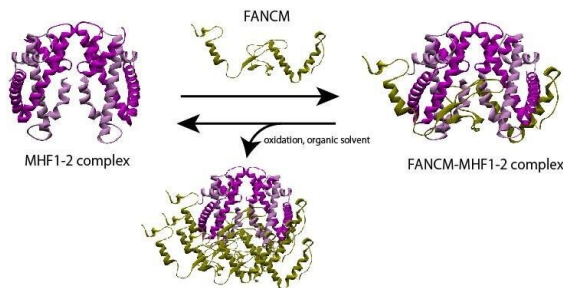


Elusive protein complex could hold the key to treating chromosomal disorders

17 March 2021



Dissociation of the FANCM-MHF complex. After X-ray crystallography (XRC), scientists found that tetrahedral and needle-shaped forms of recombinant FANCM-MHF complex contained only MHF without FANCM. Upon biochemical analysis, they found that this was due to the organic solvent used in sample preparation for XRC and exposure to oxidizing conditions. Credit: Tatsuya Nishino from Tokyo University of Science

One of the most vital functions performed by the cells in our body is DNA repair, a task so crucial to our well-being that failing to execute it can lead to consequences as dreadful as cancer. The process of DNA repair involves a complex interplay between several gene pathways and proteins. One such pathway is the "Fanconi anemia (FA) pathway," whose genes participate in DNA repair. FANCM, a component of this pathway, is tasked with the elimination of harmful DNA "inter-strand cross-links," and interacts with another component called MHF in order to function. The importance of the FANCM-MHF complex is well-documented: its loss can result in chromosomal instabilities that can lead to diseases such as FA itself and cancer. However, little is known about its structure and the basis of its stability.

Against this backdrop, Associate Professor Tatsuya Nishino and his colleague Dr. Sho Ito from Tokyo University of Science decided to explore the crystalline [structure](#) of this intriguing complex using

X-ray diffraction techniques. "DNA damage and chromosome segregation are mechanisms necessary for the maintenance and inheritance of genes possessed by all organisms. MHF (also known as CENP-SX) is an enigmatic complex that plays a role in DNA repair and chromosome segregation. We wanted to find out how it performs these two different functions in the hope that it might give us insights into novel phenomena," explains Prof. Nishino. Their findings are published in *Acta Crystallographica Section F: Structural Biology Communications*.

The scientists prepared a recombinant version of the FANCM-MHF complex, consisting of FANCM from chickens and MHF1 and MHF2. They were able to purify three different types of protein crystals—tetrahedral, needle-shaped, and rod-shaped—from similar crystallization conditions. Surprisingly, upon determining the structure with X-ray crystallography, they found that two of the crystal forms (tetrahedral and needle-shaped) contained only the MHF complex without FANCM.

Intrigued by this discovery, the scientists used biochemical techniques to examine what caused the FANCM-MHF complex to disassemble. They attributed it to the presence of a compound called 2-methyl-2, 4-pentanediol (MPD), an [organic solvent](#) commonly used in crystallography, and exposure to an oxidizing environment.

But, how exactly does the dissociation happen? The scientists believe that this may have been caused partly by certain non-conserved [amino acids](#) in the chicken FANCM which causes the complex to aggregate with other FANCM-MHF complexes and disassemble. Additionally, they surmise that the small, flexible structure of MPD may have also allowed it to bind to and facilitate the release of FANCM, dismantling the complex.

The findings are extraordinary and can be used to improve the stability of the FANCM-MHF complex

for future studies on its structure and function. Dr. Ito believes we have much to expect in the future from this complex. "A good understanding of this complex can help us treat cancer and [genetic diseases](#), create artificial chromosomes, and even develop new biotechnological tools," he speculates.

Thanks to Prof. Nishino and Dr. Ito's efforts, we are already one step closer to that goal.

More information: Sho Ito et al, Structural analysis of the chicken FANCM–MHF complex and its stability, *Acta Crystallographica Section F Structural Biology Communications* (2020). [DOI: 10.1107/S2053230X20016003](#)

Provided by Tokyo University of Science

APA citation: Elusive protein complex could hold the key to treating chromosomal disorders (2021, March 17) retrieved 15 October 2021 from <https://phys.org/news/2021-03-elusive-protein-complex-key-chromosomal.html>

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