Marine bacterium sheds light on control of toxic metals

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An ocean-dwelling bacterium has provided fresh insights into how cells protect themselves from the toxic effects of metal ions such as iron and copper, in research led by the University of East Anglia (UEA).

Although essential to life, metal ions can also generate reactive oxygen species (ROS) - highly reactive molecules that damage cells as they try to form bonds with other molecules.

In humans, reactive oxygen species are linked to ageing and also to diseases such as cancers.

To reduce the toxic effects of iron, a family of proteins called ferritins detoxify and store the metal ions within their football-shaped protein shell, generating a safe but accessible deposit that can be drawn on by the cell when iron in the environment becomes scarce.

Working with researchers at the University of Essex and the Scripps Institute in California, the UEA team have discovered how a ferritin in one particular marine bacterium succeeds in carrying out this detoxification process.

Unusually, the bacterium produces the ferritin in response to high levels of copper, not iron.

The team discovered that there was no direct interaction between the ferritin and the copper, but instead the ferritin catalysed a new kind of reaction between oxygen and iron. This generated a form of the ferritin that has an enhanced ability to detoxify ROS directly, whilst also carrying out its iron storage and detoxification roles.

Prof Nick Le Brun, from UEA's School of Chemistry, said: "We believe the iron involved in this new pathway has been displaced from other iron-containing proteins by the copper, and the bacterium manages the toxicity of the displaced iron by producing the ferritin. This of particular interest because the ferritin involved more closely resembles those in animals than in other bacteria."

This type of process has not previously been spotted by scientists and confirms that there are many different ferritin mechanisms at work across different organisms.

Dr. Dima Svistunenko, from the University of Essex, said: "The chemistry between iron and O2, that generates harmful ROS, has been studied in many systems, and that includes a number of ferritins from a range of organisms. But, here, we saw reactivity that is entirely new, pointing to an unprecedented detoxification process that involves long-range electron transfer across the protein molecule."

A search of genomic databases carried out by the team also revealed that many other similar marine bacteria may produce similar ferritins under conditions of stress.

The team now plan to expand their research to investigate how widespread the new mechanism is.

"None of the previously studied ferritins, or indeed iron enzymes in general, react in the way this newly discovered ferritin does," said Prof Le Brun.

"This novel chemistry not only represents a breakthrough for our understanding of natural anti-oxidant processes, it also reveals new possibilities for future engineered biocatalysts that could, for example, find use in drug development."

'Reaction of O2 with a di-iron protein generates a mixed valent Fe2+/Fe3+ center and peroxide' is published in *PNAS* on January 14, 2019.

More information: Justin M. Bradley el al., "Reaction of O2 with a diiron protein generates a mixed-valent Fe2+/Fe3+ center and peroxide," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1809913116

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