The discovery and role of *ADAM33*, a new candidate gene for asthma

John W. Holloway, Donna E. Davies, Robert Powell, Hans-Michael Haitchi, Tim P. Keith and Stephen T. Holgate

Asthma is a complex disorder in which major genetic and environmental factors interact to initiate the disease and propagate it as a chronic relapsing disorder. Until recently, genetic factors implicated in the disease pathogenesis have been restricted to variants in known molecules involved in the inflammatory or remodelling pathways. This review discusses evidence for a new susceptibility gene for asthma, *ADAM33*, which was identified by positional cloning and shown to be selectively expressed in mesenchymal but not immune or inflammatory cells. ADAM33 belongs to a family of membrane-anchored metalloproteinases that also have fusagenic, adhesion and intracellular signalling properties. ADAM33 might play a key role in predisposing to the reduced lung function characteristic of asthma, possibly by influencing airway wall remodelling.

Asthma is a disorder of the conducting airways in which the inflammation mediated by T helper 2 (Th2) cells interacts with structural changes to cause variable airflow obstruction (Ref. 1). It is a serious global health problem with over 100 million people affected worldwide, and the prevalence is increasing, especially among children (Refs 2, 3). Careful epidemiological studies have identified

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several risk factors for the development of asthma in children, including genetic susceptibility, maternal smoking, exposure to a Western lifestyle and urban environment, allergen exposure and obesity.

How these very different factors translate themselves into clinical asthma is an area of much research interest. It is clear that in addition to inflammation these factors contribute to the structural changes characteristic of asthma, including epithelial mucous metaplasia, increase in smooth muscle, vasculogenesis and neurite development, as well as the deposition of matrix proteins. Together, these lead to thickening of the airway walls. Fundamental to disordered airway function is the concept of bronchial hyper-responsiveness (BHR), in which the airways constrict too much and too easily to a range of stimuli. In chronic severe asthma, the inflammation and structural changes both become more intense (Ref. 4) and are paralleled by an increase in BHR that is only partially or is nonresponsive to treatment with corticosteroids (Ref. 5). Morphometric studies have shown an increase in smooth muscle mass in proportion to disease severity, and computer modelling has revealed that a combination of airway wall thickening and altered contractility are the most plausible explanations for BHR, particularly corticosteroid-insensitive BHR (Refs 6, 7).

Airway re/pre-modelling in asthma

It is well established that both for the early phenotype of wheezing in young children and for later atopic asthma, both baseline airway function and bronchial responsiveness measured in the newborn period (and hence dependent on fetal lung development) are significant predictors of asthma (Ref. 8). Recent evidence from an Australian cohort has shown that, independent of allergic sensitisation, BHR in newborns is a predictor of the subsequent development of asthma (Ref. 9), and in 'high-risk infants' BHR becomes fully developed by 6 months of age (Ref. 10). There might also be an important interaction between atopy [a genetically determined state of increased generation of immunoglobulin (Ig) E against common environmental allergens] and lung development, as shown by a recent study of a clear relationship between early lung function [specific airways resistance (sR_{AW}) measured at age 3 years] and a child's risk of atopy (Ref. 11).

These early alterations in lung function result from the interaction of environmental factors with the developing lung, which, in susceptible individuals, could lead to structural changes in the airways. This hypothesis is supported by the recent observation that thickening of the lamina reticularis in bronchial biopsies from young children is present at the start of asthma in early childhood and several years before the disease becomes clinically manifest (Ref. 12). Studies in nonhuman primates have shown that prenatal exposure to nicotine causes collagen deposition around the large airways (Ref. 13), whereas exposure to dust-mite allergens results in sub-basement membrane thickening and a large increase in smooth muscle associated with BHR that persists for up to two years after allergen exposure is withdrawn (Refs 14, 15).

The observation that environmental agents impact on the bronchial epithelium and that structural remodelling is associated with tissue injury has led to a study of these processes with the following conclusions. First, susceptibility of the asthmatic bronchial epithelium to oxidant stress is greater than normal, as revealed by the occurrence of premature apoptosis, and reflects a fundamental difference that has potential to translate gene–environment interactions (Ref. 16). It is suggested that this increased susceptibility results from a reduced ability of the epithelium to protect itself against oxidative insults, leading to mitochondria-triggered activation of caspases 8 and 9. Second, epithelial repair in asthma is prolonged as a result of impaired epithelial proliferation caused by an imbalance of cell cyclins and their inhibitors, specifically $p21^{WAF}$ (Ref. 17). Third, consequential to impaired primary repair, the altered epithelium communicates with the underlying mesenchyme to form an 'epithelial–mesenchymal trophic unit' (EMTU) that propagates and amplifies remodelling events from the epithelial surface to the submucosa through activation of subepithelial effector fibroblasts, resulting in their conversion to more-active myofibroblasts (Ref. 18). Fourth, through cell-surface molecules and mediator secretion, the EMTU favours localisation of Th2-mediated inflammation, enabling interleukin (IL)-4 and IL-13 to work in concert with the EMTU to maintain and amplify remodelling and inflammatory processes (Ref. 19).

This new concept of asthma helps explain: why in chronic persistent disaease there is incomplete

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disease resolution with corticosteroids; why in moderate or severe disease, inhaled long-acting β-agonists are more effective than increasing the dose of inhaled corticosteroids and even then resolution is often incomplete; and why, beyond atopy, a range of locally acting environmental factors (passive tobacco smoke exposure, air pollutants, enzymically active allergens and virus infections) are important risk factors for the development and consolidation of this disease. Similar mechanisms involving reciprocal signalling between epithelial and mesenchymal cells are being advanced to explain other chronic human diseases, including fibrosing alveolitis, chronic atopic dermatitis, alcohol-induced liver cirrhosis, multiple sclerosis and chronic glomerulonephritis.

It follows that Th2-mediated inflammation and activation of the EMTU might be parallel rather than sequential events, each interacting with the other and each varying between patients and across time. In this context, the asthmatic airway could be considered as a chronic wound where there are cycles of injury and impaired repair and, as a consequence, tissue restructuring and persistent inflammation.

The genetic basis of asthma

Asthma has a high heritability of up to 75% (Ref. 20), involving a few genes with moderate effects rather than many genes with small effects (Ref. 21). Asthma can be termed a complex genetic disease in that there are multiple genetic effects that interact with the environment to modify both susceptibility and severity of the disease (Ref. 22). Family-based studies of asthma have identified that in addition to a genetic predisposition to atopy, which alters susceptibility to asthma as well as other allergic disorders, there are also genetic effects that relate solely to asthma and possibly regulate susceptibility of the lung to both allergic- and other environmental induced inflammation. Linkage studies have led to the identification of candidate regions for asthma genes, and polymorphisms associated with disease phenotypes have been detected in candidate genes (Ref. 22).

Although it is clear that asthma results from the interaction between environmental and genetic factors, the contribution of environmental factors has proven difficult to define because cohorts with extensive environmental exposure data are not available for genetic analysis, there are problems in defining and quantifying exposure, and most studies have lacked statistical power. However, a recent study in a Chinese population that identified an interaction between cigarette smoking and β_2-adrenoceptor genotype in determining susceptibility to asthma (Ref. 23) indicates the importance of investigating both genetic and environmental factors in the same cohort. This approach has already revealed subphenotypes that utilise the lipopolysaccharide receptor CD14 in manifesting atopy and asthma (Ref. 24). The identification of T-cell immunoglobulin mucin 1 (TIM-1) protein – a critical determinant in the differentiation of T cells into a Th2 phenotype – as the receptor for hepatitis A virus (Ref. 25) might also explain the powerful protective effect that this infection has on atopy and asthma (Ref. 26).

ADAM33 as an asthma-susceptibility gene

We have recently reported the first novel asthma-related gene identified by positional cloning (Ref. 27) (Fig. 1). In a five-year collaboration with Genome Therapeutics Corporation (Waltham, MA, USA) and Schering Plough (Kenilworth, NJ, USA), a genome-wide screen using multipoint linkage analysis and 401 microsatellite markers at a density of 9 cM has been undertaken involving 362 families from the UK and 98 from the USA with at least two siblings with asthma. For physician-diagnosed asthma, suggestive evidence of linkage [maximum lod score (MLS) of 2.24] was found on chromosome 20 at 9.99 cM. The addition of 13 more markers at 1–2 cM increased the MLS to 2.94 at D20S482 (12.1 cM), and this further increased to 3.93 when BHR was included in the definition of asthma, thereby exceeding the threshold for genome-wide significance (Ref. 28). By contrast, when asthma was included as a diagnosis only in the presence of elevated serum total IgE or allergen-specific IgE, the MLS fell to 2.3 at 11.6 cM and 1.87 at 12.1 cM, respectively, suggesting the presence of a gene(s) more closely linked to altered airway function than to allergic inflammation per se. Confirmation of chromosomal linkage to asthma and BHR on 20p13 has come from separate analysis of the UK and US families (Ref. 27), and from separate genome-wide studies in other US outbred populations (Ref. 29).

Physical mapping and direct cDNA selection identified 40 genes in the region under the peak of linkage at 20p13 (Ref. 27). Single-strand

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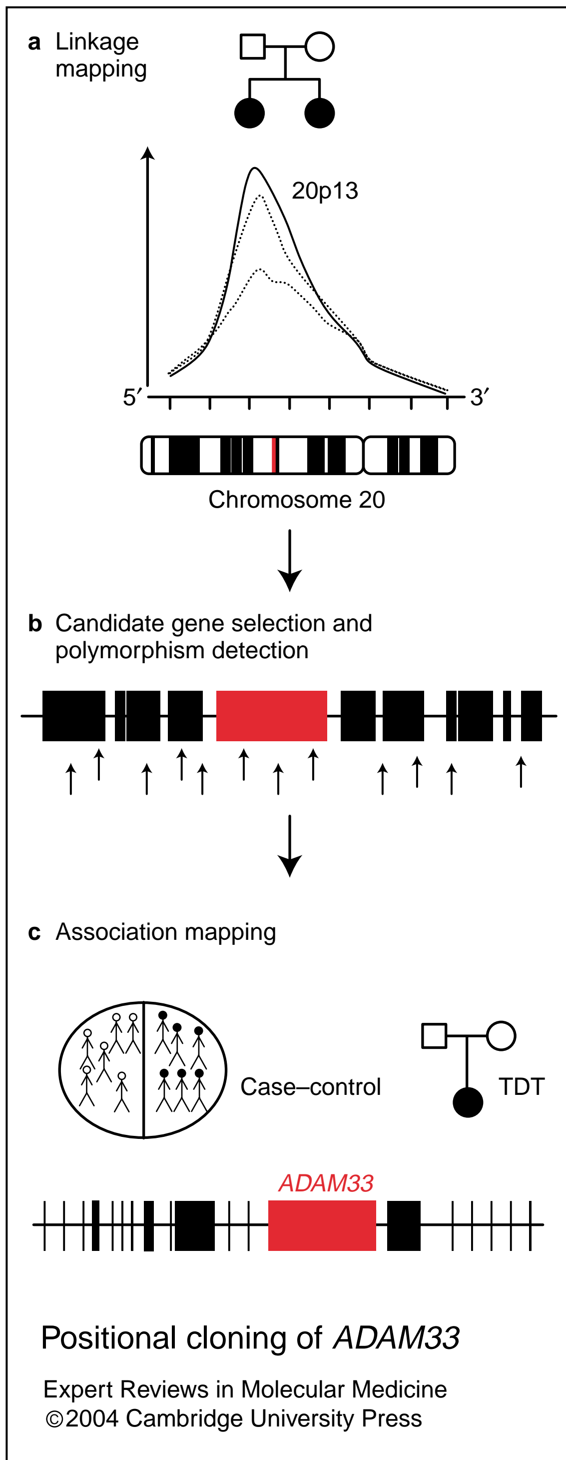

Figure 1. Positional cloning of *ADAM33*. *(See next column for legend.)*

Figure 1. Positional cloning of *ADAM33*. (a) Microsatellite linkage analysis involving 460 asthma-enriched families led to the identification of a region on chromosome 20p13 that linked to asthma and bronchial hyper-responsiveness. [The dotted lines represent asthma in which high total IgE (upper dotted line) or allergen-specific IgE (lower dotted line) was also present.] (b) Subsequent fine mapping and cloning of overlapping segments of DNA underlying this region into bacterial artificial chromosomes followed by sequencing and gene identification led to the selection of 29 candidate genes; these were then typed for single-nucleotide polymorphisms (SNPs; represented by arrows). c) The SNPs were used in case–control studies and transmission disequilibrium tests (TDTs) (in association studies) to locate the gene most likely to account for the linkage to asthma, thereby identifying *ADAM33*.

conformation polymorphism (SSCP) analysis and direct sequencing was used to identify single-nucleotide polymorphisms (SNPs) in association studies involving 130 identical-by-descent affected individuals and 217 hypernormal controls. In 23 genes spanning a 90% confidence interval around the microsatellite marker D20S482, 105 SNPs were typed, of which 25 localised to a cluster of five genes showing significant association with both asthma and BHR. Fourteen of these SNPs lay within a single gene identified as *ADAM33*, a novel member of the ADAM (for 'a disintegrin and metalloprotease') family, achieving a significance of $P = 0.005–0.05$. Both in the combined populations and in the UK and US samples when analysed separately, additional SNP typing strengthened the location of the signal to *ADAM33* and this was further confirmed both by haplotype analysis (5–7 SNP combinations at $P = 0.000001–0.005$) and transmission disequilibrium testing (10 SNP combinations at $P < 0.005$). Because the alleles on the *ADAM33* gene that conferred increased risk of developing asthma and BHR were so common, their effects translate into a substantial population attributable risk for having asthma (Ref. 27). Replication of the association between *ADAM33* SNPs and asthma has been seen in studies of African American, Hispanic and US Caucasian outbred populations, as well as a Dutch (Ref. 30), two German (Ref. 31) and Korean (Ref. 32) populations (Table 1). However, a study by Lind et al. (Ref. 33) has failed to demonstrate association of *ADAM33* SNPs and asthma pathogenesis in US Puerto Ricans and Mexicans – although BHR, a phenotype that showed the strongest association with *ADAM33* SNPs in most of the positive studies, was not measured. The

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Table 1. Summary of single nucleotide polymorphisms (SNPs) associated with asthma or its partial phenotypes in different populations

Study	SNPs[a]	Ref.
Van Eerdewegh et al.		
(Case–control)		
UK (*n* = 362 sib pairs)	F+1, Q–1, S1, S2, ST+4, V–1, V4	27
US (*n* = 98 sib pairs)	I1, L–1, M+1, T1, T2, T+1	
Combined (UK + US)	Q–1, S1, ST+4, ST+7, V–1, V4	
Howard et al.		
African Americans (*n* = 160)[b]	S2, ST+4, V4	30
White (*n* = 219)	S2, T1, T2	
Hispanic (*n* = 112)	S2 , ST+4, T1, T2, V–1	
Dutch (*n* = 153)	S1, S2, ST+7, V4	
Werner et al.		
German families (*n* = 732)	F+1, ST+4, ST+5	31
Case–control (*n* = 590)	ST+7	
Simpson et al.		
Low lung function; children aged 3 and 5 years[c] (*n* = 302 and 504, respectively)	F+1, Q–1, M+1, T1, T2, ST+5, ST+5, V–1	39
Lee et al.		
Korea (*n* = 326)	T1	32
Jongepier et al.		
Dutch 20-year decline in lung function (*n* = 200)	S–2, T–1, T–2, V–4	40

[a] The SNP designations are derived from the exon labelling (see Fig. 2).
[b] Number of cases matched by similar number of normal controls.
[c] Children born of atopic and asthmatic parents.

significance of *ADAM33* for asthma is strengthened by the existence of a syntenic region on mouse chromosome 2 at 74 cM that has been linked to BHR (Ref. 34), overlying an orthologue of *ADAM33* that exhibits approximately 70% homology with its human counterpart (Ref. 35).

ADAM33 comprises 22 exons, which, when spliced together as the full-length molecule, generate a protein with eight domains (discussed further below) (Fig. 2). The *ADAM33* gene contains at least 55 SNPs, many of which are in introns and in the 3' noncoding region (V) (Fig. 3). The 3' noncoding region has an important role in modifying intracellular processing of ADAM33 RNA (Ref. 36). Altogether, seven SNPs lead to amino acid changes. The L1 SNP (Ala395Val) in the catalytic domain would likely alter substrate specificity, and the F1 SNP (Thr178Ala) would influence the function of a cysteine residue that affects access to the active site (Ref. 37). The individual SNPs that have so far been reported to be associated with asthma or its partial phenotypes are presented in Table 1. At present it is not known which SNP(s) are responsible for susceptibility to disease expression since there is considerable linkage disequilibrium between them (Refs 27, 30).

ADAM33 and early-life origins of asthma

Recent findings published in abstract form suggest ADAM33 mutations might predispose to altered lung function in early infancy. *ADAM33* SNPs correlated with lung function measured at age 3 years in a cohort of children from Manchester, UK (the MAAS Study) (Ref. 38). Seventeen SNPs spanning 11 kb of the *ADAM33* gene were analysed in 302 children from a prospective birth cohort in which respiratory questionnaires and measurements of lung function (sR_{AW}) were completed at age 3 years.

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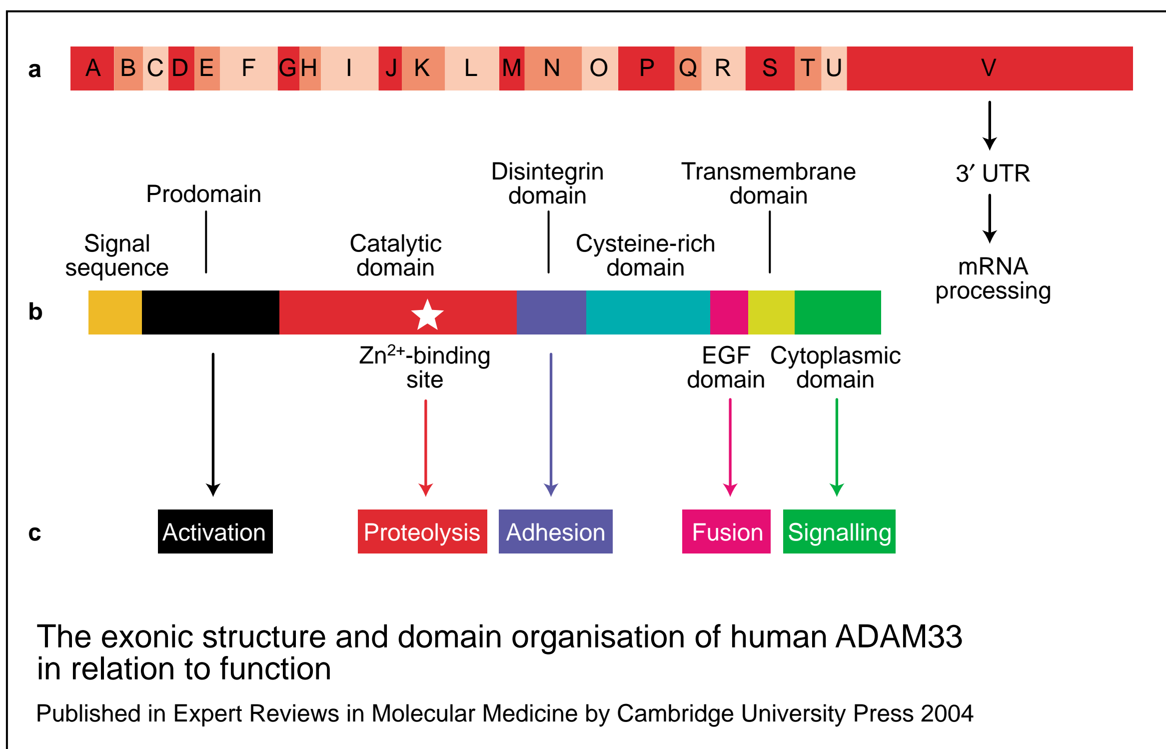

Figure 2. The exonic structure and domain organisation of human ADAM33 in relation to function. (a) The *ADAM33* gene comprises 22 exons, labelled A–V. (b) The encoded protein has eight domains: the signal sequence and pro-, catalytic, disintegrin, cysteine-rich and epidermal growth factor domains, a transmembrane domain that anchors the protein to the cell surface, and a cytoplasmic domain with signalling functions. The 3' noncoding region has an important role in modifying intracellular processing of ADAM33 RNA. (c) ADAM proteins have diverse functions that reflect the complex domain structure of these molecules, including proteolysis, adhesion, fusion and signalling. Adapted from *Nature* (Ref. 27; Copyright © 2002, Macmillan Publishers Ltd).

Here was a significant association between sR_{AW} and six SNPs (V–1, Q–1, ST+7, F+1, T1 and T2) in *ADAM33*. In all cases it was the rare allele that was associated with a higher sR_{AW} value and therefore poor lung function. Analysing the same SNPs in 504 of the original MAAS cohort when the children had reached 5 years of age showed persistence of statistical association between F+1, V–1 and T2 SNPs and sR_{AW} that was lost after administration of a bronchodilator, suggestive of a link to responsiveness of smooth muscle (Ref. 39). These data support the hypothesis that impaired early-life lung function is in part a genetically determined trait involving *ADAM33* that might increase the risk of chronic asthma.

ADAM33 SNPs as a predictor of severe and progressive asthma

Recent epidemiological studies support a role for ADAM33 as a susceptibility gene for more-severe and progressive disease. In 200 asthmatics in The Netherlands, in whom longitudinal data on asthma and FEV_1 (forced expiratory volume in 1 s) was available over a 20-year period, investigation of nine SNPs of *ADAM33*, controlled for other variables such as atopy and smoking, showed that four (S–2, T–1, T–2 and V–4) were significantly associated with a progressive decline in FEV_1 when compared with normal controls, giving an excess decline in FEV_1 for individuals homozygous for the rare allele of 23.7–30.0 ml/year (Ref. 40).

ADAM33 function

The ADAM33 protein

ADAM33 is the most recently reported member of the *ADAM* gene family encoding Zn^{2+}-dependent matrix metalloproteinases (MMPs). ADAM proteins have a complex organisation involving eight domains: the signal sequence and pro-, catalytic, disintegrin, cysteine-rich and EGF

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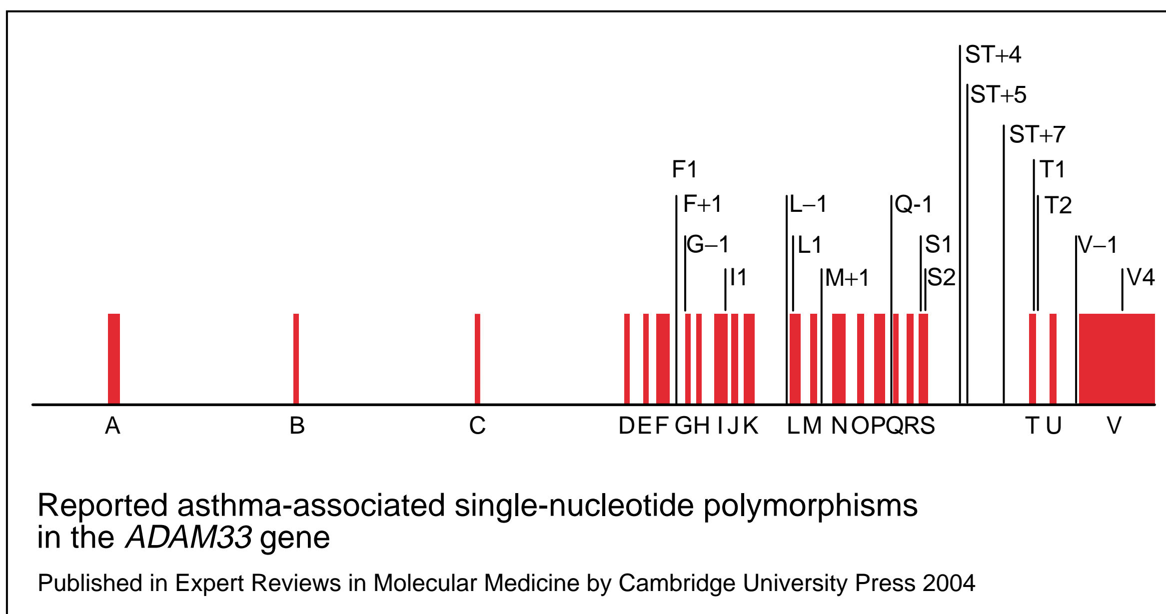

Figure 3. Reported asthma-associated single nucleotide polymorphisms in the *ADAM33* gene. Exons (labelled A–V)and introns of the *ADAM33* gene are shown. The single-nucleotide polymorphisms (SNPs) that have been associated with asthma and bronchial hyper-responsivenes are marked; for further details see Table 1. Adapted from *Nature* (Ref. 27; Copyright © 2002, Macmillan Publishers Ltd).

domains (Ref. 41), a transmembrane domain that anchors the protein at the cell surface, and a cytoplasmic domain with sequences involved in signalling. ADAM proteins have diverse functions that reflect the complex domain structure of these molecules (Ref. 34). Although certain functions can be attributed to an individual domain [e.g. ectodomain shedding to the metalloproteinase domain (Ref. 42) and cell adhesion to the disintegrin domain (Ref. 43)], it is likely that the other domains play important regulatory roles in these functions by conferring specificity and selectivity. ADAM33 belongs to the ADAM12, ADAM15, ADAM19 and ADAM28 subfamily. Members of this family have been shown to possess proteolytic activity (i.e. sheddase activity) for heparin-binding epidermal growth factor (ADAM12), insulin-like growth factor binding protein 3 and 5 as well as fibronectin (ADAM9), and tumour necrosis factor α (TNF–α) (ADAM17) (Refs 41, 44). However, when Zhou et al. (Ref. 45) examined the capacity of human ADAM33 to cleave a wide range of substrates, only 4 out of 39 were cleaved – stem cell factor (SCF, c-kit), β-amyloid precursor protein (APP), TNF-related activation-induced cytokine (TRANCE) and insulin B – and with kinetics suggesting that these might not be the natural substrates. In a cell-based transfection assay, ADAM33 was also shown to exert sheddase activity, but its natural substrates have yet to be identified.

The ADAM33 catalytic domain has recently been crystallised and its three-dimensional structure determined using Marimastat, a nonspecific MMP inhibitor, to aid in the generation of appropriate crystals (Ref. 37). The catalytic site shares the typical features of other MMPs with a Zn^{2+}-binding site, but differs in structure at the entrance of the substrate pocket, suggesting the possibility of developing selective active-site inhibitors (Ref. 37). Indeed, the overall amino acid homology of ADAM33 with ADAM17 (TACE) is only 27%, with most of the differences at the entrance to the catalytic site. In addition, ADAM33 shares with some, but not all, ADAMs a Ca^{2+}-binding site that helps stabilise the tertiary structure. The inhibitor profile of ADAM33 reveals that the substrate-binding pocket of its active site shares some similarities with but also has some distinct features from those of other MMPs (Ref. 45). For example, of the naturally occurring tissue inhibitors of metalloproteinases (TIMPs), TIMP-3 and -4 were highly active, TIMP-2 much less so and TIMP-1 not at all. This appears to be a unique inhibitory profile not reported with other members of the ADAM family (Ref. 45).

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ADAM33 gene expression

The *ADAM33* gene contains the canonical splice sequence (CT/AG) at each of its splice junctions. Northern blot analysis has identified two transcripts of *ADAM33*, of 5.0 and 3.5 kb; the 5 kb is 2–5-fold more abundant than the 3.5 kb transcripts (Ref. 36) but only the latter has been found in cytoplasmic RNA (Ref. 27). In situ hybridisation using antisense *ADAM33* probes has shown that *ADAM33* is preferentially expressed in smooth muscle, myofibroblasts and fibroblasts of asthmatic airways, but is not expressed in epithelium, endothelium, T cells or inflammatory leukocytes (Ref. 36). Using an antibody directed to the intracellular domain we have also shown expression of ADAM33 protein is restricted to airway mesenchymal cells (Refs 27, 36). The *ADAM33* gene is expressed during embryonic development in the mouse (Ref. 46), with preliminary studies revealing that transcripts are present in embryonic lungs at the start of branching morphogenesis, increase with gestation and remain present into adulthood (Ref. 47).

Alternatively spliced forms of ADAM33 have been identified in lung-derived cDNA, and protein variants have been detected – at least six of which lack the proteolytic domain (Ref. 48). One of the splice variants of ADAM33 is predicted to generate a soluble form (Ref. 48). For mouse ADAM33, alternative splicing impacts on the intracellular processing of the protein (Ref. 49). Although ADAM proteins are normally anchored in the trans-Golgi network or plasma membrane, in some cases secreted splice variants have been identified. Interestingly, in the case of ADAM 12, an evolutionarily close relative of ADAM33, ectopic expression of the secreted form of the molecule (ADAM12S) in rhabdomyosarcoma cells results in growth of tumour xenografts that are infiltrated with large numbers of host-derived smooth muscle cells (Ref. 50).

ADAM33 in asthma

The selective expression of *ADAM33* in mesenchymal cells of asthmatic airways strongly suggests that alterations in its activity might underlie abnormalities in the function of airway smooth muscle cells and fibroblasts linked to BHR and remodelling in asthma.

One function relevant to this is the ability of ADAM33 to serve as a cell surface 'sheddase' to release growth factors and modify cell-surface receptor expression (Fig. 4). As indicated above, two asthma-associated SNPs of interest are L1 (Ala395Val) in the catalytic domain, which is predicted to influence substrate binding, and F1 SNP (Thr178Ala), which is sited next to a cysteine residue (Cys179) influencing access to the active site of the enzyme and could affect proteolytic activity (Ref. 37). However, other functions of this unique molecule could be of equal importance in translating its asthmagenic potential; for example, it might act as a dominant negative regulator (through the active site of the proteinase), fusagen (through the cysteine-rich and EGF domains) or an enhancer of a mesenchymal cell migration (through the disintegrin domain) (Fig. 4).

ADAM33 function might be linked to the action of transforming growth factor β (TGF-β) (and related bone morphogenetic proteins), whose release from bronchial epithelial cells is increased in response to damage; TGF-β increases ADAM33 expression transiently as part of the differentiation trajectory of the common fibroblastic progenitor (primitive mesenchymal cells) of components of the EMTU to myofibroblasts, which are believed to be important in chronic wound repair (Refs 17, 18, 51, 52, 53). In this context, the highest level of ADAM33 mRNA observed by in situ hybridisation of a range of mesenchymal cells and tissues was in the granulation areas of a duodenal ulcer where myofibroblasts were plentiful in driving a repair response, supporting the idea that ADAM33 is strongly upregulated within injured/repairing tissue (Ref. 36). Relating to this observation, asthmatic (myo)fibroblasts are unusual in that they have the capacity to proliferate in the absence of exogenous growth factors (Ref. 18) and in this way are similar to asthmatic smooth muscle cells in vitro (Ref. 54).

As discussed above, expression studies have shown *ADAM33* expression in the lung during embryogenesis. It is thus possible to speculate that ADAM33 functions in lung growth and development in utero, and that altered *ADAM33* gene function might alter lung morphogenesis before birth to lead to altered responsiveness of airways and increased risk of asthma.

Concluding comments

Applying genetics to a complex disease such as asthma is beginning to realise its potential. In addition to *ADAM33*, novel candidate genes that have been discovered from positional cloning efforts include *PHF11* on chromosome 13q14, the

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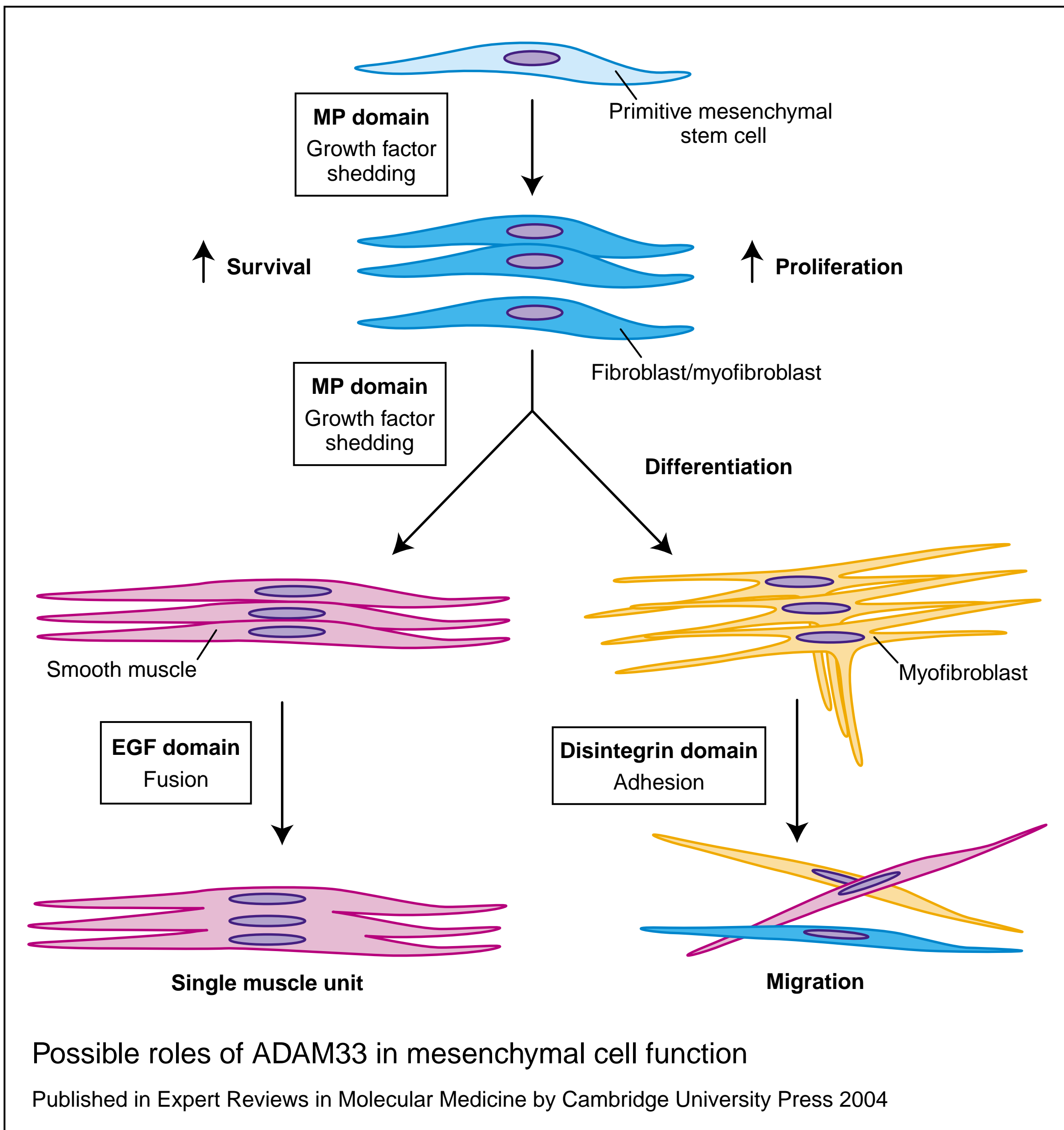

Figure 4. Possible roles of ADAM33 in mesenchymal cell function. Four possible functions are shown; the proteolytic (metalloproteinase; MP) domain of ADAM33 might act in growth factor shedding to influence proliferation and/or differentiation; the EGF domain might function in cell fusion; and the disintegrin domain might influence migration. Reprinted, after modification, from Ref. 57 (Copyright © 2003, American Academy of Allergy, Asthma and Immunology), with permission from the American Academy of Allergy, Asthma and Immunology.

gene product of which contains two PHD zinc fingers that regulate transcription involved in IgE synthesis (Ref. 55), and *DPP10* on chromosome 2q14, which encodes a homologue of dipeptidyl peptidases capable of cleaving terminal peptides from cytokines and chemokines (Ref. 56). Understanding how *ADAM33* and these new genes relate to asthma and allergy in a functional setting will be a challenge. What is certain is that the application of new genetic technologies will identify further novel genes involved in the onset and persistence of atopy and asthma that will undoubtedly reveal new ways to prevent and treat this complex disorder.

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Further reading, resources and contacts

The GeneCard entry for *ADAM33* provides expression information and links to other bioinformatics database entries for *ADAM33*:

http://bioinfo.weizmann.ac.il/cards-bin/carddisp?ADAM33&search=adam33&suff=txt

The Genetic Association Database at the US NIH is an archive of human genetic association studies of complex diseases and disorders, which enables searches by gene (e.g. ADAM33) or disease (e.g asthma):

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Features associated with this article

Figures

Figure 1. Positional cloning of *ADAM33*.
Figure 2. The exonic structure and domain organisation of human ADAM33 in relation to function.
Figure 3. Reported asthma-associated single-nucleotide polymorphisms in the *ADAM33* gene.
Figure 4. Possible roles of ADAM33 in mesenchymal cell function.

Table

Table 1. Summary of single-nucleotide polymorphisms (SNPs) associated with asthma or its partial phenotypes in different populations.

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