Sputum periostin in patients with different asthma phenotypes

Thesis

Submitted for Partial Fulfillment of

Master Degree in Internal Medicine

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Amr Helmy Elbanna

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List of Abbreviations

AERD	:	Aspirin Exacerbated Respiratory Disease
AHR	:	Airway Hyperresponsiveness
AR	:	Allergic rhinitis
ATS	:	American thoracic society
BALF	:	Bronchoalveolar lavage fluid
BMI	:	Body mass index
BMP	:	Bone morphogenic protein
Ch5q	:	Long arm of chromosome 5
CRS	:	Chronic rhinosinusitis
DNA	:	Deoxyribonucleic acid
DTT	:	Dithiothreitol
ECM	:	Extracellular matrix
EIB	:	Exercise induced bronchospasm
ELSIA	:	Enzyme linked immunosorbent assay
EMI	:	Emergency management institute
FDA	:	Food and drug administration
FeNO	:	Fractional exhaled nitric oxide
FEV1	:	Forced expiratory volume in one second
FVC	:	Forced vital capacity
GERD	:	Gastroesophageal reflux disease
GINA	:	Global initiative for asthma management and prevention
GM-CSF	:	Granulocyte macrophages colony stimulating factor
GPR-35	:	G- protein coupled receptor
GRE	:	Glucocorticoid receptor element
GWAS	:	Gene wide association studies
HDMs	:	House dust mites
HRCT	:	High resolution computed tomography
HRP	:	Horseradish peroxidase
HRV	:	Human rhinovirus
ICS	:	Inhaled corticosteroids
IgE	:	Immunoglobulin E
IL	:	Interleukin
KDa	:	Kilodalton
LABA	:	Long acting β-2 agonist
LT	:	Leukotriene
LTRA	:	Leukotriene receptor antagonists
MMP	:	Matrix metalloproteinase
mRNA	:	Messenger ribonucleic acid
NIH	:	National institute of health
NP	:	Nasal polyposis
NPP	:	Negative predictive value
NSAIDs	:	Non steroidal anti-inflammatory drugs
4-PL	:	Four parameter logestic

PCR	:	Polymerase chain reaction
PEF	:	Peak expiratory flowmeter
PFT	:	Pulmonary function test
PPV	:	Positive predictive value
PSTN	:	Periostin
RGDsequence	:	Binding site for integrins
RNAI	:	Ribonucleic acid interference
RSV	:	Repiratory synsitial virus
SABA	:	Short acting β2- agonist
Sag	:	Superantigen
SARP	:	Severe asthma research program
SBM	:	Subepithelial basement membrane
SCG	:	Sodium cromoglycate
SD	:	Standard deviation
SMART	:	Sametrol multicenter asthma research
SPT	:	Skin prick test
TGF-β	:	Transforming growth factor β
Th	:	T-helper lymphocytes
TLC	:	Total leukocytic count
TNF	:	Tumor necrosis factor
USA	:	United states of America

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Introduction

Asthma is defined as a clinical syndrome of intermittent respiratory symptoms triggered by viral upper respiratory infections, environmental allergens or other stimuli, and is characterized by nonspecific bronchial hyperresponsiveness and airways inflammation **(1,2)**. The National Asthma education and Prevention Program and Global Initiative for Asthma guidelines divide asthma severity based on lung function (FEV1), daytime and nocturnal symptoms, and frequency of rescue bronchodilator use **(1, 2)**. There is increasing evidence, however, that this approach does not reflect the heterogeneous characteristics of this disease that are observed in populations with asthma **(3–5)**. Identification of heterogeneity and classification of asthma by phenotypes provides a better understanding of the underlying pathobiology of the phenotypes and lead to targeted therapies for individual phenotypes **(6, 7)**

The treatment of severe asthma both in adults and children still relies heavily on the maximal optimal use of corticosteroids and bronchodilators, and other controllers recommended for moderate to severe asthma.The addition of the first targeted biological treatment approved for asthma, a monoclonal anti-IgE antibody, has led to renewed optimism of improvement in outcomes in some patients with allergic severe asthma. There is a potential for other add-on benefits of additional biological agents to providing benefit in severe asthma, especially if appropriate responder specific phenotypes of patients can be identified and selected for these highly specific treatments. This prospect provides the impetus for

searching mechanisms, pathways and biomarkers in severe asthma which are under intense study. It is hoped that the current emerging understanding of the immunopathobiology, biological agents emerging inflammatory and molecular phenotypes of severe asthma; will generate and lead to safe and effective biomarker-driven approaches to the therapy of severe asthma **(8)**.

Periostin originally termed osteoblast specific factor 2 is a matricellular protein, which is a 90 - kDa member of the fasciclin-containing protein family and is upregulated by (IL-4) and (IL-13) stimulation from airway epithelial cells and other structural cells **(9)**.

The role of periostin in asthma and type 2 inflammatory responses is an area of active research. Recently,Sehra et al. and Gordon et al. demonstrated that periostin protects mice from allergic airway inflammation,whereas Blanchard et al. showed that periostin accelerates allergen-induced eosinophil recruitment in the lung and esophagus **(10-12)**. A similar protocol using intranasal administration of Aspergillus fumigatus (A. fumigatus) led to different outcomes, thereby suggesting that the role of periostin in allergic airway inflammation remains unclear **(13)**.

Aim of the work

The aim of this study is to identify the different clinical, inflammatory, functional, and molecular phenotypes in a group of asthmatic patients; and to evaluate the role of periostin in bronchial asthma and its different cellular phenotypes and its correlation with eosinophilic asthma and asthma severity.

Patients and Method

Study population

Forty eight asthmatic patients with severe asthma selected according to (GINA) criteria and forty eight asthmatic patients with mild to moderate asthma attending the Allergy and immunology Clinic, Ain Shams University Hospitals and ten healthy control subjects will be included in this study. All patients will provide a written informed consent. The study will be reviewed by the local ethical committee.

Demographic and clinical data will be collected: age, sex, body mass index (BMI), smoking status; clinical characteristics of asthma such as age of onset, asthma exacerbations, symptoms control, and asthma-related medication; and coexisting conditions and comorbidities such as aspirin/nonsteroidalanti-inflammatory drugs (NSAIDs) hypersensitivity, chronic rhinosinusitis (CRS), nasal polyposis (NP), gastroesophageal reflux, allergic rhinitis, and obesity. Asthma severity will be classified according to GINA 2016 criteria. **(14)**

The following investigations will be performed:

1. Skin prick test (SPT) to common allergens, histamine and normal saline (0.9%) were used as positive and negative controls, respectively. Hypersensitivity is defined as the presence of at least one skin prick test to common allergens,

with a wheal diameter of 3 mm or greater than the negative control,

2. pulmonary function tests (PFT).
3. Induced sputum by nebulized hypertonic saline to detect inflammatory cells and periostin in the supernatant by ELISA technique.