Abstract

The DNA damage response is essential for preserving genome integrity and eliminating damaged cells. Although cellular metabolism plays a central role in cell fate decision between proliferation, survival, or death, the metabolic response to DNA damage remains largely obscure. Here, we show that DNA damage induces fatty acid oxidation (FAO), which is required for DNA damage-induced cell death. Mechanistically, FAO induction increases cellular acetyl-CoA levels and promotes N-alpha-acetylation of caspase-2, leading to cell death. Whereas chemotherapy increases FAO related genes through PPARα, accelerated hypoxia-inducible factor-1α stabilization by tumor cells in obese mice impedes the upregulation of FAO, which contributes to its chemoresistance. Finally, we find that improving FAO by PPARα activation ameliorates obesity-driven chemoresistance and enhances the outcomes of chemotherapy in obese mice. These findings reveal the shift toward FAO induction is an important metabolic response to DNA damage and may provide effective therapeutic strategies for cancer patients with obesity.