Apes show dramatically different early immune responses compared to monkeys

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A new study out of the University of Chicago and the University of Illinois Urbana-Champaign in humans, chimpanzees, rhesus macaques and baboons has found key differences in early gene expression in

response to pathogen exposure, highlighting the importance of choosing the right animal model for the right questions. The study was published on March 26 in *Proceedings of the National Academy of Sciences.*

The researchers previously studied differences in primate immunity and immune responses and wanted to conduct a large-scale, whole transcriptomic investigation into the differences in gene expression seen after exposure to viral and bacterial stimulation.

Often, macaques and baboons are used as research models for studying immune conditions such as sepsis, a widespread inflammatory condition triggered by a severe infection that can cause profound organ damage if it goes untreated. However, while only very small amounts of certain pathogens are required to induce septic shock in humans, much higher doses are needed to induce similar symptoms in some of our closest relatives, such as rhesus macaques or baboons.

"There are massive differences between species in the susceptibility to certain infectious diseases," said co-senior author Luis Barreiro, Ph.D., an associate professor of medicine at UChicago. "For example, humans are very susceptible to septic shock triggered by certain types of bacteria, while some African and Asian monkeys are incredibly resistant. We wanted to know if we could understand what might be the immunological differences underlying such differences in disease susceptibility."

To conduct the study, the team coordinated with investigators throughout the U.S. to conduct identical blood draws and transcriptional analysis in groups of chimpanzees and humans, as well as in two African and Asian monkey species—rhesus macaques and olive baboons.

Blood samples were exposed to either hexa-acylated lipopolysaccharide (LPS) or gardiquimod (GARD), which mimic bacterial and viral

infections, respectively. After either a four- or 24-hour exposure period, investigators conducted whole genome transcriptome analysis of the leukocytes within the samples and examined the changes in gene expression after the stimulation.

The results showed that the apes mounted a much stronger early response and activated a broader array of defense molecules in response to both types of stimulation compared to African and Asian monkeys. This indicates that upon early pathogen exposure, apes mount a strong, nonspecific response that is costly in terms of energy expenditure and possible tissue damage, with the trade-off of being more efficient at killing those pathogens.

The difference in response may be due to differences in life history, according to the investigators. Apes, including chimpanzees and humans, tend to live much longer and are larger, increasing their lifetime risk of pathogen exposure and making a rapid, robust pathogen detection and elimination response evolutionarily beneficial, despite the potential costs.

The finding that African and Asian monkeys showed a much more specific response when compared to apes was a surprise. "I was expecting to see a huge, amplified response from the ape lineage, and the same response but more blunted in the African and Asian monkeys," said co-senior author Jessica Brinkworth, Ph.D., an assistant professor of anthropology at the University of Illinois Urbana-Champaign. "Like the response in apes would be the same, just louder. But instead we saw this specificity of the genes and the ways the networks activated—the patterns were different than we expected."

Understanding the differences and similarities in the early immune response is important for both understanding the nature of the human immune system and for determining which model organisms can most

accurately recapitulate the human immune response when developing drugs and therapies.

"If we're going to talk about human health and look for drugs or genes you can target to improve that health, then we need to appreciate why those genes are there in a species and what they are doing," said Brinkworth. "That requires understanding the evolution of the animal model and how it compares to our own. This study suggests, for example, that African and Asian monkeys are likely not strong models for certain types of sepsis because their immune response doesn't reflect what we see when we compare them to humans and chimpanzees."

More information: Mohamed B. F. Hawash et al, Primate innate immune responses to bacterial and viral pathogens reveals an evolutionary trade-off between strength and specificity, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2015855118

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