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REVIEW ARTICLE

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Unveiling the hidden power of noncoding RNAs in pediatric respiratory diseases

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Abstract
Respiratory diseases in children are common health problems that significantly impact their quality of life and health status, and this has its own unique challenges compared to adults. A growing body of research has focused on epigenetic mechanisms that relate with the development of various diseases, such as pediatric respiratory diseases. Noncoding RNAs (ncRNAs), especially long noncoding RNAs, microRNA, and circular RNA, are reported to play a regulatory role in pediatric respiratory diseases whose mutations or aberrant expressions are strongly associated with the development of these diseases. In this review, we mainly discussed the functions of these three ncRNAs in pediatric respiratory diseases.

Introduction

Many ribonucleic acids (RNAs) are present in cells that do not encode proteins but play important regulatory roles. In fact, these noncoding RNAs (ncRNAs) occupy a very large percentage of eukaryotic transcriptome and include a variety of classes.[1] Increasing evidence has proved that ncRNAs are widely involved in growth, differentiation, development, immunity, and even have important regulatory roles in tumor formation.[2-4] The rapid development of high-throughput sequencing technologies and computational platforms has accelerated the discovery of ncRNAs. A variety of ncRNAs have been discovered, and, based on their roles in biology, are categorized into housekeeping ncRNAs and regulatory ncRNAs.[5] They have a role in gene regulation at different levels, including messenger RNA (mRNA) processing, transcription, translation, and chromatin modification Figure 1).[6]

Respiratory diseases, the most common diseases in children, are a major risk to their lives and health.[7] More than 6.6 million deaths of children aged <5 years are reported annually, mainly caused by respiratory diseases.[8] A global survey estimates that 14% of children suffer from asthma, and its prevalence is increasing.[9] Approximately 13,000 and

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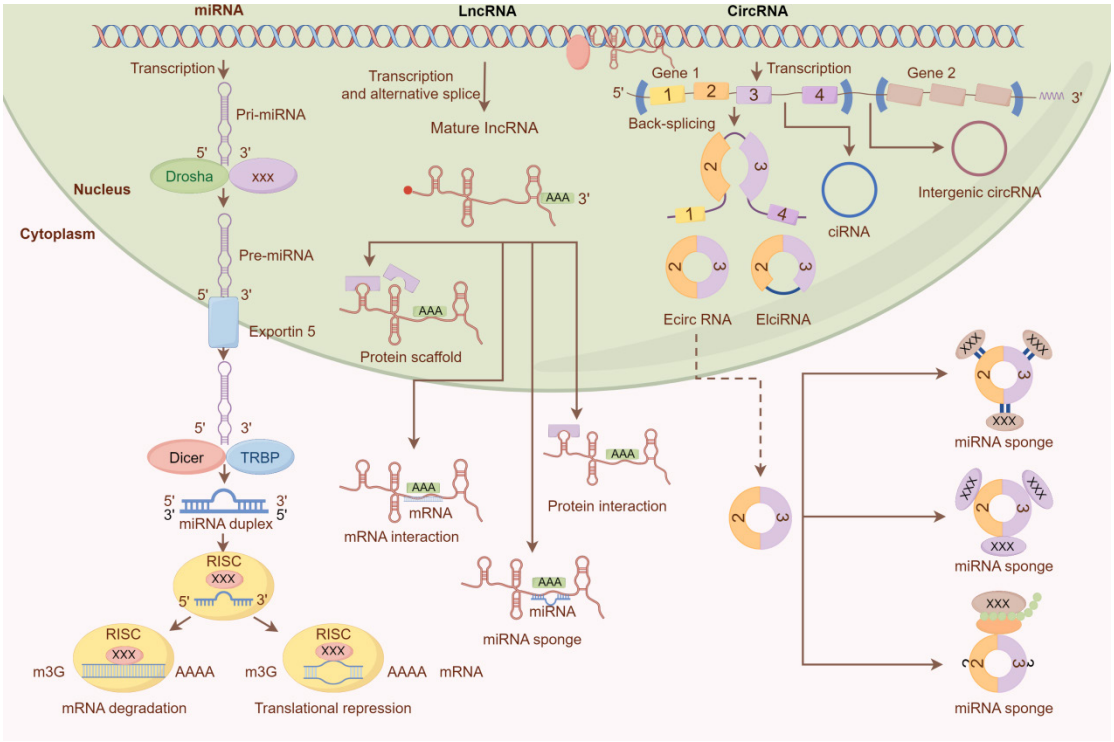

Figure 1 Functions of several ncRNAs. MiRNAs perform their biological functions by participating in the regulation of the translation of their downstream genes. LncRNAs are involved extensively in a variety of important regulatory processes, such as chromosome silencing, genomic imprinting, chromatin modification, transcriptional activation, transcriptional interference, and intranuclear transport. Biological functions of circRNAs include acting as miRNA sponges, regulating transcription, and facilitating protein–protein interactions. (This figure was created in Figdraw.)

14,000 live births are affected by cystic fibrosis (CF) every year globally, which is the second most common chronic respiratory disease in children.[10]

Many pediatric respiratory diseases remain incurable, contributing to the growing burden of noncommunicable respiratory diseases among adults.[8] We have chosen three common pediatric respiratory diseases: childhood asthma, CF, and respiratory syncytial virus (RSV) infection. In this review, we summarize the existing research on ncRNAs as pathogenic factors and biomarkers of these diseases.

Noncoding RNAs and childhood asthma

Asthma is a chronic airway disease characterized by chronic airway inflammation.[11] The clinical manifestations are recurrent wheezing, shortness of breath, chest tightness or cough, which often occurs or worsens at night or in early morning. Asthma being a common respiratory disease endangers the health of children. Its incidence is high, often manifested as a repeated chronic disease course, seriously affecting not only the learning, life, and activities but also the growth and development of children.[12] In many case child asthma eventually develops into adult asthma because of delayed or improper treatment; lung function is impaired and some children even lose physical activity completely. Acute attacks of asthma can be fatal if not treated promptly and effectively. Although prevalence of asthma in children has increased over decades, no definitive explanation is known for this trend.[13] Despite the fact that clinical manifestations of asthma alleviates in most children with effective asthma control by avoiding triggering factors, managing the disease rationally, and taking medications, no full cure is available to date. Furthermore, diagnosing asthma in children is difficult, since many childhood conditions exhibit symptoms similar to asthma, such as shortness of breath, wheezing, and coughing. Above all, there is a need to explore the pathogenesis and treatment of childhood asthma from a new perspective. In the face of these challenges, the discovery of long noncoding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (cirRNAs) has provided new opportunities to understand the pathogenesis and treatment of childhood asthma.

MicroRNAs and childhood asthma

MicroRNA is a small noncoding RNA that binds to the 3' untranslated region (3' UTR) of target genes to promote degradation or inhibition of the translation of mRNA.[3] The processing and maturation of miRNAs is a multistep sophisticated reaction that undergoes spatial transition from the nucleus to the cytoplasm and is coordinated by various enzymes and auxiliary proteins, regulated at multiple levels.[14] Since microarrays and new-generation sequencing techniques have been developed in the past few decades, it is possible to determine the expression and sequence

of many miRNAs simultaneously. Kho et al. collected 153 children serum samples that were profiled for 754 miRNAs. MiR-146b, miR-206, and miR-720, involved in nuclear factor *kappa B* (NF-kß) and glycogen synthase kinase 3-protein kinase B (GSK3/AKT) signaling pathways, were found to have excellent predictive power with childhood asthma exacerbation.[15] Small-RNA (sRNA) sequencing was performed with whole blood samples of 374 asthmatic children (aged 6–14 years), and miR-451b, miR-7-5p, miR-532-3p, miR-296-5p, and miR-766-3p were related to childhood asthma.[16] Analysis of plasma metabolite principal components from asthmatic children discovered miR-143-3p to be associated with metabolites and lung function trajectories in childhood asthma.[17]

MicroRNAs are implicated in asthma pathogenesis by the regulation of inflammatory reactions. According to miRNA profiling, levels of let-7e miRNA, miR-98, and miR-497 were more than two-fold higher in moderate-to-severe asthma patients than in controls. In addition, let-7a miRNA regulated interleukin 13 (IL-13), a cytokine critical for allergic lung disease expression, and let-7 miRNA inhibition suppressed allergic cytokine production and phenotype of asthma.[18] Evidence was discovered that miR-21 levels were elevated in the serum of asthmatic patients, suggesting that it could be a biomarker of asthma.[19] By utilizing transgenic mice that overexpressed IL-13, researchers identified that miR-21 expressed differently in animals with induced inflammation, compared to those averting induced allergic inflammation.

Airway remodeling is influenced by miR-133a, which negatively regulates the small G protein RhoA expression and contraction of bronchial smooth muscle cells.[20] Furthermore, miR-26a promotes the hypertrophy of human airway smooth muscle cells.[21] According to the next-generation sequencing, miR-10a was identified as the highest abundance miRNA accounting for over 20% of the sRNA reads from primary human airway smooth muscle cells, and regulated airway remodeling by reducing proliferation of cells.[22] Let-7i-5p, whose level was related to particulate matter 2.5 (PM2.5) exposure in asthmatic children, was obviously overexpressed in asthmatic plasma, and m*echanistically* extracellular vesicles-packaged let-7i-5p could mediate remodeling during PM2.5-induced asthma attacks.[23]

Childhood asthma could be controlled and prevented with inhaled corticosteroids (ICS), and miR-155-5p and miR-532-5p could be the pharmacogenomic predictors of their response.[24] Another study found that a poor response to ICS treatment was associated with immune dysregulation caused by miR-339-3p.[25]

Circular RNAs and childhood asthma

CircRNAs regulate transcription and splicing processes through specific interactions with DNA, RNA, and proteins via subcellular localization, modulate cytoplasmic mRNA stability and translation, interfere with signaling pathways, and serve as templates for translation in diverse biological and pathophysiological settings.[26,27] The emerging applications of circRNAs in interfering with cellular processes, modulating immune responses, and directly translating proteins are opening up new ideas for biomedical research.[28-30] Emerging applications are providing new ideas for pediatric asthma research.

Liang et al. found that circS100A11, which is predominantly expressed in monocytes, is significantly upregulated in children with asthma by microarray analysis of circRNAs sequencing profile. CircS100A11 can promote *S100A11* gene translation by competitively binding to cell cycle associated protein 1 (*CAPRIN1*) coding gene to reduce the inhibition of host gene *S100A11* translation by *CAPRIN1*. *S100A11* then releases SP3 from nucleolin and promotes SP3 binding to the signal transducer and activator of transcription 6 (STAT6) promoter, thereby enhancing STAT6 expression and M2a macrophage activation. Meanwhile, specific knockdown of *S100A11* in macrophages attenuates lung inflammation in the murine asthma model.[31] Circ_0000029 has been proved as a potential target for childhood asthma treatment because it regulates *KCNA1* gene expression by targeting miR-576-5p, which finally inhibits the abnormal migration and proliferation of airway smooth muscle cells.[32] Currently, the study of circRNAs for asthma is focused mainly on phenotypes of adult patients. Therefore, more studies are needed to screen significantly altered circRNAs using childhood asthma samples or by using computational algorithms (such as deep learning models) to offer more potential candidate circRNAs, and explore the mechanism of action in conjunction with molecular biology experiments, in order to search for potential diagnostic and therapeutic targets of childhood asthma.[33] Most importantly, more attention is required to the experimental limitations of the study for the participation of these circRNAs in human pathologies, including echnological and ethical and methodological challenges for obtaining biological samples in humans.[34]

Long noncoding RNAs and childhood asthma

Long noncoding RNAs are a class of RNA molecules that are more than 200 nucleotides (nt) in length and do not encode proteins. It has been found that lncRNAs have a conserved secondary structure, can interact with proteins, DNA, and RNA, and are involved in the regulation of genomic imprinting, chromatin modification, transcriptional activation or repression, transcriptional interference, and intranuclear transport, which are closely related to the occurrence and development of various diseases.[35-37] The pathogenesis of asthma is influenced by gene signaling pathways, and lncRNA can regulate transcription and mRNA stability by various gene targets, contributing to airway remodeling and therapy-resistance.

A systematic transcriptome analysis of 10 asthmatic children prior to and after desensitization treatment showed that long intergenic non-protein coding RNA 2145 (*LINC02145*) and GUSB pseudogene 2 (*GUSBP2*) were identified as implicated in childhood asthma by involving in immune and inflammatory response.[38] LncRNA *CASC2* was shown to discriminate between healthy individuals and asthmatic children by quantitative real-time polymerase chain reaction (qRT-PCR) detection of mRNA levels in the serum of healthy and asthmatic children. In platelet-derived growth factor subunit B (PDGF-BB)-induced cell

models, by sponging miR-31-5p, *CASC2* inhibited cell proliferation, migration, and inflammation.[39] Besides, lncRNA CDKN2B-AS1 was found to be significantly elevated in the plasma of children with asthma, and silencing *CDKN2B-AS1* enhanced cell viability by inhibiting apoptosis and inflammation cytokine production in cell inflammation models. Consistently, in ovalbumin-induced mouse models, inflammation and hyper-responsiveness of the airways were alleviated by silencing *CDKN2B-AS1*.[40] By detecting peripheral blood mononuclear cells and inflammatory cytokines in serum, lncRNA THRIL was proved to correlate with inflammatory cytokines and increase the risk and severity of childhood asthma.[41]

Dai et al. found that asthmatic children had high peripheral blood levels of lncRNA PTTG3P. In 16HBE cells, *PTTG3P* knockdown could inhibit epithelial–mesenchymal transition, proliferation, and migration, and through targeting miRNA-192-3p/CCNB1, *PTTG3P* could promote childhood asthma progression.[42] A significant increase in *lnc-BAZ2B* gene expression was associated with childhood asthma, while a decrease in lncRNA-PTPRE-AS1 expression was associated with macrophage polarization, which contributes to type II inflammation.[43] Recently, Zheng et al. found that exosomal lncRNA PM2.5-associated exosomal transcript (*PAET*) participated in childhood asthma by increasing DNA damages regulating m6A RNA-dependent oxidative phosphorylation (OXPHOS).[44]

In conclusion, the above studies suggest that lncRNAs can be involved in childhood asthma by modulating immune response, airway inflammation, and regulation of cytokine expression. Unfortunately, the mechanism by which lncRNAs are regulated in childhood asthma is unclear.

Most importantly, these findings indicate that ncRNAs play a role in childhood asthma pathogenesis not only by mediating inflammation and airway remodeling but also by immune response (Table 1).

Further studies are needed to screen significantly altered NcRNAs using childhood asthma samples (such as peripheral blood, sputum, bronchoalveolar lavage fluid, and exhaled breath condensate) using the latest sequencing technology, and explore the mechanism of action in conjunction with molecular biology experiments, in order to search for potential diagnostic and therapeutic targets of childhood asthma.

Noncoding RNAs and Cystic Fibrosis

Cystic fibrosis is an inherited disease that primarily affects the gastrointestinal and respiratory systems. It is usually characterized by chronic obstructive lung lesions, pancreatic exocrine dysfunction, and abnormally elevated sweat electrolytes.[58] CF is primarily caused by mutations in the cystic fibrosis transmembrane receptor (*CFTR*) gene, and the lung disease is significantly affected by chronic inflammation and infection, both being secondary events contributing to CF.[59]

MicroRNAs and cystic fibrosis

The role of miRNAs in regulating the expression of the *CFTR* gene is thoroughly studied in numerous studies. Gillen et al. reported that miR-145 and miR-494 directly target discrete sites in the 3'UTR of the *CFTR* gene to

Table 1 ncRNAs in childhood asthma pathogenesis.

Class of ncRNAs	Subject	Functions
MicroRNAs	let-7i-5p	Modulating the mitogen-activated protein kinase (MAPK) signaling pathway.[23]
	miR-143-3p	Drivers of poor lung function trajectories.[17]
	miR-145-5p	Increasing airway smooth muscle cell proliferation.[45]
	miR-106a-5p/18a-5p/144-3p/ 375/21	Promising biomarker for diagnosis.[46,47]
	miR-146a-5p/210-3p	Correlating with T regulatory cells frequency.[48]
	miR-192	Suppressing T follicular helper cell differentiation.[49]
	let-7a/miR-155	Potential biomarkers for diagnosis and severity.[50]
	miR-451a	Contributing to T helper 2 (Th2) cell differentiation.[51]
	miR-21	Regulating bronchial epithelial cell proliferation.[52]
	miR-451a	Inhibiting airway remodeling by targets of *cadherin 11* (CDH11).[53]
CircRNAs	circS100A11	Enhancing M2a macrophage activation and lung inflammation.[31]
	circ_0005519	Increasing IL-13/IL-6.[54]
	circ_0000029	Repressing the abnormal airway smooth muscle cells (ASMCs) migration.[32]
LncRNAs	CASC2	Inhibiting ASMCs proliferation, migration, and inflammation.[39]
	CDKN2B-AS1	Inhibiting *ZFP36* promoter methylation and increasing nuclear receptor 4A1 (NR4A1).[40]
	PAET	Enhancing DNA damage.[44]
	LINC02145/GUSBP2	Involving in immune response and inflammatory response.[38]
	THRIL	Correlating with inflammatory cytokines.[41]
	PTTG3P	Promoting progression of childhood asthma.[42]
	LINC01559/SNHG8	Correlating with progression of childhood asthma.[55]
	BAZ2B	Promoting M2 macrophage activation and inflammation.[56]
	TUG1	Promoting proliferation and migration.[57]

regulate its expression.[60] The bronchial brushings of CF patients showed higher levels of miR-145, miR-223, and miR-494 than non-CF brushings, illustrating the complexity of *CFTR* post-transcriptional regulation.[61,62] *In vitro*, miR-101 and miR-494 regulated the *CTFR* gene expression, whereas miR-138 inhibited *SIN3A*, causing increase in the *CFTR* gene expression.[63,64] Overexpression of MiR-138 enhanced CFTR molecule binding to the surface of cells, which is a potential therapeutic target of the *CFTR* gene.[64] Oligonucleotide sequences specifically target and inhibit miR-101, miR-145, and miR-509-3p, successfully rescuing CFTR protein levels.[65] In primary lung epithelial cells from CF patients, miR-16 restores functional expression of the cyclic AMP-activated apical chloride channel, F508del-*CFTR*.[66] Since miRNAs act upstream of correctors and potentiators, miRNA-based therapies enhancing the *CFTR* gene expression may increase the effectiveness of the current *CFTR* modulators being tested in CF patients.

It is essential to carry out further research in order to develop biocompatible materials that are capable of delivering therapeutics efficiently at local sites because of barriers in the lungs with CF.

MicroRNAs may also control inflammatory responses in CF, particularly during pulmonary exacerbations, by affecting gene expression during inflammation. MiRNA-126 was the first described miRNA in CF; it decreased in airway epithelial cells regulating the *TOM1* gene expression, involved in the ubiquitinated proteins trafficking and negative regulation of toll-like receptor 2 (TLR2), TLR4, and IL-1R1 pathways.[67] In CF lung epithelial cells, increased miR-155 reduced SHIP1 expression, thereby triggering phosphatidylinositol 3-kinase–protein kinase B (PI3K/Akt) signaling and thereby promoting proinflammatory expression of IL-8.[68] In another study, compared with healthy groups, miR-145 and miR-494 were obviously increased in nasal epithelial tissues of CF patients.[69] There was a decrease in miR-17 levels in CF bronchial brushings and a decrease in miR-17 and miR-93 expressions in pseudomonas-induced bronchial epithelial cell lines, thus increasing the level of IL-8.[70,71]

Furthermore, macrophages from patients with CF are not capable of killing bacteria inside the cell. In CF cells, miR-181b is overexpressed, impairing some mechanisms of inflammation resolution dependent on N-formyl peptide receptor 2 (ALX/FPR2).[72] In this regard, miR-181b targeting may contribute to the enhancement of anti-inflammatory and anti-microbial defenses in CF.

Long noncoding RNAs and cystic fibrosis

In a microarray analysis of lncRNAs, 1063 differentially expressed lncRNAs were detected in CF patients and non-CF patients, and several lncRNAs were divergently transcribed as gene promoters, suggesting a connection between lncRNAs and proteins.[73] There are a number of reasons for this: (a) these heterogeneous findings can be attributed to a number of factors, such as age, gender, pulmonary function, microbial colonization, and use of medication; (b) because the sample size was small, it did not provide a high level of statistical power.

Saayman et al. found that lncRNA BGas modulated the local chromatin and DNA architecture of intron 11 of the *CFTR* gene in concert with HMGA1, HMGB1, and WIBG.[74] Biotin-labeled oligonucleotides are used to identify the mechanism of how BGas modulates *CFTR* expression, as well as non-histone chromosomal proteins (HMG-14 and HMG-17), high mobility group protein B1 (HMGB1), and partner of Y14 and mago (WIBG), which are DNA-binding proteins that are capable of altering chromatin architecture to regulate transcription.[75] In conclusion, BGas modulates *CFTR* expression by tethering chromatin architectural modifying proteins to intron 11 of the *CFTR* gene.

Noncoding RNAs and Respiratory Syncytial Virus Infection

Respiratory syncytial virus belongs to the family *Paramyxoviridae*, and is one of the major causes of lower respiratory tract infection in young children. A global estimate indicates 24.8 million cases of RSV and about 70–80K deaths reported annually, with 54% occurring in children aged ≤5 years.[76] Clinical manifestations of RSV infection are related to age, underlying disease, environmental exposures, and history of previous respiratory infections. RSV leads to severe infections in high-risk children, with involvement of organs other than the respiratory system.[77] NcRNAs are important for regulating gene expression and protein functions, and figuring out their role in RSV infection could reveal mechanism of the disease.

MicroRNAs and RSV infection

In a miRNA microarray of RSV-infected A549 cells, five miRNAs were induced and two miRNAs were repressed.[78] The expression of miR-24, miR-29a, and miR-6087 in RSV-infected cell models was also demonstrated in other studies using qRT-PCR.[76] Similarly, in human bronchial epithelial cell models, two miRNAs were upregulated and 24 downregulated when infected with RSV, among which miR-221 was obviously downregulated by RSV and inhibited nerve growth factor (NGF) and tropomyosin receptor kinase A (TrKA), finally increasing apoptosis and reducing viral replication and infectivity.[79] Furthermore, according to a sequencing of exosomes from RSV-infected A549 cells, RSV-infected exosomes had an increased miRNA content.[80]

A study collected nasal mucosa cytology specimens of 19 healthy infants, 16 mild patients, 7 moderate patients, and 19 severe patients to perform deep sequencing. The result showed that compared with the healthy group, eight miRNAs were upregulated and three miRNAs were downregulated in the mild or severe group. One miRNA was upregulated in the severe group but downregulated in the mild group.[81] Downregulation of miRNA-140-5p was observed in peripheral blood samples of children with bronchiolitis having RSV infection or healthy children. Further study showed that decreased miRNA-140-5p was related to RSV infection by targeting TLR4.[82] A recent study identified miRNA targets in RSV-infected lung cells by using a biochemical method (CLEAR-CLIP) and found that miRNA-26 and miRNA-27 regulated cell cycle, metabolism, and antiviral immunity.[83] Therefore, the altered miRNA profile

is dramatically related to RSV infection, and RSV-regulated miRNAs are crucial for host responses to RSV infection.

Long noncoding RNAs and RSV infection

Long noncoding RNA was found to promote RSV replication by targeting miRNA miR-509-3p/Rab5c axis regulating vesicle transport.[84] Tao et al. found that the lncRNA MEG3 expression was reduced when infected by RSV but the mRNA levels of TLR4, TNF-α, and IL-8 increased in patients' samples and cell models, indicating MEG3 ameliorated RSV infection by suppressing TLR4 signaling.[85]

LncRNA n337374 is a promising target in RSV infection-induced asthma treatment because its overexpression could suppress dendritic cells maturation and relieve the symptoms of RSV-induced asthma by downregulating the CD86–ERK pathway.[86]

Circular RNAs and RSV infection

CircRNAs play a significant role in the interaction between cells and viruses. Yao et al. first characterized 53,719 cellular circRNAs and 2280 differentially expressed cellular circRNAs in RSC cell models, and profiled the general characteristics of both cellular and viral circRNAs.[87] Their results revealed novel aspects of the host–RSV interaction, as well as circRNAs that could serve as novel therapeutic targets or biomarkers. It is currently believed that host circRNAs act as miRNA sponges, competing with other RNAs for miRNA binding sites, leading to indirect regulation of miRNA target genes and pathways.[88] Future research into the functioning and mechanism of host circRNAs will enhance understanding of their roles in the onset and progression of viral diseases.[89]

Limitations and future outlook

Limitations were observed to the use of ncRNA, such as how to locate nucleic acid drugs at specific targets or specific organs, and whether specific chemical modifications could be made to nucleic acid drugs because of natural mechanisms of degradation, as well as potential off-target effects. In addition, most of the evidences were based on animal and cell models, and these evidences must be carefully transposed to the case of human diseases. Thus, future research should pay more attention to human settings, and identify and validate more ncRNAs by collecting peripheral blood, sputum, and exhaled breath condensate from patients in combination with deep sequencing, bioinformatics analysis, and experimental validation (Figure 2).

Conclusions

The study of ncRNAs has a wide range of applications in the field of medicine, such as the treatment of relevant diseases or as markers of disease onset and progression by regulating the expression of specific ncRNAs.[90–92] In pediatric respiratory diseases, miRNAs are studied most extensively, but lncRNA and circRNA also have potential for analysis. Furthermore, treatments based on synthetic ncRNAs or inhibitors could prove a breakthrough in treating pediatric respiratory diseases.

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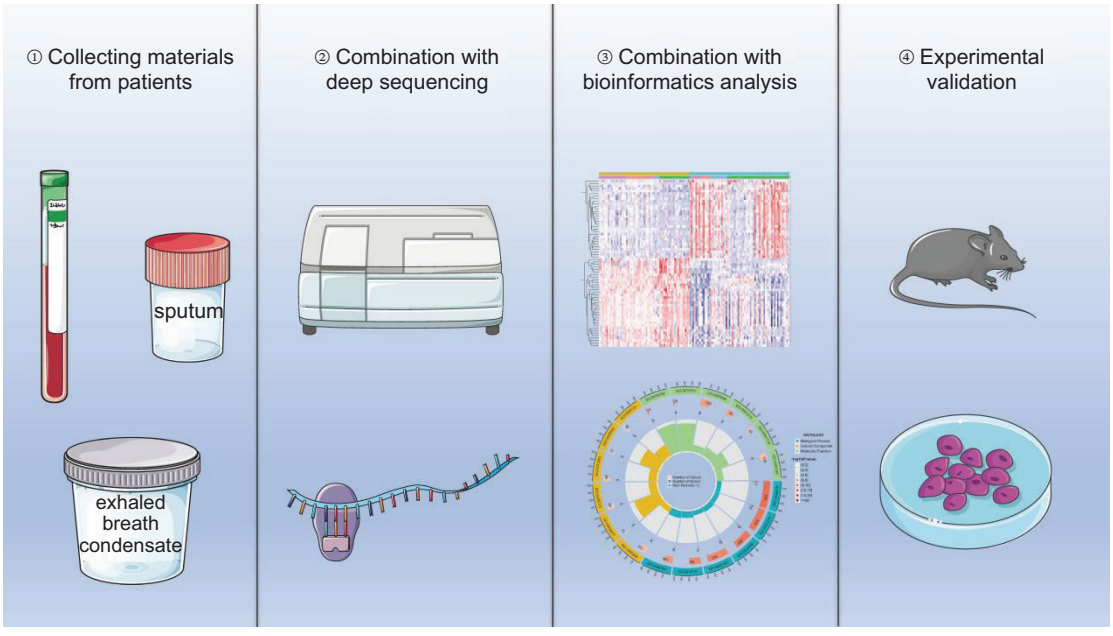

Figure 2 The overall flowchart of ncRNA research.

Competing Interests

The authors had no relevant financial or nonfinancial interests to disclose.

Author Contributions

Shishu Yu and Lili Chen wrote the text of main manuscript and Mingyao Zhang collected the data. All authors reviewed the manuscript.

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