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Review

Epigenetic changes: An emerging potential pharmacological target in allergic rhinitis

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ABSTRACT

The importance of epigenetics has increased due to identification of its role in the pathophysiology of a number of diseases including allergic rhinitis. Amongst the different epigenetic changes in allergic retinitis, deacetylation of histone proteins by histone deacetylase (HDACs), hypermethylation of DNA by DNA methyltransferases (DNMT) and alteration in post-transcriptional process by the changes in the levels of miRNA are widely studied. Studies conducted related to allergic rhinitis have shown the elevation in the levels of HDAC1, 3 and 11 in the nasal epithelia and HDAC inhibitors have shown effectiveness in decreasing the symptoms of rhinitis. Their beneficial effects are attributed to restoration of the expression of TWIK-related potassium channel-1, correction of cytokine profile along with normalization of Th1/Th2 imbalance. Another epigenetic change due to increase in DNMT activity may induce DNA hypermethylation in CpG sites in the airway epithelial cells and $CD4^+$ T-cells. The reduction in DNA methylation decreases allergic symptoms and normalizes the over-reactive immune system. Mechanistically, allergens may promote the hypermethylation in the promoter region of IFN-γ gene in $CD4^+$ T cells via activation of ERK pathway to decrease the expression of IFN-γ. In allergic rhinitis patients, there is also a downregulation of certain miRNAs including miR-135a, miR-146a, miR-181a, miR-155 and upregulation of miRNA19a. This review discusses the studies describing the epigenetic changes taking place in the host cells in response to allergen along with possible mechanisms.

1. Introduction

Epigenetics includes the heritable alterations in the gene expression without any alteration in the DNA sequence. Indeed in recent years, the importance of epigenetics has increased tremendously [1] and it is being accepted nowadays that alteration in gene functioning, without any change in a DNA sequence, is critical in the pathophysiology of a number of diseases [2,3]. Accordingly, scientists have started targeting enzymes and processes involved in inducing epigenetic changes so as to control and manage the diseases [4,5].

Amongst the principal mechanisms involved in inducing epigenetic changes, acetylation/deacetylation of the histone proteins, methylation/demethylation of DNA regions and changes in the levels of miRNAs are widely studied. Histone deacetylases (HDACs) are the enzymes that help in removing the acetyl groups from the lysine residues in histone proteins. About eighteen different types of HDACs have been characterized and these have been classified into 4 classes including I, II, III and IV. In class I, there are HDAC 1, 2, 3 and 8; in class II, there are HDAC 4, 5, 6, 7, 9 and 10; class III HDAC, also termed as sirtuins, there are sirtuins 1 to 7 and in class IV, there is HDAC 11 [6,7]. The removal of the acetyl groups from the lysine residues increases the positive charge on the histone proteins, which increases the affinity of positively charged histone proteins for the negatively charged DNA. It leads to formation of a compacted chromatin and accessibility of enzymes for transcription is reduced, which eventually results in inhibiting gene transcription [8]. The attachment of a methyl group to the C5 position of cytosine residues in CpG dinucleotide sequences by a covalent linkage is another principal epigenetic change in the DNA. DNA methylation is generally catalyzed in the presence of an enzyme, DNA methyl transferases (DNMT) and CpG methylation is one of important mechanisms to induce gene repression [9]. Scientists also describe miRNA-mediated interference with the post-transcriptional process and subsequently, inhibition of gene expression as a part of the epigenetic machinery. Indeed, miRNAs are the non-protein coding RNA

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molecules that interfere with the post-transcriptional process by cleaving/inhibiting the target mRNA. Due to the silencing of DNA-derived mRNA, there is inhibition of all the steps involved in gene expression after transcription [10,11].

Throughout the world, allergic diseases are the most prevalent chronic diseases in all ages, particularly in childhood [12]. It has been a challenging task for the health care practitioners to overcome the allergic disorders, particularly allergic rhinitis. In recent years, the importance of epigenetic changes in making the persons more prone to allergic stimuli has increased [13–15]. Studies have shown the role of epigenetics including DNA methylation, histone acetylation and alteration in miRNA levels in the development and persistence of allergic rhinitis [16]. Indeed, it has been shown that there are changes in the DNA methylation [17–20], histone acetylation [21–24] in the host DNA, particularly peripheral blood cells in response to persistent allergic reactions. Not only this, the effects of these changes may be transmitted from the allergic mothers to the newborn babies too [25–27]. Apart from histone acetylation/deacetylation and DNA methylation/demethylation, the changes in the levels of miRNA have also been documented in preclinical models and in allergic rhinitis patients [28–31]. There has been a decrease in the levels of certain miRNA including miR-135a [31], miR-146a [29,30,32], miR-181a [29,30,33], miR-149 [28] and miR-155 [34] in children and rodent models of allergic rhinitis. The present review discusses the studies describing the epigenetic changes taking place in the host cells, especially histone deacetylation, DNA methylation and changes in miRNA in response to allergens along with possible mechanisms.

2. Pathogenesis, current treatment and need of epigenetic studies in allergic rhinitis

In allergic rhinitis patients, the entry of allergen evokes type I hypersensitivity with the key role of IgE antibodies, mast cells, histamine, cytokines, leukotrienes and immune cells. The interaction of IgE with the mast cells leads to the release of histamine during the early phase and the synthesis of lipid-derived mediators including leukotrienes during the delayed phase. During the repeated exposure to allergen, there is a development of mucosal hypersensitivity, termed as priming, in which even a very small amount of allergen is able to evoke the same or higher magnitude of inflammatory response as evoked earlier in the presence of higher amount of allergen. Due to this priming, the allergic reactions may be evoked even in the presence of other allergens [35,36]. Considering the significant role of histamine, mast cells, IgE and leukotrienes in the pathogenesis of allergic rhinitis, scientists have developed interventions on the basis of these targets to combat the disease. Currently, the drug therapy of allergic rhinitis is mainly symptomatic and aims to reduce the symptoms associated with rhinitis. Apart from avoidance of allergen, the use of drugs in allergic rhinitis is dependent on the severity of the disease. In mild or intermittent cases, oral/nasal second generation anti-histamines or intranasal corticosteroids are generally given in the patients. In moderate to severe conditions, other drugs including leukotriene antagonists and anti-cholinergics are generally employed as add on therapy to anti-histamines or intranasal corticosteroids. The other drugs that may be employed include mast cell stabilizers and anti-IgE monoclonal antibodies. However, the major limitation of the presently available pharmacotherapy is that the beneficial effects are not long lasting and symptoms start appearing on stopping the medication [36]. In very severe cases, allergen-specific immunotherapy involving repeated subcutaneous or sublingual administration of allergens may also be used to induce relatively long lasting effects in allergic rhinitis patients [37,38]. However, it has been reported that the treatment with immunotherapy has to be given for a long period (usually more than 2 years) to produce clinically visible effects [39,40]. Considering the long term use of immunotherapy and the development of allergen-associated side effects [41,42], there is a need to identify and explore other suitable drug targets for the effective and long lasting management of allergic rhinitis.

Studies have shown that cytokines derived from the epithelial cells control the activation of the immune cells including T cells and a cross-talk between the cytokines and T cells may serve as a 'master switch' in allergic diseases [43]. Accordingly, specific targeting of cytokines and T cells may also yield potentially beneficial effects in allergic rhinitis patients. Amongst the different mechanisms, the key role of epigenetics has emerged in the regulating the long term synthesis of cytokines and proliferation of T cells [15]. Therefore, scientists have started exploring epigenetics as a potential drug target in the pathogenesis of allergic rhinitis with an aim to inhibit the alteration in cytokine profile and T cell imbalance by normalizing the gene expression in allergic patients. Particularly, the role of epigenetics in allergic rhinitis becomes more significant considering the fact that the effects of epigenetic changes are long lasting [44]. It may also be possible that the long lasting effects of priming, a key feature of allergic rhinitis, are secondary to allergen-induced changes in the epigenetics in an individual. Moreover, studies have also shown that the beneficial effects of immunotherapy observed in patients may also be secondary to the epigenetic changes induced during immunotherapy [29,30,45,46]. The following sections discuss the significance of epigenetic changes in the animal models of allergic rhinitis and discuss the studies employing epigenetics as a potential new pharmacological target to overcome this disease.

3. Elevation in the levels of histone deacetylase in allergic rhinitis and beneficial effects of histone deacetylase inhibitors

Based on the studies performed in allergic rhinitis patients, animal models of allergic rhinitis and the immune cells isolated from allergic rhinitis patients, it has been proposed that there is a rise in the levels of histone deacetylase (HDAC) in the immune cells and HDAC inhibitors are beneficial in improving the condition of allergic rhinitis. In a study comprising of allergic rhinitis patients, the expression of HDAC1 was shown to be up-regulated in the nasal epithelia in comparison to healthy control persons [23]. Another study has identified the increased expression of HDAC1 in the human and rat nasal epithelial cells in allergic rhinitis. Moreover, exposure to interleukin-4 (IL-4) was shown to produce the deleterious effects in the form of nasal epithelial barrier dysfunction by increasing the expression of the HDAC1. Moreover, selective HDAC1 inhibitor (trichostatin A) as well as non-selective HDAC inhibitor (sodium butyrate) attenuated IL-4-induced rat nasal epithelial barrier dysfunction in a significant manner [47,48]. Administration of trichostatin A (1 mg/kg) was shown to decrease the allergic nasal symptom scores, including frequency of rubbing and sneezing, along with decrease in the eosinophil infiltrations and IgE levels in ovalbumin-induced allergic rhinitis in mice [21]. In another study, intranasal administration of sodium butyrate attenuated the increase in the expression levels of HDAC1 and HDAC3, and decreased the H3 acetylation at lysine 9 site in allergic rhinitis model in mice. Furthermore, treatment with sodium butyrate decreased ovalbumin-induced increase in the levels of IgE, improved the symptoms along with the improvement in nasal mucosal epithelial morphology [22]. Other studies have also shown the beneficial effects of sodium butyrate in allergic rhinitis model and it has been shown to inhibit the production of IgE by inhibiting the activation of HDAC1 [24]. Apart from the good number of studies showing the key role of HDAC1 in allergic rhinitis, studies have also documented that there is also a significant role of HDAC 11 in the development of allergic rhinitis. Based on the studies in allergic rhinitis patients or B cells isolated from the rhinitis patients, it has been shown that there is an increase in the expression of HDAC 11 in the B cells [49–52].

3.1. Upregulation of HDAC may decrease the expression of TREK1 to produce allergic symptoms of rhinitis

TWIK-related potassium channel-1 (TREK-1) is the one of the most

widely described 2- pore domain K^+ channels and its presence is well documented in the different parts of the body. There have been studies documenting the role of TREK-1 in allergic rhinitis and it has been shown that the expression of TREK-1 is significantly reduced in patients with allergic rhinitis [47,48,53]. Moreover, it is reported that the up-regulation of HDAC1 during allergic rhinitis may modulate the expression and functions of TREK1 to regulate the epithelial barrier function of the nasal mucosa. It has been shown that there is a correlation between the increased expression of HDAC1 and decreased levels of TREK1 in the human and rat nasal epithelial cells. Furthermore, exposure of the nasal mucosa to IL-4 markedly suppressed the expression of TREK1 and produced epithelial barrier dysfunction by up regulating the expression of HDAC1. The role of HDAC1 in decreasing the TREK1 expression was supported by the finding that HDAC1 inhibitors trichostatin A or sodium butyrate abolished IL-4-induced rat nasal epithelial barrier dysfunction and increased the expression of TREK1 [47,48]. Another study has also showed a parallelism between the up-regulation of HDAC1 and down-regulation of TREK1 channels in the nasal epithelial cells in inducing epithelial nasal barrier dysfunction. Moreover, treatment with antigen-specific immunotherapy led to up-regulation of TREK1 expression and down-regulation of HDAC1 in the nasal mucosa suggesting the close relationship between these two in the pathogenesis of allergic rhinitis [23]. Accordingly, it may be proposed that upregulation of HDAC in the nasal epithelial cells may decrease the expression of TREK1 to produce deleterious effects in allergic rhinitis.

3.2. Upregulation of HDAC may modulate the levels of cytokines during allergic rhinitis

There is an important role of cytokines in the pathogenesis of allergic rhinitis and it has been well documented there is an increase in the levels of IL-4, TNF-α (pro-inflammatory cytokines) along with decrease in the levels of IL-10 (anti-inflammatory cytokine) [54,55]. Accordingly, scientists have attempted to delineate the relationship between the elevation in the levels of HDAC and alterations in the cytokines profile in allergic rhinitis. It has been shown that inhibition of HDAC1 using trichostatin A increases the levels of IL-10 and expression of Forkhead box p3 (Foxp3) [21]. Foxp3, a member of Fox protein family, is a transcriptional factor and it is reported as a master regulator in development and function of regulatory T cells, which are important to turn off the excessive activation of immune response [56]. Therefore, it may be suggested that inhibition of HDAC1 may produce beneficial effects by promoting the functions of regulatory T cells through increased expression of Foxp3 and IL-10. Other studies have also shown that sodium butyrate inhibits the activation of HDAC1 in the antigen specific B cells to induce the expression of IL-10 and decrease the production of IgE in allergic rhinitis model [24]. In the mouse model of allergic rhinitis, treatment with sodium butyrate is shown to correct the Th1/Th2 imbalance by increasing the serum levels of IFN-γ and decreasing the serum levels of IL-4 [22]. Apart from these, the beneficial effects of low-level laser therapy (radiotherapy therapy) in allergic rhinitis have been attributed to histone modification at TNF-α and IL-10 gene promoter area suggesting that histone modifications may participate in enhancing the endogenous immune system to control allergic diseases [57].

Along with the role of HDAC1 in altering the cytokine profile, an increase in HDAC11 is also shown to deregulate the profile of cytokines in allergic rhinitis. Exposure of allergic rhinitis patient's B cells to specific allergens has been shown to increase the expression of HDAC11 along with the suppression of IL-10 suggesting the reciprocal relationship between HDAC11 and IL-10 expression in allergic rhinitis [49]. There have been other studies from the allergic rhinitis patients showing an increase in the levels of HDAC11 and decrease in the levels of IL-10. Moreover, the blockade of HDAC11 was shown to block the expression of IL-10 in the dendritic cells in response to recombinant IL-4 exposure [50,51]. In a recent study also, a reciprocal relationship between the expression of HDAC11 and IL-10 has been documented. There has been a decrease in the expression of IL-10 in the allergic patients and in the B cells of healthy individuals exposed to TNF-α. Moreover, inhibition of HDAC11 restored the expression of IL-10 in TNF-α exposed B cells suggesting that TNF-α suppresses the expression of IL-10 in B cells via enhancing the expression of HDAC11 [52]. Therefore, it may be proposed that there exists a reciprocal relationship between HDAC and TNF-α. On the one hand, an increase in HDAC may increase the expression of TNF-α and HDAC inhibitors attenuate the production of TNF-α [58]. On the other hand, TNF-α may also act as a stimulus for increasing the expression of HDAC [52]. Overall, it may be hypothesized that an increase in HDAC activity may increase the levels of pro-inflammatory cytokines and decrease the levels of anti-inflammatory cytokines to contribute in the pathogenesis of allergic rhinitis.

4. Down-regulation of silent information regulator 1 (SIRT1) in allergic rhinitis

SIRT1 is a nicotinamide adenine dinucleotide-dependent histone deacetylase and is a member of class III HDAC family. In contrast to other HDACs, SIRT1 is reported to produce protective effects in different tissues [59–62]. In allergic rhinitis also, it is reported that the down-regulation of SIRT1 may contribute in its pathogenesis. In ovalbumin-induced allergic rhinitis, the mRNA and protein expressions of SIRT1 were reported to be impaired. Additionally, intranasal administration of recombinant SIRT1 was reported to attenuate allergic symptoms along with normalization of the levels of IgE, leukotriene C4, eosinophil cation protein and other inflammatory cytokine mediators in the serum and nasal lavage fluid. Moreover, administration of SIRT1 also reduced the genes of high-mobility group protein B1/toll-like receptor 4 (HMGB1/TLR4) signaling pathway in the murine model. HMGB1/TL4 is one of the principal signaling pathways that is augmented during different types of inflammatory conditions [61,62] and its activation may also be involved in development of allergic rhinitis [63]. Therefore, it may be suggested that SIRT1 may be a promising therapeutic agent to control allergic rhinitis and its activation may produce beneficial effects by down-regulating the HMGB1/TLR4 signaling [64].

5. Allergic rhinitis is associated with the changes in DNA methylation in CpG sites

5.1. Evidences revealing the changes in DNA methylation during allergic rhinitis

Studies have shown that the allergic patients may be differentiated from the healthy persons on the basis of changes in the DNA methylation. Indeed, the alterations in DNA methylation patterns in $CD4^+$ T-cells have been identified in allergic patients. The changes in the DNA methylation were also correlated with the changes in the number of $CD4^+$ T-cells in the allergic rhinitis. Moreover, the changes in the DNA methylation pattern were also identified in in vitro test in which purified peripheral blood cells were challenged with allergen [20]. The study of Stefanowicz et al. in allergic children revealed that there are changes in the DNA methylation pattern at CpG sites in the airway epithelial cells and peripheral blood mononuclear cells in diseased children [65]. In two independent cohorts from Beijing and Liaoning, the decrease in DNA methylation at CpG38 was documented in house dust mite-sensitized allergic rhinitis patients ($n = 60$) [18,19].

There have been other studies also documenting the change in DNA methylation pattern in seasonal allergic rhinitis patients [17]. Indeed, it has been shown that allergens may induce epigenetic changes in the peripheral blood cells in form of DNA hypermethylation very rapidly, in about 3 h, in allergic rhinitis patients [66]. In patients ($n = 30$) suffering from respiratory allergies, the efficacy of sublingual

immunotherapy in terms of decrease in rhinoconjunctivitis scores, reduction in response to allergens in skin prick tests or nasal disk challenges, a decrease in the IgE levels was associated with increase in Foxp3 positive memory regulatory T cells along with reduction in DNA methylation of CpG sites within the Foxp3 locus. It suggests that immunotherapy led to epigenetic changes in the memory regulatory T cells in terms of decrease in DNA methylation at CpG sites within the Foxp3 locus, which led to upregulation of regulatory T cells. Accordingly, it may be suggested that DNA methylation may be an important epigenetic mechanism contributing in development of resistance to allergens [45]. Another study also revealed the increase in DNA methylation at CpG sites within Foxp3 locus (−127 and −250) in the peripheral blood cells of allergic rhinitis patients ($n = 20$). However, treatment with sublingual immunotherapy led to significant reduction in DNA methylation in CpG sites in Foxp3 locus suggesting the significant role of DNA methylation in the pathogenesis of allergic rhinitis [46].

5.2. Influence of DNA hypermethylation in allergic rhinitis parents on offsprings

The scientists have linked the Foxp3 DNA hypermethylation to the passage of allergic disease from the mother to the offsprings. Normal female mice were exposed to Der p1 (an allergen) to create an allergic rhinitis model in mice, which were mated with normal male mice to obtain offsprings. The analysis of spleen lymphocytes revealed the hypermethylation of DNA at Foxp3 promoter region in the offsprings at 3rd and 5th week of birth along with increase in the levels of IL-4 and decrease in IL-10 levels. Interestingly, the alterations in the cytokines levels and Foxp3 DNA hypermethylation in the offsprings returned to normal state by 8th week in the absence of subsequent exposure to allergen. It suggests that due to the existence of allergic disorder in mother, there are chances of an abnormal immune state in offsprings at the time of birth, which is mainly due to the hypermethylation of DNA at Foxp3 promoter region. However, if further exposure to allergens is prevented, then the offsprings tend to recover from the abnormal state and may achieve the normal immune state on maturity [27]. The previous study also demonstrated the contribution of epigenetic changes in passing the traits of allergic rhinitis from the mothers to new born offsprings. In comparison to normal offsprings, there was an increase in the levels of IL-4, IL-17 along with a decrease in the levels of IL-10 and regulatory T cells in the neonatal offsprings obtained from Der p 1-exposed female mice. Furthermore, a positive correlation was reported between the Foxp3 DNA hypermethylation in mothers and the development of allergic rhinitis symptoms in offspring [26]. Genetic analyses in the family members of asthma patients also revealed the alterations in the DNA methylation at CpG sites and thus, it may be possible to suggest that DNA hypermethylation-related epigenetic changes may be passed to subsequent generations [25].

5.3. DNA hypermethylation in the promoter region of IFN-γ gene leads to its decreased expression

In allergic rhinitis, the key role of IFN-γ has been identified and it has been shown that there are decreased levels of IFN-γ in the allergic rhinitis patients [67,68]. In relation to epigenetic changes, it has been proposed that hypermethylation of DNA leads to decreased expression of IFN-γ, which may be a contributory factor in the development of allergic rhinitis. In a study on pediatric allergic rhinitis patients ($n = 35$), the changes in DNA methylation in the promoter region of IFN-γ gene were documented. More specifically, the changes were recorded in CpG^{-299}, CpG^{+119}, CpG^{+168} and the level of IFN-γ expression were negatively correlated to mean level of methylation in IFN-γ promoter region. In other words, there was an increase in DNA methylation in IFN-γ promoter region in allergic rhinitis patients, which led to decrease in the expression of IFN-γ [18,19]. Another study from these scientists in pediatric allergic rhinitis patients ($n = 105$) documented that exposure to PM2.5 led to selective increase in the DNA methylation in the promoter region of IFN-γ gene in the CD4+ T cells with concomitant decrease in IFN-γ expression, without affecting IL-4 methylation and IL-4 mRNA expression [59,60]. A very recent study from the same group of scientists verified these finding and reported an increase in DNA methylation in the promoter region of IFN-γ gene in $CD4^+$ T cells after exposure to PM2.5 in allergic rhinitis model. Indeed, there was a significant increase in the expression of DNA methyl transferase (DNMT) enzyme, which led to hypermethylation in promoter region of IFN-γ gene. These epigenetic changes were associated with a significant decrease in the percentage of $CD4^+$ T cells in allergic rhinitis model. Moreover, PM2.5 exposure also led to the activation of ERK pathway in the CD4+ T cells, and selective inhibition of this pathway attenuated the deleterious effects of PM2.5 in allergic rhinitis model [69]. ERK is an important member of mitogen activated protein (MAP) kinase and earlier studies have shown the role of ERK in controlling the production of IFN-γ [70]. Therefore, it may be suggested that PM2.5 exposure exacerbates allergic rhinitis by increasing the DNA methylation at the IFN-γ gene promoter region in the $CD4^+$ T cells via activation of ERK pathway.

5.4. Other mechanisms induced due to changes in DNA methylation

From the two independent cohorts from Beijing and Liaoning, the decrease in DNA methylation at CpG38 region was negatively correlated with the mRNA expression of IL-33 and IgE. In fact, significantly increased serum levels of IL-33 and IgE levels due to DNA hypomethylation were reported [18,19]. Another study has revealed the change in the methylation pattern at the CpG site within the melatonin receptor 1A gene, which may contribute in transmitting the effects of allergic rhinitis parents to the offsprings [25]. The study of Stefanowicz et al. revealed that there are changes in DNA methylation at the CpGs site in signal transducer and activator of transcription 5A (STAT5A) and cysteine-rich intestinal protein (CRIP1) gene in allergic rhinitis children. Indeed, the changes in DNA methylation led to decrease in the STAT5A gene expression along with increase in CRIP1 gene expression [65]. Nevertheless, further studies are required to establish the correlation between changes in the DNA methylation and expression of STAT5A, CRIP1 and melatonin receptors in allergic rhinitis.

6. Allergic rhinitis is associated with changes in the levels of MicroRNA

MicroRNAs (miRNAs) are the endogenous non-protein coding small RNA molecules (about 22 nucleotides in length) that interfere with post-transcriptional process by cleaving/inhibiting the target mRNA. In other words, miRNAs affect gene expression by silencing the mRNA encoded from DNA and hence, prevent the subsequent steps following transcription. Many scientists have described miRNA-mediated regulation of gene expression as a part of the epigenetic machinery [10,11]. There have been studies documenting the key role of different types of miRNAs in the pathogenesis of allergic rhinitis [33,34,71]. Even scientists have documented that the circulating miRNA may also serve as biomarkers of allergic rhinitis in patients [72,73]. The study of Chen et al. identified the correlation between the change in miRNA expression in the neonatal leukocytes with the elevation in IgE levels and the development of allergic rhinitis. The authors identified the alterations in the expression of 157 miRNAs, particularly a decrease in miR-21 and miR-126 expression in the mononuclear leukocytes in allergic rhinitis children [74]. In miRNA microarray chip analysis-based study, Shaoqing et al. identified the differential expression of about 421 miRNAs in the nasal mucosal samples isolated from eight allergic rhinitis patients [75]. Another study reported the changes in the profile of miRNAs in allergic rhinitis patients, which included the down-regulation of miR-18a, miR-126, let-7e, miR-155, miR-224 and upregulation

of miR-498, miR-187, miR-874, miR-143 and miR-886-3p [76].

Apart from the studies showing the widespread changes in miRNA expression, scientists have also focused on individual miRNAs to delineate their specific role in allergic rhinitis. In an allergic rhinitis model, a decrease in the expression of miR-135a in the nasal mucosa along with an increase in the levels of IL-4 and IgE has been reported. Moreover, these changes were associated with an imbalance in the ratio of Th1/Th2 cells with an increase in the percentage of Th1 cells and decrease in the percentage of Th2 cells. Moreover, exogenous application of miR-135a was shown to normalize the expression of cytokines, the levels of IgE and imbalance of Th1/Th2 cells [31]. Additionally, intranasal administration of miR-135a is also shown to prevent mast cell activation/degranulation by down-regulating the expression of GATA binding protein 3 (GATA-3) in allergic rhinitis model [77]. An important role of miR-146a has also been delineated as its decreased levels have been detected in the nasal epithelial cells and its exogenous administration was shown to attenuate the symptoms of allergy. The beneficial effects of miR-146a in preclinical model have been attributed to increase in the production of anti-inflammatory cytokine viz. interleukin 10 in the monocytes [29,30,32]. It has also been shown to specifically enhance the effects of immunotherapy in allergic rhinitis model [29,30]. Moreover, an increase in the expression of miR-146a has been noted in the children suffering from allergic rhinitis following immunotherapy suggesting that the beneficial effects of immunotherapy may also be secondary to increase in the levels of miR-146a [78]. Other studies have shown a decrease in the levels of miR-181a [29,30,33,34], miR-149 [28] and miR-155 [33,34] in children and rodent models of allergic rhinitis. Indeed, a correlation has been found between the levels of miR-181a, miR-155 and T cell regulatory cells in patients of allergic rhinitis. In other words, a decrease in the levels of miR-181a, miR-155 is associated with decrease in the levels of T regulatory cells and IL-10 suggesting that these miRNAs may serve as key regulatory mechanisms to control the proliferation and differentiation of regulatory T cells [33,34]. Scientists have also shown that an increase in the expression of miR-143 [79], miR-133b [80], miR-487b [81], miR-375 [82] and miR-16 [83] produce beneficial effects in allergic rhinitis models. Mechanistically, miR-16 prevents IL-13-induced deleterious by inhibiting IκB/NF-κB pathway [83], miR-375 prevents apoptosis of nasal mucosa cells by inhibiting JAK2/STAT3 pathway [82] and miR-487b mitigates allergic rhinitis by inhibiting IL-33/ST2 pathway [81].

In contrast to above described studies showing a decrease in the levels of different types of miRNAs in allergic rhinitis, scientists have found an opposite role of miR-19a in this disease. In allergic rhinitis, an increase in the levels of miR-19a has been directly correlated with the development of disease [49,84]. Moreover, it has been shown that miR-19a participates in the development of allergic rhinitis by decreasing the production of IL-10 in peripheral B cells [50,51]. Moreover, studies in allergic rhinitis patients have shown the relationship between HDAC11 and miR-19a. It has been shown that an increase in the expression of miR-19a in the peripheral B cells isolated from allergic rhinitis patients in response to exposure to allergens is also associated with a concomitant increase in the expression of HDAC11 [49]. In allergic rhinitis patients also, a parallel increase in the expression of miR-19a and HDAC11 has been documented. The knockout of miR-19a gene in the dendritic cells or blockade of HDAC was shown to attenuate allergen-induced suppression of IL-10 in the peripheral dendritic cells. In other words, miR-19a gene removal or HDAC inhibitor increased the levels of anti-inflammatory cytokine i.e. IL-10 [50,51]. It suggests that HDAC acts in concert with miR-19a in the development of allergic rhinitis.

7. Epigenetic changes produce dysregulation of the immune response

On the basis of preclinical studies it may be deduced that the primary outcome of epigenetic changes during allergic rhinitis is the dysregulation of immune response in terms of imbalance in Th1/Th2, changes in cytokine profile, increase in IgE and decrease in the number of T regulatory cells. Normally, naïve $CD4^+$ cells convert into Th1 cells in the presence of IFN-γ [85]; Th2 cells in the presence of IL-4 and T regulatory cells in the presence of TGF-β [86]. Moreover, the naïve cells may change into Th9 cells in the combined presence of IL-4 and TGF-β [87]; while Th17 cells may be formed in the combined presence of IL-6 and TGF-β [88]. During allergic rhinitis, the epigenetic changes decrease the secretion of IFN-γ, increase the secretion of IL-4 and IL-6 to produce an imbalance in Th1/Th2. It is also associated with an increase in the number of Th9 and Th17 cells [18,19,21,22,56]. Furthermore, there is a decrease in the transcriptional activity of Foxp3 resulting in the decrease in the number of T regulatory cells, decrease in the secretion of IL-10 and overactivation of immune system [21,45]. Th1 cells inhibit the differentiation of Th2 cells and keep the proliferation of Th2 cells under control. Due to decrease in the number of Th1 cells, there is a corresponding increase in the number of Th2 cells, which is followed by increase in the secretion of IL-4 to promote the activation of B cells to release IgE [89]; increase in the release of IL-13 to induce mucus secretion and hyper responsiveness [90]; increase in the secretion of IL-5 to promote eosinophil recruitment and activation [91]; increase in the release of IL-9 (also released by Th9 cells) to promote mast cell activation [92]. Accordingly, inhibition of epigenetic changes in the form of inhibition of histone deacetylase enzyme, activation of DNA demethylase and miRNA mimetics may possibly overcome allergens-induced overactivation of immune system (Fig. 1) and hence, may serve as potentially useful pharmacological agents to overcome allergic rhinitis.

8. Current epigenetic therapy in clinics and their adverse effects

At present, the drugs modulating epigenetic changes are not prescribed for the disease management in clinics. However, histone deacetylase inhibitors and miRNA mimetics are being evaluated in clinical trials for their safety and efficacy in cancer and viral diseases, respectively. Indeed, there are a good number of histone acetylase inhibitors which are under different phases of clinical trials including vorinostat, panobinostat, mocetinostat and abexinostat [93,94]. These drugs have been currently evaluated in phase I and phase II clinical trials for their safety and efficacy in different types of cancers in the form of add-on therapy [95]. Most of these trials have reported the relative safety of these drugs in comparison to conventional anticancer drugs and the typical side effects of histone deacetylase inhibitors as anti-cancer drugs are related to disturbance in the bone marrow function including development of anemia, neutropenia and thrombocytopenia along with fatigue, nausea and diarrhea [96–99]. The mimetics of miRNA have been clinically evaluated for the management of hepatitis C virus [100,101] and advanced solid tumors [102]. No significant safety-related issues were observed and miRNA mimetics were found to be significantly safe agents in virus-related studies [100,101]. However in cancer management study, the common adverse events included the development of fever, fatigue, back pain, nausea, diarrhea, anorexia, lymphopenia, neutropenia and thrombocytopenia [102]. It suggests that the development of side effects of a given drug depends on the disease for which it is given. Since the drugs modulating epigenetic changes have not been evaluated clinically in the allergic rhinitis patients, therefore, it is not possible to precisely describe the side effects and efficacy of these drugs in allergic rhinitis patients. Nevertheless, it is possible to hypothesize that the clinical effects of epigenetic modulators may be long lasting and these drugs may normalize the hyperactive immune system to inhibit the pathogenesis of allergic rhinitis. However, the potential side effects due to inhibition of immune response may also arise during epigenetic therapy. Accordingly, future clinical studies shall be planned to explore the efficacy and safety of these drugs in allergic rhinitis patients.

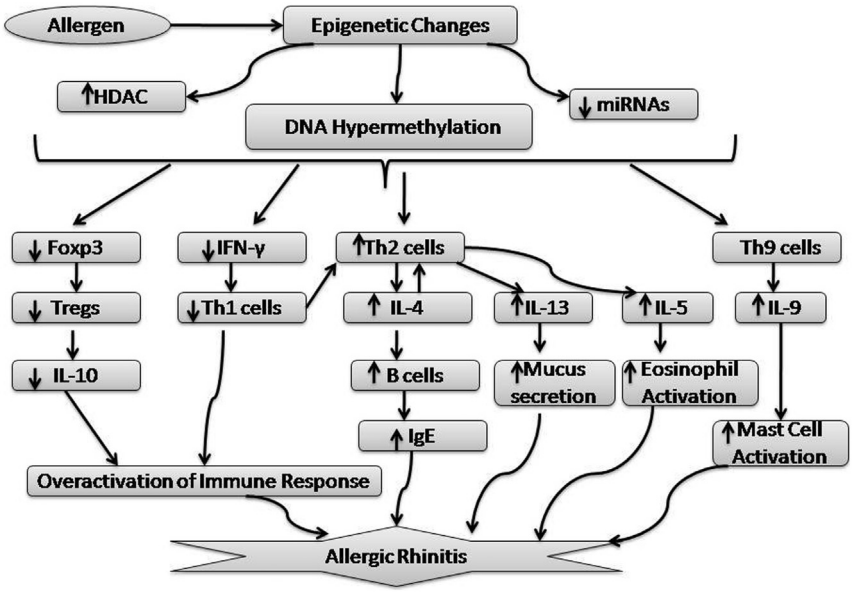

Fig. 1. Schematic representation of role of epigenetic changes in inducing dysregulation in immune response in response to allergen, which subsequently results in the development of allergic rhinitis. Treg: T regulatory cells; HDAC: Histone deacetylase; miRNA: MicroRNA.

9. Conclusion

Exposure to allergens may induce the epigenetic changes in the form of increase in histone deacetylation, increase in DNA methylation and alteration in miRNAs levels in the respiratory epithelial cells and peripheral $CD4^+$ cells in the host system to change the cytokine profile, dysregulate the balance of T regulatory cells, which may be manifested in the form of development of symptoms of allergic rhinitis. The effective control of histone acetylation using histone deacetylase inhibitors, DNA hypermethylation using DNA methyl transferase inhibitors and post-transcriptional gene expression using miRNA mimetics may help in managing allergic rhinitis.

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