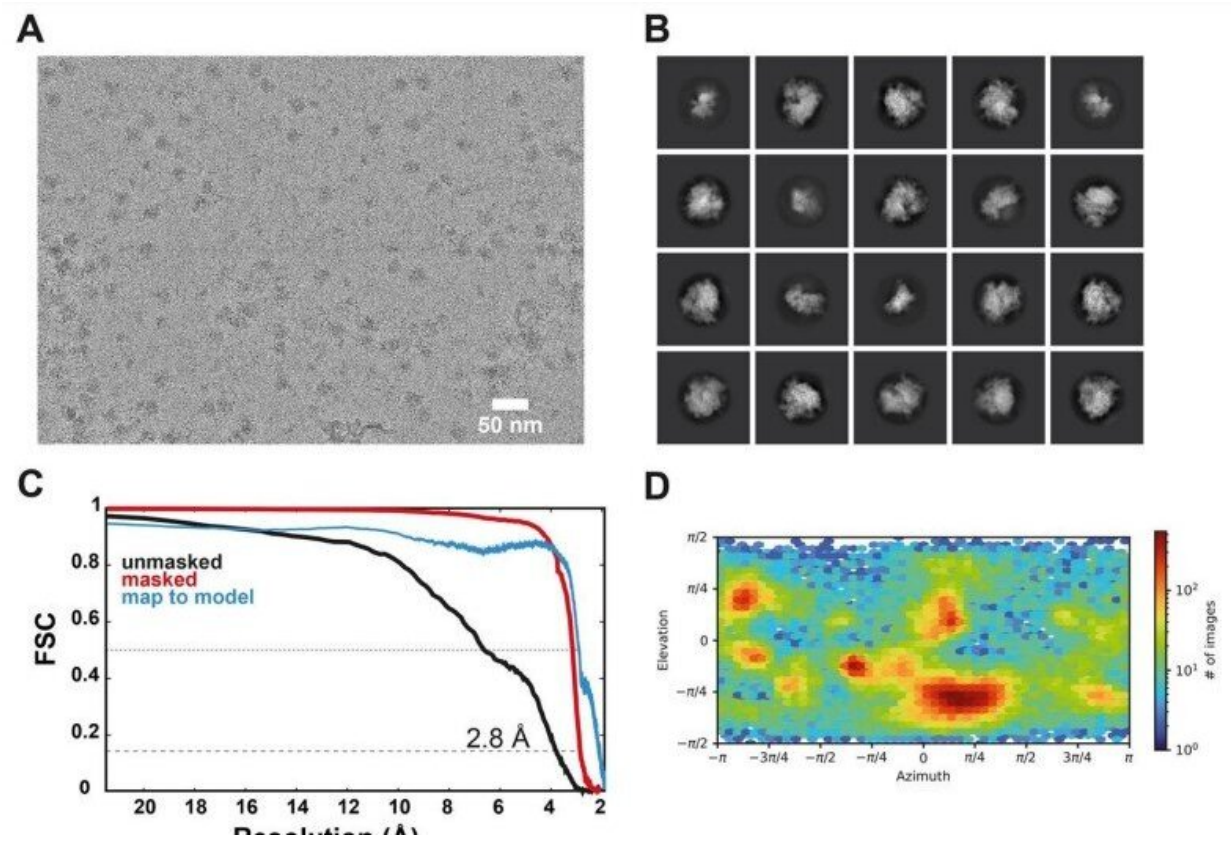
Researchers observe vital cellular machinery behind the body's incorporation of selenium

June 17 2022, by Kitta MacPherson



CryoEM analysis of the 80S-Selenosome dataset. (A) Representative cryo-electron micrograph of the fully assembled 80S-Selenosome sample. Scale bar represents 50 nm in the image. (B) Class averages after reference-free 2D classification generated with cryoSPARC. (C) Resolution estimation by gold-standard Fourier-shell-correlation. (D) Angular distribution plot after NU refinement with cryoSPARC shows moderate orientation bias which turned out not to be limiting for the reconstruction. (E) Local resolution as determined with cryoSPARC. The cryoEM density surface is colored according to the resolution

estimates, ranging from 2.3 Å (blue) to 10.3 Å (red) depicted from the with view on the GAC (left) and rotated by 180° (right). Low resolution regions mainly reside in the periphery. Credit: *Science* (2022). DOI: 10.1126/science.abg3875

A Rutgers scientist is part of an international team that has determined the process for incorporating selenium—an essential trace mineral found in soil, water and some foods that increases antioxidant effects in the body—includes 25 specialized proteins, a discovery that could help develop new therapies to treat a multitude of diseases from cancer to diabetes.

The research, detailed in *Science*, includes the most in-depth description yet of the process by which selenium gets to where it needs to be in cells, which is crucial for many aspects of cell and organismal biology. First, selenium is encapsulated within selenocysteine (Sec), an essential amino acid. Then, Sec is incorporated into 25 so-called selenoproteins, all of them key to a host of cellular and metabolic processes.

Understanding the workings of these vital mechanisms in such a detailed manner is critical to the development of new medical therapies, according to researchers including Paul Copeland, a professor in the Department of Biochemistry and Molecular Biology at Rutgers Robert Wood Johnson Medical School.

"This work revealed structures that had never before been seen, some of which are unique in all of biology," said Copeland, an author of the study.

Copeland and the team were able to visualize the cell mechanisms by using a specialized cryo-electron microscope, which uses beams of electrons rather than light to form three-dimensional images of complex

biological formations at nearly atomic resolution. The process uses frozen samples of molecular complexes and then applies sophisticated image processing—employing today's vast computing power to string together thousands of images to produce three-dimensional cross-sections and even stop-motion animation conveying a sense of motion within the biomolecules. As a result, scientists can view representations of the intricate structure of proteins and other biomolecules and even how these structures move and change as they function as cellular "machines."

The incorporation of selenium takes place deep within an individual cell's intricate machinery. Scientists already knew which proteins and molecules of RNA—a nucleic acid present in all cells involved in the production of proteins—enabled the process. However, they were not able to discern the critical step of how these factors worked in tandem to complete the cycle, dictating the function of the cell's ribosome—a large macromolecular machine that binds RNA to make more proteins. What they found was that the processes that occur are not like any understood to take place anywhere else in the human body.

"This amino acid gets attached to a unique RNA molecule and that has to be carried to the ribosome via a unique protein factor," said Copeland, whose lab has spent the past 20 years working to understand how these biomolecules function on a biochemical level. "And all of this evolved in humans specifically to allow selenium to be incorporated into this handful of proteins."

Once Sec is ensconced in the selenoproteins, the proteins perform a wide range of vital functions necessary for growth and development. They produce nucleotides, the building blocks of DNA. They break down or store fat for energy. They create cell membranes. They produce the thyroid hormone, which controls the human body's metabolism. And they respond to what is known as oxidative stress by detoxifying

chemically reactive byproducts in cells.

Diseases and disorders such as cancer, heart disease, male infertility, diabetes and hypothyroidism can arise when the production of selenoproteins is disrupted.

"Understanding the mechanism by which Sec is incorporated is a foundational part of developing new therapies for a multitude of disease states," Copeland said.

More information: Tarek Hilal et al, Structure of the mammalian ribosome as it decodes the selenocysteine UGA codon, *Science* (2022). DOI: 10.1126/science.abg3875

Provided by Rutgers University