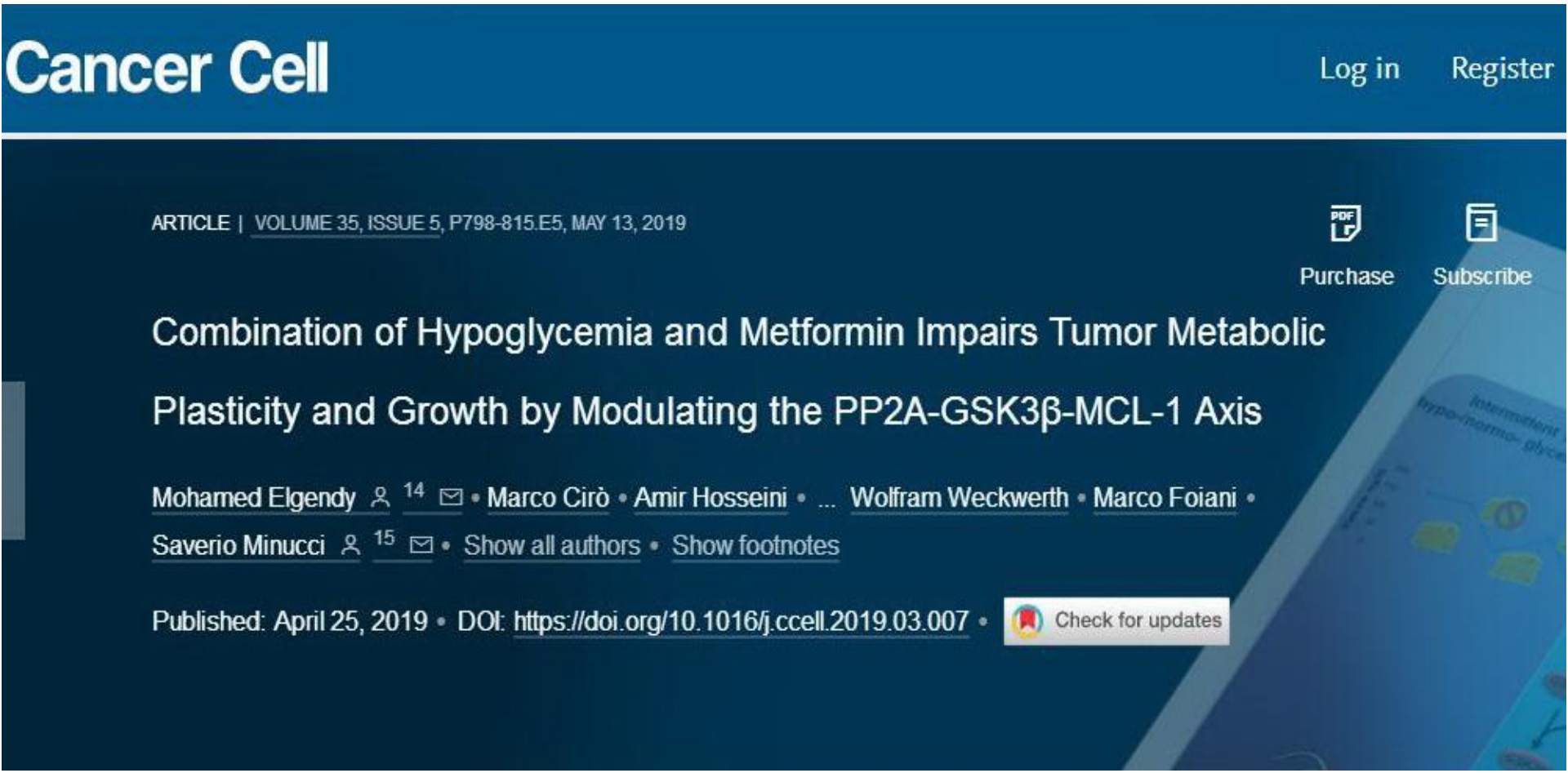

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Article

Combination of Hypoglycemia and Metformin Impairs Tumor Metabolic Plasticity and Growth by Modulating the PP2A-GSK3β-MCL-1 Axis

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Introduction

❖ Therapeutic strategies aimed to tackle metabolic alterations in tumors are gaining greater attention.

❖ Dietary limitation through caloric restriction (CR) or intermittent fasting (IF) is an emerging approach to target tumor metabolism that has been shown to protect against tumorigenesis and to enhance the response to chemotherapy*.

❖ CR has been reported to limit tumor growth, but its clinical use is complicated by factors such as weight loss, fatigue, nausea, delayed wound healing, and impaired immunity.

* ***Longo and Mattson (2014)..Cell Metab. 19, 181–192.***

Introduction

❖ IF, using a limited time of a severely restricted diet has been shown to protect mice and cancer patients from the toxic effects of chemotherapeutic agents without causing chronic weight loss, making it a possibly safer approach*.

❖ Tumor metabolism can also be targeted pharmacologically.

❖ Metformin, the most widely used drug for treating type 2 diabetes (T2D), exhibits anti-cancer activities that are supposedly due to its activity on tumor metabolism.

❖ Direct effects of metformin on cancer cells have been proposed to involve the activation of the AMP-activated protein kinase (AMPK).

* ***Raffaghello et al. (2008). Proc. Natl. Acad. Sci. U S A 105, 8215–8220.***

Introduction

❖ However, accumulating reports have described the AMPK-independent anti-proliferative effects of metformin.

❖ Metformin has been shown to inhibit mammalian target of rapamycin complex 1 signaling and to decrease phosphorylation of multiple receptor tyrosine kinases independently of AMPK..

❖ Given the favorable safety profile of metformin, several clinical trials are now exploring its potential as an adjuvant cancer therapeutic used in combination with other treatments.

Introduction

❖ Metformin accelerates the growth of BRAF-mutant melanoma cells in preclinical models. A dual effect of metformin has also been shown in initial clinical studies in breast cancer.

❖ Optimization of the clinical use of metformin in cancer would therefore benefit from a better understanding of how it exerts its anti-neoplastic effects.

Aim of Study

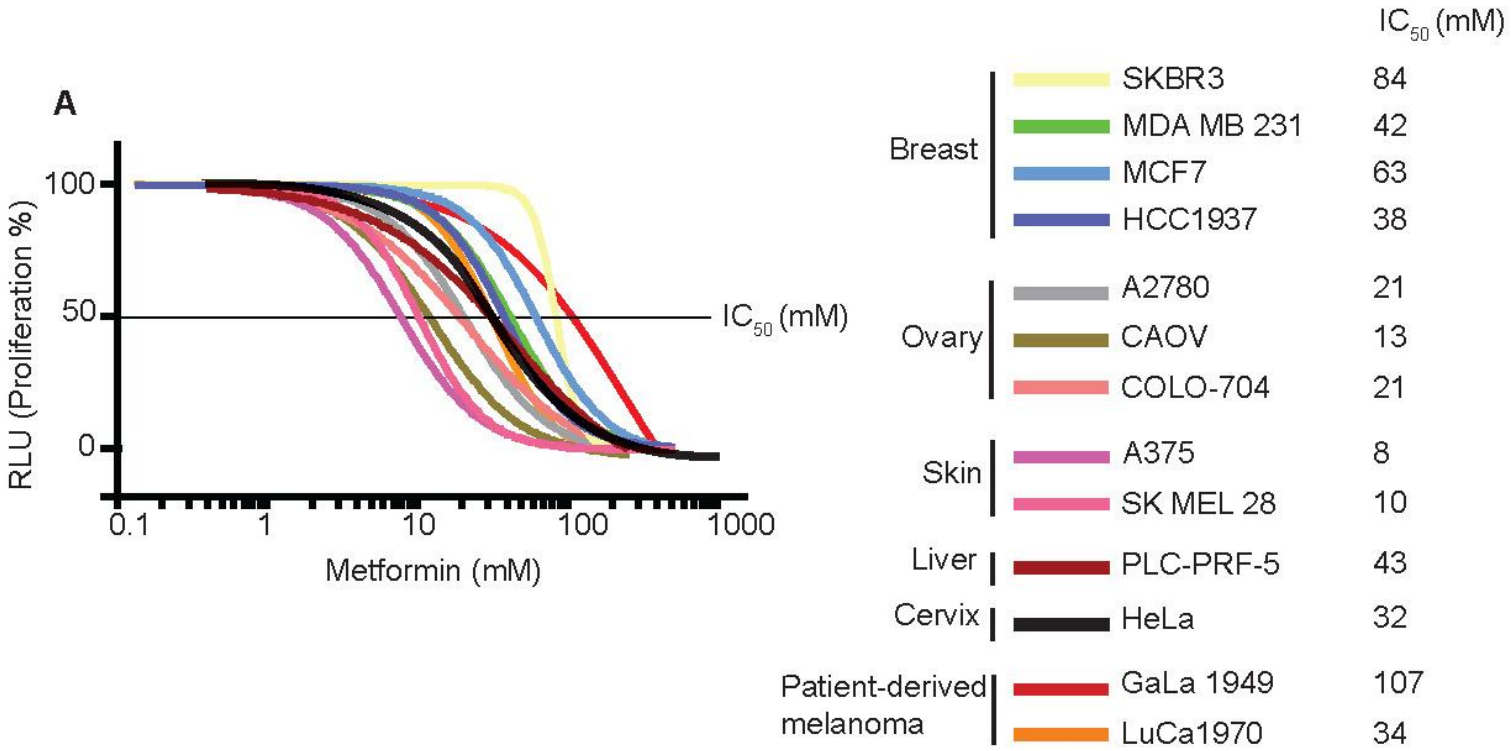
❖ in many cases, tumor cells can alternate between dependency on glycolysis or oxidative phosphorylation (OXPHOS) to adapt to metabolic challenges. Targeting one specific metabolic pathway could thus be ineffective.

❖ In the present study, they examined the effect of targeting tumor metabolism by a combination of inhibitions of glycolysis and OXPHOS.

❖ Dissect the molecular mechanisms of the synergistic effect of the combination and exploited the gained mechanistic insight to tailor pharmacological approaches ready for immediate clinical testing, being based on the repurposing of marketed drugs.

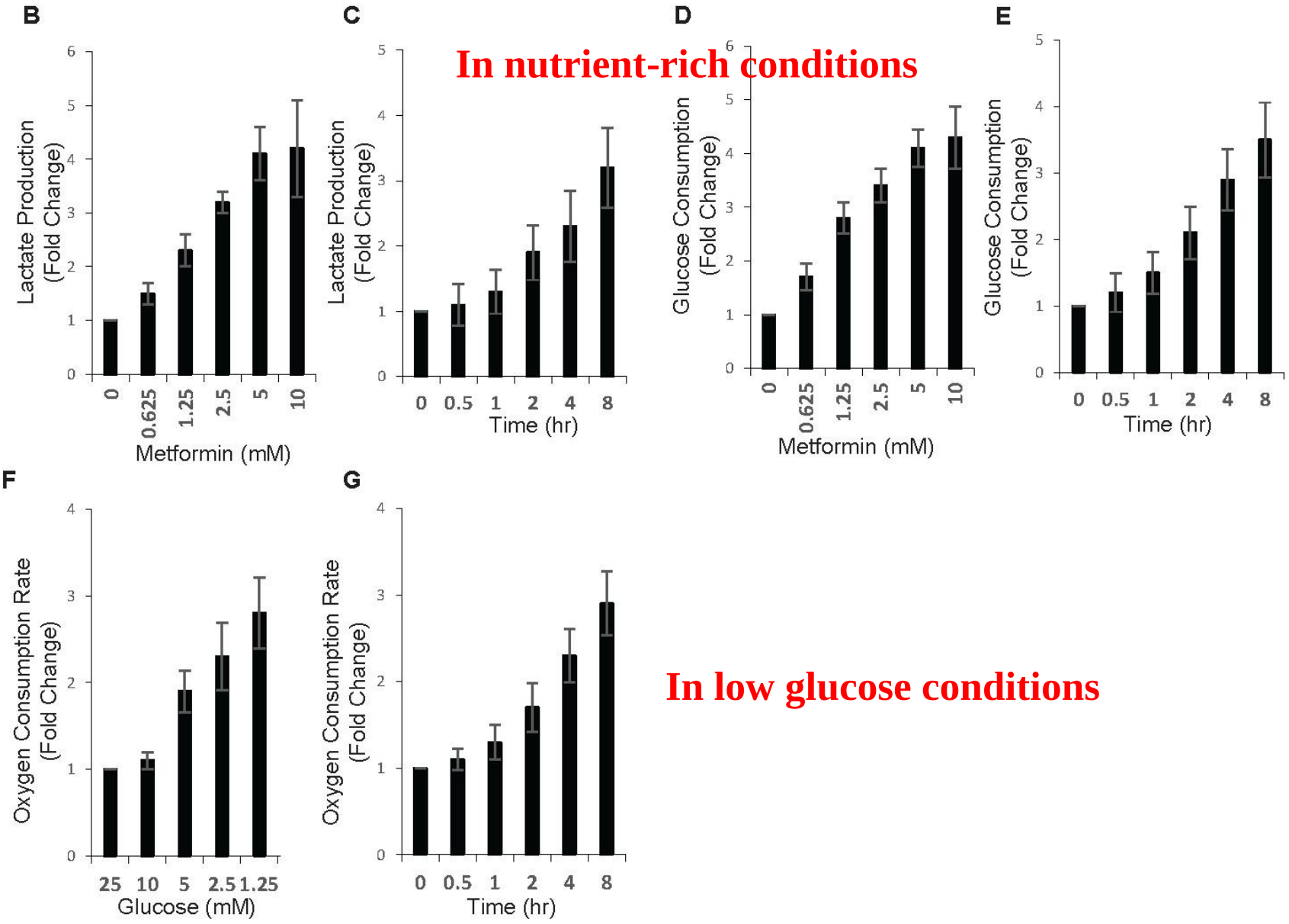
Experimental Models: Cell Lines		
MCF7	ATCC (the American Type Culture Collection)	
A2780	ECACC (The European Collection of Authenticated Cell Cultures)	
COLO-704	DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH)	
A375	IZSLER (Istituto Zooprofilattico Sperimentale della Lombardia e dell'emilia Romagna)	
SK MEL 28	ICLC (IRCCS AOU San Martino - IST Istituto Nazionale per la Ricerca sul Cancro)	
PLC-PRF-5	ATCC (the American Type Culture Collection)	
IGR-1	DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH)	
G-361	ICLC (IRCCS AOU San Martino - IST Istituto Nazionale per la Ricerca sul Cancro)	
COLO 858	ICLC (IRCCS AOU San Martino - IST Istituto Nazionale per la Ricerca sul Cancro)	
C32	IZSLER (Istituto Zooprofilattico Sperimentale della Lombardia e dell'emilia Romagna)	
MALME 3M	ATCC (the American Type Culture Collection)	
IPC-298	DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH)	
SK-MEL30	DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH)	
SK-MEL3	DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH)	
WM266-4	ECACC (The European Collection of Authenticated Cell Cultures)	
MEWO	ICLC (IRCCS AOU San Martino - IST Istituto Nazionale per la Ricerca sul Cancro)	
IGR-37	DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH)	
RPMI 7951	DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH)	
COLO-679	DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH)	
GaLa1949	This paper	N/A
LuCa1973	This paper	N/A
Experimental Models: Organisms/Strains		
CD1 nude mice (CD1-Foxn1nu)	Charles River Laboratories	N/A

Results: Hypoglycemia-Metformin Combination Effectively Restrains Tumor Growth



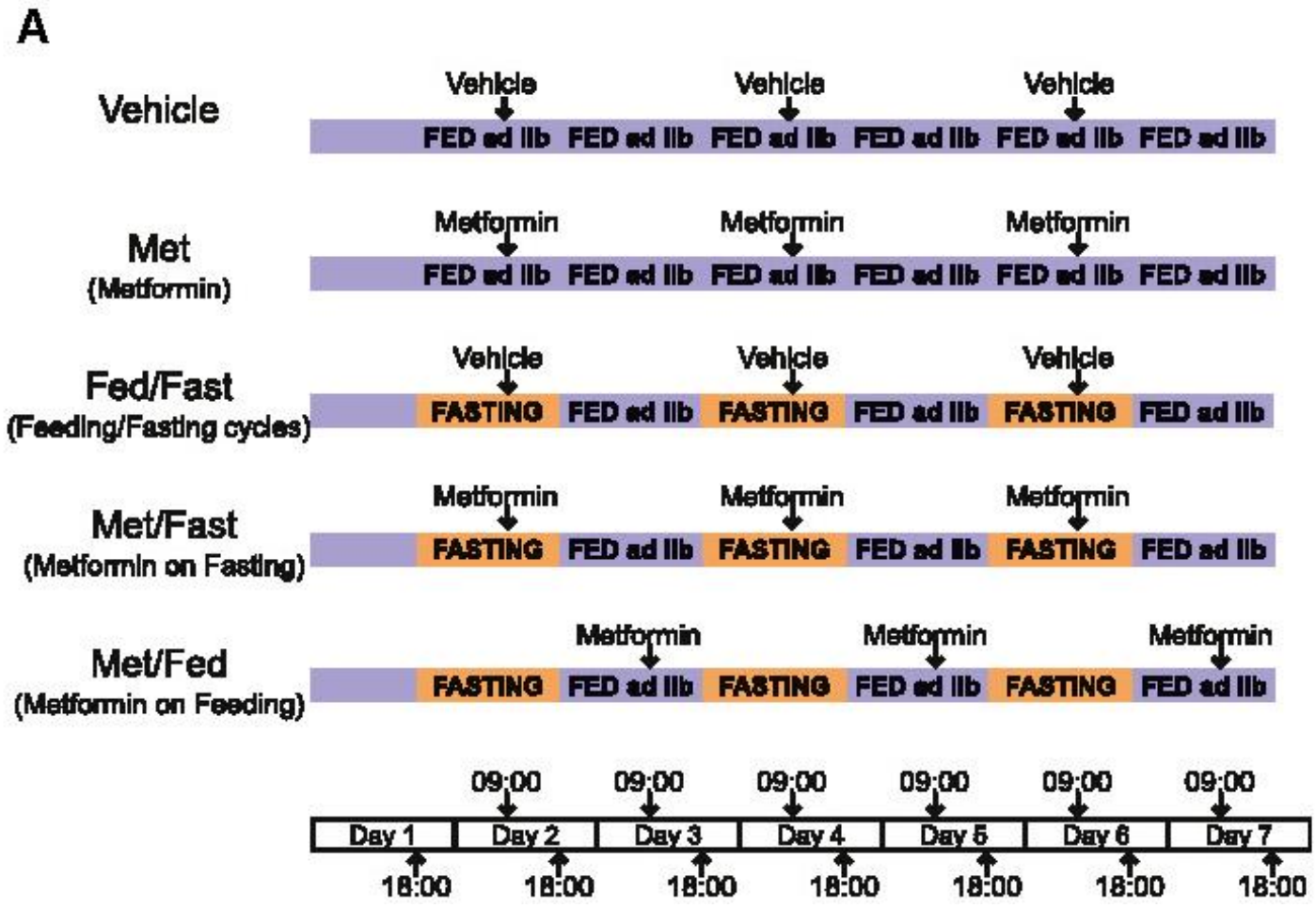
In nutrient-rich conditions

Results: Hypoglycemia-Metformin Combination Effectively Restrains Tumor Growth



Results: Hypoglycemia-Metformin Combination Effectively Restrains Tumor Growth

in vivo metabolic approach



Metformin was administered at 200 mg/kg (n = 5 per group)

Results: Hypoglycemia-Metformin Combination Effectively Restrains Tumor Growth

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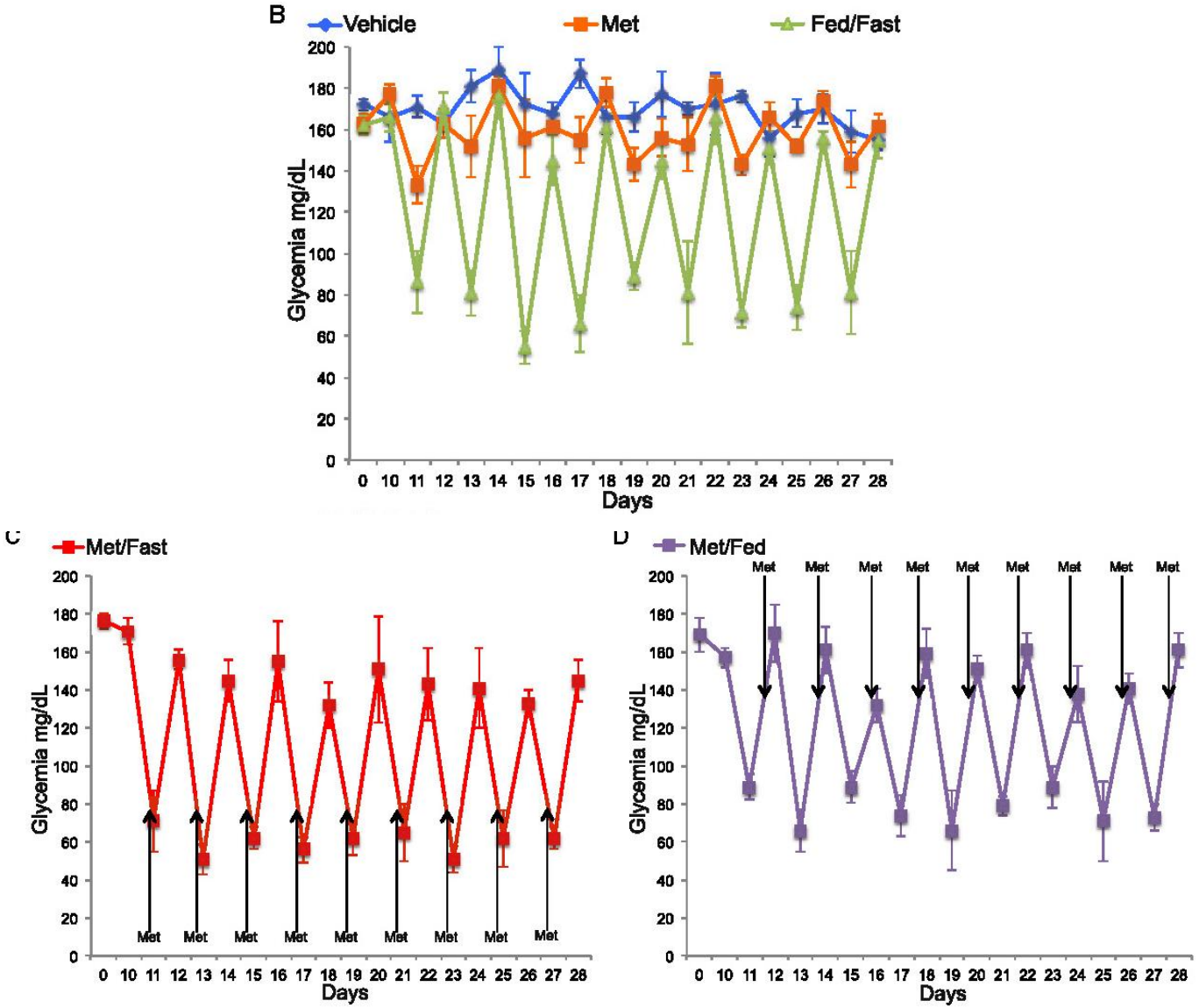

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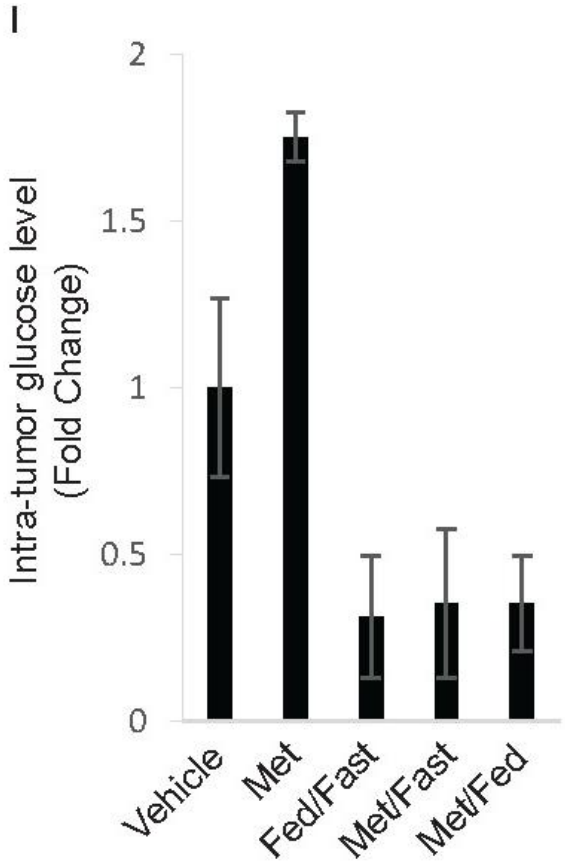

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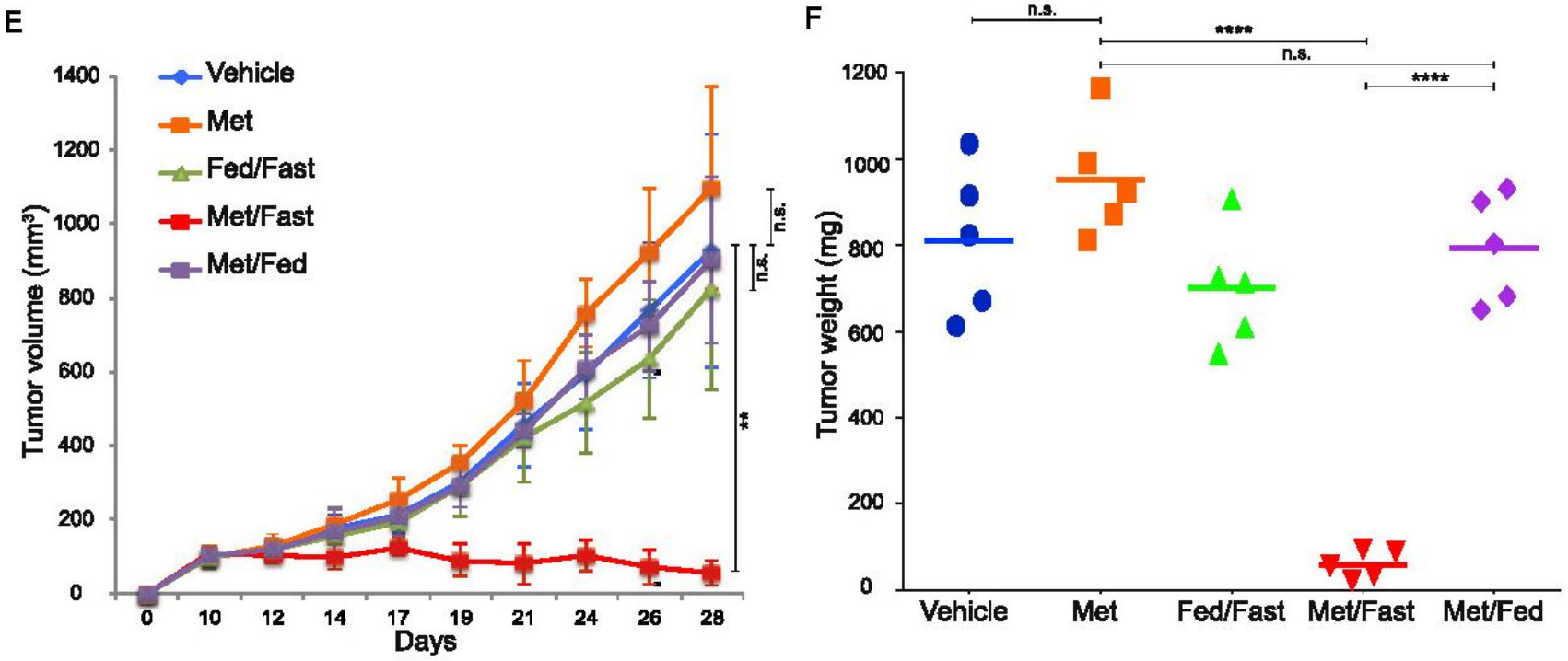
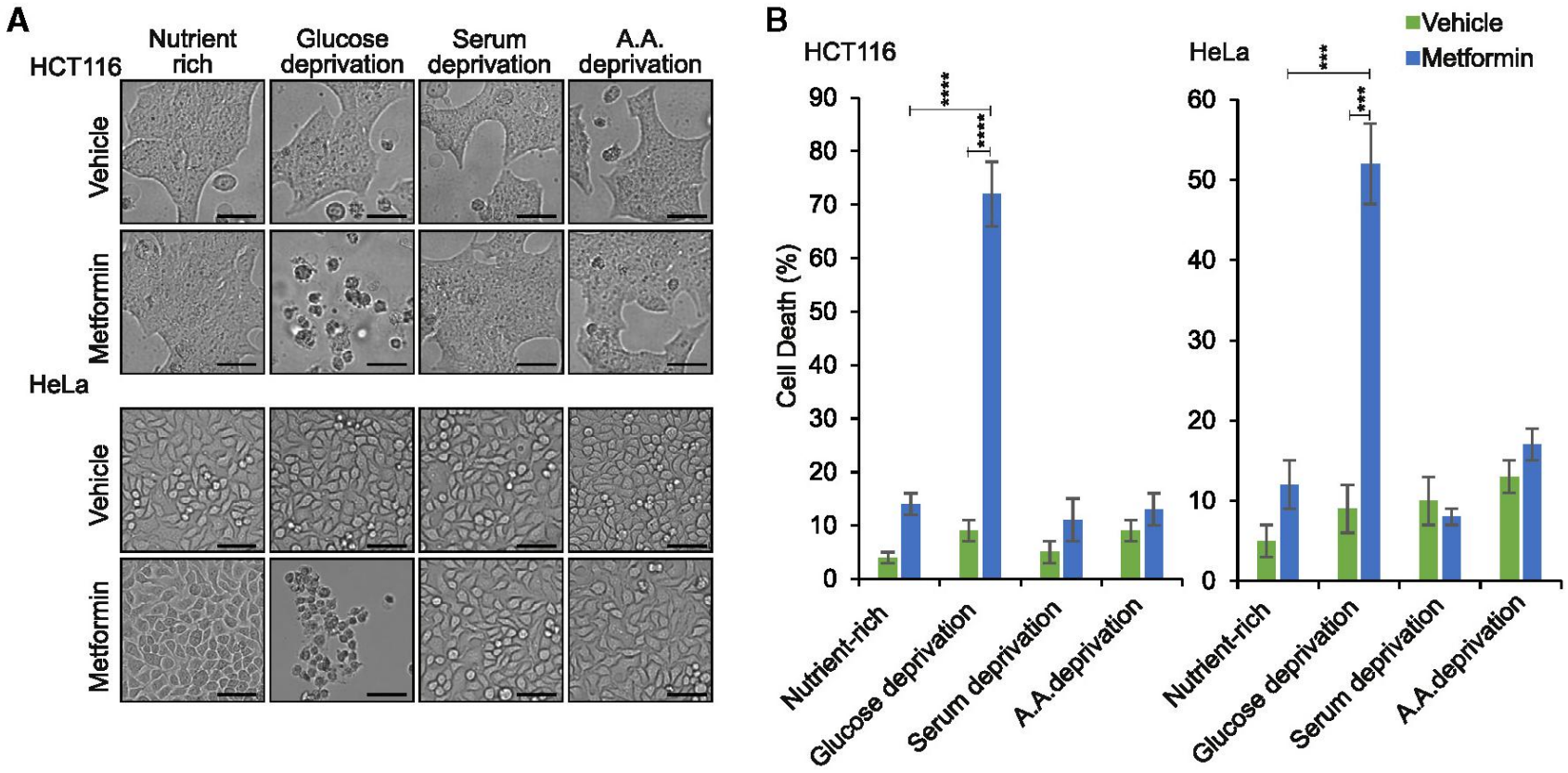


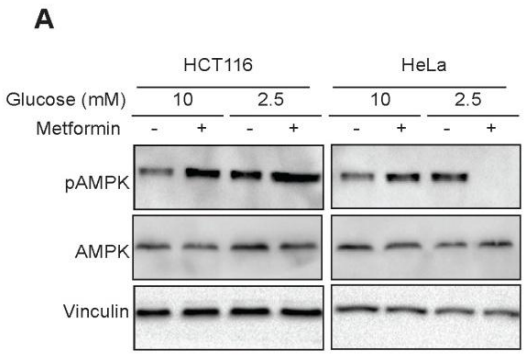
Results: Activation of GSK3β Mediates the Synergistic Cytotoxicity of Low Glucose/Metformin Combination

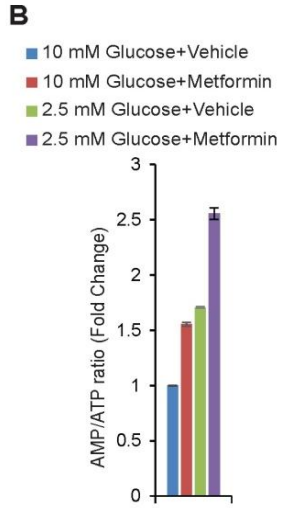
Fasting reduces the blood levels of glucose but it also results in a decrease in circulating growth factors and nutrients

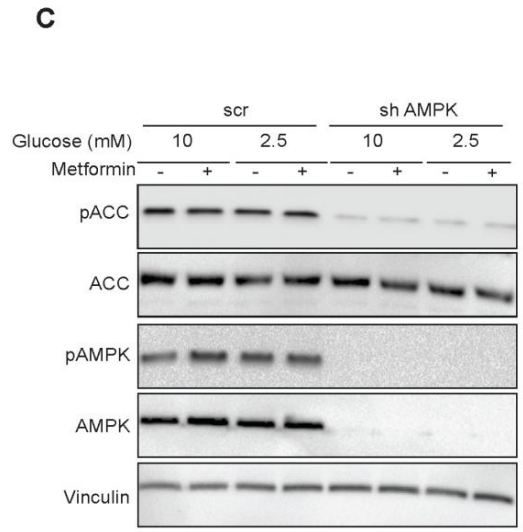


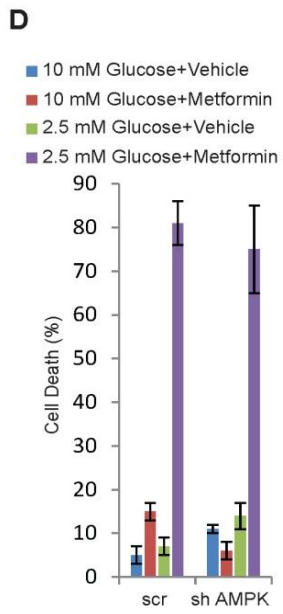
Results: Activation of GSK3β Mediates the Synergistic Cytotoxicity of Low Glucose/Metformin Combination

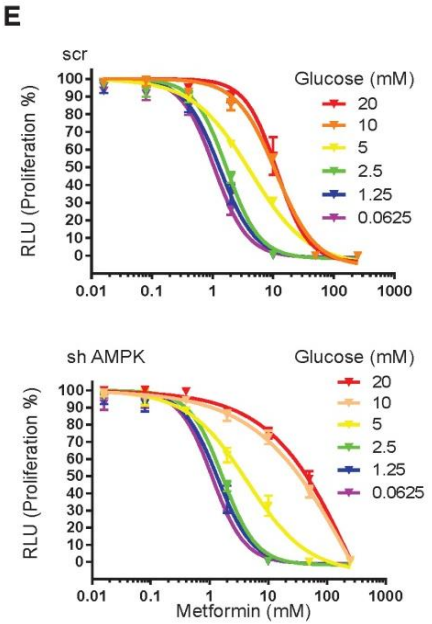
The activation of AMPK is the most widely accepted mechanism to explain the anti-cancer effects of metformin





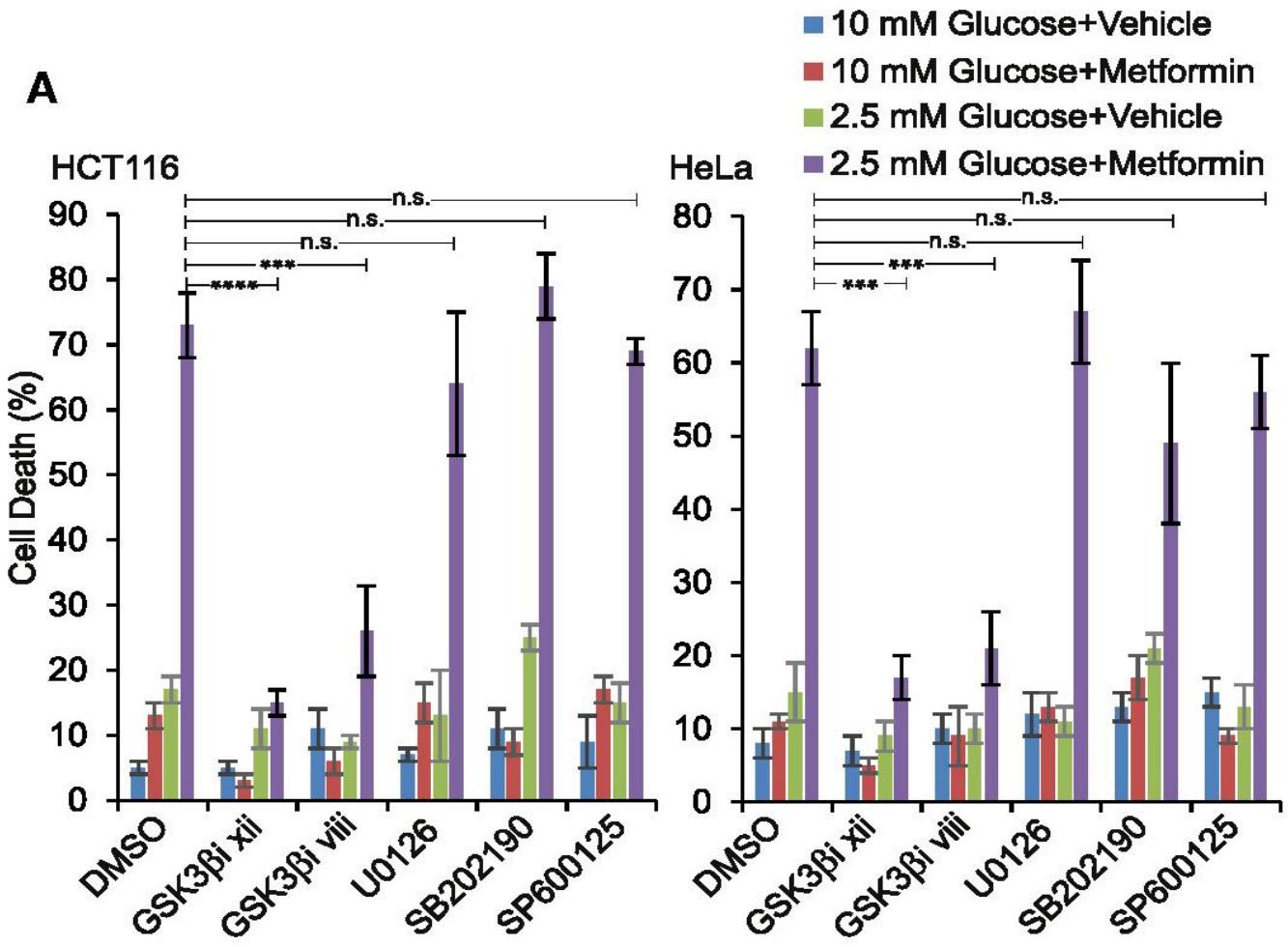






Suggesting that the observed synergistic cytotoxicity of the metformin/low glucose combination is AMPK independent.

Results: Activation of GSK3β Mediates the Synergistic Cytotoxicity of Low Glucose/Metformin Combination



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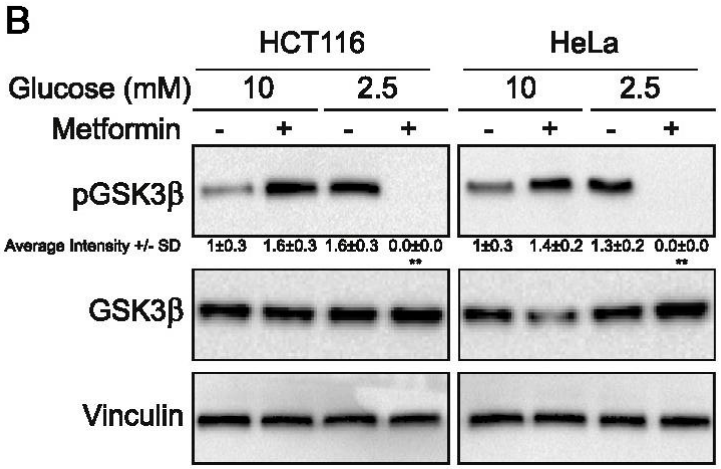
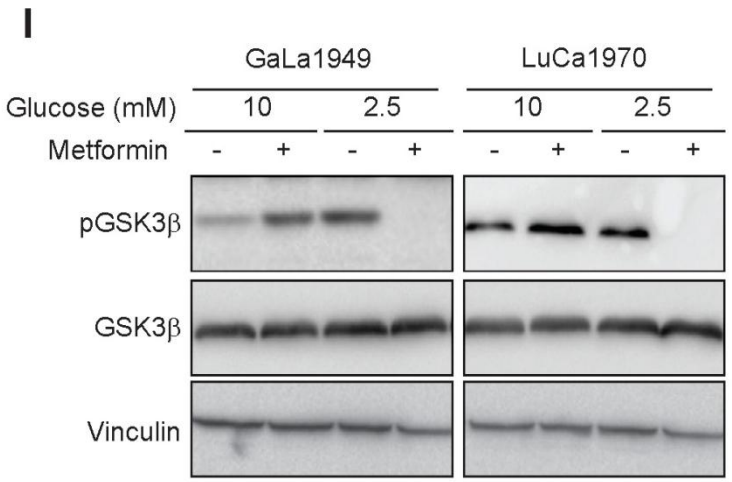
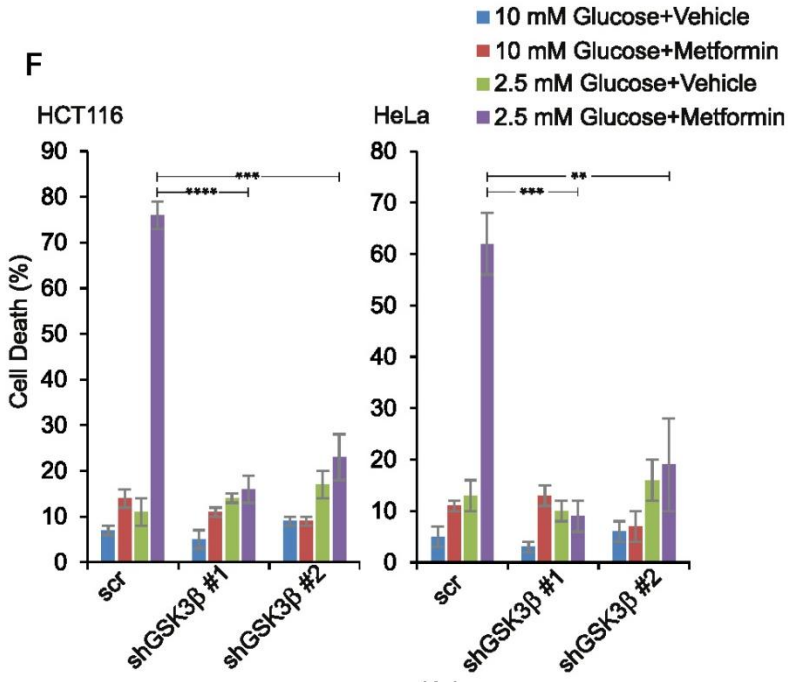
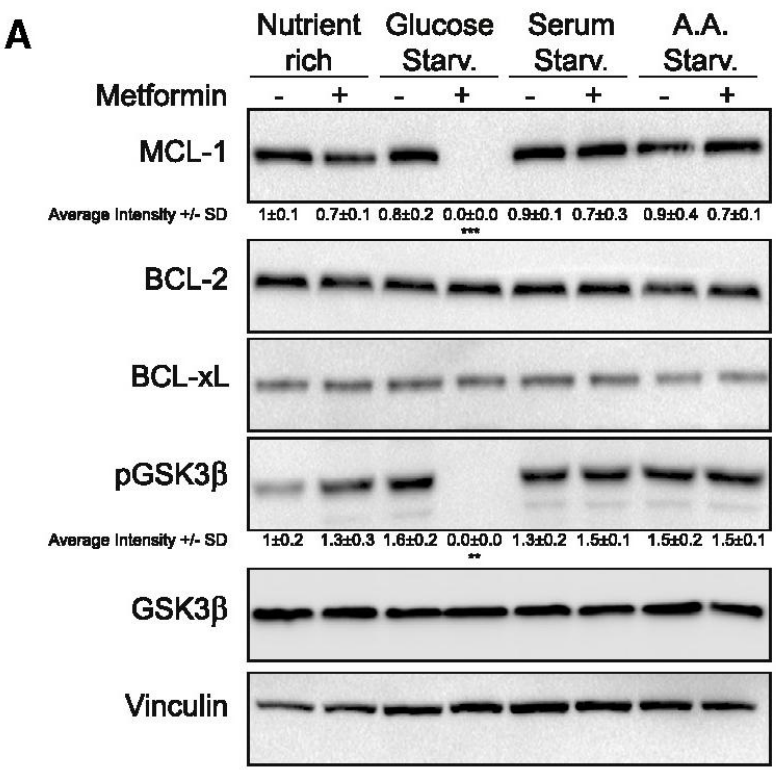


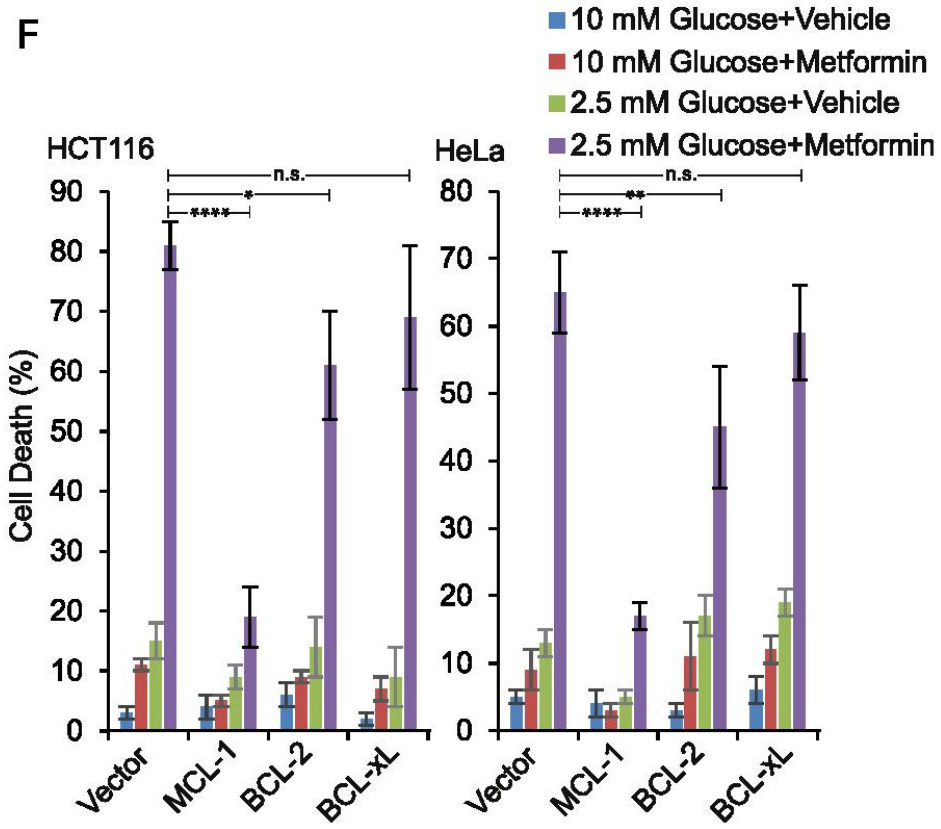




Results: A GSK3b-Dependent Decline in MCL-1 Levels Mediates the Synergistic Cytotoxicity of the Low Glucose/Metformin Combination

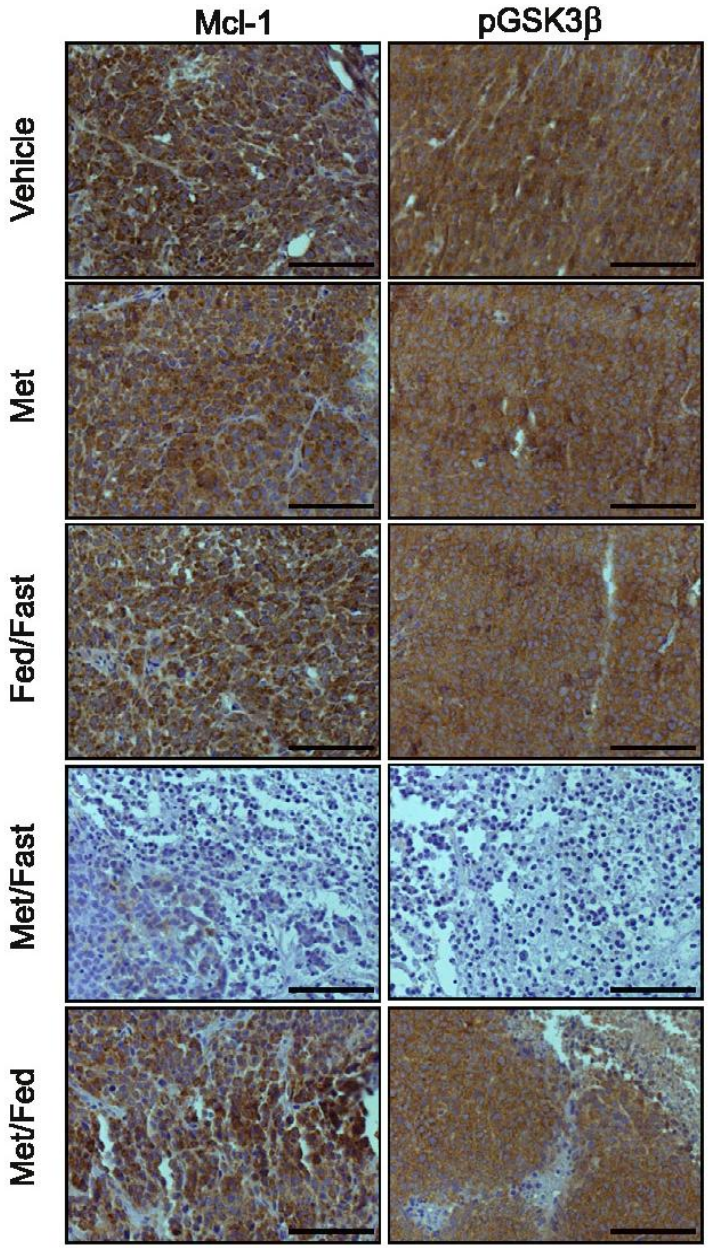
GSK3β activation enhanced proteasomal degradation of MCL-1, a pro-survival member of the BCL-2 family of proteins, and mediated cell death*.





*Maurer et al. (2006). Mol. Cell 21, 749–760.

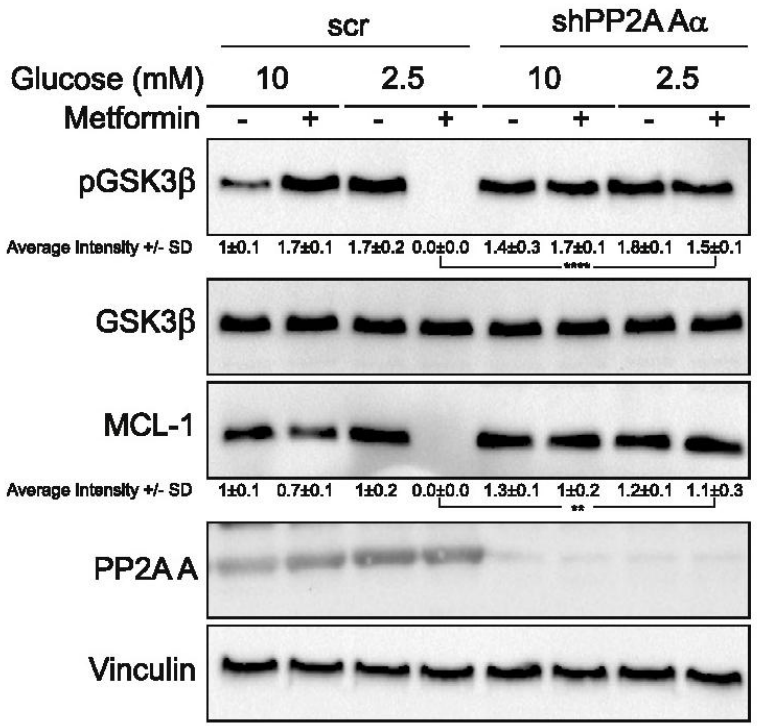
Results: A GSK3b-Dependent Decline in MCL-1 Levels Mediates the Synergistic Cytotoxicity of the Low Glucose/Metformin Combination

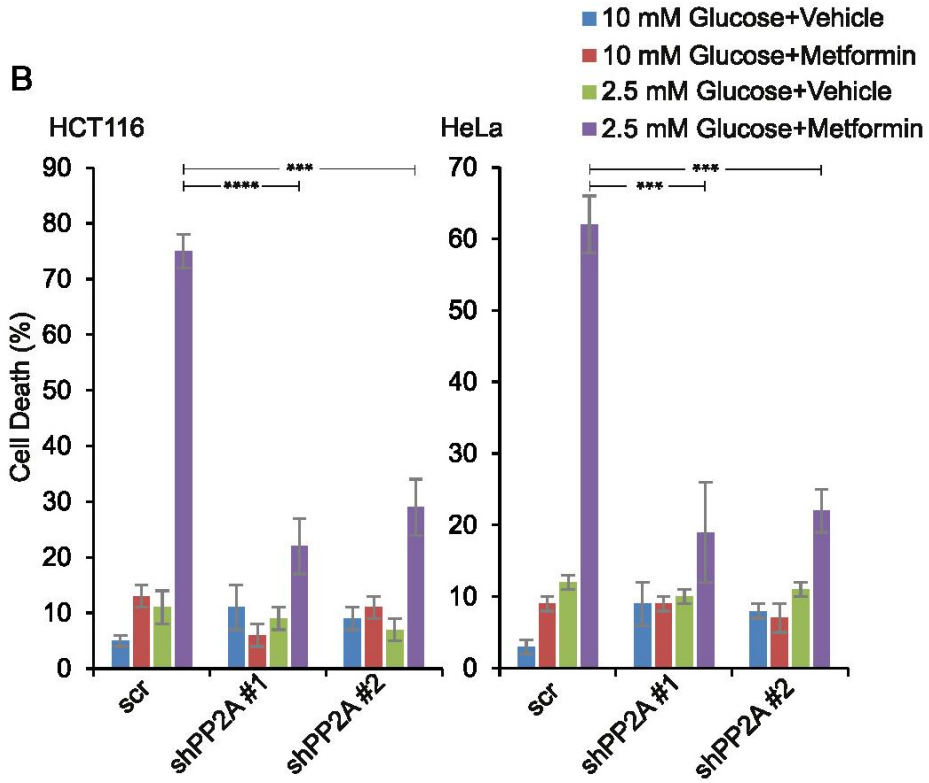


Results: PP2A Mediates the Synergistic Cytotoxicity of Low Glucose/Metformin Combination

Protein phosphatase 2A (PP2A) is a major serine-threonine phosphatase in mammalian cells that acts as a tumor suppressor.

PP2A has been shown to regulate GSK3β activity by removing phosphorylation *

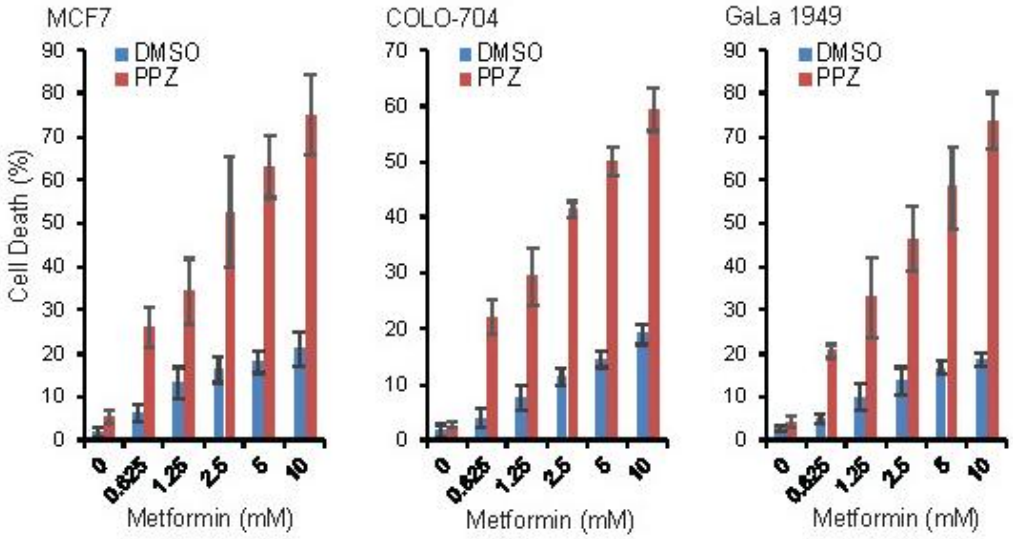


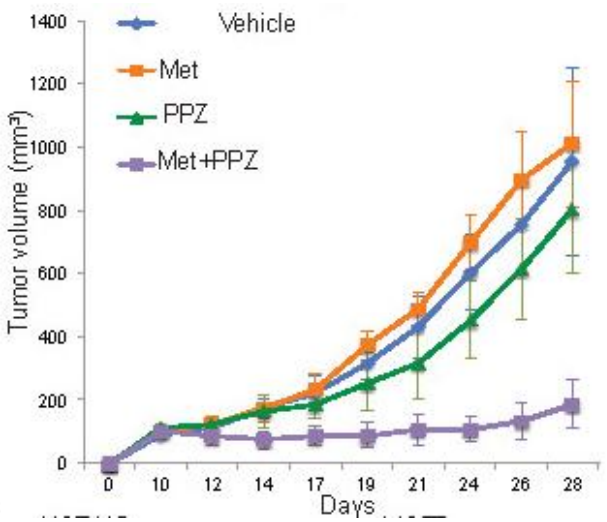


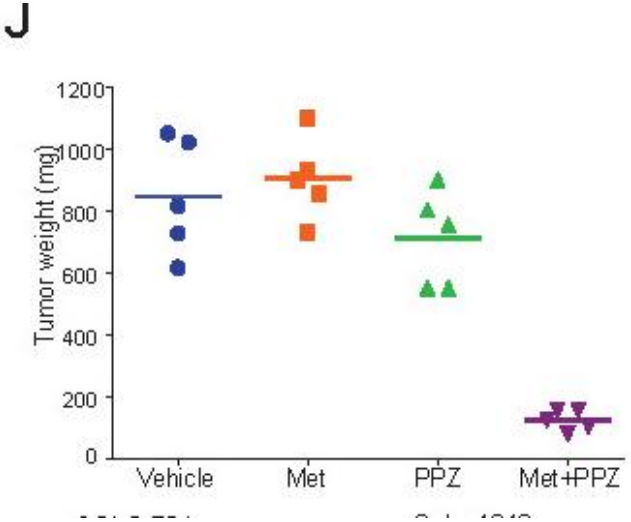
Mitra et al. (2012). Oncogene 31, 4472–4483.

Results: PP2A Mediates the Synergistic Cytotoxicity of Low Glucose/Metformin Combination

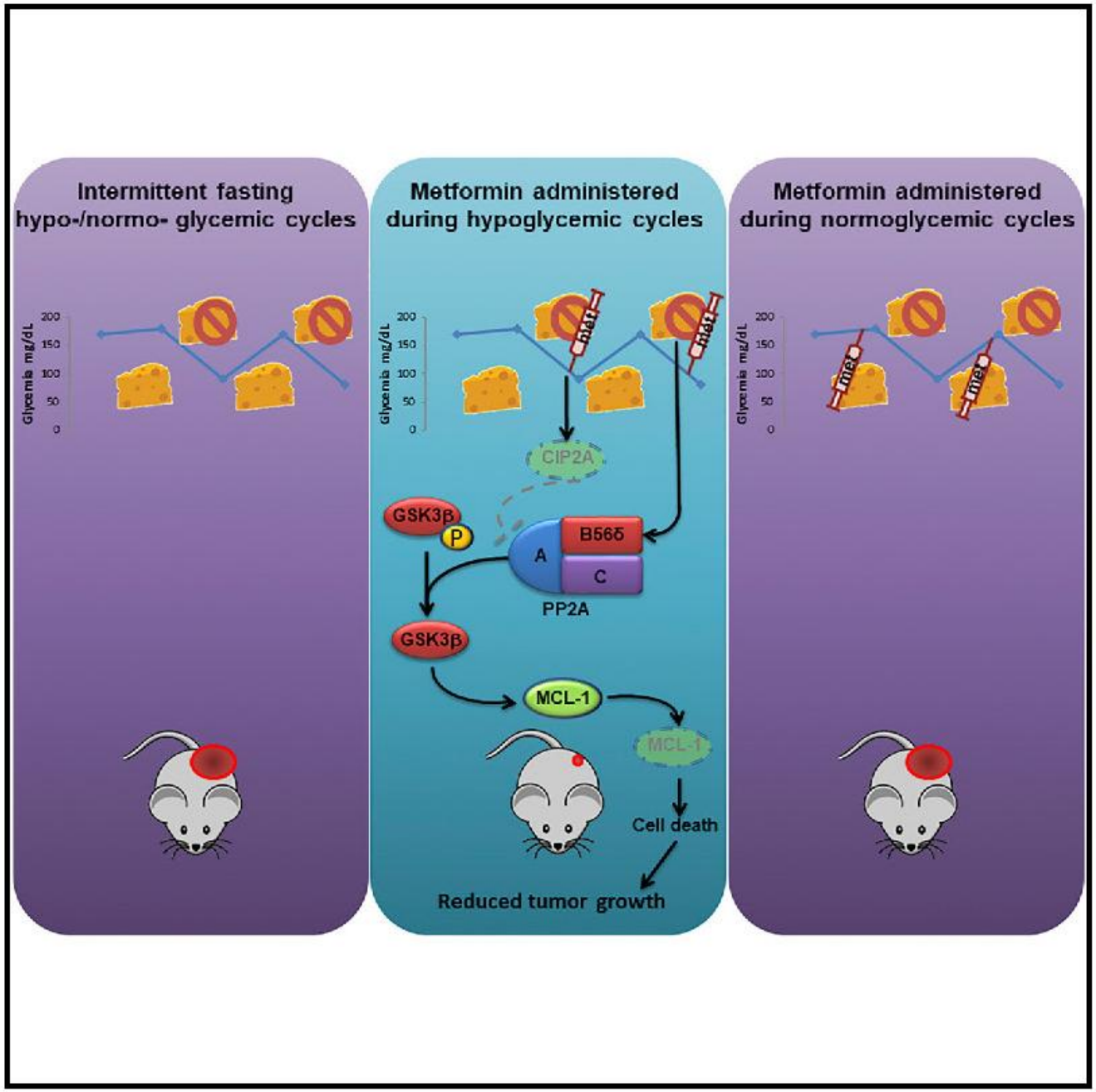
Anti-psychotic drug (perphenazine and Thioridazine) are PP2A activator.







Graphical Abstract




Thank you for
attention