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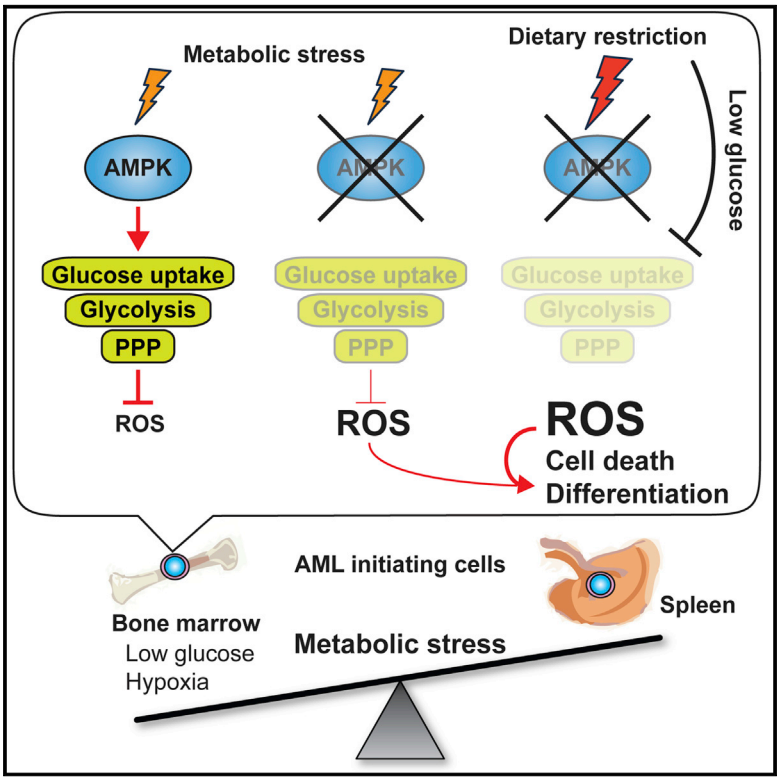
Cell Stem Cell

# AMPK Protects Leukemia-Initiating Cells in Myeloid Leukemias from Metabolic Stress in the Bone Marrow

## Graphical Abstract




## Highlights

- AMPK is activated upon metabolic stress and promotes survival of AML
- AMPK deletion disrupts glucose metabolism of AML cells and increases ROS
- AMPK is more important for LICs in the bone marrow compared to those in the spleen
- AMPK deletion sensitizes AML to metabolic stress caused by dietary restriction

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## In Brief

Saito et al. show that deletion of *AMPK* from AML cells disrupts their glucose metabolism and redox homeostasis and that deletion of *AMPK* synergizes with metabolic stress caused by dietary restriction to suppress AML.

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# AMPK Protects Leukemia-Initiating Cells in Myeloid Leukemias from Metabolic Stress in the Bone Marrow

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## SUMMARY

**How cancer cells adapt to metabolically adverse conditions in patients and strive to proliferate is a fundamental question in cancer biology. Here we show that AMP-activated protein kinase (AMPK), a metabolic checkpoint kinase, confers metabolic stress resistance to leukemia-initiating cells (LICs) and promotes leukemogenesis. Upon dietary restriction, MLL-AF9-induced murine acute myeloid leukemia (AML) activated AMPK and maintained leukemogenic potential. *AMPK* deletion significantly delayed leukemogenesis and depleted LICs by reducing the expression of glucose transporter 1 (Glut1), compromising glucose flux, and increasing oxidative stress and DNA damage. LICs were particularly dependent on AMPK to suppress oxidative stress in the hypoglycemic bone marrow environment. Strikingly, AMPK inhibition synergized with physiological metabolic stress caused by dietary restriction and profoundly suppressed leukemogenesis. Our results indicate that AMPK protects LICs from metabolic stress and that combining AMPK inhibition with physiological metabolic stress potently suppresses AML by inducing oxidative stress and DNA damage.**

## INTRODUCTION

A fundamental question in cancer biology concerns how cancer cells residing in metabolically adverse conditions with low oxygen, glucose, and nutrient levels strive to proliferate and whether this feature of cancer cells can be turned into vulnerability by interventions (Cairns et al., 2011; Schulze and Harris, 2012). Dietary restriction (DR) causes systemic changes in metabolic parameters such as reduced insulin, insulin-like growth factor 1 (IGF-1), and glucose levels (Masoro, 2005), and it delays the incidence and growth of various tumor models (Colman et al., 2009; Curry et al., 2013; Kalaany and Sabatini, 2009; Longo and Fontana, 2010; Mattison et al., 2012; Mihaylova et al., 2014), demonstrating that cancer cells can be targeted by modulating systemic metabolic parameters. Nonetheless, some cancer cells acquire adaptive mutations, such as activating mutations in the phosphoinositide 3-kinase (PI3K) pathway, and become insensitive to the insulin/IGF-1-lowering effects of DR (Curry et al., 2013; Kalaany and Sabatini, 2009). It is, however, still unknown whether the PI3K pathway mutations are the sole determinant of DR sensitivity, or whether cancer cells are equipped with other protective mechanisms independent of their mutation status. Moreover, how DR affects expansion of cancer cells by regulating cancer-initiating cells is unexplored.

AMP-activated protein kinase (AMPK) orchestrates the cellular metabolic state with proliferation by promoting catabolism and inhibiting anabolism (Hardie et al., 2012). AMPK is a heterotrimeric complex consisted of a catalytic $\alpha$ subunit and two regulatory subunits ($\beta$ and $\gamma$). Energetic stress increases the AMP:ATP ratio, upon which AMPK is activated in a manner dependent on the phosphorylation by the tumor suppressor kinase Lkb1 (Shackelford and Shaw, 2009). Activated AMPK promotes multiple catabolic processes to maintain metabolic homeostasis, such as glucose uptake via glucose transporters Glut1 and Glut4 (Barnes et al., 2002; Kurth-Kraczek et al., 1999), glycolysis (Almeida et al., 2004), fatty acid uptake and oxidation (Hardie et al., 2012), and mitochondrial biogenesis (Jäger et al., 2007; Zong et al., 2002). Furthermore, AMPK activation suppresses anabolic processes such as protein and lipid synthesis. Of note, AMPK inhibits the mammalian target of rapamycin (mTOR) pathway, which promotes protein translation and cell growth, and is thus frequently over-activated in many cancers (Laplante and Sabatini, 2012). Consistent with the tumor-suppressive role of the Lkb1-AMPK pathway, AMPK-activating drugs suppress cancer cell proliferation and tumor formation (Shackelford and Shaw, 2009), while disruption of AMPK promotes some tumors (Faubert et al., 2013). On the contrary, AMPK can promote cancer cell maintenance in vitro and in xenograft models by regulating redox homeostasis (Jeon et al., 2012). Thus, it remains elusive how AMPK function affects cancer in a physiological setting (Faubert et al., 2015; Liang and Mills, 2013; Saito and Nakada, 2014).

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, and it appears increasingly with age with devastating prognosis for elder patients (Ferrara and Schiffer, 2013). AML is a heterogeneous disease caused by various genetic lesions, among which a translocation between the mixed lineage leukemia (MLL) and AF9 genes (producing MLL-AF9) is often found, and they have poor prognosis (Krivtsov and Armstrong, 2007; Muntean and Hess, 2012). Leukemia-initiating cells (LICs), a cell population capable of initiating leukemias, have been functionally identified in murine AML models as well as in human AML specimens through transplantation assays, and