

Researcher solves mystery about proteins that package the genome

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A Florida State University College of Medicine researcher has solved a century-old mystery about proteins that play a vital role in the transfer of the human genetic code from one cell to another. The discovery could lead to finding new ways to help the body fight a variety of diseases, including cancer.

For more than a hundred years, the best scientific evidence supported a belief that histones - responsible for packaging DNA inside the nucleus of cells - are highly stable proteins not rapidly degraded by the body. Yet, researchers have not previously been able to explain why free histones, if they are not degraded as other proteins are, do not accumulate in large amounts within human cells.

Akash Gunjan, an assistant professor in the department of biomedical sciences, has found evidence supporting his hypothesis that there actually are two pools of histones: one used in packaging DNA that is very stable and remains in the cell for more than a year in some cases and the other made in excess by the cells to ensure that enough histones are available for packaging the DNA. Not having enough histones results in cell death. Those excess histones, Gunjan suggests, are rapidly degraded as are other proteins.

The discovery is important because it sheds light on the way the body is able to regulate proteins for various complex tasks. Such knowledge may allow scientists to learn how to manipulate protein regulation to fight cancerous cells and thwart other disease processes. Gunjan and co-authors Rakesh Kumar Singh, Marie-Helene Miquel Kabbaj and Johanna Paik, all from the College of Medicine, published their findings in the journal *Nature Cell Biology*.

'This has major ramifications for all the different things the DNA does,' Gunjan said. 'Because if DNA contains genes and DNA is packaged around histones, then histones are at the most fundamental level regulating whether those genes are turned on or off.'

If scientists are able to determine how genes for cancer and other diseases are turned on or off, it might lead to ways to help the body rid itself of or better control disease.

For decades scientists have been captivated by the way the body selectively uses proteins in essential functions, storing or disposing of them when they are not needed. For example, eating a hamburger requires a certain set of enzyme proteins for digestion. If the enzymes are not deactivated or degraded following digestion, the consequences would be disastrous.

'They'll start to digest things you do not want them to digest,' Gunjan said. 'After finishing your hamburger, if these enzymes started digesting proteins in your intestines, in your stomach wall and so on, that would not be a good thing.'

To manage proteins when they are not needed, the body naturally degrades them through a process known as proteolysis. Histones in most cases, however, must be preserved for long periods of time because they make it possible to fold strands of DNA measuring about 3 feet in length within the microscopic nucleus of a typical human cell. Histones used in that process must be able to avoid degradation to preserve the body's ability to pass on its genetic code from cell to cell.

Histones, the first proteins to be purified, have been a topic of research by scientists for nearly 125 years. The mystery evolved as scientists discovered that cells have multiple copies of histone genes and make far more histones than what is needed for wrapping DNA, yet were unable to explain the apparent contradiction.

'On the one hand, you cannot find the excess histones,' Gunjan said. 'On the other hand, if you propose it gets degraded, then you try to measure its rate of degradation and you find that it hangs around for several months to more than a year.'

Gunjan spent five years seeking answers to the mystery before his discovery of two separate pools of histones.

'Not only did we show for the first time that histones are unstable - they get rapidly degraded - we also showed this has important consequences for DNA damage and repair processes that have a major impact on cancer formation,' Gunjan said.

Additionally, previous studies published by other researchers suggest that the newly discovered regulated histone proteolysis may make significant contributions to many diverse biological processes, from the resetting of epigenetic marks on histones that help regulate gene expression, to sperm formation.

'All of this together suggests this is a very important phenomenon,' Gunjan said.

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