

Review Article

Immune and genetic aspects of asthma, allergy and parasitic worm infections: evolutionary links

J. HOPKIN

Institute of Life Science, School of Medicine, Swansea University, Swansea, UK

SUMMARY

There are important parallels in the immunobiology of allergy and asthma, and of the human host's response to parasitic worms. Th-2 immune actions with 'weep and sweep' mucosal biology are common to both – pathological in the first and protective in the second. Common up-regulating genetic variants of Th-2 immunity, notably in IL13 and STAT6, predict increased risk of asthma and allergy, but diminished intensity of infection by Ascaris and Schistosoma. Endemic exposures of humans to parasitic worms may have been one evolutionary force selecting for genetic variants that promote asthma and allergy.

Keywords: genetics, TH-2 immunity, asthma, helminth

THE BIOLOGY OF ASTHMA AND ALLERGY

Allergy is a state of hypersensitivity to environmental antigens of relatively limited type called allergens. The commonest clinical allergy syndrome is atopy – where individuals suffer a complex of asthma, rhino-conjunctivitis and eczema in variable combination. It is a hypersensitivity disorder prominently affecting the mucous membranes and skin (1).

This article will consider asthma as the exemplar allergic disorder – a disease which is the commonest cause of chronic illness in children and young adults in developed countries and showing a strong rise in its prevalence in more affluent populations across the 1960s to 1990s. Asthma has long been accepted as a polygenic disorder – where multiple genetic effects, each of moderate contribution, interact with environmental factors to determine disease. Multiple positional genetic linkage and candidate mechanism genetic association studies have been conducted – and also multiple epidemiological studies have focused on the rise in its prevalence. Concomitantly, mechanistic studies on the immunology and mucosal biology in both humans and experimental animals have provided novel insights (2).

Asthma is a chronic inflammatory disorder of the bronchial mucosa, including its mucus secreting, ciliated columnar epithelium and associated underlying tissues and smooth muscle. The clinical picture is of periodic symptoms that include chest tightness, wheeze, and cough, and of variable obstruction of airflow through the bronchi. Current treatment has and continues to be dominated by relatively selective β -adrenergic sympathomimetic agonists (with short-acting limited anti-inflammatory action but potent smooth muscle relaxation action, making them valuable in swift, partial relief of symptoms) and synthetic corticosteroids (with profound but nonspecific immune-regulating and metabolic effects) which can limit symptoms when taken regularly.

The bronchial inflammation of asthma is orchestrated by cells of the innate immune system (dendritic cells, mast cells,

Correspondence: Julian Hopkin, Institute of Life Science, School of Medicine, Swansea University, Swansea SA2 8PP, UK (e-mail: j.m.hopkin@swansea.ac.uk).

Received: 28 August 2008

Accepted for publication: 14 January 2009

Disclosures: Non-Executive Director ABM University NHS Trust. Director, with equity holdings, in Allerna Therapeutics Ltd (a start-up company from the Institute of Life Science, developing novel therapeutics for asthma and allergy).

eosinophils, neutrophils, macrophages and NK-cells) and by cells of the adaptive immune system ($CD4^+$ T-lymphocytes, and often antigen-specific IgE secreting B-lymphocytes). The innate and adaptive cells are of Th-2 class – secreting the cytokines IL-13 and IL-4 prominently or responding to these cytokines through their transduction and transactivating molecule STAT6 (3). Thus ingress into the bronchus of these cells and release or secretion of many mediators (e.g. heparin, reactive lipids or eicosanoids, and enzymes including tryptase and chitinase) lead to increased permeability of blood vessels and consequent oedema or water-logging, increased mucus production, and exaggerated smooth muscle contraction (1,2,4). All of these contribute to airflow obstruction and the symptoms described above. Continued inflammation results in remodelling of the airway – with TGF- β driven metaplasia of the epithelium, increased vascularity, thickening of the basement membrane, and muscular hypertrophy – leading to lasting airflow obstruction and breathlessness (5,6). In a mouse model of asthma – with allergen induced bronchial inflammation – the disorder is fully prevented by genetic knock-out of STAT6, thus emphasizing the centrality of Th-2 inflammatory mechanisms (7,8).

Many puzzling aspects of this immunopathology remain, as follows.

Why does Th-2 immune activation occur? One factor on first presentation of allergen peptide by dendritic cells to $CD4^+$ lymphocytes, is the balance of competitive co-signalling factors (dendritic CTLA-4 and CD80/86 vying for T-lymphocyte CD28). Another is the cytokine environment where lesser levels of Th-1 stimulating IL-12 allow Th-2 rather than Th-1 development. What are the very first external and internal initiators of the Th-2 response? Low allergen dose itself may promote Th-2 response. Co-exposures may influence the result and certain microbes (9,10), for example mycobacteria which promote strong Th-1 responses through IL-12, may limit Th-2 response (see hygiene hypothesis below). Genetic variants also influence the outcome as described later. What does the activity of neutrophils and macrophages in asthmatic inflammation represent? It may imply the development of mixed Th-1/Th-2 mechanisms as the disease progresses. Alternatively it may represent alternative activation of these cells through Th-2 mechanisms when macrophages can be IL-4R α + and arginase+ (11–13).

What makes a potent allergen? One clue is that many common allergens (house dust mites, pollens, fungal spores, mammalian products) include proteases (14) – e.g. DerP1 from dust mites – and it is now plain that signals from enzyme-damaged bronchial epithelium (e.g. thymic stromal lymphopoietin, TSLP) strongly prime Th-2 response (15), and also that proteases can act directly through protease activated receptors (PARs) to stimulate Th-2 actions (16).

Other factors also operate – so that certain allergens contain the glycan, chitin, which is intrinsically Th-2 promoting (13).

How is asthma of similar severity produced in the presence or absence of the potentiating antibody IgE to allergens on mucosal mast cells? One explanation is that mucosal Th-2 mechanisms may be triggered by allergens through innate cell responses (17,18). Another is that imbalance across a second immune axis (pro-inflammatory IL-17 $^+$ rather than regulatory $CD4^+$ $CD25^+$ lymphocytes) contributes (19). Viruses can also induce release of IL-13 from innate immune cells including macrophages (20). Some individuals may have epithelia intrinsically susceptible to damage or less effective repair – for example when they are filaggrin deficient. In some asthmatics, there is an evident and dominant extrinsic factor such as occupational exposure to di-isocyanates, which may also damage epithelium and hence promote TSLP driven Th-2 activation (12).

Why should asthma now be so common, especially in developed countries? There are multiple hypotheses but no explanation as yet. Among these (e.g. changing diet, pollution, hygiene), the hygiene hypothesis has received most attention, because of a plausible mechanism supported by some experimental data. Thus certain infections could inhibit or diminish Th-2 responses by inducing IL-12, or by inducing more general immune-regulation through promotion of IL-10, and development of $CD4^+$ $CD25^+$, *FoxP3* expressing T-regulatory cells (21). For example, administration of the mycobacterium BCG limits experimental asthma in mice (9,10). Many but not all studies suggest that parasitic worm infection may limit the expression of clinical allergic disease (22,23) – putatively through the induction of regulatory mechanisms (24,25). Hence, environments where infectious exposures and diseases are restrained (because of improved sanitation, better nutrition and housing, immunization, and antibiotic usage) may show more allergy.

THE GENETICS OF ASTHMA AND ALLERGY

The impact of specific genetic factors has been examined in the context of long-standing observations of familial aggregation of atopy and asthma, and twin studies providing heritability estimates of 60–70% (26). The general messages from the very many studies so far conducted on asthma and atopy may be summarized as follows and further detailed information found in a recent meta-analysis of genetic linkages (27), a review of the field (28), and a genome-wide association study of global gene expression (29).

Asthma is evidently a polygenic disorder with a whole set of reproducible genetic linkages observed (of relatively low lod score and many with broad localizations) – including 2q33, 3p22, 5q31, 6p22, 11q13, 12q12–24, 13q12–14, 16p11, 17p12-q24 and X.

Genetic association studies, based on linkage findings or mechanism based testing, show variants of high population frequency (heterozygosity frequently 10–30%) at many loci and which associate with different phenotypes of the asthma – allergy syndrome in different populations: (i) mucosa and supporting tissues (filaggrin, vascularization factor *ADAM33*, myosin light chain kinase, transmembrane protein *ORMDL3*); (ii) inflammatory mediators (prostaglandin E2 receptor, cysteine leukotriene receptor 1, eosinophil cationic protein, chitinase); (iii) innate and adaptive immunity (different toll-like receptors, *CD14*, HLA Class 2, *IL17F*, *IL13*). The common variants recognized generally produce moderate functional change – through simple amino acid substitution, or through influence on transcript production (variants in 5' or 3' gene regulatory regions or in dinucleotide repeat length) – see section on Th-2 signalling variants to follow. There is evident heterogeneity in the linkage and associations across populations and ethnic groups. Moreover, the true functional role of these common variants and the resultant population risks for asthma from their occurrence in combinations, and how these relate to environment risk factors, are yet to be determined. Finally, the high frequency of these disease promoting genetic variants requires explanation.

The example of filaggrin mutations is striking. Filaggrin is a protein with important functions in the terminal differentiation of the skin's epidermis, and hence the securing of the skin's barrier function to diverse extrinsic agents. Common loss of function variants have been identified (R501X and 2782del14) – and have been shown in many populations to be striking risk factors for atopic dermatitis or eczema in children and eczema persisting into adulthood; odds ratios are approximately 7 for heterozygotes and approximately 150 for homozygotes (30). Of further note is that these filaggrin variants also associate with allergen sensitization and with asthma in the context of eczema, even though filaggrin is not expressed in the bronchial airway (31). Hence it has been proposed that the loss of skin barrier function may allow stronger and hence more diverse allergen exposure and hence more general Th-2 priming in early life, with promotion of subsequent asthma (32).

Also striking are the observations accumulating around genetic variants of Th-2 immune signalling – seen to be one central pathway in the mucosal pathology of asthma – genetic variants of *IL13*, of one chain (*IL4RA*) of IL-13's heterodimer receptor, and its unique transduction molecule *STAT6*. Common up-regulating variants of *IL13* – in particular 5' –1112C/T, –1055T/C and Gln110Arg (33–35) – relate to a number of asthma and atopy phenotypes across different populations – eosinophil counts, IgE levels, asthma in general, di-isocyanate induced asthma, prolonged wheezing after respiratory syncytial viral infections, and

worsening lung function in smokers (36–40); the 5' variants enhance gene promoter function, while Gln150Arg enhances IL-13 actions through reduced binding to its decoy receptor IL13R α 2 (34,35). Many common amino acid substitutions of *IL4RA* have been identified – including Ile50Val, Glu551Arg and which associate with asthma associated with high IgE levels and diminished lung function especially in Asian and Black populations (40–43); a fuller understanding of the functional effects of the different variants – singly or in combination – is needed. Whilst *STAT6* shows no common variants causing amino-acid substitutions, there are common variants that include a dinucleotide repeat in exon 1 (44), and a number in the 3' and 5' regions where different elements determine, respectively, transcript half-life and transcriptional activation, and hence function (45); these variants relate to IgE levels, sensitization to allergens, and allergic respiratory symptoms (46–49). Notably, the presence together of variants at these different loci (*IL13*, *IL4RA* and *STAT6*) is a particularly strong risk factor (odds ratios 10+) for raised IgE levels and childhood asthma (50).

PARASITIC WORMS – AND THE HUMAN'S IMMUNE RESPONSE

Though the parasitic worms (helminths) are diverse and distributed across two phyla, it is now broadly accepted that their induction of Th-2 innate and adaptive immune mechanisms is typical (17,51) – even though mixed Th-2/1 responses are observed with certain worms or when certain host organs are involved. Hence, there are remarkable parallels between the immune phenomena that underlie allergy and asthma and those observed in response to helminth infection (1,2,17,51).

This discussion will thus risk dealing with helminths and host responses in general – but will focus on *Ascaris lumbricoides* and *Schistosoma haematobium* in particular when considering data on genetic variants of human Th-2 immunity.

The burden of helminth infection on humans is enormous – with many regions of the world currently showing endemic levels of infection; thus some two billion people in developing countries across Asia, Sub-Saharan Africa, and Latin America show infection, transmission driven by overcrowding of large populations and poor sanitation (52).

A number of striking observations have been made (17, 51,52), which are relevant to our consideration of genetic factors. The geographical prevalences of helminth infection and allergy trend towards the opposites of developing and developed countries. Children and adolescents suffer the greatest burden of helminth infection – which suggests that there is increasingly effective immune response with age. It also means that the burden of ill health falls principally on

the young. Infections are chronic and recurring and may involve more than one helminth. The degree of ill-health relates to the intensity of infection rather than the state of being infected. Intensity can be quantified simply in some infections (e.g. parasite eggs per gram of stool in ascariasis, or eggs per mL of urine in *S. haematobium*).

Of great note, there is regularly observed heterogeneity in the intensity of infection for helminth infections in any exposed community, and where usually some 15–20% of humans show high intensity infection and act as the greatest repository of parasites (53). The factors influencing this heterogeneity of infection intensity include local circumstances that affect transmission of disease – such as soil type, rain fall, niche for any vectors, household clustering, and nutrition (54). Heritable human factors are also important, as we shall see later.

The burden of ill health from helminth infection is only now being fully recognized as very high (52). Besides whatever obvious, organ specific complications may ensue, heavily infected individuals, especially children and adolescents, show poor nutritional status, poor growth, anaemia, fatigue and impaired cognition. This ill-health impacts adversely on education and life prospects, the risk of and outcome from other infectious diseases, and hence biological fitness (reproduction and successful rearing of children). We shall see later that the latter is relevant to proposed evolutionary effects of helminth infections on genetic variation in human immunity.

As stated earlier, Th-2 immune mechanisms are the dominant form of human immune response to helminths – and it is now accepted that these Th-2 immune mechanisms are protective (51). These Th-2 actions are also accompanied by significant immune-regulatory actions (17,24) – and which may represent a compromise between limiting infection and excessive, immunity-induced tissue damage. This is consistent with the pattern of chronic infection and resistance being achieved later in life, as above (52).

The details of Th-2 immune mechanisms in helminth response and in allergy show further remarkable parallels on deeper inspection of cell and cytokine biology and animal models. Thus, proteases prominently secreted by different life stages of helminths cause epithelial damage and thus release of Th-2 stimulating TSLP, or stimulate PARs leading to loosening of epithelial tight junctions and direct cytokine and chemokine release from mast cells and eosinophils. Helminths bear plentiful Th-2 promoting carbohydrate (chitin). Both innate and adaptive Th-2 mechanisms are mutually supportive and prominent with involvement of mast cells, basophils, eosinophils and the release of diverse mediators that cause tissue or epithelial oedema, excessive mucus production and smooth muscle activity which in the gut can be described as a ‘weep and sweep’ response that

promotes expulsion of the worm; alternative Th-2 activation of macrophages occurs (55) with release of arginase, chitinase, and resistin-like molecules (RELMS). There is production of IgE (though its protective effect is not decisive). Orchestration of the whole is by Th-2 cytokines where IL-13 in particular is central, acting through STAT6. Genetic knockout of STAT6 renders mice incapable of clearing helminth gut infections (56,57).

The admixture of immune-regulatory activities involving the actions of IL-10 and the development of CD4⁺ CD25⁺ regulatory T-cells may be a protective adaptation by the host, but it is unclear to what degree the helminth itself may promote immune regulation. Helminths do display a range of evasive and subversive tactics – so for example, *Ascaris* secretes inhibitors of human trypsin, assimilates human blood group antigens as mimetics, has pyrophosphatases vital to moulting (inhibited by the medication, piperazine), and utilizes chromatin diminution to sustain its genome (58,59).

The trend towards reverse distributions of helminth infection and allergy according to a population's economic and social development, and the observations of the induction of regulatory immune mechanisms by helminths has led to the idea that helminth infections may directly inhibit allergic disease – see hygiene hypothesis above (21). In this respect some, but not all, studies on migrants and therapeutically de-wormed individuals support this idea (22,23). Hence variables such as the intensity of worm (52) and human genetic variables (see below) may underlie different results – and point to a complex picture where parasitic worm infection can inhibit allergic phenomena under certain circumstances – but where human genetic variation can influence the expression of allergic disorders.

GENETIC VARIANTS OF TH-2 IMMUNE SIGNALLING AND THE INTENSITY OF HELMINTH INFECTION

The observations of shared Th-2 immune phenomena in helminth infections and in allergy, and the observation that common genetic variants of Th-2 immune signalling relate to allergy and asthma, provide the background for the hypothesis that the origin of these allergy-promoting variants derives from evolutionary mechanisms and their selection in the presence of widespread, endemic helminth infection.

Genetic linkage studies provided the first observational support for this – with a study of *S. mansoni* in both Brazil and Senegal showing significant linkage between intensity of *S. mansoni* infection and an unidentified locus on chromosome 5q31–q33 (60). It was noted that a number of loci for immune function are located here, including the loci for the

Th-2 cytokines, IL-4, IL-5 and IL-13. Genetic association studies, focused on a range of specific loci related to immune function, have now built on and extended this finding.

Studies of genetic variants of immune signalling have been conducted in Xing-Chang (61,62), a rural area of the Shanghai province of China, where most of the population in 2002/2003 was involved in subsistence agriculture, where many farmers used fresh night soil to fertilize leaf vegetables, and where infection with *A. lumbricoides* was endemic with infection in children being greatest. *Ascaris lumbricoides* is a round worm in which there is faecal-oral spread of infection and re-infection; its life cycle involves transient passage of blood borne larvae across the lung, and then the residence of mature worms in the small intestine where the females excrete eggs into the faeces. Children show the greatest infection, and approximately 600 children were studied – among whom some 20% showed high intensity infection.

Common genetic variants from 14 loci were studied in these Xing-Chang children (61) – encompassing Th-2 signalling, Th-1 signalling, and immune-regulatory function (*IL10* and its receptor). Discriminant and logistic analysis showed that a-3' UTR variant of *STAT6* (location, chromosome 12) was the principal predictor of intensity of *Ascaris* infection (GG 506, GA 1195, AA 1417 epg); lesser but also significant associations were found for the -1055 variant of *IL13*, and an interaction between the *STAT6* variant and a variant of *IFN γ* . A second study (62) examined a detailed set of *STAT6* variants in this population, also considering total serum IgE levels, and comparing results with a young British population in whom allergy and asthma were common but *Ascaris* infection absent. Haplotypes of the genetic variants spanning *STAT6* were constructed and segregated significantly into two groups relating either to high IgE levels and allergy and asthma in the British and low intensity *Ascaris* infection in the Chinese, or to low IgE levels with lesser risk of allergy in the British and greater risk of high intensity *Ascaris* infection in the Chinese. Included in the variants was a dinucleotide repeat, where short repeats had been shown to result in increased *STAT6* transcription, and which related to higher IgE levels with more allergies but less intense *Ascaris* infections in the British and Chinese, respectively (62).

Studies on genetic variants of Th-2 immune signalling have also been conducted in Dogon populations in Mali (45,63), testing for association with the intensity of *S. haematobium* infection. This *Schistosoma* infection is endemic in the region, gaining initial human access through the skin, followed by migration through blood and lymphatic vessels (including several passages through the lung) before settling as adult worms in pelvic veins related to the bladder, genital tract and lower gut. High intensity infection

(gauged by egg counts per mL of urine) is associated with high general morbidity (as described earlier) but also other special features that include ureteric inflammation and fibrosis with renal impairment, and genital involvement which in the female in particular can limit fertility.

In a first study of this Dogon population (63), variants of *IL4*, *IL5* and *IL13* were tested in children and their parents; one variant T/C of position -1055 of *IL13* related to intensity of infection, with TT homozygotes showing significantly less infection. Notably, this is the same protective allele observed for *Ascaris* in Chinese children (above), and which relates to asthma in developed country populations, and which shows up-regulation of *IL13* transcription. In a second study of the same population (45), there was in-depth analysis of more variants of Th-2 immune signalling – encompassing the loci *IL4*, *IL13*, *IL4RA*, *IL13RA1*, *IL13RA2*, *STAT6* and *GATA3*. Two alleles related significantly to intensity of infection – the previously recorded T/C at -1055 in the promoter region of *IL13*, and the rs324013 variant in the 5' promoter region of *STAT6*. Moreover, when present together there was an additive effect of these *IL13* and *STAT6* variants on the intensity of infection. *In silico* modelling suggested that the variants at both 5' sites would alter gene transcription – through quantitative (*IL13*) or qualitative effects (*STAT6*'s C allele creating a binding site for ATF and poly A transcription factor, its allele T for NIT2 and GATA-1 & 2) on transcription factor binding. Electrophoretic mobility shift assays confirmed that the variants at both sites modulated factor binding (45).

These study findings from independent research groups in distinct populations (African and Asian) and for two distinct helminths (*S. haematobium* and *A. lumbricoides*) are remarkably consistent. Together, they provide strong support for the hypothesis that geographically widespread helminth infections have been potent factors in selecting for up-regulating, genetic variants of Th-2 immunity. Implicit in this is that those carrying such variants have diminished intensity of worm infection in comparison to those without such variants, and hence enjoy better health and show greater reproductive capacity (52) – thereby leading to enhanced transmission of such variants in to the next human generation.

These same up-regulating Th-2 immune variants promote the risk of allergy and asthma. While part of a complex biological and genetic picture (64), the studies further emphasize the importance of variants in IL-13 signalling, with its powerful actions through *STAT6* in orchestrating mucosal Th-2 immune mechanisms (2,51) in relation to both asthma and allergy, and to parasitic worm infections.

The study findings above also suggest one possible explanation for the variable relationship between escape from worm infection (by de-worming or migration) and the

subsequent development of asthma or allergy (22,23,52) and where data on genetic variants have not been taken account of, to date. In one respect, removal of helminth infection has the potential to diminish associated immune-regulatory mechanisms (19,24), and thus promote asthma and allergy. But in another respect this development of asthma and allergy is more likely in those individuals with Th-2 up-regulating variants, those who would also have shown lower intensities of helminth infection originally. Hence, it can be proposed that active parasitic worm infection may on the one hand limit the expression of asthma and allergy by the induction of immune-regulatory mechanisms – but in contrast, promote asthma and allergy more remotely by providing a selective force for the transmission of up-regulating Th-2 immune variants.

Further studies in this area – and encompassing data on genetic variation in Th-2 immunity – may provide further interest and clarity – and may be helpful to scientists and clinicians searching for more effective prevention and treatment of parasitic worm infections, and asthma and allergy.

REFERENCES

- Galli SJ, Tsai M & Piliponsky AM. The development of allergic inflammation. *Nature* 2008; **454**: 445–454.
- Holgate ST. Pathogenesis of asthma. *Clin Exp Allergy* 2008; **38**: 872–897.
- Webb DC, Cai Y, Matthaai KI & Foster PS. Comparative roles of IL-4, IL-13, and IL-4R α in dendritic cell maturation and CD4⁺ Th2 cell function. *J Immunol* 2007; **178**: 219–227.
- Bloemen K, Verstraelen S, Van Den Heuvel R, Witters H, Nelissen I & Schoeters G. The allergic cascade: review of the most important molecules in the asthmatic lung. *Immunol Lett* 2007; **113**: 6–18.
- James AL, Maxwell PS, Pearce-Pinto G, Elliot JG & Carroll NG. The relationship of reticular basement membrane thickness to airway wall remodeling in asthma. *Am J Respir Crit Care Med* 2002; **166**: 1590–1595.
- Puxeddu I, Pang YY, Harvey A, *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.
- Tomkinson A, Kanehiro A, Rabinovitch N, Joetham A, Cieslewicz G & Gelfand EW. The failure of STAT6-deficient mice to develop airway eosinophilia and airway hyperresponsiveness is overcome by interleukin-5. *Am J Respir Crit Care Med* 1999; **160**: 1283–1291.
- Hoshino A, Tsuji T, Matsuzaki J, *et al.* STAT6-mediated signaling in Th2-dependent allergic asthma: critical role for the development of eosinophilia, airway hyper-responsiveness and mucus hypersecretion, distinct from its role in Th2 differentiation. *Int Immunol* 2004; **16**: 1497–1505.
- Major T, Wohlleben G, Reibetanz B & Erb KJ. Application of heat killed *Mycobacterium bovis*-BCG into the lung inhibits the development of allergen-induced Th2 responses. *Vaccine* 2002; **20**: 1532–1540.
- Hopfenstirger MT & Agrawal DK. Airway hyperresponsiveness, late allergic response, and eosinophilia are reversed with mycobacterial antigens in ovalbumin-prensensitized mice. *J Immunol* 2002; **168**: 2516–2522.
- Kang K, Reilly SM, Karabacak V, *et al.* Adipocyte-derived Th2 cytokines and myeloid PPAR δ regulate macrophage polarization and insulin sensitivity. *Cell Metab* 2008; **7**: 485–495.
- MacKinnon AC, Farnworth SL, Hodgkinson PS, *et al.* Regulation of alternative macrophage activation by galectin-3. *J Immunol* 2008; **180**: 2650–2658.
- Reese TA, Liang HE, Tager AM, *et al.* Chitin induces accumulation in tissue of innate immune cells associated with allergy. *Nature* 2007; **447**: 92–96.
- Reed CE & Kita H. The role of protease activation of inflammation in allergic respiratory diseases. *J Allergy Clin Immunol* 2004; **114**: 997–1008.
- Liu YJ, Soumelis V, Watanabe N, *et al.* TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. *Annu Rev Immunol* 2007; **25**: 193–219.
- Zhang Z, Zhang H, Yang H, *et al.* Induction of T-helper type 2 cytokine release and up-regulated expression of protease-activated receptors on mast cells by recombinant American cockroach allergen Per a 7. *Clin Exp Allergy* 2008; **38**: 1160–1167.
- Hammad H & Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. *Nat Rev Immunol* 2008; **8**: 193–204.
- Kato A & Schleimer RP. Beyond inflammation: airway epithelial cells are at the interface of innate and adaptive immunity. *Curr Opin Immunol* 2007; **19**: 711–720.
- Diaz A & Allen JE. Mapping immune response profiles: the emerging scenario from helminth immunology. *Eur J Immunol* 2007; **37**: 3319–3326.
- Grayson MH, Cheung D, Rohlfing MM, *et al.* Induction of high-affinity IgE receptor on lung dendritic cells during viral infection leads to mucous cell metaplasia. *J Exp Med* 2007; **204**: 2759–2769.
- Renz H, Blümer N, Virna S, Sel S & Garn H. The immunological basis of the hygiene hypothesis. *Chem Immunol Allergy* 2006; **91**: 30–48.
- Hagel I, Cabrera M, Hurtado MA, *et al.* Infection by *Ascaris lumbricoides* and bronchial hyper reactivity: an outstanding association in Venezuelan school children from endemic areas. *Acta Trop* 2007; **103**: 231–241.
- Obihara CC, Beyers N, Gie RP, *et al.* Respiratory atopic disease, *Ascaris*-immunoglobulin E and tuberculin testing in urban South African children. *Clin Exp Allergy* 2006; **36**: 640–648.
- Capron A, Dombrowicz D & Capron M. Helminth infections and allergic diseases: from the Th2 paradigm to regulatory networks. *Clin Rev Allergy Immunol* 2004; **26**: 25–34.
- Elliott DE, Summers RW & Weinstock JV. Helminths as governors of immune-mediated inflammation. *Int J Parasitol* 2007; **37**: 457–464.
- Willemsen G, van Beijsterveldt TC, van Baal CG, Postma D & Boomsma DI. Heritability of self-reported asthma and allergy: a study in adult Dutch twins, sibs and parents. *Twin Res Hum Genet* 2008; **11**: 132–142.
- Denham S, Koppelman GH, Blakey J, *et al.* Meta-analysis of genome-wide linkage studies of asthma and related traits. *Respir Res* 2008; **9**: 38.
- Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008; **8**: 169–182.
- Dixon AL, Liang L, Moffatt MF, *et al.* A genome-wide

- association study of global gene expression. *Nat Genet* 2007; **39**: 1202–1207.
- 30 Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–446.
 - 31 Palmer CN, Ismail T, Lee SP, *et al.* Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007; **120**: 64–68.
 - 32 Marenholz I, Nickel R, Rüschendorf F, *et al.* Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006; **118**: 866–871.
 - 33 Heinzmann A, Mao XQ, Akaiwa M, *et al.* Genetic variants of IL-13 signalling and human asthma and atopy. *Hum Mol Genet* 2000; **9**: 549–559.
 - 34 Arima K, Umeshita-Suyama R, Sakata Y, *et al.* Upregulation of IL-13 concentration in vivo by the IL13 variant associated with bronchial asthma. *J Allergy Clin Immunol* 2002; **109**: 980–987.
 - 35 Andrews AL, Buccieri F, Arima K, *et al.* Effect of IL-13 receptor $\alpha 2$ levels on the biological activity of IL-13 variant R110Q. *J Allergy Clin Immunol* 2007; **120**: 91–97.
 - 36 Sadeghnejad A, Meyers DA, Bottai M, Sterling DA, Bleecker ER, Ohar JA. IL13 promoter polymorphism 1112C/T modulates the adverse effect of tobacco smoking on lung function. *Am J Respir Crit Care Med* 2007; **176**: 748–752.
 - 37 Hunninghake GM, Soto-Quirós ME, Avila L, *et al.* Polymorphisms in IL13, total IgE, eosinophilia, and asthma exacerbations in childhood. *J Allergy Clin Immunol* 2007; **120**: 84–90.
 - 38 Ermers MJ, Hoebee B, Hodemaekers HM, Kimman TG, Kimpfen JL & Bont L. IL-13 genetic polymorphism identifies children with late wheezing after respiratory syncytial virus infection. *J Allergy Clin Immunol* 2007; **119**: 1086–1091.
 - 39 Bernstein DI, Wang N, Campo P, *et al.* Diisocyanate asthma and gene-environment interactions with IL4R α , CD-14, and IL-13 genes. *Ann Allergy Asthma Immunol* 2006; **97**: 800–806.
 - 40 Battle NC, Choudhry S, Tsai HJ, *et al.* Ethnicity-specific gene-gene interaction between IL-13 and IL-4R α among African Americans with asthma. *Am J Respir Crit Care Med* 2007; **175**: 881–887.
 - 41 Wenzel SE, Balzar S, Ampleford E, *et al.* IL4R alpha mutations are associated with asthma exacerbations and mast cell/IgE expression. *Am J Respir Crit Care Med* 2007; **175**: 570–576.
 - 42 Mitsuyasu H, Izuhara K, Mao XQ, *et al.* Ile50Val variant of IL4R alpha upregulates IgE synthesis and associates with atopic asthma. *Nat Genet* 1998; **19**: 119–120.
 - 43 Yabiku K, Hayashi M, Komiya I, *et al.* Polymorphisms of interleukin (IL)-4 receptor alpha and signal transducer and activator of transcription-6 (Stat6) are associated with increased IL-4Ralpha-Stat6 signalling in lymphocytes and elevated serum IgE in patients with Graves' disease. *Clin Exp Immunol* 2007; **148**: 425–431.
 - 44 Gao PS, Heller NM, Walker W, *et al.* Variation in dinucleotide (GT) repeat sequence in the first exon of the STAT6 gene is associated with atopic asthma and differentially regulates the promoter activity in vitro. *J Med Genet* 2004; **41**: 535–539.
 - 45 He H, Isnard A, Kouriba B, *et al.* A STAT6 gene polymorphism is associated with high infection levels in urinary schistosomiasis. *Genes Immun* 2008; **9**: 195–206.
 - 46 Li Y, Wu B, Xiong H, Zhu C & Zhang L. Polymorphisms of STAT-6, STAT-4 and IFN- γ genes and the risk of asthma in Chinese population. *Respir Med* 2007; **101**: 1977–1981.
 - 47 Pykäläinen M, Kinos R, Valkonen S, *et al.* Association analysis of common variants of STAT6, GATA3, and STAT4 to asthma and high serum IgE phenotypes. *J Allergy Clin Immunol* 2005; **115**: 80–87.
 - 48 Amoli MM, Hand S, Hajeer AH, *et al.* Polymorphism in the STAT6 gene encodes risk for nut allergy. *Genes Immun* 2002; **3**: 220–224.
 - 49 Tamura K, Arakawa H, Suzuki M, *et al.* Novel dinucleotide repeat polymorphism in the first exon of the STAT-6 gene is associated with allergic diseases. *Clin Exp Allergy* 2001; **31** (10): 1509–1514.
 - 50 Kabesch M, Schedel M, Carr D, *et al.* IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J Allergy Clin Immunol* 2006; **117**: 269–274.
 - 51 Anthony RM, Rutitzky LI, Urban JF Jr, Staderker MJ & Gause WC. Protective immune mechanisms in helminth infection. *Nat Rev Immunol* 2007; **7**: 975–987.
 - 52 Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ & Jacobson J. Helminth infections: the great neglected tropical diseases. *J Clin Invest* 2008; **118**: 1311–1321.
 - 53 Turner JD, Jackson JA, Faulkner H, *et al.* Intensity of intestinal infection with multiple worm species is related to regulatory cytokine output and immune hyporesponsiveness. *J Infect Dis* 2008; **197**: 1204–1212.
 - 54 Hagel I, Lynch NR, Puccio F, *et al.* Defective regulation of the protective IgE response against intestinal helminth *Ascaris lumbricoides* in malnourished children. *J Trop Pediatr* 2003; **49**: 136–142.
 - 55 Anthony RM, Urban JF Jr, Alem F, *et al.* Memory T (H) 2 cells induce alternatively activated macrophages to mediate protection against nematode parasites. *Nat Med* 2006; **12**: 955–960.
 - 56 Urban JF Jr, Schopf L, Morris SC, *et al.* Stat6 signaling promotes protective immunity against *Trichinella spiralis* through a mast cell and T cell-dependent mechanism. *J Immunol* 2000; **164**: 2046–2052.
 - 57 Urban JF Jr, Noben-Trauth N, Donaldson DD, *et al.* IL-13, IL-4R α , and Stat6 are required for the expulsion of the gastrointestinal nematode parasite *Nippostrongylus brasiliensis*. *Immunity* 1998; **8**: 255–264.
 - 58 Islam MK, Miyoshi T, Yamada M & Tsuji N. Pyrophosphatase of the roundworm *Ascaris suum* plays an essential role in the worm's molting and development. *Infect Immun* 2005; **73**: 1995–2004.
 - 59 Bachmann-Waldmann C, Jentsch S, Tobler H & Müller F. Chromatin diminution leads to rapid evolutionary changes in the organization of the germ line genomes of the parasitic nematodes *A. suum* and *P. univalens*. *Mol Biochem Parasitol* 2004; **134**: 53–64.
 - 60 Marquet S, Abel L, Hillaire D, *et al.* Genetic localization of a locus controlling the intensity of infection by *Schistosoma mansoni* on chromosome 5q31–q33. *Nat Genet* 1996; **14**: 181–184.
 - 61 Peisong G, Yamasaki A, Mao XQ, *et al.* An asthma-associated genetic variant of STAT6 predicts low burden of *Ascaris* worm infestation. *Genes Immun* 2004; **5**: 58–62.
 - 62 Moller M, Gravenor MB, Roberts SE, Sun D, Gao P & Hopkin JM. Genetic haplotypes of Th-2 immune signalling link allergy to enhanced protection to parasitic worms. *Hum Mol Genet* 2007; **16**: 1828–1836.
 - 63 Kouriba B, Chevillard C, Bream JH, *et al.* Analysis of the 5q31–q33 locus shows an association between IL13–1055C/T and IL-13–591A/G polymorphisms and *Schistosoma haematobium* infections. *J Immunol* 2005; **174**: 6274–6281.
 - 64 Williams-Blangero S, Vandenberg JL, Subedi J, Jha B, Corrêa-Oliveira R & Blangero J. Localization of multiple quantitative trait loci influencing susceptibility to infection with *Ascaris lumbricoides*. *J Infect Dis* 2008; **197**: 66–71.