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Title: THE ROLE OF GLUTATHIONE IN LIPID METABOLISM

Abstract

The antioxidant glutathione (GSH) scavenges free radicals and prevents the detrimental effects of oxidative stress. As a result, GSH levels are associated with protection from stress-related conditions, such as aging and cancer. Recent evidence, however, implicates GSH in protecting cancer cells from oxidative stress and promoting their survival. Thus, these data suggest that the relationship between antioxidants and diseases is much more complex and that there is potentially outstanding aspects to GSH biology that remains to be discovered, especially regarding its in vivo roles. By elucidating these roles, we can identify its intricate crosstalk with other cellular pathways, and potentially improve of the efficacy of therapeutic interventions for diseases, including cancer. Here, we show that GSH plays a key role in the maintenance of lipid homeostasis in the body. Using a model of systemic, inducible Gclc deletion, we find that loss of GSH synthesis causes overt weight loss, a dramatic reduction in fat mass, and decreased circulating triglycerides. We also show that in liver tissue from Gclc-/- mice, GSH depletion causes a compensatory activation of the NRF2 transcription factor and downstream antioxidant enzymes and cofactors, as well as a dramatic repression of lipogenic enzymes. These results indicate that, in addition to its detoxification-related activities in the liver, abundantly synthesized GSH functions to sustain low NRF2 activity, potentially allowing for full expression of lipid-producing genes. Overall, these findings suggest an important function for GSH in the maintenance of circulating lipids levels and lipid depots, possibly as a mechanism to prevent lipid peroxidation and redox imbalances. This also highlights a potential novel mechanism by which GSH regulates lipid production and suggests a possible link between oxidative stress (caused by GSH deficiency) and cachexia (commonly characterized by loss of fat and lean mass), a disorder linked to cancer but poorly understood. Consequently, by elucidating the contributions of GSH to lipid homeostasis, we can better understand the basic biology surrounding GSH and obtain critical insight into potentially improving the treatment of cancer-related cachexia.