Indian J Med Res 137, March 2013, pp 447-450

Commentary

Unravelling the role of *ADAM 33* in asthma

Asthma, a chronic inflammatory disease of the airways, mediated by a Th2 dependent inflammation is an important cause of morbidity in both children and adults worldwide[1]. It is associated with recurrent bouts of cough and wheezing and some of the main concerns are non-responsiveness to steroids, progressive and accelerated lung function decline in a sub-set of patients[1]. The prevalence of asthma in many countries around the world is around 5 per cent in adults and 10 per cent in children[1]. In a large multicenter study in India, the prevalence of asthma was lower and estimated to be about 2.4 per cent among the Indian adults[2]. The smaller percentage still translates to a huge burden of disease in the community taking into account the population of India.

Asthma is a complex disease which needs significant genetic and environmental interactions for the disease to manifest[3,4]. A large number of genes have been identified to have an association with asthma in case-control, family and twin studies[5,6]. One of the first genes to be discovered in the Caucasian population was *ADAM33* by Eerdewegh *et al* in 2002[7]. Since then, many studies have confirmed the association of *ADAM33* polymorphisms and its association with asthma, though many studies have not been able to replicate the same polymorphisms in different ethnic populations[5]. *ADAM33* polymorphisms have been associated with asthma in the Caucasian, African American, Dutch, US White, US Hispanic, Korean, Japanese, and North Indian but not in Latino, Mexican and south Indian population[8-10].

ADAM 33 is a disintegrin and metalloproteinase glycoprotein[11] involved in intercellular and cell-matrix interactions and plays an important role in both health and disease. In normal subjects, these proteins are involved in fertilization, myogenesis, neurogenesis, inflammatory response and apoptosis[1,12] and exert their role by proteolysis, cleavage or influencing cell adhesion and cell signalling[11]. It could be important for normal lung development in the embryo as the expression of *ADAM 33* can be observed as early as 8-12 wk after gestation[3,11]. It could be involved in determining lung functions throughout life[13]. Several studies have demonstrated an association between *ADAM33* and various features of asthma such as bronchial hyperresponsiveness[14,15], progression of wheezing illness[16], airway remodelling[17,18], lower lung functions[19], accelerated lung function decline[17], higher specific airway resistance in children 3 yr of age[20,21] and in one study, even though subjects used steroids (inhaled and in some cases even oral) regularly, it did not influence *ADAM33* expression suggesting steroid non-responsiveness in these subjects[1]. *ADAM33* has been associated with intermediate asthma phenotypes such as atopy or elevated total and specific serum IgE levels and skin test responsiveness in some studies[12,18] but not in others[16,20]. Identification of *ADAM33* paved the way for recognition of non-atopic mechanisms involving proliferation of fibroblasts and smooth muscles and deposition of matrix proteins causing sub-epithelial fibrosis, leading to airway remodelling, an important mechanism for maintaining disease chronicity and progression (Figure). Airway remodelling is postulated to be due to aberrant communication between airway epithelium and mesenchymal tissue with *ADAM33* playing an important role[22].

Though *ADAM33* is associated with airway remodelling via non-inflammatory mechanisms, it can also promote inflammation via altered ADAM33 protein function leading to impaired or enhanced release of cytokines and growth factors[22]. Interactions between ADAM33 proteins and environmental factors could be important in the pathogenesis of

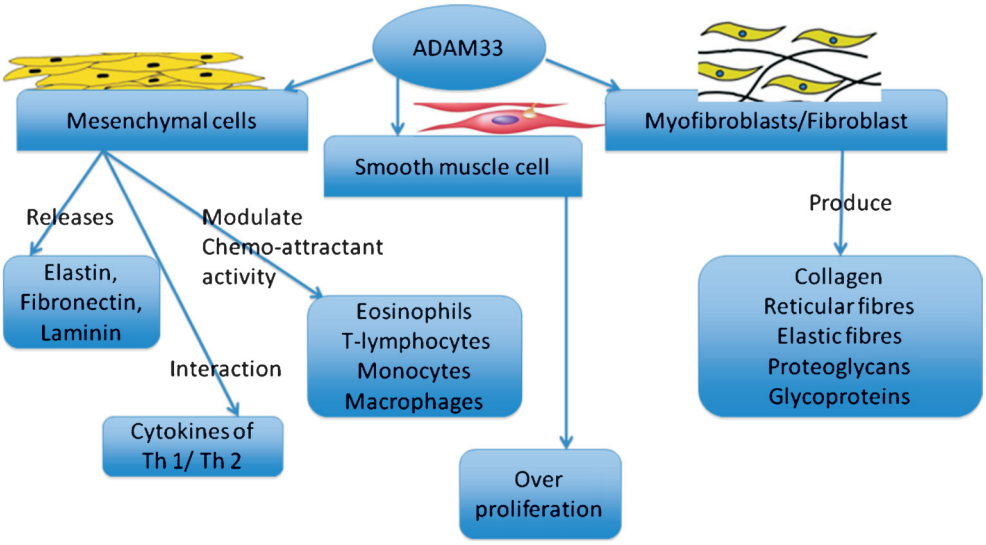

Fig. Key cells influenced by *ADAM33* in airway remodelling in asthma.

asthma[22]. It has been demonstrated that the loss of membrane anchor and regulatory cytoplasmic domain of ADAM33, leads to a soluble form of ADAM33 (sADAM33), that can result in a disease-related gain of function wherein the abnormal localization of the ADAM33 metalloproteases results in inappropriate cleavage of angiogenic substrates to cause increased angiogenesis in the airway wall, contributing to airway wall thickening, one of the key findings in airway remodelling in asthma[23]. This leads to fixed airway obstruction and accelerated lung function decline in patients with asthma[23].

There is a change in the perception that airway remodelling from being due to long-term uncontrolled chronic inflammation, seen only in adults, to being programmed *in utero* in the foetus and in young children even before they develop symptoms of asthma[22,24]. ADAM33 is ubiquitously expressed in the foetal tissue and is one of the prime candidates for these changes in the foetal lungs[22]. In the normal foetus, *ADAM33* is likely to be responsible for epithelial mesenchymal cross talk, branching of the airways and differentiation of the cells in the lungs[25]. Multiple single nucleotide polymorphisms in *ADAM33* have been identified as being associated with asthma and it has been observed that combinations of SNPs confer a higher risk of asthma than single polymorphisms[7,22]. Subjects with both moderate and severe asthma have shown an increased expression of *ADAM33* mRNA in endobronchial biopsy specimens as compared to normal subjects and subjects with mild asthma[1].

Though *ADAM33* located on chromosome 20p13 was identified to be important in asthma pathogenesis a decade ago, there is a need for concerted effort to elucidate its full implications, including its role in normal physiology, which is still unclear. The key reason for this is the complexity of the gene itself with multiple SNPs having been associated with asthma. Unravelling the *ADAM33* would necessitate completely mapping all the SNPs in that gene region in all ethnic populations of the world, understanding the role of each SNP in health and disease, effect of these SNPs on gene transcription and resultant changes in the protein structure, protein levels and conformational changes in the tertiary protein structure that could potentially affect its functioning, thus leading to disease. It is also observed that alternative splicing could lead to different proteins with loss of or altered functions[22]. Studies have demonstrated that the downstream effects of the SNPs are complex and may not be related to simple gain or loss of function of ADAM33 proteins[1,3,13,26] since the amount of protein seems to be similar in bronchial biopsies of both asthmatic subjects and normal controls[3]. In addition, the role of other ADAMs such as *ADAM8* which has been identified to be important in asthma[1] and its interactions with *ADAM33* need to be evaluated. Finally, all the potential interactions between other related pathways in asthma and *ADAM33* may need to be studied in a systematic manner using a systems biology approach which will explain differential responses in different individuals and populations.

In this issue, Tripathi *et al*[27] have demonstrated the presence of *ADAM33* protein not only in the airway smooth muscle and mesenchymal cells but also in the airway epithelium, which is an important finding. Earlier studies has demonstrated that *ADAM33* is expressed in fibroblasts and smooth muscle cells but not in airway epithelium[7,22] and only a few studies have demonstrated that *ADAM33* is expressed in the airway epithelium[1]. Higher expression of both isoforms of ADAM 33 proteins have been demonstrated in the airway smooth muscle, but not in airway epithelium[22]. Though the study by Tripathi *et al*[27] has multiple limitations, it is a step in the right direction for unravelling the complex role of *ADAM33* in asthma. The key limitations include, small sample size, paucity of controls, selection bias in including both cases and controls for the study as both cases and controls had additional co-morbidities other than asthma which could have confounded the results and the majority of the subjects were smokers. No significant difference was observed between moderate and persistent asthma, which could be due to low sample size. They observed a higher expression of *ADAM33* protein in the asthmatic airway epithelium and smooth muscle cells as compared to controls. The role of *ADAM33* in the airway epithelium and its role in the pathogenesis of asthma need to be further elucidated. With impaired epithelial barrier function identified as one of the key factors in the initiation of asthma[20], the presence of *ADAM33* in the airway epithelium warrants further research into its role in epithelial barrier function in health and disease. Further, study in *ADAM33* proteins should expand into identifying the isoforms and splice variants and functional assays of these proteins need to be performed. In this era of biomarker discovery, whether total or different isoforms of *ADAM33* protein levels could be an important biomarker to determine susceptibility for asthma in children and adults, accelerated decline in lung functions, airway remodelling and poor steroid responsiveness make an exciting field for future research.

Acknowledgment

The author thanks Ms. Sangeetha V. for help in preparing the Figure.

Mahesh P.A.
Department of Pulmonary Medicine
JSS Medical College, JSS University
Mysore 570 004, India
mahesh1971in@yahoo.com

References

1. Foley SC, Mogas AK, Olivenstein R, Fiset PO, Chakir J, Bourbeau J, *et al*. Increased expression of *ADAM33* and *ADAM8* with disease progression in asthma. *J Allergy Clin Immunol* 2007; *119* : 863-71.
2. Aggarwal AN, Chaudhry K, Chhabra SK, D'Souza GA, Gupta D, Jindal SK, *et al*. Prevalence and risk factors for bronchial asthma in Indian adults: a multicentre study. *Indian J Chest Dis Allied Sci* 2006; *48* : 13-22.
3. Haitchi HM, Powell RM, Shaw TJ, Howarth PH, Wilson SJ, Wilson DI, *et al*. *ADAM33* expression in asthmatic airways and human embryonic lungs. *Am J Respir Crit Care Med* 2005; *171* : 958-65.
4. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev* 2011; *242* : 10-30.
5. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008; *8* : 169-82.
6. Bijanzadeh M, Mahesh PA, Ramachandra NB. An understanding of the genetic basis of asthma. *Indian J Med Res* 2011; *134* : 149-61.
7. Van Eerdewegh P, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J, *et al*. Association of the *ADAM33* gene with asthma and bronchial hyperresponsiveness. *Nature* 2002; *418* : 426-30.
8. Awasthi S, Tripathi P, Ganesh S, Husain N. Association of *ADAM33* gene polymorphisms with asthma in Indian children. *J Hum Genet* 2011; *56* : 188-95.
9. Hirota T, Hasegawa K, Obara K, Matsuda A, Akahoshi M, Nakashima K, *et al*. Association between *ADAM33* polymorphisms and adult asthma in the Japanese population. *Clin Exp Allergy* 2006; *36* : 884-91.
10. Bijanzadeh M, Ramachandra NB, Mahesh PA, Mysore RS, Kumar P, Manjunath BS, *et al*. Association of IL-4 and *ADAM33* gene polymorphisms with asthma in an Indian population. *Lung* 2010; *188* : 415-22.
11. Blakey J, Halapi E, Bjornsdottir US, Wheatley A, Kristinsson S, Upmanyu R, *et al*. Contribution of *ADAM33* polymorphisms to the population risk of asthma. *Thorax* 2005; *60* : 274-6.
12. Howard TD, Postma DS, Jongepier H, Moore WC, Koppelman GH, Zheng SL, *et al*. Association of a disintegrin and metalloprotease 33 *(ADAM33)* gene with asthma in ethnically diverse populations. *J Allergy Clin Immunol* 2003; *112* : 717-22.
13. Holgate ST, Davies DE, Powell RM, Holloway JW. ADAM33: a newly identified protease involved in airway remodelling. *Pulm Pharmacol Ther* 2006; *19* : 3-11.
14. Holgate ST, Davies DE, Murphy G, Powell RM, Holloway JW. *ADAM 33*: just another asthma gene or a breakthrough in understanding the origins of bronchial hyperresponsiveness? *Thorax* 2003; 58 : 466-9.
15. Lee JH, Park HS, Park SW, Jang AS, Uh ST, Rhim T, *et al*. *ADAM33* polymorphism: association with bronchial hyper-responsiveness in Korean asthmatics. *Clin Exp Allergy* 2004; *34* : 860-5.
16. Blakey JD, Sayers I, Ring SM, Strachan DP, Hall IP. Positionally cloned asthma susceptibility gene polymorphisms

and disease risk in the British 1958 Birth Cohort. *Thorax* 2009; *64* : 381-7.

17. Jongepier H, Boezen HM, Dijkstra A, Howard TD, Vonk JM, Koppelman GH, *et al*. Polymorphisms of the *ADAM33* gene are associated with accelerated lung function decline in asthma. *Clin Exp Allergy* 2004; *34* : 757-60.
18. Kedda MA, Duffy DL, Bradley B, O'Hehir RE, Thompson PJ. *ADAM33* haplotypes are associated with asthma in a large Australian population. *Eur J Hum Genet* 2006; *14* : 1027-36.
19. Lee JY, Park SW, Chang HK, Kim HY, Rhim T, Lee JH, *et al*. A disintegrin and metalloproteinase 33 protein in patients with asthma: Relevance to airflow limitation. *Am J Respir Crit Care Med* 2006; *173* : 729-35.
20. Holloway JW, Yang IA, Holgate ST. Genetics of allergic disease. *J Allergy Clin Immunol* 2010; *125* (2 Suppl 2): S81-94.
21. Simpson A, Maniatis N, Jury F, Cakebread JA, Lowe LA, Holgate ST, *et al*. Polymorphisms in a disintegrin and metalloprotease 33 *(ADAM33)* predict impaired early-life lung function. *Am J Respir Crit Care Med* 2005; *172* : 55-60.
22. Cakebread JA, Haitchi HM, Holloway JW, Powell RM, Keith T, Davies DE, *et al*. The role of *ADAM33* in the pathogenesis of asthma. *Springer Semin Immunopathol* 2004; *25* : 361-75.
23. Puxeddu I, Pang YY, Harvey A, Haitchi HM, Nicholas B, Yoshisue H, *et al*. The soluble form of a disintegrin and metalloprotease 33 promotes angiogenesis: implications for airway remodeling in asthma. *J Allergy Clin Immunol* 2008; *121* : 1400-6, 6 e1-4.
24. Payne DN, Rogers AV, Adelroth E, Bandi V, Guntupalli KK, Bush A, *et al*. Early thickening of the reticular basement membrane in children with difficult asthma. *Am J Respir Crit Care Med* 2003; *167* : 78-82.
25. Black JL, Johnson PR. Factors controlling smooth muscle proliferation and airway remodelling. *Curr Opin Allergy Clin Immunol* 2002; *2* : 47-51.
26. Drazen JM, Weiss ST. Genetics: inherit the wheeze. *Nature* 2002; *418* : 383-4.
27. Tripathi P, Awasthi S, Husain N, Prasad R, Mishra V. Increased expression of *ADAM 33* protein in asthmatic patients as compared to non-asthmatic controls. *Indian J Med Res* 2013; *137* : 507-14.