PNAS PROFILE

Profile of Andreas J. Bäumler

Sandeep Ravindran

Andreas J. Bäumler became interested in the life sciences during his high school years in Bavaria, Germany. "I had a biology teacher who motivated me to study biology; that was my first influence," he says. His interest in infectious diseases and molecular biology drew him toward microbiology. "Much of eukaryotic biology wasn't very molecular or genetic at the time, whereas microbiology was using genetics since it was first available, so I kind of liked that," he says.

So began Bäumler's long and distinguished career in microbiology, during which he has made many contributions to the field. He has studied how the pathogenic bacterium *Salmonella* colonizes the intestine and how the host responds to *Salmonella* infection. Bäumler's research on how pathogens cause inflammation and disrupt the gut microbiota has enabled him to identify host factors involved in balancing gut microbial communities. Among other things, he has found that cells of the intestinal epithelium, particularly those involved in cellular respiration and energy metabolism, influence the composition and function of the human gut microbiota and can result in "dysbiosis," a condition in which the microbial composition of the gut is thrown out of balance. Bäumler's work has important implications for several diseases, including infectious colitis, colorectal cancer, diabetes, and chronic kidney disease.

In his Inaugural Article (1), Bäumler reviews his efforts to understand the mechanisms that lead to gut dysbiosis and highlights the role of host changes in causing dysbiosis. Now a professor at the University of California, Davis, Bäumler was elected to the National Academy of Sciences in 2023.

Andreas J. Bäumler. Image credit: Kathy West (photographer).

Perspective on the Microbiome

Bäumler earned his diploma and PhD in microbiology from the University of Tübingen in 1992. "At Tubingen, there was a strong [emphasis on] environmental microbiology and microbial physiology, so my initial background was in understanding microbial metabolism," he says. After his PhD, Bäumler became a postdoctoral fellow in microbial pathogenesis at the Oregon Health Sciences University in Portland, Oregon. "During my postdoc, I studied pathogenesis for the first time, which was in the enteric pathogen *Salmonella*, and I became…interested in the intestinal phase of infection," he says.

In 1996, Bäumler started his own lab at the Texas A&M University Health Science Center, where he continued his studies on *Salmonella* intestinal colonization. "I had a nice collaboration with Garry Adams at Texas A&M that allowed us to look at the intestinal phase of infection a little better because Garry had a calf model," he says. "When the calves are infected with *Salmonella*, they develop a localized gastroenteritis just like humans, whereas mice infected with *Salmonella* get a systemic infection. So the calf model better represents the human disease," says Bäumler. Studies in the calf model allowed Bäumler to better understand the intestinal pathology of *Salmonella* and sparked his interest in host immunology. "Using the calf model, I was getting deeper into the host response and studied inflammation and the pathways triggering inflammation, and so that kind of got me more and more familiar with immunology," he says.

When Bäumler joined UC Davis in 2005, he started studying another key player in the gut—the microbiota. "Since I was already interested in an enteric pathogen and the intestinal phase of infection, it was fairly easy for me to incorporate microbiota because that was always happening in the background," he says.

Bäumler says his scientific background and interests gave him a vantage point on the microbiome. "I would say I'm probably an outsider in the microbiome field, and bringing this microbiologist viewpoint, I think, makes me look at most of the questions quite differently," he says. In particular, Bäumler's knowledge of microbial physiology allowed him

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to understand differences in how the microbiota grew, and his work on *Salmonella* intestinal infections speeded his understanding of host immunology and inflammation. "The host has a strong influence, and of course when inflammation changes the environment, that can change the microbial community," he says.

Holistic View of the Microbiome

At UC Davis, Bäumler started working with germ-free mice, which exist in a sterile environment completely devoid of microorganisms. He hoped to examine the gut microbiota in more detail. "You can give defined communities or you can do Fecal Microbiota Transplantations (FMTs)," he says. In FMT, fecal matter from a donor is transferred into the intestinal tract of a recipient to directly change the recipient's gut microbial composition. FMTs have been used to successfully treat recurrent *Clostridium difficile* infection. "That tool made it possible to manipulate the microbiota, and we could also manipulate the mouse and pathogen genetically, which made it possible to become pretty mechanistic in our approach," he says.

Baumler has always taken a holistic view of the microbiome. "The microbiome is more than just the microbes or their genes and gene products. It's the microbiota and its environment, which includes the host organ in which the microbiota resides," he says. "What I was trying to get across in my Inaugural Article is that without incorporating the host in the picture, you don't understand dysbiosis," says Bäumler (1).

Among other things, Bäumler was able to show that oxygen is one of the major drivers of microbial community structures in the gut, and to understand the mechanisms by which oxygen levels are controlled. Bäumler says a key breakthrough came in a 2010 article with Sebastian Winter on the electron acceptor tetrathionate (2). "That showed for the first time that a host response can generate some sort of electron acceptor that helps pathogens bloom in the gut," he says. "Tetrathionate was a very exotic electron acceptor [that] only a few bacteria can use, and it had been used for many decades in clinical labs to enrich for *Salmonella* in samples contaminated with other microbes," explains Bäumler. *Salmonella* used tetrathionate as an electron acceptor and outgrew other microbes in these samples. "We found basically the same thing happening in the gut, except tetrathionate is only generated during inflammation by the inflammatory host response oxidizing sulfur compounds in the gut," he says.

Another major finding was that epithelial hypoxia was a major driver of community composition. "If the epithelium in the colon is hypoxic, with less than 1% oxygen, very little oxygen diffuses out to keep the lumen anaerobic, and we showed in a 2016 paper with Fabian Rivera Chavez [and colleagues] that *Salmonella* eliminates hypoxia during infection and increases oxygen levels," he says (3). Another paper the same year with Chris Lopez [and colleagues] showed that another pathogen, *Citrobacter rodentium*, achieved the same effect in mice, albeit using a different mechanism (4). "Then, a very influential 2017 paper with Mariana Xavier Byndloss [and colleagues] showed the mechanism by which oxygenation of the epithelium changes," says Bäumler (5). The researchers identified the regulator in the epithelium, a molecule called PPAR-γ that responds to butyrate as a signal and activates mitochondrial activity (5). In the absence of butyrate, the metabolism changes so that oxygen is no longer consumed in the mitochondria but diffuses into the lumen.

"Those three papers…put oxygen and mitochondrial activity of the epithelium in the picture, and after that, we found that [in] every disease we studied, that pathway is affected," says Bäumler. "There are so many conditions where this metabolism of epithelial cells seems to affect the environment and the metabolism of the microbiota. We can just move from disease to disease and make contributions," he says.

Variety of Diseases

The gut microbiome has wide-ranging effects. "The nice thing about microbiome research is that it affects so many diseases, and if you understand the drivers of dysbiosis, you can work on these diseases and make a contribution," says Bäumler. "One approach is to target the metabolism of the microbiota, for example, with tungsten to block respiratory metabolism of *Enterobacteriacae* (6). [Another] approach is to target the host so that you prevent resources from diffusing into the gut that promote the growth of potentially harmful bacteria, so you can treat the host and therefore prevent or ameliorate dysbiosis," he says.

Bäumler is particularly interested in PPAR signaling pathways and suggests that using agonists to activate the regulators could return the epithelium to a healthy state. "That usually fixes the problems we look at," he says. One project Bäumler is currently working on involves *Candida albicans*, an opportunistic pathogen that affects people with cancer and people receiving transplants who are on antibiotic therapy. "If you block the oxygenation of the epithelium, you can prevent *Candida* from blooming and therefore causing candidemia," he says.

Bäumler says an advantage of blocking *Candida* bloom with a PPAR-γ agonist that targets the host is that the fungi cannot become resistant. Targeting the host could help develop therapeutic approaches against other opportunistic pathogens as well—without leading to resistance. "If you're looking for therapeutics, going beyond just the microbiota and considering the host seems like a potentially fruitful line of inquiry," says Bäumler.

Understanding the microbiome could result in unexpected dividends. "Many diseases that are leading causes of death, such as cardiovascular disease, diabetes, and chronic kidney disease, are associated with an elevated level of uremic toxins in the blood, and uremic toxins are produced only by the microbiota," says Bäumler. "These patients have dysbiosis and a changed composition in the microbiota, so I think there's a large group of patients… that perhaps can be targeted by microbiota-based therapies to reduce the production of uremic toxins," he says. Bäumler currently has a project exploring chronic kidney disease and has also examined conditions such as inflammatory bowel disease and colorectal cancer.

Bäumler is working on understanding why such conditions are associated with changes in the microbiota composition and whether such dysbiosis increases the production of uremic toxins. "It looks like changes in the gut environment are

key to accelerating the production of these compounds," he says.

Bäumler is optimistic about the long-term therapeutic potential of his work. "Treatments that would normalize the composition [of the microbiota] could be beneficial for many of these conditions, so that's a future area that is very promising simply because these conditions affect so many people," he adds.

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