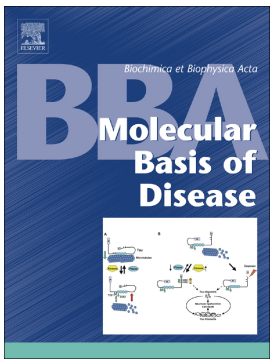

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Inhibition of mTOR complexes protects cancer cells from glutamine starvation induced cell death by restoring Akt stability

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Running title: *Enhanced autophagy protects cancer during starvation*

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ABSTRACT

Glutamine, a well-established oncometabolite, anaplerotically fuels mitochondrial energy metabolism and modulates activity of mammalian/mechanistic target of rapamycin complexes (mTOR). Currently, mTOR inhibitors are in clinical use for certain types of cancer but with limited success. Since glutamine is essential for growth of many cancers, we reasoned that glutamine deprivation under conditions of mTOR inhibition should be more detrimental to cancer cell survival. However, our results show that when cells are deprived of glutamine concomitant with mTOR inhibition, hepatocarcinoma cells elicit an adaptive response which aids in their survival due to enhanced autophagic flux. Moreover, inhibition of mTOR promotes Akt ubiquitination and its proteasomal degradation however we show that Akt degradation is abrogated by increased autophagy following glutamine withdrawal. Under conditions of glutamine deficiency and mTOR inhibition, the enhanced stability of Akt protein may provide survival cues to cancer cells. Thus, our data uncovers a novel molecular link between glutamine metabolism, autophagy and stability of Akt with cancer cell survival.