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Original Article

Sirtuin 1 Expression Enhances the Inflammatory Response in Allergic Rhinitis Combined with Asthma

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Abstract

Asthma (ASTH) is a chronic inflammatory disease that affects the lung airway and leads to occasional breathing difficulties. Previous studies have presented links between allergic rhinitis (AR) and ASTH. Recently, it was suggested that *SIRT1*, a NAD-dependent class III histone deacetylase protein, was involved in the pathogenesis of ASTH. However, the protective roles of *SRIT1* in ASTH are still unclear. This study aimed to investigate the role of *SRIT1* in the inflammatory response in ASTH and AR. The study involved 30 patients with ASTH, 40 patients with AR, 40 ASTH with AR, and 30 healthy subjects as control. A 5 ml blood sample was taken from all the participants. 1 ml was used for complete blood count (CBC) and Neutrophils/lymphocytes ratio analysis. Serum was separated from other 4 ml of blood by centrifugation for *SRIT1* and exotoxin (*CCL11*) assays analyzed by ELISA. Nasal fluids (0.5 ml) were also collected from all patient groups and controlled to measure *SRIT1* and *CCL11* by ELISA. The results showed a significant increase in eosinophil counts and Neutrophils/ lymphocytes ratio (N/L) in ASTH with the AR group compared to other patient groups and control (P<0.05). High *SIRT1* and *CCL11* levels were observed in serum and nasal patient groups compared to control (P<0.05**)**. These findings may go some way towards explaining the numerous roles of *SRIT1* in patients with ASTH. SIRT1 may regulate *CCL11* levels after that, affecting ASTH pathogenesis. *SRIT 1* in nasal secretion is a new biological characteristic of pulmonary airway diseases.

Keywords: Immune System, Pulmonary Diseases, Gene Expression

1. Introduction

ASTH is a common chronic airway disease characterized by variable airflow limitation secondary to airway narrowing, airway wall thickening, and increased mucus (1).

Airway narrowing results from chronic airway inflammation secondary to plasma extravasation and the influx of inflammatory cells such as eosinophils, neutrophils, lymphocytes, macrophages, and mast cells. Airway hyperresponsiveness (AHR) is an important physiologic feature of ASTH. Although ASTH is often defined as reversible airway obstruction, it can evolve into irreversible lung function impairment (2). Increasing mucus production in the airway lumen is one of the possible causes of persistent airflow obstruction. Another mechanism of persistent airflow obstruction is airway remodeling, including pathologies such as goblet cell hyperplasia, excessive subepithelial collagen deposition, decreased epithelial and cartilage integrity, airway smooth muscle hyperplasia, and increased vascularity (3).

Chronic Allergic Rhinitis (RA) is an inflammatory disorder of the nasal mucosa which negatively affects the quality of life and is responsible for significant work and school absenteeism. The condition is often classified as AR and non-AR(NAR) (4). AR constitutes

a relatively homogenous phenotype resulting from IgE-sensitisation to environmental allergens. Conversely, NAR comprises a heterogeneous group of diseases where immune-mediated inflammation is not always apparent. AR patients are by definition positive for skin prick test (SPT) and/or serum-specific (s) IgE (5). Rhinitis is a general term that describes the appearance of nasal symptoms as nasal congestion, rhinorrhea, sneezing, and pruritus (itching/ nasal rubbing), resulting from an inflammatory process and/or dysfunction of the nasal mucosa (6).

Rhinitis is one of the most common diseases worldwide, and it is estimated that about 25% of the world population suffers from AR; more importantly, it is a risk factor for the development of ASTH and other chronic respiratory diseases such as rhinosinusitis (7, 8).

The Combined AR and ASTH syndrome (CARAS) is a single disease related to upper and lower airway inflammation. AR and ASTH have shown an intimate connection in their genesis, the concept of coexistence, and similarities such as a. triggered by the same etiological agents; have the same inflammatory cell profile present in the respiratory system (9).

The CARAS is associated with a predominant TH2 immune response (TH2 phenotype), and its physiopathology profile is directly related to atopic individuals, which are genetically predisposed to stimuli (aeroallergens) and develop an immediate hypersensitivity (10).

Recruitment of inflammatory cells, including eosinophils, basophils, and T cells, results in further release of histamine and leukotrienes, as well as other compounds, including proinflammatory cytokines and chemokines, sustaining the allergic response and promoting the late phase response that may occur 6–9 hours after allergen exposure. Chronic inflammation and remodeling contribute to airway wall thickening, encroaching upon the airway lumen, and increasing resistance to airflow. Airway secretions also contribute to the pathology of ASTH and especially to the consequences of acute, severe, life-threatening exacerbations (11).

Silent information regulator 1 (SIRT1) belongs to the mammalian sirtuin family, which is composed of seven NAD+-dependent protein deacetylases (SIRT1-7) (12). Sirtuins are highly conserved nicotinamide adenine dinucleotide–dependent deacetylases that regulate lifespan in lower organisms31 and affect aging-related pathology in mammals, such as diabetes, inflammation, and neurodegenerative disease.32 In mammals, there are 7 sirtuin homologs, SIRT1 to SIRT7. Among them, SIRT1 has garnered the most attention. SIRT1 is known to deacetylate transcription factors that control the aging process33 and suppress inflammation.

Chemokines are among the various mediators of the inflammatory process thought to be significant leukocyte mediators differentiation and influx in several disease processes, including asthma and COPD (13). Several experimental studies, especially in models of ASTH, have shown an essential role of chemokines in leukocyte migration into the lungs (14). Some studies have demonstrated a positive correlation between eotaxin (CCL11) and eosinophils or eosinophil-derived products in asthmatic individuals (15).

There are three forms of eotaxin: eotaxin-1(CCL11), eotaxin-2(CCL24), and eotaxin-3(CCL26), respectively. CCL11 will accelerate basophilic cell accumulation via lgE-mast-cell-FaRI cascades, which further cause an allergic reaction. Another chemical called RANTS/CCL5, which is closely linked to allergic inflammation, is regulated by normal activation of T cells, and a secret porous factor is found to be high in Allergic RHIN in epithelial or endothelial bowel mucosa cells (16). Eotaxin-1/CCL11 is a chemokine originally implicated in the selective recruitment of eosinophils into inflammatory sites during allergic reactions, being thoroughly investigated in ASTH, AR, and other eosinophil-related conditions (17). Eotaxin-1/CCL11 is also involved with a skewed immune response toward a type-2 (Th2) profile.

The study aimed to address the evidence that links between SIRT1 upregulation and inflammatory response in patients with ASTH and AR.

2. Materials and Methods

2.1. General Characteristics of the Patients and Control Groups

Thirty patients with ASTH (mean age: 48.27±1.68; 22 Females, 8 male), 40 patients with AR (mean age: 42.43±1.76,1 7 females, 23 male), 40 patients that have ASTH with AR (mean age: 42.83±1.62 24 females, 16 males). Subjects were enrolled in this study between November 2020 to May 2021 at the Al-Diwanyah Teaching Hospital. Thirty healthy subjects as control with mean age (44.567±1.88 years; 14 females, 16 female) who visited the hospital for a routine check-up without any history of ASTH or AR, with no chronic diseases, acute illness, or infection. All laboratory tests analysis was performed in Diwaniyah Teaching Hospital and the Clinical Chemistry Research Lab, College of Medicine, University of Al- Qadisiyah.

All clinical and hemodynamic variables are summarized in table 1.

2.2. Sampling and Assays

A blood sample (5 ml) was collected from all study groups. The blood (1 ml) was immediately put in dipotassium-EDTA Vacutainer® tubes. The complete blood count (CBC) Neutrophils/lymphocytes ratio analysis was performed directly in HematoiogyAnalyser CBC (Sysmex, Japan) technique**.**other4 ml of blood was allowed to clot for 30 min, then serum was separated by centrifugation at (4000 rpm) for 15- 20 min at Room temperature 37°C. The separated serum was preserved using Eppendorf tubes at -20˚C for biochemical analysis. Serum SIRT1and CCL11were quantified using the sandwich ELISA. Also, nasal samples were collected from patients and control, a 0.5 ml nasal fluid diluted by 1.5 Distil water in plane tubes and kept at - 20 ˚C for SIRT1, CCL11 measurements by ELISA.

2.3. Statistical Analysis

Data are expressed as means±standard error of the mean (SEM). Statistical analysis was carried out using SPSS, and the significant differences between groups were determined using one-way ANOVAs. The probability of (P<0.05) was considered significant throughout.

Table 1. General characteristics of the patients and control groups

Parameters	Groups			
	ASTH	**AR**	**ASTH with AR**	**Control**
Total Number	30	40	40	30
Sex				
Females, n (%)	22 (73.3%)	17 (42.5%)		14 (46.6%)
Males, n (%)	8 (26.7%)	23 (57.5%)	24 (60%)	16 (53.3%)
			16 (40%)	
Age(y)				
Mean±SEM	48.27±1.68	42.43±1.76	42.83±1.62	44.567±1.88
Family history with diseases				
Yes	11 (36.6%)	14 (35%)	16 (40.0%)	0
NO	19 (63.3)	26 (65%)	23 (60.0%)	0
Other diseases				
Hypertension	5 (16.6%)	5 (10%)	7 (17.5%	0
Diabetes	6 (20%)	5 (10%)	8 (20%)	0
Smoking				
Smoking	4 (13.3%)	10 (%)	4 (10%)	7 (%)
Non-smoking	26 (86.6)	30 (%)	36 (90%)	23 (%)
O_2%				
Mean±SEM	94.4±0.212	94.7±0.18	94.5±0.119	96.4±0.1496

3. Results

3.1. Neutrophils/Lymphocytes as a Marker of Inflammation in ASTH, AR, and ASTH with AR

Eosinophils, Neutrophils, lymphocytes, and Neutrophils/ lymphocytes ratio (N/L)was calculated in the present study as markers of inflammatory responses in patients with ASTH, AR, and ASTH with AR. A significant increase was observed in eosinophil counts in ASTH with AR patients compared to other patient groups and control ($P \leq 0.05$), as shown in table 2. Also, the results indicate that NLR is significantly changed in all patient groups compared to the control ($P \leq 0.05$).

3.2. Biochemical Measurements in Serum Samples

3.2.1. SIRT-1 level in ASTH, AR, and ASTH with AR

Serum SIRT1 concentrations were measured using ELISA. The results showed high SIRT1 levels in patient groups with ASTH or AR only and ASTH with ARgroups compared to control ($P<0.05$) (Figure 1). Also, significant changes were shown between ASTH with AR and other groups.

3.2.2. CLL11 Levels in ASTH, AR, and ASTH with AR

The Results showed that serum levels of CCL۱۱were increased significantly in the patient groups with ASTH or AR only and ASTH with ARgroups compared to control ($P<0.05$) (Figure 2).

Table 2. Neutrophil count, Lymphocyte count, NLR with DN, T2DM, and control groups

Study groups	Eosinophils	Neutrophil count (10^3/ml) (mean±SEM)	Lymphocyte count (10^3/ml) (mean±SEM)	NLR (mean±SEM)
ASTH	2.458±0.489	6.63±0.66[a]	2.42±0.155[a]	3.207±0.50[a]
AR	2.91±0.683	5.69±0.416[a]	2.33±0.15[a]	3.2±0.50[a]
ASTH with AR	4.283±0.3065[a]	6.275±0.495[a]	2.46±0.16[a]	2.996±0.315[a]
Control	2.282±0.28	2.96±0.09	1.80±0.088	1.64±0.0895
P-value	$P \leq 0.05$	$P \leq 0.05$	$P \leq 0.05$	$P \leq 0.05$

a significant compared to control ($P<0.05$)

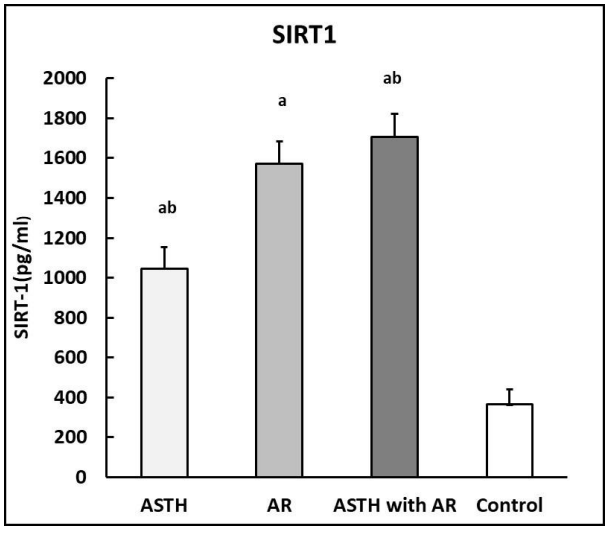

Figure 1. Serum SIRT1 level in patients with ASTH, AR, and ASTH with AR and control groups. Data are expressed as means±SEM; a indicates significant differences compared to the control, and b significant differences between patient groups ($P<0.05$)

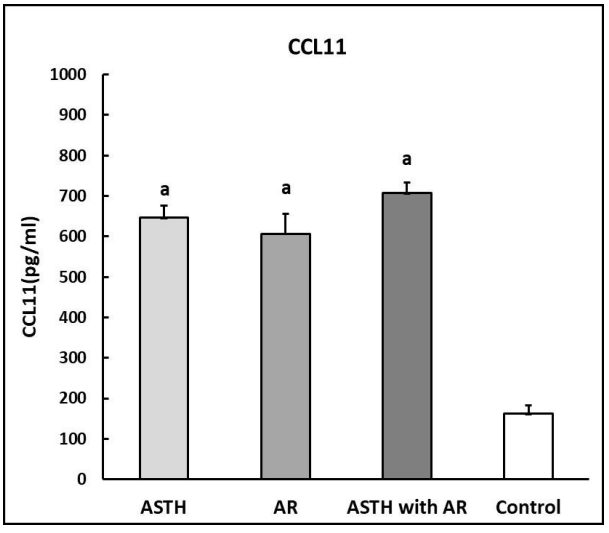

Figure 2. Serum CCL۱۱ levels in patients with ASTH, AR, and ASTH with AR and control groups. Data are expressed as means±SEM, (a) indicating significant differences compared to the control ($P<0.05$)

3.3. Biochemical Measurements in Nasal Samples

3.3.1. SIRT-1 Level in ASTH, AR, and ASTH with AR

The present study suggested that the nasal fluid may serve as a valuable biomarker for monitoring ASTH and AR status. SIRT1 levels in nasal secretion were significantly increased in ASTH, AR, and ASTH with AR groups compared to control (P<0.05) (Figure 3). Also, significant changes in Sirt1 levels were observed between patient groups (P<0.05).

3.3.2. CLL11 Levels in ASTH, AR, and ASTH with AS

An elevation of nasal CCL11was found in the patient's group compared to the control (P<0.01) (Figure 4), and higher levels were detected in the AR group than in other patients and control groups (P<0.01).

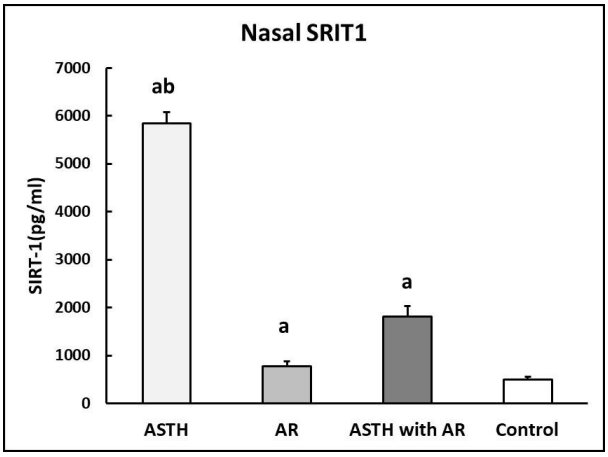

Figure 3. Nasal SIRT-1 level in patients with ASTH, AR, and ASTH with ARand control groups. Data are expressed as means±SEM; a indicates significant differences compared to the control, and b significant differences between patient groups (P<0.05)

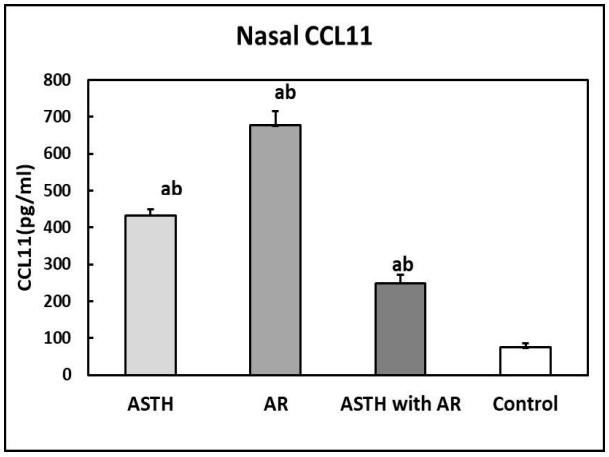

Figure 4. Nasal CCL11 level in patients with ASTH, AR, and ASTH with ARand control groups. Data are expressed as means±SEM; a indicates significant differences compared to the control (P<0.05)

4. Discussion

4.1. Neutrophils, Lymphocytes, and Eosinophil Counts in ASTH, AR, and ASTH with AR

Recently was reported that eosinophils have an essential role in developing ASTH exacerbation (18). The results showed a significant increase in eosinophils counts in ASTH with AR compared to other patient groups and control (P<0.05). To infiltrate sites of inflammation, eosinophils leave the bloodstream and pass through the endothelium in four steps: rolling, adhesion, transendothelial migration, and chemotaxis. Adhesion molecules, such as VCAM1, play an important role in adhesion to endothelial cells (19). High eosinophils are associated with a high-risk factor for virus-induced ASTH exacerbation (20). NLR was significantly increased in ASTH, AR, and ASTH with AR compared to the control (P<0.05). NLR correlates well with disease activity measurements in patients with ASTH, Neutrophils, lymphocytes, and monocytes. Immigration into peripheral tissues is one of the principal purposes for inflammation, bringing to a site of injury the immune-system cells, which can combat infection and clean up damaged tissue (21). The rise is because neutrophils are highly motile and quickly congregate at a focus of infection, attracted by cytokines expressed by activated endothelium, mast cells, and macrophages (22). Neutrophils express and release cytokines, which amplify inflammatory reactions by several other cell types. Neutrophils undergo chemotaxis via amoeboid movement, which

allows them to migrate toward sites of infection or inflammation (23). Cell surface receptors allow neutrophils to detect chemical gradients of molecules such as interleukin-8 (IL-8), interferon-gamma (IFN-γ), C3a, C5a, and Leukotriene B4, which these cells use to direct the path of their migration (24). It has been shown that in certain conditions, neutrophils have a specific type of migration behavior referred to as neutrophil swarming, during which they migrate in a highly coordinated manner and accumulate and cluster to sites of inflammation (25).

4.2. SIRT1 Levels in ASTH, AR, and ASTH with AR

The present study showed an increase in serum levels of SIRT 1 in a patient with ASTH, AR, and ASTH with AR compared to the control ($P<0.05$). A significant increase was found in AR combined ASTH. Suppression of SIRT1 prevented ASTH progression, alleviated airway hyperresponsiveness, decreased inflammatory cell numbers around the airways, and decreased IL4, IL5, and IL13 levels in BALF in OVA inhaled mice (26).

The increased activation and expression of SIRT1 could enhance autophagy, while its inhibition suppressed autophagy in vascular adventitial fibroblasts (27). A study revealed that SIRT1 protected cardiomyocytes from hypoxic stress by promoting autophagic flux induced by AMPK activation. SIRT1 has also been involved in the pathogenesis of Ovalbumin (OVA) induced ASTH in mice, and airway inflammation and hyperresponsiveness were attenuated after its inhibition (28).

In the present study, the results demonstrated that serum SIRT1 levels increased in patients with ASTH. In the OVA-sensitized and challenged mice, SIRT1 increased in the serum but decreased in the lung tissues coupled with eosinophils, lymphocytes, macrophages, and neutrophil infiltration (29). The high-serum SIRT1 levels were due to airway inflammation and the subsequent release of SIRT1 from inflammation cells. SIRT1 is a multifunctional molecule and is involved in a variety of pathways. The loss of SIRT1 may lead to multiple molecular pathway disorders and weaken the anti-inflammatory functions of various types of cells (30). A recent study demonstrated that lung SIRT1 levels decrease in other inflammatory diseases such as COPD and emphysema. As an anti-aging and anti-inflammatory factor, lung SIRT1 decrease may be responsible for the uncontrolled airway inflammation of ASTH. Present findings may be due to changes in protein expression or the leakage of SIRT1 from the lung tissues (31). Although the exact function of SIRT1 in the setting of ASTH remains unclear, our study indicates that high levels of serum SIRT1 are a biological characteristic of ASTH, and modulating SIRT1 with activators may be a topic of therapeutic strategy in the treatment of ASTH.

4.3. CCL11 Levels in ASTH, AR, and ASTH with AR

The present study showed a significant difference in serum levels of eotaxin 1(CCl11) between all patient groups and the control ($P\leq0.05$). Lei, Sun (32) suggested that the serum of CCL11 levels was significantly elevated in the patients during AR compared with the control group.

A significant increase in the CCL11 level after exposure of the patient with AR to pollen compared with a healthy group was shown by Branicka, Jura-Szołtys (33). Chemokine is a series of acti retina cytokines liable to allergic inflammation of leukocytes such as T/B lymphocytes, monocytes, neutrophils, and basophils. Many chemokines and their receptors now play an important role in the pathogenesis of AR (34).

CCl11 may be associated with allergic inflammation because eosinophils in patients with AR are recruited and activated by chemotaxis. Eotaxin, a specific eosinophil attractant, was elevated in seasonal AR (SAR) over the perennial AR(PAR) group (35). Our results confirm the findings of Gökkaya, Damialis (36), who found elevated levels of eotaxin in nasal secretions of patients with SAR under natural allergen exposure. Moreover, an increase of eotaxin-positive cells and eosinophils in nasal biopsies was reported after allergen provocation (37). Concerning CCL-11, there was a

significant elevation in SAR over PAR, while the differences between the AR groups and the controls were insignificant (37). RANTES is known to attract eosinophils and cause activation of eosinophils and basophils, resulting in inflammatory mediator release. Further, elevated levels were reported after nasal allergen challenge (38).

The present study showed a significant increase in basal levels of SIRT1 in all patient groups compared to the control (P<0.05). To our knowledge, this is the first study regarding the role of SIRT1 in nasal secretions. Despite the lack of related literature, a few reports support our findings. However, in these studies, the specific mechanism related to the effect of SIRT1 could not be elucidated. However, it was known to suppress inflammation by targeting peroxisome proliferator-activated receptors and NF-kB (39). The regulation mechanism of SIRT1 expression is not fully understood. It has been reported that the SIRT1 protein could be suppressed by the tumor repressor HIC1 (hypermethylated in cancer 1) and the microRNA miR-34a (40). Taken together, SIRT1 might play a defensive role in CRS, and it seems that SIRT1 loss aggravates sinonasal mucosa inflammation, finally leading to epithelial remodeling, including polygenesis. The present study showed significantly increased nasalCCL11 in patients with ASTH ARand ASTH with AR compared to healthy subjects (P<0.05). A previous study demonstrated that eotaxin/CCL11 levels in nasal lavage fluid were significantly higher in chronic eosinophilic rhinosinusitis (ECRS) mice compared with control (41). Recently, serum IL-17 levels were higher in asthmatic patients than in healthy subjects. IL-17 activated the release of eotaxin from airway smooth muscle cells and also induced the release of inflammatory mediators from human eosinophils (42).

Authors' Contribution

Study concept and design: A. J. A.
Acquisition of data: A. A.
Analysis and interpretation of data: A. S. K.
Drafting of the manuscript: A. J. A.
Critical revision of the manuscript for important intellectual content: A. S. K.
Statistical analysis: A. J. A.
Administrative, technical, and material support: A. S. K.

Ethics

All subjects signed a written informed consent form, and the Ethical Committee approved all Diwaniyah Teaching Hospital study methods and the University of Al- Qadisiyah (Al-Diwaniyah, Iraq).

Conflict of Interest

The authors declare that they have no conflict of interest.

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