 also disrupt the second gene structure and reduce the tendency to bind to HNRNPD and chromatin and, accordingly, allows inflammatory genes to be expressed. Complete decoding of the mechanisms by which lnc13 promotes inflammation may elucidate some mechanisms of gene expression regulation as well as other unknown targets for use in the diagnosis and treatment of inflammatory diseases such as CeD [39].

The GWAS conjugation analysis indicates the presence of six polymorphisms as Haploblock (highly related nucleotides) in this region. The most important polymorphism in lnc13, rs917997 is located at 2q21, and is 1.5 kb away from the il18 receptor accessory protein (IL18RAP) encoding genes. Although the lnc13 and the IL18RAP gene overlap, they have distinct and distinct transcripts. The rs917997 contained in the lnc13 is associated not only with CeD, but with other autoimmune diseases [50].

Interestingly, the interaction between these two elements occurs due to gene sequences rs917997. When the genomic sequence "TT" is replaced by the wild type CC," the interaction significantly decreases and the expression of the pro-inflammatory genes increases [50]. Due to the role of lnc13 in other inflammatory diseases, such as arthritis, Crohn's disease, or rheumatoid arthritis, there are also risk-based variants associated with the onset of symptoms in any disease. However, the type of undesirable allele related to the disease varies depending on the context of the disease. In other words, for each specific cell, the risk allele is related to rs917997 in celiac T, whereas in T1D, the allele is a

risk factor C [4,50].

5. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is accomplished with symptoms such as abdominal pain, diarrhea, and weight loss. IBD is likely to frequent in around the world, and five million people suffer from IBD worldwide [51]. The exact etiology of IBD remains unclear; however, epidemiologists and genetics scientists estimate that genetic associated immune dysregulation accomplished with environmental factors underlie the IBD correlated pathological events. Remarkably, eightfold to tenfold risk for IBD appearance for relative's IBD patients have shown the genetic interplay for IBD incidence in the population. Likewise, 23 % and 16 % heritability were reported for CD and UC, respectively, by GWAS. In accordance to 98 % of non-coding RNA out of whole-genome in the human and undeniable regulatory role of ncRNAs in autoimmune diseases, the function of lncRNAs in IBD cannot be ignored and required more investigation and analyzing [2].

6. LncRNA in IBD

It is well-known that the pathogenesis of multi-factorial IBD is joining with inflammation incidence and epithelial barrier injury and the most common forms of which include Crohn's disease CD and ulcerative colitis UC. The IBD pathogenesis associated mechanisms remained to be fully illuminated. The human genome contained at least 10,000 lncRNAs, and 58,000 species of lncRNAs has been identified. The various investigations explained the widespread dysregulation of lncRNAs in both inflamed and non-inflamed CD and UC. The lncRNAs in IBD associated studies is more that celiac diseases; therefore, various kinds of interfering lncRNA in IBD incidence, severity and promotion was discussed separately, in the following [5].

6.1. NEAT1

A study on the coca2 cell line revealed that over-expression of lncRNA H19 increased cell permeability and lowered the gene expression of junction-associated proteins via mir-675 mediation. Nuclear paraspeckle assembly transcript 1 (NEAT1) lncRNA recognized as the recently discovered lncRNA with nuclear localization. Previously, the linkage between Neat-1 and counting types of cancers were demonstrated by various studies. The pieces of evidence showed that genes of inflammatory cytokines that mediated a key regulatory in innate immune response might be directed by Neat1 LncRNA in a nuclear position. Albeit, it was performed a few kinds of research around the Neat1 in IBD. According to the Neat1 function is tightly linked with epithelial permeability and blood-cancer barrier may be hypothesized its role in IBD associated ineffective intestinal epithelial barrier as a strong evidence in the IBD. Rui Liu et al. illustrated that over-expression of Neat1 in IBD model mice, and regulating of inflammatory response and healthy epithelial barrier were achieved in the following of Neat1 inhibition [3].

eQTL or expression qualitative trait loci is a beneficial technique to illustrate the genetic variation associated fluctuations in gene expression. Cis-eQTLs and trans-eQTLs are referred to as the maps that can regulate nearby and distant genes, respectively. Surprisingly, SNPs that occur in non-coding regions are greater than coding regions. The last investigations report that disorder-correlated SNPs placed in non-coding regions especially in non-coding RNA associated regulatory sequences, could potentially alter the functional motif of ncRNAs and molecular interaction, and therefore cause disorder incidence.

R620W, rs2476601 in protein tyrosine phosphate non-receptor type 22 (PTPN22) is associated with Crohn's disease (CD) and T1D. [6,8]. Besides, Neat1 join to STAT3 promoter of naïve T helper, and TH0 polarize to TH17 subsequently. Traditionally, IBD was considered to be mainly mediated by Th1 cells in CD or Th2 in UC; however, it is well known that Th17 and associated cytokines are significant mediators in both conditions. Th17 cells and interleukin 17A frequently found in IBD inflamed intestine that is subsequently intensifying the inflammatory process [10].

6.2. IFNG-AS1

The lncRNA Interferon gamma-antisense 1(IFNG-AS1), was reported for over-expression in active inflamed IBD patients. It is accentuated by associated single nucleotide polymorphism rs7134599, which correlated with IBD subtypes incidence. CD4 and CD8 T-cells, B-cells, and NK cells are the main origins of IFNG-AS1 secretion in the colon that lead to IFNG transcription regulation. Thus, IFNG-AS1 plays an essential role in the transcription of IFN-ɤ and Th1 response. Likewise, IFNG-AS1 contributing to other autoimmune diseases such as Hashimoto's Thyroiditis. The activation of IFNG-AS1 is positively linked with IFNG and t-bet expression. One possible regulatory function of IFNG-AS1 is that IFNG-AS1 joined to the MLL/SET1 histone methylation complex surrounding of IFNG genes that lead to the expression of IFN- associated genes in the colon of IBD patients. It seems that IFNG-AS1 has a differential impact on Th1 versus Th2 polarization. Also, IFNG-AS1 strongly related to UC severity [11]. Some studies showed that the adverse allele of rs7134599 was frequent in the Hispanic population. Maybe rs7134599 could regulate the splicing of IFNG-AS1, but exact mechanisms remain unknown and adverse allele of rs7134599, improving the IBD and other risks of other autoimmune disorders such as Hashimoto's Thyroiditis [12].

6.3. DQ786243

One of the oldest knowns of lncRNA is DQ786243 in active IBD patients. Likewise, GAWAS studies demonstrated elevated expression of DQ786243 in Crohn's disease patients, and similar studies in Jurkat cells illustrated that regulatory function of DQ786243 on regulatory T cells (Treg) utilizing alteration in cAMP response element-binding protein (CREB) and forkhead box P3 (Foxp3) expression level. The evidence showed that Treg had equilibrated the immune system to defend and prevent the autoimmune reaction; therefore, imbalance of Treg interplay leads to autoimmune attack and injury of body tissue in IBD [29].

The investigations on colorectal cancer showed that DQ786243 causes proliferation and metastasis of cancer cells and in vitro knocking down of DQ786243 lead to inhibition of cancer cell proliferation, invasion and migration. The possible variation of DQ786243, such as SNPs and different models of disease, may be factors, which should be studied in the DQ786243 function and impact on Treg action [23].

6.4. CDKN2B-AS1 (ANRIL)

Long antisense LncRNA, CDKN2B-AS, also be famous as ANRIL (antisense non-coding RNA in the INK4 locus), including 19 exons with 126.3 kb in length in INK4 location on 9p2.3 region. P15/CDKN2B-p16/CDKN2A-p14/ARF gene cluster surrounded ANRIL in the antisense direction.

ANRIL associated SNPs correlate with several human diseases containing coronary artery, diabetes, and some cancers. ANRIL exerts an inhibitory function through the binding of chromobox 7 (CBX7) within the polycomb repressive complex1 and to SUZ12. IBD accompanied with ANRIL reduced expression versus of types of cancers. Yarani et al. showed that 8 isoforms of ANRIL showed downregulation in inflamed UC colon pinch biopsies and inflamed CD in comparison with non-inflamed UC and healthy control, respectively. One research showed that ANRIL down-regulation fold in UC patients is 12-fold, and in CD patients is 4.9-fold. It has been further shown that ANRIL is mediated in the NFK-β pathway. ANRIL or CDKN2B-AS1 located in the neighboring CDKN2A-AS that encode two cell cycle regulatory elements named

P15INK4B and P16INK4A. Therefore, ANRIL epigenetically represses the neighbor CDKN2A-AS and subsequently, cell cycle. Up-regulation of P15INK4B and P16INK4A lead to high cell proliferation, which subsequently observed ANRIL down-regulation or knocking down [14]. ANRIL associated lncRNAs including ENST00000422420.1 and ENST00000428597.1 up-regulate in pinch biopsies of CD. ENST00000422420.1, ENST00000428597.1, ENST00000585267.1, ENST00000580576.1, ENST00000577551.1, ENST00000581051.1, ENST00000582072.1, ENST00000421632.1 regarded to ANRIL down regulate in pinch biopsies of UC patients [30].

Further studies are required for more illustration of ANRIL regulatory function on apoptosis or cell proliferation and defect of epithelial obstacle in IBD.

6.5. H19

LncRNA H19 regulates several genes involved in human genetic disorders and cancers. Recently, LncRNA H19 was correlated to vitamin D receptor. This linkage is investigated to inflammatory disorders, including osteoarthritis and IBD. The barrier between the internal environment and lumen contained form epithelial intestinal cells with tight junctions. A defective tight junction leads to leaky gut in the initiation and progression of UC.

The active form of vitD3, 1, 25 (OH)2D3, is mediated by nuclear factor VDR in the human body and has revealed for the protective role against epithelial injuries. Dysregulation of VDR signaling has been an emerging role in inflammatory and cancer diseases and destructive influence on the tight junction in the intestinal barrier. Reduced expression of VDR cause to over-expression of H19 and disruption of intact barrier function and increasing permeability in the leaky gut [52].

The role of H19 in intestinal barrier function is implicated by presenting as a precursor for microRNA- 675(mir-675), therefore redundancy of mir-675 is induced by H19 over-expression which leads to repressing the protein junction translation including tight junction protein ZO-1 and adhering junction E-cadherin, resulting in epithelial barrier injuries. However, RNA binding protein HuR prevents of H19 as a precursor for mir-675, thus by inhibition of mir-675 function resulting into normal levels of ZO-1 and E-cadherin and recovery of epithelial barrier function. Zou et al. demonstrated that targeted deletion of HuR leads an abundant of mir-675 in epithelial cells mucosa and remaining epithelial injuries [53].

6.6. BC012900

BC012900 lncRNA as the UC associated-lncRNA stimulated by inflammatory cytokines and play a regulatory role in apoptosis in intestinal epithelial cells. Wu et al. reported that BC012900 is placed downstream of DUSP4, but they showed that DUSP4 mRNA and BC012900 exist as independent transcripts [54]. It seems that inflammatory cytokines stimulate the up-regulation of BC012900 in epithelial cell lines of HCT116 and HT29, which lead to remarkable inhibition of cell proliferation but promote the apoptosis level. Thus, BC012900 may be considered an interesting target for further studies in IBD therapeutic investigations [23].

6.7. GUSBP2, AF113016

In the investigation for the study of lncRNA associated plasma biomarkers for CD, it was demonstrated that the expression of GUSBP2, AF113016 was remarkably altered in CD, and up-regulated and down-regulated respectively [23,55].

6.8. DIO3OS

DIO3OS demonstrated downregulation in plasma and tissue of IBD patients in comparison with healthy control. It detected that DIO3OS have the potential for IBD associated biomarker [37].

There were at least 6 DIO3OS associated lncRNAs that down-regulated in pinch biopsies of CD patients including ENST00000553575.1, ENST00000554694.1, ENST00000557532.1, ENST00000557109.1, ENST00000554441.1, ENST00000554735.1 [30]. In the study performed by Reza Yarani et al., downregulation of DIO3OS was demonstrated in the colonic samples in contrast with chen et al. that observed upregulation of DIO3OS in plasma samples. This contrast is maybe due to different samples for investigations [23].

6.9. CCAT1 and UCA

The accumulating data supported an effective role of the long non-coding RNA colon cancer-associated transcript 1 (CCAT1) in multiple types of cancer. It was reported the potential application of CCAT1 in cancers. CCAT1 improves cancer promotion by migration, invasion, and cancer cell proliferation. It was further demonstrated contribution of the CCAT1 in inflammation incidence in the initiation of colorectal cancer. Unexpectedly, the CCAT1 up regulate in UC and CD patients by expression profile study. How high expression of CCAT1 improves the inflammatory response in IBD pathogenesis remains unclear.

The intestinal epithelial barrier, including both tight and adherent junctions, protects the intestinal cells against microorganisms and immune stimulation. Tight junction mainly controls the permeability of the intestinal barrier. Myosin light chain kinase can phosphorylate the myosin II regulatory light chain and subsequently increase the intestinal tight junction permeability. Therefore, any disruption in intestinal obstacles leads to intestinal inflammation and maybe contribute to IBD progression. It was further conducted that lncRNAs.

6.10. HNF4A-AS1, LINC01272, KIF9-AS1

MALAT1 and CDKN2B-AS1 are not the only lncRNAs that demonstrate nuclear enrichment, but also, HNF4A-AS1 showed condensation in nuclear function in the Caco2 model system. The nuclear enrichment proposes a transcriptional regulatory function in intestinal epithelia. There are common HNF4-AS1 and CDKN2B co-expressed genes containing RP11-347E10.1, FOXD1-AS1, RP11-64D22.5, RP11-91P17.1, CDKN2B-AS1, RP11-116D2.1, RP11-245G13.2, RP11-132E11.2, HNF4A-AS1, RP11-143A12.3, RP11-689K5.3, RP11-1223D19.1, RP11-122K13.7, RP11-798K3.2 and RP11-680F8.1 with significant down regulation as expressed ileal lncRNA genes.

Upregulated differentially expressed ileal lncRNA genes included CTB-61M7.2, RP11-598F7.3, LUCAT1, LINC01272, RP11-290L1.3, LINC00694, RP11-44K6.2, LINC01235, FAM225A, RP11-536O18.1, RP11-115D19.1, LINC00582, WISP1-OT1, RP11-638I2.8, CTD-2589M5.4. Of the top 15 upregulated lncRNAs, LINC01272 showed the highest number of 187 upregulated co-expressed genes [56].

The recent investigation in 2017 by Wang and et al. showed that KIF9-AS1, LINC01272, was remarkably up-regulated in tissue and plasma of IBD patients compared with healthy individuals.

KIF9-AS1 associated ENST00000429315.2 and ENST00000429315.2 upregulated in pinch biopsies of UC and CD patients respectively [30].

6.11. GAS5

Lucafo et al. evaluated the growth arrest specific5 (GAS5) lncRNA expression and compared it with the protein level of MMP2 and MMP9 in the sample of colon biopsies acquired from IBD patients. They demonstrated decreased expression in inflamed tissues of IBD patients versus healthy controls. They estimated that GAS5 downregulation is inversely correlated with MMPs expression. It is proposing a regulatory function of this lncRNA in handling the activity of MMP molecules [57].

The studies showed that GAS5 could be a potential marker for Glucocorticoid resistance, and influence on efficacy of steroids in order

to inhibition of proliferation in colon and ovarian cancer associated cell lines. Lucafo et al. in 2018 measured GAS5 level in 19 paediatric IBD patients for diagnosis of GCs. They found that an upregulation of GAS5 is related to unfavorable steroid response and GAS5 could be considered as a novel biomarker for GC therapy in children with IBD [58].

NR_037605 related GAS5-AS1 was significantly found as an upregulated lncRNA in the blood sample of CD patients [30].

7. Conclusion

The expression of lncRNA as a factor influencing gene expression settings offers a more specificity than mRNA. Due to the specialized role of lncRNAs in their regulatory activities, it can be concluded that changes in the cell lncRNAs profile cause a large proportion of immunogenetic abnormalities. Therefore, analysis of different classes of lncRNAs in the population may lead to the identification of relevant markers of disease progression and, in turn, to the development of therapeutic approaches. Besides, manipulating epigenetic mechanisms such as altering the expression of lncRNA genes in GI-associated inflammatory disease may lead to effective therapeutic strategies being discovered. Given the relatively high prevalence of celiac and IBD disorders in the community, this issue becomes even more important if we obtain comprehensive information on modifiers factors and causes. Although our knowledge of the various types of genetic factors involved in CeD and IBD has increased substantially, the existence of lncRNAs and their multi-functional polymorphisms makes it difficult to achieve successful therapeutic strategies. Finally, our study confirms the notion that many genetic variants that cause the risk of GI-associated diseases may alter the expression of lncRNA associated with enhancer, which in turn affects the expression of the protein-coding genes desired, which leads to change cell phenotypes. The knowledge about the molecular mechanisms of lncRNAs involved in inflammation and autoimmunity and their biological function is increasing, if our understanding of how the SNPs influence the function of lncRNA results in the possibility of targeting such lncRNAs for diagnostic and therapeutic purposes.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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