ABSTRACT

Reactive oxygen species (ROS) are byproducts of normal cellular processes. While low or moderate levels of ROS promote and sustain oncogenic properties of cancer cells, excessive amounts are detrimental. Cancer cells counterbalance increased ROS production by engaging ROS-scavenging systems, which heavily rely on the antioxidants GSH and NADPH that can be synthesized from glutamine (GLN). Although GLN is not an essential amino acid, some cancer cells depend on exogenous GLN for survival, a phenotype known as GLN addiction. GLN plays versatile roles in cells from synthesis of macromolecules to redox balance. However, why GLN dependence for survival varies among different cancer cell types is not fully understood. This thesis tested the hypothesis that GLN addiction phenotype is ROS dependent. We first showed that loss of Hace1, a tumor suppressor that regulates ROS levels, results in increased GLN metabolism and GLN addiction. Inhibition of ROS reverses GLN addiction phenotype of Hace1 deficient cells, providing the first evidence that loss of a tumor suppressor leads to GLN addiction due to increased ROS levels. Using a panel of human cancer cell lines we established that GLN deprivation induces cell death in GLN addicted cells primarily by depleting intracellular antioxidant pools, resulting in increased ROS levels and oxidative damage. Furthermore GLN deprivation results in ROS-dependent elevation of glucose uptake in GLN addicted cells, which exacerbates oxidative stress causing cell death. Finally, we showed that GLN addicted cells are more sensitive to exogenous oxidants without GLN, and that AMPK mediated upregulation of ASCT2 expression and GLN uptake confers resistance to oxidative stress in GLN addicted cells. These studies establish the reciprocal regulation of GLN metabolism and oxidative stress in cancer cells.