Baboons shed light on antimicrobial resistance

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Antibiotic resistance is an ancient feature of gut microbial communities and sharing habitat with humans has had an important impact on the structure and function of gut microbiota of non-human primates, according to a study involving wild and captive baboons. The study,

published in the journal *mSystems*, is one of the first to provide a glimpse of the pre-antibiotic resistome of primates.

"The gut microbiomes of baboons look very different from humans, and within the baboon sets, the microbiomes of the captive baboons were different from the wild ones, supporting the hypothesis that something about captivity and human contact shifts the microbiomes," said principal study investigator Gautam Dantas, Ph.D., professor of pathology and immunology at Washington University in St. Louis, Missouri. "There is a gradient in the compositional differences of the gut microbiomes between humans with different lifestyles, with people living in developed nations and cities having similar microbiomes and then microbiomes looking less and less similar the further away you move toward the agrarian and hunter-gather lifestyle. This study shows you can now put non-human primates on that same gradient too."

By using wild versus captive nonhuman primates as a model for the human microbiome, the investigators showed very clearly that antibiotic resistance exists, even without human-produced antibiotic selection pressure, and that the microbiome of animals looks very different in wild populations. "As soon as you have contact with humans and human medicines, you shift the composition of the microbiome toward an industrialized human state and you enrich for antibiotic resistance, which tells us that this is a great risk factor," said Dr. Dantas.

"It is very difficult to find what the pre-antibiotic resistome looks like. That is what motivated this study," said Dr. Dantas. A major roadblock to understanding the impact of antibiotics on the human microbiome is finding samples from humans that have never been exposed to antibiotics.

The study was a collaborative effort between Dr. Dantas's laboratory, which performed the microbiology and genomics work, and several

anthropologists with access to wild and captive primate populations. "We were very fortunate to get not just the samples, but the intellectual contributions of the anthropologists," said Dr. Dantas.

The researchers compared their data with published metagenomic datasets from humans and baboons to test the hypothesis that human contact correlated with substantial shifts in microbiota composition, function and resistome profiles compared to 'antibiotic naïve' baboon gut microbiota. Using the same genome sequencing technology employed by the Human Microbiome Project, the researchers analyzed fecal samples from baboons in regions of Zambia where the animals had minimal contact with humans and compared them to samples from captive baboons in the Southwest National Primate Research Center, in Texas.

After sequencing the DNA in the baboon fecal samples, the researchers mapped the metagenomic data to databases of resistance genes. Because these databases are biased towards known pathogens and human-related samples, the researchers used functional metagenomics, which allowed them to identify both known and novel resistance genes. "We take the fecal samples from the baboons and, before we do any sequencing, we clone the fecal metagenomic DNA recombinantly into an *Escherichia coli* (*E. coli*) expression system. Then, every clone in the *E. coli* library contains a random genetic fragment from the baboon microbiome. We plate those libraries of *E. coli* recombinants on petri dishes with antibiotics that will kill wild type *E. coli* and the only recombinants that can survive are those expressing a functional resistance gene from the baboon microbiome," explained Dr. Dantas.

The researchers identified functional antibiotic resistance genes in the gut microbiota of wild and captive baboon groups and marked variation in microbiota architecture and resistome across habitats and lifeways. Some of these resistance genes had never been described. Wild baboons had the lowest number of resistance genes, lower than captive baboons,

and even lower than humans. Comparing the gut microbiomes of baboons and humans from the United States, Venezuela, Italy, and Malawi, as well as the remote Hadza tribe in Tanzania that was recently identified as being relatively antibiotic naïve, the researchers found that the captive baboons' microbiome and resistome resembled the isolated tribe most closely.

Finding resistance genes in populations that have not been exposed to human produced antibiotics is not novel. "Antibiotics are molecules that have been produced by soil bacteria for hundreds of millions of years. In the 1930s and 1940s, humans figured out how to bioprospect these molecules and produce them on a large scale and that changed the face of treating infectious diseases. Then resistance started increasing in pathogens, but resistance has existed in other bacteria for eons," said Dr. Dantas. "We believe that the wild baboons represent an ancestral state of antibiotic resistance and they have resistance genes, not because they have seen any human produced antibiotics, but rather, the ancient antibiotic resistance genes likely came from exchange with microbes from environments like the soil."

One surprising finding from the study was that wild baboon populations were enriched with Actinobacteria, a group of microbes that are important for digesting human breast milk and are normally associated with infancy in humans. "As human kids transition to solid food, those bacteria are depleted," said Dr. Dantas. "We were very, very surprised to find that particular class was highly enriched in the wild baboons, even in the adult baboon populations. We don't currently have a good explanation for this, but it probably has something to do with their diet." Bioprospecting these potentially beneficial bacteria from wild non-human primates could lead to new probiotic therapies.

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