IU role in Human Microbiome Project exposes battle history between bacteria, viruses in human body

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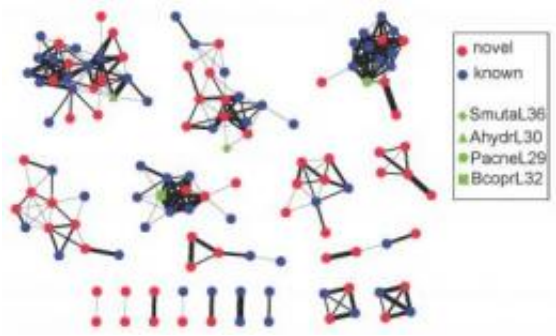

This is a visualization of a network of 150 CRISPRs, each represented as a node. Blue nodes are known CRISPRs; red nodes are novel CRISPRs. CRISPRs sharing more genomic repeats are connected by thick lines; those sharing fewer repeats are connected by thin lines. Credit: Indiana University

An Indiana University team of researchers has conducted the most in-depth and diverse genetic analysis of the defense systems that trillions of micro-organisms in the human body use to fend off viruses. The work is among a collection of 16 research papers released today by the Human Microbiome Project Consortium, a National Institutes of Health-led effort to map the normal microbial make-up of healthy humans.

Led by IU Bloomington assistant professor of informatics and computing Yuzhen Ye, the team of bioinformaticists and biologists

reconstructed arrays of clusters of regularly interspaced short palindromic repeats -- CRISPRs -- which function as immune systems to the bacteria that play a vital role in human health. Between genomic repeats, CRISPR locations carry short strands of foreign DNA called spacers, which provide a history of past exposures to outside invaders like plasmids and bacteriophages (viruses that infect bacteria), and allow the bacteria to fight off viruses they have already encountered.

"By studying CRISPRs and their sequences, we ask the same types of questions we ask about viral infections in humans and other animals: Do individuals make antibodies to a particular virus? If they do, we then know they have been exposed to that virus," Ye said. "By examining CRISPR sequences, we learn about what viruses there have been infecting different species of bacteria in a particular environment."

Bacteriophages are the most abundant life form on the planet and are in a constant arms race with bacteria, which in the human body outnumber human cells by 10 to 1. Scientists want to better understand how microbes -- a group that contributes more genes responsible for human survival than humans themselves do -- battle the viruses that seek to infect them.

Using a targeted assembly strategy to reconstruct CRISPR arrays that otherwise are impossible to identify from whole metagenome assemblies, the team identified the distributions of 64 known and 86 novel types of CRISPRs (based on the CRISPR repeat sequences) from the 751 shotgun datasets (containing 3.5 terabases of genomic sequences) of microbial DNA extracted from the 242 healthy U.S. volunteers participating in the Human Microbiome Project.

The Human Microbiome Project collected tissues from 15 body sites in 129 men and from 18 body sites in 113 females, with up to three samples taken from each volunteer's mouth, nose, skin and lower

intestine, in addition to three vaginal sites in women. The entire research consortium included 200 researchers at nearly 80 universities and institutions, and today's release of new data is the result of five years of work and an investment of $173 million.

The IU team confirmed that by using targeted assembly, longer CRISPR arrays were produced that allowed more spacers to be identified for analyzing CRISPR evolution. The Streptococcus CRISPR SmutaL36, for example, was observed in 38 of 751 datasets using whole metagenome assembly, but targeted assembly identified SmutaL36 in 386 datasets. For 142 out of 150 CRISPRs, their traces were identified in more datasets by targeted assembly as compared to whole metagenome assembly, and for 36 CRISPRs, they were seen in at least 10 times more datasets.

"We know that CRISPRs adapted to a virus or other infectious agent are extremely important to the bacteria carrying those CRISPRs: They live or die," Ye said. "But we really don't understand how this leads to changes in the entire biology of an individual."

Looking at what could be the nuanced differences in the evolution of CRISPR defenses, the team found that in one case involving known streptococcal CRISPRs in the mouth (where targeted assembly revealed 8,000 unique spacers), most spacers were shared at the same oral site of resampling for the same individual, while different oral sites from the same individual shared significantly fewer CRISPRs. Different individuals had almost no common spacers.

The team found a skin-specific CRISPR (PacneL29) in Propionibacterium acnes -- the only skin-specific CRISPR found in the Human Microbiome Project datasets -- and P. acnes is linked to the skin condition acne, which is one of the many cases where a complicated interaction between host and bacteria exist. While most people have the

bacteria, they don't have acne.

"Overall, this work demonstrates the applications of CRISPRs to tracing the virus exposure of individuals," Ye said. "And it indicates the importance of effective identification and characterization of CRISPR loci to the study of the dynamic ecology of microbiomes."

The lack of common spacers between individuals probably reflects different individual virus exposure and indicates that the battle between bacteria and viruses is constant, with bacteria adapting to viruses and viruses finding new ways to avoid CRISPR defenses.

"One constant message of the Human Microbiome Project is that people are each really unique in the balance of bacteria inhabiting their bodies. CRISPR arrays can be a unique characteristic of an individual at a certain time, so we may be able to use spacer changes as historical markers," Ye said. "We might also be able to use CRISPR loci as a new molecular fingerprint to identify and trace human individuals from human residues for forensic purposes."

More generally, scientists want to use CRISPRs to follow the ecology of the human microbiome, and Ye said they can't wait for different datasets to study -- particularly datasets from samples taken from the same individual over months and years.

"From what we've seen in the lab, CRISPR arrays can change quickly, and one could argue that scientists often learn the most from long-term observations that follow changes at particular sites," Ye concluded.

More information: "Diverse CRISPRs evolving in human microbiomes" was published today in *PLoS Genetics*.

Provided by Indiana University