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Review

Emerging role of non-coding RNAs in allergic disorders

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ABSTRACT

RNA transcripts that not undergo translation into polypeptides recently came into focus of research. Long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs (circRNAs) comprise the most important groups of these transcripts. LncRNAs have a length over 200 nucleotides and like mRNAs, have regulated transcription in a tissue specific manner. Biogenesis and function of lncRNAs is related to cell differentiation, response to stimuli and regulation of immune responses. LncRNAs can interact with both miRNAs and mRNAs. MiRNAs are characterized by a length of 22–24 nucleotides. MiRNAs regulate expression of genes at the post-transcriptional level. LncRNAs together with miRNAs are considered as regulators of the immune system. Alterations in their biogenesis is an important mechanism in the development immune related disorders. CircRNAs are products of aberrant maturation of protein-coding transcripts in a process of back-splicing, in which a single strand RNA molecule attains a closed circle shape. Despite a low expression, some circRNA were found to titrate miRNAs and interfere with maturation of legitimate protein-coding transcripts. We summarize the current knowledge on the role of non-coding transcripts in allergic disorders: asthma, atopic dermatitis, allergic rhinitis and urticaria. The reviewed data suggest lncRNA and miRNAs as therapeutic targets and biomarkers of allergic disorders.

1. Introduction

Some sequences of a genome are transcribed but not translated into polypeptides. These non-coding RNA (ncRNA) can be detected in the cytoplasm or in extracellular fluids. Deep RNA sequencing and bioinformatics tools allowed to study (ncRNAs). Participation of ncRNA in RNA splicing, transposon reassembly or genes rearrangements [1] was known for long time. However, regulatory ncRNAs constitute a large proportion of ncRNAs. The most recently described circular RNAs are produced from protein-coding transcripts by abnormal splicing and have a closed circle shape. Some circRNA were found to trap miRNAs and interfere with maturation mRNA [2]. Other ncRNA are named long ncRNAs (lncRNAs, length > 200 nucleotides) or microRNAs (miRNAs, length 22–24 nucleotides) [2,3]. MiRNAs regulate translation of polypeptides at post-transcriptional level [4] contributing to epigenetic regulation. All ncRNAs are encoded by their respective genes and regulate many biological processes in an evolutionary conserved manner [5]. Both lncRNAs and miRNAs participate in the regulation of immunity by the preservation of hematopoietic stems cells, differentiation and apoptosis of myeloid cell and the stimulation of monocytes, macrophages and dendritic cells (DCs) [6]. Moreover, several lncRNAs regulate proliferation, differentiation and induction of immune cells from inactive state. During innate or adaptive immune responses monocytes, macrophages, DCs, neutrophils, T and B lymphocytes change their expression of ncRNAs [7]. Assessment of expression of lncRNAs in CD8+ and CD4 + T cells led to identification of numerous RNAs species with a phase- or tissue-specific signatures [8,9]. Similarly, miRNAs were showed to alter cell development, differentiation and release of inflammatory cytokines [10]. The role of miRNAs in regulation of innate immune responses, especially macrophages and granulocytes, was well established [11]. MiRNAs also participate in a control adaptive immune responses and abnormal expression of miRNAs was found in autoimmune disorders [11]. We summarize the available data about the role of these ncRNA in asthma, atopic dermatitis (AD), allergic rhinitis (AR), and urticaria.

2. Asthma

Asthma is an inflammatory disorder of the lower airways with reversible obstruction of the airflow and chronic airway remodeling [12].

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A histopathological component of asthma is hyperplasia and hypertrophy of airway smooth muscle cells (ASMCs). Epigenetic mechanisms have prominent roles in the regulation of these cells [13]. Austin et al. reported on differential expression of lncRNAs comparing ASMCs from patients with non-severe and those with severe asthma. Also, a lower expression of PVT1 lncRNA was found in patients with corticosteroid-sensitive non-severe asthma, whereas over-expression of this lncRNA was present in asthmatics with corticosteroid-insensitive severe phenotype. Functional studies showed the role of PVT1 in the regulation of cell proliferation and IL-6 production of ASMCs [14]. Zhu et al. assessed expression of lncRNAs in peripheral blood samples of patients with eosinophilic asthma, neutrophilic asthma and healthy controls using RNA-sequencing. Several differentially expressed lncRNAs were identified. Over-expression of LNC_000127 in eosinophilic asthma was replicated in Jurkat immortalized human T lymphocytes and isolated human CD4 + T cells following stimulation with phorbol ester or anti-CD28. The function of this lncRNA in Th2 inflammation pathway was thus verified [15]. Ye et al. examined expression of ANRIL lncRNA in patients with asthma during exacerbation (BA-E), patients at remission (BA-R) and healthy controls. Of interest, a higher expression of ANRIL/miR-125a axis was observed in BA-E patients compared with BA-R or control groups. Expression of this regulatory axis negatively correlated with respiratory functional tests results in the study participants. Another correlation was found between ANRIL/miR-125a axis expression and severity of asthma, particularly in exacerbations [16]. In addition, receiver operating characteristic curve showed that the axis expression could discriminate disease status with a performance comparable to the measurements of TNF-α, IL-1β, IL-6 and IL-17 cytokines [16]. Presented results are consistent with the role of ANRIL/miR-125a axis in regulation of immune response and suggest its involvement into the pathogenesis of asthma [17,18]. Some other studies also reported aberrant expression of a number of lncRNAs in asthma. Fig. 1A shows the role of *TIMMDC1* and *lncTCF7* in the pathophysiology of asthma. Fig. 1B illustrates TUG1 lncRNA in the control of miR-590-5p regulated bronchial remodeling. The profile of expression and a tentative function of lncRNAs in asthma are summarized in the Table 1.

Several studies assessed the role of miRNAs in asthma. A group of miRNAs which regulate the balance between Th1 and Th2 cells are particular candidates for immunoregulation of the disease. Qui et al. evaluated expression of miRNAs that targeted the transcription factor Runx3 contributing in differentiation of T helper cells. They showed an imbalance of Th1/Th2 cells in the asthmatic patients they studied. Moreover, a lower expression of Runx3 and higher expression of a several miRNAs targeting this transcription factor in the CD4 + T cells was detected in asthmatic patients. Experimentally, it was verified that miR-371, miR-138, miR-544, miR-145, and miR-214 could directly bind to the 3'-UTR of Runx3. These miRNAs could contribute to the Th1/Th2 imbalance in asthma by regulating Runx3 [26].

Several other miRNAs participate in suppression of inflammation in airways, thus down-regulation of these miRNAs contribute to the pathogenesis of asthma. MiR-21 role in regulation of allergic asthma model in mouse is illustrated by the Fig. 2. Ma et al. established a mouse model of asthma by sensitizing and challenging the mice with ovalbumin. In this animal model, they showed that miR-20b mimic reduced both the number of the total leukocytes, neutrophils and eosinophils in the bronchoalveolar lavage fluid (BALF) and mucus production in the airway. Moreover, this treatment decreased VEGF levels in BALF [53]. The role of some other miRNAs in the pathogenesis of asthma was evaluated in human subjects. Zhang et al. found decreased abundance of miR-192 in asthmatic children as compared with controls. In vitro experiments documented that miR-192 inhibited activation pathway of T follicular helper cells by targeting CXCR5 [43]. Table 2 shows the list

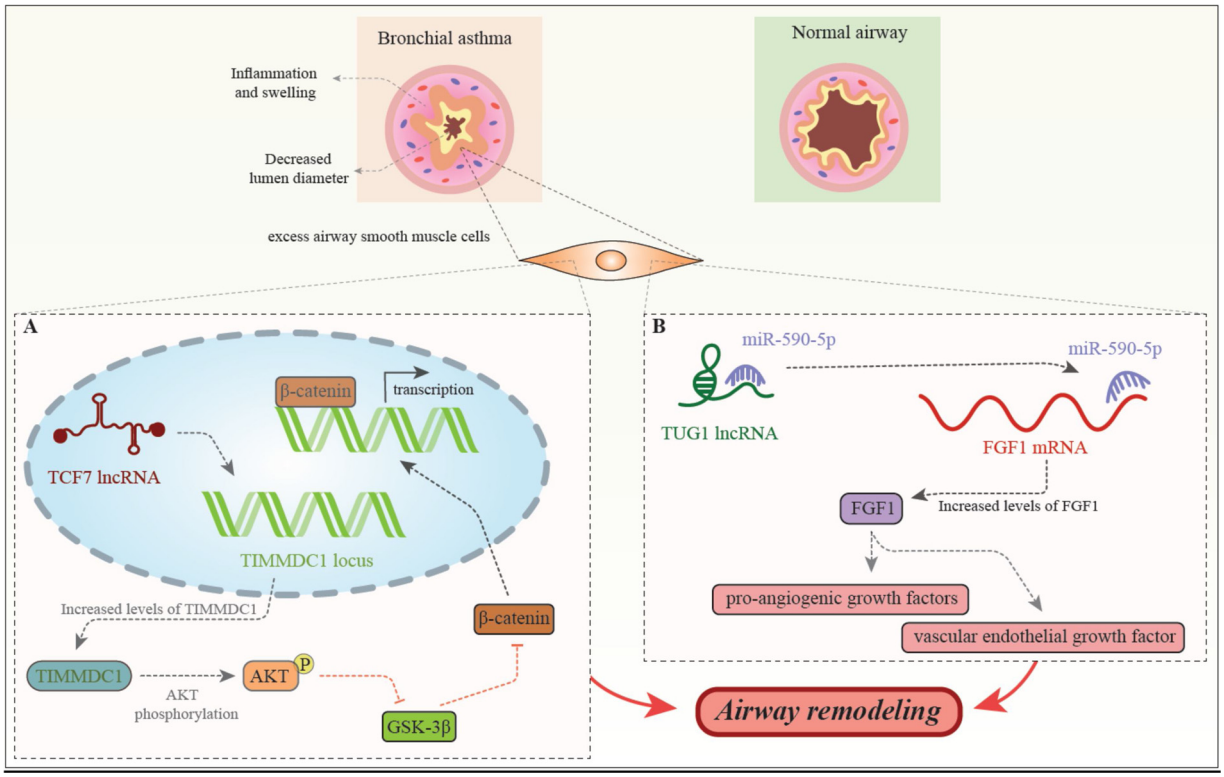

Fig. 1. (A) *TIMMDC1* and *lncTCF7* have been shown to be up-regulated in asthma. *LncTCF7* enhances transcription of *TIMMDC1*. Knock-down of *lncTCF7* has led to down-regulation of TIMMDC1 at transcript and protein levels. Up-regulation of TIMMDC1 increases phosphorylation and activation of AKT. Activated AKT increases expression of β-catenin through inhibition of GSK-3β leading to modulation of expression of genes which are involved in the airway remodeling [19]. (B) *TUG1* acts as a competing endogenous RNA to decrease miR-590-5p levels. miR-590-5p has a role in suppression of FGF1 expression through binding with its 3' UTR region, thus inhibition of this miRNA by *TUG1* increases expression of FGF1. FGF1 is a pro-angiogenic growth factor and vascular endothelial growth factor, therefore it is involved in the airway remodeling [20].

Table 1
Expression and function of lncRNAs in asthma.

LncRNA	Expression pattern	Numbers of clinical samples	Targets/ Regulators	Signaling Pathways	Function	Ref
PVT1	Upregulated	Primary ASMCs from patients with non-severe (n = 9) or severe (n = 9) asthma and healthy subjects (n = 9)	IL-6	–	PVT1 increased in corticosteroid-insensitive severe asthma and decreased in corticosteroid-sensitive non-severe asthma. PVT1 reduced increased cellular proliferation and IL-6 release from ASMCs in severe asthma.	[14]
BCYRN1	Upregulated	–	TRPC1	–	BCYRN1 promoted proliferation and migration of rat airway smooth muscle cells.	[21]
TUG1	Upregulated	–	miR-590-5p	FGF1	TUG1 via sponging miR-590-5p/FGF1 promoted airway smooth muscle cells proliferation and migration in asthma.	[20]
BCYRN1	Upregulated	–	miR-150	–	autophagy activator schisandrin B by downregulating BCYRN1 expression inhibited proliferation and migration of rat ASMCs	[22]
TCF7	Upregulated	asthmatic patients (n = 12) and healthy controls (n = 12)	TIMMDC1	AKT	TCF7 via targeting the TIMMDC1/Akt axis facilitated growth and migration of ASMCs in asthma	[19]
LNC_000127	Upregulated	patients at onset of Eos asthma (n = 12), at onset of Neu asthma (n = 6), healthy controls (n = 12)	–	–	in Eos asthma, targeting LNC_000127 was effective in reducing Th2 inflammation in vitro	[15]
Malat1	Upregulated	ASMCs isolated from 3 patients following lung resection	miR-150	eIF4E/Akt	Malat1 upregulated in ASMCs stimulated with platelet-derived growth factor BB (PDGF-BB). Silencing of Malat1 using miR-150 and block of eIF4E/Akt signaling inhibits PDGF-BB-induced ASMC proliferation and migration.	[23]
ANRIL	Upregulated	plasma of 90 patients with asthma at remission (BA-R) and 90 patients with asthma at exacerbation (BA-E), and 90 healthy controls	miR-125a	–	expression of ANRIL/miR-125a used to investigate the disease exacerbation, exacerbation severity, and inflammation for asthma has a discriminant value.	[16]
ENST00000444682, ENST00000566098, ENST00000583179	Upregulated	108 patients with asthma and 45 healthy controls	–	–	specific lncRNAs aberrantly expressed in $CD4^{+}$T cells useful as biomarkers for diagnosis	[24]
MM9LINCRNAEXON12105+, AK089315	Upregulated	–	–	–	some of the altered lncRNAs involved in the alleviation of iPSC-MSC airway inflammation in mouse asthma	[25]

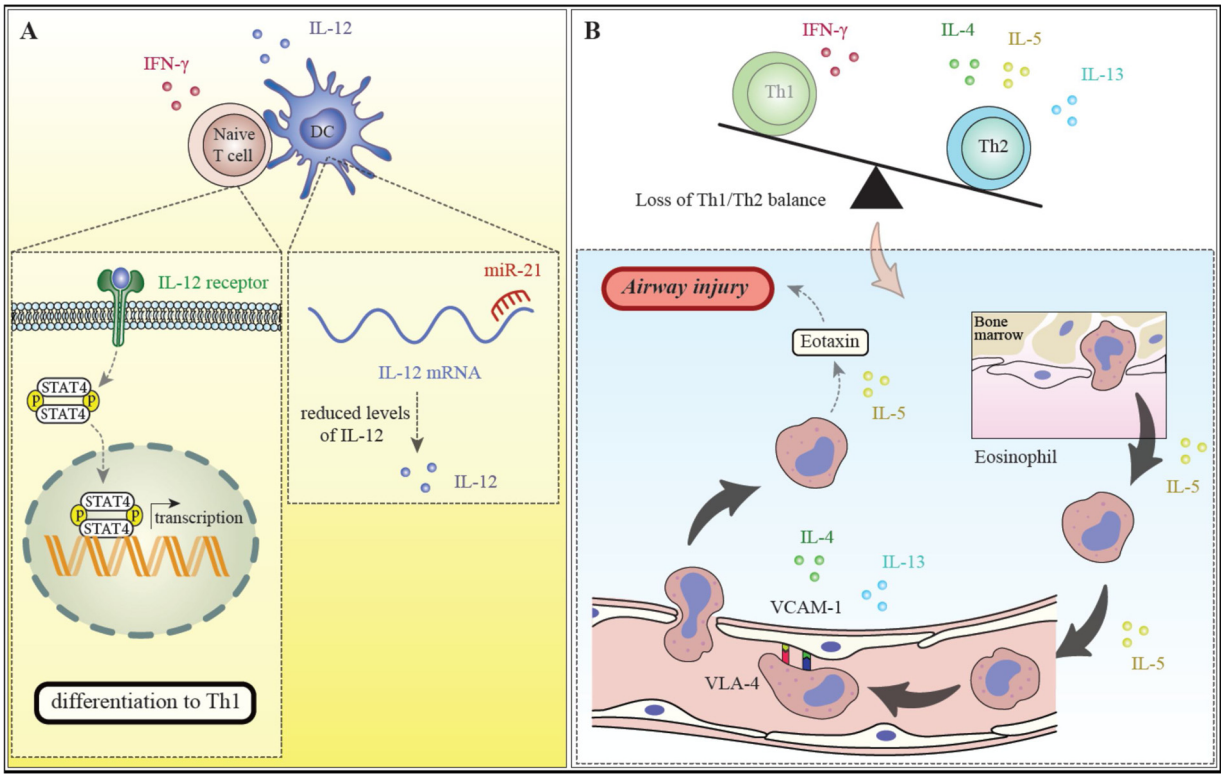

Fig. 2. (A) miR-21 has been shown to be increased in allergic asthmatic mice, while IL-12 and STAT4 are decreased. These factors are involved in regulation of Th1/Th2 balance. Dysregulated expression of these factors in asthma leads to Th2 dominance [29]. (B) IFN-γ is one of the Th1 cytokines which inhibits Th2 differentiation. IL-4, -5 and -13 are Th2 cytokines which enhance production of eosinophils in the bone marrow and their transport to the lungs. While production of eosinophils is increased by IL-5, IL-4 and -13 enhance expression of VCAM-1 on endothelial cells. Binding of VLA-4 molecules on eosinophils with VCAM-1 molecules leads to extravasation of eosinophils. Then, IL-5 acts as an exotoxin to enhance transport of these cells to the lungs. Th2 cytokines increase survival of eosinophils as well [54,55].

of up- and down- regulated miRNAs in asthma and their functions.

3. Atopic dermatitis (AD)

Wang et al. established an fluorescein isothiocyanate-induced animal model of AD. Next, they assessed expression of ncRNAs and mRNAs in this model using microarray technique. They showed dysregulation of 5766 lncRNAs, 4025 mRNAs, and 202 miRNAs after provocation of the AD recurrence. Most notably, expression of 419 lncRNAs, 349 mRNAs and 23 miRNAs remained altered in the remission stage [56]. *In silico* prediction steps led to identification of seven lncRNAs that were subjected to expression assay in the ear tissue of animals by qRT-PCR. They reported upregulation of lincRNA0016+, uc008thl.1, uc029qxr.1, and AK077345, and down-regulation of uc029ycn.1, ENSMUST00000164311, and ENSMUST00000149791. Finally, they selected five lncRNAs (AK077345, uc008thl.1, uc029ycn.1, ENSMUST00000164311, and ENSMUST00000149791) with the highest expression change to identify their potential mRNA targets [56]. These lncRNAs have been suggested as novel targets for modulation of AD recurrence in mice [56].

Several studies assessed the role of miRNAs in the development of AD. Expression profiling of miRNAs in AD facilitated identification of pathogenetic pathways and helped in differentiation of this allergic condition from other disorders like cutaneous T-cell lymphoma (CTCL) or mycosis fungoides (MF). Ralfkiaer et al. showed differential expression of 38 miRNAs between early MF vs. AD. While miR-155, miR-146a, 146b-5p, miR-342-3p and let-7i* were down-regulated in AD, miR-203 and miR-205 had the opposite trend [57]. It is worth mentioning, that up-regulation of a certain miRNA in AD tissues does not necessary imply the pathogenic role of this miRNA in the development of this disorder. Rebane et al. described higher expression of miR-146a in keratinocytes and chronic lesions of the skin in patients with AD. However, the role of this miRNA was confirmed as suppression several proinflammatory transcripts such as IFN-γ-inducible and AD-associated chemokines CCL5, CCL8, and ubiquitin D (UBD) in vitro. Moreover, in vivo experiments confirmed the presence of more robust inflammatory responses in miR-146a-deficient mice. Functional studies revealed that this miRNA inhibits the nuclear factor kappa-B signal transducers [58]. The function of up-regulated and down-regulated miRNAs in AD was summarized in Table 3.

4. Allergic rhinitis (AR)

AR is characterized by induction of the inflammatory response in the nasal mucosa after exposure to an allergen. The inflammatory responses comprise an immediate IgE-mediated mast cell degranulation followed by recruitment of eosinophils, basophils, and T cells. Cells that contribute in the late phase produce Th2 cytokines such as IL-4 and Il-5 which facilitate IgE synthesis and expansion of eosinophils [64]. Based on the role of lncRNAs and miRNAs in the regulation of Th2 responses, it is not surprising that altered expression of these transcript contributes to the pathogenesis of AR. Ma et al. assessed lncRNA signature in nasal mucosa of AR patients to predict possible function of these transcripts in the pathogenesis of AR Their microarray investigation demonstrated differential expression of a total of 2 259 lncRNAs (1,033 up-regulated and 1,226 down-regulated) in the nasal mucosa of AR patients compared with healthy controls. Analysis of lncRNA-mRNA co-expression showed their enrichment in cellular signaling pathways associated with AR development such as positive regulation of IL-13 production, Fc-epsilon receptor-1 and NF-kappa B signaling pathways [65]. Another microarray-based analysis reported differential expression several lncRNAs including 110 upregulated and 48 downregulated lncRNAs in

Table 2
MiRNAs up- or down- regulated in asthma and summary of their function.

Up-regulated microRNA	Numbers of clinical samples	Targets/ Regulators	Signaling Pathways	Function	Ref
miR-1248	serum of asthmatics (n = 10) and non-asthmatic (n = 10) controls	IL-5	–	miR-1248 elevates Th2 cytokine levels.	[27]
miR-371, miR-138, miR-544, miR-145, miR-214	asthmatics (n = 30) and healthy subjects (n = 25)	Runx3	–	mirRNAs capable of combinatorial regulation of Runx3, modulates Th1/Th2 balance in asthma.	[26]
miR-98	asthma patients(n = 20) and healthy subjects (n = 20)	TSP1, IL-13		miR-98 suppresses TSP1 expression in peripheral B cells of allergic asthmatics.	[28]
miR-21	–	IL-12, STAT4	–	Axis of miR-22/IL-12/STAT4 participates in development of allergic asthma.	[29]
miR-21	40 asthmatic children without inhaled corticosteroid, 40 steroid-sensitive asthma children, 15 steroid-resistant asthma children, and 80 healthy children	IL-12p35	–	Circulating blood miRNA-21 predicts therapeutic response to ICS in asthma.	[30]
miR-146a	asthmatic children (n = 30) and healthy children (n = 30)	EGFR	–	Upregulation of miR-146a inhibits proliferation and promotes apoptosis of ASMCs in asthma.	[31]
miR-19a	airway epithelial cells isolated from mild asthmatic subjects (n = 9), and severe asthmatic subjects (n = 6), and healthy controls (n = 9),	TGFbR2	–	miR-19a targets TGFbR2 gene in severe asthma enhances proliferation of bronchial epithelial cells.	[32]
miR-21, miR-146a	asthmatic children (n = 27) and non-asthmatic children (n = 21)	–	–	miR-21 and miR-146a correlates with eosinophilic asthma, useful as biomarker.	[33]
miR-146a	–	IL-5, IL-13	–	miR-146a decreases influx of inflammatory cells into lung, suppresses OVA-specific IgE and Th2 cytokines, attenuating airway hyper-responsiveness and allergic inflammation, mouse model.	[34]
miR-21, miR-126	asthmatics treated with inhaled corticosteroids (n = 19) or without inhaled corticosteroids (n = 16) and non-asthmatic controls (n = 12)	IL-13	–	miRNAs increased in asthmatics compared to controls, expression in bronchial epithelia of asthmatics positively correlated with IL-13	[35]
miR-155	–	IL-33	–	miR-155 required for allergen-induced ILC2 expansion and IL-33 production, asthma mouse model	[36]
miR-21	–	HDAC2	PI3K	miR-21 induced in the lung by infection, during steroid-insensitive allergic airway disease (SSIAAD) in BALB/c. miR-21. Amplifies PI3K–mediated suppression of HDAC2 driving severe steroid-insensitive experimental asthma.	[37]
miR-21	–	PTEN	PI3K/Akt	miR-21 through PTEN /PI3K/Akt signaling pathway modulates human ASMCs proliferation and migration in asthma.	[38]
miR-21	–	IL-12p35	IL-13Rα1, STAT6	miR-21 through the IL-13Rα1-independent pathway overexpressed in mouse allergic asthma	[39]
miR-155	7 asthmatics and 5 healthy subjects	COX-2	PGE2	miR-155 assists overexpression of COX-2 in asthmatic ASMCs	[40]
miR-221	4 asthmatics and 4 healthy subjects	–	–	asthmatics and OVA-induced allergic mice have miR-221 upregulated, reduced airway inflammation	[41]
miR-1165-3p	53 asthmatics and 22 healthy subjects	–	–	circulating miR-1165-3p useful as a biomarker of asthma.	[42]
miR-221	25 asthmatics and 22 healthy subjects	SIRT1	–	overexpression of miR-221 by targeting SIRT1 induces apoptosis and inhibits proliferation in bronchial epithelial BEAS2B cells.	[43]
Down-regulated microRNA					
miR-221-3p	77 asthmatics and 36 healthy subjects	CXCL17	p38, MAPK	miR-221-3p upregulates anti-inflammatory chemokine CXCL17, protective against airway eosinophilic inflammation.	[44]
miR-192	7 mild asthmatics and 4 healthy subjects	–	–	decreased miR-192 in blood of asthmatics	[45]
miR-20b	–	–	–	intranasal administration of miR-20b increased the percentage of Gr1 + CD11b + myeloid-derived suppressor cells (MDSCs) and increased TGF-β in the lung of asthmatic mice	[46]
miR-20b	–	–	–	miRNA-20b promotes accumulation of CD11b + Ly6G + Ly6C^{low} MDSCs in asthmatic mice.	[47]
miR-485	–	Smurf2	TGF-β/Smads	miR-485 targeting Smurf2 through the TGF-β/Smads signaling pathway, suppresses cell proliferation and promote cell apoptosis in mice with chronic asthma.	[48]
miR-142-3p	mild (n = 5) and severe (n = 16) asthmatics	–	WNT	miR-142-3p regulates the balance between proliferation and differentiation of ASMCs	[49]
miR-26a, Let-7a, Let-7d, mir-323, miR-21	serum of asthmatics (n = 10) and non-asthmatic (n = 10) controls	–	–	miRNAs useful as a biomarkers for diagnosis of asthma.	[27]
miR-17	asthmatics (n = 30) and healthy controls (n = 25)	–	–	miR-17 useful as a biomarker for the diagnosis of asthma.	[26]

(*continued on next page*)

Table 2 (*continued*)

Up-regulated microRNA	Numbers of clinical samples	Targets/ Regulators	Signaling Pathways	Function	Ref
let-7a	bronchial biopsies of 24 asthmatics and 10 controls	–	–	let-7a useful as a biomarker to discriminate between asthma phenotypes.	[50]
	–	IL-13	–	exogenous let-7 mimic by targeting IL-13 alleviates asthmatic phenotype in OVA allergic mice.	[51]
miR-410	–	IL-4, IL-13	–	intranasal miR-410 targeting IL-4/IL-13 attenuates airway inflammation in OVA-induced asthmatic mice.	[52]

Table 3
MiRNAs up-regulated in AD and summary of their function.

Up-regulated microRNA	Numbers of clinical samples	Targets/ Regulators	Signaling Pathways	Function	Ref
miR-203, miR-205	atopic dermatitis (AD, n = 20), mycosis fungoides (MF, n = 13), cutaneous T-cell lymphoma (CTCL, n = 42)	–	–	miRNA profiling in AD improves both diagnosis and risk prediction	[57]
miR-155	serum of AD patients (n = 32) and healthy subjects (n = 31)	SOCS1	–	miR-155 drives differentiation of Th17 cells, directly inhibits SOCS1 in AD enhancing function of Th17 cells	[59]
	skin biopsy from and patients with AD (n = 18) and healthy subjects (n = 29)	CTLA-4	–	miR-155suppresses CTLA-4 and by enhancing T-cell proliferation is involved in the regulation of T-cell responses	[60]
miR-151a	blood leukocytes from AD patients (n = 117) and healthy subjects (n = 166)	IL12RB2	–	miR-151a regulating IL12RB2 involved in the pathogenesis of AD	[61]
miR-29b	skin biopsy from AD patients (n = 21) and healthy control subjects (n = 12)	BCL2L2	–	miR-29b/Bcl2L2 axis is involved in the pathogenesis of AD	[62]
miR-146a	serum of patients with AD (n = 25) and healthy controls (n = 16)	SUMO1	–	miR-146a by targeting SUMO1 involved in the pathogenesis of AD	[63]
miR-146a	–	CCL5	NF-kB	in AD miR-146a controls NF-kB–dependent inflammatory response	[58]
miR-155-5p, miR-3473b, miR-146a-5p	–	–	–	specific non-coding RNAs reveal therapeutic targets against AD recurrence, mice model	[56]
Down-regulated microRNA					
miR-155, miR-146a, miR-146b-5p, miR-342-3p, Let-7i	atopic dermatitis (AD, n = 20), mycosis fungoides (MF, n = 13), cutaneous T-cell lymphoma (CTCL, n = 42)	–	–	miRNA profiling in AD improves both diagnosis and risk prediction	[57]
miR-677-3p, miR-770a-5p, miR-5119	atopic dermatitis (AD, n = 20), mycosis fungoides (MF, n = 13), cutaneous T-cell lymphoma (CTCL, n = 42)	–	–	specific non-coding RNAs reveal therapeutic targets against AD recurrence, mice model	[56]

Table 4
LncRNAs up- or down- regulated in AR and summary of their function.

Upregulated lncRNA	Numbers of clinical samples	Function	Ref
GABPA-9:1, NR_103763, CCL21, APOA2, RAD9B-1:4	nasal mucosal from 19 patients with AR and 14 non-allergic patients	Expression of lncRNAs in AR patients provide insight into AR pathogenesis.	[65]
FR022494, FR255904, FR169472	–	Expression of lncRNAs in CD4 + T cells of AR murine model provide insight into AR pathogenesis.	[66]
ANRIL	nasal mucosal from 96 patients with AR and 96 controls	lncRNA ANRIL involved in the pathogenesis of AR	[67]
Down-regulated lncRNA			
GAS5	nasal epithelium from AR (n = 30) and healthy subjects (n = 30)	GAS5 suppresses Th1 differentiation and promotes Th2 differentiation through downregulated EZH2 and T-bet in AR.	[68]
UBLCP1-4:2, RTL1-8:1, NR_121637, NST00000505668	nasal mucosa from 19 AR and 14 non-allergic subjects	Expression of lncRNAs in AR patients providing an insight into AR pathogenesis.	[65]
FR288904, FR301516, FR285768	–	Expression of lncRNAs in CD4 + T cells of an AR murine model provides insight into AR pathogenesis.	[66]

the CD4 + T cells in an AR murine model. Differentially expressed genes were enriched in some pathways such as regulation of calcium ion transport, B cell activation and chemokine-signaling [66]. In a human study, Qian et al. compared expression of ANRIL in nasal mucosa samples between AR patients and non-atopic obstructive snoring patients. Notably, up-regulation of ANRIL characterized AR patients. Moreover, expression of this lncRNA positivly correlated with levels of TNF-α, IL-4, IL-6, IL-13, and IL-17, whereas, it negatively correlated with IL-10 and IFN-γ levels [67]. ANRIL expression also positively correlated with: increased AR risk, severity and inflammation indices, showing some diagnostic properties of this transcript in AR (Sensitivity = 81.3 % and specificity = 56.3 %) [67]. Table 4 summarize the results of studies which reported up-regulation and down-regulation of lncRNAs in AR.

Function of miRNAs was also investigated in the pathophysiology of AR. Jia et al. assessed miRNA signature in nasal mucosa of AR patients and non-atopic subjects using microarray technique and qRT-PCR. Up-regulation of miR-126-5p, miR-19a-5p and miR-26a-5p was reported in AR patients as compared to healthy subjects [69]. Hou et al. assessed expression of miRNAs in AR mice before and after treatment with ipratropium bromide (IB) effective in the control of AR symptoms. Differential expression of 87 miRNAs in IB group was found by comparison with the placebo group. Notably, mmu-miR-124-3p/5p, -133b-5p, -133a-3p/5p, -384-3p, -181a-5p, -378a-5p and -3071-5p were among the most up-regulated miRNAs. Based on these observations, authors suggested that IB treatment regulated expression of immune-associated miRNAs in the nasal mucosa of allergic mice and corresponded with amelioration of the nasal allergic symptoms [70]. Table 5 summarizes the results of studies which reported up-regulation or down-regulation of miRNAs in AR.

One of the most practical aspects of miRNA profiling in human disorders is application of differentially expressed molecules as predictive disease biomarkers. However, only a few studies assessed diagnostic performance of miRNA in diagnosis of AR. Table 6 summarizes the results of these studies.

5. Urticaria

Urticaria is an acute or chronic dermal edema which is caused by dilatation of vessels and leakage of fluid into the skin. Chronic spontaneous urticaria (CSU), also called chronic idiopathic urticaria (CIU), is characterized by spontaneous development of wheals and/or angioedema for more than 6 weeks without obvious triggering factors [93]. Mast cells granules mediators have essential roles in the pathogenesis of this disorder. CSU/CIU is an autoimmune disease [94]. A few studies evaluated ncRNAs in the pathophysiology of this disorder. Lin et al. reported on identification of miRNAs in CIU. By assessment of miRNAs in plasma, profiles of these molecules were obtained in groups comprising active hives or no hives and presence or absence of CIU. Differentially expressed 16 miRNAs were found in patients with active hives. MiR-2355-3p, miR-4264, miR-2355-5p, miR-29c-5p and miR-361-3p were over-expressed in exacerbated CIU patients. Target prediction of these miRNAs showed their enrichment in regulatory pathways such as TGF-β, glucocorticoid receptor, and p53 signaling. Some other enriched terms were p21-activated kinase, phosphoinositide-3 kinase, protein kinase B and neuroactive ligand-receptor interaction [95]. Zhang et al. explored the role of miRNAs in the CIU. Up-regulation of miR-125a-5p and CCL17 was found in patients sera. Although serum levels of miR-125a-5p were even higher in refractory CSU patients, its levels were down-regulated in patients who experienced remission [96]. Table 7 summarizes the results of studies that reported alterations of expression of miRNAs in urticaria.

6. Discussion

The current research on lncRNAs and miRNAs in allergic disorders is summarized, however, no circRNA studies were conducted so far. These data could be used for design of novel therapeutic strategies. Integrative assessment of lncRNAs, miRNAs, circRNA with mRNA-encoded proteins production is proposed as competing endogenous (ce) network. This approach was successfully applied in AD [56]. A similar analysis in AR identified mRNA-lncRNA network and suggested possible therapeutic targets [65]. More recently, comprehensive assessment of lncRNA-miRNA and mRNA-miRNA interaction data led to a construction of lncRNA-miRNA-mRNA ceRNA network in asthma. These analyses showed the importance of lncRNAs in the disease. Moreover, results suggested tentative novel targets for treatment via drug repositioning techniques [97]. Assessment of miRNAs/lncRNAs expression in paired tissue and serum samples to compare patients vs. healthy subjects facilitates identification of disease biomarkers and explores the correlation between their expressions in two tissues. The latter can elucidate source of alterations in peripheral blood. Such comparative analyses seems highly recommended in allergic diseases.

An imbalance between Th1 and Th2 responses is a common finding in allergic conditions. Assessment of the specific roles of miRNAs and lncRNAs in the regulation of these cells and identification of the ceRNA network would facilitate recognition of biomarkers for these disorders. This approach can be applied using the available expression profiles from high-throughput studies. Moreover, variable expression of ncRNAs in different stages of a disorder, e.g. remission or exacerbation, is necessary to fully address the function of these transcripts. Similarly, a response of ncRNA levels to a treatment evaluated by appropriate clinical scores would confirm importance of the observed alterations. For example, alterations in the expressions of miRNAs were reported in nasal mucosa after specific immunotherapy for AR in mice, thus inflicting miRNA in specific immunotherapy [98].

Table 5
MiRNAs up- or down-regulated in AR and summary of their function.

Up-regulated microRNA	Numbers of clinical samples	Targets/ Regulators	Function	Ref
miR-221,miR-142-3p	nasal mucosa from 85 AR and 57 non-atopic subjects	–	miR-221 and miR-142-3p expressions novel and promising biomarker for risk of AR	[71]
miR-30-5p, miR-199b-3p, miR-203	extracellular vesicles from nasal mucus of 44 AR and 20 healthy controls	–	vesicle miRNA is regulator for the development of AR	[72]
miR-375	–	IL-4, IL-13, TSLP	miR-375 is a regulator for the development of AR	[73]
miR-135a	–	–	miR-135a corrects Th1/Th2 imbalance in AR mice	[74]
miR-155	nasal mucosa from 28 AR and 26 non-atopic subjects	IL-4, IL-5, IL-9, IL-13	miR-155 regulates Th2 factor expression and allergic inflammatory response in ILC2 cells in AR	[75]
miR-126-5p, miR-19a-5p, miR-26a-5p	nasal mucosa from 48 AR and 50 control subjetcs	–	miR-126-5p, miR-19a-5p and miR-26a-5p novel biomarkers for AR risk	[69]
miR-19a	peripheral blood AR patients (n = 20) and healthy subjects (n = 20)	IL-10	vitamin D3 represses mir-19a promoting specific immunotherapy (SIT) in AR	[76]
miR-155, miR-205, miR-498	159 young adults stratified: AR + asthma (n = 36), nonallergic rhinitis (n = 39), control (n = 34), AR (n = 50)	–	miR-155, miR-205, and miR-498 importance in allergic inflammation of nasal mucosa	[77]
Let-7a	–	OPN	Let-7a regulates OPN expression promoting AR development in a mouse model	[78]
miR-202-5p	peripheral blood from 30 AR and 10 healthy subjects	MATN2	miR-202-5p via targeting MATN2 participates in regulatory T-cells differentiation and function	[79]
miR-202-5p	nasal mucosa from AR patients (n = 30) and healthy subjects (n = 10)	MATN2	miR-202-5p by targeting MATN2 promotes M2 polarization in AR	[80]
Down-regulated microRNA				
miR-487b	nasal mucosa from 20 patients with AR and 20 control patients	IL-33, ST2	miR-487b through inhibition of the IL-33/ST2 signaling pathway mitigates allergic rhinitis	[81]
miR-133b	–	Nlrp3	overexpression of miR-133b via targeting Nlrp3 inhibits OVA-specific IgE and allergic symptoms in AR mice	[82]
miR-874, miR-28-3p, miR-875-5p	extracellular vesicles from nasal mucus from 44 AR patients and 20 healthy controls	–	vesicle miRNA regulates development of AR	[72]
miR-146a	nasal mucosa from 24 AR children and 20 healthy controls	Foxp3, TRAF6, IL-10	miR-146a considered as a biomarker for management of AR patients.	[83]
miR-21	20 cord blood samples with and without elevated cord blood IgE (CBIgE) elevation and in 20 children with and without allergic rhinitis	TGFBR2, IL-12A, IRF3, HMGB2	lower expression of miR-21 and higher expression of TGFBR2 in.CB associated with antenatal IgE production and development of AR.	[84]
miR-let-7e	nasal mucosa from 23 patients with AR and 18 control patients	SOCS4, JAK1/STAT3	miR-let-7e through the SOCS4/JAK1/STAT3 signaling pathway regulates progression and development of AR.	[85]
miR-21	–	PTEN	traditional chinese medicine yupingfeng upregulates PTEN-induced miRNA-21 while improving imbalance in theTh1/Th2 ratio in allergic rhinitis	[86]
miR-155, miR-181a	25 AR children and 20 healthy children	IL-10	decreased regulatory cells (Tregs)-derived miR-155 and miR-181a correlated with reduced number and function of Tregs in AR children.	[87]
let-7e	159 young adult subjects subdivided into control (n = 34), AR (n = 50), AR + asthma (n = 36), and non-allergic rhinitis (NAR, n = 39)	–	let-7e importance in allergic inflammation of nasal mucosa.	[77]
miR-106b	–	Egr-2	miR-106b by targeting Egr-2 regulates pro-allergic properties of dendritic cells and Th2 polarization in vitro	[88]
miR-143	nasal mucosal from AR (n = 23) and non-AR sibjects (n = 18).	IL13Ra1	miR-143 by targeting IL13Ra1 inhibits IL-13-induced inflammatory cytokine and mucus production in nasal epithelial cells of AR patients	[89]
miR30a-5p	20 AR and 20 control subjects	SOCS3	miR30a-5p/SOCS3 involved in the pathogenesis of AR	[90]
miR-181a, miR-155	20 AR and 20 healthy subjects	SOCS1, SIRT1, IL-10, TGF-β, PI3K/Akt	miR-155 and miR-181a closely correlated with the proliferation and function of Tregs in AR	[91]
miR-15a-5p	nasal mucosa of 20 patients with long-term AR and 20 non-AR subjects	ADRB2	in AR stimulated by IL-13, ADRB2 inhibits inflammatory response of NECs, miR-15a-5p has a negative regulatory effect on ADRB2	[92]
miR-375	–	JAK2, STAT3	miR-375 via inhibiting JAK2/STAT3 pathway ameliorates AR and prevents nasal mucosa cells from apoptosis in mice mode.	[73]

Table 6
Diagnostic power of miRNAs in AR.

Samples number	Area under curve	Sensitivity	Specificity	Univariate cox regression	Multivariate cox regression	Ref
nasal mucosa from 85 patients with AR and 57 non-atopic patients	0.622 for miR-221 and 0.762 for miR-142-3p	35.3 % for miR-221 and 78.8 % for miR-142-3p	86.0 % for miR-221 and 64.9 % for miR-142-3p		–	[71]
nasal mucosa from 48 AR patients and 50 controls	0.685 for miR-126-5p, 0.742 for miR-19a-5p, 0.719 for miR-26a-5p	89.6 % for all	70% for all	expression positively correlated with the risk of AR.	expression independently associated with increased risk of AR.	[69]

Table 7
Summary of urticaria studies that reported alterations in expression of miRNAs.

microRNA	Expression pattern	Numbers of clinical samples	Targets/ Regulators	Function	Ref
miR-2355-3p, miR-4264, miR-2355-5p, miR-29c-5p, miR-361-3p	Upregulated	12 patients stratified to: normal chronic urticaria index and no active hives; positive disease index no active hives; active hives with a negative disease index; active hives and positive disease index	–	modulation of inflammation-related pathways	[95]
miR-125a-5p	Upregulated	20 active CIU patients and 20 healthy controls	CCL17	miR-125a-5p could serve as potential serum biomarkers for CIU.	[96]

The presented data appeals for the role of both lncRNAs and miRNAs, and possibly circRNAs in the pathogenesis of asthma, AR, AD and urticaria. Identified miRNAs/lncRNAs alterations awaits replication studies.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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