Periostin as a systemic biomarker of eosinophilic airway inflammation in asthmatic children

Thesis

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List of Abbreviations

ADAM33	A disintegrin and metalloprotease 33 gene
AEC	Absolute eosinophilic count
AHR	Airway hyperreactivity
APC	Antigen-presenting cells
ARIA	Allergic rhinitis and its impact on asthma initiative
AS	Ankylosing spondylitis
BA	Bronchial asthma
BAL	Bronchoalveolar lavage
BD	Positive bronchodilator
BMI	Body mass index
CD	Clusters of differentiation
COPD	Chronic obstructive airway disease
COX-1	Cyclo-oxygenase 1 enzyme
DPI	Dry powder inhaler
EBC	Exhaled breath condensate
ECM	Extracellular matrix
ECRS	Eosinophilic chronic rhinosinusitis
ED	Emergency department
EIA	Exercise induced asthma
EIB	Exercise-induced bronchospasm
ELISA	Enzyme linked immune-sorbent assay
FCE RI	High-affinity fragment crystalline receptors for ige
FDA	Food and drug administration
FEF	Forced expiratory flow
FENO	Fractional exhaled no
FEV1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GINA	Global initiative for asthma
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HDM	House dust mite
HFA	Hydro fluoroalkane
HO-1	Hemeoxygenase-1

HPA	Hypothalamic-pituitary-adrenal axis
HRP	Horseradish peroxidase
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IFN	Interferon
IG	Immunoglobulin
IGE	Immunoglobulin E
IIPS	Idiopathic interstitial pneumonias
IL	Interleukin
IPF	Idiopathic pulmonary fibrosis
KDA	Kilo dalton
LABA	Long acting B agonist
LTRA	Leukotriene receptor antagonist
LTS	Leukotrienes
MCP	Monocyte chemotactic protein
MCS	Mast cell stabilizers
MDCS	Macrophage-derived chemokines
MIP-1A	Macrophage inflammatory protein -1 alpha
NAEPP	The national asthma education and prevention program
NK	Natural killer
NO	Nitric oxide
NSAID	Nonsteroidal anti-inflammatory drugs
OCS	Oral corticosteroids
OD	Optical density
OVA	Ovalbumin
PAF	Platelet-activating factor
PCR	Polymerase chain reaction
PEF	Peak expiratory flow
PGD2	Prostaglandin d2
PGF2A	Prostaglandin f2 alpha
PN	Periostin
PV	Positive predictive value
RAST	Radio allergosorbent tests
ROC	Receiver-operating characteristic
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus

RV	Residual volume
SABA	Short-acting β2-agonist
SPSS	Statistical package for social science
TAP1	Translational asthma phenotype 1
TARCS	Thymus and activation-regulated chemokines
TGF	Transforming growth factor
TGF-β	Transforming growth factor –β
TH1	T-helper cell1
TH2	T-helper cell2
TLC	Total lung capacity
TLR	Toll-like receptor
TNF- α	Tumor necrosis factor
TMB	Trimethylbenzidine
URTIS	Upper respiratory tract infections
VC	Vital capacity
α	Alpha
β	Beta
γ	Gamma
µg	Micro-gram
µl	Micro liter

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Abstract

Background and Aim:

Th2_eosinophilic inflammation has been considered to be the dominant inflammatory pattern in asthma. Eosinophilic disease is a strong predictor of corticosteroid responsiveness. Direct airway sampling is technically challenging and impractical.Serum periostin may be a biomarker of eosinophilic asthma and it may help in asthma stratification prior to therapeutic interventions.The aim of this study is to explore serum Periostin as potential systemic biomarker in eosinophilic asthma in children and to correlate it with type of asthma.

Subjects and methods:

This is a cross sectional study, 60 asthmatic children with varying degree of severity, aged from 1-12 years were recruited from allergy and pulmonology clinic at Abo El Rish children's hospital, Cairo University and studied in comparison to 20 healthy age and sex matched children. Serum periostin level and complete blood picture including absolute eosinophilic count are measured in both asthmatics and controls.

Results:

Serum periostin levelis higher in asthmatic children compared to controls with with p-value <0.001, Serumperiostinlevel was significantly higher in severe asthmatics inspite maximum ICS compared to mild-moderate asthmatics with p-value<0.0001.There is positive correlation between serum periostin level and degree of severity of asthma with p-value<0.0001. Serum periostin level has highest value in allergic rhinitis compared to allergic conjunctivitis and eczema, no significant correlation was found between periostin level and patients with positive family history of atopy p-value=0.187.

Conclusion:

These findings imply that serum periostin level may be involved in the pathogenesis of eosinophilic asthma. Serum level of periostin as a biomarker has the potential to be used as noninvasive inflammatory markers for evaluation of airway inflammation in asthma.

Key words: Bronchial asthma- asthmatic children- biomarkers-periostin-ICS.

Introduction and Aim of work

There are few biomarkers that can be easily accessed in clinical settings and may reflect refractory Th2_eosinophlic inflammation and remodeling of the asthmatic airways ***(Szefler et al., 2013)***.

Serum periostin may be one such biomarker to aid our understanding of the pathobiophysiology of asthma and stratification prior to therapeutic interventions.Periostin is a disulfide linked 90-kDa heparin-binding N terminus-glycosylated protein, containing four tandem fasciclin (Fas1) domains. Periostin has been confirmed in many tissues and pathologies and its expression is known to be prominent in fibrotic conditions, including sub-epithelial fibrosis in bronchial asthma ***(Takayama et al., 2006)***.

Matricellular protein is a recent concept that was coined for an extracellular matrix protein that causes a vicious cycle of inflammation and remodeling. Periostin is one of these matricellular proteins and is upregulated by IL-4 and IL-13 stimulation from airway epithelial cells and other structural cells ***(Sidhu et al., 2010)***. Serum periostin has been identified as the single best predictor of airway eosinophilia in patients with severe asthma who remain symptomatic despite maximal inhaled corticosteroid treatment ***(Jia et al., 2012)***.

Therefore biomarkers that identify asthmatic patients likely to have Th2-driven inflammation in their airways might aid in the identification and selection of the patients most likely to respond to targeted therapies of asthma ***(Jia et al., 2012)***.

Aim of the work

The aim of this study is to explore serum Periostin as potential systemic biomarker in asthmatic children and to correlate it with type of asthma according to Global Initiative for Asthma guidelines (GINA) classification.

Introduction

Asthma is a chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm. Bronchial asthma has increasing incidence and prevalence worldwide. It is currently the most prevalent chronic disease in pediatric patients. During several years, studies have been performed to ascertain airway inflammation and consequently develop phenotype-specific and personalized therapies for asthma patients ***(Wenzel, 2012)***.

Airway inflammation and remodeling are fundamental features of asthma. Th2_eosinophilic inflammation has been considered to be the dominant inflammatory pattern in asthma ***(Woodruff et al., 2009)***. Although asthma is traditionally thought to result from aeroallergen-induced inflammation driven by Th2 processes and is commonly characterized by eosinophilic infiltration of the airways, there is increasing evidence that there are other subtypes of asthma driven by alternative pathogenic mechanisms ***(Galliet al., 2008)***. An emerging concept holds that the nature and intensity of granulocytic infiltration of the airways, in particular the presence or absence of increased numbers of eosinophils, defines pathophysiologically and clinically distinct subsets of the disease ***(Wardlawet al., 2005)***.

Eosinophilic disease is a strong predictor of corticosteroid responsiveness in asthmatic patients ***(Cowan et al., 2010)***. Direct airway sampling through sputum induction or bronchoscopy is technically challenging and often impractical in clinical practice, and hence noninvasive systemic biomarkers of airway eosinophilia are desirable for the rational management of asthma with existing and emerging targeted molecular therapies ***(Green et al., 2002)***.

Review of literature

Chapter 1

Bronchial Asthma