Malmutrition

The Human Gut Microbiota and Undernutrition

Jeffrey I. Gordon,1* Kathryn G. Dewey,2 David A. Mills,3,4 Ruslan M. Medzhitov5

Childhood malnutrition is a global health problem that cannot be attributed to food insecurity alone. The gut microbiota may contribute to this devastating health disorder. In this Perspective, we call for the application of tools and concepts emerging from studies of the human gut microbiota to better understand the nutritional needs of infants and children and the role of the microbiota in the pathogenesis and treatment of undernutrition. This effort will require elucidation of the interrelationships between breast milk composition and the development of the microbiota and immune system in the context of the maternal-infant dyad.

WHAT DO WE MEAN BY MALNUTRITION?

Malnutrition is a general term that encompasses many different manifestations of inadequate nutrition, including delayed growth of children as well as signs and symptoms of deficiencies in vitamins, minerals, essential fatty acids, and protein. Malnutrition includes both under- and overnutrition, but here we will focus on undernutrition. Child growth has been used as an indicator of undernutrition for decades, but the most commonly measured outcome—low weight-for-age—is not the optimal indicator because it can reflect either acute or chronic undernutrition or both. Characterizing growth in terms of both height-for-age (reflective of chronic undernutrition) and weight-for-height (reflective of acute undernutrition) is more useful. Low height-for-age, typically defined as less than 2 standard deviations (SD) below the median based on the World Health Organization (WHO) Child Growth Standards, is termed “stunting.” Low weight-for-height is termed “wasting”; wasting is considered “moderate” if between –2 and –3 SD below the median and “severe” if less than –3 SD below the median. Stunting and certain specific nutritional deficiencies are key risk factors for diminished survival, poor child and adult health, decreased learning capacity, and lost future productivity (1, 2).

Challenges to reducing stunting. Worldwide, stunting affects 27% of children under 5 years of age in low- and middle-income countries, or a total of 170 million children (3). Stunting often goes unrecognized by families who live in communities where short stature is so common that it is construed as normal. Even among health workers, stunting generally does not receive the same attention as being underweight or wasting, especially if height is not routinely measured as part of community health programs. In low- and middle-income countries, stunting is more prevalent than underweight (low weight-for-age, 16%) or wasting (9%) (3). This is probably because growth in height is highly sensitive to poor dietary quality, not just quantity (4).

Intrauterine growth retardation, inadequate nutrition to support the rapid growth and development of infants and young children, and frequent infections during early life are the factors most frequently invoked as causes of stunting (5, 6). Although a child may not be classified as “stunted” until 2 to 3 years of age, the process of becoming stunted typically begins in utero. Thus, stunting usually reflects the cumulative effects of poor nutrition and other insults that often span several generations (2). Undernutrition during critical periods of development has been linked to insulin-like growth factor-1 (IGF-1) and growth hormone signaling pathways, which appear to modulate height in response to an unfavorable environment, whether in utero or postnatally (7, 8). This may “program” the child’s future growth, which may explain why reductions in stunting in response to nutritional interventions are typically rather modest. It often takes several generations to see substantial declines in stunting rates (9).

The archaeological record indicates that the average height of preagricultural humans was similar to that of well-nourished modern populations and that it declined in many prehistoric societies after the introduction of agriculture ~10,000 years ago (10). Average height has increased over the past ~100 years in most industrialized countries; this has been attributed to improved nutrition (such as increased consumption of animal-source foods) and a reduction in infectious diseases. However, in low-income populations that obtain most of their calories from cereal-based diets, stunting remains widespread. Preagricultural humans consumed a wide variety of animal-source foods, including wild game, fish, shellfish, and insects. It is estimated that human hunter-gatherers obtained 45 to 65% of their energy from animal-source foods (11). In combination with a wide variety of wild plant foods such as leaves, flowers, roots and tubers, nuts, seeds, berries, and other fruits (but virtually no cereal grains), the nutritional quality of the prehistoric diet is thought to have been very high compared to modern diets (12). The decline in dietary quality that accompanied the agricultural revolution is likely to be a major reason for the high rates of stunting that persist today.

Infection and subclinical conditions. Epidemiological studies indicate that food insecurity alone cannot explain the incidence of moderate to severe forms of malnutrition in various human populations (6). Infections are very common in early life, with children under 2 experiencing an average of three to five episodes of diarrhea per year in developing countries (13). The incidence of diarrhea peaks at 6 to 11 months of age, as infants eat increasing amounts of complementary foods that may be contaminated, and begin to crawl and explore their environment, thus putting them in direct contact with multiple sources of pathogens (14). During an infection, the immune system requires a broad range of nutrients to mount a defense against the invading organism.

Subclinical conditions may also have a strong, perhaps cumulative effect on gut function, metabolism, and growth. One condition likely to be prevalent in developing countries is environmental enteropathy (also known as tropical enteropathy). This condition often has no outward manifestation, but it can cause nutrient malabsorp-
tion by changing gut structure and function and may decrease the efficacy of nutritional interventions (14).

A fundamental challenge for understanding environmental enteropathy is the absence of noninvasive assays for its diagnosis, classification and assessment of therapeutic responses. Biopsy of the small intestine has been the most definitive test. Changes associated with enteropathy include reductions in the height of small intestinal villi and increases in the number of intraepithelial lymphocytes and lamina propria T cells with a predominating Th1 helper 1 (Th1) phenotype. Functional tests have shown impaired mucosal barrier integrity. No single pathogen or constellation of pathogens has been identified in the gut microbiota of a majority of individuals diagnosed with environmental enteropathy. This has led to the notion that this disorder could be the result of colonization with microbial consortia that induce inflammation in the context of a susceptible host. What constitutes a “normal” immune repertoire in a healthy gut may vary considerably depending upon a person’s environmental exposures and microbiota configuration (15). Thus, linking the term “environmental” together with “enteropathy” is sensible because it underscores the importance of placing a host’s immune system and gut microbiota community in the context of exposures to various environmental factors.

The first 1000 days. There is a growing consensus that pregnancy and the first 2 years of life are the most critical time period for interventions to improve child growth and development. This is the age of greatest vulnerability to undernutrition and infection. Potentially irreversible long-term physical and mental damage due to undernutrition occurs during this period; for example, it is difficult to reverse stunting if intervention begins after age 2. In addition, the gut microbial community is established within the first 3 years of life, and repair of defects in the development of this metabolic “organ” during this time period may promote healthy growth.

Although a variety of environmental and genetic factors have been postulated to influence the development of moderate to severe forms of undernutrition, the underlying mechanisms remain poorly defined. For example, in Malawi, discordance for moderate to severe malnutrition between twins within the same household and fed similar diets is only approximately 40% (16). This finding raises a number of questions. Do different gut community configurations predispose one co-twin to malnutrition? Is the incidence of discordance for moderate or severe forms of malnutrition different in monoyzygotic compared to dizygotic twin pairs? Both the microbiota and breast milk are “transmitted” from mother to infant, yet we have much to learn about how breast milk and the infant microbiota codevelop during the suckling period when a mother is healthy or when she is malnourished. Important feedback mechanisms may be revealed. Undernutrition may delay the maturation of the infant’s gut microbiota or skew it toward a different and persistent configuration that either lacks necessary functions for healthy growth or increases the risk for disease, including immunoinflammatory disorders. If this is the case, would nutrient repletion return the gut microbiota to a “normal” pre-deficient state, or are there persistent structural and functional perturbations that require continued nutritional supplementation to correct?

BREAST MILK, THE GUT MICROBIOTA, AND UNDERNUTRITION.

Human milk, the ultimate “functional food,” helps to orchestrate development of the infant. In addition to its nutritional components, human milk contains a constellation of bioactive and immunological factors that drive maturation of the infant intestine and companion microbial community. Various studies have shown that breast-feeding protects infants in both economically developed and less developed countries (17–19). Protection is afforded by an array of bio-molecules, including secretory IgA (sIgA), lactoferrin, lysozyme, α-lactalbumin, complex lipids, as well as free oligosaccharides and other glycoconjugates. Secretory IgA, which is present at high concentrations in peripartum breast milk (colostrum) (19), complements the lack of sIgA production in newborns, thus providing the neonate time to develop its capacity for immunoglobulin production. Free oligosaccharides, which serve as decoy receptors for epithelial binding sites, are also found at higher concentrations in colostrum than in mature milk (20, 21), thereby reducing colonization by pathogens while simultaneously promoting establishment of beneficial members of the microbiota, including Bifidobacterium spp. (through mechanisms that remain to be defined) (22). Colostrum contains higher concentrations of total protein than mature milk, and there are changes in overall protein composition over the course of lactation (23). Milk proteins also undergo dramatic changes in glycosylation during lactation (24). Changes in milk protein glycosylation are known to impact protein function, stability, and structure (25) and to influence interactions with pathogens (26).

Other factors that modulate the gut microbiota are activated during transit of milk components through the infant gastrointestinal tract. Proteolytic processing of the glycoprotein κ-casein releases glycomacropeptide, which likely acts as a receptor analog preventing colonization of the gut by pathogens (27). Similarly, lactoferrin is converted by proteolysis to lactoferracin, a potent antimicrobial (28).

Milk provides an array of lipids to the growing infant. This component includes complex lipid structures: eicosanoids (29), phospholipids, glycosphingolipids, free cholesterol, cholesterol esters, and cholesteryl intermediates. The fatty acid composition of maternal milk is reflective of maternal stores, diet, and synthesis in the mammary gland (30, 31). Long chain polyunsaturated fatty acids such as docosahexaenoic and arachidonic acids are necessary for growth and neurological development, yet concentrations vary globally among low- to high-income countries (32). Fatty acid composition changes over the course of lactation, with colostrum generally possessing less linoleic and alpha-linolenic acids and a higher percentage of long chain polyunsaturated fatty acids (33). Mean triglyceride content increases during the first week postpartum and then remains constant throughout lactation. In contrast, cholesterol decreases over the course of lactation (34), whereas the phospholipid concentration remains stable (35).

Human milk also contains a number of other factors, including cytokines and chemokines, whose production is delayed in the neonate (36). Human epidermal growth factor, which produces a variety of biological responses, including repair of damaged mucosa, is found at the highest concentration in breast milk produced during the first few days after parturition and then declines over the first month of lactation (37). Together, these programmed modulations attest to the amazingly dynamic (and little studied) nature of the assemblage of milk factors delivered to the developing infant.

The gut microbiota and postnatal development. Studies of infants, children,
teenagers, and adults living in countries with different life-styles and cultural traditions are beginning to reveal shared as well as distinct features of the gut microbiota during postnatal development. In a recent survey of 531 individuals, fecal samples were obtained from families of Guahibo Amerindians residing in two villages located near Puerto Ayacucho in the Amazonas State of Venezuela, from families living in four rural communities in Malawi, and from families distributed across the United States (38) (Fig. 1). In each population of breast-fed healthy children sampled, the gut microbiota did not reach an adultlike configuration until ~3 years of age. The fecal bacterial species assemblages in Malawian and Amerindian gut microbiotas were more diverse and clustered together compared to Western gut communities. This difference in diversity was apparent in children at 3 years of age. Shared features of the functional maturation of gut microbiomes across the three populations included higher representation of genes involved in folate biosynthesis in infants with a later shift to folate metabolism and reduced representation of genes involved in (i) synthesis of cobalamin (vitamin B12), biotin (vitamin B7), and thiamine (vitamin B1), (ii) fermentation and methanogenesis, and (iii) metabolism of certain amino acids (arginine, lysine, glutamate, aspartate) in children compared to adults. However, differences in Amerindian and Malawian children compared to children in the United States are also evident. Amerindian and Malawian children have gut microbiomes with a greater proportional representation of genes that produce riboflavin (vitamin B2). The same is true for the genes encoding glycoside hydrolases that process glycans in breast milk and in the gut mucosa. The microbiomes of children living in non-Western environments also exhibit more prominent representation of genes encoding urease, which breaks down urea, an important source of nitrogen in breast milk, into ammonia. Microbes can use ammonia for production of essential and nonessential amino acids. Urease production by the microbiome would be beneficial when protein is not very abundant in the diet. Differences in the representation of genes in the microbiomes of adults in the United States compared to Malawian and Amerindian adult microbiomes follow differences in diet (38).

![Fig. 1. Tackling the scourge of undernutrition.](image)

Characterizing the interrelationships between the gut microbiota and nutritional status involves surveys of healthy and malnourished individuals representing different geographical locations, cultural traditions, and life-styles. These surveys require a comprehensive biospecimen collection effort including sampling of breast milk from mothers during the course of lactation, together with assessments of maternal and infant nutritional and metabolic status and microbial ecology. The images shown were taken at sites where sampling of infants, children, and their mothers are being conducted by the authors and their colleagues. (A to F) Malawi, (G) Amazonas state of Venezuela, (H and I) Bangladesh.

INTERACTIONS OF THE IMMUNE SYSTEM AND GUT MICROBIOTA

Host-microbial relations have been traditionally considered in the context of antagonistic interactions between pathogens and the immune system. Accordingly, the best-understood function of the immune system is to detect invasive pathogens and to promote their destruction and elimination. Furthermore, many view the immune system as having been specifically designed to attack pathogenic microbes while sparing, ignoring, or tolerating nonpathogenic (beneficial) symbionts. However, the immune system clearly detects and responds to myriad components of the microbiota: Antimicrobial defensins and IgA are just two examples of immune defenses directed at gut microbiota constituents [see Review by Hooper et al. (39)]. The current framework of host-microbial interactions does not fully explain the decision-making process of the immune system when it comes to these resident microbes.

There is increasing appreciation for the fact that different resident members of the microbiota can have a positive or negative
impact, depending on their relative abundance, community structure, and status of the host. When host defenses are compromised, normal microbial community structure is disrupted, resulting in an outgrowth of detrimental microorganisms or the conversion of normally innocuous microorganisms into pathogens (pathobionts) if their "virulence" depends on their abundance. This suggests that the immune system can somehow suppress the expansion of detrimental microorganisms yet maintain the abundance of beneficial microbes. However, it is not clear how the immune system maintains the appropriate density, composition, and overall configuration of the gut microbiota. It is likely that additional modes of interaction between microbes and the immune system exist that, on the one hand, allow the immune system to detect specific configurations of the gut microbiota, whereas, on the other hand, promote configurations that are beneficial to the host. For the purpose of this discussion, "microbiota configuration" can be loosely defined as microbial consortia (with their specific characteristics) that are relevant to the fitness of the host. Some configurations are beneficial to the host, whereas others are detrimental. Therefore, an optimal configuration of the gut microbiota must exist for a given host in a given environment.

It is conceivable that the host plays an important role in determining the microbiota configuration. The most obvious example is the provision of human milk oligosaccharides (HMOs) to HMO-consuming *Bifidobacterium* spp. in the gut. Thus, host-derived HMOs promote the expansion and maintenance of a coevolved bacterial clade beneficial to the infant. Conversely, a variety of antimicrobial agents (including HMOs) in breast milk suppress bacteria that are detrimental to an infant’s fitness. Lactation in mammals and analogous secretions in birds (such as “crop milk”), and other processes such as premastication, regurgitation, and consumption of feces (coprophagy) across many types of animals, may facilitate optimal microbial colonization of the gut in the offspring.

**Immune sensing of microbiota configurations.** The immune system may not only protect from invasive pathogens but also promote the optimal configuration of the gut microbiota. Although such a function would have an obvious evolutionary and physiological rationale, it is not clear how immune system function could modulate microbial ecology. We suggest that the immune system has a sensing mechanism that evaluates the configuration of the gut microbiota. Pattern recognition by the innate immune system cannot fulfill this role, as it does not have the requisite level of resolution to discriminate between different classes and characteristics of microbes. An additional mode of communication between the microbiota and the host immune system could be based on sensing metabolites [see Review by Holmes et al., this issue (40) and Review by Nicholson et al. (41)]. There are three groups of metabolites that could be involved.

The first group of metabolites would be uniquely produced by different classes of microbes from precursors present in the diet (such as short-chain fatty acids). These metabolic signals would be sensed by the digestive system (enteroendocrine cells of the gut mucosa, cells of the pancreas and liver, and adipocytes), where they would report on the quality and quantity of incoming nutrients. The immune system could sense these metabolites to evaluate the characteristics of the gut microbiota. Some of these small-molecule metabolites sensed by the immune system may not be unique to microbes but rather may be produced in amounts or locations characteristic of a microbial origin. The metabolites may have anti- or proinflammatory activity depending on whether the microbial communities they "report on" are desirable or detrimental to the host.

The second group of metabolites would be unmodified nutrients that the immune system could use to evaluate the presence of microbes that metabolize the nutrients into forms that can no longer be sensed. The amounts of these nutrients could be an indicator of the relative densities of the microbes that metabolize them. Certain micronutrients, such as retinoic acid, may fall into this category. These micronutrients would be expected to have anti-inflammatory activity and their concentrations would be a function of the abundance of "detrimental" microbes that metabolize them. To function in this manner, the concentrations of micronutrients with signaling capabilities should not be limited by the host’s dietary intake (they should be abundant in the "natural" diet). This feature could be one factor that discriminates Western from non-Western diets.

The third group of metabolites would be produced by the host but metabolized by specific members of a microbial consortia. Bile acids produced by the liver and secreted into the jejunum can be either reabsorbed into the ileum or metabolized into secondary bile acids (for example, deoxycholic and lithocholic acids) by 7α-dehydroxylase mediated by microbes in the colon. Both primary and secondary bile acids have signaling functions, including potentially anti-inflammatory activities (42). Although mechanistic details still need to be elucidated, secondary bile acids may be an example of “molecular probes” that report to the host on the presence and abundance of specific enzymatic activities of certain microorganisms, such as bacteria that produce the enzyme 7α-dehydroxylase. In all three cases, metabolite sensing could provide the immune system with information about the presence and abundance of specific metabolic activities and configurations of microbial consortia. Although the impact of microbial metabolites and some nutrients on the immune system has been described (15, 43), the logic of this mode of host-microbial communication has been unclear. We propose that the host immune system’s ability to sense microbial metabolites and dietary micronutrients may serve the function of reporting on the “quality” of a gut microbiota configuration. Relative abundance of metabolites with anti-inflammatory or immunosuppressive activities (for example, short-chain fatty acids) should reflect the desired microbiota configuration. If the gut microbiota is suboptimal, immune responsiveness would be tuned up (or specific effector responses would be up-regulated) to promote reconfiguration to a more optimal state. This could be achieved through specific effects of IgA, less specific effects of innate effectors (such as defensins), or nonspecific effects such as diarrhea, which the host uses as a last resort to eliminate undesirable microbial communities and to prepare niches for recolonization with more optimal microbial consortia.

**TESTING HYPOTHESES**

Studying how the gut microbiota and the immune system codevelop in healthy and undernourished infants and children, and the role of breast milk in this process, would allow testing of several hypotheses.

**Hypothesis 1.** The gut microbiota is a metabolic organ that is needed for healthy postnatal development. Malnutrition affects the assembly of metabolic functions encoded and expressed by the gut microbiome. The assumption being tested is that the gut micro-
biota is both a biomarker and mediator of key metabolic functions needed to promote the nutritional health of mothers and the healthy growth of their offspring. A related assumption is that the maturation of breast milk during the course of lactation impacts the assembly of the infant gut microbial community, thereby shaping the microbiota’s metabolic potential and expressed metabolic activities. A corollary is that periods of malnutrition may have long-lasting effects on microbiota-based metabolic activities that extend beyond the period of overt nutrient deficiency. This would require sustained nutrition support to ensure rescue of the normal development of microbial and host physiological functions.

This hypothesis addresses the possibility that the effects of undernutrition on the developmental program of the gut microbiota could be modified at key stages of postnatal life by administering live microbes that fill missing metabolic niches (probiotics) or prebiotics that boost metabolic functions of key microbes in the gut microbiota. A combination of prebiotics and probiotic consortia (synbiotics) could be required for restoration of a beneficial microbiota. The hypothesis raises an important question about microbiota-directed therapeutics. Would therapeutic interventions have greater efficacy if implemented early during community assembly when the microbiota manifests greater instability and seemingly stochastic behavior, or later, when directed movement toward a particular functional configuration is more apparent (although by this time, attempted “repair” of the microbiota may be more difficult to achieve)?

**Hypothesis 2.** The functions of the normal developing innate and adaptive immune systems are modulated by the metabolic activities of the gut microbiota. The constituents in breast milk have a major effect on these metabolic activities and thus on the immune system. This testable hypothesis is motivated by the view that innate and adaptive immune cells may have sensors that respond to breast milk constituents or to their breakdown products generated by microbial metabolism. These sensors and their associated signaling pathways may modulate immune cell subsets, including activities relevant to maturation of intestinal barrier function, resistance and responses to infection, and robust responses to enteric vaccines. This hypothesis emphasizes the need to delineate the effects of breast milk–dependent bioactive compounds—that is, breast milk components presented after processing by the host, by the microbiota, and by host-microbial catabolism—on major components of the intestine’s immune system.

**Hypothesis 3.** Immunopathological states associated with childhood undernutrition are caused by the co-occurrence of several interrelated factors, including nutrient availability, defects in gut microbiota maturation, abnormal nutrient processing by the microbiota, aberrant nutrient sensing by immune cells, and the presence of enteropathogens. If this hypothesis is true, the gut microbiota and its metabolic activities may be useful biomarkers for diagnosing and classifying immunopathological states associated with malnutrition. Administering gut microbiota constituents from healthy donors and breast milk components could reshape microbial community metabolism and immune function in ways that mitigate the risk for developing environmental enteropathy.

**THE VALUE OF HUMAN STUDIES**

There are several reasons we believe that twins, particularly twins discordant for moderate or severe malnutrition, will be informative for clinical studies of the role of the gut microbiota in disease, especially if both cotwins in a discordant pair are subjected to the same nutritional intervention (16). First, substantial interpersonal differences in microbial community configurations normally exist between unrelated healthy individuals; intra- and interpersonal variations are particularly great during the early postnatal period (38). Second, there may be a relatively large number of microbiota configurations associated with malnutrition in children, each shared by relatively few individuals. Third, if given the same therapeutic food intervention, each sib in a discordant twin pair could serve as his or her own control, with the healthy cotwin in the discordant pair serving as another control. Fourth, comparing discordant monozygotic and dizygotic twin pairs allows initial broad assessment of the role of host genetics in defining disease.

A logical question arising from such twin studies would be whether differences are causally or casually related to malnutrition. Recent work has shown that it is possible to transplant a previously frozen fecal microbiota (or a collection of cultured microbes generated from the fecal sample), from a given human donor (representing an age, phenotype, and cultural tradition of interest) into multiple germ-free mice. There is efficient capture of the genes and taxa of the donor’s gut microbiota in the gastrointestinal tracts of these recipient gnotobiotic mice (44, 45), and these communities can be transmitted from one generation to the next. In addition, recipient mice can be fed diets that are representative of those consumed by the human donor. These types of experiments provide an opportunity to determine how much of a donor’s phenotype can be transmitted to gnotobiotic animal recipients (and their offspring) via the microbiota and to perform proof-of-concept therapeutic tests with prebiotics, probiotic consortia, or synbiotics. In principle, these approaches can be used to determine whether the effects of nutrient supplements and supplement-responsive taxa can be generalized to humans living in multiple geographic locations with distinct cultural traditions and diets. Such preclinical platforms could also allow identification and validation of new surrogate- and mechanism-based biomarkers of efficacy, as well as dosing schemes and safety tests that will inform clinical study design. The advantage of these “personalized” gnotobiotic models is that the targeted human population of interest has to be defined at the very onset of model creation, thereby facilitating subsequent translation.

The discovery pipelines created by these preclinical models and the clinical studies that could support raise a number of challenges for regulatory agencies, issues about ownership of microbes, and ethical challenges related to how microbiota-directed therapeutics could or should be applied to mothers and infants. They also represent formidable challenges and tremendous opportunities for the agricultural, food, and pharmaceutical industries; government agencies; and other elements of society. With the world’s human population predicted to top 9 billion by mid-century, new approaches and their implementation to improve nutritional health cannot come soon enough.

**REFERENCES AND NOTES**


Acknowledgments: We thank the Bill & Melinda Gates Foundation for challenging us to better understand the relationship between breast milk, gut microbiome, immunity, and the healthy growth of children worldwide. We are grateful to our colleagues who are members of the Breast Milk, Gut Microbiome, and Immunity (BMMI) Project funded by the Bill & Melinda Gates Foundation: Kenneth Maleta, Per Ashorn, Nahed Ahmed, Gagandeep Kang, Pascal Bessong, Aldo Lima, Margaret Kosek, Michael Gottlieb, Dennis Lang, Jeremy Nicholson, Elaine Holmes, Linda Saf, Rob Knight, Michael Barra- kert, Karen Seibert, David D’Argenio, and Andrew Serazin. JIG thanks Mark Manary, Indi Trehan, Michelle Smith, and Tanya Yatsunenko for their collaboration with twin studies of childhood malnutrition in Malawi. DAM thanks Jennifer Smlowitiz for her contributions to the description of changes in breast milk following parturition. Funding: Authors are supported by grants from the Bill & Melinda Gates Foundation (J. I. G., K. G. D., D. A. M.), the NIH (J. I. G., D. A. M., R. M. M.), the Crohn’s and Colitis Foundation of America (J. I. G.), the California Dairy Research Foundation (D. A. M.), the University of California Discovery Program (D. A. M.), and the Howard Hughes Medical Institute (R. M. M.).


Acknowledgments: We thank the Bill & Melinda Gates Foundation for challenging us to better understand the relationship between breast milk, gut microbiome, immunity, and the healthy growth of children worldwide. We are grateful to our colleagues who are members of the Breast Milk, Gut Microbiome, and Immunity (BMMI) Project funded by the Bill & Melinda Gates Foundation: Kenneth Maleta, Per Ashorn, Nahed Ahmed, Gagandeep Kang, Pascal Bessong, Aldo Lima, Margaret Kosek, Michael Gottlieb, Dennis Lang, Jeremy Nicholson, Elaine Holmes, Linda Saf, Rob Knight, Michael Barra- rket, Karen Seibert, David D’Argenio, and Andrew Serazin. JIG thanks Mark Manary, Indi Trehan, Michelle Smith, and Tanya Yatsunenko for their collaboration with twin studies of childhood malnutrition in Malawi. DAM thanks Jennifer Smlowitiz for her contributions to the description of changes in breast milk following parturition. Funding: Authors are supported by grants from the Bill & Melinda Gates Foundation (J. I. G., K. G. D., D. A. M.), the NIH (J. I. G., D. A. M., R. M. M.), the Crohn’s and Colitis Foundation of America (J. I. G.), the California Dairy Research Foundation (D. A. M.), the University of California Discovery Program (D. A. M.), and the Howard Hughes Medical Institute (R. M. M.).
