doi:10.1038/nature17895

IMMUNOLOGY

Mum's microbes boost baby's immunity

The microorganisms that colonize pregnant mice have been shown to prime the innate immune system in newborn offspring, preparing them for life in association with microbes.

MIHIR PENDSE & LORA V. HOOPER

Babies emerge from the womb into a world brimming with microbial life. Mammalian young inhabit a microbiologically sterile environment during fetal development, but are exposed to microbes from the moment of birth. The newborn intestine subsequently becomes colonized with trillions of microorganisms that promote digestion, block invading organisms and synthesize certain vitamins. How does the immature newborn immune system deal with this microbial onslaught? Writing in *Science*, Gomez de Agüero *et al.*[1] show that the bacteria that live in a pregnant mother's intestine provide signals that promote the development of her newborn's immune system, readying it to cope with large numbers of microbes.

Microbial colonization during the first days and weeks of newborn life has profound effects on immune-system development[2]. Many of these effects have been teased out by studies in germ-free mice, which are reared in a completely sterile setting. Germ-free mice exhibit numerous immune-system deficiencies, such as a dearth of the B and T cells that respond to foreign invaders[2]. But what happens before birth? Although the fetus lacks its own resident microorganisms, might the mother's own microbes provide cues that guide immune-system development in her offspring?

Gomez de Agüero *et al.* addressed this question using a clever experimental trick in which they exposed germ-free mice to bacteria only during pregnancy. They chose a normal bacterial resident of the gut, *Escherichia coli*, but genetically hobbled it so that it wouldn't persist in the intestine for more than a few days[3]. Pregnant mice became colonized with the hobbled strain (called *E. coli* HA107) but then returned to a germ-free state before giving birth. Thus, the developing offspring were exposed to bacteria and their products only during pregnancy — not after birth.

The authors then studied the immune systems of offspring born to the transiently colonized mice. The newborns had increased numbers of two key immune cells that circulate throughout intestinal tissues and help to fight foreign invaders: group 3 innate lymphoid cells (ILC3s)[4] and intestinal mononuclear cells (iMNCs)[5]. Both cells are agents of the innate immune system, which is tasked with unleashing a rapid but nonspecific response to infection. Interestingly, ILC3 numbers remained elevated for several weeks after birth, suggesting that even transient colonization during pregnancy has long-term consequences for the offspring's immune system.

Although intestinal B- and T-cell numbers are boosted by colonizing germ-free mice after birth, these cells were unaffected by pregnancy-specific colonization of the germ-free mice. B and T cells are agents of the adaptive immune system, which confers long-term, specific immunity to microorganisms. Thus, pregnancy-specific colonization seems to preferentially affect cells of the innate immune system, whereas cells of the adaptive immune system are shaped largely by microbial exposure after birth.

Gomez de Agüero *et al.* found that pregnancy-specific colonization also elevates the expression of large swathes of genes in the newborn intestine. These include genes involved in metabolism, oxidative stress and innate immunity. For example, there was increased expression of the gene encoding RegIIIγ, a secreted protein that minimizes bacterial attachment to the intestinal surface[6]. These findings suggest that maternal microbes trigger a wide range of intestinal adaptations that go beyond the changes in immune-cell numbers.

How do maternal gut microbes signal to the fetus to prime development of the innate immune system? The authors first ruled out direct exposure of the fetus to live bacteria as a possible mechanism. But when they transferred serum from a mother colonized with *E. coli* HA107 into a germ-free mother, the offspring born to the serum-transplanted mice displayed the same boost in ILC3 numbers and RegIIIγ expression. Interestingly, this boost depended partly on the mother's

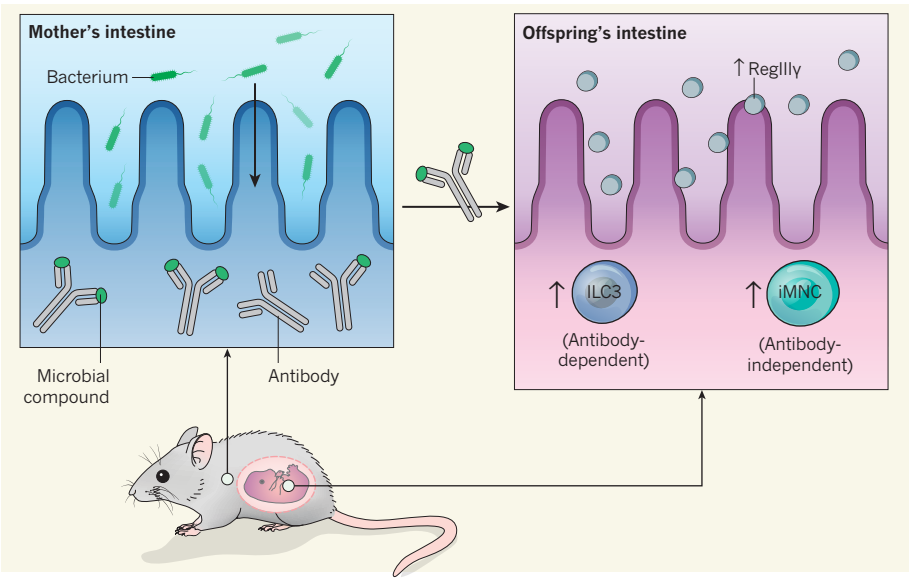

Figure 1 | Preparation for the outside world. Gomez de Agüero *et al.*[1] show that the presence of bacteria in the intestines of pregnant mice increases innate immunity in the offspring, and that this effect depends partly on the mother's circulating antibodies. Through an unclear mechanism, the antibodies promote transfer of microbial compounds to the developing fetus. This results in increased numbers of group 3 innate lymphoid cells (ILC3s) and increased expression of the *RegIIIγ* gene, which encodes the antimicrobial protein RegIIIγ, made by the intestinal epithelial lining. Numbers of intestinal mononuclear cells (iMNCs) are also boosted by pregnancy-specific colonization, but this increase is independent of the mother's antibodies.

antibodies — circulating immune molecules that bind tightly to specific antigen molecules, including those derived from bacteria. Bacterial compounds from the mother were indeed present in newborn tissues, and maternal antibodies enhanced transfer of the compounds to the offspring. It is still not clear whether this antibody-facilitated transfer is due to direct antibody binding to microbial compounds. But these findings suggest that maternal antibodies bind to microbial molecules, enter the circulation and deliver the molecules to the developing fetus, where they prime immune-system development (Fig. 1).

When the authors investigated the chemical composition of the immunity-stimulating compounds, several were known binding partners of the aryl hydrocarbon receptor (AhR), which is essential for the development of key intestinal immune cells, including ILC3s[7]. Thus, AhR might be part of the mechanism by which maternal bacterial compounds are received by the offspring's immune system.

Do maternal microbes confer any advantages to newborns in dealing with microbial exposures? When Gomez de Agüero *et al.* exposed newborns to intestinal bacteria, those born to pregnancy-colonized mothers were better able to limit the numbers of bacteria that penetrated to deeper tissues than were those born to germ-free mothers. This suggests that the immunity boost from the mother's microbes helps to protect neonates against the pathogenic effects of bacteria, and prepares the offspring for association with large microbial communities after birth.

There are several fascinating questions that remain to be addressed. Are there other receptors besides AhR that receive maternal microbial signals in the newborn immune system? Do maternal microbial communities associated with the skin and airways also prime newborn immunity? And do maternal intestinal bacteria affect immunity in any other organs of the newborn?

A major goal in studying gut bacteria is to use their beneficial properties to improve human health. Gomez de Agüero *et al.* have laid some groundwork by identifying maternal bacterial compounds such as indole-3-carbinol — a naturally occurring ligand of AhR — that stimulate newborn immunity when fed to a pregnant mother. The work may point to new therapeutics for neonatal infectious diseases, and should encourage further investigation of how bacterial molecules augment immunity in humans. ■

Mihir Pendse *and* **Lora V. Hooper** *are in the Department of Immunology, University of Texas Southwestern Medical Center, Dallas, Texas 75390, USA.* **L.V.H.** *is also in the Howard Hughes Medical Institute, University of Texas Southwestern Medical Center.*
e-mail: lora.hooper@utsouthwestern.edu

1. Gomez de Agüero, M. *et al. Science* **351,** 1296–1302 (2016).
2. Round, J. L. & Mazmanian, S. K. *Nature Rev. Immunol.* **4,** 313–323 (2009).
3. Hapfelmeier, S. *et al. Science* **328,** 1704–1709 (2010).
4. Killig, M., Glatzer, T. & Romagnani, C. *Front. Immunol.* **5,** 142 (2014).
5. Gross, M., Salame, T. M. & Jung, S. *Front. Immunol.* **6,** 254 (2015).
6. Vaishnava, S. *et al. Science* **334,** 255–258 (2011).
7. Stockinger, B., Di Meglio, P., Gialitakis, M. & Duarte, J. H. *Annu. Rev. Immunol.* **32,** 403–432 (2014).