New screen offers hope for copper deficiency sufferers

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Copper deficiency diseases can be devastating. Symptoms can range from crippling neurological degeneration in Menkes disease - a classic copper deficiency disease - to brittle bones, anaemia and defective skin pigmentation in gastric bypass patients. Unfortunately, very little is known about how the body uses this essential nutrient.

Knowing that melanocytes (the cells that give rise to hair, skin and eye pigmentation) are dramatically affected by the effects of copper deficiency, Elizabeth Patton from the University of Edinburgh, UK, and other colleagues from UK- and US-based labs decided to find out how melanocytes metabolise copper. Patton and her colleagues publish their results in *Disease Models and Mechanisms* on August 17, 2010.

Patton explains that zebrafish are a valuable research tool because they are an intermediate organism between mammals and the simpler creatures that scientists routinely use to study genetic disorders. She usually uses zebrafish to understand how melanocytes develop and how these cells can give rise to malignant melanoma, a lethal form of cancer. Testing compounds that she hoped might prevent malignant melanoma symptoms in zebrafish, she was puzzled to find a compound that caused the fish to lose their characteristic zebra-stripe patterns. After spending months trying to determine why the fish lost their stripes, she crossed paths with Jonathan Gitlin, a copper deficiency specialist from Vanderbilt University, USA, and realised that the stripeless fish might have copper deficiency.

To understand the molecular pathways involved in copper deficiency, Patton and Gitlin teamed up with Mike Tyers from the University of Edinburgh and developed an elegant method to probe copper metabolism in zebrafish. First, the team identified compounds that caused zebrafish to lose their stripes - indicating copper deficiency. Next, they identified the genes that each compound targeted by applying the compounds to yeast cells. Patton explains that most of the genes that control copper metabolism are very similar in yeast, zebrafish and humans, so the genes identified in this study should increase our understanding of what makes certain people susceptible to copper deficiency.

The team found that mutations in certain proteins that move nutrients around cells (trafficking components) increase the risk that carriers will be susceptible to copper deficiency when the copper supply is restricted, such as after gastric bypass surgery. Patton says, "You might have people with polymorphisms [variations in a single gene] in some of these trafficking components that are fine, but under certain environmental conditions some of the weaknesses are revealed."

This work demonstrates the utility of the coupled zebrafish-yeast approach for studying copper deficiency, but it can also be applied for studying other complex multifactorial diseases, particularly those with an environmental component. "There have been some beautiful studies looking at transport components in melanocytes, which have linked copper metabolism pathways with transport. What's new here is that we can investigate a gene-environment interaction," says Patton, who hopes to apply the method for studying cardiofaciocutaneous syndrome, a rare genetic disorder with crippling symptoms ranging from skin abnormalities to heart defects. In addition, her team plans to apply the method to investigate how drug candidates function in vivo.

More information: dmm.biologists.org/

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