

The Research Progress of Long Noncoding RNAs in Autoimmune Diseases

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Abstract

Long Noncoding RNAs (lncRNAs) are transcribed RNAs molecules greater than 200 nucleotides in length. Nowadays, lncRNAs are found to have lots of functions including regulating transcription, post-transcriptional RNA processing, translation, gene rearrangement and chromatin modification. Abnormal expressions and functional abnormality of lncRNAs may play an important role in the development and progress of autoimmune diseases. Thus a systematic and comprehensive profiling of lncRNA will help us to have a deeper understanding of the pathogenesis of the diseases. This article will focus on the latest research progress of lncRNA in autoimmune diseases, which will contribute to clinical applications for diagnosis, prognosis and treatment of autoimmune diseases.

Keywords: Long Noncoding RNAs; Autoimmune diseases; Research strategy; Systemic lupus erythematosus; Rheumatoid arthritis; Multiple sclerosis; Psoriasis; Sjogren's syndrome

Introduction

Over the past few decades research has generally focused on the protein encoding gene. However in recent years, through genome-wide transcriptional analysis research shows that transcription without choice of mammalian genomes may be common. There are a variety of codes of noncoding RNA (ncRNA) [1,2]. Prior to a period of time within noncoding transcription has been considered junk DNA and transcription of "noises" [3]. However recent studies indicate that, these ncRNA are also involved in the maintenance of tissue homeostasis and other physiological processes of nucleus [4-6]. According to its size ncRNAs can be roughly divided into two main categories: small ncRNAs (<200 nt), such as micro RNA (miRNAs); long chain ncRNA (≥ 200 nt). In the pathogenesis of inflammatory and autoimmune diseases, miRNA has been shown to be an important regulatory factor of numerous genes and signaling pathways, such as Systemic lupus erythematosus (SLE), Rheumatoid arthritis (RA), Psoriasis (Systemic sclerosis, SSc), Primary Sjogren's syndrome (SS) and Multiple sclerosis (MS) [7,8]. Recently ncRNAs in another major category, long noncoding RNA (lncRNAs) has been widespread concern in the field of molecular biology. A growing body of evidence suggests that this type of RNA can be processed protein coding mRNA and participate in a variety of physiological and biological processes such as cell proliferation, differentiation, apoptosis and immune response [9-13]. Previous studies have found that, lncRNAs focused on exploring the relationship between genomic imprinting, cancer and cell differentiation. On the other hand, current studies have found lncRNAs in innate and acquired immune system, differentiation and activation of immune cells, which play an important regulatory role. This suggests that, lncRNA play a key role in the autoimmune process and autoimmune diseases. In this review, we will briefly introduce the biological effects of lncRNA and summarizes its development in pathogenesis, representing several autoimmune diseases in the current research progress.

Overview of long noncoding RNA

Long noncoding RNA (lncRNA) is longer than the RNA molecule 200 nt; itself does not encode proteins with a specific secondary structure, expression of tissue specificity and temporal specificity, often located in the nucleus or inside cytoplasm in the form of RNA in gene transcription regulation, epigenetic level, chromatin modification, post-transcriptional regulation and other multi-level, multi-participatory biological processes. Recent studies have found, lncRNA general transcription, mutation and regulatory function abnormalities can cause a variety of human diseases [14]. Brief description of the classification and functions lncRNAs are following.

According to lncRNA relative position in the genome encodes protein is mainly divided into five categories: (1) justice lncRNA (2) an antisense lncRNA, both separately are protein-coding sequence of one or more exons encoding forward, reverse overlap (3) two-way lncRNA, refers to this lncRNA expression and protein-coding sequence adjacent to a promoter sequence and is located on the antisense strand, both opposite direction of transcription (4) gene lncRNA, it refers to its sequence entirely by another transcript intron derived lncRNA (5) between gene lncRNA, is located between two genes means independent, not associated with any protein-coding gene sequences transcribed from neighboring lncRNA [15,16]. Most characteristic lncRNA are not exactly accurate classification within the genome. According to their characteristics, these lncRNA are: activated lncRNA (lncRNA-a) gene, ultra-conserved elements gene (pseudogene), telomere associated noncoding RNA (TERRAs), transcription (T-UCRs), enhancer RNAs (eRNAs), ring-type RNA [17-20]. These noncoding transcripts often associated with the coding region of the corresponding mRNA or minimal overlap, whether or not it may encode proteins, but these mRNA has its inherent function. lncRNAs has been involved in a variety of ways by a wide range of biological functions, but there is still little known about the molecular mechanism. We understand, lncRNAs major genetic influences can output within genes almost every stage of the life cycle, from remodeling and epigenetic regulation of chromatin, transcriptional and post-transcriptional regulation to protein metabolism [21,22]. Part lncRNAs involved in chromatin remodeling complex formation and

mediated gene silencing [23]. However lncRNAs recycling is achieved within more binding regulatory proteins, RNA and DNA interactions probably by modularity [24]. It also can be used as noncoding DNA which is inherited evolutionary conservation of the transcript, this effect may be related to regulation of cell differentiation [25], genomic rearrangements and inactivation of tumor suppressor genes [4]. LncRNAs has been confirmed, it can adjust the adjacent (cis-acting) within a large number of genomes or remote (trans-acting) of the gene product, or trans-acting transcription-dependent transcription lncRNA called cis-acting lncRNA dependence [26]. Recently, Marques and Ponting nucleus by the appropriate organizations lncRNA genomic features were set target screening and found that most low Shunyi lncRNA characteristic variation while antisense lncRNA characteristic variability may be higher [27]. In addition, a variety of molecular mechanisms and biological functions lncRNA is relevant [28], but research is still limiting its precise understanding of specific mechanisms. Therefore, lncRNAs dysfunctional performance and a variety of human polygenic diseases from cancers of different organs [29] to non-cancerous diseases, such as Alzheimer's disease [30], coronary heart disease [31], myocardial infarction [32] and X chromosome inactivation transcribed (Xist) membranous nephropathy [33]. Meanwhile, lncRNA congenital or acquired immune system are affected alternately, their further research may help us better understand infectious and inflammatory diseases [34,35].

Long noncoding RNA and autoimmune diseases

Over time, autoimmune disease progressed by interaction of genetics and environmental factors, arising from a complex disease. Although significantly progressed the new treatments but for many patients, the long-term effect is still not ideal [36-38]. Therefore, we need a better understanding of the etiology of autoimmune diseases. There are many types of autoimmune diseases, such as: Systemic lupus erythematosus (SLE), Rheumatoid arthritis (RA), Multiple sclerosis (MS), Psoriasis and Sjogren's syndrome (SS) etc. Although autoimmune diseases have significant clinical differences, but there are many clinical features and pathogenesis those are substantially the same. For example: SLE, RA, SS and Psoriasis have a chronic inflammatory joint symptoms [39], SLE and SSc exist within the cycle of anti-intracellular antigens autoantibodies; such as antinuclear antibodies (ANAs) [40]. Currently, lncRNAs regulate normal immune function in a variety of evidence that is quite more. However it is not yet in-depth understanding that, lncRNAs disorder is associated with the pathogenesis of autoimmune diseases. But new evidence has shown that, lncRNAs dysfunction may in autoimmune diseases such as SLE, RA, MS, SS etc., which play a key role [41,42].

Long noncoding RNA and Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a typical which is involving in congenital and acquired sophisticated interactivity between systemic autoimmune disease of the immune system, which is lost since nuclear antigen immune tolerance and produce autoantibodies [43]. The main feature of this disease is to produce anti double-stranded DNA (dsDNA) autoantibodies and anti-nuclear autoantigens, other autoantibodies. Despite a lot of research, but there are still many mysteries cause of SLE is now recognized: genetic and epigenetic predisposition; as well as familiar and unfamiliar environmental factors play a pivotal role in the development of SLE [44]. Recently, Genome-wide association studies (GWAS), has identified chromosome 1q25 region which are associated with SLE. A Long noncoding RNA

called GAS5 may be a prime candidate for chromosome 1q25 locus associated with SLE. Thus, genetic evidence suggests that: GAS5 is remainder of SLE susceptibility [23,45]. In addition, in a mouse model, GAS5 increased SLE susceptibility, suggesting that the results may influence the effect of glucocorticoids as immunosuppressive agents [23]. The loss of GAS5 promoter Sp1 binding sites can result in low expression of GAS5. So, author guess GAS5 may inhibit cell cycle and apoptosis, which may be exposed and autoantibody production by promoting antigen, involving the incidence of autoimmune diseases [46]. In a recent study, Shi and others in their small sample study, nine cases of female SLE patients monocytes were purified whole transcriptome analysis, gene expression and by comparison with eight healthy control group; they have found that the presence of specific selectivity SLE splicing, alternative polyadenylation, transcription of new sites and reproducible effect on the control monocytes LPS treatment [47]. In addition, the study confirmed that, the carrier in a mouse model of type I interferons, the non-coding RNA expression Aicardi Goutieres syndrome is reduced. Primary miRNA (Pri-miRNA) is clearly induced in the pathogenesis of SLE; these small non-coding RNA is processed to inhibit transcription and regulation of several specific Messenger RNA. Compared with the healthy control group; there are two specific pri-miRNA in SLE monocytes which is significantly increased and the two of miRNA message level is declining, suggesting that pri-miRNA in SLE monocytes are functionally -related. lncRNAs compared additionally to other types of RNA - is unlikely to change in SLE, while those with a significant change in the position of suggesting that, lncRNA involved in the pathogenesis of SLE development. For example, Human immunodeficiency virus type I enhancer binding protein-2 (HIVEP2) itself and an lncRNA (about 800-1500 base) are in the Transcription start site (TSS) upstream of expression in SLE were significantly up-regulated. In SLE monocytes, located in lncRNAs on chromosome 6q25.3 has generally offset [41].

Long noncoding RNA and Psoriasis

Psoriasis is a chronic skin and joint manifestations of hyper-proliferative diseases, currently affecting the normal life about 2-3% of the total population [48]. Thickening of the skin of patients in psoriasis is mainly due to abnormal basal keratinocyte proliferation and differentiation of cells [49]. Changes in gene expression of Psoriasis have been well documented. In addition to protein-coding gene has its own characteristic features, Long non-coding RNA a newly discovered - PRNS (under stress-induced psoriasis-related non-protein-coding RNA), has been demonstrated in patients with psoriasis is not exists in the epidermis, and psoriasis in contrast skin lesions and normal skin are highly expressed; this indicates that PRINS may play an important role in psoriasis susceptibility rather than in psoriatic lesions from the skin to maintain the role [50]. Moreover, some studies have shown that, PRINS play a protective role [50-52] in cellular stress reactions. In addition, Szegedi [53], who found that, PRINS over expressed in psoriasis and adjust G1P3. G1P3 is an anti-apoptotic gene in cancer cells. High expression of G1P3 may help to maintain the development of psoriatic lesions keratinocyte hyperplasia cells, which assist the progress of psoriatic lesions [53]. Therefore, these studies show that, in the epidermis, elevated expression levels of PRINS may play an important role in psoriasis. In addition, RNA interference can reduces RNA PRINS after serum starvation level, but not in normal serum conditions on cell viability. It is proven that, PRINS can also act as "riboregulator" to manage the expression of other genes involved in cell display stress proliferation and survival. Another lncRNA gene, was

named PSORS1C3 (psoriasis susceptibility 1 candidate 3); its closer HLA-C, and is located within the PSORS1 sites may also be psoriasis susceptibility gene [54]. To 178 Chinese people with psoriasis vulgaris patients PSORS1C3 correlation analysis of whole genome, we can confirm PSORS1C3 patients with psoriasis vulgaris gene is an important psoriasis susceptibility genes [55].

Long noncoding RNA and Sjogren's syndrome

Sjogren's syndrome (SS) is an autoimmune disease characterized by major exocrine glands, such as salivary, lacrimal gland invasion by inflammation, leading to dry mouth, dry eyes and other symptoms [56]. Age of onset is usually 40-50 years old and mostly is women. SS logo is the performance of B-cell function hyperthyroidism, such as hypergammaglobulinemia, circulating immune complexes and anti-Ro / SSA, anti-La / SSB autoantibodies [57]. In the minor salivary glands (MSG) RNA in a sample study, primary SS may be made Coxsackie B4 virus (CVB4) p2A gene 94bp fragment length; this study may clarify that, CVB4 may induce and maintain effects of primary Sjogren's syndrome [58]. However, in PubMed and MeSH database, Sjogren's syndrome research lncRNA cannot be retrieved; research shows there is still a great prospect.

Long noncoding RNA and Multiple Sclerosis

Multiple sclerosis (MS) is characterized by chronic inflammatory demyelinating, oligodendrocytes apoptosis and axonal degeneration. Burfoot [59], who demonstrated that, HLA-A*2 and A*3 multiple sclerosis plays an important role in sensitivity, and myelin oligodendrocyte glycoprotein (MOG) regulate gene HLA-DRB1 complete after two encoded multi-normality which also have an important influence on multiple sclerosis susceptibility. Often due to infection TMEV, an important means of experimental mouse model of multiple sclerosis. Therefore, the role of T cell regulation IFNG-AS1 (Tmevpg1) is considered to be involved in another important means in lncRNA multiple sclerosis disease development [60]. However, lncRNA research in multiple sclerosis more or less, the only research is still at the primary level.

Conclusion

All in all, lncRNA is longer than 200 nt RNA and RNA does not encode proteins, plays an important role in autoimmune diseases such as: Systemic lupus erythematosus, Rheumatoid arthritis, Psoriasis, etc., and a variety of multiple genes in human diseases. Immune cell activation, differentiation and unbalanced expression, T cells, B cells and NK cells in autoimmunity can change is directly linked with lncRNA [41]. However in autoimmune diseases, identification of functional performance of lncRNA still needs to study furthermore. For example, why lncRNA expression in autoimmune diseases is exceptions and what is the specific mechanism? How in the etiology and pathogenesis of autoimmune diseases distinguish lncRNAs and other non-coding RNA, or other association epigenetic factor? In addition, it is unclear whether the change lncRNAs plays a causal role in disease progression, whether manipulation of lncRNAs can play a beneficial effect in the treatment of autoimmune diseases? Most of the transcribed noncoding DNA can encode RNA. The relative proportions of noncoding genomic DNA increases the complexity of the development, which indicates that more ncRNA may have their important biological functions as well as in autoimmune diseases like cancer in different organs. In near future, further research will be both in vitro and in vivo application of advanced molecular biology

techniques, such as: gene chips and next generation gene sequencing. This will reveal the mysteries disease regulation of lncRNA. Overall, studies of functional lncRNA biology and autoimmune diseases can further deepen the development of autoimmune diseases and understanding of the pathogenesis [41]. In near future, further studies of lncRNAs may contribute to the clinical diagnosis of autoimmune diseases [42]; as well as its clinical application may open up a whole new range of opportunities for treatment [61].

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