Scientists find cellular backup plan for keeping iron levels just right

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Iron is essential for cells to function, but excess iron can damage cells. Accordingly, cells have sophisticated molecular mechanisms to constantly sense and adjust iron levels. Disorders of cellular iron metabolism affect, by some estimates, more than a third of the world's population. In addition to well-known disorders like anemia, caused by overall insufficient levels of iron in the human body, iron deficiency can impair brain function in the young and reduce muscle strength in adults. Iron may be dysregulated at the level of individual cells in neurological disorders such as Parkinson's disease, and disordered iron metabolism contributes to congenital conditions such as Friedrich's ataxia.

Researchers in the Nutritional Sciences department at the University of Wisconsin have uncovered a new connection in the network of checks and balances underlying cellular iron regulation. The research will be published in the Sept. 22 issue of the *Journal of Biological Chemistry*.

When iron levels in human and other mammalian cells are low, iron regulatory proteins, or IRPs, spring into action. IRPs prevent iron that enters cells from being improperly stored away, allowing the cell to use iron to produce essential iron-containing proteins. When there is excess iron, IRPs are inactive, leading to increased iron storage thereby lowering its potential toxicity and reserving it for when iron availability is reduced. Too much or too little IRP activity can be dangerous for cells.

Richard Eisenstein's research group at the University of Wisconsin

studies what controls IRPs' activity. For decades, it's been thought that the main method by which IRP-1 is inactivated involves essential compounds called iron-sulfur clusters. When there is sufficient iron in the cell, an iron-sulfur cluster is inserted into IRP-1, inactivating it. Thus, the activation or suppression of IRP-1 is directly related to how much iron is available in the cell to produce iron-sulfur clusters.

However, there was some evidence of another method by which IRP-1 could be stopped when it was not needed: namely, that a protein called FBXL5 could add molecular tags to IRP-1 to tell the cell to degrade the protein altogether.

"The idea that IRP1 is also regulated by protein degradation was controversial when it was first discovered by others," Eisenstein said. "There's been a belief that IRP1 was really regulated by this iron-sulfur cluster mechanism, and that the protein degradation mechanism wasn't so important."

To test whether this was the case, Eisenstein's team performed experiments in which they suppressed the production of iron-sulfur clusters. Even when iron-sulfur clusters production was reduced, IRP-1 activity could still be suppressed. The team confirmed that this was indeed due to the activity of FBXL5. This supported the idea that protein degradation was a backup mechanism that reduced IRP-1 action in cells with high iron.

The results have implications for understanding how iron is sensed, used and regulated in different tissues. Different tissues have different levels of oxygen, but the iron-sulfur cluster production system functions best at low oxygen whereas FBXL5 functions best at high oxygen. Therefore, these two systems may trade off taking the lead in controlling IRP-1 in different parts of the body. Because iron-sulfur clusters and FBXL5 play many different important roles in cell growth, this balance between these

functions could help different types of cells control how they utilize iron.

"Diseases of iron metabolism caused by diet or by genetic perturbations are major public health issues," Eisenstein said. "To combat such diseases and develop effective treatments for those afflicted with them, it is essential to understand iron-sensing and iron-regulatory pathways."

More information: Nathan B. Johnson et al, A synergistic role of IRP1 and FBXL5 in coordinating iron metabolism during cell proliferation, *Journal of Biological Chemistry* (2017). DOI: 10.1074/jbc.M117.785741

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