Correlation between early-life regulation of the immune system by microbiota and allergy development

Thomas Gensollen, PhD, and Richard S. Blumberg, MD *Boston, Mass*

Early postnatal life is a key time for development of the immune system and colonization of the host by microbiota. Recent studies have shown that specific limbs of the immune system can be regulated by microbiota in a time-restricted period during early life. Studies in mouse models have shown that perturbations of the microbiota during early life can cause immune effects that can persist into adulthood and create increased host susceptibility to certain diseases. Here we discuss the role of early-life regulation of the immune system by the microbiota and how it can be related to allergy development. (J Allergy Clin Immunol 2017;139:1084-91.)

Key words: *Allergy, microbiota, early-life, window of opportunity, neonate*

Abbreviations used
GF: Germ-free
iNKT: Invariant natural killer T
SPF: Specific pathogen-free
Treg: Regulatory T

Human subjects are colonized by trillions of microorganisms that include fungi, ***archaea***, viruses, ***protozoans***, and bacteria. The greater numbers of these microbes can be found in the intestinal tract and in the colon in particular. The past decades have shown a growing interest in studying the phenotype and function of the microbiota in the gut and its roles in immunity and health outcomes. Analyses of microbiota composition in adult human subjects have revealed numerous associations between specific bacterial phyla and disease and elucidated a number of pathways through which this can occur. Perhaps the earliest example is the relationship described between the gut microbiome and the phyla-level changes associated with metabolic pathways and obesity.[1,2] Since that time, there have been numerous other examples in which alterations in microbiota composition or function, as imputed by metagenomics or direct analysis of the microbiota, are associated with human diseases. For example, type 2 diabetes is characterized by decreased quantities of butyrate-producing bacteria[3] in comparison with cardiovascular disease, which is associated with an increased gut microbiota, driving the production of inflammatory lipid mediators.[4] In the gut itself microbial dysbiosis is also strongly associated with inflammatory bowel disease development.[5] This latter example has been quite instructive because it been difficult to determine whether the microbial alterations are primary and causative or secondary events that are derived from intestinal inflammation itself.[6]

Of recent interest is the possibility that many of the disease-associated microbial changes that have been observed and their immune consequences might originally develop during the earliest days of life. During the early postnatal period, the microbiota is in the process of colonizing the host, and its composition is highly unstable. This time of early-life bacterial colonization also correlates with development of the immune system and its education, which allows it to tolerate its environment to fight pathogens and avoid allergy and autoimmunity.

Increasing evidence shows that certain immune cell populations can be regulated by microbiota in a time-restricted fashion. Furthermore, perturbations of the microbiota during a specific early-life time period can have persistent effects on the immune system later in life. This has predicted the existence of a window of opportunity during the early life of the host that is amenable to environmental manipulation. This review describes the immune processes that are regulated by microbiota specifically during early life and their relation to disease development and allergy in particular.

ESTABLISHMENT OF THE MICROBIOTA DURING EARLY LIFE

Mucosal tissues are colonized by microbes that have the capacity to interact with the host. In the adult the gut microbiota can regulate the host's immune response,[7] metabolism,[8] and digestion,[9] which in the latter case provides the mucosa with specific enzymes and other proteins that would not be otherwise produced.[10] Four principal phyla generally comprise a healthy gut

From the Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School.

Supported by National Institutes of Health grant RO1 DK44319 and the Harvard Digestive Diseases Center (to R.S.B.) and Crohn's and Colitis Foundation of America grant no. 418509 (to T.G.).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication December 19, 2016; revised February 15, 2017; accepted for publication February 22, 2017.

Corresponding author: Richard S. Blumberg, MD, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Thorn Biomedical Research Building, Room 1419, Boston, MA 02115. E-mail: rblumberg@bwh.harvard.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00

© 2017 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2017.02.011

Terms in boldface and italics are defined in the glossary on page 1085.

microbiome: Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria.

Although the fetal compartment has long been considered sterile, colonization of the host by microbes seems to be initiated before birth. Maternally derived bacteria can be isolated from umbilical cord blood of healthy neonates born by means of cesarean section.[11] Bacteria are detected in the meconium of preterm human babies.[12] Labeled *Enterococcus faecium* orally inoculated to pregnant mice can be retrieved in the meconium of the fetus 1 day before birth.[13] In addition, by using a mutant strain of *Escherichia coli*, a recent study has shown that transient intestinal colonization of a pregnant mouse can exert effects on the offspring's immune system.[14]

Newborns are exposed to a large ***diversity*** of maternal bacteria during birth. Logically, the composition of the newborn microbiota is deeply influenced by the mode of delivery and exposure to bacteria. The microbiota composition of infants born by means of vaginal birth is similar to that of the maternal vaginal and gut microbiota,[15] whereas babies born by means of cesarean section harbor a microbiota resembling the human skin microbiota.[16] These differences in microbiota composition between infants born by means of vaginal birth and cesarean section are persistent, with microbes associated with cesarean section still detectable 2 years after birth.[17] The infant microbiota structure is highly unstable and has low diversity[18] compared with the adult microbiota.[19] The first major shift in intestinal microbiota composition was initially thought to be associated with the introduction of solid food.[20-22] A more recent study has shown that differences in microbial composition and function associated with solid-food introduction do not become apparent until the infant discontinues breast-feeding, suggesting that the latter rather than the transition to a solid-food diet is the major factor that determines a shift of the microbial ecology toward an adult-like configuration in 12-month-old infants.[15] The human intestinal microbiota further evolves with age and stabilizes after 3 years of life.[23] However, even at 5 years after birth, the gut microbiota might still not be definitely established.[24] Thus the precise time after which the microbiota switches to an individual specific adult type remains to be firmly determined. Dietary and environmental factors are important in molding the composition of the microbiota after birth. Antibiotic use[25] and breast-feeding/formula feeding[26,27] are associated with modifications of microbiota composition. The infant genotype can also influence the early gut microbiota composition, as shown in infants carrying the human leukocyte antigen DQ2 haplotype.[28] Therefore the infant microbiota evolves with age and reflects the history of exposure to external factors, as well as host genetics, before stabilizing to an individual adult microbiota arrangement (Fig 1).

This period of microbiota evolution to an adult configuration during early life coincides with development of the immune system. Emerging evidence from rodent studies suggests that part of the immune system is educated by microbiota during early life in a time-restricted fashion. This has been recognized to occur during the neonatal period of life, especially before weaning.[29] However, the specific details of these temporal effects in rodents and especially in human subjects remain to be defined. It has also been shown that the immune influences induced by the microbiota during this specific window of time might be a determining factor in resistance or susceptibility to diseases, such as allergy, during infancy and potentially during adulthood.

EARLY-LIFE COLONIZATION AND ALLERGIC DISEASES

The increased incidence of allergy worldwide in the context of progressive urbanization and industrialization has led to investigations about the influence of environmental and dietary factors associated with "westernized" countries that might be involved in the development of allergies. It is now well established that early-life sensitization to allergens influences susceptibility to allergic disease development in later life.[30,31] The hygiene hypothesis is based on the initial observation that family size and position in the household in childhood were associated with the development of hay fever, asthma, and atopic

GLOSSARY

ARCHAEA: A domain of primitive single-celled microorganisms that lack a nucleus, as well as organelles. Archaea and bacteria make up the 2 domains of Prokaryotae. Archaea are thought to have arisen from extreme settings, such as hot, salty, and/or acidic environments.

DIVERSITY: A term used in bacterial community metrics analysis that includes both richness (ie, the number of different species represented in the community) and evenness (ie, equality in abundance of the species).

ENZYME A20: A cytoplasmic zinc finger protein that inhibits nuclear factor κB (NF-κB) activity and TNF-mediated programmed cell death. NF-κB signaling cascades are heavily controlled by ubiquitination, and several proteins, including A20, can interfere with these processes. Genome-wide association studies have identified A20 as a susceptibility gene in patients with inflammatory disease.

GROUP 3 INNATE LYMPHOID CELLS (ILC3s): Innate immune cells with lymphoid features that do not have antigen receptors. They can quickly respond to multiple tissue-derived factors, such as cytokines, eicosanoids, and alarmins, by producing multiple proinflammatory and immunoregulatory cytokines. ILC classification into groups based on their transcription factors and cytokines parallels helper T-cell subsets. ILC3s resemble T_H17 cells. ILC3s are defined by production of IL-17A and IL-22 and expression of retinoic acid–related orphan receptor γt. They have been implicated in immunity against extracellular bacteria and autoimmune diseases.

HELIOS-NEGATIVE REGULATORY T CELL: Natural regulatory T (nTreg) cells are forkhead box protein 3 $(Foxp3)^+$ and usually are thymic derived. However, some $Foxp3^+$ Treg cells can be peripherally induced. A subset of Treg cells express Helios, a transcription factor with a poorly understood function in Treg cells, but might represent an additional way to differentiate subsets of Treg cells.

INVARIANT NATURAL KILLER T CELLS: A subset of lymphocytes that express surface molecules characteristic of both natural killer (NK) cells (CD16) and T cells (CD3). All NKT cells recognize lipids bound to CD1, an MHC-like molecule. They are capable of rapidly secreting cytokines after stimulation. The T-cell receptor α chains in invariant NKT cells have limited diversity and are characterized by a unique Vα24-Jα18 rearrangement in humans.

PROTOZOANS: Motile single-celled organisms, such as amoeba, containing nuclei and organelles. They are often divided based on kinetic properties. Examples include *Plasmodium* species, *Entamoeba histolytica*, *Trypanosoma* species, *Leishmania* species, *Giardia lamblia*, *Cryptosporidium* species, and *Toxoplasma gondii*.

The editors wish to acknowledge Daniel Searing, MD, for preparing this glossary.

Download English Version:

https://daneshyari.com/en/article/5647103

Download Persian Version:

https://daneshyari.com/article/5647103

Daneshyari.com