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Molecular interaction network and pathway studies of *ADAM33* potentially relevant to asthma

Sangeetha Vishweswaraiah, MSc^{*}; Avinash M. Veerappa, PhD^{*};
Padukudru A. Mahesh, MBBS, DTCD, DNB[†]; Biligere Siddaiah Jayaraju, MBBS, MD, DM[†];
Chaya Sindaghatta Krishnarao, MBBS, DTCD, DNB[†]; and Nallur B. Ramachandra, PhD^{*}

^{*} Genetics and Genomics Laboratory, Department of Studies in Zoology, University of Mysore, Mysore, Karnataka, India

[†] Department of Pulmonology, JSS Hospital, Mysore, Karnataka, India

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ABSTRACT

Background: Asthma is a complex disease caused by gene–gene, gene–protein, and protein–protein interactions and the influence of environment, which plays a significant role in causing asthma pathogenesis. *ADAM33* is known to be an important gene involved in asthma pathogenesis. No one single gene is a causal factor of asthma; rather, asthma is caused by a complex interaction of multiple genes having pathogenetic and protective effects.

Objective: To identify and understand the interacting genes and proteins of *ADAM33*.

Methods: The Ingenuity Pathway Analysis and GeneMANIA tools and a literature survey were used to identify the interacting candidates of *ADAM33* and the WEB-based GENE Set Analysis Toolkit was used to perform enrichment analysis of the proteins identified.

Results: Keeping *ADAM33* as a major hub, the authors identified some proteins whose interaction with *ADAM33* had been associated with asthma and they recognized some proteins, such as amyloid β (A4) precursor protein, ataxin-7, α_4 -integrin, α_5 -integrin, α_9 -integrin, tissue inhibitor of metalloproteinase-4, and ubiquitin-4, that had not been previously associated with asthma.

Conclusion: The proteins identified in this study were enriched for various mechanisms that are involved in airway hyperresponsiveness, and through the interaction with *ADAM33*, they may have potential relevance in asthma.

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Introduction

Asthma is a complex disease that involves many pathologic features such as airway wall thickening, edema, inflammatory cell infiltration, connective tissue deposition, subepithelial fibrosis, myofibroblast hyperplasia, mucus metaplasia, and epithelial hypertrophy leading to blockage in airways and causing difficulty in breathing.^{1,2} No one single gene is a causal factor of asthma; rather, asthma is caused by a complex interaction of multiple genes having pathogenetic and protective effects.³ A disintegrin and metalloprotease-33 (*ADAM33*) is one such gene involved with the complexities associated with asthma and the involvement of this gene was first proved by positional cloning⁴ and then by association studies. *ADAM33* belongs to the ADAM family of genes located on

chromosome 20p13, which is a type I transmembrane protein, and ubiquitously expressed.⁵ This gene has been linked to multiple biological processes involving cell–cell and cell–matrix interactions, cell proliferation, cell differentiation, cell migration, muscle development, fertilization, and neurogenesis.^{6,7} There are 2 transcript variants of approximately 3.5-kb and approximately 5-kb transcripts produced by alternative splicing.^{8,9} *ADAM33* encompasses multiple domains, namely signal sequence, pro-domain, catalytic, metalloprotease, disintegrin, cysteine-rich, epidermal growth factor domain, transmembrane, and cytoplasmic domains.⁴ *ADAM33* exhibits altered function that can translate into bronchial hyperresponsiveness by the contraction of airway smooth muscle cells into a single unit.¹⁰ It remains to be identified whether asthma-related phenotypes are directly linked to the *ADAM33* polymorphism alone or is a result of gene–gene or gene–environment interactions.¹¹ Hence, it is important to understand the molecular interaction and behavior of other proteins interacting with *ADAM33* to understand the etiology and manifestation of asthma.

ADAM33 is one of the genes associated with asthma phenotypes. The fate of *ADAM33* programmed by the gene and protein

Reprints: Nallur B. Ramachandra, PhD, Genetics and Genomics Laboratory, Department of Studies in Zoology, University of Mysore, Mysore 06, Karnataka, India; E-mail: nallurbr@gmail.com.

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regulatory network can be understood by genomic insight, which is significant for understanding the role of ADAM33 in the pathogenesis of a complex disease such as asthma. The purpose of the present study was to identify the pathways and processes critical to asthma by assessing the functional and regulatory roles of several proteins interacting with ADAM33 and to construct interaction networks among those genes and their products to discern the complex effect of genes involved in the manifestation of asthma.

Methods

Network Prediction

The pathways and molecular interactions were generated through a systems biology approach using Ingenuity Pathway Analysis (IPA; www.qiagen.com/ingenuity) to identify interactions between genes, protein–protein interactions, biological mechanisms, and the location and function of target genes. IPA is a high-throughput network database regarded as a “global molecular network” consisting of approximately 3,000,000 biological and chemical interactions based on scientific evidence. In IPA, the Fisher exact test is used to calculate the *P* value to check the significance of associations among genes, pathways, and networks.^{12,13} The IPA database also uses a resilient set of people, technologies, and processes for curating and mining better-quality datasets from peer-reviewed journals and public and private biomedical databases (<http://www.ingenuity.com/science/knowledge-base>). Some major databases used in the IPA include the National Center for Biotechnology Information databases (EntrezGene, RefSeq, and OMIM), targets and pharmacologic relevance of Food and Drug Administration–approved and clinical trial drugs, clinical biomarkers, gene ontology annotations, a normal gene expression body atlas for more than 30 tissues and the NCI-60 panel of cancer cell lines, microRNA–mRNA target databases, and genomewide association study databases (<http://www.ingenuity.com/science/platform/content-sources>). Gene and chemical searches were used to explore the information on protein families, protein signaling, metabolic pathways, and the normal cellular activity of protein. Genes and their protein products are shown based on their location. An edge (line) is used to represent the relation between 2 nodes. Each edge in the network was represented by underpinning the information in the IPA knowledge base and references from the available literature. A cascade of protein–protein interactions or protein binding, molecular cleavage, activation, upregulation, downregulation, and expression of mRNA by targeting the mature miRNA network was analyzed. The interacting genes also were identified using the GeneMANIA tool, which identifies the interacting molecules based on the existing genomics and proteomics data and the datasets from the Gene Expression Omnibus, Biological General Repository for Interaction Datasets, Pathway Commons, and Interologous Interaction Database (I2D).¹⁴ In addition, a literature survey was conducted to accumulate data on the interactions of ADAM33 with other genes and proteins using PubMed and Google Scholar to identify further interactions of ADAM33.

Categorization of Genes

Function-based categorization of genes obtained from the network was performed using the WEB-based GEne SeT Analysis (Webgestalt) toolkit, a Web-based enrichment analysis tool. The enrichment is built on different biological contexts comprising gene ontology, pathway, network module, and gene–phenotype, gene–disease, and gene–drug associations. Enrichment analysis began with the 17 genes involving ADAM33 and its interacting partners. The hypergeometric statistical method using the Benjamini-Hochberg procedure was applied as a multiple test

adjustment to calculate the false discovery rate for each *P* value and a significance level no higher than 10. The gene ontology classification (biological process, cellular component, and molecular function) was performed using the Webgestalt classification system.¹⁵

Results

Molecular Interaction Network

Figure 1 presents the molecular interaction network based on the location of the interacting proteins and regulating miRNAs with ADAM33. Analysis of the ADAM33 protein exhibited 17 protein–protein interactions and 52 mature miRNA interactions. Of the 17 proteins, 8 were located in the extracellular matrix, 6 were located on the plasma membrane, 2 proteins were located in the cytoplasmic region, and 1 protein was situated in the nucleus of the cell. Many functionally diverse proteins were shown by the network in which ADAM33, a peptidase protein, was the major hub, located in the transmembrane site, with its interacting molecules present in various cellular locations. Paths between genes represent protein–protein interactions, regulation, and phosphorylation activities.

Biological Process, Molecular Function, and Cellular Components of Genes Interacting with ADAM33

Seventeen genes involved in the ADAM33 protein–interaction network were categorized using the Webgestalt based on biological process, molecular function, and cellular component. In the biological process (Table 1), most genes (12 genes) were involved in system development (multicellular and anatomic structures; $P = 9.05e^{-06}$) and the fewest genes (4 genes) were involved in the positive regulation of leukocyte proliferation ($P = 1.33e^{-05}$). For molecular function, 9 genes were involved in the receptor binding process ($P = 6.31e^{-07}$) and only 1 gene was involved in vascular endothelial growth factor receptor binding ($P = 3.06e^{-05}$). The cellular component showed approximately 10 genes located in the extracellular region ($P = 5.09e^{-06}$), whereas only 2 genes were present in the $\alpha_9\beta_1$ integrin complex ($P = 1.57e^{-05}$). The significantly enriched biological process, molecular function, and cellular components of gene products interacting with ADAM33 are presented in Table 1.

Genes interacting with ADAM33 also were examined to determine functional relevance and disease pathways relevant to asthma. Seventeen coding and 52 miRNA genes were included in the IPA. Functional and disease categories were ranked based on enrichment for all genes. The top 17 ranked categories included functional and disease categories related to cell–cell interaction and signaling, hematologic system development and function, immune cell trafficking, inflammatory response, cellular movement, adhesion of mast cells, migration of cells, adhesion of immune cells, infiltration by lymphocytes, and invasion of cells. The IPA also was used to search for biological relations between the ADAM33 interacting genes and previously identified asthma genes. A comparison between normal and asthmatic airways is illustrated in Figure 2. eTable 1 presents those miRNA genes that regulate ADAM33.

Discussion

The molecular pathway was built primarily using IPA. The authors performed IPA on the upstream and downstream elements of ADAM33 and identified several targets accountable for various asthma phenotypes relating to airway wall thickening, edema, inflammatory cell infiltration, connective tissue deposition, subepithelial fibrosis, myofibroblast hyperplasia, mucus metaplasia, and epithelial hypertrophy. This phenotype and genotype

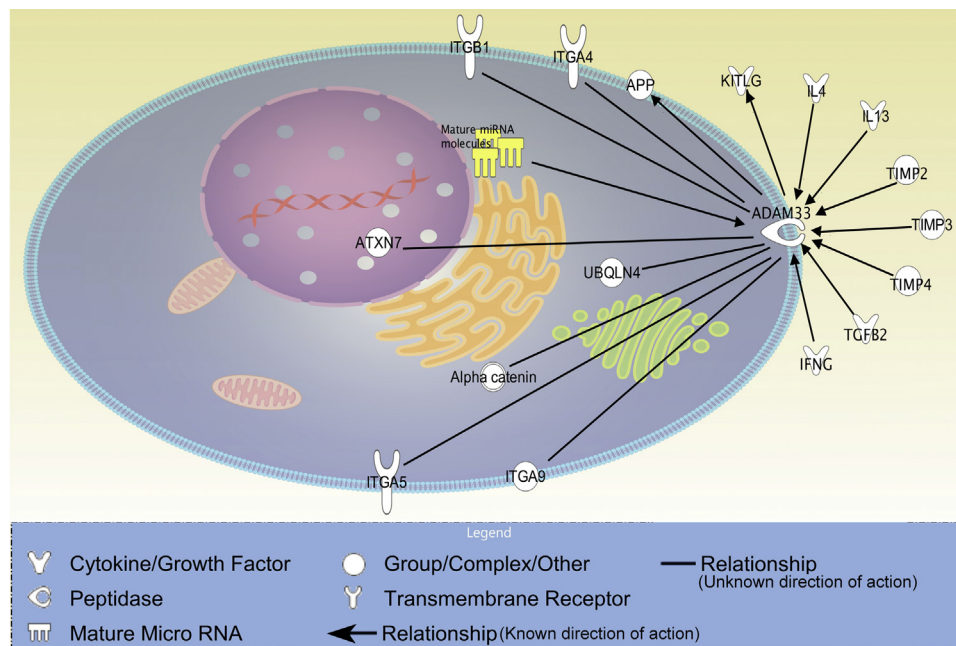


Figure 1. Representation of the molecular interaction network of ADAM33 based on location in a cell. Symbols represent molecule types and lines represent the relation between molecules. Arrows indicate the direction of the action of the molecules. Lines without arrows indicate the molecules that are interacting but the direction of interaction is unknown. ADAM33, A disintegrin and metalloproteinase; APP, amyloid β (A4) precursor protein; ATXN7, ataxin-7; IFNG, interferon- γ ; IL13, interleukin-13; IL4, interleukin-4; ITGA4, α_4 -integrin; ITGA5, α_5 -integrin; ITGA9, α_9 -integrin; ITGB1, β_1 -integrin; KITLG, KL-1 ligand; TGF β 2, transforming growth factor- β_2 ; TIMP2, tissue inhibitor of metalloproteinase-2; TIMP3, tissue inhibitor of metalloproteinase-3; TIMP4, tissue inhibitor of metalloproteinase-4; UBQLN4, ubiquitin-4.

correlation could lead to a better understanding of the molecular interaction and behavior of proteins interacting with ADAM33 in asthma.

Molecular Interaction Network

Using the systems biology approach, this study has identified new proteins (tissue inhibitor of metalloproteinase [TIMP] 4; α_4 , α_5 , and α_9 integrins [ITGA4, ITGA5, and ITGA9, respectively]; amyloid β (A4) precursor protein [APP]; ubiquitin-4 [UBQLN4]; and ataxin-7 [ATXN7]; Figure 1) hitherto not associated with asthma as important in various mechanisms associated with airway hyperresponsiveness through the interaction with ADAM33 in addition to KL-1, interleukin-4 (IL4), interleukin-13 (IL13), interferon- γ (IFNG), transforming growth factor- β_2 (TGF β 2), TIMP2, TIMP3, alpha-catenin, and β_1 integrin (ITGB1), which have been observed in previous studies to influence asthma pathogenesis.

Gene Enrichment Analysis

The proteins identified in the present study that interact with ADAM33 were analyzed further using the Webgestalt toolkit based on gene ontology by grouping them into 3 categories: biological process, molecular function, and cellular components. Under the biological process, most genes were involved in system development (multicellular and anatomic structures), with smaller numbers of genes associated with the positive regulation of leukocyte proliferation. The genes that interact with ADAM33 are involved in cell activation, cellular development, and cell differentiation; these processes lead to the propagation of muscle cells and eventually the muscle mass increases, which are the probable causes for airway remodeling.¹⁶ Immune system process and leukocyte migration are the 2 processes that are relatively causal for airway hyperresponsiveness.¹⁷ These multiple proteins involved in such signaling pathway mechanisms interact with ADAM33, indicating a direct or indirect influence of ADAM33 in leading these signaling pathways.

For molecular function, more genes code for receptor binding processes. These proteins that interact with ADAM33 are involved chiefly in the process of receptor binding (vascular endothelial growth factor receptor binding and cytokine receptor binding), metalloenzyme regulation and inhibition, peptidase inhibition, endopeptidase regulation, and inhibition activities. The activity of ADAM33 is directly or indirectly regulated by all these processes. During regulation, any slight deviation might lead to the manifestation of airway pathogenesis. The cellular component showed more genes in the extracellular region and the fewest in the α_9 - β_1 integrin complex. The proteins also were present in the cell surface, namely in the external side of the plasma membrane, and in the cytoplasmic regions. This explains why the interaction of ADAM33 with other proteins is not limited to any single location; rather, the interaction is regionally diverse and is not biased.

Pathway Analysis

The transcription factors that transcribe ADAM33 are yet to be identified but many upstream and downstream regulators have been identified. ADAM33 is upregulated by IL-4, IL-13, TGF β 2^{18,19} and downregulated by TIMP3, TIMP4, TIMP2, and IFNG.^{20,21} ADAM33 is involved in the regulation of some genes, where it upregulates KL-1 expression and downregulates APP expression.²⁰ Also, there is an interaction between α -catenin and ADAM33 but there is no available literature on how α -catenin is regulated by ADAM33. Further, there might be a protein–protein interaction between ATXN7–ADAM33 and UBQLN4–ADAM33. Similarly, a group of 4 integrins (ITGA4, ITGA5, ITGA9, and ITGB1) might form a protein complex with ADAM33 (Fig 2).

The role of ADAM33 is vital in asthma pathogenesis, which interacts with many other proteins with diverse mechanisms. It has expression in various types of cells, such as smooth muscle cells, fibroblast cells, myofibroblast cells, blood vessels, mesenchymal cells, and epithelial cells.²² Thus, it plays a key role with various other molecules that are along the ADAM33 pathway and regulates

Table 1Significantly enriched gene ontology categories by biological process, molecular function, and cellular components of gene products interacting with ADAM33^a

Serial no	Gene ontology	Genes involved	P value
Biological process			
1	response to wounding	TIMP3, ITGA4, CTNNA1, IL13, ITGB1, IL4, ITGA5, ITGA9, TGFβ2, APP	7.76e ⁻⁰⁷
2	leukocyte migration	ITGA5, IFNG, ITGA9, TGFβ2, ITGA4, ITGB1	5.86e ⁻⁰⁶
3	cell adhesion	IFNG, ITGA4, CTNNA1, ITGB1, ITGA5, KITLG, ITGA9, TGFβ2, APP	9.05e ⁻⁰⁶
4	system development	IFNG, TIMP2, ITGA4, CTNNA1, IL13, TIMP4, IL4, ITGA5, TGFβ2, ITGB1, KITLG, ITGA9	9.05e ⁻⁰⁶
5	cellular response to chemical stimulus	IFNG, TIMP3, TIMP2, CTNNA1, IL13, ITGB1, IL4, ITGA5, ITGA9, TGFβ2	9.05e ⁻⁰⁶
6	response to external stimulus	IFNG, TIMP3, IL13, ITGB1, IL4, ITGA5, ITGA9, TGFβ2, APP	1.29e ⁻⁰⁵
7	cell activation	IFNG, ITGA4, IL13, ITGB1, IL4, TGFβ2, APP	1.33e ⁻⁰⁵
8	positive regulation of leukocyte proliferation	KITLG, IFNG, IL13, IL4	1.33e ⁻⁰⁵
9	cell differentiation	IFNG, TIMP2, ITGA4, IL13, ITGB1, IL4, KITLG, ITGA5, ITGA9, TGFβ2, APP	1.48e ⁻⁰⁵
Molecular function			
1	cytokine receptor binding	KITLG, ITGA5, IFNG, TGFβ2, IL13, IL4	1.71e ⁻⁰⁷
2	receptor binding	IFNG, TIMP2, IL13, ITGB1, IL4, KITLG, ITGA5, TGFβ2, APP	6.31e ⁻⁰⁷
3	cytokine activity	KITLG, IFNG, TGFβ2, IL13, IL4	1.83e ⁻⁰⁶
4	metalloenzyme inhibitor and regulator activity	TIMP2, TIMP3, TIMP4	2.92e ⁻⁰⁶
5	endopeptidase inhibitor and regulator activity	TIMP3, TIMP2, APP, TIMP4	4.47e ⁻⁰⁵
6	vascular endothelial growth factor receptor binding	ITGA5	3.06e ⁻⁰⁵
7	growth factor activity	KITLG, TGFβ2, IL4	4.37e ⁻⁰⁵
Cellular component			
1	cell surface	IFNG, TIMP2, TIMP4, IL13, ITGB1, IL4, ITGA5, TGFβ2, APP	7.77e ⁻⁰⁸
2	extracellular region part	IFNG, TIMP3, TIMP2, IL13, ITGB1, TIMP4, IL4, KITLG, TGFβ2	1.42e ⁻⁰⁷
3	integrin complex	ITGA5, ITGA9, ITGA4, ITGB1	6.85e ⁻⁰⁷
4	external side of plasma membrane	ITGA5, IFNG, ITGA4, IL13, ITGB1, IL4	1.26e ⁻⁰⁶
5	extracellular region	IFNG, TIMP3, TIMP2, IL13, ITGB1, TIMP4, IL4, KITLG, TGFβ2, APP	5.09e ⁻⁰⁶
6	alpha9-beta1 integrin complex	ITGA9, ITGB1	1.57e ⁻⁰⁵
7	extracellular space	IFNG, IL13, TIMP4, IL4, KITLG, TGFβ2	2.06e ⁻⁰⁵
8	basement membrane	TIMP3, TIMP2, TGFβ2, ITGB1	2.53e ⁻⁰⁵
9	secretory granule	TGFβ2, APP, CTNNA1, ITGB1	6.51e ⁻⁰⁵
10	plasma membrane part	IFNG, ITGA4, CTNNA1, IL13, ITGB1, IL4, ITGA5, ITGA9, APP	8.96e ⁻⁰⁵

Abbreviations: ADAM33, A disintegrin and metalloproteinase; APP, amyloid β (A4) precursor protein; CTNNA1, α-catenin-1; IFNG, interferon-γ; IL13, interleukin-13; IL4, interleukin-4; ITGA4, α₄-integrin; ITGA5, α₅-integrin; ITGA9, α₉-integrin; ITGB1, β₁-integrin; KITLG, KL-1 ligand; TGFβ1, transforming growth factor-β₁; TGFβ2, transforming growth factor-β₂; TIMP2, tissue inhibitor of metalloproteinase-2; TIMP3, tissue inhibitor of metalloproteinase-3; TIMP4, tissue inhibitor of metalloproteinase-4.

^aAnalysis parameters: data: organism: hsapiens, ID type: gene_symbol, ref set: genome, statistic: hypergeometric, significance level: top 10, MTC: BH, minimum: 2.

various types of activities of cells in the lungs, ultimately contributing to the pathogenic features of asthma.

Extracellular matrix and smooth muscle

Molecules in the extracellular matrix regulate changes in smooth muscle cells during asthma pathogenesis.²³ Smooth muscle hyperplasia is a major characteristic of airway hyper-responsiveness.²⁴ TIMPs regulate the activity of the ADAM family of genes during tissue remodeling at different levels, such as transcription and pro-enzyme activation, and during inhibition by endogenous inhibitors. TIMP3 is expressed on the extracellular matrix and controls the level of ADAM33²⁰ and the remaining 2 TIMPs (those predicted by IPA), TIMP2 and TIMP4, also might regulate ADAM33 in same way. The water molecule binding to the catalytic zinc atom of matrix metalloproteinases is cleaved by the bidentate chelated N-terminal amino group and carbonyl group of cysteine-1 of TIMP proteins.²⁵ Through this mechanism, TIMPs might regulate the protease activity of ADAM33, wherein the zinc-bound water molecule is a critical component for the catalytic zinc site to be active.²⁶ Similarly, a study on human airway smooth muscle cells has shown that IFNG downregulates ADAM33 mRNA expression by acting on the promoter region; failing to do so might result in the loss of the inhibitory effect of IFNG on ADAM33, leading to irregularity in migration and proliferation of airway smooth muscle cells.²¹ Protein–protein interaction occurs between ATXN7 and ADAM33, where ATXN7 protein has a role in the regulation of cytoskeletal dynamics.²⁷ The actin cytoskeleton of smooth muscle cells plays an essential role in the regulation and development of mechanical tension and material properties of smooth muscle tissues.²⁸ Thus, the binding between ADAM33 and ATXN7 proteins that was predicted by IPA and GeneMANIA is probably involved in the regulation of the

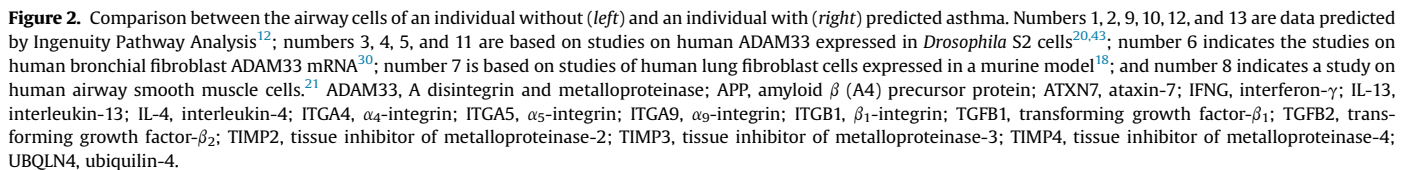
mechanical properties of airway smooth muscle cells that might affect the contraction and relaxation of smooth muscles in airways.

Fibroblasts

Airways are significantly affected by activated fibroblasts and fibrocytes, leading to airway remodeling.²⁹ Expression of ADAM33 is a prime reason for the proliferation of fibroblasts and it leads to bronchial hyperresponsiveness by fibroblast differentiation into myofibroblast and smooth muscles.²⁴ Two cytokines, IL-4 and IL-13, studied using human lung fibroblast cells, regulate the expression of ADAM33 mRNA by binding at the 3' untranslated region in fibroblast cells and activating fibroblast cells. The stimulation of ADAM33 mRNA expression is significantly high when IL-4 and IL-13 activate ADAM33 together compared with stimulation of ADAM33 by IL-4 or IL-13.¹⁸ Similarly, in fibroblasts, the mRNA expression of ADAM33 is decreased by TGFβ2 by promoter histone modification without affecting DNA methylation, which has been reported in a study on human bronchial fibroblast ADAM33 mRNA.³⁰ The expression of growth factor receptors might become impaired during the loss of function of ADAM33⁶ and the lower level of fibroblast growth factors might decrease elastin production.³¹ Abnormal fragmentation and absence of elastic fibers are the reasons for increased lung stiffness³² because the resulting rigidity might increase and the flexibility or stretching capacity of the lung might decrease.

Epithelial cells

Epithelial cell abnormalities, such as epithelial denudation, ciliary destruction, and growth factor and receptor expressions, are the major causes of exacerbation in asthma.³³ Alpha-catenin, a cadherin-associated protein, appears to play a central role in



Matrix metalloproteinases has a remarkable function in the ubiquitylation pathway in which UBQLN4 is a major hub.⁴⁶ UBQLN4 is a ubiquitously expressing protein that is involved in inhibiting proteosomal protein degradation, depending on the

event,^{47,48} because it has low-level expression in the lungs according to the European Bioinformatics Institute expression atlas,⁴⁹ although the lung cells that express this protein have not been identified. The IPA and GeneMANIA tools predict that ADAM33 is found binding with UBQLN4 and this binding might be involved in the peptide degradation of ADAM33 and possibly might regulate the required level of ADAM33 protein in the lungs.

ADAM33 also may be relevant in the expression of specific phenotypes of asthma, such as aspirin-sensitive asthma, through downregulation of APP. According to Zou et al.,²⁰ ADAM33 is involved the downregulation of APP. However, the loss of function of ADAM33, resulting in upregulation of APP, leads to higher expression of fibrous sheath interacting protein 1 gene in the airway epithelium, causing increased inflammation.⁵⁰ In contrast, there is evidence from gastric cancer cell studies showing that vascular endothelial growth factor-D (c-fos–induced growth factor) induced ADAM33 regulates the expression levels of interleukin-18 (IL-18), where pro-IL-18 is converted to mature IL-18 by ADAM33.⁵¹ Interleukin-18 is expressed in the airway epithelium and smooth muscle cells, where excess expression results in inflammation and airway hyperresponsiveness.⁵² Because the interaction among c-fos–induced growth factor, ADAM33, and IL-18 has been identified in different diseased cells, the authors predict that the this interaction also might occur in lung cells, but further experimental evidences are required to disclose the actual interaction among these proteins in the lungs.

Role of microRNAs

MicroRNAs are a group of noncoding RNAs that are approximately 22 nucleotides long, located in exons, introns, or intergenes in the genome, and predominantly silence the target mRNA.⁵³ Through IPA, the authors identified 52 mature miRNA genes that are predicted to be involved in the regulation of ADAM33 activity (eTable 1). Polymorphisms in these miRNAs could significantly alter the expression levels by the deregulation of ADAM33 and may play an important role in the pathogenesis of asthma. Thus, it is necessary to study the activity of these miRNAs to understand the molecular activity of ADAM33 in causing asthma.

In conclusion, ADAM33 is a ubiquitously expressed protein, with widespread extracellular and intracellular interactions, that may be associated with asthma and bronchial hyperresponsiveness. Based on the present study using a system biology approach, the authors observed novel interactions of ADAM33 with TIMP4, ITGA4, ITGA5, ITGA9, APP, UBQLN4, and ATXN7, participating in pathways involving peptidase regulator activity, leukocyte migration, integrin complex, and histone modification. These were identified from IPA and GeneMANIA analysis, and the authors have hypothesized the role of these interactions and their relevance in asthma pathogenesis, which have yet to be confirmed with experiments on various asthma models. Unraveling these complex interactions with ADAM33 would further the understanding of asthma.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.07.009>.

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eTable 1

List of miRNA genes regulating ADAM33 predicted by Ingenuity Pathway Analysis

Serial no	miRNA	SI no	miRNA
1	miR-1182	27	miR-4299
2	miR-122-5p	28	miR-4303
3	miR-1233-3p	29	miR-431-5p
4	miR-1275	30	miR-4314
5	miR-1303	31	miR-4421
6	miR-1913	32	miR-4435
7	miR-1964-5p	33	miR-4487
8	miR-1976	34	miR-4530
9	miR-22-3p	35	miR-4697-3p
10	miR-296-5p	36	miR-4701-5p
11	miR-298-5p	37	miR-4707-5p
12	miR-3103-5p	38	miR-4710
13	miR-3175	39	miR-4715-3p
14	miR-3176	40	miR-4723-5p
15	miR-3194-3p	41	miR-4746-3p
16	miR-3194-5p	42	miR-4757-5p
17	miR-3199	43	miR-4800-5p
18	miR-329	44	miR-484
19	miR-330-5p	45	miR-492
20	miR-3665	46	miR-511
21	miR-3677-5p	47	miR-542-5p
22	miR-3690	48	miR-642a-5p
23	miR-370-3p	49	miR-760-3p
24	miR-3934-5p	50	miR-764
25	miR-4254	51	miR-766-3p
26	miR-4290	52	miR-873-5p