

MicroRNAs in Allergic Disease

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Abstract

Purpose of Review MicroRNAs (miRNAs) are short, single-stranded, non-coding RNAs that are increasingly being recognized as important epigenetic regulators. They have been implicated in the pathogenesis of many diseases including cancer, cardiovascular diseases, connective tissue diseases, and neuromuscular disorders.

Recent Findings A few miRNAs have already been recognized as a core set of miRNAs important in allergic inflammation. These include let-7, miR-21, miR-142, and miR-146.

Summary This review aims to bring together some of the recent findings on how miRNAs regulate allergic inflammation with special focus on asthma, atopic dermatitis, allergic rhinitis, and eosinophilic esophagitis. We will also touch upon extracellular miRNAs and future perspective of this field of study.

Keywords microRNAs · Inflammation · Asthma · Atopic dermatitis · Allergic rhinitis · Eosinophilic esophagitis

Introduction

One of the main reasons that epigenetics are of increasing interest is that single-nucleotide polymorphisms (SNPs) identified by genome-wide association studies have been unable to account for a certain proportion of the phenotypic variance, as seen in the case of asthma, in spite of the fact that these diseases have a strong genetic component [1, 2]. MiRNAs are one of the central epigenetic regulators that are highly conserved throughout species. They are small, non-coding RNAs that are about 18–22 nucleotides in length that inhibit target gene expression through mRNA degradation or translation repression [3]. A single miRNA can act on several hundred mRNAs, which can be direct targets of a particular miRNA. On the other hand, a single mRNA can be the target of multiple miRNAs. This overlap of activity may at a glance seem redundant but actually reflects the regulatory impact of miRNAs: while a lone miRNA may have minimal effect on its target, the concerted effect of multiple miRNAs will be cumulative and robust.

Role of MicroRNAs in Allergic Inflammation

In relation to allergic diseases, miRNAs may have several possible modes of action. Rebane and Akdis proposed the following three mechanisms of action: (1) Th2 polarization, (2) innate immune cells in inflamed tissue, and (3) chronic inflammation in epithelium and tissue remodeling [4]. The possible mechanisms are summarized in Table 1.

These interlacing interactions leave us with a complicated network of regulatory pathways and targets. As we see it, each

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Table 1 Functions on miRNAs in allergic diseases

Disease	MiRNAs involved	Mechanism of action	Target tissue	Target gene
Asthma	let-7a	Intravenous LNAs decreased allergic airway inflammation in OVA-induced asthma model [9] Decreased IL-13 levels when let-7 mimic was administered intranasally to OVA-induced model [10]	Th2 cells	IL-13
Asthma	miR-126	Inhibition decreased eosinophilic airway inflammation May <i>not</i> be involved in airway remodeling [12]	BECs	?
Asthma AD	miR-155	Th2-mediated eosinophilic inflammation in OVA-induced mouse model [16] May regulate lymphocyte emigration from thymus and peripheral lymphoid organs [13–15] Downregulates the negative regulator CTLA4 promoting T cell activation [47]	Th2 cells	PU.1 S1pr1 CTLA4
Asthma	miR-145	Inhibition causes decreased airway inflammation in HDM-induced model [17]	Lower airway tissue	?
Asthma Contact dermatitis AR EoE	miR-21	Upregulation promotes Th2 polarization in murine model [7] Elevated in steroid-naïve asthmatic children [42] Upregulated in allergen-challenged skin in mice and humans [46] Downregulation in cord blood monocytes with high IgE levels [56] Upregulated in esophageal biopsies [59]	T cells Plasma Lesional skin Monocytes Esophageal epithelium	IL-12p35 TGFB2 IL-12
Asthma	miR-24 and miR-27	Upregulation inhibits IL-4 in Th2 cells of OVA-induced model [18]	Th2 cells	GATA3
Asthma	mmu-miR-106a	Upregulation decreases IL-10 in HDM-induced murine model [19]	Lung parenchymal tissue	IL-10
Asthma	miR-203	Downregulation in BECs of adult asthmatics elevates <i>AQP</i> which regulates vessel wall permeability [36]	BECs	AQP
Asthma	miR-19	Promotes Th2 cytokine production [25]	BECs	PTEN, SOCS1, A20
Asthma	miR-181-5p	Downregulation causes an increase in IL-13-induced production of IL-1 β and CCL11 [26]	BECs	SPP1
Asthma	miR-133a	Downregulation in mouse BSMs causes downregulation of RhoA in IL-13 treated murine BSM [28]	BSM	RhoA
Asthma	miR-323-3p	Promotes TGF β and IL-22 production [36]	T cells	TGF β
Asthma	miR-15a	Downregulation increases VEGFA [38]	Th2 cells	VEGFA
Asthma	miR-221 and miR-485-3p	Overexpressed in mouse and pediatric asthmatic lung tissue [39]	Murine lung parenchymal tissue Lymphocytes of pediatric asthmatics	Spred-2
AD	miR-143	Overexpression suppresses IL-13-induced dysregulation of skin barrier proteins [49]	Epidermal keratinocytes	IL-13R α 1
Chronic AR	miR-125b	Overexpression enhances IFN production by suppressing 4E-BP1 [55]	Nasal mucosal epithelium	4E-BP1
EoE	miR-375	Overexpression decreases eosinophil infiltration, Th2 cytokine production, and mast cell activation [62]	Esophageal epithelium	?
EoE	miR-146a	Upregulation selectively suppresses Th1 differentiation [63]	Th1 cells	?

miRNA may need to be studied in its own disease or cellular context. This review brings together some of the latest

available knowledge on miRNAs in their role in allergic inflammation.

Allergic Asthma

Asthma is a heterogeneous disease, characterized by chronic airway inflammation and tissue remodeling. The structural changes in asthma include subepithelial fibrosis, smooth muscle hypertrophy and hyperplasia, neovascularization, goblet cell hyperplasia, and epithelial alterations leading to bronchial hyperresponsiveness, airway narrowing, airway edema, and mucus hypersecretion [5]. It is currently believed that the release of epithelial cytokines such as IL-25, IL-33, and TSLP are of primary importance in initiating allergic inflammation that cascades down to Th2 cell activation. The subsequent release of IL-4, IL-5, and IL-13 execute the allergic reaction in which IL-5 mediates eosinophilia and IL-13 causes the induction of chemokines and goblet cell hyperplasia [6].

MiRNA Expression in Experimental Models of Asthma

MiR-21 in T Cell Polarization

In multiple models of experimental asthma induced by allergens including OVA, HDM, IL-13 and *Aspergillus fumigatus*, miR-21 was one of the significantly overexpressed miRNAs in lung tissue [7]. IL-12p35 is a direct target of miR-21 and it has been suggested that miR-21 might promote Th2 polarization during allergic airway inflammation [7]. More recent evidence for miR-21 in relation to pediatric asthma is discussed later in this section.

Let-7 in the T Cell Effector Response

The let-7 family of miRNAs was the first to be discovered in humans and has been shown to be of importance in asthma on several occasions. This miRNA family that is conserved across species includes let-7a to let-7k of which let-7h, let-7j, and let-7k are not expressed in humans and mice [8]. IL-13 has been shown to be a direct target of let-7 with T helper 1 (Th1) cells having significantly higher let-7a expression than T helper 2 (Th2) cells do. Subsequent inhibition of let-7a by locked nucleic acid (LNA) antagomiR resulted in the upregulation of IL-13 mRNA expression in T cells [9]. In vivo experiments failed to duplicate the results with the finding that inhibition by LNA antagomiR resulted in reduced inflammatory cells in the bronchoalveolar lavage fluid (BALF) and decreased IL-4, IL-5, and IL-13. On the other hand, Kumar et al. showed that a let-7 mimic delivered intranasally alleviated ovalbumin (OVA)-induced experimental asthma [10]. These discrepancies in the results could be due to the differences in the experimental methods of the two groups, including the inhibitory miRNAs used and the frequency of the allergen challenge. Although these studies suggest the involvement of the let-7 family in the pathogenesis of asthma, more studies are needed to identify the possible role of the let-

7 family in asthma including the variable response to different allergens.

MiR-126, MiR-155, and MiR-145 in the Inflammatory Response

A study on a house dust mite (HDM)-induced model of asthma showed the TLR-4 and MyD88- dependent upregulation of miR-126 [11]. In contrast, a chronic model of asthma only showed early upregulation of the same miRNA with levels declining to normal after 6 weeks of allergen challenge [12]. AntagomiR-based inhibition of miR-126 decreased the number of intraepithelial eosinophils in the conducting airways but had no effect on goblet cell hyperplasia and subepithelial fibrosis. As the authors suggested, these results may mean that the prolonged dysregulation of miRNAs are not essential for the changes associated with chronic asthma.

Using *miR-155*^{-/-} T cells, Okoye et al. showed that miR-155 was necessary for the Th2 immune response partly through the regulation of the sphingosine-1-phosphate receptor gene (*S1pr1*) [13]. *S1pr1* has been shown to be important for the emigration of lymphocytes from the thymus and peripheral lymphoid organs [14, 15]. Malmhall et al. used a miR-155 knock-out murine model and challenged it with OVA and found that the absence of miR-155 alleviated eosinophilic inflammation in the lungs by reducing the Th2 response through the negative regulator PU.1 [16]. These two studies have clearly demonstrated that miR-155 has a wide range of targets and does indeed have a role in allergic inflammation. As it is involved in the regulation of T lymphocytes from their origin to the effectors, the possible use in therapeutics will need to be tightly regulated in order to prevent undesirable immunosuppression.

Another HDM-induced allergic airway murine model showed the anti-inflammatory effects of inhibiting miR-145 in the form of inhibited eosinophilic inflammation, mucus hypersecretion, Th2 cytokine production, and airway hyperresponsiveness. They also showed that the anti-inflammatory effects of miR-145 antagonism were similar to that of steroid treatment [17]. This steroid-sparing effect of miRNA-based therapy will be helpful in decreasing the adverse effects of long-term steroid use, especially in pediatric asthma.

MiR-24, MiR-27, and MiR-106a in the Suppression of Allergic Inflammation

Pua et al. identified that miRNAs 24 and 27, encoded in the genome in the *Mirc 11* and *Mirc 22* clusters in mice and humans, directly targeted GATA-binding protein 3 (GATA3) and thereby regulated IL-4 production in Th2 cells. In an OVA-induced model of allergic asthma, they showed that these miRNAs were endogenous inhibitors of Th2 cytokine

production [18]. In a murine model of allergic airway inflammation, Sharma et al. reported that mmu-miR-106a was greatly increased while IL-10 was decreased. They also observed that the administration of anti-mmu-miR-106a after the establishment of experimental asthma was able to assuage most features of asthma while increasing IL-10 levels [19].

Both of these studies demonstrate the involvement of miRNAs in maintaining a non-inflammatory cytokine milieu. In this context, at least miR-106a has the potential to be explored as an option that can reverse the changes associated with asthma and also be used as maintenance therapy.

MiRNA Expression in Adult Asthma

Although much of the evidence for miRNA involvement in the pathogenesis of asthma comes from extensive studies on murine models, there are a growing number of studies showcasing miRNA involvement in human asthma. Here, we will discuss the tissue-specific roles of miRNAs identified in adult asthmatics.

Bronchial Epithelium

In one of the earliest studies on miRNAs in asthma, Williams et al. showed that 227 miRNAs showed no difference in the expression in bronchial biopsies between mild asthmatics and normal individuals even after corticosteroid treatment. As the authors suggest, this may be due the fact that the mild asthma in these patients made the miRNA changes undetectably low [20]. On the other hand, Jardim et al. succeeded in validating three differentially expressed miRNAs, miR-203, in the bronchial epithelial cells (BECs) of adult asthmatics and showed that the Cox2, IL-8, TNF- α , and aquaporin (AQP), predicted to be targets of these miRNAs, were significantly elevated while IL-6 was reduced compared to healthy subjects. By analyzing molecular networks, they identified AQP as a novel asthma-associated gene [21]. AQPs have been shown to regulate the permeability of the vessel wall and to cause mucus hypersecretion in asthma and have been shown to be possible biomarkers of asthma [22, 23].

The miR-34/449 family (miR-34b-5p, miR-34c-5p, miR-449a, and miR-449b-5p) has been shown to be highly repressed in vivo and in vitro in BECs [24]. Simpson et al. looked at the BALF of asthmatics and identified miR-19a to be consistently upregulated in all the steroid-naïve asthmatics and those on inhaled corticosteroids (ICS). They also reported that miR-19 promoted Th2 cytokine production by targeting the inositol phosphatase PTEN, the signaling inhibitor SOCS1 and the deubiquitinase A20 which are inhibitors of the NF- κ B, STAT, and PI(3)K pathways [25]. MiR-181b-5p was shown to be downregulated in BECs and in the plasma of asthmatic patients and showed

increased plasma levels following ICS therapy. It was also found that miR-181-5p regulated IL-13-induced IL-1 β and CCL11 by targeting SPP1 and that treatment with dexamethasone reversed these changes [26].

Maes et al. reported that the expression of miR-223-3p, miR-142-3p, and miR-629-3p are increased in the sputum of patients with severe asthma. These miRNAs were found to influence inflammatory pathways and in particular neutrophilic airway inflammation [27] and therefore may not be involved in allergic asthma.

As described, many miRNA changes have been observed in the BECs of adult asthmatics, but the data implicate many different miRNAs and pathways of action. More clinical data may be necessary to understand how these miRNAs act together to bring about the symptoms of asthma.

Bronchial Smooth Muscle

In cultured human bronchial smooth muscle (BSM) cells treated with IL-13, Chiba et al. demonstrated an upregulation of RhoA and a downregulation of miR-133a while the BSM of OVA-challenged mice also showed similar changes. The authors conclude that RhoA expression is negatively regulated by miR-133a in BSMs and that IL-13 might at least partly contribute to this decrease [28]. RhoA is highly expressed in contractile BSM and has been shown to cause hypercontractility when upregulated [29, 30]. The Rho/Rho kinase pathway is being explored as a possible alternative to β_2 -adrenoceptor agonist and corticosteroid treatment [31].

BALF

The exosomal miRNA contents of the BALF of patients with mild, intermittent, stable asthma has shown the downregulation of the let-7 and miR-200 family miRNAs [32]. This finding is significant because it has been reported that exosomes are important modes of intercellular communication and can transfer their contents to other cells [33–35]. It might be of importance to verify the cellular sources of these exosomes which in turn will make it possible to understand the pathways regulated by the miRNAs they contain.

PBMCs, Plasma, and Peripheral Blood

In order to explore the functions of miRNAs in IL-22/IL-17-producing T cells, Kärner et al. looked at IL-22 and IL-17 producing T cells in human peripheral blood and identified that miR-323-3p showed the highest expression in IL-22 and IL-17 double-positive T cells and that it was involved in the regulation of the transforming growth factor β -producing pathway and IL-22 production in T cells [36].

In a recent study, 30 differentially expressed miRNAs were identified in the plasma of patients with asthma or allergic rhinitis compared to healthy individuals. Using miRNA expression as a phenotypic tool, the researchers identified five expression groups which to varying degrees reflect the association between these two allergic diseases [37].

MiRNA Expression in Pediatric Asthma

Pediatric asthma has been an area of study with a few reports discussing the involvement of miRNAs. Nevertheless, understanding the miRNA profiles of children as the disease-specific changes are initiated may provide a significant understanding of their roles in the pathogenesis and disease progression. Nakano et al. found an inverse correlation between miR-15a and the expression of vascular endothelial growth factor A (VEGFA) in peripheral blood CD4⁺ T cells of pediatric asthma patients. They did not find any association between miR-15a and ICS usage, serum VEGFA, or *VEGFA* expression [38].

MiR-221 and MiR-485-3p were shown to be upregulated in the lung tissue of an OVA-induced murine asthma model as well as in asthmatic children. It was also shown that the target of these two miRNAs, Spred-2, was downregulated in the murine model [39]. MiR-221 has been shown to have two different roles in mast cells: in the resting state of the cell, miR-221 regulates the cell cycle and the cytoskeleton, while in the activated cell miR-221, it regulates cell adherence, degranulation, and cytokine production [40].

Midyat et al. profiled miRNAs according to the severity of asthma in children and found that the expression of ten miRNAs, including miR-638, was higher in severe asthma as well as in severe acute exacerbations, while miR-497, let-7e, and miR-98 were significantly higher in moderate persistent/severe asthmatic children [41]. Elbehidy et al. found significantly elevated miR-21 levels in asthmatic children not receiving inhaled corticosteroid therapy irrespective of their sensitivity to inhaled corticosteroids compared to healthy controls. They found that miR-21 could be used to differentiate steroid-sensitive from steroid-resistant asthma and a negative correlation between serum miR-21 and serum IL-12p35 levels. As miR-21 is stably detectable in serum, the authors recommend it as a potential biomarker for asthma [42]. MiR-146a has been found to be associated with asthma in several studies, and a single nucleotide polymorphism in this miRNA has been shown to be important in the pathogenesis of asthma [43, 44]. Jiménez-Morales et al. genotyped a pediatric cohort to find an association between this SNP and the development of allergic/immunological diseases. They observed that this SNP may be associated with a tendency to develop childhood-onset asthma, but not other diseases such as systemic lupus erythematosus or juvenile rheumatoid arthritis [44].

Although there are numerous reports available on the role of miRNAs in asthma, a clear picture of their interconnections and definitive roles is just appearing on the horizon. More studies are needed to understand the role of miRNAs in relation to asthma.

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory condition of the skin. A central role in the pathogenesis of AD is played by a defective skin barrier compounded by a mixed Th1/Th2 inflammatory response. This results in the clinical manifestations of intense pruritus and recurrent eczematous lesions [45]. Some of the miRNAs mentioned earlier in relation to asthma including miR-21 and miR-223 have been shown to be involved in allergic contact dermatitis in humans and mice alike [46]. In addition, Sonkoly et al. described how miR-155 is overexpressed in AD by increasing in Th1 and Th2 cell responses through the downregulation of cytotoxic T lymphocyte-associated antigen-4 (CTLA4) [47]. In one study where miRNAs in serum and urine from children were profiled, the authors concluded that elevated serum miR-485-3p in children with AD may indicate other allergic diseases, while decreased miR-203 may be used as a biomarker of the severity of AD [48]. A recent in vitro study showed that miR-143 acts on IL-13 receptor alpha 1 (IL-13R α 1) to suppress IL-13 in human epidermal keratinocytes [49]. IL-13 is associated with a decrease in the expression of epidermal barrier proteins including filaggrin, loricrin, and involucrin leading to defective barrier function [50–52], and the authors suggest the possibility of therapeutic use of miR-143 in AD [49].

Allergic Rhinitis

A few reports are available on the role of miRNAs in allergic rhinitis (AR). In the nasal mucosa from a group of patients with AR who underwent surgery for nasal obstruction and non-allergic controls, the downregulation of miR-143, miR-187, and miR-224 was observed [53]. In a study on the miRNA profiles in the nasal mucosa in allergic and non-allergic AR in asthma, Suojalehto et al. identified that currently symptomatic AR patients had elevated miR-155, miR-205, and miR-498 but decreased let-7e. They also observed that concomitant asthma had little effect on the miRNA profile in AR [54]. MiR-125b has been found to be overexpressed in the sinonasal mucosal epithelium of patients with chronic rhinosinusitis with nasal polyps, which enhances type I IFN production by suppressing 4E-BP1 protein expression in airway epithelial cells [55]. In cord blood samples with elevated IgE levels, downregulated miR-21 was associated with increased transforming growth factor beta receptor 2

(TGFB β 2) expression in cord blood monocytes. The same study found that miR-21 and miR-126 were significantly downregulated in the monocytes of 6-year-old children with AR [56]. Contradictorily, miR-21 has been shown to upregulate IL-12 and reduce the severity of the inflammatory response in delayed-type hypersensitivity [7, 57].

With limited and inconsistent data on AR, it is still not possible to determine the role of miRNAs in AR. Also, as there maybe a significant change in the miRNA profiles when the acute condition progresses to chronic state with the formation of nasal polyps.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) can be called an emerging disease. It is characterized by intense inflammation of the esophageal mucosa that is unresponsive to acid-suppressive therapy [58]. Lu et al. profiled the miRNA expression in esophageal biopsies of patients with active EoE and those with glucocorticoid-induced disease remission. The expression profiles were compared with healthy controls and chronic non-eosinophilic esophagitis, and it was found that miR-21 and miR-223 were the most upregulated on miRNAs, while miR-375 was the most downregulated in EoE and correlated with esophageal eosinophil levels [59]. Another independent study identified miR-21 as a downregulated miRNA in EoE [60]. As mentioned earlier, miR-21 has been shown to regulate IL-12 expression and may have a similar role in EoE [7].

In a study on pediatric EoE, miR-375 showed the greatest reduction by fold change while miR-203 showed a twofold reduction which the authors attribute to basal layer hyperplasia and the loss of differentiated epithelium in EoE [61]. When the expression of miR-375 was analyzed in different cell types, the primary esophageal epithelium showed the greatest expression levels followed by primary bronchial epithelium. They also confirmed that miR-375 levels inversely correlated with the degree of inflammation, including eosinophil infiltration and Th2 cytokine and mast cell-specific (*CPA3* and *TPSAB1*) gene expression levels in esophageal biopsies of EoE patients [62].

MiR-146a and miR-146b have also been found to be upregulated in EoE [59]. As miR-146a has been shown to selectively suppress Th1 differentiation [63], miR-146a upregulation could prevent the differentiation of IFN- γ -producing Th1 cells which in turn will cause unopposed Th2 cell activation [64]. MiR-146a, miR-146b, and miR-223 have also been found to be differentially regulated in the plasma of EoE patients [59]. In contrast to these findings, the study by Zahm et al. did not find the miRNA changes in the esophageal biopsies reflected in the serum [61]. As studies on the miRNA changes in EoE are limited, there is a definite need for more studies to understand their role in this disease.

Extracellular MiRNAs

Extracellular miRNAs have been detected in blood, serum, plasma, BALF, saliva, and urine in relation to allergic disease [27, 32, 37, 48]. These miRNAs are found in many forms: within exosomes, within lipoprotein complexes, and bound to Argonaute proteins outside vesicles.

Extracellular miRNAs have been shown to be transferred between mouse dendritic cells via exosomes, from T cells to antigen-presenting cells in exosomes, and between macrophages and epithelial cells in microvesicles at least in vivo [65–67]. It was also reported recently that the exhaled breath condensates of patients with pulmonary diseases, including asthma, contained extracellular vesicles with miRNAs [68, 69].

Their stable expression in the extracellular compartment, the ease of obtaining clinical samples, and the ease of detection have made extracellular miRNAs attractive candidates as biomarkers.

In the coming years, there will be definitely more interest and research in to this field to identify possible candidates for diagnosis and monitoring of treatment efficacy.

Conclusions and Future Perspectives

The current evidence suggests that miRNAs play an important role in some of the crucial steps in the pathogenesis of allergic diseases. Nevertheless, it can be said that the true potency of miRNAs is yet unknown. With the identification of an “allergic march” which progresses from food allergy to asthma, allergic diseases provide a unique opportunity to understand how the miRNA profile changes from one disease to another. Moreover, as in the case of early childhood asthma and food allergies, some allergic diseases are known to be “grown-out” of; there is another opportunity to identify miRNA changes in disease resolution. The combination of miRNA profiles in the pathogenetic and resolution phases will make it possible to predict the course and outcome in patients.

There is a set of miRNAs that have been repeatedly referred to in this review and others, with let-7, miR-21, miR-142, and miR-146 being among them. Apparently, these miRNAs are generally key effectors in allergic inflammation. It will be interesting, and is indeed worth the effort, to see how these miRNAs interact and act together in a single setting. This is of vital importance on the one hand to understand disease pathogenesis better and on the other to move the field forward toward personalized miRNA-based therapeutics.

As miRNAs may have tissue-specific roles, once again, there is a need for more studies that comprehensively look at the source and the multiple tissue targets of miRNAs in a single-disease context. The understanding of individual and

collaborative miRNA action is also important because miRNAs mainly act by mRNA cleavage or by translational inhibition, meaning that miRNA-based therapeutics could be used for symptomatic and preventive treatment simultaneously.

MiRNAs have gained much attention over the past decade or so but is in its infancy as a field of study. Many concerted effort will give a better understanding and thereby better treatment options for allergic diseases that have hitherto not been clearly understood with existing science.

Compliance with Ethical Standards

Conflict of Interest Drs. Dissanayake and Inoue declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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