ASTHMA

Asthma: Undoing millions of years of coevolution in early life?

Maria Gloria Dominguez-Bello[1]* and Martin J. Blaser[1,2,3]*

Early microbiome composition can predict asthma risk, and asthma development can be subverted when missing protective microbes are restored (Arrieta *et al.*, this issue).

Why has there been an explosive worldwide rise in asthma over the past three human generations? Although human genetic variation may predispose some individuals, the dramatic rise in incidence strongly suggests the involvement of environmental changes. The environmental reasoning might be further divided into two alternative explanations. First, our environment has changed because we are "too clean"—in other words, our exposure to soil, dust, farm animals, pets, and "germs" in general is not what it used to be (which is consistent with the "hygiene hypothesis"). Second, the change in our environment concerns our internal milieu, our ancient and conserved microbiome, with continuing changes that result from modernization (*1*, *2*). Although these two hypotheses are not exclusive, their respective foci suggest that solutions will take markedly different forms.

In this issue of *Science Translational Medicine*, Arrieta *et al.* (*3*) address the importance of the very early life microbiome in the predisposition of children to develop asthma and provide important perspectives. They studied a birth cohort of Canadian infants and compared those who developed wheezing and skin atopy at age 1 year with those who remained well. The authors found that early exposure (in the first year of life) to antibiotics was associated with the presence of wheeze and atopy, which together are a strong marker for the later development of asthma. Other microbiome disruptors, such as Caesarean (C)-section birth (versus vaginal) and exclusive formula feeding (versus breastfeeding), trended with asthma risk, although the differences were not significant.

Using bioinformatics analyses, Arrieta *et al.* identified particular genus-level bacterial taxa that were depleted in the intestines of the 3-month-old infants who later developed wheezing and atopy in relation to the healthy controls. By 1 year of age, most of these differences were gone, suggesting that the microbiota in the first few months of life might be crucial determinants of the asthma risk. To determine whether the microbes that were depleted might play a causal role, the authors introduced cultured members of these taxa into a "depleted" infant fecal specimen or not and then humanized germ-free mice with these suspensions. In a subsequent provocative assay of lung allergy in these experimental mice, they provided evidence that restoring these depleted taxa played a protective role against airway inflammation. That normalizing the abnormal 3-month-old fecal microbiome reduced the associated asthma-related end points points to the potential role of the early-life indigenous microbes in diagnosing, preventing, and treating allergic disorders. These findings emphasize the importance of the early, maternally transmitted microbiome in health (Fig. 1).

VERTICAL TRANSMISSION OF MICROBIOTA

All animal species have evolved in the context of a microbial world that predated them. Through natural selection, cooperation between microbes and humans evolved, with further (secondary) selection and continued coevolution. The congruent phylogeny of the composite fecal microbiome and its hosts provides evidence for intergenerational "vertical" transmission, thus suggesting the coevolution of microbiota and host over a time scale of millions of years or longer (*4*). At the time when they are born, mammals are inoculated with maternal birth canal microbes, which are relevant to the exclusive maternal milk diet during early development. The extent of microbiota acquisition in utero is uncertain and may not be large in magnitude. The major introduction of the naïve human fetus to the world of microbes occurs during labor, when the water breaks and the microbes ascend the birth canal, even as the baby is descending face backward. Nature has provided an extensive opportunity for the child being born to acquire its mother's vaginal and fecal microbiota, at the start of the new life.

The microbiota cover the baby's skin and are in the mouth, so that the baby's first suckling inoculates the breast with microbes that then might flourish there. With the particular substrates in breast milk that favor their growth, this synbiotic combination—prebiotics including particular oligosaccharides and urea, and probiotics that include *Bifidobacterium* and *Lactobacillus* species—seeds the founding populations in the infant's gastrointestinal (GI) tract. This cycle involving mothers and their daughters—vaginal-rectal, skin-mouth, breast, GI tract, and then to the vagina and rectum for the next generation—has been uninterrupted since time immemorial (Fig. 1). The soft skin of the baby may provide an essential way station and reservoir for the eventual seeding of other loci. This nonrandom, nonaccidental transmission would then provide the microbiota (and their preferential substrates) that perform essential functions in development: for example, to guide developing organs in energy expenditure and saving, to inform the developing brain about certainty or not, and to train the naïve immune system in the GI tract about what self and nonself may mean.

In humans, there is much evidence that at least some proportion of the adult microbiota is a consequence of who our mother was, and what she carried. This concept of verticality is of critical importance because it then implies that as the young of the species are developing toward their adult forms, their residential microbes are communicating, via chemical and physical signals, with their own (host) cells. The long-term conservation (*4*) further implies that the communication is choreographed, that it is in fact a central part of the development of the young. For young mammals, we are particularly concerned with the development of metabolic systems, immunity, and cognition. There is increasing evidence that the early microbiome is a player in host de-

[1]Division of Translational Medicine, Department of Medicine, New York University Langone Medical Center, (NYULMC) New York, NY 10016, USA. [2]Department of Microbiology, NYULMC, New York, NY 10016, USA. [3]Department of Veterans Affairs New York Harbor Medical Center, New York, NY 10010, USA.
*Corresponding author.
E-mail: maria.dominguez-bello@nyumc.org (M.G.D.-B.); martin.blaser@nyumc.org (M.J.B.)

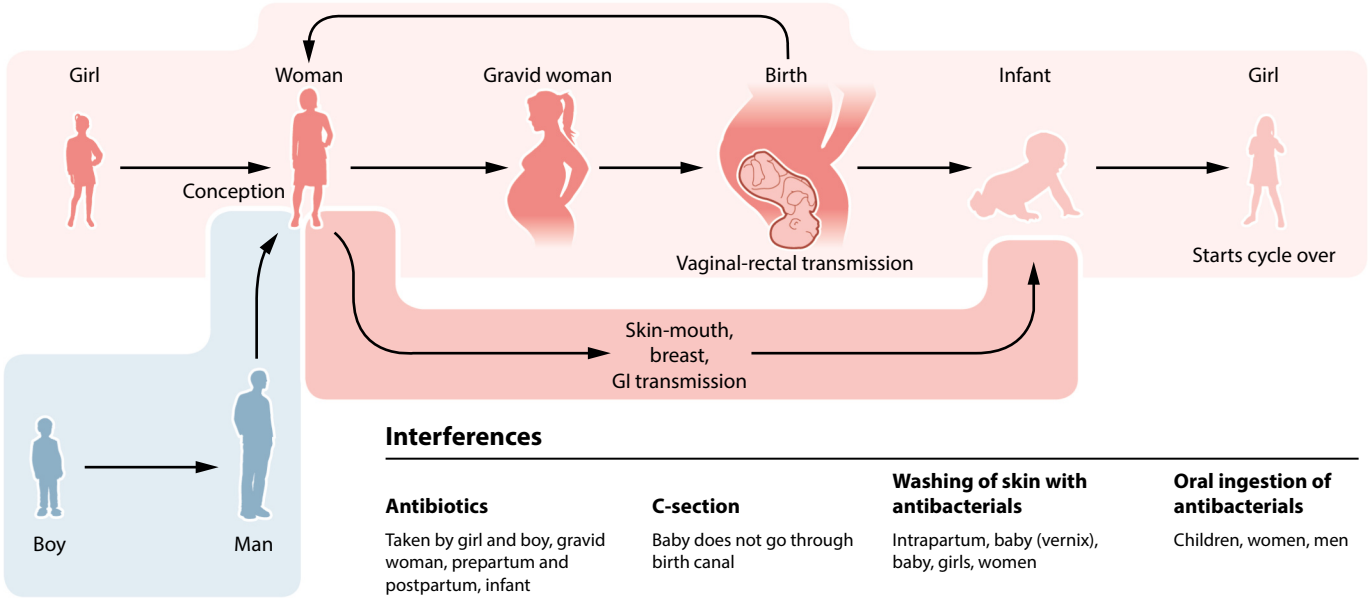

Fig. 1. The cycle of healthy microbiota transmission and host development. In utero, introduction to microbiota is minimal in health, but exposures to girls and mothers that affect microbiota composition before intergenerational transmission are important. During birthing, practices that eliminate or minimize acquisition of vaginal-rectal microbiota, including C-section, early/extensive washing, and antibiotic exposures, may have costs. Human milk is designed for nurturing the transmitted microbes during nursing, often without competition for substrate between favored microbes and host. Formula feeding means loss of this function and substitution with substrates that have alternative selective properties. The early-life microbiota during infancy and youth, especially but not exclusively in the GI tract, interacts with human cells and forms part of the developmental matrix, affecting signals to lymphoid organs, metabolic organs (including intestine, liver, muscle, and adipocytes), and the central nervous system through chemical (neurotransmitter) signals and neural pathways. Lastly, girls become women, preparing for the next generation.

velopment and that there are critical "windows" when key events occur; perturbation during such early-life windows can have lifelong consequences (*5*). The study results by Arrieta *et al.* (*3*) are consistent with and extend these ideas in the domain of immunity, considering propensity for asthma as one consequence of disordered immunological development and illustrating the potential for microbial therapies.

SECULAR TRENDS IN MICROBE POPULATIONS

Human cultural evolution is exerting pressure on the microbiome that had previously been restricted to natural selection. It has become increasingly clear that we humans have been losing microbial diversity as we have adopted modern practices (*2*); the scale of our loss might be in the neighborhood of 50% (*6*). If true, when and how did it happen? One hypothesis is that it has been cumulative across recent generations (*1*). As we better understand the importance of vertical (intergenerational) transmission and the essential hand-off of the microbiota, it becomes evident that if the mother does not have a particular microbe, the baby has a low chance of acquiring it. These effects are compounded by many factors. First, we must consider antibiotics; evidence suggests that babies who receive early-life antibiotics are more likely to develop not only asthma but also milk allergy—and the more courses, the higher the risk (*7*). In addition, it is not just the baby's exposure but also the mother's exposure to antibiotics while pregnant and before pregnancy that also were found to be significant (*7*). These observations make sense in the context of the intergenerational hand-off.

Next, there is elective C-section in which the newborn misses the acquisition of mom's vaginal-rectal bacteria during labor and delivery. In many countries, C-section accounts for a third to more than half of all births; the baby's microbiome is abnormal early (*8*) and may not reach normality for months, creating a window of abnormality during development. Breast milk selects for favorable microbes, but infant formula is a deficient imitation lacking the "know-how" of millions of years of natural selection. There are other factors that perturb or irrevocably alter the early-life microbiota (Fig. 1). Although Arrieta *et al.* focus on the colonic microbiota, other evidence suggests that *Helicobacter pylori*, the dominant microbe in the human stomach with strong maternal transmission, and now "disappearing" (*1*, *6*), is also part of the protection against asthma (*9*, *10*).

EARLY-LIFE PERSPECTIVE

It is becoming clear that early life is indeed the crucible for healthy development and that the vertically transmitted and now progressively disappearing microbiota have been of critical importance for optimizing later health. The study by Arrieta *et al.* (*3*) provides new pieces of the puzzle, with a direct focus on disordered immunological development leading to asthma. Confirmation and extension of these findings should allow us to develop better approaches to prevention, including restoration of microbiota, as well as treatments based on the microbial cross-talk with hosts. Important unanswered questions include careful definition of the most important conserved actors, ways to identify their fingerprints, as well as the key molecules that promote regulatory T cells and other effectors modulating immunity. When does the window open and when does it close? How can we recognize problems early enough to intervene? Stay tuned.

REFERENCES AND NOTES

1. M. J. Blaser, S. Falkow, What are the consequences of the disappearing human microbiota? *Nat. Rev. Microbiol.* **7**, 887–894 (2009).
2. T. Yatsunenko, F. E. Rey, M. J. Manary, I. Trehan, M. G. Dominguez-Bello, M. Contreras, M. Magris, G. Hidalgo, R. N. Baldassano, A. P. Anokhin, A. C. Heath, B. Warner, J. Reeder, J. Kuczynski, J. G. Caporaso, C. A. Lozupone, C. Lauber, J. C. Clemente, D. Knights, R. Knight, J. I. Gordon, Human gut microbiome viewed across age and geography. *Nature* **486**, 222–227 (2012).
3. M.-C. Arrieta, L. T. Stiemsma, P. A. Dimitriu, L. Thorson, S. Russell, S. Yurist-Doutsch, B. Kuzeljevic, M. J. Gold, H. M. Britton, D. L. Lefebvre, P. Subbarao, P. Mandhane, A. Becker, K. M. McNagny, M. R. Sears, T. Kollmann, the CHILD Study Investigators, W. W. Mohn, S. E. Turvey, B. B. Finlay, Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci. Transl. Med.* **7**, 307ra152 (2015).
4. A. H. Moeller, Y. Li, E. Mpoudi Ngole, S. Ahuka-Mundeke, E. V. Lonsdorf, A. E. Pusey, M. Peeters, B. H. Hahn, H. Ochman, Rapid changes in the gut microbiome during human evolution. *Proc. Natl. Acad. Sci. U.S.A.* **111**, 16431–16435 (2014).
5. L. M. Cox, S. Yamanishi, J. Sohn, A. V. Alekseyenko, J. M. Leung, I. Cho, S. G. Kim, H. Li, Z. Gao, D. Mahana, J. G. Zárate Rodriguez, A. B. Rogers, N. Robine, P. Loke, M. J. Blaser, Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* **158**, 705–721 (2014).
6. J. C. Clemente, E. C. Pehrsson, M. J. Blaser, K. Sandhu, Z. Gao, B. Wang, M. Magris, G. Hidalgo, M. Contreras, Ó. Noya-Alarcón, O. Lander, J. McDonald, M. Cox, J. Walter, P. L. Oh, J. F. Ruiz, S. Rodriguez, N. Shen, S. J. Song, J. Metcalf, R. Knight, G. Dantas, M. G. Dominguez-Bello, The microbiome of uncontacted Amerindians. *Sci. Adv.* **1**, e1500183 (2015).
7. J. Metsälä, A. Lundqvist, L. J. Virta, M. Kaila, M. Gissler, S. M. Virtanen, Mother's and offspring's use of antibiotics and infant allergy to cow's milk. *Epidemiology* **24**, 303–309 (2013).
8. M. G. Dominguez-Bello, E. K. Costello, M. Contreras, M. Magris, G. Hidalgo, N. Fierer, R. Knight, Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 11971–11975 (2010).
9. Y. Chen, M. J. Blaser, Inverse associations of *Helicobacter pylori* with asthma and allergy. *Arch. Intern. Med.* **167**, 821–827 (2007).
10. I. C. Arnold, N. Dehzad, S. Reuter, H. Martin, B. Becher, C. Taube, A. Müller, Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cells. *J. Clin. Invest.* **121**, 3088–3093 (2011).

Funding: R01 DK090989 from the National Institutes of Health, Diane Belfer Program for Human Microbial Ecology, Emch Fund.

10.1126/scitranslmed.aad2741

Citation: M. G. Dominguez-Bello, M. J. Blaser, Asthma: Undoing millions of years of coevolution in early life? *Sci. Transl. Med.* **7**, 307fs39 (2015).

Science Translational Medicine

Asthma: Undoing millions of years of coevolution in early life?

Maria Gloria Dominguez-Bello and Martin J. Blaser

Sci Transl Med **7**, 307fs39307fs39.
DOI: 10.1126/scitranslmed.aad2741