Researchers uncover some of the ancient mysteries of leprosy

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Research at The University of Texas MD Anderson Cancer Center is finally unearthing some of the ancient mysteries behind leprosy, also known as Hansen's disease, which has plagued mankind throughout history. The new research findings appear in the current edition of journal *PLOS Neglected Tropical Diseases*. According to this new hypothesis, the disease might be the oldest human-specific infection, with roots that likely stem back millions of years.

There are hundreds of thousands of new cases of leprosy worldwide each year, but the disease is rare in the United States, with 100-200 new cases annually. Leprosy is known for attacking a patient's skin and nerves. Effective antimicrobial treatments exist today. However, when misdiagnosed or untreated, the disease can lead to extensive skin lesions, deformities in the patient's face and extremities, disabilities, and even death. Leprosy carries a social stigma and diagnosis is frequently and notoriously delayed.

An incidental yet important discovery

Work led by MD Anderson pathologist Xiang-Yang Han, M.D., Ph.D., a professor in laboratory medicine, resulted in the discovery in 2008 of a new leprosy-causing species, called *Mycobacterium lepromatosis*. Before that time, only one species of bacteria, called *Mycobacterium leprae*, was known to cause leprosy.

In the past several years, Han and other researchers have found the new leprosy agent in patients from Mexico, Canada, Brazil, Singapore, and Myanmar. Han's team, in collaboration with Francisco Silva, an evolutionary geneticist from Spain, analyzed 20 genes of *Mycobacterium lepromatosis* and compared them with those of *Mycobacterium leprae*.

They found the two leprosy bacteria came from a last common ancestor around 10 million years ago. Before the divergence, the common bacteria ancestor had undergone a massive reductive evolution that resulted in inactivation of approximately 40 percent of all the genes in its genome. Those genes went on to become non-functioning pseudogenes or were even lost. This reductive evolution, unique among all pathogenic bacteria known so far, was unearthed from genome sequencing of *Mycobacterium leprae* several years ago before the discovery of *Mycobacterium lepromatosis*, by another research team.

A unifying theory

In the newly published study, Han and Silva came to the hypothesis that leprosy has existed for millions of years. This theory was built by connecting the dots from several known facts and published studies.

One piece of evidence is the fact that leprosy is a strict human disease without other hosts or reservoirs. Once outside of the human body, leprosy bacteria are unable to grow in artificial media. One caveat is that *Mycobacterium leprae* is found in wild armadillos, but only in North America and South America. It's believed the animals likely first acquired the infection from early American explorers a few hundred years ago.

A second piece of evidence suggesting a long history of leprosy lies within the bacterial genome. All worldwide *Mycobacterium leprae* strains analyzed so far, more than 400 in total, have been found to have

essentially identical genomes, or be clonal. This suggests human beings carried the leprosy bacteria when departing Africa around 100,000 years ago to populate the rest of the world. It also means that leprosy bacteria are extraordinarily stable within their human hosts, a sign of mature parasitic life far older than 100,000 years.

A third piece of evidence relates to the last common ancestor of the two known leprosy bacteria, which completed reductive evolution around 10 million years ago, resulting in a lean genome and the loss of free-living ability. A well-adapted lean parasite is confined to its specific host species and is unlikely to switch to other host species.

Lastly, the oldest age of the leprosy bacteria's pseudogenes suggest that gene inactivation began approximately 20 million years ago. This is likely the point when the ancestor of leprosy bacteria jumped to our early human ancestors and transitioned from free-living to strictly parasitic. In essence, the theory unifies the reductive evolution of the leprosy bacteria and their strict parasitic lifestyle in humans into a single continuous, long process.

Insights into the pathogenesis of leprosy

Han and Silva also brought human evolution, host genetic diversity, and host immunity into the complex picture of leprosy. Their hypothesis that leprosy existed for millions of years offers new insights into disease pathogenesis.

For example, the parasitic adaptation of the leprosy bacteria inside hominid-human hosts is similar to a very long hide-and-seek game. In this scenario, the parasite hides by mutating or removing harmful molecules while retaining protective ones. In the end, this leads to evasion from host immunity, a phenomenon commonly seen in leprosy. Finally, Han and Silva concluded that leprosy can be viewed as a natural

consequence of a long parasitism.

Han, a clinical microbiologist, routinely diagnoses secondary infections caused by various kinds of microbes in patients with cancer. "Many patients who come to MD Anderson suspected of having cancer turn out to have infections instead and we make such game-changing diagnoses nearly every day" said Dr. Han.

"Discovering the new leprosy agent *Mycobacterium lepromatosis* was incidental. However, locating this additional leprosy cause significantly adds to our understanding of the ancient disease. In particular, tracing the ultimate origin of leprosy through the parasitic adaptive evolution of the leprosy bacteria is rather insightful, not only for this single disease but also for our better understanding of the mechanism behind other human infections. Medical historians and anthropologists may appreciate this also."

Han's team is currently focused on the decoded genome of *Mycobacterium lepromatosis* and its assembly.

Provided by University of Texas M. D. Anderson Cancer Center

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