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**Title: GlUTATHIONE CATABOLISM MAY BE A CRITICAL AMINO ACID SOURCE FOR CANCER CELL SURVIVAL**

**Abstract:**
Amino acids are crucial to cancer initiation, progression, and drug resistance. Restricting amino acids from tumors is an emerging therapeutic strategy which holds significant promise. Glutathione (GSH), a tripeptide comprised of cysteine, glutamate, and glycine, is abundantly present in the tumor microenvironment. While it is typically thought of as an intracellular antioxidant, extracellular GSH is also catabolized to supply amino acids, which could support tumor metabolism. The extent to which GSH-derived amino acids are essential to cancers is unclear. Here, we find that catabolism of extracellular GSH is crucial for tumor cell survival and growth. We show that cultured cells can be rescued from a lethal depletion of cystine upon supplementation with GSH or its catabolic product cysteinylglycine. Further, we find that GSH is highly elevated in the plasma and tumor microenvironment compared with standard cell culture medium. Finally, we demonstrate that while systemic reduction in GSH synthesis blocks tumorigenesis, tumor-intrinsic depletion of GSH does not perturb tumor growth, suggesting that tumor-extrinsic extracellular GSH potentially drives tumors. These findings support the hypothesis that GSH has important non-canonical functions in supporting tumor survival by acting as vehicle for amino acid delivery. Understanding the mechanisms by governing GSH catabolism could dramatically shift our understanding of tumor metabolism. Further, depriving tumors of extracellular GSH or inhibiting its catabolic enzymes could prove to be a tractable therapeutic approach in otherwise intractable tumors.