

Oh, the Microbes You'll Meet!

Fred Hutch Cancer Center immunologist discovers a biological mechanism sprung in the first week of life that trains a mouse pup's immune system to tolerate harmless gut bugs and new foods.

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When a baby enters the world, a world of microbes enters the baby.

[With apologies to Dr. Seuss](#), the story of how the developing immune system makes peace with the tiny squatters that populate the infant gut could go like this:

"Oh, the microbes you'll meet! They're mostly good or at least discreet, but some are scoundrels, thieves and cheats."

Most of the microbiota setting up shop in the intestines are helpful or innocuous, but a few can be deadly, and the baby's immune system must learn to tell the difference.

A study by Fred Hutch Cancer Center immunologist [Meghan Koch, PhD](#), recently published in the journal [Science](#) describes how this learning in mice begins in the first week of life with a maternal antibody passed through breastmilk.

The mechanism Koch and her colleagues discovered tunes the developing immune system so that it doesn't overreact to harmless microbes or new foods encountered during development.

A better understanding of how it works in mice could shed light on how humans have evolved to solve the same problem, and lead to potential therapies for food allergies in newborns and infants.

The prevailing model of how mothers transfer immunity to infants through breastmilk is incomplete

Koch's lab in the [Basic Sciences Division](#) at Fred Hutch focuses on how the immune systems of mothers and infants interact before and after birth. She studies how these interactions train the babies' developing immune systems to establish and preserve a healthy balance with the emerging microbiota, the complex community of microbes that colonize the mammalian gut immediately following birth.

It's well-established that antibodies passed from mothers through breastmilk regulate gut immunity, but Koch wanted to understand the precise mechanism(s) that keep the peace between the microbiome and the baby's immune system.

The prevailing model of how that works is largely based on studies in adult mice of antibodies that target bacteria, viruses, parasites and other enteric pathogens typically ingested through contaminated food or water.

But an infant's gut is different than an adult's and so are the microbiota inhabiting it.

Finding the mechanism in mice

Sorting out interactions between maternal antibodies, the gut microbiota and the infant immune system required developing a genetically engineered mouse model that would allow Koch and her team to precisely control the timing of antibody transfer and other variables.

"Then we could just take away everything and then add it back," Koch said. "And by being able to do that, we can really do a bunch of different tricks and manipulate all these aspects."

Postdoctoral researcher [Meera K. Shenoy, PhD](#), who led the research, developed an approach that essentially starts with a blank slate — pups that haven't received any maternal antibodies — and then tracks what happens when the researchers systematically introduce antibodies one at a time under controlled conditions.

"Cage-to-cage differences in the microbiota are a confounding factor in most studies that use genetic mouse models, so I wanted a way of teasing apart the influence of maternal antibodies from maternal microbes," said Shenoy, who is now a principal investigator at the Singapore Immunology Network. "By isolating different antibody subtypes and feeding them to pups in the same litter, we could ensure that any observed developmental differences were due to ingested antibody type rather than differences in microbiota."

The team confirmed that breastmilk antibodies mattered, and one class of antibody called [immunoglobulin G](#), or IgG, stood out as particularly important for shaping the developing immune system.

They found that feeding IgG to infant mice that had not received any maternal antibodies could restore normal immune function. IgG worked whether the mice were raised in Seattle or in Berkeley, California, though the group in each city had different communities of microbiota growing in the pups' guts.

They discovered that whatever work IgG is doing, a little goes a long way. Feeding pups low levels of IgG was extremely effective at regulating immune responses up to weeks later, a point at which the IgG was no longer detectable.

Koch said that raised an interesting question: “How is the IgG changing this immune response later when it’s not even present anymore?”

They don’t have the complete answer to that question, but they’ve connected enough dots to form a rough picture.

All the magic of IgG happens within the first week of life when the antibody binds to harmless bacteria inside the gut and forms a complex.

Normally, that complex would stay inside the intestine, but in the first week of life the intestinal wall is permeable enough to allow the complex to slip through and enter the body, where it can be sensed by the pup’s developing immune system.

The immune system becomes familiar with the IgG-bound microbes that have slipped through and tolerates their presence, saving an all-out attack for the real threats.

That mechanism trains the immune system to not overreact to the good bugs taking up residence in the gut.

Koch’s team wondered whether IgG also regulated immune responses to molecules in food that can sometimes provoke an allergic response. They found that feeding baby mice IgG in the first week of life made them more tolerant to a new dietary protein they were fed weeks later, after weaning.

IgG had the same broad dampening effect, keeping the immune system from overreacting to new foods.

Why it matters for humans

The IgG that mice pass to their pups during breastfeeding is much more abundant than it is in human breastmilk. As such, the function of IgG in human breastmilk hasn’t aroused much scientific curiosity.

The few studies on IgG in human breastmilk have focused on its role in combating infection, rather than understanding how it helps the infant maintain a healthy balance with the microbiome.

But Koch wonders if we use IgG the same way as mice.

It’s also possible that we have evolved ways to do the same thing with a close cousin of IgG called Immunoglobulin A, or IgA.

Understanding how it works in humans will require more research, but Koch’s study suggests that newborns of women who cannot or choose not to breastfeed could benefit from IgG delivered in the first three days of life, which might be enough to get the job done.

“We think there might be a role for milk IgG, and it’s OK that there is not a lot of IgG because it only really needs to do its work in the first window of life,” Koch said.

It may also help babies cope with food allergies.

But Koch said it’s important to understand that maternal antibodies delivered through breastmilk aren’t critical for survival and her study shouldn’t cause a new round of parent anxiety over breastfeeding.

“These mice that don’t get antibodies from their mom are fine,” she said.

Besides, humans who do breastfeed may not always pass on the key antibodies Koch is studying, and their babies turn out fine, too.

But knowing how the mechanism works on a fundamental level may yield insights that could improve babies’ gut health right from the start.

“It’s cool to study these things in milk and understand what they can do,” Koch said. “Potentially, we can use this knowledge and leverage it to help. The more we know, the more we can do.”

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