Scientists sequence genome of pathogen responsible for pneumocystis pneumonia

December 26 2012

Scientists have sequenced the genome of the fungus *Pneumocystis jirovecii*, an advancement that could help identify new targets for drugs to treat and prevent Pneumocystis pneumonia, a common and often deadly infection in immunocompromised patients. The study will be published on December 26, 2012 in *mBio*, the online open-access journal of the American Society for Microbiology. The organism cannot yet be isolated and grown for study in the laboratory, so details about Pneumocystis pneumonia, the biology of *P. jirovecii*, and its pathogenicity are hard to come by. The genome sequence represents a wealth of new information for doctors and researchers tackling this disease.

Pneumocystis pneumonia is an opportunistic infection that strikes most often in individuals with diminished immune systems. The corresponding author of the study in *mBio*®, Philippe Hauser of the Centre Hospitalier Universitaire Vaudois and University of Lausanne, in Switzerland, says the disease gained importance in the 1980s.

"Recognized first among malnourished infants, *P. jirovecii* pneumonia became a public issue with the advent of the HIV epidemic," says Hauser. Today, the disease most commonly affects HIV-infected persons who are unaware of their status as well as solid organ transplant recipients and patients with hemato-oncologic or autoimmune diseases. Since the organism cannot be grown in the lab for study, researchers have long made do with studying *P. jirovecii*'s lab-friendly relatives, species that infect animals and plants, in order to explore the secrets of

the human disease.

"It is obviously better to study [*P. jirovecii*'s] genes rather that those of Pneumocystis species from animal models. The genome has both medical and evolutionary interests for the scientific community," says Hauser.

Under normal circumstances, scientists sequencing the genome of a microorganism simply extract DNA from thick cultures of cells they grow in the lab. Since they were unable to grow *P. jirovecii* cells for their genomic DNA, Hauser and his colleagues took a different approach. They took a sample of bronchoalveolar lavage fluid from an individual infected with Pneumocystis pneumonia, then concentrated the *P. jirovecii* cells using immuno-precipitation and created copies of the DNA in the sample using a technique called random DNA amplification. This mixture of DNA strands, from *P. jirovecii*, human, and other microbes from the lungs of the infected patient, was then sequenced using high throughput technologies.

According to Hauser and his colleagues, the fact that the sequence data represented DNA from many different species created the biggest challenge they faced. "The major challenge of the study was the in silico sorting of the reads out of a mixture representing the human host and different organisms present in the lung microbiome," he says. This challenge was met through a collaboration with Marco Pagni of the Vital-IT group of the SIB Swiss Institute of Bioinformatics, who provided indispensable expertise and infrastructure.

Once the sorting task was accomplished, the researchers assembled the sequences into a genome and attempted to identify the functions of *P. jirovecii*'s genes. This is the first time scientists have assembled the genome of a fungus from a mixed pool of DNA from a single source, often called a metagenome. Their analyses reveal a surprising fact: *P.*

jirovecii is a parasite that must live within the human body to survive.

P. jirovecii lacks the genes necessary for creating some of the essential ingredients of life, a hallmark of obligate parasites, organisms that must rely on another creature for sustenance. "It implies that they need their host to provide these molecules. Thus, this has been quite an important finding which implied that human beings represent the reservoir of this pathogen," says Hauser. This is useful information, since it means that people are the only significant source of the organism and that both infected people and healthy carriers represent the only control points for limiting the spread of the disease.

The genome also shows that *P. jirovecii* apparently lacks the ability to make toxins and virulence factors, molecules that enable a microbe to invade and take advantage of its host. This makes sense, since *P. jirovecii* does not cause disease in healthy people, but only runs out of control when it is not confronted with an immune response.

In the study of infectious disease, access to the genome of a pathogen provides new information that can be pivotal in combating the diseases is causes. The hope is that the genome of *P. jirovecii* will lead to new advances in therapies for those suffering from Pneumocystis pneumonia. The current drugs of choice for treating Pneumocystis pneumonia are antifolates, but certain isolates of *P. jirovecii* have already developed resistance to antifolates, an ability that is very likely to spread. Now that the genome of *P. jirovecii* is assembled and available to researchers all over the world, scientists can tease out clues about the organism that will help identify targets for some badly needed new drugs.

Provided by American Society for Microbiology