Allergology International 65 (2016) 243–252

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited review article

Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine

Ioana Agache [a, *], Cezmi A. Akdis [b, c]

[a] Faculty of Medicine, Transylvania University, Brasov, Romania
[b] Swiss Institute for Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland
[c] Christine Kühne-Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

ARTICLE INFO

Article history:
Received 17 April 2016
Accepted 25 April 2016
Available online 6 June 2016

Keywords:
Allergic diseases
Asthma
Biomarkers
Endotypes
Precision medicine

Abbreviations:
AD, atopic dermatitis; AHR, airway hyperreactivity; AR, allergic rhinitis; BAL, bronchoalveolar lavage; Bcl-2, B-cell lymphoma 2 protein; BNA, Bayesian Network Analysis; CCL, CC chemokine ligand; CGBN, Conditional Gaussian Bayesian Network; CD, cluster of differentiation; CLP, chitinase-like proteins; COPD, chronic obstructive lung disease; CpG, 5′—Cytosine—phosphate—Guanine—3′; CRS, chronic rhinosinusitis; CRTH2, chemokine receptor homologous molecule expressed on Th2 lymphocytes; CXCL, CXC chemokine ligand; CXCR2, CXC chemokine receptor 2; eNO, exhaled nitric oxide; FA, food allergy; FDA, Food and Drug Administration; Gal, galectin; GATA, gamma-amino-n-butyrate transaminase; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; IFN, interferon; LCA, latent class analysis; LIGHT, tumor necrosis factor superfamily member 14; MAIT, mucosal associated invariant T cell; MARS, multivariate regression splines; MAP-kinase, mitogen-activated

ABSTRACT

Discoveries from basic science research in the last decade have brought significant progress in knowledge of pathophysiologic processes of allergic diseases, with a compelling impact on understanding of the natural history, risk prediction, treatment selection or mechanism-specific prevention strategies. The view of the pathophysiology of allergic diseases developed from a mechanistic approach, with a focus on symptoms and organ function, to the recognition of a complex network of immunological pathways. Several subtypes of inflammation and complex immune-regulatory networks and the reasons for their failure are now described, that open the way for the development of new diagnostic tools and innovative targeted-treatments. An endotype is a subtype of a disease condition, which is defined by a distinct pathophysiological mechanism, whereas a disease phenotype defines any observable characteristic of a disease without any implication of a mechanism. Another key word linked to disease endotyping is biomarker that is measured and evaluated to examine any biological or pathogenic processes, including response to a therapeutic intervention. These three keywords will be discussed more and more in the future with the upcoming efforts to revolutionize patient care in the direction of precision medicine and precision health. The understanding of disease endotypes based on pathophysiological principles and their validation across clinically meaningful outcomes in asthma, allergic rhinitis, chronic rhinosinusitis, atopic dermatitis and food allergy will be crucial for the success of precision medicine as a new approach to patient management.

* Corresponding author. Allergy and Clinical Immunology, Faculty of Medicine, Transylvania University, Bvd. Eroilor nr 29, Brasov 500030, Romania.
E-mail address: ibrumaru@unitbv.ro (I. Agache).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2016.04.011

protein kinases; MMP, matrix metalloproteinase; MUC, mucin; NF, nerve fibers; NGF, nerve growth factor; NK, natural killer; NNCS, non-neuronal cholinergic system; NP, nasal polyps; ORA, over-representation analyses; PGE2, prostaglandin E2; PGP, proline-glycine-proline; PPIN, protein–protein interaction network; RAR, retinoic acid receptor; ROC, receiver operating characteristic curves; RUNX, Runt-related transcription factor X; S1P, sphingosine 1-phosphate; SCORAD, scoring atopic dermatitis; SNP, single-nucleotide polymorphism; SR, steroid resistant; SS, steroid sensitive; TDA, topological data analysis; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor; Treg, T regulatory cell; TSLP, thymic stromal lymphopoietin; VCAM, vascular endothelial cellular adhesion molecule; YKL-40, chitinase-3-like protein 1

The concept of endotypes, phenotypes, biomarkers and precision medicine

The three key words endotype, phenotype and biomarker will be one of the main topics of research on the way of building blocks of precision medicine and precision health.[1–3] The word "endotype" uncovers molecular mechanisms underlying observable disease characteristics known as "phenotype".[4,5] Assigning unique mechanisms and biomarkers for each endotype is crucial for the validity of the endotype.[5,6] So far only few (if any) valid endotypes have been identified in allergic disease, all with therapeutic implications. To further elaborate on the definition of an endotype one must recognize that one major pathogenic pathway such as type 2 immune response is highly complex, including several determinants with nonlinear dynamic interactions (Fig. 1) and heterogeneous, since not all determinants are present in all patients or, in a given patient, at all time points.[6,7] We therefore must embrace the concept of a "*complex endotype*" consisting of several sub-endotypes as opposed to an endotype that encompasses a single molecular mechanism.[7]

Epigenetics and endotypes of allergy and asthma

Epigenetic programming during early life influences is crucial for the development of the endotypes of allergic diseases. Increased knowledge on developmental endotypes addressing disease inception and progression are needed for the outset of early prevention and disease modifying strategies. Crucial determining factors for complex immune regulation and barrier function include respiratory infections, microbiome, and nutrition. Epigenetic mechanisms link gene regulation to environmental influences and developmental trajectories.[8] Developmental programming induced by the intrauterine environment (cigarette smoke, nutrition, and stress) affects the fetus and its germ line, with intergenerational epigenetic effects. Developmental programming can be transmitted across generations (trans-generational effects) and cannot be anymore attributed to direct environmental exposure.

Several time-dependent DNA methylation signatures associated with allergic disease developmental endotypes are described. The Tucson Infant Immune Study identified in cord blood mononuclear cells 589 differentially methylated regions associated with

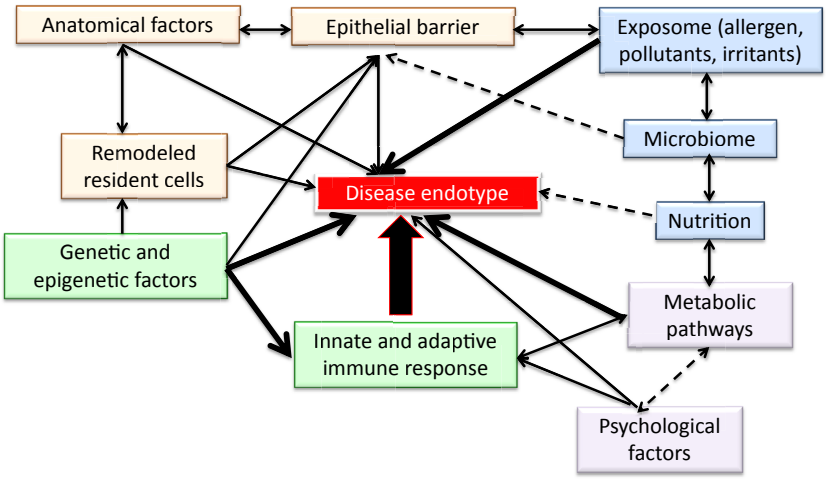

Fig. 1. Factors that affect a disease endotype in allergic diseases. For precision medicine in allergic disease, more mechanistic approaches are needed, based on an integrated understanding of the individual patient's biological mechanisms, including the interplay between the immune response and the exposome, infections and microbiome, genetics, epigenetics, psychosocial factors, nutrition, anatomical factors and metabolic pathways.