October-2012

- HUMAN LEUKOCYTE ANTIGENS (HLA) ASSOCIATED DRUG HYPERSENSITIVITY: CONSEQUENCES OF DRUG BINDING TO HLA (Yun J, Adam J, Yerdy D, Pichler WJ. Allergy 2012; 67: 1338–1346).
ALLERGY:

- **HUMAN LEUKOCYTE ANTIGENS (HLA) ASSOCIATED DRUG HYPERSENSITIVITY: CONSEQUENCES OF DRUG BINDING TO HLA** (Yun J, Adam J, Yerly D, Pichler WJ. Allergy 2012; 67: 1338–1346):
  
  - Genetic and environmental factors → drug hypersensitivity. Certain HLA alleles are associated with hypersensitivity to particular drugs.
  
  - Drugs are small sized molecules. How do they become immunogenic? Mechanisms: 1) **hapten** (or metabolized prohapten) joins to a self protein (carrier) and creates neoantigens → antigen presenting cells uptake the conjugate, process it and present drug peptides in HLA molecules to T cells → adaptive immune activation. 2) **p-i concept** (pharmacological interactions with immune receptors): drug (or metabolites) interacts directly with HLA molecules and TCRs → adaptive immune activation.
  
  - Drugs that act as hapten/prohapten can join several different proteins and, after processing, form multiple drug-bound peptides, which can be loaded onto different types of HLA alleles → less HLA restriction.
  
  - **Pro-hapten concept**: a drug may become a hapten after metabolism (e.g. sulfamethoxazole). Metabolizing enzymes and specific sites of modification remain largely unknown.
  
  - Haptens/prohaptens need innate immune activation to become immunogenic (e.g. metabolism of SMX to nitroso SMX in DCs results in their activation). Consequently, haptens/pro-haptens do not often elicit immune responses.
  
  - Stimulation of innate immunity is not sufficient to induce hypersensitivity (e.g. nickel activates TLR4 but not always induces hypersensitivity; imiquimod activates TLR7 but rarely induces hypersensitivity).
  
  - In the p-i concept, T cell activation does not need innate immune system activation. T cells that react in p-i manner arise from the memory pool.
  
  - **Penicillin** has a propensity to bind to lysine residues. There is a vast array of available lysine residues in human proteins, so many different neoantigens can be generated → elicited immune responses are expected to be variable.
  
  - Certain TCR repertoires are required for immune activation after interaction between carbamazepine and HLA-B*15:02. This explains why most individuals carrying this allele can tolerate the drug. HLA-B*15:02 allele should be checked prior to initiation of carbamazepine therapy in some populations.
  
  - **Abacavir** joins non-covalently to HLA-B*57:01 molecules → self-peptide loading onto HLA-B*57:01 is altered → new endogenous peptides are displayed on the cell surface of APC (alteration in the presented peptide repertoire) → polyclonal T-cell response is generated. This may explain drug-
dependent autoimmunity. HLA typing is mandatory before starting therapy with abacavir (PPV=47.9%).

- **HLA-B*58:01** allele increases risk of allopurinol hypersensitivity (PPV=2.7%).

- Although HLA-B*57:01 is closely related to HLA-B*58:01, abacavir and allopurinol hypersensitivity are exclusively associated with HLA-B*57:01 and HLA-B*58:01, respectively. In contrast, HLA-B*15:02 molecule and HLA-A*31:01 molecule are structurally remote but are both associated with carbamazepine hypersensitivity. The reasons are not determined.

- Yang et al. predicted the interaction of HLA-B*57:01 molecule with abacavir using a bioinformatics approach. Such methods will be invaluable tools for drug hypersensitivity research and for the pharmaceutical industry.


- **WDEIA:** anaphylactic reactions after wheat ingestion and physical exercise. Cofactors (aspirin, alcohol, infections, stress, menstruation) can substitute for or synergize with exercise.

- **Wheat proteins:** a) water/salt-soluble proteins (e.g., alpha-amylase inhibitor); b) water/salt-insoluble glutens: gliadins (α/β-, γ- and ω-gliadins) and glutenins.

- The majority of WDEIA patients have IgE antibodies to ω5-gliadin.

- The authors demonstrate the value of IgE to α/β- and γ-gliadin in the diagnosis of WDEIA, in particular in ω5-gliadin IgE-negative patients.


- This is a Task Force Report from the EAACI Ocular Allergy Interest Group on Diagnosis and Management of Ocular Allergy, which: (i) unifies nomenclature and classification; (ii) summarizes diagnostic and therapeutic options.

- **2 key points:** 1) differentiate allergic conjunctivitis from more severe diseases (atopic and vernal keratoconjunctivitis); 2) determine the severity correctly, to give an appropriate therapy.

**PERCEIVED STRESS AND RISK OF ADULT-ONSET ASTHMA AND OTHER ATOPIC DISORDERS: A LONGITUDINAL COHORT STUDY (Rod NH, Kristensen TS, Lange P, Prescott E, Diderichsen F. Allergy 2012; 67: 1408–1414):**
• **Stress** is strongly associated in adults with: a) asthma incidence; b) asthma hospitalization; c) use of asthma medication; d) allergic rhinitis; e) atopic dermatitis.


  - When we analyze epidemiological studies about the relationship between diet and asthma, we should consider factors that may act as potential confounders: living on a farm, socioeconomic status, physical activity, obesity, etc.

  - Methods to address, analyze and rule out confounding factors: direct acyclic graphs (DAGs), marginal structural models (MSM), Mendelian randomization.

• **RISK FACTORS FOR THE DEVELOPMENT OF EGG ALLERGY: PROGRESS TO DATE AND FUTURE DIRECTIONS** (Nwaru BI, Sheikh A. Allergy 2012; 67: 1325–1326):

  - Koplin et al. showed in their study that: a) ownership of a dog at home, having older siblings $\rightarrow$ ↓ risk of egg allergy; b) family history of allergy $\rightarrow$ ↑ risk of egg allergy; c) Cesarean section delivery, use of antibiotics, attendance to daycare, maternal age $\rightarrow$ not associated with egg allergy.

  - However, there are some methodological issues that should be considered: cross-sectional design, exploratory nature, potential confounders.


  - Eicosanoid imbalance has a role in the development of CRS, especially in the context of nasal polyps and aspirin-exacerbated respiratory disease (AERD): a) ↓ levels of anti-inflammatory molecules (PGE2, lipoxins); b) ↑ levels of pro-inflammatory molecules (CysLTs, PGD2, 15-HETE).

  - Staphylococcal enterotoxins can amplify inflammation in CRS, asthma and atopic dermatitis by activating epithelial cells and influencing Th2 responses.

• **SPECIFIC IMMUNOTHERAPY CAN GREATLY REDUCE THE NEED FOR SYSTEMIC STEROIDS IN ALLERGIC RHINITIS** (Aasbjerg K, Torp-Pedersen C, Backer V. Allergy 2012; 67: 1423–1429):

  - Subcutaneous IT against grass (Phleum pratense), birch (Betula verrucosa) or both can greatly reduce the need for steroids in patients with allergic rhinitis.

  - Retrospective study (39,173 patients) $\rightarrow$ mean annual steroid injections were 1.6 in the steroid-only group and 1.0 in the SCIT group ($P<0.0001$). Of the SCIT-treated patients, 84% did not need steroids after SCIT treatment ($P<0.0001$).
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- Systemic steroid use was defined as ≥1 steroid injection during April–July for at least 3 consecutive years.

  - CRTh2 (chemoattractant-receptor homologous molecule expressed on Th2 cells): chemokine receptor expressed by Th2 cells and eosinophils.
  - Authors show an association between CRTh2 rs533116 SNP and allergic asthma, possibly mediated by ↑ expression of CRTh2. This finding adds to previously reported SNPs in CRTh2 (rs11571288, rs545659, rs634681) that ↑ allergy risk.

  - Specific IT is the only treatment with the potential to modify the natural history of allergic diseases. Subcutaneous and sublingual route have some problems (side effects, low compliance). Alternative routes are being investigated (intralymphatic, epicutaneous).
  - Authors show in mice that transcutaneous IT via laser microporation is equally efficient (↓ airway hyperresponsiveness, ↓ leukocyte infiltration in the lungs) and safer (↓ of Th1/Th2/Th17 responses) compared with subcutaneous IT.
  - Successful therapy was associated with ↑ IgG2a and ↑ FOXP3+ CD4+ T cells.

  - Original ARIA classification of AR severity is based on four items (sleep; school performance; daily activities/sport/leisure; troublesome symptoms) → mild AR (no affected items); moderate/severe AR (≥1 affected items).
  - Modified ARIA (m-ARIA) classification allows discrimination between moderate (1 to 3 affected items) and severe AR (all of 4 affected items) in children 6-12 years old (the same has been shown in adults).
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:


  • 90 asthmatic children sensitized only to HDM → 30 who had completed 3 years of HDM subcutaneous immunotherapy (SIT3 group), 30 who had completed 5 years of HDM SIT (SIT5 group), 30 whose parents had refused HDM SIT although they had indication to receive it (control group).

  • Patients were followed for 3 years after SIT discontinuation. Effectiveness of SIT was assessed primarily by ↓ in ICS dose, ↑ in FEV1 and asthma remission.

  • 84 children completed the study → a) Asthma remission: SIT3 (50%), SIT5 (54%), significant against control (3.3%). b) ↓ in ICS dose: significantly higher in SIT3 and SIT5 groups (no difference between them at 3-year follow up). c) FEV1: slightly higher increase in the SIT5 group compared with the SIT3 group.

  • Conclusion: 3 years of SIT therapy is an adequate duration for children with asthma and HDM sensitization; 2 more years of SIT added no clinical benefit.


  • Normal respiratory cycle: vocal folds widely abduct on inspiration and slightly adduct (<30%) on expiration.

  • PVFM (vocal cord dysfunction): involuntary adduction of vocal cords during inspiration → acute upper airway obstruction.

  • Prevalence is unknown. Affected individuals are of all ages and of both sexes.

  • Many factors may be involved: psychological disorders (the most important?), postnasal drip, gastroesophageal reflux (GER), laryngopharyngeal reflux (LPR), upper respiratory tract infections, abnormal response to exercise.

  • Clinical presentation: sudden onset of asthma symptoms (mainly on inspiration) and/or throat symptoms (choking, tightening of the throat, dysphonia or aphonia); spontaneous remission; triggers: exercise, irritants, etc.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- Analysis of 1020 patients: dyspnea (73%), wheeze (36%), stridor (28%), cough (25%), chest tightness (25%), throat tightness (22%), changes in voice (12%).

- PVFM and asthma can coexist. 10% of patients referred for inpatient evaluation of refractory asthma had PVFM; 30% had both PVFM and asthma.

- When to suspect PVFM? Asthma symptoms with discordant physical examination, tracheal symptoms, no response to asthma therapy, normal spirometry, normal oxygen saturation during acute attacks.

- Diagnostic tools: history, spirometry (25% of patients may show variable extrathoracic obstruction on flow volume loops), methacholine bronchoprovocation test (may reproduce symptoms), flexible laryngoscopy, laryngeal videography, high resolution CT.

- Fiberoptic laryngoscopy during attacks is the gold standard for diagnosis of PVFM. It may be normal during asymptomatic periods.

- Methacholine bronchoprovocation testing with concomitant flexible laryngoscopy are excellent tools for the evaluation of asthma and PVFM.

- Differential diagnosis of PVFM: asthma, GER, LPR, rhinosinusitis, oropharyngeal thrush, laryngomalacia, laryngospasm after airway instrumentation, aberrant arytenoids closure, vocal fold paralysis, mass effect from adjacent structures.

- Treatment for acute attacks: heliox (80% helium + 20% oxygen, ↓ airflow turbulence and resistance by promoting laminar flow); continuous positive airway pressure.

- Long-term therapy: speech therapy and breathing exercises (mainstay); psychological therapy; identification and treatment of associated conditions and triggers; inhaled ipratropium before exercise for patients with exercise-induced symptoms (blockage of the vagus nerve stimulation?).

**EXERCISE-INDUCED HYPERVERVENTILATION: MORE COMMON THAN APPRECIATED**


- Exercise-induced respiratory symptoms are not always caused by asthma.

- Hyperventilation during exercise (excessive to metabolic requirements) can be misdiagnosed as asthma or exercise-induced bronchoconstriction.

- 12 non-asthmatic patients suspected of exercise-induced hyperventilation are reported in this article.

- How to differentiate exercise-induced hyperventilation from asthma? Paresthesias, syncope/presyncope, absence of rhinitis or nocturnal symptoms, high oxygen saturation, poor response to bronchodilators, normal or non-symptom-reproducing methacholine test.
• **Symptoms may occur only during competition**, can be absent in practice exercise. Exercise under supervision may not reproduce symptoms.

• **Intermittent laryngeal dysfunction** during exercise should be excluded.

• **Treatment strategies**: education about the benign nature of the disease (explain the patient that symptoms are due to hypocapnea and respiratory alkalosis); breathing retraining; pharmacotherapy has limited value.


• **Macrolides**: a) Broad-spectrum antibiotics: erythromycin, clarithromycin, azithromycin; b) Immunosuppressive drugs: tacrolimus, sirolimus, everolimus, temsirolimus.

• Immediate or delayed allergic reactions to macrolides are uncommon: 0.4–3%.

• ¿Is there cross-reactivity among macrolides? Largely unknown. A large lactone ring with varying numbers of atoms is the main structural component of macrolides. Differences in the structure and side groups of the lactone ring theoretically prevent cross-reactivity. At least 1 hypersensitivity reaction has been described with use of tacrolimus in a clarithromycin-allergic patient.

• This article reports a patient with erythromycin allergy who underwent successful graded-dose challenge to sirolimus.

A 37-year-old woman with refractory adult T cell lymphoma was admitted for HSCT. Sirolimus was needed as GVHD prophylaxis. 2 years before she had anaphylaxis after erythromycin use (azithromycin was previously tolerated). Concern: ¿risk of allergy to sirolimus?

• Procedures performed: 1st) SPT and intradermal test to erythromycin (0.05 mg/mL) → no reaction (however, erythromycin skin testing is not validated; a negative result does not rule out drug-specific IgE). 2nd) Graded-dose challenge with sirolimus → drug was tolerated without adverse reactions.

• Graded-dose challenge with sirolimus: 0.16 mg (1/100th of the target dose) → 1.5 mg → 14 mg. 30-minute intervals between doses.

• In macrolide-allergic patients who need macrolide therapy, desensitization results in a temporary state of allergen-specific tolerance.

• Graded-dose challenge is different from desensitization; it is a procedure where the drug is introduced cautiously in patients with low risk for allergic reactions. Unlike desensitization, no modification of the immune response is seen in graded-dose challenges. With a successful graded-dose challenge, patients do not require repeat challenging for subsequent dosing.
SUCCESSFUL TREATMENT OF EXERCISE-INDUCED ANAPHYLAXIS WITH OMALIZUMAB

- **Omalizumab (anti-IgE):** approved for severe allergic asthma. Reports have shown efficacy in idiopathic, mastocytosis-associated and venom-induced anaphylaxis.

- **Exercise-induced anaphylaxis (EIA):** a potentially life-threatening syndrome that occurs during or shortly after exercise; independently or in association with specific food ingestion (food-dependent EIA).

- **Physiopathology** of EIA is not well understood. Proposed mechanisms: IgE-mediated; changes in plasma osmolality, blood pH, blood flow distribution, gut permeability, tissue transglutaminase.

- **Current treatments for EIA:** exercise avoidance, food avoidance in FDEIA, pre-exercise medications (antihistamines, cromolyn, montelukast).

- The article reports the **first case of successful use of omalizumab in EIA.**

- 14-year-old competitive male athlete; 2 episodes of anaphylaxis 5 min after running; normal baseline tryptase; pre-exercise medication (montelukast 10 mg, fexofenadine 180 mg, cromolyn 200 mg, ranitidine 150 mg) and food avoidance did not prevent new episodes, even after minimal exercise; another reaction occurred after taking 200 mg of ibuprofen.

- Omalizumab 300 mg monthly was added → 4 months later exercise was resumed (current exercise routine: 2 hours of gym activity: warm-up sessions, weight lifting, intermittent cardio-exercises; he eats before exercise without restrictions; no need for epinephrine or emergency visits). He continues his premedication regimen. He has not yet resumed competitive running.

- The **mast cell stabilizing effect of omalizumab** likely contributed to the clinical response in this patient.
CURRENT OPINION IN ALLERGY AND CLINICAL IMMUNOLOGY:

  
  - Exposure to a farming environment prenatally or early in life (2-3 first years) → modulation of the immune response → protection against asthma and atopy.
  
  - ¿Protective factors? Diet; bacterial and fungal diversity and its products (endotoxin, muramic acid, β-glucans).
  
  - Contact with cows and straw and consumption of farm milk account for virtually all the protective farm effect for asthma.
A MECHANISM FOR URTICARIA/ANGIOEDEMA IN PATIENTS WITH THYROID DISEASE
(Kirkpatrick CH. J Allergy Clin Immunol 2012; 130: 988-990):

- Thyroid autoimmunity is present in ±15% of patients with chronic urticaria.
- What is the relationship between thyroid autoimmunity and chronic urticaria/angioedema (UAE)? Six patients with antihistamine-refractory chronic urticaria and evidence of thyroid autoimmunity were studied.
- Activation of the classical complement pathway (↑ levels of C4a) occurred during active UAE. Complement activation was minimal during remissions.
- L-thyroxine improved or resolved chronic UAE in patients with thyroid autoimmunity. Two patients with chronic urticaria but without thyroid autoimmunity did not respond to L-thyroxine.
- Hypothesis: complement is activated by the complement controller domain of thyroperoxidase → mast cells are activated by complement anaphylotoxins (C3a, C5a) → mast cell products, such as tryptase, generate additional cleavage of complement proteins → chronic course of UAE.
- Why patients with chronic UAE do not have symptoms of asthma or anaphylaxis? Because mucosal-type mast cells do not have receptors for C3a and C5a, contrary to cutaneous mast cells.
- Some patients with chronic UAE have anti-FcεRI. Complement has an essential role in mast cell/basophil activation after anti-FcεRI targets FcεRI.


- ADA deficiency usually causes SCID. Hypomorphic mutations can lead to a variable phenotype including immune dysregulation; diagnosis is challenging.
- Are there any clues to suspect hypomorphic ADA mutations? Autoimmunity and severe infections; chronic lymphopenia, eosinophilia and ↑ IgE levels; ↓ KRECs and ↑ adenosine metabolites at newborn screening.
- ↓ KREC copy numbers at birth should also raise suspicion of combined ID.
- In this article authors report 2 ADA-deficient patients with delayed-onset (patient 1, P1) and late-onset phenotype (patient 2, P2).

IL-13 IN ASTHMA AND ALLERGY: ASTHMA PHENOTYPES AND TARGETED THERAPIES
(Ingram JL, Kraft M. J Allergy Clin Immunol 2012; 130: 829-842):
• **Approach to individualized therapy:** standardization of asthma subphenotypes according to clinical and laboratory data, including biomarkers → development of targeted therapies. Problem: the complex heterogeneity of asthma.

• Approximately 50% of asthmatic patients show a TH2-driven phenotype.

• **Biomarkers associated with TH2 inflammation** in airways: sputum eosinophils, peripheral blood eosinophils, serum IgE, FENO, periostin levels. Advantages and limitations of these markers are extensively discussed in the article.

• **Periostin:** extracellular matrix protein induced by IL-4 and IL-13 in airway epithelial cells and lung fibroblasts; it plays a role in cell adhesion, TGF-β production and subepithelial fibrosis in asthma airways.

• On the basis of analyses of **airway inflammatory cell profiles** in induced sputum samples, 4 subtypes of asthma have emerged: (1) eosinophilic; (2) neutrophilic or noneosinophilic; (3) mixed granulocytic; and (4) paucigranulocytic asthma (normal levels of neutrophils and absent eosinophils).

• **IL-13** is a key cytokine for Th2 responses, asthma and allergy. However, not all the pathways involved in human asthma are IL-13 driven.

• **IL-13 and IL-4R polymorphisms** are associated with asthma susceptibility, airways hyperresponsiveness (AHR), and ↑ IgE levels.

• **IL-13 actions:** ↑ survival and migration of eosinophils; isotype switching for IgE production; ↑ activation of macrophages; ↑ permeability, mucus production and nitric oxide production by airway epithelial cells; ↑ transformation of fibroblasts to myofibroblasts; ↑ AHR and remodeling.

• **Focused therapies** are in development: IL-4 variant; mAbs to IL-4Rα or IL-13; inhibitory RNAs and peptides specific for STAT6.

• **Serum periostin levels** might be a useful biomarker to identify patients with asthma who would be most responsive to anti–IL-13 therapies.

• **SCIENCE FROM A BLACK BOX (Aalberse RC. J Allergy Clin Immunol 2012; 130: 902-903):**

  • Production of IgE against an epitope predisposes to generation of IgE against different epitopes on the same allergen or other allergens (epitope spreading, “IgE breeds IgE”). This is not the same to immunologic memory (generation of more antibody of the same specificity).

  • **How does IgE production start at the first time?** Are there “more allergenic” molecules that induce IgE production (initiator allergens)?

  • Hatzler et al investigated which allergen qualified most as an initiator allergen in 126 children with seasonal allergic rhinoconjunctivitis and IgE (+) to grass →
the winner was Phl p 1 (it was present in 75% of the first positive serum samples). Method: ISAC allergen microarray (Phadia, Uppsala, Sweden).

- What about the 25% negative results for Phl p1 in the first samples? Do they exclude a role of Phl p1 as an initiator allergen in these patients? A technical issue might explain these negative results: Phl p 1 is a recombinant protein on the ISAC array (it has been reported that rPhl p 1 was not a suitable candidate as a reference protein because of low IgE reactivity). We don’t know if the rPhl p 1 used in Hatzler’s study is a new (different) recombinant protein with more IgE reactivity. This would obviously alter the interpretation of Hatzler’s results.

- A problem to understand in vitro tests is that information about reagents (process of manufacture, composition) is not full available. Some reagents are obtained as a “black box”, mostly due of proprietary reasons.

- Black box: “a device, system or object which can be viewed solely in terms of its input, output and transfer characteristics without any knowledge of its internal workings”.

- **THE MYTH OF HYPOALLERGENIC DOGS (AND CATS)** (Lockey RF. J Allergy Clin Immunol 2012; 130: 910-911):
  - Vredegoor et al → there is no difference between Can f1 levels in hair and homes from “hypoallergenic” vs “nonhypoallergenic” dog breeds.
  - However, >80% of allergic owners of “hypoallergenic” dogs referred less symptoms with these vs other dogs (although similar Can f 1 in their home; which other factors may be involved?).
  - USA is the country with more pets (62% houses, 78.2 million dogs, 86.4 million cats; average cost: $750/year; estimated total cost: $123 billion/year, equal to the gross national product of the 57th of the 182 countries of the world).
  - Evidence about protective effects of having a cat or dog in the home during the 1st year of life to prevent allergic disease is controversial. Acquiring or avoiding a pet cannot be justified as a measure to prevent allergy in an infant.
  - The concept of hypoallergenic pets is not supported by scientific evidence.

- **THYMIC STROMAL LYMPHOPOIETIN (TSLP) AND ALLERGIC DISEASE** (Ziegler SF. J Allergy Clin Immunol 2012; 130: 845-852):
  - TSLP is a distant paralog of IL-7. Its receptor is formed by 2 subunits: TSLPR (shares 24% identity with the common γ chain) and IL-7Rα.
  - Which cells express TSLP receptor? T cells, B cells, monocyte/macrophages, NKT cells, basophils, DCs, epithelial cells.
  - TSLP receptor signals by JAK1, JAK2, STAT1, STAT3 and STAT5.
• TSLP is expressed by epithelial cells, especially in lung and skin. Dysregulated TSLP expression can result in the development of allergic diseases.

• Hypothesis: epithelium activation (allergens, air pollutants, microbes, genetic susceptibility) → TSLP production by epithelial cells → OX40L upregulation and CCL17/CCL22 production by CD11c+ dendritic cells → differentiation and proliferation of TH2 cells after OX40L-OX40 interaction; attraction of TH2 cells by CCL17/CCL22 → production of IL-4, IL-5, IL-13 and TNF-α.

• Functions of TSLP: thymocyte proliferation; differentiation and survival of TH2 cells; induction of Tregs in tolerogenic environments; B-cell lymphopoiesis; cytokine production from mast cells, NKT cells and eosinophils; IL-3–independent basophil hematopoiesis.

• Increased TSLP expression has been seen in asthma, atopic dermatitis, allergic rhinitis, food allergy, allergic conjunctivitis, chronic sinusitis, nasal polyposis and eosinophilic esophagitis.

• SNPs of TSLP gene were associated with ↑ asthma susceptibility or protection.

• Nucleotide-binding oligomerization domain–containing proteins (NODs): PRRs that detect muropeptides from peptidoglycan; NODs are expressed in DCs, epithelial cells, neutrophils; they seem important for homeostasis in intestinal lymphoid tissue; mutations in NOD2 are associated with Crohn disease.

• Peripheral-induced Treg cells are CD80/86 independent (important for tolerance). Congenital absence of Foxp3+ Treg cells → IPEX syndrome.

• Phase II trials for asthma are underway using a fully humanized anti-TSLP antibody (AMG 157; Amgen, Thousand Oaks, Calif) or a human anti-OX40L antibody (Genentech, South San Francisco, Calif).

• Netherton syndrome (NS): a severe ichthyosis in which affected subjects have a significant predisposition for atopic diseases. Mechanisms: mutations in the serine protease inhibitor Kazal-type 5 (SPINK5) gene, which encodes the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI) → LEKTI deficiency → increased activity of kallikrein 5 → activation of protease-activated receptor 2 (PAR-2) → induction of TSLP expression by keratinocytes or airway epithelial cells → development of severe atopic diseases.