Molecular structure could help explain albinism, melanoma

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Arthropods and mollusks are Nature's true bluebloods - thanks to hemocyanin, an oxygen-carrying large protein complex, which can even be turned into the enzymatically active chemical phenoloxidase.

Scientists have long known that members of the phenoloxidase family are involved in skin and hair coloring. When they are mutated, they can cause albinism - the loss of coloring in skin and hair. Produced over abundantly, they are associated with the deadly skin cancer melanoma.

In an elegant structural study, a team of Baylor College of Medicine and German researchers explain how hemocyanin is activated - a finding that could lead to a better understanding of both ends of the skin and hair color spectrum. A report of their work appears in the current issue of the journal *Structure*.

When Dr. Yao Cong, a postdoctoral researcher in the laboratory of Dr. Wah Chiu, displays the computer representation of hemocyanin, it glows like a four-part jewel on the computer screen. Chiu is professor of biochemistry and molecular biology at BCM and director of the National Center for Macromolecular Imaging.

"It is very large and composed of 24 molecules," Cong said. In fact, it consists of four hexamers, each with six monomers.

Just getting this far required using single particle electron cryomicroscopy (cryo-EM) to produce three dimensional density maps of the molecule at sub-nanometer resolution.

"Cryo-EM is becoming a structural tool that can be used for understanding structural mechanism of large protein, which has translational and biotechnological application as demonstrated in this study," said Chiu, a senior author.

"There are some critical structural features are very well resolved in our maps," said Cong. "which could not be captured using other techniques."

She and her colleagues used the detergent SDS, which is usually used as denaturant to degrade protein, to activate hemocyanin. At certain high concentrations, instead of destroyomg the complex, it turns hemocyanin into an enzymatically active phenoloxidase.

Each monomer of the protein particle has three domains.

"It is very interesting," said Cong. "One domain is more flexible than the other two domains because it has much less interaction with neighboring subunits as compared with the other two domains."

Upon activation, there is an overall conformational change of the complex. The most obvious is formation of two bridges in the previously vacant middle of the protein, which strengthens the interaction between the two halves of the complex.

"Zoom into the active site," said Cong. The intrinsically flexible domain twists away from the other two domains, dragging away a blocking residue and exposes the entrance to the active site. This movement is then stabilized by enhanced interhexamer interactions."

"This is all about interaction," said Cong. "A single change in the local domain of a subunit can result in conformation changes in the entire complex and make it work cooperatively. This is really a molecular machine."

Using hemocyanin as a model system, scientists can learn about the activation mechanism of other phenoloxidase enzymes in the same family, opening the door to new understanding of both melanoma and albinism, she said.

"If you know the mechanism of activating the protein, you could mutate it to enhance the interaction or inhibit it - depending on what you want to accomplish," she said.

Not only does this research have implications for human disease, it could also play a role in agriculture, where enzymes in this protein family are responsible for fruit and vegetables turning brown as they age.

More information: www.cell.com/structure/

Source: Baylor College of Medicine (news : web)