January 12, 2021

Health & Physiology

More than meets the eye: the histones revealed as enzymes

by Oscar A. Campos[1] | Postdoctoral scholar; Siavash K. Kurdistani[2] | Professor

doi.org/10.25250/thescbr.brk449

[1]: Department of Biological Chemistry at the David Geffen School of Medicine, University of California, Los Angeles

This Break was edited by Isa Ozdemir, Scientific Editor - TheScienceBreaker

Histones have been known as proteins that package the DNA of eukaryotes and regulate gene expression. We discovered that histones also function as enzymes that convert copper ions into a usable form for cells. The enzymatic function changes how we think about the roles of histones in health and disease. It may have also been a critical driver for emergence of eukaryotes in the first place.

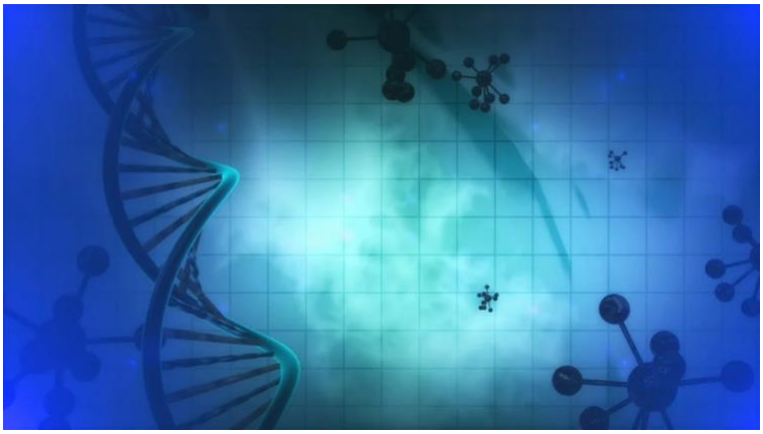

Image credits: Pixabay

If you traveled back in time to approximately two billion years ago, you would see an Earth completely devoid of animals and plants. Yet, at microscopic levels, life is on the brink of one of the greatest and unique developments in history. Two single celled organisms are about to enter a partnership, with one living inside the other, to form a new class of living beings—the Eukaryotes.

This partnership gave rise to humans, as well as all other animals, plants, fungi, and protists, and is still occurring today. Mitochondria, the powerhouses of the cell, are the modern-day descendant of the single celled organism that took residence inside the other. How that partnership came to be has remained a difficult puzzle, but one that inspired us to ask whether histones had anything to do with it.

Scientists have studied histones since the 1950's, first for their ability to form a scaffolding structure for our DNA and later as regulators of DNA-based processes such as gene regulation or DNA replication and repair. However, our group's interest in them comes from the fact that the cell that hosted the future mitochondria had a histone-based DNA packaging system. We wondered whether the histones could have been one reason why the partnership was established successfully.

Interestingly, the first eukaryotes appeared when oxygen was starting to accumulate on the planet. Presence of oxygen changed the abundance of certain nutrients including copper ions. This is the same copper element in electrical wires and water pipes. Interestingly, a section of the histone proteins can bind a copper ion. We discovered that the histones not only bind copper but catalyze electron

transfer to it, revealing histones for the first time to be enzymes. Why is this new histone enzyme activity important? It turns out that the form of copper produced by histones is a critical resource for mitochondria. Thus, the enzymatic ability of histones enables more effective use of copper for mitochondrial function. This suggests that the histones could have been essential for the success of the microscopic partnership that gave rise to Eukaryotes.

Our reasoning and eventual discovery was not the result of some grand epiphany, a sudden moment of lightning-like inspiration. Our investigation was a painstakingly long process including years of trial and error (mostly error!). One challenge was to isolate the histone proteins by themselves, away from cells, and devise a way to observe a chemical process that no one had observed with histones before. After years of tinkering, we arrived at a set of chemical parameters that allowed us to detect for the first time the enzymatic capability of histones.

Another challenge was to show that histones performed this chemical activity inside living cells, and that this enzyme activity was important for optimal function of mitochondria and other processes that depend on copper. We examined the histones in baker's yeast, the same organism used in baking bread or brewing beer. With the power of genetic manipulation, we performed various experiments in which we disrupted the histone enzymatic activity and observed the predicted changes in the levels of copper they produce as well as copper-dependent mitochondrial function. Our results provided the evidence to conclude that histones are indeed enzymes that enhance the use of copper as a resource in cells.

Our findings raise many intriguing possibilities including the opportunity of gaining knowledge on the potential role that histones may play in various copper-related diseases that range from neurodegenerative conditions to cancer. We have also only scratched the surface of the new function of histones. In particular, human cells have many more types of histones that present a tougher but welcome challenge for investigation of their enzymatic activity. Ultimately, we envision a future where a deeper understanding of the histone enzyme activity will serve as a common thread linking the origin of Eukaryotes to human disease.