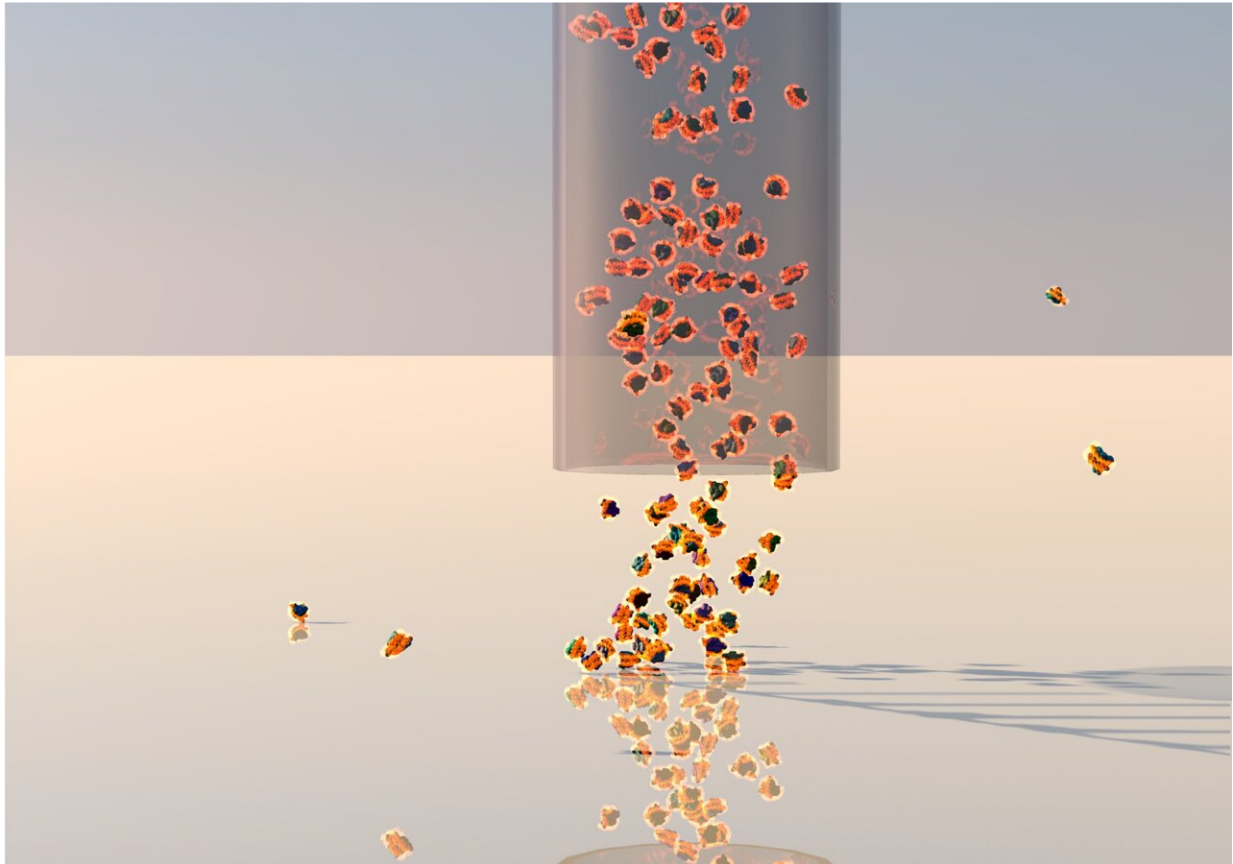


# New method to analyze nucleosomes

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Artistic representation of the study of nucleosome particles by mass spectrometry, with a shadow forming their representative spectrum. Credit: Luis Schachner

Northwestern Medicine scientists have developed a new method to analyze the protein composition of intact nucleosomes without losing

combinatorial information present in chromatin. The technique, called Nuc-MS, could help scientists more efficiently uncover the mechanisms behind mutation-driven diseases such as some cancers, according to Neil Kelleher, Ph.D., professor of Medicine in the Division of Hematology and Oncology, director of the Proteomics Center of Excellence and senior author of the study published in *Nature Methods*.

"Other techniques shred nucleosomes and their histone proteins into little pieces and you only get the minority of the pieces back," said Kelleher, who is also a professor of Biochemistry and Molecular Genetics and a professor at the Weinberg College of Arts and Sciences. "If we can keep the whole [nucleosome](#) intact, we can preserve the co-occurrence of all these little switches that we're trying to figure out in [chromatin](#) biology and cancer epigenetics."

Chromatin is a complex comprised primarily of DNA and protein found in cells. Its primary function is packaging our DNA into compact structures. Chromatin is comprised of a structured fiber of nucleosome particles and [histone proteins](#), similar to how suspension bridge cable is constructed from smaller strands of wire.

Histones are modified by post-translational modifications, part of the system of epigenetic regulation that ensures the correct genes are expressed at the right time. Previous studies have indicated that the precise arrangement of histone marks on nucleosomes are also necessary for epigenetic regulation.

These two systems are deeply intertwined, but current analysis techniques for histones are highly destructive, breaking down the histone and nucleosomes into tiny pieces and forcing scientists to infer their composition and their impacts on gene expression.

"There's already enough inferences in biology; let's remove a few of

them through more direct measurements," Kelleher said.

Instead, Kelleher and his collaborators developed Nuc-MS. The technique uses a "top down" approach to controllably disassemble the nucleosomes using [high performance mass spectrometry](#), measuring the masses and characterizing the histones and their modifications.

"These nucleosomes are about 100 times heavier, compared to little things like a peptide," Kelleher said.

Nuc-MS displays the entire landscape of histone variants and their post-translational modifications in a single mass spectrum, offering a new readout of nucleosome-level biology. Many cancers are driven by mutations in histone biology that help maintain chromatin, so this method could help scientists figure out exactly what is damaged downstream of those mutations.

"This preserves the biological information that can help clarify the picture of how alterations in [histone](#) code can lead to cancer," Kelleher said.

**More information:** Luis F. Schachner et al, Decoding the protein composition of whole nucleosomes with Nuc-MS, *Nature Methods* (2021). [DOI: 10.1038/s41592-020-01052-9](https://doi.org/10.1038/s41592-020-01052-9)

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