Iron-sulfur cluster research offers new avenues of investigating disease

May 30 2018

Many important proteins in the human body need iron-sulfur clusters, tiny structures made of iron and sulfur atoms, in order to function correctly. Researchers at the National Cancer Institute (NCI), the National Institutes of Health (NIH) and the University of Kentucky have discovered that disruptions in the construction of iron-sulfur clusters can lead to the buildup of fat droplets in certain cells. These findings, which will be published in the May 25 issue of the *Journal of Biological Chemistry*, provide clues about the biochemical causes of conditions like nonalcoholic fatty liver disease and clear cell renal carcinoma.

"Iron-sulfur clusters are delicate and susceptible to damage within the cell," said Daniel Crooks, the postdoctoral fellow who led the new study. "For this reason, the cells in our body are constantly building new iron-sulfur clusters."

Crooks began studying the enzymes that build iron-sulfur clusters during his graduate studies in Tracey Rouault's lab at the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the NIH. Mutations in one of these enzymes can cause ISCU myopathy, a hereditary condition in which patients, despite seeming strong and healthy, cannot exercise for more than a short time without feeling pain and weakness.

Therefore, it was clear to Crooks that lifelong deficiency of iron-sulfur clusters caused profound changes in how cells processed energy. But he wondered exactly what happened in a cell in the first moments after

something went wrong with iron-sulfur cluster production. Which of the many proteins that need iron-sulfur clusters were affected first, and what effect did this have on cell metabolism?

Crooks developed experimental methods to abruptly stop iron-sulfur clusters from being manufactured in cells and to monitor what happens to how these cells process glucose. Ordinarily, over a series of metabolic steps, cells would convert glucose into energy. But without iron-sulfur clusters, an enzyme called aconitase that carries out one of the steps in this process doesn't work. As a result, the cells quickly accumulated an intermediate metabolic product called citrate, which was eventually converted into droplets of fat.

Over-accumulation of fats in tissues where they're not normally found is a hallmark of numerous diseases, including nonalcoholic fatty liver disease, a risk factor for cirrhosis and liver cancer. These findings suggest that this state could be caused by failures of iron-sulfur cluster production, for example due to cellular stressors or toxin exposure.

"We're hoping that the people who are working so hard on nonalcoholic fatty liver disease will find our paper helpful to their research," Rouault said.

Crooks, working in the laboratory of surgeon and scientist W. Marston Linehan at NCI, is now examining the role of iron-sulfur cluster formation and aconitase function in cancers, for example clear cell carcinomas. Various cancers are often characterized by excessive fat accumulation in cells. In fact, this accumulation of lipid droplets is where clear cell carcinomas get their name: when a slice of a such a tumor is fixed on a slide and its proteins are stained, the large areas of lipid accumulation in the cells look transparent.

"We really want to look at the beginnings of cancer... to understand

whether the lipids were formed from glucose or other fuels and whether the lipids are important for pathogenesis, or whether they're just bystanders that form in response to metabolic reprogramming which is likely to include disruption of iron sulfur protein activities," Crooks said.

More information: Daniel R. Crooks et al, Acute loss of iron–sulfur clusters results in metabolic reprogramming and generation of lipid droplets in mammalian cells, *Journal of Biological Chemistry* (2018). DOI: 10.1074/jbc.RA118.001885