Loosely coiled DNA helps trypanosomes make their escape

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(PhysOrg.com) -- To escape the grip of the human immune system, Trypanosoma brucei, which causes African sleeping sickness, performs its acclaimed disappearing act. Every time the host's immune cells get close to eliminating the infection, a small number of trypanosomes avoid detection by changing their surface 'coat.' Now, after 30 years of contradictory and inconclusive findings, Rockefeller University researchers reveal that trypanosomes' ability to strategically coil their DNA is part of the mechanism by which they make their stealthy escape.

The work, led by George A.M. Cross, head of the Laboratory of Molecular Parasitology, and Luisa Figueiredo, a former postdoc in the lab, clarifies past findings and also points to a never-before-known layer of regulation that plays an important role in T. brucei's disappearing act. "The implications are huge," says Figueiredo. "We've entered a new paradigm in the understanding of how trypanosomes change their surface coat and outsmart the human immune system."

Throughout the trypanosome's genome, the genes that encode the surface coat are transcribed from 15 to 20 regions known as bloodstream expression sites, only one of which is in use at a time. When the host's immune system has just about killed all of the parasites, some survivors rearrange their DNA at one of their expression sites (or switch transcription between expression sites without any DNA rearrangements), causing the surface coats to change their molecular identity and enabling a new wave of trypanosome multiplication. During the cat-and-mouse game that follows, the immune system never gains the

upper hand — and the victim typically dies.

In their work, Cross and Figueiredo found that the DNA of active expression sites is coiled much less tightly than the DNA of inactive sites, and less tightly than DNA on other regions of the genome. “This research wouldn’t have been possible without techniques that allow you to compare the chromatin structure of individual expression sites,” says Figueiredo. “By comparing the chromatin structure of active and inactive sites, we were able to see that they were dramatically different.”

In order for DNA to fit into the nucleus of a cell, it must be packaged into nucleosomes, which consist of proteins called histones around which the DNA is wrapped. A string of nucleosomes is called chromatin — the stuff of chromosomes. The researchers found that there are far fewer nucleosomes in active than in inactive sites and that the remaining nucleosomes are irregularly spaced.

“What this means is that there must be a new level of regulation at these sites and that this regulation is controlled by chromatin remodeling,” says Figueiredo. “It means that there needs to be specific machinery that removes these nucleosomes from active expression sites. If we can understand how this machinery is recruited and how it interacts with the DNA, we might be able to develop a new way to interrupt the processes that allow trypanosomes to get the upper hand during chronic infections.”

Before the 1980s, researchers believed that there were no differences between active and inactive blood expression sites in trypanosomes. With the development of better tools, researchers then claimed there were slight differences, probably from a distortion of the DNA. “Now,” says Figueiredo, “the differences are clear.”

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Nucleosomes are depleted at the VSG expression site transcribed by RNA polymerase I in African trypanosomes{triangledown} Luisa M. Figueiredo and George A.M. Cross

Provided by Rockefeller University

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