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Immune biomarkers in the spectrum of childhood noncommunicable diseases

Chrysanthi Skevaki, MD, PhD,[a,b] Jolice Van den Berg, PhD,[a,c] Nicholas Jones, BSc,[a,d] Johan Garssen, MD, PhD,[a,e] Peter Vuillermin, MD, PhD,[a,f] Michael Levin, MD, PhD,[a,g] Alan Landay, PhD,[a,c] Harald Renz, MD,[a,b] Philip C. Calder, PhD,[a,h] and Catherine A. Thornton, PhD[a,d] *Marburg, Germany, Chicago, Ill, Swansea, Wales, Utrecht, The Netherlands, Geelong, Australia, Cape Town, South Africa, and Southampton, United Kingdom*

A biomarker is an accurately and reproducibly quantifiable biological characteristic that provides an objective measure of health status or disease. Benefits of biomarkers include identification of therapeutic targets, monitoring of clinical interventions, and development of personalized (or precision) medicine. Challenges to the use of biomarkers include optimizing sample collection, processing and storage, validation, and often the need for sophisticated laboratory and bioinformatics approaches. Biomarkers offer better understanding of disease processes and should benefit the early detection, treatment, and management of multiple noncommunicable diseases (NCDs). This review will consider the utility of biomarkers in patients with allergic and other immune-mediated diseases in childhood. Typically, biomarkers are used currently to provide mechanistic insight or an objective measure of disease severity, with their future role in risk stratification/disease prediction speculative at best. There are many lessons to be learned from the biomarker strategies used for cancer in which biomarkers are in routine clinical use and industry-wide standardized approaches have been developed. Biomarker discovery and validation in children with disease lag behind those in adults; given the early onset and therefore potential lifelong effect of many NCDs, there should be more studies incorporating cohorts of children. Many pediatric biomarkers are at the discovery stage, with a long path to evaluation and clinical implementation. The ultimate challenge will be optimization of prevention strategies that can be implemented in children identified as being at risk of an NCD through the use of biomarkers. (J Allergy Clin Immunol 2016;137:1302-16.)

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Noncommunicable diseases (NCDs) are one of the major global challenges of the 21st century.[1] NCDs have been termed a "slow-motion disaster"[2] and a global crisis[3] as their prevalence increases in all countries, in all income groups, and at all ages. NCDs, often called chronic diseases, are generally considered one of 4 main types: cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes. Allergic disease has been suggested as a fifth group given its high prevalence and early onset,[4] but neurocognitive diseases, inflammatory bowel diseases (IBDs), and others are also important NCDs. Worldwide, 2 of every 3 deaths each year are attributable to NCDs, with one third of those who die being less than 60 years of age.[5] In all regions of the world, the prevalence of NCDs is increasing because of an aging population and the globalization of common risk factors.[5] The main risk factors for NCDs, accounting for two thirds of all cases, are tobacco use; foods high in saturated and trans-fats, salt, and sugar; physical inactivity; and alcohol consumption.[6] NCDs not only directly threaten health, they influence economic development to compound the effect on health. The World Economic Forum ranks NCDs as one of the top global threats to economic development: a 10% increase in mortality caused by NCDs reduces annual economic growth by 0.5%.[7]

A shared feature of all NCDs is chronic low-grade inflammation promoted by modern diets, environmental pollutants,

From [a]International Inflammation (in-FLAME) Network of the World Universities Network; [b]the Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Philipps University Marburg, University Hospital Giessen and Marburg GmbH Baldingerstr, Marburg; [c]the Department of Immunology/Microbiology Rush University Medical Center Chicago; [d]the Institute of Life Science, Swansea University Medical School, Swansea University; [e]Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacology, Beta Faculty, Utrecht University; [f]the Child Health Research Unit, Barwon Health, School of Medicine, Deakin University, Geelong; [g]the Division of Asthma and Allergy, University of Cape Town, and the Department of Pediatrics and Child Health, Red Cross Children's Hospital, Cape Town; and [h]the Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, and NIHR Southampton Biomedical Research Centre, Southampton University Hospital NHS Foundation Trust and University of Southampton.

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Corresponding author: Catherine A. Thornton, PhD, Swansea University, Institute of Life Science, School of Medicine, Singleton Park, Swansea SA2 8PP, United Kingdom. E-mail: c.a.thornton@swansea.ac.uk.

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Terms in boldface and italics are defined in the glossary on page 1303.

Abbreviations used
ASD: Autism spectrum disorder
CD: Crohn disease
CRP: C-reactive protein
EMP: Endothelial microparticle
EPC: Endothelial progenitor cell
FoxP3: Forkhead box P3
IBD: Inflammatory bowel disease
miRNA: MicroRNA
MS: Mass spectrometry
NCD: Noncommunicable disease
OIT: Oral immunotherapy
sFasL: Soluble Fas ligand
UC: Ulcerative colitis

microbial exposure, and psychological and biological (eg, oxidative or endoplasmic reticulum) stress.[1,8] This low-grade inflammation differs from classical inflammation, which occurs in response to a threat or injury and leads to tissue repair and restoration of the basal homeostatic state. The low-grade inflammation in patients with NCDs is chronic; without effective treatment, basal homeostasis cannot be restored, and the damage might already be done.[9] Inflammatory pathways in NCDs are multifactorial and part of a metabolic cascade, including cellular oxidative stress and insulin resistance, which induces allostatic overload, dysmetabolism, and ultimately chronic disease.[10] Changes in the gut microbiome have emerged as one of the pathways leading to chronic low-grade inflammation.[11] Altered gut colonization and reduced microbiome diversity occur in response to both changed nutritional patterns and the built environment; a diverse microbiome is essential for normal immune development and regulation.[12] There is global interest in gut dysbiosis in multiple NCD settings, including beta-cell autoimmune disease,[13] atopic dermatitis,[14] and IBDs.[15] Despite the clear link between the gut microbiome and development of these diseases and obesity, cardiovascular disease, and metabolic disorders more generally, the causal relationship between alterations in the gut microbiome and ill health is likely to be complex. There can be multiple different pathways for different organisms; these pathways might or might not overlap in some of their stages. However, specific microbe-derived metabolites, such as short-chain fatty acids, have emerged as examples whereby cross-talk between the microbiome and host is achieved.

Although NCDs are most prominent in adulthood, development in early life influences predisposition to NCDs. This starts as

GLOSSARY

ADIPOKINES: Cytokines secreted by adipose tissue.

FILAGGRIN: A filament-associated protein that binds to keratin fibers in epithelial cells and is essential for regulation of epidermal homeostasis.

FLOW CYTOMETRY: A technology that is used to analyze the physical and chemical characteristics of particles in a fluid as it passes through at least 1 laser. Cell components are fluorescently labeled and then excited by the laser to emit light at varying wavelengths. Flow cytometry allows for the characterization and separation of immune cells.

IL-4: A pleiotropic cytokine produced by activated T cells, this cytokine is a ligand for the IL-4 receptor that also binds to IL-13, which can contribute to many overlapping functions of this cytokine and IL-13.

IL-5: A major maturation and differentiation cytokine expressed by T_H2 cells and eosinophils in mice and human subjects. IL-5 has been shown to play an instrumental role in eosinophilic inflammation in patients with allergic diseases.

IL-10: A cytokine produced primarily by monocytes and, to a lesser extent, by lymphocytes that has pleiotropic effects in immunoregulation and inflammation by limiting the immune response to pathogens and thereby preventing damage to the host.

IL-12: A cytokine produced by dendritic cells, macrophages, and human B-lymphoblastoid cells in response to antigen stimulation. IL-12 is involved in the differentiation of naive T cells into T_H1 cells. It is known as a T cell–stimulating factor that can stimulate the growth and function of T cells. It stimulates the production of IFN-γ and TNF-α from T cells and natural killer cells and reduces IL-4–mediated suppression of IFN-γ.

IL-13: A cytokine produced primarily by T_H2 cells that is involved in several stages of B-cell maturation and differentiation and is critical to the pathogenesis of allergen-induced asthma but operates through mechanisms independent of IgE and eosinophils.

LPS: An endotoxin found in the outer membrane of gram-negative bacteria that elicits a strong immune responses in animals.

MASS CYTOMETRY: A mass spectrometry technique that analyzes cell properties using antibodies tagged with rare earth elements.

MASS SPECTROMETRY: An analytic technique that separates ions by their mass.

RAPAMYCIN (MECHANISTIC TARGET OF RAPAMYCIN): A macrolide produced by the bacterium *Streptomyces hygroscopicus*, which has immunosuppressant functions in human subjects. It prevents activation of T and B cells by inhibiting IL-2 production.

REGULATORY T (TREG): A subset of T cells that control inflammation and induce tolerance by secreting anti-inflammatory cytokines. They are $CD4^+CD25^+$ T cells under the control of the transcription factor FoxP3 that develop and emigrate from the thymus to perform their key role in immune homeostasis. Treg cells secrete immunosuppressive soluble factors, such as IL-9, IL-10, and TGF-β.

T_H2 CELLS: A distinct lineage of $CD4^+$ effector T cells that secrete IL-4, IL-5, IL-9, IL-13, and IL-17E/IL-25. These cells are required for humoral immunity and play an important role in coordinating the immune response to large extracellular pathogens.

T_H17 CELLS: A subset of activated $CD4^+$ T cells that are responsive to IL-1R1 and IL-23R signaling. They are regulated by the IL-6/signal transducer and activator of transcription 3/retinoic acid–related orphan receptor γt lineage control and produce the cytokines IL-17A, IL-17F, IL-17AF, IL-21, IL-22, IL-26 (human), GM-CSF, macrophage inflammatory protein 3α, and TNF-α. T_H17 cells act as a bridge between adaptive and innate immunity, where they promote neutrophil activation, immunity to pathogens, and inflammation.

TNF-α: Secreted primarily by macrophages, this cytokine's primary role is the regulation of immune cells. Moreover, it is involved in the regulation of a wide spectrum of biological processes, including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation.

TOLL-LIKE RECEPTOR (TLR): A class of receptors expressed on macrophages and dendritic cells that recognize conserved microbial particles that can activate an immune response.

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