UA medical scientists first in the world to look at structure of vital molecule

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Molybdenum is an essential metal required in all living beings from bacteria to plants to humans. But as vital as this metal is, no one understood the importance of its structure until the Faculty of Medicine & Dentistry's Joel Weiner and his team jumped on the case.

Molybdenum plays critical roles in human health. It does not act alone but is found attached to certain proteins, called molybdenum enzymes, by a very large organic molecule. The organic molecule that holds the molybdenum in place in a protein is extraordinarily complex. and "expensive" for the cell to make, b But the structure of this molecule should make sense to scientists now, thanks to Weiner and his research team.

For starters, the research group found that the molecule occurs in nature in two forms based on their appearance – flat or distorted. Weiner's team was able to show that the distorted form and flat form have very different functions. The distorted molecule plays a role in the transfer of electrons to the molybdenum, whereas the flat molecule prepares and co-ordinates positioning of the enzyme so it can be part of a biochemical reaction.

"This is important because molybdenum is so essential throughout biology," said Weiner. "We need to understand why the cell goes to all this trouble."

The distorted form is found in proteins involved in metabolic, respiratory and cardiac diseases. The flat form occurs in a protein required for brain development, and defects in this protein cause death in infancy. Understanding of this flat form could help lead to treatment of this defect.

It all started for Weiner and his research group in the Department of Biochemistry about three years ago. Although scientists worldwide had known the overall structure of molybdenum in proteins for many years, no one understood why it is so complicated. It was a summer student, Matthew Solomonson, who noticed that one of the structures holding molybdenum was very flat while the other group was distorted. As curiosity-based research goes, the summer student and Weiner's research team wondered if it was significant. The answer is yes.

"When you bring in a new student it's really good because they have a fresh way of looking at things," says Weiner of Solomonson who is now a grad student at the University of British Columbia.

"This discovery is a major one for my lab and will have a huge impact on molybdenum biochemistry research."

Now the team will use protein-engineering techniques to change the protein environment around the molybdenum.

"This is a critical next step," said Weiner. "We hope to finally start understanding the chemistry of these enzymes at atomic resolution, and to modulate their activities to better understand human disease and explore potential biotechnology and biomedical applications."

This work is published in the high-impact journal *Proceedings of the National Academy of Sciences*.

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