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.

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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-
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.genecodegenes.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 dereting 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 than 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 acknowledged 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 autoimmune [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 (LRRK2), 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 NONHSA044354 associated with IBD-candidate gene BACH2. In addition, seven structure-disruptive SNPs (rs5763746, rs1476514, rs41176, rs3757247, rs597325 and rs602662) were found to harbour in IBD-associated lncRNAs. Four of these SNPs (rs5763746, rs1476514, rs41176 and rs41158) nest in the NONHSA033653, a lncRNA which is also near the NORMAD2 (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 NONHSA044354 was strongly associated with IBD candidate gene BACH2 in the whole blood. In addition, antisense lncRNA NONHSA026183 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].

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, GAS5-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. The 10 most up-regulated and the 10 most down-regulated lncRNAs in ileal genes from paediatric CD patients [62].

Table 1a

<table>
<thead>
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Table 1b

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

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

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<td>ANRIL (CDKN2B-AS1)</td>
</tr>
<tr>
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<td>ANRIL (CDKN2B-AS1)</td>
</tr>
<tr>
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<td>ANRIL (CDKN2B-AS1)</td>
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<td>ENST00000426588.1</td>
<td>DPP10-AS1</td>
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<tr>
<td>ENST00000421632.1</td>
<td>ANRIL (CDKN2B-AS1)</td>
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Table 3c
The 10 most down-regulated lncRNAs in CD pinch biopsies [61].

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<tr>
<td>ENST00000585267.1</td>
<td>ANRIL (CDKN2B-AS1)</td>
</tr>
<tr>
<td>ENST00000580576.1</td>
<td>ANRIL (CDKN2B-AS1)</td>
</tr>
<tr>
<td>ENST00000581051.1</td>
<td>ANRIL (CDKN2B-AS1)</td>
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<td>ENST00000426588.1</td>
<td>DPP10-AS1</td>
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<tr>
<td>ENST00000421632.1</td>
<td>ANRIL (CDKN2B-AS1)</td>
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Table 4
The pairwise correlations for six intersecting IBD loci-associated lncRNAs and protein-coding genes [61].

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<th>Protein-coding genes</th>
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<td>ENST00000497961.1 (rs1004620)</td>
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<td>ENST00000487021.2 (rs1287920)</td>
<td>RP11-115901.9, RP11-187801.7</td>
</tr>
</tbody>
</table>

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 diagnosis 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 INF- 

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].

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].
As it was expected, it has already been found significant co-expression between the IBD loci-associated IncRNAs and their overlapping or cis-neighbouring protein-coding genes. Mirza et al. pointed six such pairs of intersecting IBD loci-associated IncRNAs 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 IncRNAs 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 IncRNAs 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 IncRNAs 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 IncRNA 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 IncRNAs 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 IncRNAs 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, IncRNAs 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 IncRNA 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, IncRNAs 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 IncRNAs found to be deregulated in IBDs (Table 6).

Disclosure statement

None declared.

Conflict of interest

None declared.

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