Genetics Day Poster Submission

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Title: EXTRACELLULAR GLUTATHIONE CATABOLISM AS AN ALTERNATIVE CYST(E)INE SOURCE IN CANCER

Abstract: Glutathione (GSH) is the most abundant antioxidant in the human body and plays an essential role in physiology and disease. Unchecked oxidative stress is involved in tumor initiation and progression. Paradoxically, various studies show that ROS-scavenging molecules such as glutathione not only fail to impede tumor growth but accelerate it. However, preliminary data from our lab show that genetically ablating tumors' ability to synthesize GSH does not affect tumor growth. This finding suggests that the favorable influence of glutathione on tumor growth may arise from external sources. Yet, the mechanism cancer cells employ to take advantage of extracellular glutathione in this context is unknown. Here we show that g-glutamyl-transpeptidase 1 (GGT1) can break down extracellular GSH, yielding the amino acid cysteine to cancer cells, which rescues the loss of cell fitness caused by cystine depletion. We found that GSH, as well as cysteinylglycine, the product of GGT1-mediated GSH breakdown, can mitigate cell death, proliferation arrest, and oxidative stress caused by cystine depletion. Inhibition of GGT1 prevented these protective effects. Cell death, but not proliferation arrest, could also be prevented by inhibiting ferroptosis. Moreover, the overexpression of human GGT1 significantly reduces the amount of glutathione needed for growth rescue. Also, a comprehensive pharmacological screening revealed that GGT1-mediated cystine acquisition contributes to the resistance of cancer cells to some metabolic inhibitors. Our findings reveal that cancer cells can access cysteine, a vital yet scarce amino acid, through GGT1's ability to break down glutathione, which is present in remarkably high concentrations within the tumor microenvironment. Although the downstream proteins involved in the transport and utilization of GSH breakdown products are yet to be identified, we anticipate this pathway has the potential to uncover novel therapeutic avenues for cancer treatment by targeting alternative pathways of nutrient acquisition that are potentially implicated in cancer progression and therapy resistance.