Fuzzy molecular threesome is basis of gene expression

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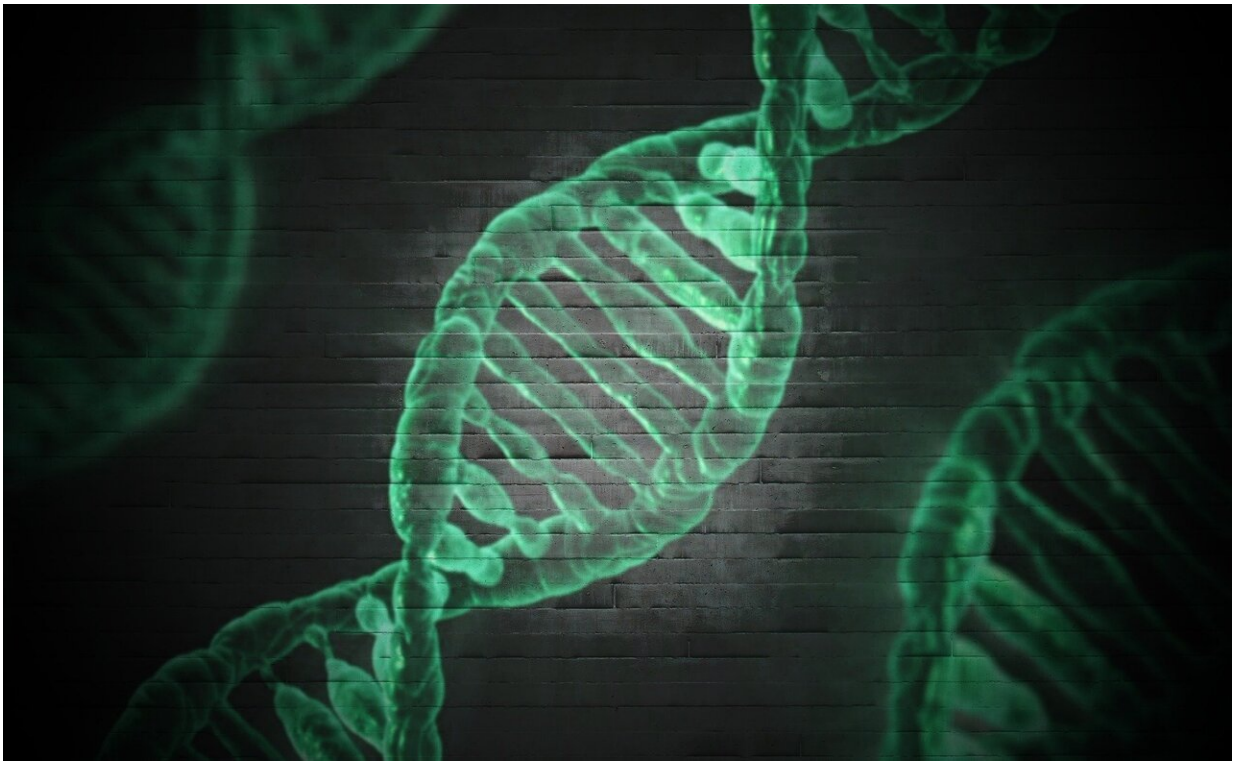

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Specific nuclear proteins act as a glue to pack genetic material in an absurdly small space in the human body. Proteins "gluing" DNA are called linker histones, and hold their secret in their electric charge. They are strongly positively charged, fusing to the strongly negatively charged

DNA.

A simple attraction of opposites is thus key to tight packing of genes; with interactions so strong, they suggest the idea of glue keeping everything together.

In new research published in *Nature Chemistry*, Dr. Davide Mercadante from the University of Auckland and a team of scientists from Switzerland, Iceland and the U.S. investigated how these genes are accessed if they are so tightly packed away. How can these molecules be broken apart to promote gene expression?

"We challenged existing notions, hypothesizing that unstructured proteins would explain the plastic and dynamic world of genes," Dr. Mercadante says. "By being fast moving, it is impossible to obtain a detailed picture of how disordered proteins take shape and from their structure we had to move our target to understand their dynamics."

The researchers first labeled histones and DNA with fluorescent dyes responding to molecular dynamics and looked at the molecules through microscopy. This didn't provide "molecular pictures" but only an idea of how molecules behaved from the indirect reading of dyes. Molecular simulations, which can provide the finest details, were then tightly coupled to experiments and instructed to give reliable "snapshots" of the investigated molecules, providing clues of how tight interactions can also be functionally dynamic to potentially unpack genes.

The strong charge complementarity in DNA-histone complexes does not allow, however, for genes to unpack easily; not in timescales compatible with life. The team hypothesized that a third molecule was needed to break the DNA-histone complex. A strongly negatively charged and unstructured protein known to interact with the linker histone is prothymosin-α. Could prothymosin-α compete with the DNA for the

binding, evicting the histone to promote gene availability?

In experiments, prothymosin-α invaded the histone-DNA complex, forming a three-way complex before dislodging the histone. "This has enormous implications, with strong but fuzzy molecular associations finely regulating gene access, this has deep repercussions on the world of biology and how we conceive protein activity," Dr. Mercadante says.

"Our work reinforces the notion that cellular processes can be mediated by unstructured proteins, challenging the historical view that function must be conveyed by specific protein structures. Here the lack of shape conveys the plasticity necessary to make the genetic material available in appreciable timescales, against the long-standing structure-to-function paradigm of biology."

Co-authors on the research include Professor Benjamin Schuler, University of Zürich, Zürich, Switzerland; Dr. Robert Best, National Institute of Health, Washington DC, U.S.; Associate Professor Pétur Heiðarsson, University of Iceland, Reykjavík, Iceland; Dr. Alessandro Borgia, St Jude Children's Hospital, Memphis, U.S.; Dr. Madeleine Borgia, St Jude Children's Hospital, Memphis, U.S.; Dr. Daniel Nettels, University of Zürich, Zürich, Switzerland; Associate Professor Beat Fierz, École polytechnique fédérale de Lausanne, Lausanne, Switzerland.

More information: Pétur O. Heidarsson et al, Release of linker histone from the nucleosome driven by polyelectrolyte competition with a disordered protein, *Nature Chemistry* (2022). DOI: 10.1038/s41557-021-00839-3

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