Scientists generate 3-D structure for the malaria parasite genome

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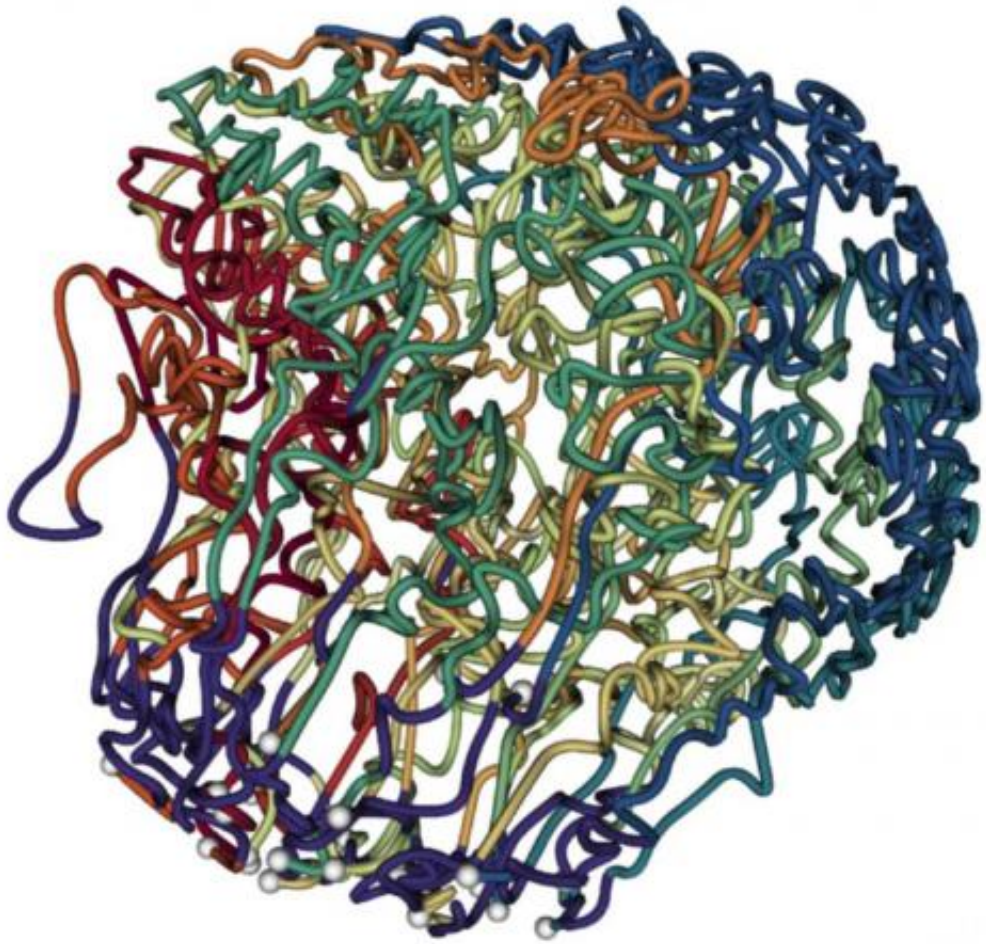

This image shows 3-D modeling of the human malaria parasite genome at one of the stages of its life cycle. Each color represents one of the 14 chromosomes of the parasite genome, the exception being purple (indicates genes known to be involved in virulence). Credit: Le Roch Lab, University of California Riverside

A research team led by a cell biologist at the University of California, Riverside has generated a 3D model of the human malaria parasite genome at three different stages in the parasite's life cycle—the first time such 3D architecture has been generated during the progression of the life cycle of a parasite.

The parasite that causes malaria in humans is *Plasmodium falciparum*. The female *Anopheles* mosquito transmits *P. falciparum* from an infected human to healthy individuals, spreading malaria in the process. According to the World Health Organization, an estimated 207 million people were infected with malaria in 2012, leading to 627,000 deaths.

"Understanding the spatial organization of chromosomes is essential to comprehend the regulation of gene expression in any eukaryotic cell," said Karine Le Roch, an associate professor of cell biology and neuroscience, who led the study.

Her research team also found that those genes that need to be highly expressed in the malaria parasite—for example, genes involved in translation—tend to cluster in the same area of the cell nucleus, while genes that need to be tightly repressed—for example, genes involved in virulence—are found elsewhere in the 3D structure in a "repression center." The 3D structure for the malaria parasite genome revealed one major repression center.

Virulence genes in the malaria parasite are a large family of genes that are responsible for the parasite's survival inside humans. Le Roch's team found that these genes, all organized into one repression center in a distinct area in the nucleus, seem to drive the full genome organization of the parasite.

Study results appeared online last week in *Genome Research*, an international, peer-reviewed journal that features outstanding original

research providing novel insights into the genome biology of all organisms. The research paper will appear in print in the June issue of the journal.

"We successfully mapped all physical interactions between genetic elements in the parasite nucleus," Le Roch said. "To do so, we used a 'chromosome conformation capture method,' followed by high throughput sequencing technology—a recently developed methodology to analyze the organization of chromosomes in the natural state of the cell. We then used the maps of all physical interactions to generate a 3D model of the genome for each stage of the parasite life cycle analyzed."

To understand the biology of an organism or any cell type, scientists need to understand not only the information encoded in the genome sequence but also how the sequence is compacted and physically organized in each cell/tissue, and how changes in the 3D genome architecture can play a critical role in regulating gene expression, chromosome morphogenesis and genome stability. In human cells, changes in chromosome organization and compaction can lead to diseases such as cancer.

"If we understand how the malaria parasite genome is organized in the nucleus and which components control this organization, we may be able to disrupt this architecture and disrupt, too, the parasite development," Le Roch said. "We know that the genome architecture is critical in regulating gene expression and, more important, in regulating genes that are critical for parasite virulence. Now we can more carefully search for components or drugs that can disrupt this organization, helping in the identification of new anti-malaria strategies."

Le Roch's lab is now looking at other stages of the malaria life cycle in order to identify components responsible for the 3D genome architecture.

"The importance of the genome architecture was initially thought to be critical for only higher eukaryotes," she explained. "But we found, to our surprise, that the genome architecture is closely linked to virulence even in the case of the malaria parasite."

Provided by University of California - Riverside