Histone H3-H4 tetramer found to be a copper reductase enzyme

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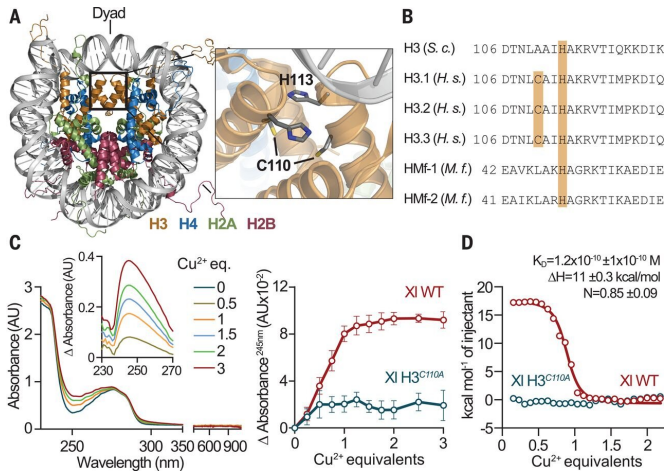

Recombinant X. laevis histone H3-H4 tetramer interacts with cupric ions. (A) Left: X. laevis (XI) nucleosome core particle structure [Protein Data Bank (PDB) 1KX5] (38). The box delineates the H3-H3? interface. Right: Interface residues H3H113 and H3C110 are shown. (B) Alignment of the C-terminal region of S. cerevisiae (S. c.) and Homo sapiens (H. s.) histone H3 and archaeal [Methanothermus fervidus (M. f.)] histones. (C) Left: UV-visible absorbance spectrum of the XI H3-H4 tetramer incubated with or without Cu2+. Inset: Differential absorbance compared to tetramer without Cu2+. Right: Buffer-corrected differential absorbance of the indicated XI tetramers. AU, absorbance units; eq., equivalents. (D) Representative ITC titration profile of the XI H3-H4 tetramer. Circles are experimental data, and the line is the fitted curve. Average dissociation constant (KD), enthalpy change (?H), and stoichiometry (N) ± SD of the H3-H4 tetramer-Cu2+ complex calculated from three experiments are shown. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr. Credit: *Science* (2020). DOI: 10.1126/science.aba8740

A team of researchers at the University of California has found that the histone H3-H4 tetramer is a copper reductase enzyme. In their paper published in the journal *Science*, the group describes two experiments they carried out that showed that histones are involved in reducing copper inside of cells. Johannes Rudolph and Karolin Luger with the University of Colorado at Boulder have published a Perspective piece in the same journal issue giving an outline of research involving histones and describing the work done by the team in California.

Histones are proteins that exist inside of eukaryotic cells. Prior work has shown that their primary function is to order DNA structures into nucleosomes. They do so by serving as spools around which DNA spirals wind, allowing them to fit inside cell nuclei. In this new effort, the researchers have found that histones have another function as well: reducing copper ions from a toxic form to a kind that can exist safely inside cells.

The researchers began their work by noting that several decades ago, other researchers had found that pairs of histidine and cysteine amino acids might be binding metal ions in the place where two types of histones met inside of cells. This suggested that histones might play a role in making copper safe for the body to use. To test this idea, the researchers set up and conducted two experiments, both involving yeast cells. The first experiment involved mutating amino acid sequences in histone proteins in the region suggested by the team in the prior study. They found that the cells with mutant histones had lower levels of Cu(I) ions, which are the safe form of copper. The researchers suggest this was evidence that histones play a role in the reduction process. In the second experiment, the researchers tested H3-H4 tetramers in test tubes and found that they did reduce Cu(II) to Cu(I).

The work by the researchers has evolutionary implications: it suggests that histones may have played a role in allowing single cell organisms to survive a suddenly globally oxygenated

environment back during life's formative years by reducing harmful copper to a harmless state, allowing it to help protect against oxygen toxicity.

More information: Narsis Attar et al. The histone H3-H4 tetramer is a copper reductase enzyme, *Science* (2020). DOI: 10.1126/science.aba8740

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