

MicroRNA and heme oxygenase-1 in allergic disease

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ABSTRACT

Background: Cumulative evidence suggests that in allergic diseases, oxidative stress and inflammation could often be detected. Therefore, the antioxidant/anti-inflammatory heme oxygenase (HO)-1 was recognized as a protective factor in allergic disorders. However, the precise underlying mechanisms of HO-1-based protection are not yet completely understood. In addition, miRNAs, a class of non-coding RNA, have been confirmed to associate with immunologic and inflammatory disorders in allergy recently. In addition, abundant studies have verified there is a complex connection between HO-1 and miRNAs. Thus, in this review, the combination of HO-1 and miRNAs (e.g. miR-155) in anti-allergy would be introduced.

Methods: To further confirm our hypothesis, GEO sequencing datasets of atopic dermatitis children were analyzed. The miR-548a-3p might regulate the cellular response to hydrogen peroxide through HO-1 and HIF-1 pathway. Meanwhile, this article reviews the latest knowledge and studies on the protective mechanisms of miRNA-HO-1 in allergy.

Results: In brief, we supposed that miRNAs/HO-1 could mediate allergy through oxidative stress pathways, transcription factors and immune cell functions such as mast cell maturation, chemokine expression in T cell and dendritic cell degranulation. Although the detailed mechanism needs further research, this review may reveal the potential application of miRNAs and HO-1 in genetic therapies of allergic disease and provide new biomarkers.

Conclusion: This article examines the latest knowledge and studies on the protective roles and mechanisms of miRNA-HO-1 in allergy. Moreover, via bioinformatics analysis of GEO dataset, it was demonstrated that miRNAs (e.g. miR-205, miR-203, and miR-483-5p) could regulate allergy process through HO-1.

1. Background

Allergic reactions differ from normal immune reactions since inappropriate or exaggerated response and sometimes damaging to the host as well as autoimmune diseases. However, the molecular and cellular mechanisms of these 2 types of reactions are same essentially. The sequence of events participated in the development of allergic reaction could be divided into sensitization stage, activation stage and effector stage [1]. Currently, there are more and more allergic diseases such as atopic dermatitis (AD), allergic asthma and contact hypersensitivity, etc. The pathogenesis of allergy has been attributed to a complex mechanism, including host susceptibility genes, environmental factors, altered skin barrier function, oxidative stress and a deregulated immune system [2]. Also, in the whole progress of allergy, immunocyte (mast cells (MCs), helper T cells, dendritic cells (DCs) and regulatory T cells (Tregs)) and various transcription factors (HO-1, Nrf2, NF- κ B, and TGF- β) have been verified to play key roles in pathology [3]. The mitochondrial enzyme HO-1 catalyzes the first and rate-limiting step in the

oxidative degradation of free heme [4]. HO-1, expressed under various pathological conditions, has an ability to influence various biological events by its enzymatic by-products. It has been the focus of considerable medical interest recently [5]. HO-1 can be induced primarily by heme and also a wide variety of stimuli, inducing hyperoxia, reactive oxygen species (ROS), hypoxia, pro-inflammatory cytokines, heat shock and ultraviolet radiation [6]. This adaptive response of HO-1 to various stimuli suggests that HO-1, besides its role in heme degradation, also functions as a cytoprotective mechanism in numerous models of cellular stress and organ pathology [7].

Innate and acquired immunity of the organism is under constant control of genes dynamic changes in expression. MicroRNAs (miRNAs), a class of small (about 22-nucleotide), noncoding RNAs, sensitively control gene expression through mRNA degradation or translation repression by directly binding to the 3'-untranslated region (3'-UTRs) of target [8]. MiRNAs are one of the fundamental epigenetic regulators that are highly conserved throughout species [9]. The mature process of miRNA involved RNase III-endonuclease type Drosha-DGCR8 (Di-

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George syndrome critical region gene 8) complex, exportin-5-RAN-GTP complex and enzyme Dicer [10–14]. Because of the large population and networked action mode, miRNAs play crucial roles in fundamental biological processes, including development, proliferation, self-renewal, and apoptosis, as well as pathological conditions such as allergy and autoimmune diseases [15–19]. Moreover, a single miRNA can act on several mRNAs while a distinct mRNA could be the target of multiple miRNAs. Thus, the mechanism of miRNA regulation is intricate and worthy of study in allergic disorders.

In this regard, this review focus on the anti-allergic mechanisms of both HO-1 and miRNAs and, with particular focus on, the potential of miRNA-HO-1 system. This information may be important for the development and patents of potential drugs that may alleviate the numerous inflammatory/allergic diseases through their regulation of miRNA-HO-1. In addition, through review the research progress of HO-1/miRNA in allergy would provide some novel biomarkers.

2. Methods

2.1. Literature search and management

A bibliographic search of scientific literature was carried out independently by two researchers (L.C., J.Z.) in the following scientific databases and search engines (Embase, PubMed, Medline, Google Scholar, and Web of Science). “MicroRNAs” combined with “skin,” “hypersensitivity,” “AD,” “allergic disease,” “allergic rhinitis” and “allergic asthma” were used as the MeSH terms. Then a simple search was conducted, from inception until March 2019. We decided to include in our analysis all research articles published in peer-reviewed scientific journals that describe the involvement of miRNAs with allergic disease. From the eligible articles, two researchers (L.C., J.Z.) independently extracted data by using a standard data extraction form. A total of 130 records were identified through database searching, with 2 additional records identified through other sources. Among these, 20 were removed based on title or language. A total of 110 abstracts were screened and, after this process, 28 further articles were excluded on account of the research target. Finally, approximate 90 full-text articles were assessed for eligibility and were included in this review. All references are managed by an editing software named EndNote X7.

2.2. Differential expression of miRNAs in serum and urine of AD compared with healthy children

A total of 27 differentially expressed miRNAs in serum and urine of children with AD were collected from the miRNA sequencing results of Lv Y's research group (GSE62406) [20]. In this study, 30 children with AD were enrolled according to the diagnostic criteria, and 28 healthy children enrolled as control. Healthy children were carefully chosen from patients undergoing pediatric surgery, excluding those with a history of atopic disorders or inflammatory skin diseases and those with total immunoglobulin E (IgE) levels in serum above the normal limit (IgE: 1.31–165.3 IU/ml). Total RNA was extracted from all children's serum and urine samples with a miRNeasy kit (#217004, QIAGEN) according to the manufacturer's protocol. Then the global miRNA profiling was performed by using the TaqMan Low-Density Array (TLDA) Human microRNA Panel version 1.0 (Capitalbio, Beijing, China) and raw cycle threshold (Ct) values were calculated by SDS 2.3 and RQ manager 1.2 software. The Ct value greater or equal to 35.0 was cutoff. To perform global normalization, all Ct values after cutoff were imported into StatMiner 4.2 (Integromics Inc., Philadelphia, PA). The resulting value was ΔCt . The $\Delta\Delta Ct$ was then calculated by subtracting average ΔCt of the normal controls from ΔCt of children with AD. By a non-Parametric Wilcoxon test, dysregulated miRNAs in serum or urine between children with AD and control individuals were dissected. A false discovery rate (FDR) was adjusted with the Benjamini-Hochberg method. An adjusted two-tailed p -value < 0.01 was considered

significant.

2.3. MiRNA target gene prediction and relevant functional analysis by GO and pathway enrichment

The potential target genes of differentially expressed miRNAs in AD patients were acquired from the widely used online databases DIANA-microT (<http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=microT.CDS/index>) [21] and TargetScanHuman 7.0 (<http://www.targetscan.org/>) [22] with conservation (aggregate PCT > 0.8) and context score (< -0.4 and percentile > 85%). The aggregate PCT is calculated as:

$$P_{CT} = 1 - ((1 - P_{CT})_{site1} \times (1 - P_{CT})_{site2} \times (1 - P_{CT})_{site3} \dots).$$

In order to reduce false positives, the predicted target genes which appeared at both databases were accepted. After that, the collection of predicted target genes of each differentially expressed miRNA was imported into DIANA-mirPath (<http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=mirpath/index>), a miRNA pathway analysis web server. All canonical pathways were identified from the Kyoto Encyclopaedia of Genes and Genomes (KEGG) databases. The results were integrated to get the intersection from those meeting the p -value threshold (Benjamini and Hochberg's FDR was applied with significant threshold set at p -value ≤ 0.05) and microT threshold (0.8 of the score). Then the interactions between miRNA and pathways were collected to construct a miRNA-pathway network via Cytoscape software. As a comprehensive set of functional annotation tools, DAVID (the Database for Annotation, Visualization, and Integrated Discovery) has been used for integrative and systematic analysis of enormous gene lists [23]. GO terms are significantly overrepresented in a set of genes from three aspects, namely the biological process, cellular component, and molecular function. In this study, the key GO terms of the predicted target genes of specific miRNAs were performed using DAVID with the thresholds of enrichment gene counts > 2 and p -value < 0.05.

3. Result

3.1. Anti-allergic effect of HO-1 and miRNA

HO-1 or miRNAs expression is dysregulated in the allergic triad (asthma [24], allergic rhinitis [25], and AD [26]), and the differential expression has been proven to be anti-allergic. However, the exact mechanism of how miRNAs/HO-1 can exert anti-allergic effects is still unclear. Both oxidative stress and inflammation are implicated in allergic reactions, the antioxidant/anti-inflammatory properties of HO-1 might play key roles. In addition, blockage of mast cell activation [27,28], inhibition of IgE production [29], and modulation of immunological functions of DCs and T cells may mediate the anti-allergic effects of HO-1 [30–32]. Meanwhile, either miRNAs alone or combined with HO-1 might be involved in these processes.

3.2. The role of miRNA/HO-1 in controlling oxidative stress

Ample evidence has shown that allergic diseases are mediated by oxidative stress [33,34]. Almolki has also reported the antioxidant role of HO-1 in allergic airway inflammation [35]. In guinea pigs sensitized with ovalbumin (OVA), oxidative stress was suppressed when HO-1 expression was induced by hemin. Moreover, in the OVA-challenged guinea pigs, the lower oxidant stress alone with higher HO-1 expression could be associated with a reduction in the number of neutrophils, eosinophils, and lymphocytes in airways. Furthermore, there were another studies have demonstrated that in neutrophils, miR-223 could ameliorate alcoholic liver injury by inhibiting the IL-6-p47phox-oxidative stress pathway [36] while high HO-1 expression stimulates autocrine IL-6 production [37]. Although both miR-223 and HO-1 could regulate IL-6/oxidative stress pathway in neutrophils, however, which

play the crucial role is unclear. However, it was confirmed that in HepG2 cells, miR-223 could decrease the Keap-1 level while the expression of Nrf2 and HO-1 was increased [38]. In addition, Ye et al. [39] have demonstrated that hyperoside, an active compound isolated from *Rhododendron*, could activate Nrf2/HO-1 pathway in turn to reduce the inflammatory cells infiltration and the levels of IL-5. In allergic asthma, miR-1248 was also verified to physically interact with the IL-5 3'-UTR and increase IL-5 expression [40]. In addition, oxidant stress is a proinflammatory factor in allergic diseases, HO-1 might reduce the effect of oxidant stress through regulating the expression of ILs as an antioxidant. In conclusion, previous studies suggested that there would be some miRNAs take part in the regulation of HO-1 in ILs but the mechanism needs to be further research.

3.3. The roles of miRNA-HO-1 in DCs functions

In allergy, except for oxidative stress, immunoreaction also plays a key role in pathogenesis. Either in allergic or normal immune reactions, antigen presentation by DCs is determined as the committed step of immunoreaction. The subsequent generation of allergen-specific CD4 + T cells, as well as transformation into regulatory T cells (Tregs), requires antigen presentation by DCs. In a mouse model of 2, 4-dinitrofluorobenzene-induced contact hypersensitivity, an HO-1 inducer strongly inhibited cutaneous inflammation. It was identified that HO-1 was mainly induced in antigen-presenting cells and suppresses the differentiation, maturation and immunostimulatory function of DCs [32]. Besides, in an allergic rhinitis mouse model sensitized by OVA, markedly lower levels of miR-146a were detected. Further analysis suggested that miR-146a might induce TGF- β in DCs which could induce naive CD4 + T cells to differentiate into Tregs [41]. Meanwhile, another study verified that miR-23b might promote tolerogenic properties of DCs in vitro through inhibiting the Notch1/NF- κ B signaling pathway [42]. However, in DCs functions, not only miRNA but also HO-1 has a correlation with TGF- β and NF- κ B. The detailed mechanism will be expounded in the following text. We concluded that in DCs mediated immune processes, both HO-1 and miRNAs might participate in the functions of DCs whether through TGF- β /NF- κ B.

3.4. MiRNA-HO-1 regulates immunological functions of effector T cell

As well known, allergen-specific CD4 + T cells play a central role in the development of allergic diseases [43]. It was detected that abundant allergen-specific CD4 + T cells were activated in the peripheral blood of allergic patients [44]. Meanwhile, HO-1 exerts a protective immunological action in the diseases mediated by effector T cells such as T-helper (Th1), Th2 and Th17 [45]. For example, HO-1 and/or CO suppressed Th2 chemokine expressions induced by cytokines [46]. Interestingly, not only HO-1 but the differential expression of miRNAs also causes several immunologic and inflammatory disorders [2]. Among them, miR-155 could participate in inflammation and immunity because of its potent upregulation in multiple immune cell lineages, including lymphocytes, MCs, macrophages, and DCs associated with the pathogenesis of allergy [12,19,47–50]. Differential expression of miR-155 has been detected in the peripheral circulation and scathing skin from patients with AD [51]. Besides, the potential regulatory effect of miR-155 on the differentiation and function of Th17 cells has also been investigated. Overall, miR-155 expression levels are positively correlated with AD peripheral CD4 + T cells /AD disease severity.

In Sonkoly et al. study [52], a global miRNA profile for 365 miRNAs were analyzed from punch biopsy specimens in healthy subjects and AD patients with house-dust mite allergy. 44 miRNAs were significantly differentially expressed in AD lesions compared with healthy skin. One of the highest-ranked up-regulated miRNAs was miR-155. To obtain further data regarding the function of miR-155 in the skin, quantification of expression in skin and other organs of healthy subjects was performed. Moreover, miR-155 was regulated by T-cell activation

signals in vitro, and it could be considered an important trigger factor of AD in vivo. There is also a study indicated that miR-155 associated with the regulation of T-cell responses through suppressing cytotoxic T-lymphocyte antigen 4 and enhancing T-cell proliferation [52]. Remarkably, in rodents, HO-1 was identified as a specific target of miR-155. Moreover, miR-155-mediated HO-1 expression in CD4 + T cells was demonstrated to promote T-cell-driven inflammation [53]. Not only in AD, miR-155 could also regulate allergy though T cells in allergic asthma. Using miR-155^{-/-} T cells, Okoye et al. showed that miR-155 was significant for the Th2-mediated immune response partly through the regulation of the S1pr1 (sphingosine-1-phosphate receptor gene) [54], which was important for the migration of lymphocytes from thymus and peripheral lymphoid organs [55]. In a word, these studies have obviously demonstrated that miR-155 does play a role in allergic inflammation via HO-1.

Apparently, except miR-155, there are various miRNAs such as miR-21 could also regulate allergic inflammation. In multiple models of experimental asthma induced by OVA, house dust mite and *Aspergillus fumigatus*, miR-21 was significantly overexpressed in lung tissue [57]. Furthermore, a correlation between miR-21 and HO-1 had been confirmed in a paraquat induced lung fibrosis model in mice [58]. It implied that miR-21 might promote Th2 polarization combined with HO-1 during allergic airway inflammation [57]. The let-7 family was the first to be discovered in humans and has been verified to be of importance in asthma on several occasions [59]. IL-13 has been shown to be a direct target of let-7a while Th1 cells have significantly higher let-7a level than Th2 cells [60]. Although the regulation of let-7 in HO-1 expression is unclear, in cardiac allograft transplantation, HO-1 mediates the immunomodulatory and anti-apoptotic effects of IL-13 in vivo and in vitro has been demonstrated [61]. Without doubt, both allergy and transplantation could cause immunoreaction and IL-13 is a key factor in specific immunity. Besides, IL-13 could also downregulate PPAR- γ /HO-1 via ER stress-stimulated calpain activation. Therefore, we speculate that IL-13 may be approved as a mediator between let-7 family and HO-1 even might regulate allergic reactions.

3.5. Regulation of Tregs functions by miRNA-HO-1

In the maintenance of peripheral tolerance and prevention of autoimmune diseases, Tregs usually play a protective role via producing immunosuppressive cytokines. IL-10, an anti-inflammatory cytokine, could induce the expression of HO-1 [62] while over-expression of HO-1 could also increase the secretion of IL-10 in return [63]. IL-10 is not only the cytokine, by which CD4 + CD25 + Tregs exert the immunoregulatory effect, it also could promote the conversion from CD4 + CD25- T cells to CD4 + CD25 + Tregs [64,65]. Moreover, numerous studies have indicated that HO-1 exerts protective action in autoimmune diseases through CD4 + CD25 + Tregs [67]. Thus, IL-10 and CD4 + CD25 + Tregs may be involved in the anti-allergic effects of HO-1 [69].

Recently, miRNAs have also been confirmed to involve in the regulation of Tregs biology and functions. Mohammadnia et al. [70] had demonstrated that in the supernatant of Tregs culture from ulcerative colitis (UC) patients, significantly lower levels of IL-10 were observed. The expression patterns of miRNAs miR-21, miR-146a, and miR-155 levels were downregulated while the miR-31 level was upregulated in CD4(+) CD25(+) CD127(-/low) FoxP3(+) Tregs of UC patients. Furthermore, Namdari et al. have demonstrated that in induced Tregs, IL-10 was increased in induced Tregs after miR-21 transfection [71,72]. In allergy, the role of miRNA-HO-1 remains unclear. According to the previous studies, we conjectured that miRNA-HO-1 might regulate functions of Tregs via IL-10.

3.6. Blockage of MCs functions by miRNA-HO-1

MCs and basophils are not only important effector cells in acute IgE-

mediated allergic reactions but also significantly contribute to the aspects of allergic responses. Studies in MC-deficient mice indicate that MCs can participate in tissue remodeling, leukocyte infiltration and long-term functional changes in the context of IgE-mediated allergy [75]. According to Ndisang et al. [76], HO-1 and its by-product CO could inhibit immunological histamine release from MCs via activation of guanylyl cyclase. In addition, MCs adhesion and degranulation, the foundation of the acute phase of allergic reactions were suppressed by biliverdin or bilirubin (HO-1 mimics) [28]. Likewise, several miRNAs have been demonstrated to involve in IgE-mediated activation of MCs degranulation (e.g. miR-221). Firstly, the result revealed the expression of miR-221 was upregulated in IgE-mediated activation of MCs. Then it was demonstrated that miR-221 promoted MCs degranulation by PI3K/Akt/PLC γ /Ca (2+) signaling pathway, in a non-NF- κ B dependent manner [77]. Interestingly, in rat experimental subarachnoid hemorrhage, HO-1 induced by PI3K/Akt pathway had been verified [78]. All results suggest miR-221 might command MCs degranulation through PI3K/Akt/HO-1 pathway based on the evidence from different experimental models.

Although NF- κ B might not participate in degranulation, it would influence other responses as a significant inflammatory factor. In Zhou's study, in murine allergic asthma model, miR-221, overexpressed in MCs, stimulated IL-4 secretion in MCs through NF- κ B/ PTEN (phosphatase and tensin homolog)/ p38 [79]. However, it was reported that HO-1 could inhibit cytokine production in MCs via selective suppression of the DNA-binding activity of AP-1 [27]. Thus, whether synergy or antagonism between miR-221 and HO-1 in cytokine production needs further research.

3.7. Modulation of transcription factors by miRNA-HO-1

Dozen transcription factors (TFs) are responsible for the increased expression of cytokines, chemokines, adhesion molecules, and growth factors, all of which are the essential features of allergic diseases with inflammation [80]. Interestingly, several TFs including NF- κ B are responsible for inflammation and remodeling, while others including TGF- β and Nrf2 show anti-inflammatory and antioxidant properties [80]. TGF- β has anti-inflammatory and immunosuppressive properties, as reflected by inhibition of immune cell differentiation (Th1 and Th2 cells and B cells) and cytokine production (IL-2). Finally, TGF- β is critical for the development and differentiation of Tregs [82]. Furthermore, the accumulated data demonstrated the concentration of TGF- β was decreased when HO-1 expressed increasingly in rat immune liver fibrosis [83]. However, Tang et al. reported a different result that revealed TGF- β enhanced the expression of HO-1 via suppressing miR-519b in human synovial fibroblasts [84]. In different cells, the correlation between transcription factors, HO-1 and miRNAs would have diversity consequentially. However, the current study is deficient and in control of allergic diseases, the hypothesis should be verified in allergy models (see Fig. 1).

4. Bioinformatic analysis of miRNA profiles in serum and urine of children with AD compared with healthy children

4.1. Canonical pathways affected by differentially expressed miRNAs

In order to verify the conclusion in preceding text, according to the sequencing datasets from GEO (GSE62406), compared with healthy control, a total of 10 and 17 miRNAs significantly differentially expressed in serum and urine respectively from AD children (Table 1). Target genes and regulatory pathways of differentially expressed miRNAs were identified by TargetScan Human 7.0 and DIANA-mirPath v2.0 software. A total of 205 pathways were significantly enriched by these dysregulated miRNAs (Fig. 2A). Among them, 34 pathways were co-regulated by more than 4 dysregulated miRNAs (average degree = 4), such as the TGF- β signaling pathway and T cell receptor

signaling pathway (Fig. 2B). Meanwhile, in previous articles, it has been demonstrated that TGF- β and T cells play key roles in allergic reactions [85]. It suggested that these dysregulated miRNAs might have significant functions in AD development. Both in serum and urine, 3 miRNAs (miR-205, miR-203, and miR-483-5p) were differentially expressed. And it has been confirmed in the peripheral blood of canine, miR-203 was elevated and associated with atopic dermatitis [86]. Thus, this content has a guiding significance for clinical detection of miRNAs as biomarkers of allergic diseases.

A total of 10,561 genes might be implicated in these pathways as targets of dysregulated miRNAs. Among them, HO-1 was a predicted target of miR-548a-3p. HO-1 was involved in 7 pathways (Table 2) include the HIF-1 signaling pathway which also be regulated by miR-548a-3p [87]. What is more, the HIF-1 signaling pathway has been verified to be involved in allergic diseases [88–90] and oxidative stress [91,92]. In an allergic rhinitis mouse model, HIF-1 α inhibitors induce anti-allergic effects by decreasing Th2 cytokine (IL-4 and IL-5) production, IgE production, and eosinophil infiltration. The higher level of HIF-1 α and VEGF were detected in patients with allergic rhinitis, showing the role of HIF-1 α in disease pathogenesis. Besides, in study of AD immunosuppressant, it was found that the expression and activity of HIF-1 α could lead to glycolysis inhibition in T cells [93]. In conclusion, the analysis suggested there are some miRNAs may participate in pathogenesis of allergic disease through HO-1.

4.2. GO functional enrichment analysis of the pivotal miRNAs target genes

Based on the above findings, especially the significantly differentially expressed miRNAs, which could be recognized as the pivotal miRNAs in the pathogenesis of AD. By employing the DAVID software, a total of 176 GO function items were enriched (p-value < 0.05). Interestingly, in BP, 3 processes include negative regulation of keratinocyte proliferation [94], cellular responses to hydrogen peroxide [95] and ER overload response may be correlative with AD. In Fig. 3, we just list the top 10 significant items from BP, CC, and MF. It was proposed that in these three biological processes, the pivotal miRNAs may influence AD pathogenesis by regulating significant target genes expression. Once again, it was confirmed that these miRNAs and target genes might not only participate in antioxidant responses and the pathogenesis of AD, they also might take part in skin damage and keratinocyte proliferation of AD. However, all the results were predicted according to the bioinformatical algorithms, whether these miRNAs could regulate allergic dermatitis or not is still unclear. In spite of this, miRNA has shown the ability for treating AD.

5. Conclusion

As showed in previous reports, miRNAs are involved in the pathogenesis of multiple disorders, from wound healing to cancer to allergy, etc. [96–99]. Currently, many researchers focus on the demonstration of the involvement of miRNAs in allergic disorders. In addition, because of the presence of oxidative stress in allergic diseases, HO-1 has also become a target of therapy. Nevertheless, the study involved both miRNAs and HO-1 simultaneously is limited. Therefore, in this review, we have to refer some researches involved other diseases such as transplantation and alcoholic liver injury. Although the pathogenesis is various, all diseases include allergy may trigger immunoreaction which is connected with MCs, T cells, etc. We believe these references also might be instructive.

Since the characters and a large number of miRNAs, it has been demonstrated that HO-1 was one target of multiple miRNAs [84,100,101]. HO-1 not only could mediate oxidative stress as an antioxidant. It also could regulate gene expression as a transcription factor. In previous studies, it has been shown that HO-1 could regulate miRNA expression. Even the single miRNA might also play various regulations on HO-1 expression. MiR-155, with high expression in

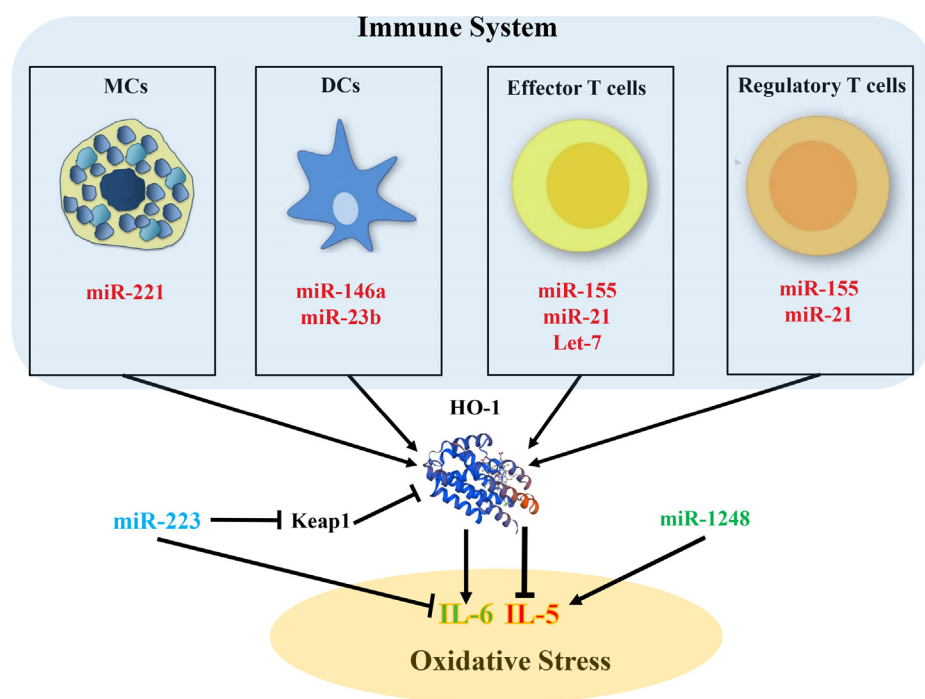


Fig. 1. The sketch map of HO-1/miRNA in allergic disease. In 4 main immune cells (mast cell, dendritic cells and 2 kinds of T cells), there are some miRNAs could interactive with HO-1. Except for immune system, HO-1/miRNA mediated oxidative stress is also involved in allergic disease through IL-5 and IL-6. Different font color represent different sources of miRNAs.

Table 1
Differently expressed miRNAs in serum and urine of children with AD.

Serum			Urine		
miRNA	-ΔΔCT	Log FC	miRNA	-ΔΔCT	Log FC
Up-regulated			Up-regulated		
miR-205*	2.886	7.309	MammU6	3.375	10.375
miR-539	2.505	5.678	miR-142-3p	2.672	6.373
miR-122	2.352	5.106	miR-20a	2.231	4.695
miR-203*	2.352	5.106	miR-548c-3p	1.793	3.465
miR-483-5p*	2.262	4.798	miR-205*	1.487	2.803
miR-134	2.086	4.246	miR-19a	1.329	2.512
let-7g	1.838	3.575	miR-483-5p*	1.118	2.170
miR-495	1.420	2.676	miR-222	1.104	2.149
miR-642	1.408	2.653	miR-92a	1.103	2.148
			miR-548a-3p	1.101	2.145
Down-regulated			Down-regulated		
miR-590-5p	-0.876	0.545	miR-203*	-2.695	0.154
			miR-125a-5p	-1.942	0.260
			miR-886-3p	-1.317	0.401
			miR-184	-1.302	0.406
			miR-886-5p	-1.253	0.420
			miR-26a	-1.107	0.464
			miR-194	-1.101	0.466

* The asterisk represents miRNA which was differently expressed in both serum and urine.

lesions of AD patients, could increase the proliferative response of CD4 + T cells [52]. Zhang et al. identified that in T cells, miR-155 could control the expression of HO-1 [53]. Nevertheless, another study has confirmed that HO-1 was induced by miR-155 via reduced BTB domain and CNC homolog 1 (Bach1) translation in endothelial cells [73]. This paradoxical finding may be explained as follows: 1, a single miRNA may have abundant targets; 2, in different kinds of tissues, the profiles and functions of miRNAs are often diverse; 3, gene expression is regulated by networks including miRNA, pathways and transcription factors not just depend on a single miRNA. Hence, when the functions of HO-1 and miRNAs in allergy are studied, the complicated relationship between them should be considered comprehensively. HO-1 could not only play an antioxidative role in allergic disorders, it also takes part in inflammatory response, a characteristic of allergic diseases. As

mentioned above, HO-1 could influence allergy via regulating the normal physiological functions of T cells, DCs and MCs, like proliferation and migration [27,45,67]. In addition, it is also regulated the release of the chemokine and cytokines (e.g. IL-10) [32]. However, a set of miRNAs also implicated in these inflammatory reactions whether through HO-1 or not [73,74].

There are abundant miRNAs in humans, and in any physiological process, many miRNAs may play a regulatory role by interacting with others by forming networks. Therefore, in order to study the role of miRNAs in allergic diseases in-depth and systematically, the miRNA network needs to be analyzed. In GSE62406, a total of 27 differently expressed miRNAs were screened in both serum and urine. In the enrichment pathways which were based on the prediction of dysregulated miRNA targets, HIF-1 pathway was also associated with HO-1. In addition, in GO analysis of dysregulated miRNAs, 3 processes correlated with HO-1 and oxidative stress (negative regulation of keratinocyte proliferation, cellular response to hydrogen peroxide and ER overload response) were verified. It further illustrated that in AD, HO-1 plays significant roles combined with miRNAs.

In summary, both miRNA and HO-1 are critical factors in the pathology of allergic diseases. However, the current studies are just devoted to research HO-1 or miRNAs, not the correlation between them. We supposed that in most allergic pathogenesis, HO-1 might play a crucial role in immune response and oxidative stress as “terminal mediator” with miRNAs control. Nevertheless, in some specific allergies or particular stages, few miRNAs might participate in allergy development directly. In this review, from an overall view, the first comprehensive analyses of the miRNA-HO-1 functions in allergy were expounded. It will provide research ideas in later researches.

6. Ethics approval and consent to participate

Not applicable.

7. Consent for publication

All authors have read and approved the final manuscript.

Availability of data and materials

All datasets analyzed are available.

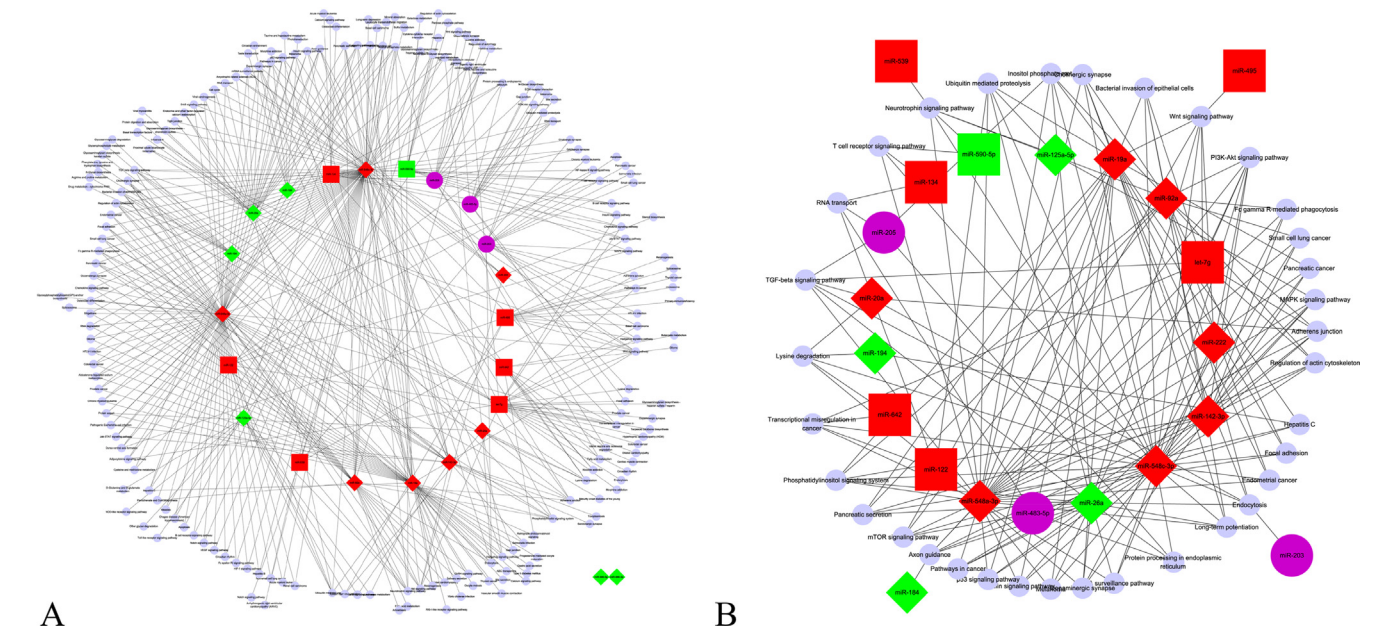


Fig. 2. The network of signal pathways and their respective dysregulated miRNAs in AD. Both in the whole network (Fig. 2A) and the hub network (Fig. 2B), the red squares represent the up-regulated miRNAs while the green squares represent down-regulated ones in serum. The red rhombus represents the up-regulated miRNAs while the green ones represent down-regulated ones in the urine. The purple nodes represent miRNAs dysregulated in both serum and urine. Other pale blue circles represent pathways associated with miRNAs. The interaction of miRNAs and pathways were predicted by DIANA database (p-value < 0.05).

Table 2
The pathways associated with HO-1.

Register ID	Pathway ID
hsa00860	Porphyrin and chlorophyll metabolism
hsa01100	Metabolic pathways
hsa04066	HIF-1 signaling pathway
hsa04216	Ferroptosis
hsa04978	Mineral absorption
hsa05206	MicroRNAs in cancer
hsa05418	Fluid shear stress and atherosclerosis

8. Competing interests

The authors declare that they have no competing interests.

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10. Authors' contributions

LC and LZ defined the topic of review and selected the key publications. All authors wrote different parts of the manuscript. All authors commented on the manuscript. All authors read and approved the final manuscript.

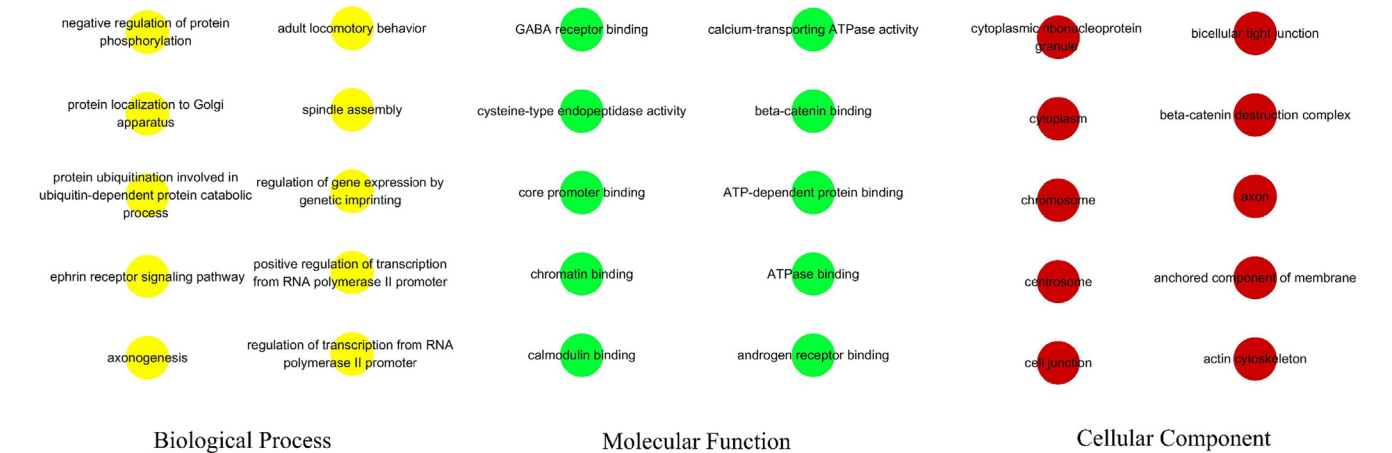


Fig. 3. GO functional enrichment analysis of the pivotal miRNAs target genes. By employing the DAVID software, a total of 176 GO function items were enriched (p-value < 0.05). The only top 10 items in biological process (BP), molecular function (MF), and cellular component (CC) were listed. The yellow circles represent biological processes. The green circles represent molecular functions. The red circles represent cellular components.

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