Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/17/20240619

Review of the association between non-coding RNAs and environmental exposure

Dongyue Wang

Department of Environmental Health Sciences, School of Public Health, University of Michigan, Ann Arbor, MI, USA.

wdongyue@umich.edu

Abstract. Disease development is a consequence of the combination of genetic and environmental factors. Epigenetics can regulate gene expression without altering DNA sequence. There are different types of epigenetic regulation, including DNA methylation, histone modification and non-coding RNAs. Research has shown epigenetic regulation plays an essential role in environmental exposure and disease development. The role of DNA methylation and histone modification is well characterized so far. While the importance of non-coding RNA in disease development has gained more attention recently, the elucidation of the exposure-non coding RNA-disease pathway is still under much investigation. This review aims to provide a general review of ncRNA functions, focusing on research progress highlighting the association between a variety of exposure and non-coding RNAs and the hope of demonstrating how non-coding RNA can serve as biomarkers for preventive and therapeutic goals upon environmental exposure.

Keywords: Epigenetics, Non-Coding RNA, Environmental Exposure, Gene Regulation.

1. Introduction

Human and public health is strongly related to the corresponding environment. Environmental exposure has been a health threat for a long time. Different kinds of exposure can cause damage to multiple organs and tissues in the human body and increase the risk of many diseases [1, 2]. Unappropriated handling of environmental exposure not only caused severe consequences but also lowered the reputation of public health officials [3]. However, due to the variety of exposure and the complexity of chemical characteristics, the specific, comprehensive mechanisms for most kinds of exposure still need to be better understood. Epigenetics refers to mitotically heritable changes in gene expression without any alterations in DNA sequences. Many different but closely related forms of epigenetic regulation have been indicated gradually with the development of technology and scientific understanding of genetics and genomics, which include DNA methylation, histone modification, chromatin structure and non-coding RNAs (ncRNA). Experimental and epidemiology research has shown that epigenetics regulation plays an important role in multiple diseases [4, 5]. Most research has focused on DNA methylation and histone modification. The cerebral cortex sampled from 23-year-old Pb exposed female monkeys exhibited AD features which were represented by overexpression of amyloid-β protein precursor (AβPP), amyloid-β(Aβ) and enhanced pathologic neurodegeneration as well as decreased expression of enzymes MeCP2, DNMT1, and DNMT3a [6]. MeCp2 regulates gene expression by chromatin modification,

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DOI: 10.54254/2753-8818/17/20240619

while DNMT1 and DNMT3a are two different types of DNA methyltransferase that are essential for the establishment of proper DNA methylation status. Genome-wide DNA-methylation profiles discriminate between the different histological stages of human hepatocarcinogenesis. The promoter regions of testis-specific Y-encoded-like protein 5 (TSPYL5), potassium voltage-gated channel, shaker-related subfamily, member 3 (KCNA3), lactate dehydrogenase B (LDHB), and serine peptidase inhibitor, Kunitz type 2 (SPINT2) displayed a rising trend of DNA methylation from cirrhotic tissue (<1%), to dysplastic nodules (≥25%), to eHCC (≥50%) [7]. Moreover, increasing DNA methylation negatively regulated gene expression, and this relationship was confirmed in genes above [7]. Another study suggested the role of DNA methylation in non-alcoholic liver disease (NAFLD) and alcoholic liver disease (ALD). They focused on the promoter regions of some fibrosis related genes, which included PPARα, PPARα, TGFβ1, Collagen 1A1 and PDGFα. Their results indicated that these genes showed different patterns of DNA methylation in patients of both NAFLD and ALD. The DNA methylation status was associated with the severity of the disease and differed between ALD and NAFLD [8].

The investigation of the role of ncRNA, which has been considered a "junk fragment" in the cell for a long time in the pathway from environmental exposure to the development of diseases has progressed a lot in the last ten to twenty years. However, the systematic review of the research breakthrough in each kind of ncRNA and their potential function is lacking. Here, this review aims at briefly introducing some main kinds of ncRNAs which are widely known and investigated with their corresponding perturbation upon different kinds of environmental exposure, with the hope of improving our understanding of ncRNA and indicating directions for future research.

2. MicroRNA

MicroRNAs (miRNA) are a set of small and highly conserved non-coding RNAs whose functions are mainly about gene regulation [9]. MiRNA is generally considered to be first identified in Caenorhabditis elegans [10]. About 2200 miRNA have been found in the mammalian genome, and over 1000 of them belong to human species [11]. MiRNA are 19-20 nucleotides in length, with the signature of 5' phosphate and 3' hydroxy ends [12, 13]. MiRNA is formed from a 60-70nt RNA hairpin precursor [14]. After transcription, miRNA go through two steps of cleavage, from primary miRNA into miRNA duplex, then it gets involved in the formation of RNA-induced Silencing Complex (RISC). RISC performs its function of negative gene regulation with the help of miRNA as a guide towards its target mRNA. Then there are two different mechanisms to be employed for down regulation of target genes, and one is through cleavage of target mRNA, the other is through translational inhibition, and the specific mechanism is determined by the degree of complementarity between miRNA and its target mRNA [9]. The majority of miRNA is transcribed by RNA polymerase II, which is also responsible for transcription of mRNA [15], while a small part of miRNA is transcribed by RNA polymerase III, which can generate other non-coding RNAs that can perform their function on cell growth and cell cycle [16]. MiRNA precursors are widely spread in clusters within intergenic regions and introns, so they were previously thought to be junk DNA fragments which might be harmful to the genome. However, with the identification of more and more miRNA in the human genome, this thought is gradually considered to be not scientifically correct. Abundant research has indicated that miRNA participates in the regulation of genes which control different cellular and metabolic pathways [17-19].

Much evidence has shown that miRNA expression can be influenced by a variety of environmental exposures. Pathway analysis indicated that perturbation of normal miRNA expression levels can be harmful for multiple tissues, organs and systems to different species.

The first evidence showing the expression of miRNA can be altered by environmental exposure came from rat experiments conducted by Izzotti and colleagues [20]. Rats were exposed to environmental cigarette smoke for 28 days, and then 484 miRNAs in lung tissues were analyzed. A total of 150 miRNA were found to be downregulated, with 24 more than three-fold. They also demonstrated the upregulation of 107 genes and 50 proteins in the same tissue, which is consistent with the knowledge that miRNA can have a negative effect on gene expression. The most important miRNAs included let-7, miR-10, miR-26, miR-30, miR-34, miR-99, miR-122, miR-123, miR-124, miR-125, miR-140, miR-145, miR-

DOI: 10.54254/2753-8818/17/20240619

146, miR-191, miR-192, miR-219, miR-222, and miR-223 which participate in different pathways including stress response, apoptosis, proliferation and angiogenesis. Air pollution not only causes miRNA changes in mice but also in humans, especially traffic-related air pollution. Particulate matter (PM) and nitrogen dioxide are the two main components of traffic-related air pollution. A cross-sectional study from Julian and colleagues indicated 54 miRNAs to be associated with PM10, PM2.5 and NO2 in a dose and species dependent manner [21]. They also utilized bioinformatic analysis to confirm the disturbance of these miRNA can serve as biomarkers for negative consequences, which were identified in different tissues like lung, heart, kidney and brain. Another research has found an association between long-term PM 2.5 exposure and miRNA alterations in serum. miR-126-3p, miR-19b-3p, miR-93-5p, miR-223-3p and miR-142-3p were increased in the six-month window, while miR-23a-3p, miR-150-5p, miR-15a-5p, miR-191-5p and miR-191-5p were increased in the 1-year window. It is remarkable that miRNA groups which have significant changes in different windows don't have much overlap. Pathway analysis suggests these miRNAs play an important role in cardiovascular-disease-related pathways, including oxidative stress, inflammation and atherosclerosis [22]. MiRNA is also suggested in arsenic exposure. It acts as a regulator in the origin and development of liver cancer. Human liver epithelial L-02 cells were exposed to arsenate, and increased expression of miR-191 was found. Phenotypes of epithelial-mesenchymal transition are also observed in this experiment, with corresponding decreased levels of BASP-1 and E-cadherin and increased levels of WT-1 and N-cadherin. In the condition of suppression of miR-191, the expression of stem-cell like properties is also inhibited. These findings indicated that miRNA can serve as a biomarker for liver cancer upon arsenic exposure [23]. Another in vivo study using a rat model has found that 2 miRNA, miR-151 and miR-183 were upregulated upon arsenic exposure, while 3 miRNA, miR-26a, miR-423, and miR-148b were suppressed. These miRNAs were further identified to target mRNAs which are associated with antioxidant function by participating in glutathione synthesis [24]. This research suggests that oxidative stress might be a mechanism by which arsenic exposure causes its toxicity. Apart from arsenic, cadmium (Cd) is also suggested to be associated with miRNA alterations by a variety of research. Cd is a potential prostate carcinogen. Human prostate cells (RWPE-1) exposed to Cd showed a significant pattern of malignant transformation, with the alterations of miR-155, miR-205, and miR-134, the effect of miRNA changes was further confirmed by the findings of increasing expression of oncogene Kirsten rat sarcoma viral oncogene homologue (KRAS) and the E2F transcription factor 1 (E2F1) gene which play a central role in prostate cancer development [25]. Cd can also cause miRNA-associated harm in lung tissue, especially considering the fact that Cd is a component in cigarettes. miR-101 and miR-144 were upregulated in human bronchial epithelial cells upon Cd exposure. These miRNAs target Cystic Fibrosis Transmembrane Regulator (CFTR) and suppress its expression, which causes perturbation of the homeostasis of airway surface fluid [26].

3. Long non-coding RNA

Long non-coding RNAs (lncRNAs) are generally defined by transcripts with a length of over 200 nucleotides and lack of the capability to code proteins [27]. Although the actual number of human lncRNA is known, the total number of identified lncRNA might still increase with the development of sequencing technology. NONCODE serves as a comprehensive non-coding RNA database and indicates there are 56018 lncRNA genes for humans and 46475 for mice [28]. LncRNA is not very conserved, and often expressed at a relatively low level, and they are more tissue and species specific [29]. They are also transcribed by RNA polymerase II, following capping, splicing and polyadenylating [30]. Based on their positions relative to protein-coding genes, lncRNA can be classified into 5 kinds, long intergenic ncRNA (lincRNA), intronic lncRNA, antisense lncRNA, transcribed pseudogene lncRNA, and enhancer RNA [31]. LncRNA were also thought to be useless and even harmful for individuals. However, unlike the miRNA, the mechanisms of lncRNA functions are not completely understood [27]. It is hypothesized that lncRNA can function as chromatin modifiers and transcriptional mediators to interact with DNA molecules, guides for correct protein folding, targeting miRNAs and modulating mRNA translation [32].

DOI: 10.54254/2753-8818/17/20240619

Much evidence has shown that lncRNAs participate in the development of multiple diseases. LncRNAs take part in the progression of breast cancer. LncRNA HOTAIR was found to be up-regulated in breast cancer tissues; researchers also found that its expression increased upon irradiation. Knockdown experiments showed decreased cell survival and increased apoptosis, further confirming its role in cell growth [33]. Pint is a long intergenic noncoding RNAs which interacts with the Polycomb Repressive Complex 2 (PRC2), and is regulated by p53. Pint is responsible for cell proliferation and survival by controlling the genes in the p53 pathways including TGF-b and MAPK [34]. Another lncRNA, myocardial infarction associated transcripts (MIAT) were first identified by Nobuaki and colleagues [35]. MIAT functions as a competing endogenous RNA involved in the process of pathological angiogenesis and may serve as a biomarker for myocardial infarction [36]. LncRNA also gets involved in central nervous system diseases like Alzheimer's Disease (AD). The BACE1-antisense transcript (BACE1-AS) is a lncRNA which is the antisense transcript for beta-secretase-1 (BACE1). BACE1 is an important enzyme in AD. BACE1-AS controls the level of BACE1 mRNA and downstream protein. Its level of expression also increases upon various cell stressors, and in AD patients, further confirming its important role in AD development [37]. MSNP1AS (moesin pseudogene 1, antisense) was found to be highly expressed in the postmortem cerebral cortex of individuals with autism spectrum disorder (ASD) and able to control the expression of moesin protein in human cells, which shows the potential for it to contribute to ASD development [38].

Although the role of lncRNAs has already been demonstrated in a variety of human diseases. The association between lncRNAs and environmental exposure is relatively limited. Using Chironomus riparius, José-Luis Martínez-Guitarte and colleagues focused on three well -characterized lncRNAs (telomeric repeats, Cla repetitive elements and the SINE CTRT1) and their response to common aquatic contaminants: bisphenol A (BPA), benzyl butyl phthalate (BBP) and Cd. BPA significantly elevated Cla transcription and upregulated telomeric transcripts, which were also activated by Cd. SINE CTRT1 is not altered by any of the three contaminants [39]. HOTAIR is also upregulated by BPA and diethylstilbestrol (DES). The findings were confirmed by using both in vivo (cultured human breast cancer cells) and in vitro (the mammary glands of rat) models [40]. Smoking is a well-known risk factor for a variety of diseases including lung cancer, cardiovascular diseases and chronic obstructive pulmonary disease (COPD). Around four hundred lncRNAs were found to be differentially expressed between smokers and non-smokers, with 87 transcripts up-regulated, Gene Ontology (GO) and pathway analysis showed that these lncRNAs are associated with metabolic pathways which are closely related to COPD development [41].

4. piRNA

The PIWI-interacting RNAs (piRNAs) are a class of small ncRNAs which are highly expressed in the germline, with an ability to combine PIWI proteins to instruct transposons silencing to maintain the integrity of the genome and regulate mRNA levels [42]. piRNAs have some unique characteristics, like a strong preference for a 5' uridine signature, an adenosine signature at position 10, and a 2'-O-methylation signature at the 3' end. PIWI protein is a class of Argonaute proteins [43]. All Argonaute proteins have certain structures in common, such as an amino-terminal domain, a PAZ domain which binds different sRNAs, a MID domain, and a PIWI domain which has catalytic functions. piRNAs associate with Argonaute protein family, specifically the PIWI protein subfamily [44]. Other well-known small interfering RNAs, such as microRNAs and siRNAs, are derived from double-strand precursors and processed by Dicer enzymes and have a length of 20-24 nucleotides. However, piRNAs are usually derived from single-strand precursors and processed by a Dicer-independent mechanism [45, 46]. It is now clear that piRNA precursors are transcribed from genomic clusters - loci harboring transposons fragments. These clusters serve as a genetic memory of past transposition invasion. Clusters are usually double-stranded in germline cells while single-stranded in somatic cells. Cluster transcripts must be specifically selected for piRNA biogenesis, explained by several models: one is by coupling the transcription of piRNA precursors to their transportation to biogenesis center, the other is based on a motif that can trigger processing [47]. Although the existence of piRNA in germline cells has been

DOI: 10.54254/2753-8818/17/20240619

investigated for decades, the expression of piRNA in somatic cells is a burgeoning field. PIWI proteins, which can serve as piRNA synthesizing types of machinery, have been found to exist in somatic cells. 26 piRNA sequences that are exclusive to somatic cells have been identified. They have shorter lengths and display a tissue-specific pattern compared to germline piRNA sequences [48].

The biogenesis of piRNAs is generally considered to be divided into 2 phases: one, the primary biogenesis on the clustered transcripts, and secondary biogenesis, the "ping-pong" cycle towards transposons mRNA at post-transcriptional levels. Recent research has revealed that the two phases are closely connected, with the promotion effect of the "ping-pong" cycle to the primary generation of mature piRNA [47]. piRNAs are known to repress genes via two mechanisms, depending on the specific Argonaute proteins. One is transcriptional gene repression, and the other is post-transcriptional gene repression through the ping-pong cycle [49]. piRNAs also serve other functions; they participate in the degradation of mRNA in the elongating spermatid phase, and regulate the ubiquitination degradation of MIWI protein, which is a murine homolog of PIWI in the late stage of spermatogenesis [50].

Studies focused on the association between piRNA and environmental exposure are limited. Some research demonstrated the response of piRNA with environmental exposures, including estrogenic exposure in Pimephales promelas models [51], while downregulation of piRNA-DQ722010 was observed in mouse models upon microcystin-leucine arginine exposure [52]. Sodium fluoride exposure to mice also induced alteration of 28 piRNA expression in mouse testes [53].

5. Discussion and Future Directions

With the rapid development of genomics, epigenetics and bioinformatics, the species and number of non-coding RNAs are expected to be constantly growing. Although the role of ncRNAs in disease development and progress has been gradually identified, the association between ncRNAs and environmental exposure needs to be fully understood. Considering the fact that ncRNAs have been verified to participate in regulating numerous essential cellular pathways, the association between ncRNAs and environmental exposure is auspicious. NcRNAs also have the potential to serve as biomarkers upon exposure for early detection and prevention of diseases. Future studies should focus on revealing the mechanisms that ncRNAs employ in driving the exposure-disease association. Both experimental studies and epidemiology research should collaborate well to demonstrate the accurate causality for this association. Due to the variety of ncRNA and the different extent of conservation among species, a comprehensive understanding of the whole ncRNA family is quite challenging.

6. Conclusions

Non-coding RNAs were previously thought to be only junk transcripts, but with the development of technology in genomics, bioinformatics and understanding of the genome, its role in regulating gene expression through multiple mechanisms such as transcriptional gene silencing, post-transcriptional gene silencing, DNA methylation, histone modification and chromatin accessibility, are gradually identified. Abundant documentary of research has shown the important role of ncRNAs in the pathogenesis of human diseases since they can regulate a variety of biological functions. The association between miRNA and environmental exposure is also well characterized. However, the environmental ncRNAs interactions are under investigation, and many questions have remained to be answered. Future studies can focus on elucidating the role of other ncRNAs in driving the exposure-disease association, revealing and confirming the new mechanisms of ncRNAs in gene regulation, and evaluating the potential for ncRNA as a biomarker for the update of preventive and therapeutic strategies. Characterization of non-coding RNA can help understand the mechanisms of diseases better and support the development of therapy.

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