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Brief Reviews

The Journal of Immunology

The Impact of Maternal Microbes and Microbial Colonization in Early Life on Hematopoiesis

Kathy D. McCoy and Carolyn A. Thomson

All body surfaces are colonized by microbes, which occurs through a dynamic process over the first few years of life. Initial colonizing microbes are transferred from the maternal microbiota to the newborn through vertical transmission. Postnatal maturation of the immune system is heavily influenced by these microbes, particularly during early life. Although microbial-mediated education of the immune system is better understood at mucosal sites, recent data indicate that the systemic immune system is also shaped by the microbiota. Bacterial products and metabolites produced through microbial metabolism can reach distal sites, and metabolites derived from the maternal microbiota can cross the placenta and are present in milk. Recent studies show that the microbiota can even influence immune development in primary lymphoid organs like the bone marrow. This review outlines our current knowledge of how the microbiota can impact hematopoiesis, with a focus on the effects of maternal and early-life microbiota. ***The Journal of Immunology*****, 2018, 200: 2519–2526.**

From the moment we are born, every surface of our body becomes colonized with a vast array of microbial species, collectively known as the microbiota. Microbes are passed vertically from mother to child during birth and are subsequently obtained via horizontal transfer from the environment. By the time we reach adulthood, we are host to trillions of microbial cells that represent thousands of species of bacteria, as well as fungi, archaea, and viruses. The precise composition of our microbiota is shaped by environmental factors that result in microbial repertoires that are as unique to the individual as our fingerprints. Our commensal microbes are more than mere silent passengers that inhabit our body surfaces; they play essential roles in immune development and function, metabolism, physiology, and even brain function. Although it is now well accepted that our microbiota influences immune responses within mucosal tissues, it is also becoming apparent that the microbiota can shape development and function of the immune system at distal tissues, including primary lymphoid organs, such as the bone marrow (BM) and thymus. In this capacity, intestinal microbes can regulate immune function via effects on the differentiation of hematopoietic progenitor cells. Not only can these processes alter the type of leukocytes produced and released from the BM, some microbial signals may even act at the epigenetic level, thereby inducing semipermanent changes in individual lineages. Understanding the timing and the mechanisms by which the microbiome can influence hematopoiesis is required for rational development of novel strategies to harness the power of the microbiome to treat and prevent disease. In this review, we discuss how hematopoiesis in the BM is shaped by microbial signals during neonatal life and adulthood and following infection and highlight our current knowledge of the molecular processes involved.

Impact of maternal microbiota and microbial colonization in early life on hematopoiesis in the neonate

Current dogma suggests that microbial colonization begins at birth via vertical microbial transmission from mother to infant. During a natural vaginal delivery, newborn babies are first exposed to the commensal microbiota of their mother's birth canal and intestinal contents and then to microbes from the maternal skin, mouth, and milk, as well as the environment (1) (Fig. 1). However, recent evidence suggests that colonization may, in fact, precede birth. As more sensitive techniques for microbial detection become available, there have been increased reports of bacterial detection in the placenta, the amniotic fluid, and the meconium (reviewed in Ref. 2). It has been suggested that a placental microbiome, seeded from the mother's intestine and oral cavity, may develop to initiate fetal colonization during gestation. However, whether this occurs in normal fetal development remains controversial. Regardless, during the first 3 y of a child's life, the intestinal microbiome becomes established through a process that is highly dynamic and reflects a period of intense microbial diversification (3). It is becoming increasingly apparent that to decrease susceptibility to disease, children should be colonized with a complex and diverse microbiota as early as possible

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Abbreviations used in this article: BM, bone marrow; CLP, common lymphocyte progenitor; DC, dendritic cell; HSC, hematopoietic stem cell; IAP, intrapartum antibiotics prophylactically; IBD, inflammatory bowel disease; ILC, innate lymphoid cell; LSK, $Lin^{-}Sca\text{-}1^{+}c\text{-}kit^{+}$; MAMP, microbe-associated molecular pattern; MPP, multipotential progenitor; RA, retinoic acid; SCFA, short-chain fatty acid.

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within this time frame. Not only can changes to the microbiome influence susceptibility to infections and sepsis, numerous studies have revealed critical links between early life dysbiosis (defined as changes in the normal composition of the microbiota) and a broad range of metabolomic, immunological, and behavioral disorders in adulthood, including asthma, allergy, inflammatory bowel disease (IBD), type 1 diabetes, autism, and obesity (1, 4). Many factors, including diet, antibiotic exposure, genotype, and method of delivery (vaginal versus caesarean), are known to shape the developing microbiome (1), and it is of crucial importance that we understand how these factors subsequently impact the developing immune system.

Bacterial infections and sepsis are major causes of infant mortality worldwide (5). Due to their underdeveloped immune system, premature babies have a particularly high risk for developing such infections; as such, it is often standard practice to use empiric antibiotics in these infants until infection has been ruled out (6, 7). Furthermore, pregnant mothers with a high risk for preterm labor are often given intrapartum antibiotics prophylactically (IAP) to reduce the risk for infection in the mother and in the neonate (8, 9). Indeed, IAP has been enormously beneficial and has vastly reduced the risk for early-onset sepsis in neonates (9). However, recent studies suggest that perinatal exposure to antibiotic treatment may have a profound and sustained impact on the developing microbiome of newborn infants. IAP treatment was shown to have more of an impact on the developing microbiome than direct exposure to antibiotics (8). This study reported higher proportions of *Leuconostaceae* (2 d after birth) and *Micrococcaceae* and *Propionibacteriaceae* (10 d after birth) in infants born to antibiotic-treated mothers. By day 30 after birth, the intestinal microbiome of infants exposed to IAP in utero had higher proportions of *Comamonadaceae*, *Staphylococcaceae, Enterobacteriaceae,* and an unclassified bacilli, along with reduced proportions of *Bifidobacteriaceae*, *Streptococcaceae*, an unclassified *Lactobacillales*, and an unclassified *Actinobacteria* (8). Treating infants with ampicillin and gentamicin within 48 h of birth has also been demonstrated to have long-lasting effects on the microbiome, resulting in increased *Proteobacteria* and concurrent reduced proportions of *Actinobacteria*, *Bifidobacterium*, and *Lactobacillus* in the intestinal microbiome compared with untreated controls (10). Although intrapartum antibiotics can prevent early-onset infections, which present within 72 h of birth, the sustained dysbiosis associated with perinatal antibiotic exposure has been linked to downstream complications and may even render newborn infants more susceptible to necrotizing enterocolitis or late-onset sepsis (6, 7), which predominantly occurs after the first week of life.

The first few hours of life are normally associated with a rapid increase in neutrophils in the BM and circulation of humans and mice (4, 11). In mice, this neutrophilia is dependent on the presence of an intact maternal microbiota and is ablated by treatment of the pregnant dam from 5 d before birth with a combination of ampicillin, gentamicin, and vancomycin (4). In antibiotic-treated pups, aberrant neutrophil development could be detected from as early as 1 d of age and was associated with loss of IL-17A production by innate lymphoid cells (ILCs) in the small intestinal lamina propria of the pups, together with significantly reduced levels of circulating G-CSF. As a result, these pups rapidly succumbed to experimental infection with *Escherichia coli* or *Klebsiella pneumoniae*. The deleterious effects of antibiotics could be reversed by treating mice with G-CSF or by adoptive transfer of microbiota from normal neonatal mice. This process was dependent on intact IL-17A signaling, highlighting a potential role for the IL-17A/G-CSF axis in mediating the effects of the microbiota on neutrophil production in the BM. It is important to emphasize that the antibiotic-mediated effects in this model must reflect vertical transfer from the mother to the pup, because the treatment was started during pregnancy and discontinued prior to weaning. These studies indicate that caution needs to be applied when considering the use of broad-spectrum antibiotics during labor or the perinatal period and perhaps suggest potential benefits of coadministering probiotics under these circumstances.

Dietary metabolites can be transferred from mother to child (12) and may have crucial roles in immune system development and inflammatory immune responses in the offspring (Fig. 1). Although an enormous body of literature describes the immune modulatory impact of short-chain fatty acids (SCFAs) in adults (13–16), the effects that maternally transferred SCFAs have on the offspring are yet to be fully defined. One recent study demonstrated that feeding pregnant dams with a high-fiber diet or acetate alone could profoundly affect immune responses in the offspring, resulting in decreased eosinophil infiltration to the lung, reduced IgE responses, and reduced disease severity following house dust mite–mediated allergic airway inflammation (17). Importantly, these phenotypes prevailed, even when pups were fostered to a surrogate mother fed a normal diet, suggesting that maternal acetate altered the immune system of the pups in utero. Further, maternally derived SCFAs have been suggested to play a role in Foxp3^{+} regulatory T cell generation in the neonatal thymus (18). Although these are the only studies directly linking maternal SCFAs to neonatal immune system education, maternal transfer of retinoic acid (RA), a metabolite of dietary vitamin A, may also play an important role. Maternal RA regulates CXCL13 production by fetal mesenchymal cells and the differentiation of lymphoid tissue inducer cells in utero, subsequently controlling the size of neonatal secondary lymphoid tissues (12). Maternal RA may also regulate hematopoiesis in the fetal liver, because treating fetal liver fragments ex vivo with RA leads to a reduction of B lymphopoiesis (19). There are no reports directly linking the maternal transfer of dietary metabolites to neonatal hematopoiesis, but the scale of immune-modulatory effects ascribed to SCFAs, coupled with the knowledge that their impact spans from mother to fetus, makes this an exciting and novel area of research.

In the experiments above, the effects of antibiotics could reflect an influence on the microbiota of the mother, the neonate, or both. To assess the impact of the maternal microbiota alone, without any influence from microbial colonization of the pups after birth, Gomez de Agüero et al. (20) transiently colonized germ-free dams during gestation with an auxotrophic mutant strain of *E. coli*, termed HA107. This model allows microbial colonization to occur only during pregnancy so that the dam becomes germ-free again prior to giving birth to her germ-free pups. This study revealed that maternal Ab-mediated vertical transfer of maternal microbial components vastly altered gene expression in the intestine of

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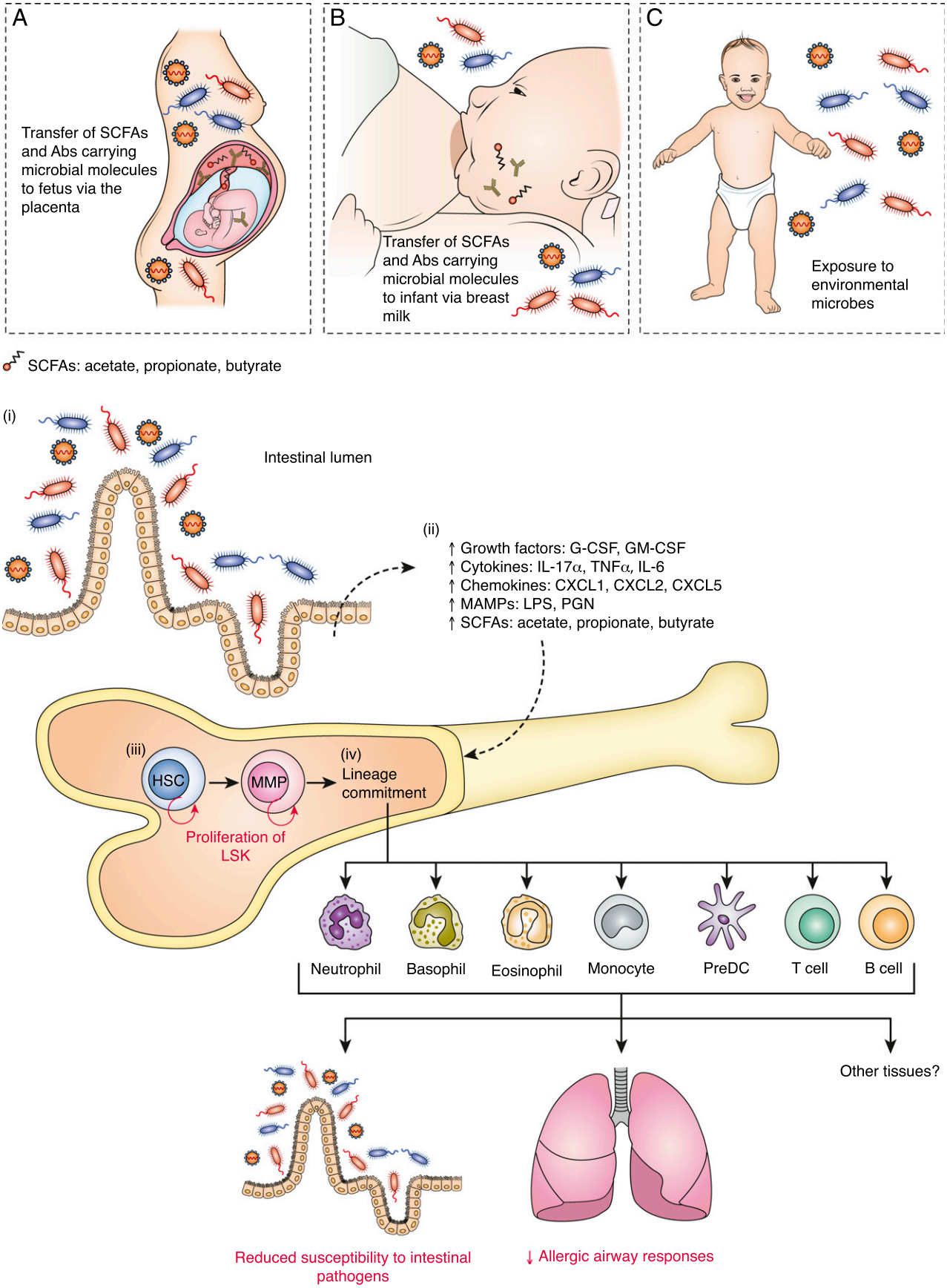

FIGURE 1. Microbial signals in early life shape the repertoire of immune cell development in the BM. A child's immune system can be modulated by microbial signals at various stages in development. Microbial metabolites, such as SCFAs, and Abs carrying microbial molecules can pass from mother to fetus during gestation (**A**) or from mother to child via breast milk (**B**). This has been shown to impact the immune cell repertoire in the intestine and may affect susceptibility to intestinal pathogens. (B and **C**) From birth onward, children are exposed to microbes in the environment (**i**), which *(Figure legend continues)*

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the pups and was responsible for more intestinal ILC3 populations (20). Gestational colonization was also responsible for increased numbers of intestinal macrophages, although Ab-mediated transfer was not involved in mediating this phenotype. These data highlight a novel pathway whereby the maternal microbiome influences the neonatal immune system. Although no changes were observed in B cell development in the neonatal BM, a general effect on BM hematopoiesis was not assessed. One intriguing possibility that may account for some of the changes in the neonatal immune system in response to maternal colonization is raised by older studies illustrating the presence of maternally derived hematopoietic stem cells (HSCs) and other hematopoietic progenitor cells in cord blood (21), from where they may seed the BM of the developing fetus. Because these cell types can be regulated by the host microbiome, dysbiosis in the mother could potentially have indirect effects on the developing neonatal BM in utero by altering the behavior of these maternally derived progenitors.

Postnatal maturation of the innate and adaptive immune systems is driven by signals arising from the intestinal microbiota. Current work supports the presence of a critical developmental window early in life when the immune system is highly susceptible to microbial influence (22). In humans, this window may encompass the first 3 y of a child's life and marks a period of intense variability in the microbiome. If the normal processes of establishing a microbiota are disrupted during this period, it may have life-long consequences for the host, leading to increased susceptibility to a number of disorders, including autoimmune diseases, IBD, asthma, allergy, obesity, and autism. Although multiple pathways are likely to be involved, it is possible that alterations in hematopoiesis in the developing BM or other tissues may result from decreased or altered microbial signals. Recent work shows that the differentiation fate of an HSC clone down a particular lineage is predetermined by epigenetic modifications that are thought to arise early during its development (23). This begs the question: could early life exposure to microbes generate epigenetic memory in the BM that has a life-long impact on host immune responses, subsequently influencing the risk for immune-mediated pathologies? Although not yet shown for cells in the neonatal BM, microbial-mediated epigenetic regulation of the chemokine ligand CXCL16 has been identified in lung and colon tissues (24). In that study, microbial colonization during neonatal life was shown to be required to limit accumulation of invariant NK T cells in the lung and colon, and this effect was mediated through microbiota-mediated epigenetic regulation of CXCL16 (24).

Exposure to microbes in early life is known to have an impact on primary B cell development that occurs in hindgut B cell structures in animals like the chicken and rabbit (reviewed in Ref. 25). Whether early B cell development can occur in the intestines of humans is not clear, although pre-B cells have been found in the human fetal small intestinal lamina propria (26). In mice, although early B cells that express RAGs are absent from the small intestine at birth, they are found to accumulate in the gut mucosa at weaning, coincident with increasing microbial colonization in early life (27). This suggests that microbes (and potentially dietary Ags) may play an important role in shaping the primary Ab repertoire in early life (28), and this may occur outside of the BM.

Microbes fine-tune hematopoiesis during steady-state

In addition to stimulation following early life colonization, recent studies have shown that steady-state hematopoiesis can be regulated by the commensal microbiota; this is likely important for fine-tuning immunity (Fig. 1). Indeed, there is evidence to suggest that even subtle changes in the commensal microbial repertoire (e.g., in response to diet or antibiotic usage) can influence immune responses via effects on progenitor cells (4, 29, 30). The absence or reduction in microbial signals in germ-free or antibiotic-treated mice is associated with reduced numbers of neutrophils and monocytes in the BM and peripheral sites (31–35). Numerous studies show that the early stages of myelopoiesis in the BM are impaired in germ-free mice (31, 34, 36, 37), with reduced numbers of HSCs, multipotential progenitors (MPPs), and common myeloid progenitors (31, 37). Treatment with broad-spectrum antibiotics, or even neomycin alone, can phenocopy these abnormalities when given to adult specific pathogen–free mice (31–33). Although one report suggested that there were no differences in the proportions or numbers of early progenitors in the germ-free BM (34), this might be due to differences in the microbiota of the specific pathogen–free mice used as a baseline in that study. As well as being reduced in number in germ-free and antibiotic-treated mice, granulocyte–monocyte precursors have been shown to have an impaired capacity to differentiate into granulocytes and macrophages ex vivo (31, 34, 36). Together, the impaired myelopoiesis seen in mice lacking a normal microbiota results in increased susceptibility to bacterial pathogens, such as *Listeria monocytogenes*, *E. coli*, and *Staphylococcus aureus* (31, 34).

Although the factors mediating emergency myelopoiesis have been characterized in some detail (see below), the regulation of steady-state hematopoiesis by the normal microbiota remains less well understood. Nevertheless, recognition of microbe-associated molecular patterns (MAMPs) is likely to be important; indeed, intestinal colonization of germ-free mice with a combination of *E. coli*, *Staphylococcus xylosus*, and *Enterococcus faecalis* stimulates myelopoiesis in a MyD88 and TRIF–dependent manner (31). Although it was unclear what cell types mediated this response, one possibility is that it reflects regulation of secondary mediator production by intestinal enterocytes stimulated by MAMPs from the commensal bacteria. This would be consistent with experiments showing that epithelial cell–derived CXCL5 can regulate the

leads to establishment of a diverse microbiota in the intestine. (**ii**) The host immune system responds to this intestinal colonization, leading to the local and/or systemic production of growth factors, cytokines, and chemokines. Microbial components, such as SCFAs and MAMPs, including LPS and peptidoglycan (PGN), can also enter the circulation from intestinal lumen. Collectively, these factors can access distal sites, such as the BM, where they may regulate the proliferation and differentiation of LSK HSCs, LSK multipotent progenitors, and their descendants (**iii**), thus shaping commitment to specific immune cell lineages (**iv**). These effects of hematopoiesis have functional consequences on host immune responses, reducing susceptibility to intestinal pathogens and modulating inflammatory responses, such as to allergic airway challenge. Future work will unravel the impact that microbe-driven effects on BM homeostasis have on other tissues or immunopathologies.

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levels of circulating G-CSF and neutrophil numbers in the BM by controlling the production of IL-17A from ILCs in the intestine (38).

The identity of the organisms mediating the effects of the steady-state microbiota on hematopoiesis is largely unknown, as are many of the mechanisms that might alter these processes during pathogenic infection or after treatment with antibiotics. Although it has long been known that diet plays a pivotal role in shaping the intestinal microbiota (39, 40), the subsequent effects on immune cells are only now being elucidated. Recent work showed that microbial dysbiosis caused by feeding mice a high-fat diet was associated with a shift in hematopoiesis in favor of myelopoiesis at the expense of the lymphoid lineage (29). These changes appeared to reflect an increase in MPPs and common myeloid progenitors and a concomitant reduction in common lymphocyte progenitors (CLPs) and immature B cells. As a result, the host mice were less able to regenerate leukocytes following BM ablation with 5-fluorouracil. Microbial dysbiosis in mice fed a high-fat diet was characterized by an increased abundance of Verrucomicrobia, Actinobacteria, and Proteobacteria species in the cecum and ileum, with a relative decrease in *Bacteriodetes* and *Firmicutes*. Importantly, the BM phenotype could be rescued by treatment with the antibiotic vancomycin, suggesting the involvement of Gram-positive organisms, and it could be phenocopied by transferring microbiota from mice fed the high-fat diet to normal mice, suggesting a causative role for the microbiota in mediating the hematopoietic changes. The increased abundance of Proteobacteria was interesting, because they are thought to be strong drivers of inflammation and metabolic disease, yet they are Gram-negative bacteria and are increased by vancomycin treatment. Similarly, Verrucomicrobia are Gram-negative and increased during vancomycin treatment; in contrast to Proteobacteria, members of this phylum, such as *Akkermansia muciniphila*, promote a healthy gut, possibly through colonizing the outer mucous layer and producing SCFAs (41). In contrast, Actinobacteria are Gram-positive and depleted by vancomycin treatment. Exactly which bacteria may be playing a role is not clear, because Actinobacteria are the third most dominant bacterial phylum in humans and can be pathogens, like *Mycobacterium*, or commensals, such as *Bifidobacterium*. Another study found that feeding mice with a fiber-rich diet led to an outgrowth of *Bacteriodetes* at the expense of *Firmicutes*, leading to an increase in the levels of the SCFAs propionate and acetate in the circulation (30). When challenged intranasally with house dust mite Ag, mice on the high-fiber diet developed less severe airway inflammation than mice fed regular chow. Allergic airway inflammation could be suppressed in mice receiving a normal diet by the administration of propionate or acetate alone, prompting the investigators to look for changes in immune cells. They found that exogenous administration of the microbial metabolite propionate led to alterations in hematopoiesis, with a reduction in macrophage and dendritic cell (DC) precursors in the BM. In addition, newly differentiated DCs expressed lower levels of MHC class II and costimulatory molecules and were less effective at reactivating effector Th2 cells. Thus, defined changes in the microbiota, resulting from antibiotic use or changes in our diet, may have drastic effects on how our immune system tackles challenges as a result of effects on hematopoiesis.

Microbial infection drives changes to the HSC pool

The capacity for hematopoietic cells within the BM to respond to microbial signals has been best characterized in response to infection. The innate immune system responds to infection by rapidly deploying newly differentiated myeloid cells from the BM into the circulation, enabling enhanced accumulation in sites of inflammation. Responding to the increased demand for innate leukocytes, the dynamics of BM hematopoiesis changes, resulting in an expansion of HSCs (42, 43) and a shift in differentiation to favor increased monocyte and granulocyte production (reviewed in Ref. 44). This phenomenon, known as emergency myelopoiesis, is a highly regulated evolutionary strategy that is designed to help the host provide an immediate response to infection (44).

A number of factors can contribute to infection-associated emergency myelopoiesis. G-CSF, M-CSF, and GM-CSF all play a key role in regulating the lineage commitment of BM progenitors in steady-state (45, 46). These growth factors are known to increase in the circulation during infection and inflammation, thereby stimulating further differentiation of progenitors down the myeloid lineage (47–49). The production of these growth factors and, thus, the driving of emergency myelopoiesis and myeloid cell deployment from the BM, are primarily driven by the activation of pattern recognition receptors, such as TLRs and NOD-like receptors, which are expressed by immune and stromal cells within the host. Many studies report a defect in myelopoiesis in animals deficient in TLRs or TLR-specific adapter molecules (42, 43, 50–52). In the case of infection with *E. coli*, a TLR4-dependent increase in circulating G-CSF leads to a massive release of mature neutrophils into the circulation, as well as an expansion of monocytes and immature neutrophils in the BM (50). These effects were abrogated in mice specifically lacking the adaptor molecule MyD88 in endothelial cells (50). Infection with *Candida albicans* drives an early TLR2-dependent expansion of $Lin^{-}Sca\text{-}1^{+}c\text{-}kit^{+}$ (LSK) cells, which include HSCs and noncommitted MPPs, ultimately leading to expanded populations of myeloid cells in the BM and the periphery (52). TLR2 is also crucial for the emergency myelopoiesis that occurs during *Mycobacterium tuberculosis* infection in mice (42).

Neutrophil release from the BM is dependent on G-CSF produced by vascular endothelial cells in response to TLR ligation. G-CSF stimulates neutrophil release from the BM via a two-pronged approach. By triggering a downregulation of CXCL12, a surface-bound chemokine expressed by BM stromal cells, and by activating neutrophil proteases, G-CSF breaks the chemokine ligand–receptor bond that usually retains neutrophils within the BM niche (53, 54). Further, G-CSF triggers the release of the neutrophil chemoattractants CXCL1 and CXCL2 from vascular endothelial cells (55). By binding to CXCR2 on neutrophils, these chemokines recruit newly differentiated neutrophils to the bloodstream. A similar process of CXCL12 regulation by the monocyte chemokine receptor CCR2 has been proposed to regulate monocyte egress from the BM under inflammatory conditions (56). Activation of CCR2 by its cognate ligand CCL2 downregulates CXCR4 expression by BM monocytes, releasing them from the BM niche. Although CCL2 was previously assumed to come from the inflamed tissues, a recent article by

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Jung et al. (57) shows that preformed CCL2 is stored in the vesicles of stromal cells within the BM itself, from where it is rapidly released after TLR4 ligation.

Although enhanced production of neutrophils and monocytes occurs in response to many forms of infection and/or inflammation, the exact nature of the alterations in hematopoiesis can be finely tuned depending on the nature of the insult. Bacterial infections tend to drive the preferential expansion and release of phagocytic cells, such as granulocytes and monocytes that are required for elimination of such pathogens. In contrast, viral infections or exposure to synthetic analogs of viral MAMPs are associated with increased production of DC precursors (58–60). Welner et al. (60) demonstrated that infecting mice with HSV caused CLPs to differentiate into plasmacytoid and conventional DCs at the expense of B cells. Plasmacytoid DCs play an important role in mediating antiviral host defenses, because they produce type I IFNs (61). This effect was largely TLR9 dependent and could be recapitulated by injecting mice with CpG (the dinucleotide CG, linked by a phosphate group), a synthetic TLR9 ligand (60). CLPs express TLR9, suggesting that viral MAMPs could directly influence CLPs in the BM. LSK cells in the BM may also respond to MAMPs directly, because they express TLRs (43, 62). Indeed, in vitro studies suggest that TNF-α, IL-6, or IFN-γ treatment may even return $Lin^{-}Sca\text{-}1^{-}c\text{-}kit^{+}$ lineage "committed" progenitors to a more primitive multipotent state (43). Although it is possible that the results in that study might reflect expansion of contaminating LSK cells, inflammatory cytokines have also been implicated in emergency myelopoiesis in vivo. For example, LSK cell expansion following *M. tuberculosis* infection could be attenuated by Ab-mediated blockade of IL-6 and TNF-α (42), whereas type I IFN production was shown to be responsible for emergency myelopoiesis following chronic TLR7 signaling (63). Although the exact mechanisms that drive emergency myelopoiesis remain to be fully elucidated, it seems safe to assume that this phenomenon can by triggered by several arms of the innate immune system and their products. By responding to environmental cues, the cellular components of the BM can drive the direction of hematopoiesis according to the nature of the immunological challenges faced by the host, thus shaping subsequent immune responses in an appropriate manner.

Impact of microbial signals on HSC function and leukocyte longevity

The microbial factors that regulate myeloid cell production and differentiation in the BM may also control their subsequent expansion and longevity after their export to the periphery. Recent work by Hergott et al. (32) demonstrated that treating mice with neomycin results in accelerated turnover of circulating monocytes and neutrophils and that these cell populations are less able to survive ex vivo. Although neomycin did not reduce the overall bacterial burden in the intestine, it did induce significant microbial dysbiosis. The ability of microbiota to enhance myeloid cell lifespan in vivo was dependent on NOD1, but not NOD2, TLR2, or TLR4, suggesting a role for specific bacterial peptidoglycans in mediating these effects. The age-prolonging effect of NOD1 ligation could be reversed by blocking IL-17A, highlighting a potential role for this cytokine in mediating the effects of the microbiota on myeloid cell development and behavior.

Until very recently, dogma surrounding microbe-driven changes in hematopoiesis suggested that LSK cells in the BM expanded and differentiated down a particular lineage in response to environmental cues. However, recent work coupling functional studies with transcriptional and epigenetic modification assays suggests that HSCs are biased in their differentiation potential (23, 64) and that specific HSC clones may be impaired in their ability to differentiate down a particular lineage pathway by cell-autonomous epigenetic constraints (23). In a landmark study, Yu et al. (23) generated the transgenic HUe mouse strain, which allowed fate mapping of endogenous HSCs in vivo, as well as isolation of distinct HSC clones and transplantation into new hosts. The majority of hematopoietic cells in the body were found to be maintained by only a few HSC clones at any given time; following transplantation into a new host, HSC clones consistently behaved in a cell-autonomous manner, expanding and differentiating down the same lineage pathway, regardless of the recipient. Furthermore, individual clones showed distinct characteristics with respect to proliferation, cell activation, and, importantly, lineage differentiation in the steady-state and following LPS challenge. These effects were attributed to differences in chromatin accessibility, DNA methylation at specific sites, and corresponding alterations in the gene-expression profiles of individual clones. Although paradigm shifting, this work does not imply that BM hematopoiesis is unaffected by environmental cues; instead, specific HSC clones may be epigenetically poised to expand and differentiate down a particular lineage given the appropriate stimuli.

Conclusions

Recent decades have seen a profound increase in the prevalence of immunopathologies, such as asthma, allergies, IBD, type 1 diabetes, and multiple sclerosis. Such rapid increases in these immune-mediated diseases have been attributed to changes in the environment and a reduction in the biodiversity of the human microbiome, which may be particularly important early in life. An explosion of research in recent years has begun to reveal how different components of the intestinal microbiota can modulate immune function in the gut and elsewhere, and we are coming increasingly closer to understanding the molecular mechanisms involved. As we discuss in this article, one way in which our microbial constituents can shape the immune response is by regulating hematopoiesis via a complex interplay among MAMPS, microbial metabolites, and secondary mediators, such as growth factors, cytokines, and chemokines. These processes allow the microbiota to drive proliferation of hematopoietic stem and progenitor cells in the BM, as well as influence lineage commitment of individual progenitor cells. Importantly, it is becoming clear that alterations in diet or antibiotic treatment can alter BM hematopoiesis in adults, resulting in profound effects on immune function.

In addition to these effects in adults, it is becoming increasingly clear that early life is a particularly critical period during which disruption of normal microbial colonization can have life-long effects on immune function. There is also emerging evidence that exposure of the mother to microbial signals during gestation or in the postnatal period can alter immune responses in infants. Whether this is a downstream consequence of altered BM hematopoiesis in the offspring remains unclear but certainly warrants further study. Elucidating

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the processes that allow the microbiota to shape immune function early in life could provide a missing link in our understanding of how immunopathologies develop and has important implications for the use of antibiotics and dietary manipulation in children and pregnant women.

Disclosures

The authors have no financial conflicts of interest.

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