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Review Article

The contribution of long non-coding RNAs in Inflammatory Bowel Diseases

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ABSTRACT

Inflammatory bowel diseases (IBDs) are multifactorial autoimmune diseases with growing prevalence but the interaction between genetic, environmental and immunologic factors in their development is complex and remains obscure. There is great need to understand their pathogenetic mechanisms and evolve diagnostic and therapeutic tools. Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that are known to interfere in gene regulation but their roles and functions have not yet been fully understood. While they are widely investigated in cancers, little is known about their contribution in other diseases. There is growing evidence that lncRNAs play critical role in regulation of immune system and that they interfere in the pathogenetic mechanisms of autoimmune diseases, like IBDs. Recent studies have identified lncRNAs in the proximity of IBD-associated genes and single nucleotide polymorphisms within IBD-associated lncRNAs as well. Furthermore, blood samples and pinch biopsies were also analyzed and a plethora of lncRNAs are found to be deregulated in Crohn's disease (CD), Ulcerative colitis (UC) or both. (Especially in UC samples the lncRNAs INFG-AS1 and BC012900 were found to be significantly up-regulated. Similarly, ANRIL, a lncRNA that nest different disease associated SNPs, is significantly down-regulated in inflamed IBD tissue.) This review aims at recording for the first time recent data about lncRNAs found to be deregulated in IBDs and discussing suggestive pathogenetic mechanisms and future use of lncRNAs as biomarkers.

1. Introduction

Inflammatory bowel diseases (IBDs) are chronic conditions of the gastrointestinal tract that mainly include Ulcerative colitis (UC) and Crohn's disease (CD). They are idiopathic relapsing disorders that are often difficult to diagnose. CD is characterized by a discontinuous pattern of transmural intestinal inflammation and could affect any part of the gastro-intestinal tract while UC involves only the large bowel, causing a continuous superficial inflammation which typically starts from the rectum and expands proximally [1].

Although IBDs tend to become a major health problem worldwide, as their incidence and prevalence continue to augment around the world during the last decades [2], little is known about their precise pathogenesis. Initial research focused on the role of mucosal adaptive immunity and provided data which suggested that CD is associated with Th1 deregulation (where IL-12 mediates increased IFN-γ production) and UC is characterized by Th2 immune response (with augmented IL-4, IL-5 and IL-13 release). Recently, innate immune system was also involved in pathogenesis of IBD. More specifically, antigen-presenting cells, like dendritic cells, monocytes and natural killer cells, and their receptors, such as toll-like and nucleotide-binding oligomerization domain-like receptors (NOD)-like receptors, were observed to have different behaviour between IBD patients and controls and CD was especially associated with autophagy deregulation.

Undoubtedly, environmental factors and human gut microbiome are included in the possible pathogenetic mechanisms. Smoking has been strongly associated with IBD. Early age antibiotic use, stress and ecological pollution have been proposed as well. Lately, much insight into the intestinal flora has been provided and significant differences between IBD patients and controls were observed [3]. Thus, it is seems that overall there is support-

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ing evidence that IBD results from an inexpedient and uncontrolled immunologic deregulation against gut commensal microbiota and intraluminal antigens in a genetic susceptible host [4]. However, the interaction between genetic, environmental and immunologic factors is complex and remains obscure. As far as the genetic predisposition is concerned, it is known that IBDs may occur in multiple familial cases and having an affected relative contributes to 8–10 fold greater risk of IBD [5]. The first gene which was associated with CD was the nucleotide-binding oligomerization domain containing 2 (NOD2) in 2001 [6]. Since then, the discovery of susceptibility loci has provided information about the immunological deregulation pathways. Genome-wide association studies (GWAS) pointed a large number of single nucleotide polymorphisms (SNPs) predisposing to autoimmune disease such as IBDs [7]. Recently, more than 200 genetic loci associated with risk of IBD were identified, some CD-specific and UC-specific and most of them shared between both [8] (http://www.immunobase.org). However, the majority of these SNPs are located in non-coding regions of the genome [9,10]. This came as a surprise and led to studies for the comprehension of the molecular mechanisms with which these regions function and may induce disease.

Since 1970s the non-coding regions of DNA were supposed to be "junk" [11]. Nowadays, genome-wide transcriptome analyses, including recent studies by the ENCODE (Encyclopedia of DNA Elements) Consortium, have revealed that mammalian genomes are pervasively transcribed, under different circumstances, into a variety of coding (mRNA) and non-coding RNA (ncRNA) transcripts. Although ~90% of the eukaryotic genome is transcribed, mRNA comprises only 1–2% of total RNA. The rest is ncRNA and can be divided into two categories: "housekeeping", such as ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), and small nucleolar RNA (snoRNA), and "regulatory" such as small ncRNA (sncRNA) and long non-coding RNA (lncRNA) [12].

There is growing interest about the "regulatory" ncRNAs as it becomes evident that they regulate gene expression contributing in the complexity of organisms and therefore they may be responsible for epigenetic processes and disease development, like IBDs [13].

Among "regulatory" ncRNAs, microRNA (miRNA) is the most studied group. It is already known that miRNAs may control gene expression by interacting with the mRNA or the translation process in the cytoplasm. They are involved in the pathogenesis of many common diseases, including IBDs, as they regulate immune response and other biological activities [14,15]. A number of studies have revealed a lot of miRNAs that are altered in mucosa and in blood of IBD patients [16,17] and they have also associated them with mRNA targets affecting inflammation pathways such as NFκB activation [18], intestinal epithelial permeability [19], deregulated autophagy [20,21] and cytokine and chemokine regulation [22,23]. There is also an effort to use miRNAs as biomarkers for diagnosis and prognosis of IBD and its subtypes [24].

While the miRNAs undergo much research and they are widely understood, very few are known about the lncRNAs. Recent studies have revealed that these molecules may facilitate gene regulation during transcription, post-transcription and epigenetic processes and interfere in development and disease [25–27]. Thus, it is promising that they may be used in the future as biomarkers and contribute in the development of targeted therapies [28,29].

In this review we will introduce lncRNAs with a focus on their role in pathogenesis of IBDs.

2. Long non-coding RNAs

LncRNAs are defined as RNA molecules longer than 200 nucleotides that have little or no protein coding potential [30,31]. There are numerous lncRNA molecules present in genome [32,33]. To date there are 90.062 lncRNA genes (and 141,353 lncRNA transcripts) identified in human genome by next generation sequencing techniques and are included in the NONCODE2016 database (http://www.noncode.org). In comparison, the current number of human protein coding genes is only 19,950 (http://www.gencodegenes.org/stats.htm).

These genome-wide analyses also revealed that lncRNAs are usually lower expressed than protein-coding genes and that their expression depends on tissue and development-stage characteristics supporting the suggestion that they play a major regulatory role in cell function [34]. LncRNAs are mainly localized in the nucleus and can be associated with chromatin. Another group of these molecules is found in the cytoplasm and even in extracellular fluids [35]. Like mRNAs, lncRNAs are transcribed by RNA polymerase II and after transcription they are capped, spliced and polyadenylated [26,36,37].

According to their genomic location they can be classified into different categories. Most of the lncRNA genes harbour in the vicinity of protein-coding genes [38]. They have been categorized into sense lncRNAs (transcribed from a part or the whole coding strand of protein-coding genes), antisense lncRNAs (transcribed from a part or the whole opposite strand, also called natural antisense transcripts-NAT), intronic lncRNAs (transcribed from an intronic region) and bidirectional lncRNAs (transcribed from a promoter towards a direction opposite to that of the protein-coding gene). Additionally, there are the long intergenic ncRNAs (lincRNAs) which do not lay into protein-coding genes, including eRNAs from distal enhancers [36,39].

Recent research has demonstrated that lncRNAs may interact with DNA, other RNA molecules and proteins like transcription factors or signalling cytoplasmic proteins [30,40] playing fundamental role in regulating gene expression. They intervene in a plethora of biological processes such as chromatin remodelling (DNA methylation, histone modification), epigenetic silencing, splicing regulation, translation control, apoptosis and cell cycle regulation, metabolism, development, localization and migration [25,27,37,41].

There are different proposed mechanisms with which lncRNAs seem to function: (1) as signals, signalling transcriptional events, (2) as decoys, binding to molecules and detering their actions, (3) as guides, aiding molecules in interacting with chromatin, (4) as scaffolds, providing stabilization in molecule complexes and (5) a combination of these mechanisms [27,30]. They may also act as enhancer RNAs or even encode short peptides with regulating function [36,42]. It is also known that they affect gene expression in either cis (in neighbouring genes) or trans (distal genes) way [28] and that they play roles in a post transcriptional level [30,35].

Currently, accumulated data suggest that lncRNAs are tissue- and development stage- specific, much more than mRNAs. In addition, other typical features is that their expression range significantly during time and that their half-lives are usually shorter that those of mRNAs. Because of these features, it is clear that identifying the "snapshot" of the lncRNA-profile of a cell type with common RNA sequencing techniques is extremely difficult, especially where complex and significantly differentiated cells are concerned [43]. The first biologic mechanisms that were attributed to lncRNAs were imprinting and X-chromosome inactivation and it was acknolewdged that the product of the Xist (X-inactive specific transcript) gene in the mammalian X-inactivation centre of X-chromosome is a lncRNA that acts as a signal of imprinting and as guide for a methylating complex (Polycomb repressive complex 2), leading to chromatin modification [30,44,45]. Since then, the regulatory role of lncRNAs has been thoroughly studied and they have been linked especially with cancer [36,46] but also cardiovascular diseases [47,48], neurological disorders [49] and microbial susceptibility [50]. Interestingly, it has also been discovered that lncRNAs

contribute in the regulation of innate and adaptive immune system and therefore are involved in the development of autoimmunity [35,51]. For instance, it was observed that lncRNA-Cox2 regulates genes that mediates immunity through Toll-like receptors and NFκB pathway [52,53]. It was shown that ~10% of SNPs associated with autoimmune disorders nest in lncRNA genes [54] suggesting a great field of future research.

3. Long non-coding RNAs in IBDs

3.1. Crohn's disease

To date, very few lncRNAs have been identified in molecular mechanisms associated with IBDs. One of the first associations between lncRNAs and IBD pathophysiology was made in 2013 when Qiao et al. investigated the levels of lncRNA DQ786243, known to be overexpressed in hepatocellular carcinoma, in patients with CD. It was shown that patients with clinical active CD express significantly higher levels of DQ786243 in peripheral blood mononuclear cells, compared with inactive disease or healthy controls. An ex vivo study also demonstrated that DQ786243 up-regulate the cAMP response element binding protein (CREB) and maybe also the TCR response element in the forkhead box P3 (Foxp3), affecting in this way Treg and leading to the hypothesis that it is involved in IBD pathogenesis [55].

Another lncRNA that has been associated with pathophysiology of CD is NRON (non-coding repressor of NFAT). This molecule takes part in a RNA-protein complex which acts like a suppressor to NFAT by preventing its nuclear translocation. The leucine-rich repeat kinase-2 (LLRK2), which was identified by GWAS as CD susceptible gene, was also found to be part of this complex. By observing that LRRK2 deficient mice were found to be more susceptible to DSS-induced colitis, a molecular mechanism of CD severity was proposed [56].

Following these observations, there was a huge effort to identify IBD-associated lncRNAs and their possible correlation with IBD-candidate genes, using the loci databases of protein-coding genes and lncRNAs. In this way, it was made possible to retrieve 3665 lncRNA genes that intersect 1168 IBD candidate genes and also another 1131 lncRNAs nearby of such genes (lincRNAs) [57].

Furthermore, SNPs in possible regulatory regions of lncRNA genes were investigated as it is known that they may cause increased susceptibility to various diseases [58]. Thus, 2063 SNPs that are located within 468 IBD-associated lncRNA genes were identified and most of them were found to be associated with binding factors like transcription factor binding, expression quantitative trait loci (eQTLs), DNAase peak, suggesting that changes in the lncRNA secondary structure may affect binding. Significant secondary structure alterations were found to be caused by 362 of these SNPs. For instance, 2 SNPs (rs3757247 and rs597325) affect the secondary structure of the sense exonic lncRNA NONHSAG044354 associated with IBD-candidate gene BACH2. In addition, seven structure-disruptive SNPs (rs5763746, rs1476514, rs41176, rs41158, rs3757247, rs597325 and rs602662) were found to harbour in IBD-associated lncRNAs. Four of these SNPs (rs5763746, rs1476514, rs41176 and rs41158) nest in the NONHSAG033653, a lncRNA which is also near the HORMAD2 (22q12.2), an IBD-candidate gene.

By examining co-expression patterns between the investigated SNPs and their candidate neighbouring genes in different tissues, it was evident that rs3757247 for IBD loci-associated lncRNA NONHSAG044354 was strongly associated with IBD candidate gene BACH2 in the whole blood. In addition, antisense lncRNA NONHSAG026183 was found to be co-expressed with its associated candidate gene FUT2 in different tissues. More research needs to be done to identify more SNPs in IBD-associated lncRNAs and their association with IBD-candidate genes [57].

Table 1a
The 10 most up-regulated lncRNAs (and their gene name) in CD blood samples [59].

lncRNA	Gene name
ENST00000466668	GUSBP2
ENST00000422548	RP5-968D22.1
ENST00000502712	RP11-68L1.2
ENST00000425364	RP11-428F8.2
NR_037605	GAS5-AS1
ENST00000562996	RP11-923I11.5
TCONS_00014043	XLOC_005955
TCONS_00012771	XLOC_005807
ENST00000569039	AC009133.20

Table 1b
The 10 most down-regulated lncRNAs (and their gene name) in CD blood samples [59].

lncRNA	Gene name
uc001ody.3	AF113016
ENST00000575787	ALOX12P2
uc010bmo.1	AGSK1
ENST00000509252	CTC-338M12.3
ENST00000413954	AC064871.3
ENST00000431104	RP11-510H23.3
uc011dhd.2	LOC729678
TCONS_00020749	XLOC_010037
NR_027074	LOC283761
TCONS_00027621	XLOC_013142

Table 2a
The 10 most up-regulated lncRNAs in CD pinch biopsies [61].

lncRNA	Gene name
ENST00000460164.1	RP11-731 F5.2
ENST00000532855.1	MMP12
ENST00000326227.5	MMP12
ENST00000419897.1	RP11-465 L10.10
ENST00000520185.1	RP11-44 K6.2
ENST00000526690.1	FAM66D
ENST00000445003.1	LINC01272
ENST00000522970.1	RP11-44 K6.4
ENST00000524555.1	SAA2-SAA4
ENST00000429315.2	KIF9-AS1

In addition, apart from research in existing databases, there is ongoing research in detecting deregulated lncRNAs in blood or pinch biopsies of IBD patients. Very recently, there was a transcriptomic analysis of plasma samples in CD patients and 1988 significantly deregulated lncRNAs were observed. The 10 most up-regulated and the 10 most down-regulated lncRNAs (and their gene names respectively) in CD plasma samples are shown in Table 1a and Table 1b respectively [59]. Of these, GA5-AS1 is already associated with different types of cancers [60] suggesting that the circulating lncRNAs need to be studied thoroughly as they could be used as biomarkers in CD.

Similarly, pinch biopsies from inflamed and non-inflamed mucosa of CD were analysed and there have been isolated 438 deregulated lncRNAs in inflamed CD mucosa versus a control group. Most of them were common between CD and UC but 100 were unique for CD. The 10 most up-regulated and the 10 most down-regulated lncRNAs in CD pinch biopsies (and their gene names respectively) are shown in Table 2a and Table 2b respectively [61]. More recently, similar findings are gathered by identifying 546 deregulated lncRNAs in ileal genes from paediatric CD patients [62].

Table 2b
The 10 most down-regulated lncRNAs in CD pinch biopsies [61].

lncRNA	Gene name
ENST00000432658.1	DPP10-AS1
ENST00000401008.2	PDZK1P2
ENST00000553575.1	DIO3OS
ENST00000554694.1	DIO3OS
ENST00000557532.1	DIO3OS
ENST00000557109.1	DIO3OS
ENST00000422420.1	ANRIL (CDKN2B-AS1)
ENST00000428597.1	ANRIL (CDKN2B-AS1)
ENST00000554441.1	DIO3OS
ENST00000554735.1	DIO3OS

Table 3a
The 10 most up-regulated lncRNAs in UC pinch biopsies [61].

lncRNA	Gene name
ENST00000460164.1	RP11-731 F5.2
ENST00000532855.1	MMP12
ENST00000326227.5	MMP12
ENST00000419897.1	RP11-465 L10.10
ENST00000429315.2	KIF9-AS1
ENST00000526690.1	FAM66D
ENST00000524555.1	SAA2-SAA4
ENST00000476886.1	CLRN1-AS1
ENST00000517774.1	RP11-1149O23.3
ENST00000578280.1	RP5-1028 K7.2

Table 3b
The 10 most down-regulated lncRNAs in UC pinch biopsies [61].

lncRNA	Gene name
ENST00000422420.1	ANRIL (CDKN2B-AS1)
ENST00000428597.1	ANRIL (CDKN2B-AS1)
ENST00000585267.1	ANRIL (CDKN2B-AS1)
ENST00000580576.1	ANRIL (CDKN2B-AS1)
ENST00000577551.1	ANRIL (CDKN2B-AS1)
ENST00000581051.1	ANRIL (CDKN2B-AS1)
ENST00000582072.1	ANRIL (CDKN2B-AS1)
ENST00000401008.2	PDZK1P2
ENST00000432658.1	DPP10-AS1
ENST00000421632.1	ANRIL (CDKN2B-AS1)

Table 4
The pairwise correlations for six intersecting IBD loci-associated lncRNAs and protein-coding genes [61].

lncRNAs	Protein-coding genes
ENST00000509204.1 (rs907611)	LSP1
ENST00000443574.1 (rs9268853, rs6927022)	HLA-DQB1
ENST00000563780.1 (rs9822268, rs3197999)	MST1
ENST00000498745.1 (rs472 8142)	TSPAN33
ENST00000417795.1 (rs2188962, rs12521868)	SLC22A5
ENST00000442524.1 (rs12994997, rs3792109)	DGKD

3.2. Ulcerative colitis

As far as UC is concerned, there are recently identified lncRNAs which are differentially expressed among active UC, UC in remission and healthy controls, offering supporting evidence that lnc RNAs may be used in diagnose and as biomarkers in UC as well [63].

The transcriptomic analysis in pinch biopsies of UC patients has already revealed 745 significantly deregulated lncRNAs versus healthy samples. 400 of them are unique for UC and the rest are shared with CD. The 10 most up-regulated and the 10 most down-regulated lncRNAs in UC pinch biopsies (and their gene names respectively) are shown in Table 3a and Table 3b respectively [61].

Knowing that lncRNAs may control gene expression in cis manner led to studying the possible co-expression patterns between lncRNAs documented to be deregulated in IBD and their neighbouring protein-coding genes. Among lncRNA molecules that are found to be deregulated in UC samples, IFNG-AS1 was found to be associated with the UC-associated SNP rs7134599 and it harbours near IFNG gene (an inflammatory cytokine). In a Jurkat cell line INFG-AS1 was found to up-regulate IFNG expression, suggesting the role of lncRNAs in inflammatory response related to IBD [61,63]. Additionally, lncRNA RP11-465 L10.10 was found to be co-expressed with the IBD- associated SNP rs1569723 [61].

Similarly, another lncRNA, BC012900, was found to be significantly up-regulated in active UC tissues and stimulated by cytokines and pathogens through known IBD molecular pathways like Toll-like and NOD2 receptors. Furthermore, it was noticed that BC012900 over-expression in epithelial cells causes significant suppression of cell proliferation and increased vulnerability to apoptosis [64].

Table 5a
The 10 most up-regulated lncRNAs in CD vs UC pinch biopsies [61].

lncRNA	Gene
ENST00000514926.1	FLJ42969
ENST00000455232.1	AC007182.6
ENST00000599411.1	RP11-542 M13.2
ENST00000453998.1	RP11-399 F4.4
ENST00000455995.1	FAM95B1
ENST00000432521.2	RP3-395 M20.8
ENST00000448624.2	RP3-395 M20.8
ENST00000426825.1	OPLAH
ENST00000534424.1	OPLAH
ENST00000592738.1	SPPL2B

Table 5b
The 10 most down-regulated lncRNAs in CD vs UC pinch biopsies [61].

lncRNA	Gene
ENST00000412518.1	AL928742.12
ENST00000540811.1	RP11-444D3.1
ENST00000427543.1	AL928742.12
ENST00000426412.2	FAM25D
ENST00000515643.1	RP11-274 N19.2
ENST00000579007.1	RP11-838 N2.4
ENST00000558941.1	RP11-279 F6.3
ENST00000559212.1	RP11-279 F6.3
ENST00000555860.1	LINC00524
ENST00000438318.1	VAV3-AS1

3.3. IBDs

CD and UC are autoimmune diseases with a lot of aspects in common, such as shared IBD-associated loci that are already registered in databases, as mentioned above. Using Immunochip data Hrdlickova et al. collected the commonest SNPs for nine autoimmune diseases (AIDs), including IBDs, and their disease-associated loci, screened them for lncRNAs and protein-coding genes and then investigated the expression levels of these AID locus-encoded genes in immune cells that are known to participate in the pathogenesis of AIDs. Eventually, it was shown that lncRNAs associated with loci shared between AIDs are highly expressed in immune cells compared to lncRNAs from the whole genome ($a < 0.005$). It was also identified that NK, Th0 and Th2 cells are enriched in IBDs ($a < 0.005$). T and B cells were associated specifically with UC. Co-expression of lncRNAs and protein-coding genes was analyzed and models of interaction between the both were suggested. For example, the IL21/IL21-AS1 locus associated with IBDs contains four protein-coding genes (KIAA1109, ADAD1, IL2, IL21) and one lncRNA (IL21-AS1). This lncRNA is clearly co-expressed with IL21 in Th1 cells and their levels are similar, predicting signalling pathways that need more research [65].

Table 6
Summary of included studies.

Study	Method-sample	Disease	Results/differentially expressed lncRNAs identified	Ref.
Liu et al.	Colon tissue	DSS-colitis	NRON	[56]
Qiao et al.	PBMCs from whole blood	CD	DQ786243	[55]
Mirza et al.	Databases (NONCODEv4, IBDsite, GWAS/Immunochip, sequence based analysis, Genotype-Tissue Expression project resource)	IBD	(a) 4272 lncRNA genes intersecting or nearby IBD candidate genes (b) 2063 SNPs (c) Tissue-specificity	[57]
Hrdlickova et al.	Databases (GENCODEv4/Immunochip)	CD, UC, IBD (shared)	(a) 14 lncRNAs for CD (b) 24 lncRNAs for UC (c) 107 lncRNAs for IBD (shared)	[65]
Mirza et al.	Pinch biopsies	CD, UC, IBD (shared)	(a) 438 lncRNAs in inflamed CD (b) 745 lncRNAs in inflamed UC (c) 96 IBD-loci associated lncRNAs	[61]
Wu et al.	Pinch biopsies	UC	455 lncRNAs	[64]
Chen et al.	Plasma	CD	1988 lncRNAs	[59]
Padua et al.	Colonic tissue	UC	1931 lncRNAs	[63]
Haberman et al.	Ileal samples	CD (pediatric naïve patients)	546 lncRNAs	[62]

As it was expected, it has already been found significant co-expression between the IBD loci-associated lncRNAs and their overlapping or cis-neighbouring protein-coding genes. Mirza et al pointed six such pairs of intersecting IBD loci-associated lncRNAs and protein-coding genes which have been linked with IBDs [8,66–69] (Table 4).

Furthermore, when pinch biopsies from inflamed CD and UC were analyzed, there were isolated 23 deregulated lncRNAs between CD and UC samples, most of them shown in Table 5a and Table 5b. However, researchers did not manage to successfully categorize these samples through unsupervised hierarchical clustering into CD and UC phenotype and further studies with larger amount of samples are possibly needed, so as to provide useful biomarkers in the future [61].

Among the various lncRNAs that have been investigated in IBDs, ANRIL (antisense non-coding RNA in the INK4 locus) is known to nest different disease-associated SNPs and to be up-regulated in leukaemia, prostate cancer, basal cell carcinoma and glioma [70,71]. Interestingly, as far as IBDs are concerned, it is significantly down-regulated in both inflamed CD [62] and inflamed UC, especially the cANRIL isoform [61]. The regulatory role of the circular RNAs is yet to be elucidated.

4. Biomarkers and targeted therapies

Taking into account the fact that lncRNAs could localize in extracellular fluids, such as plasma, and that they are recognized to have significant specificity as far as tissue, cell and development stage are concerned [43], seems feasible that they will be proven as excellent biomarkers. It is already mentioned that there is ongoing research on that field [28,35]. Nevertheless, the lncRNA molecules that are isolated in IBD tissues or blood samples have not been well characterized yet as IBD specific. Interestingly, a great overlap, especially among autoimmune diseases but also between autoimmunity and cancer, has been observed. Were the physiological mechanisms of lncRNAs further understood, specific molecules would be attributed to certain diseases.

5. Discussion

In recent years, research in genetic mechanisms of complex diseases has shifted towards the non-coding regions of genome and it is now evident that lncRNAs seem to play a crucial role in gene regulation. They could be the missing step between genetics and epigenetics and could provide explanation for the cause of multifactorial health disorders. Up to date, lncRNAs are better understood in different types of cancers but there is on-going research in their contribution in autoimmune diseases as well, like IBDs.

Hundreds of lncRNA molecules are shown to be deregulated in IBD patients and some of them have been associated with neighbouring genes suggesting molecular disease mechanisms that remain to be confirmed. Furthermore, lncRNAs that are isolated from blood or tissue samples could be used as biomarkers, providing non-invasive diagnostic tools and aiming in personalized treatment. This review aims at recording for the first time recent data about lncRNAs found to be deregulated in IBDs (Table 6).

Disclosure statement

None declared.

Conflict of interest

None declared.

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