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Two isoforms of sphingosine kinase, SK1 and SK2, catalyze the formation of the bioactive lipid sphingosine 1-phosphate (S1P) in mammalian cells. We have previously shown that treatment of androgen-sensitive LNCaP prostate cancer cells with a non-selective SK isoform inhibitor, 2-(p-hydroxyanilino)-4-(p-chlorophenyl)thiazole (SKi), induces the proteasomal degradation of SK1. This is concomitant with a significant increase in C22:0-ceramide and sphingosine levels and a reduction in S1P levels, resulting in the apoptosis of LNCaP cells. In contrast, we show here that a SK2-selective inhibitor, (R)-FTY720 methyl ether (ROME), increases sphingosine and decreases S1P levels but has no effect on ceramide levels and does not induce apoptosis in LNCaP cells. We also show that several glycolytic metabolites and (R)-S-lactoylglutathione are increased upon treatment of LNCaP cells with SKi, which induces the proteasomal degradation of c-Myc. These changes reflect an indirect antagonism of the Warburg effect. LNCaP cells also respond to SKi by diverting glucose 6-phosphate into the pentose phosphate pathway to provide NADPH, which serves as an antioxidant to counter an oxidative stress response. SKi also promotes the formation of a novel pro-apoptotic molecule called diadenosine 5’,5”’-P(1),P(3)-triphosphate (Ap3A), which binds to the tumor suppressor fragile histidine triad protein (FHIT). In contrast, the SK2-selective inhibitor, ROME, induces a reduction in some glycolytic metabolites and does not affect oxidative stress. We conclude that SK1 functions to increase the stability of c-Myc and suppresses Ap3A formation, which might maintain the Warburg effect and cell survival, while SK2 exhibits a non-overlapping function.