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INTEGRIN BETA 4 mRNA EXPRESSION LEVELS IN BRONCHIAL ASTHMA PATIENTS

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ABSTRACT

Integrin beta 4 (ITGβ4) is one of the integrin families that is engaged in the maintenance of the integrity of airway epithelial cells. The aim of this work was to evaluate the relationship between ITGβ4 mRNA expression level and asthma susceptibility; and to analyze the relevance of atopic asthma with the alteration of ITGβ4mRNA expression level.Seventy five asthmatic patients and thirty age and gender matched healthy controls were enrolled in this study. Serum total IgE was measured by ELISA and mRNA expression of ITGβ4 was assessed by reverse transcriptase PCR (RT-PCR) using real time PCR.**.** ITGβ4 mRNA expression was significantly down regulated with increased serum total IgE in patients with asthma compared to controls. Moreover, ITGβ4 expression was significantly reduced with increased total IgE in atopic asthmatics compared to non-atopic asthmatics.From this study, it could be concluded thatdown-regulation of ITGβ4 expression is associated with asthma susceptibility mainly in atopic cases irrespective of the degree of severity.

Key words: Integrin β4, expression, asthma, atopy and RT- PCR.

INTRODUCTION

Bronchial asthma is an airway disorder with an allergic nature **(Xiang et al., 2014)**. It is characterized by chronic inflammation with typical structural damage and airway epithelial cells dysfunction **(Liu et al., 2010b)**, including shedding and metaplasia of epithelial layer, basement membrane thickening with increased susceptibility to outer stimuli **(Holgate, 2007)**.

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Membrane glycoprotein molecules, named as adhesion moleculesare expressed on the surface of many cell types **(Charalambopoulos and Karachalios, 2000)**.They are responsible for the contact between two adjacent cells or between the cell and the extracellular matrix.They are involved in the physiological and pathological processes of asthma (**Johansson and Mosher, 2013)**.

The integrin family of adhesion molecules, heterodimeric receptors that consist of paired α and β subunitsthatfunction in adhesion and transduction**(Acosta et al., 2016)**, are involved in migration, survival, proliferation , growth and differentiation of cells **(Barczyk et al., 2010)**. One of these integrin families is integrin beta 4 (ITGβ4) that is engaged in the maintenance of the integrity of airway epithelial cells**(Liu et al., 2010b)**. ITGβ4 is a laminin receptor that mediates the stable adhesion of epithelial cells to the basement membrane through hemidesmosomes architecture **(Liu et al., 2010a)**. Damage of airway epithelial cell was common in asthmatic airway epithelial cells **(Watt, 2002 and Sheppard, 2003)**.

Atopic asthma is characterized by Th2-mediated inflammation and typically impaired airway epithelial cells. In the airways of asthmatic patients, exposure to allergens induces an increase in Th2 cell infiltration and Th2 cytokine expression **(Holgate and Davies, 2009 and Liu et al., 2012)**.

A previous study found that there was downregulation of integrin β4 in the airway epithelium of asthmatic patients. As the airway epithelium is considered as the first barrier to allergen stimulation, downregulation of ITGβ4 enhanced the invasion of inhaled allergens and regulated the local T cell immune inflammation through antigen presentation process**(Liu et al., 2010b)**.

The aim of the present study is to evaluate the relationship between ITGβ4 mRNA expression level and asthma susceptibility, and to analyze the relevance of atopic asthma with the alteration of ITGβ4 mRNA expression level.

MATERIALS AND METHODS

This study was carried out in Medical Biochemistry and Chest Departments, Faculty of Medicine, Menoufia University. 105 subjects were enrolled in the study; they were 75 asthmatic patients (36 males and 39 females) with mean age of32±7.9 and 30 age and

gender matched healthy controls (14 males and 16 females)with mean age of 33.9±9.9The study was approved by ethical committee of Faculty of Medicine, Menoufia University. A written informed consent was obtained from all subjects. A clinical diagnosis of bronchial asthma wasbasedonthe characteristic pattern of respiratory symptoms such as wheezing, shortness of breath (dyspnea), chest tightness or cough, evidence of expiratory airflow limitation (FEV1/FVC less than 0.7).Bronchodilator (BD) reversibility test was carried out and was considered positive if there was an increase in FEV1 of >12% and >200 mL from baseline, 10–15 minutes after 200 mg salbutamol inhalation**(GINA.2016)**.

Patients were classified into atopic and non atopic groups based on the family history of atopy, presence of history of identified allergen sensitivity and by measuring the level of immunoglobulin E (IgE) in serum. **(Global Initiative for Asthma, 2016 and National Heart Lung and Blood Institute,2007)**.Serum IgE level ≥100 IU/ml is considered atopic and level<100 IU/mlisconsidered non-atopic**(Abnova, USA)**. Severity of bronchial asthma in patients was assessed based on the GINA guidelines 2016 **(Global Initiative for Asthma, 2016)**and ERS/ATS guidelines **(Chung KF et al., 2014)** into mild, moderate and severe groups:

•Mild asthma is asthma that is well controlled with Step 1 or Step 2 treatment (i.e. with as-needed reliever medication alone, or with low-intensity controller treatment such as low dose ICS, leukotriene receptor antagonists or chromones).

•Moderate asthma is asthma that is well controlled with Step 3 treatment (e.g. low dose ICS/LABA).

•Severe asthma is asthma that requires Step 4 or 5 treatments (e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment).

All patients who had any other cardiopulmonary disorders, acute exacerbation of asthma or evidence of other allergic diseases were excluded from the study.

Methods:

All subjects were subjected to: full history taking, general and local clinical examinations, chest X ray and pulmonary function tests (before and after bronchodilators, for asthmatic patients) including forced expiratory volume in one second / forced vital capacity ratio (FEV1/FVC) and postbronchodilator forced expiratory volume in one

second(BDFEV1). Serum level of IgE was determined by ELISA technique **(Abnova, USA)**. Measurement of Integrin β4 mRNA expression was performed using reverse transcriptase PCR (RT-PCR) using real time PCR.

Samples collection:

Seven milliliters (ml) of venous blood were withdrawn from each subject anddivided as follows: 3 mL in a vacutainerplain test tube andwas left to clot, and then centrifuged at 3000rpm for 10 minutes, serum was then separated and stored at -80°C until used for measurement of serum IgElevel by ELISA. 4 mL of venous blood were delivered in a vacutainerEDTA-containingtube for detection of integrin β4 mRNAexpression.

Reverse transcriptase PCR (RT-PCR):

RNA was isolated from peripheral blood leukocytes using QIAamp RNA BloodMiniKit (Qiagen, USA, 2013), then assuring RNA concenrtation and purity by Nanodrop. First step-PCR: Complementary DNA was synthesized using QuantiTect Reverse Transcription Kit (Qiagen,AppliedBiosystems, USA, 2012),second step- PCR (real time PCRstep): it was performed using QuantiTect SYBR Green PCR Kit with ready made quantiTect Primer Assay, Qiagen.For measurement of integrin β4 mRNAlevels, the following primers were used: forward and reverse primers of human integrin β4, 5-AGACGAGATGTTCAGGGACC-3 and 5-GGTCTCCTCTGTGATTTGGAA-3, respectively; forward and reverse primers for human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) 5-CCACTCCTCCACCTTTGAC-3 and 5-ACCCTGTTGCTGTAGCCA-3, respectively. PCR was conducted under the following conditions: 40 cycles; denaturation at 94 C for 5sec ،annealing at 60 C for 30 sec and extension at 72 C for 30 sec.

Statistical analysis:

The data collected was tabulated and analyzed by SPSS (statistical package for the socialscience) software version 16. Chi-square test is used to study the association between two qualitative variables. Student's t test was used to assess the statistical significance of parametric data. Mann–Whitney and Kruskal Wallis Test were used for nonparametric data.Spearman'scorrelation was used for skewed distributed quantitative variables. Values less than 0.05 were considered significant.

RESULTS

The study enrolled 75 asthmatic patients and 30 age(P=0.3) and gender(P=0.9) matched apparently healthy individuals. Also, BMI (P=0.08) revealed non significant difference between the studied groups (table1).

There was a significant decrease in the level of Integrin β4 mRNA expression in asthmatic patients (2.88±2.44Iu/ml) compared to controls (41.5±5.5Iu/ml) (P<0.0001).While a significant increase in the serum level of Ig E was found in these patients (287.1±184.7Iu/ml) compared to controls (34.8±2.7Iu/ml) (P<0.0001) (table 1).

Regarding the asthmatic patients56 % were atopic and (44%) of them were non- atopic patients, who revealed non- significant difference regarding airway obstruction parametersFEV1/FVC(P=0.98) & BDFEV1% (P=0.94) (table 2).

The serum IgElevels were significantly increased in atopic patients (442.7±36.3Iu/ml) compared to non-atopic ones (76.2±15.5Iu/ml) (P<0.0001). While there was a significant decrease of integrin β4 mRNA expressionlevels in atopic patients (1.6±1.96Iu/ml) compared to non-atopic (4.6±1.92Iu/ml) (P<0.0001) (table 2).

Concerning the severity of asthma 33.3% of patients had mild degree of asthma, 40% had moderate degree and 26.7% suffered from severe asthma, who revealed non significant difference in the levels of Integrin β4 mRNA expression (P=0.53) and serum IgE(P=0.75) (table 3).

In asthmatic patients Integrin β4 mRNA expression levels showed a significant negative correlation with serum levels of Ig E (r=-0.39, P<0.001)and a significant positive correlation with BMI (r=0.24, P=0.043) while there was no significant correlation between levels of both integrin β4 mRNA expression and serum IgE and the other parameters (table 4&5).

Table 1: Demographic, clinical and laboratory characteristics of studied groups

Characteristics	Studied groups		P-value
	Patients (n=75)	Controls (n=30)	
Age (years): Mean±SD Range	32±7.9 18-42	33.9±9.9 20-50	0.3
Gender (n,%): -Male -Female	36 (48) 39 (52)	14 (46.7) 16 (53.3)	0.90
BMI (kg/m^2): Mean±SD Range	25.8±1.15 23.44 – 28.3	25.4±0.96 23.4 – 27.6	0.08
FEV1/FVC: Mean±SD Range	62.8±6.9 48 – 75	-	-
BDFEV1 (%): Mean±SD Range	70.4±12.9 45 – 87	-	-
Atopy (n, %): -Atopic -Nonatopic	42 (56%) 33 (44%)	-	-
Severity (n, %): -Mild -Moderate -Severe	25 (33.3) 30 (40) 20 (26.7)	-	-
Integrin β4 mRNA expression (Iu/ml): Mean±SD Median(Range)	2.88±2.44 2.29(0.02 – 5.83)	41.5±5.5 43.3 (35.0 – 48.7)	<0.0001*
IgE serum level (Iu/ml): Mean±SD Median(Range)	287.1±184.7 402 (47 – 499)	34.8±2.72 35 (31 – 39)	<0.0001*

BMI: body mass index, FEV1: forced expiratory volume in one second, FEVC: forced vital capacity, BDFEV1: bronchodilator forced expiratory volume in one second, t: t test, #Chi square test- *Mann-Whitney test

Table (2): Demographic, clinical and laboratory characteristics of atopic and non-atopic patients

Characteristics	Patient group (n=75)		P-value
	Atopic cases (n=42)	Non-atopic cases (n=33)	
Age (years) **Mean±SD** **Range**	**31.5±7.7** **18-40**	**32.7±8.2** **19-42**	**0.52**
Gender (n,%): **-Male** **-Female**	**23 (54.8)** **19 (45.2)**	**13 (39.4)** **20 (60.6)**	**0.19**
BMI (kg/m^2): **Mean±SD** **Range**	**25.6±1.1** **23.9-27.89**	**26±1.2** **23.44-28.3**	**0.16**
Sever asthma (n,%)	**12 (28.6%)**	**8 (24.2%)**	**0.33#**
FEV1/FVC: **Mean±SD**	**62.8±6.8**	**62.8±7.1**	**0.98**
BDFEV1 (%): **Mean±SD**	**70.3±12.6**	**70.6±13.5**	**0.94**
Integrin β4 mRNA expression (Iu/ml): **Mean±SD** **Median(Range)**	**1.6±1.96** **0.7 (0.06-5.8)**	**4.6±1.92** **5.38 (0.02-5.83)**	**<0.0001***
IgE serum level (Iu/ml): **Mean±SD** **Median(Range)**	**442.7±36.3** **432 (390-499)**	**76.2±15.5** **79 (47-96)**	**<0.0001***

BMI: body mass index, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, BDFEV1: bronchodilator forced expiratory volume in one second, t: t test, #Chi square test -*Mann-Whitney test

Table (3): Statistical comparison of integrin β4 mRNA expression and IgE serum levels among different degrees of severity in patients group

	Patient group (n=75)			P value
	Mild (n=25)	Moderate (n=30)	Severe (n=20)	
Integrin β4 mRNA expression (Iu/ml): Mean±SD Median (Range)	**2.87±2.37 2.3 (0.02-5.77)**	**2.94±2.55 2.28 (0.06-5.8)**	**2.77±2.48 1.9 (0.08-5.8)**	**0.53**
IgE serum level(Iu/ml): Mean±SD Median (Range)	**244±199.2 90 (48-499)**	**305.5±180.2 405(60-498)**	**291.1±178.6 401.5 (47-499)**	**0.75**

Kruskal Wallis Test

Table (4): Correlation between integrin β4 mRNA expression and studied parameters among patients

Studied parameters	Integrin β4 mRNA expression (Iu/ml)	
	r	P value
Age (years):	0.07	0.52
BMI (kg/m^2):	0.24	**0.043**
FEV1/FVC:	0.12	0.32
BDFEV1 (%):	-0.07	0.55
IgE serum level (Iu/ml):	-0.39	**0.001**

BMI: body mass index, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, BDFEV1: bronchodilator forced expiratory volume in one second,r:
Spearman correlation coefficient

Table (5): Correlation between IgE serum level and studied parameters among patients

Studied parameters	IgE serum level (Iu/ml)	
	r	P value
Age (years):	-0.06	0.64
BMI (kg/m^2):	-0.02	0.89
FEV1/FVC:	0.02	0.87
BDEFV1 (%):	0.08	0.49

BMI: body mass index, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, BDFEV1: bronchodilator forced expiratory volume in one second, r: **Spearman 's correlation coefficient**

DISSCUSION

Bronchial Asthma is a complex disease of gene-environment interactions. The need is increasing for better understanding of the molecular mechanisms and identification of further susceptibility gene in asthma, some of which could be useful for diagnosis and improving treatments targeted to individual disease phenotypes **(Blume and Davis2013)**.

In our study, we observed a significant decrease in the level of ITGβ4 mRNA expression in asthmatic patients mainly atopic casesirrespectiveof the degree of severity, confirming its relation to the asthma susceptibility (tables1-3).

Our data supported previous studies regarding ITGβ4 mRNA expression and bronchial asthma.The airway epithelial barrier is often disrupted in asthma patients, with evidence of shedding of airway epithelial cells and impaired expression of genes (**Bucchieri et al., 2000**).

Liu et al. 2010 Provided evidences that ITGβ4 was involved in the structural integrity and functional homeostasis of airway epithelial cells (**Liu et al., 2010b**).

The results of Zhou et al., 2008 and Xiang et al., 2014, showed that the expressions of integrin β4 were down-regulated in asthma patients, and that it was associated with the variation in5'flanking region.

It is likely that down-regulation of ITGβ4 in bronchial asthma contributes to the structural disruption and dysfunction of airway epithelial cells and may result in decreased wound repair and anti-oxidation ability (**Evans and Koo 2009 &Siddiquiad Martin 2008**).
Moreover, Sheppard 2003 showed that integrinβ4 expression was clearly elevated after airway epithelialinjuryand could be detected in many cell types, which suggest that integrin β4 might be involved in the repair processes of airway epithelium (**Sheppard 2003**).
Xiang et al., 2014 found thatmutations in 5′ flanking region of integrin β4 gene result in reduced integrin β4 expression, and that it was related to increased risk of asthma (**Xiang et al., 2014**).
ITGs are heterodimeric receptors that mediate cell adhesion, migration and tissue organization(**Staunton et al., 2006**) and might be a death factor in endothelial cells (**Hiran et al., 2003**).
It is reported that disintegrin is increased in asthma.And it is related to asthma severity which may relates to downregulation of integrin(**Ji-Yeon et al., 2006**) .
The study by Liu et al. 2012 demonstrated that downregulation of integrinβ4 expression in airway epithelial cells could impair the antigen presentation ability of these cellswith decreased Th1 cytokine production and increased Th2 cytokine production, which further regulates airway inflammation reaction in allergic asthma (**Liu et al., 2012**).
It is known that airway inflammation and airway hyper-responsiveness in asthma models were suppressed by Th1 cytokines(**Park et al., 2009**).On contrary, Th2 cytokines, such as IL-4 and IL-5, induce eosinophil infiltration and asthmatic airway hyper-responsiveness(**Holgate, 2008**).
Integrins are cellular receptors that regulate attraction of eosinophils from the bronchial circulation to the airway wall and airspace (Barthel et al., 2008).
This could explain the significant association of ITGβ4 down-regulation and increased serum total IgE among asthmatic patients in our study. It has been shown that the presence and the degree of airway hyper-responsiveness were related to the total IgE as expressed by the occurrence of asthma exacerbation or an asthma severity score (**Wever-Hess J, 2000**).

Scarpelli et al. 2016 indicated increased postmortem serum total IgE in atopic individuals, irrespective of the cause of death (**Scarpelli et al., 2016**).

Also, Sky et al. (2016) stated that a one-year follow up study on a well controlled adult patients with atopic asthma showed that treatment with inhaled corticosteroids and leukotrienes receptor antagonists resulted in a marked decrease in elevated total serum IgEAb concentration with improvement in asthma control and asthma related quality life (**Sky et al., 2016**) proving the role of serum total IgE in atopic asthma.

In contrast, our data revealed a non-significant correlation regarding ITGβ4 mRNA expression and serum IgE with asthma severity indices or patients` demographics (Tables 4,5). This could be attributed to the presence of atopy regardless of the severity of asthma or patients`characteristics.Also, the distribution of atopic cases among the severity range of asthma could explain the non- significant association of lung function with atopic status in our study.

Conclusion:

From this study, it could be concluded that, down-regulation of ITGβ4 expression was significantly associated with asthma susceptibility especially in atopic cases irrespective of the degree of asthma severity.

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الملخص العربى

مستوى تعبير الحامض النووي الريبوزي الرسول انتجرين بيتا٤ فى المرضى المصابين بالربو الشعبى

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يعتبر انتجرين بيتا ٤ واحد من مجموعة الانتيجرين المسؤله على الحفاظ على سلامة الخلايا الظهاريه فى مجرى الهواء. الغرض من هذا البحث هو تقييم العلاقه بين مستوى تعبير الحامض النووي الريبوزي الرسول انتجرين بيتا٤والقابليه للاصابه بالربو الشعبي.أجريت هذه الدراسة علي ٧٥من المرضى المصريين المصابين بالربو الشعبى و ٣٠ من الاشخاص الاصحاء كمجموعه ضابطه. وقد تم تقسيم مرضى الربو الشعبى حسب مستوى الاجسام المناعيه الى مجموعه مصابه بالربو التحسسي ومجموعه اخرى غير مصابه بالربو التحسسي. وقد تم اخذ التاريخ المرضى لجميع المشاركين، كتلة الجسم، مستوى الاجسام المناعيه ه بالاليزا وايضا مستوى تعبير الحامض النووي الريبوزي الرسول انتجرين بيتا ٤عن طريق الناسخ العكسي تفاعل البلمرة المتسلسل. أظهرت نتائج هذه الدراسة أن مستوى تعبير الحامض النووي الريبوزي الرسول انتجرين بيتا ٤ينخفض انخفاضا ملحوظا مقارنه بالمجموعه الضابطه خاصة فى مرضى الربو التحسسى ولكن لا توجد علاقه بين انخفاض مستوى تعبير الحامض النووي الريبوزي الرسول انتجرين بيتا ٤ وشدة الربو الشعبى. يمكن الاستنتاج بأنانخفاض مستوى تعبير الحامض النووي الريبوزي الرسول انتجرين بيتا ٤ يرتبط بالاصابه بمرض الربو الشعبى خاصة الربو التحسسى بغض النظر عن شدة الربو.