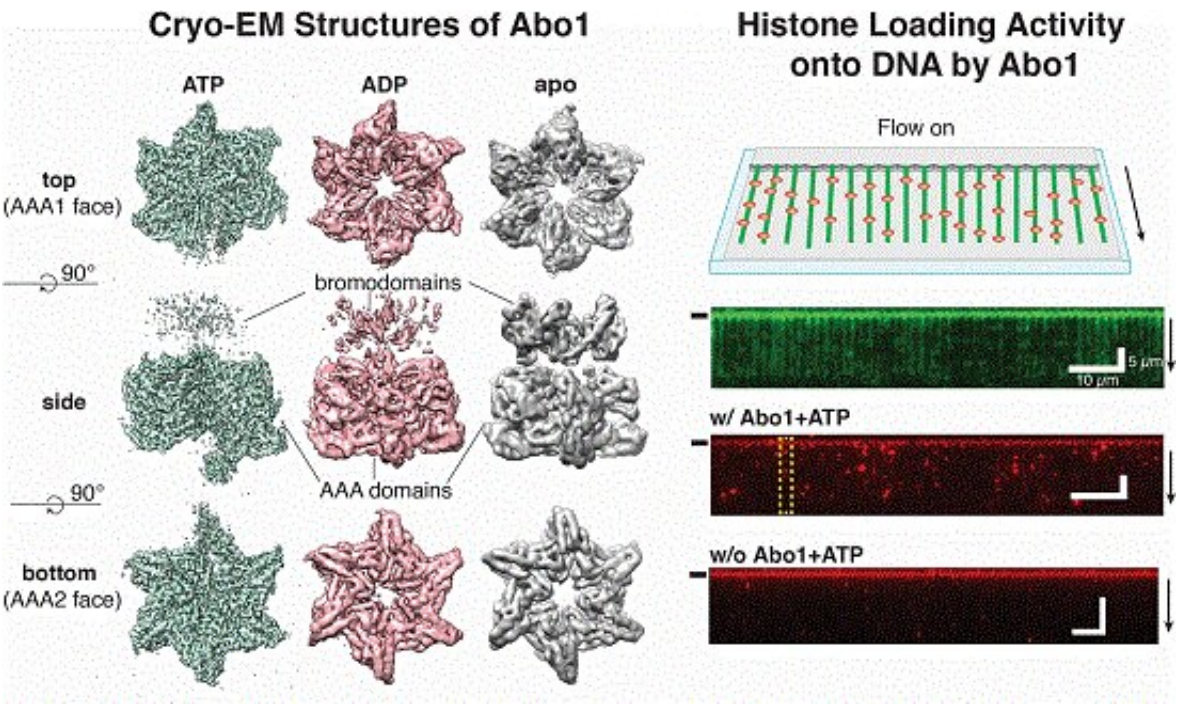
Scientists discover the mechanism of DNA high-order structure formation

January 23 2020



Molecular structures of Abo1 in different energy states (left), Demonstration of an Abo1-assisted histone loading onto DNA by the DNA curtain assay. Credit: The Korea Advanced Institute of Science and Technology (KAIST)

The genetic material of our cells—DNA—exists in a high-order structure called chromatin. Chromatin consists of DNA wrapped around histone proteins and efficiently packs DNA into a small volume. Moreover, using a spool and thread analogy, chromatin allows DNA to be locally wound or unwound, thus enabling genes to be enclosed or

exposed. The misregulation of chromatin structures results in aberrant gene expression and can ultimately lead to developmental disorders or cancers. Despite the importance of DNA high-order structures, the complexity of the underlying machinery has circumvented molecular dissection.

For the first time, molecular biologists have uncovered how one particular mechanism uses energy to ensure proper histone placement onto DNA to form chromatin. They published their results on Dec. 17 in *Nature Communications*.

The study focused on proteins called histone chaperones. Histone chaperones are responsible for adding and removing specific histones at specific times during the DNA packaging process. The wrong histone at the wrong time and place could result in the misregulation of gene expression or aberrant DNA replication. Thus, histone chaperones are key players in the assembly and disassembly of chromatin.

"In order to carefully control the assembly and disassembly of chromatin units, histone chaperones act as molecular escorts that prevent histone aggregation and undesired interactions," said Professor Ji-Joon Song in the Department of Biological Sciences at KAIST. "We set out to understand how a unique histone chaperone uses chemical energy to assemble or disassemble chromatin."

Song and his team looked to Abo1, the only known histone chaperone that utilizes cellular energy (ATP). While Abo1 is found in yeast, it has an analogous partner in other organisms, including humans, called ATAD2. Both use ATP, which is produced through a cellular process where enzymes break down a molecule's phosphate bond. ATP energy is typically used to power other cellular processes, but it is a rare partner for histone chaperones.

"This was an interesting problem in the field because all other histone chaperones studied to date do not use ATP," Song said.

By imaging Abo1 with a single-molecule fluorescence imaging technique known as the DNA curtain assay, the researchers could examine the protein interactions at the single-molecule level. The technique allows scientists to arrange the DNA molecules and proteins on a single layer of a microfluidic chamber and examine the layer with fluorescence microscopy.

The researchers found through real-time observation that Abo1 is ring-shaped and changes its structure to accommodate a specific histone and deposit it on DNA. Moreover, they found that the accommodating structural changes are powered by ADP.

"We discovered a mechanism by which Abo1 accommodates histone substrates, ultimately allowing it to function as a unique energy-dependent histone chaperone," Song said. "We also found that despite looking like a protein disassembly machine, Abo1 actually loads histone substrates onto DNA to facilitate chromatin assembly."

The researchers plan to continue exploring how energy-dependent histone chaperones bind and release histones, with the ultimate goal of developing therapeutics that can target cancer-causing misbehavior by Abo1's analogous human counterpart, ATAD2.

More information: Carol Cho et al. Structural basis of nucleosome assembly by the Abo1 AAA+ ATPase histone chaperone, *Nature Communications* (2019). DOI: 10.1038/s41467-019-13743-9

Provided by The Korea Advanced Institute of Science and Technology

(KAIST)