Energy Sensing and Metabolism in Cancer

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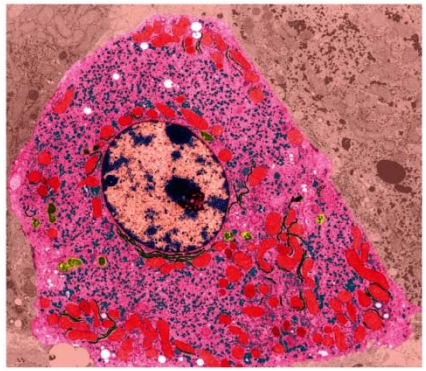
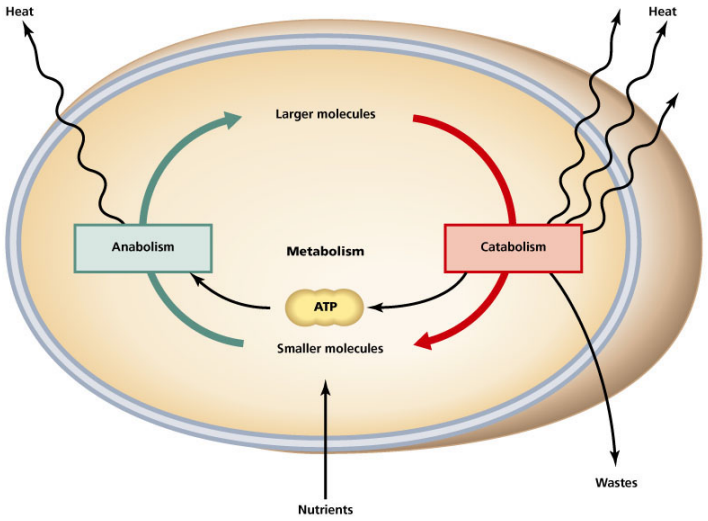
The distinguishing features of living organisms

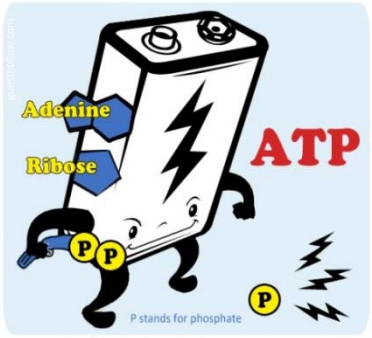


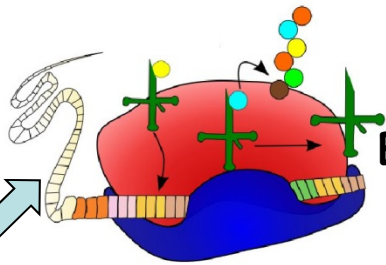
1. A high degree of chemical complexity and microscopic organization.
2. Systems for extracting, transforming, and using energy from the environment.
3. Defined functions for each of an organism's components and regulated interactions among them.
4. Mechanisms for sensing and responding to alterations in their surroundings.
5. A capacity for precise self-replication and self-assembly.

(Lehninger Principles of Biochemistry, 6th edition)



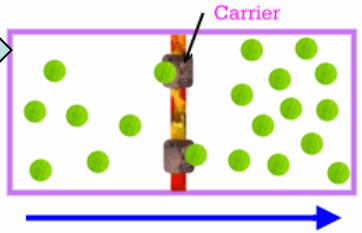
ATP: the "molecular unit of currency" of intracellular energy transfer



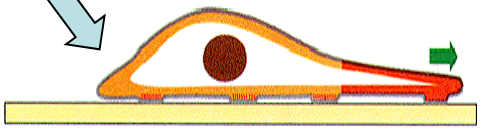


Biosynthesis

Muscle contraction

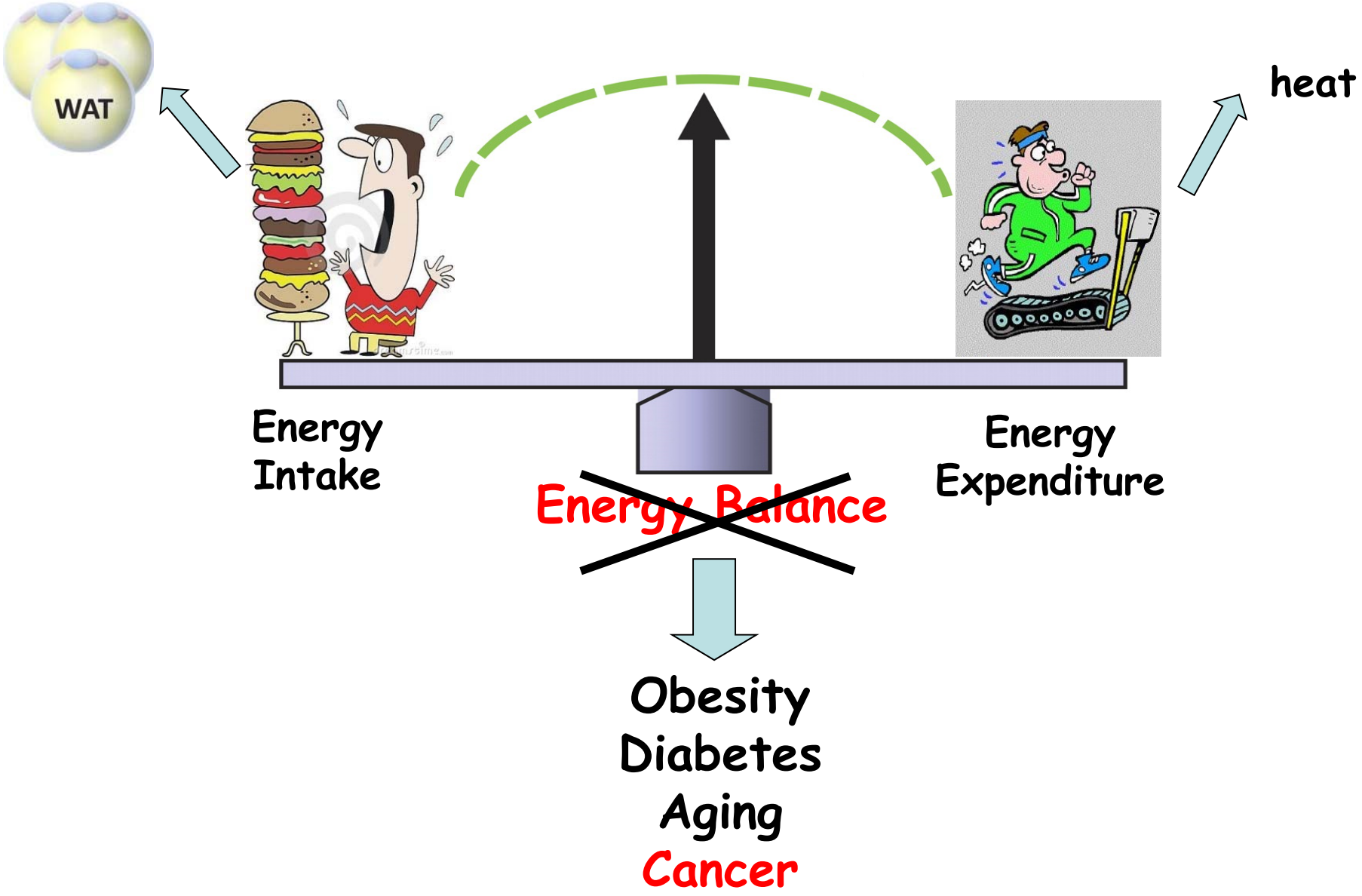


Membrane transport



Cellular movement

1. How cells sense and respond energy and nutrient availability?
2. How cancer cells adapt to survive and grow under metabolic stress?

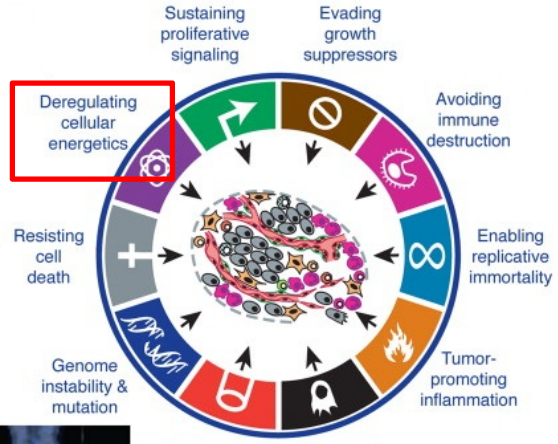

WAT
heat
Energy
Intake
Energy
Expenditure
Energy Balance
Obesity
Diabetes
Aging
Cancer

Energy Metabolism and Cancer Development

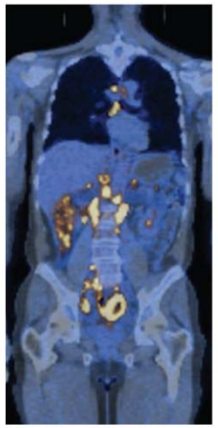
- **Obesity** is the second greatest risk factor for cancer development in USA (only after tobacco use).

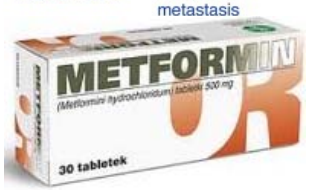
cause	cancers caused (percent of total)	number of deaths in US (annual)	magnitude of reduction possible (percent)
smoking	33	189,000	75
diet, overweight, and obesity	25	143,000	50
lack of exercise	5	28,600	85
viruses	5	28,600	100
alcohol	3	17,200	50
UV and ionizing radiation	2	11,400	50
occupational carcinogens	5	28,600	50

- **Deregulated energy metabolism** is an emerging hallmark of cancer.



- Our understanding of energy metabolism in cancer has been translated into cancer detection (**FDG-PET**) and treatment (**metformin**, the widely used drug to treat diabetes, is associated with decreased tumor incidence and mortality.





(Molecular Biology of the Cell, 6th edition; Hallmarks of cancer: the next generation. Hanahan, Weinberg, Cell, 2011; The biology of cancer, 2nd edition, Weinberg, 2014)

Research Topic:

Energy Sensing and Metabolism

Cancer

Research Questions:

1.How normal/cancer cells sense energy availability?

2.How cancer cells adapt to survive and grow under energy stress?

3.How to translate our understanding of energy metabolism in cancer into novel cancer therapeutics?

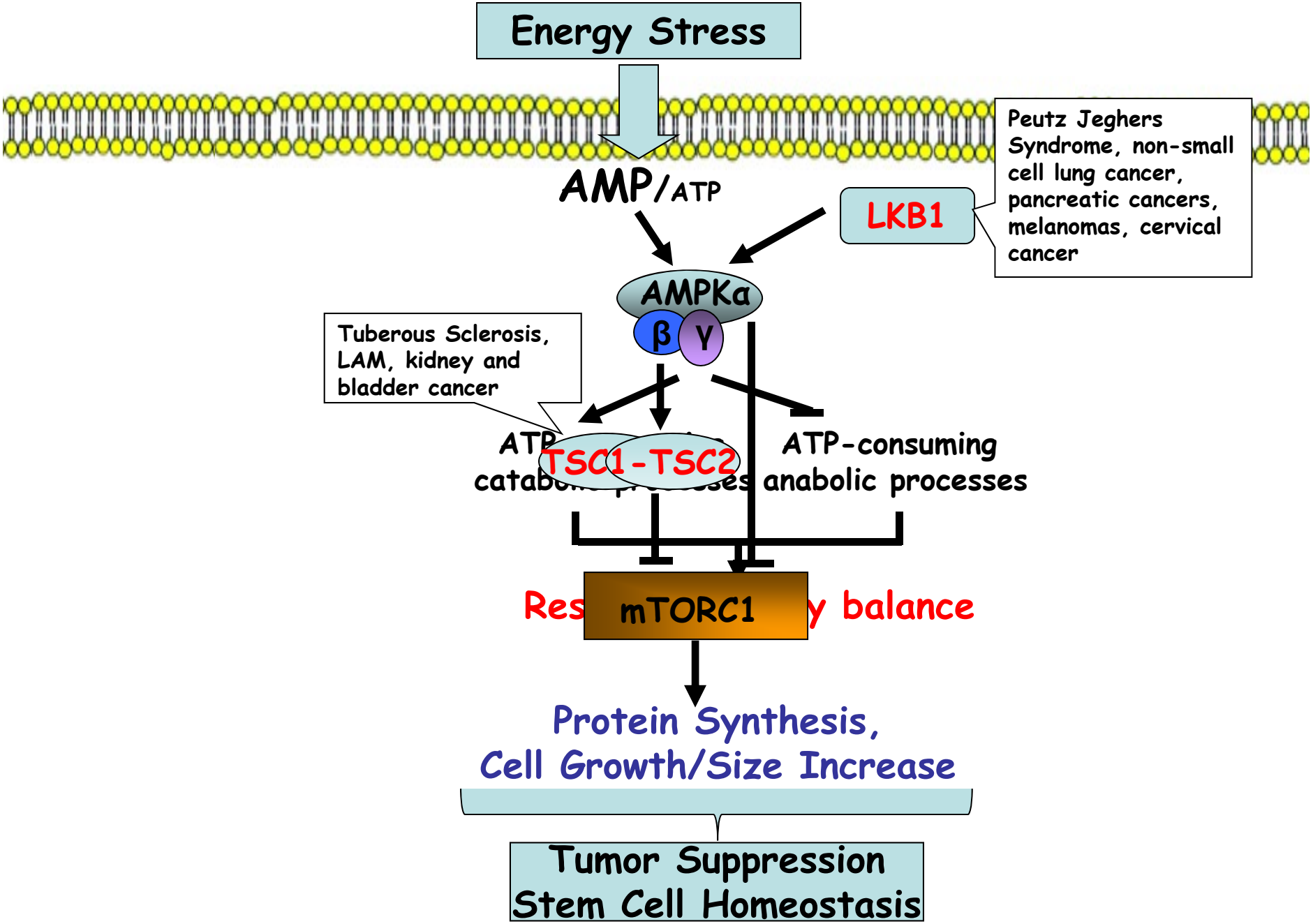
Presentation Outline:

→Regulation of energy sensor AMPK by lncRNA NBR2.

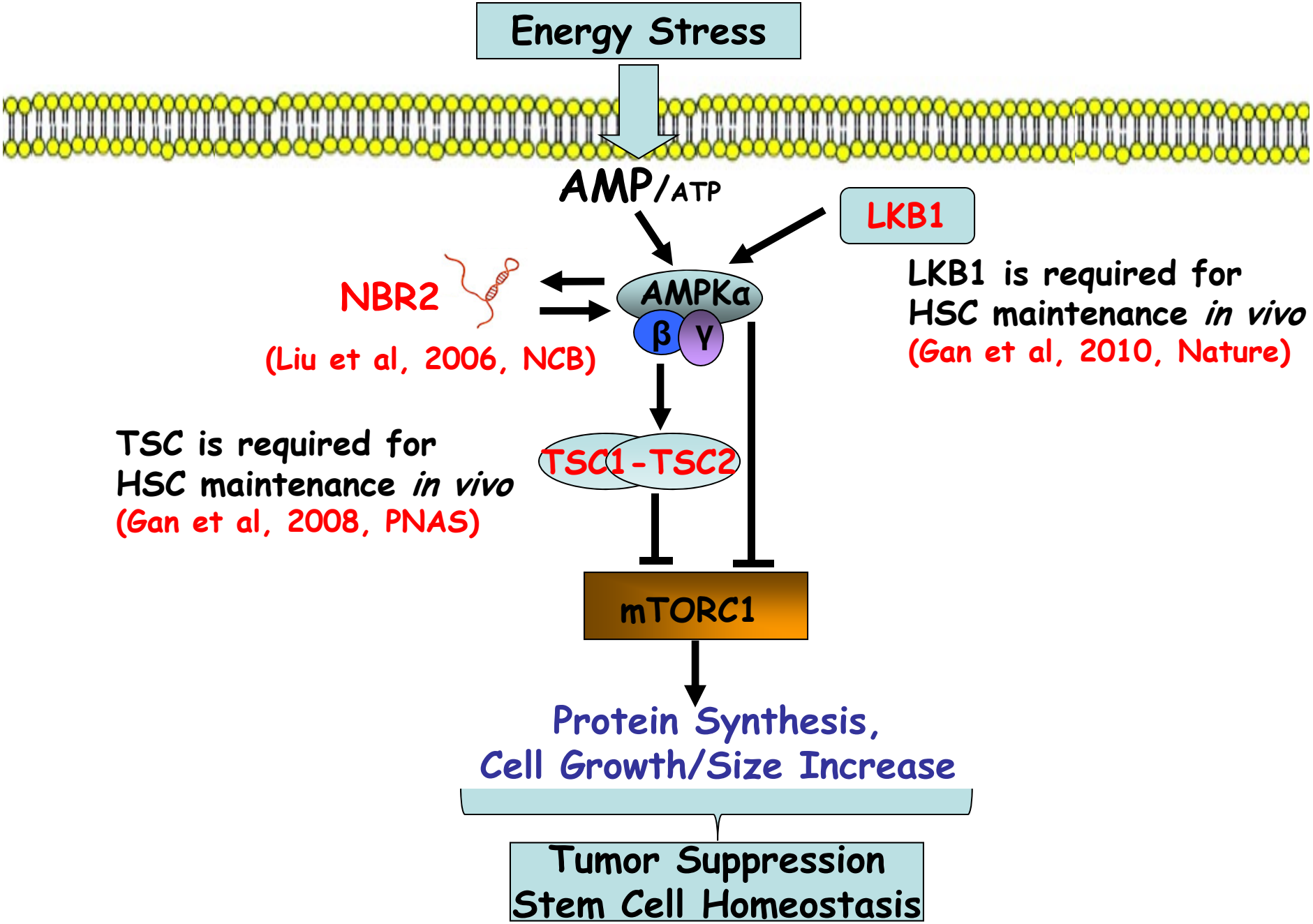
→Energy stress-induced lncRNA FLINC1 regulates energy metabolism and tumor suppression.

→Glutamate/cystine antiporter SLC7A11 regulates glucose dependency in cancer cells.

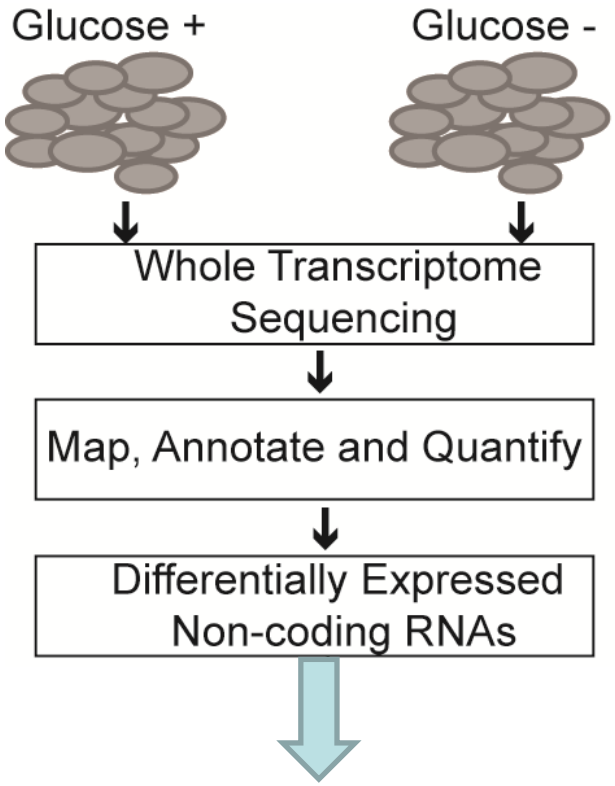
AMPK-mediated Energy Sensing Signaling



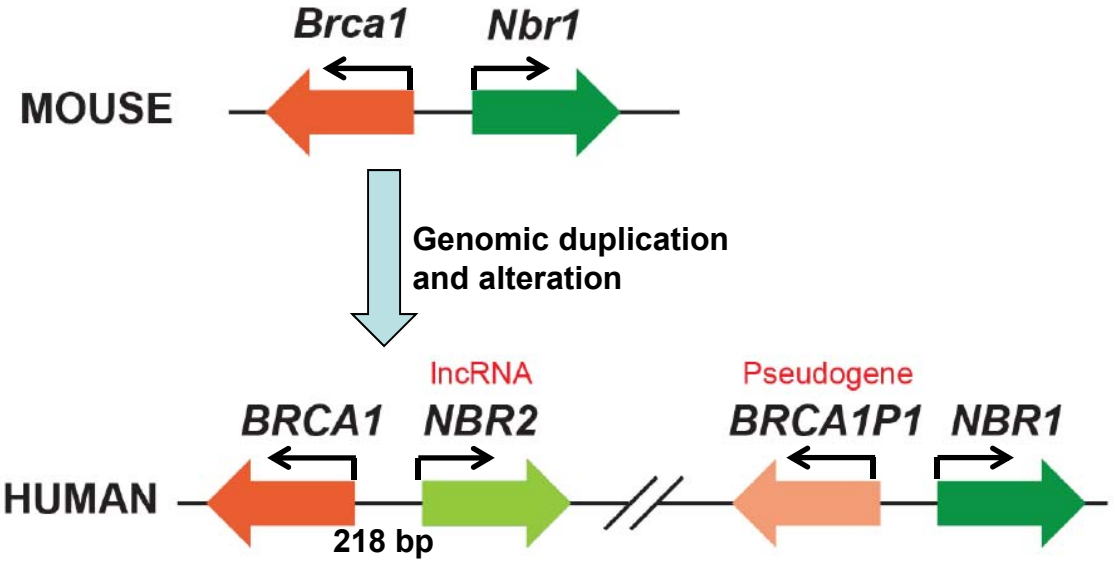
AMPK-mediated Energy Sensing Signaling



Glucose starvation induces lncRNA NBR2 expression



NBR2 (neighbor of BRCA1 gene 2) for further study



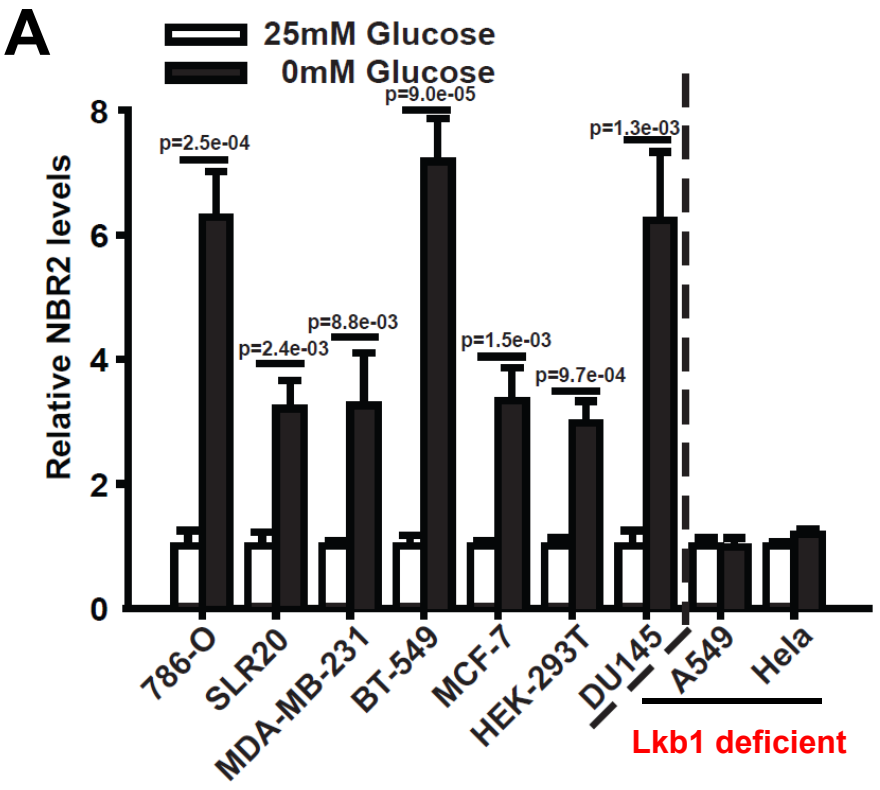
BRCA1: protein-coding gene, regulate DNA damage response and genome integrity

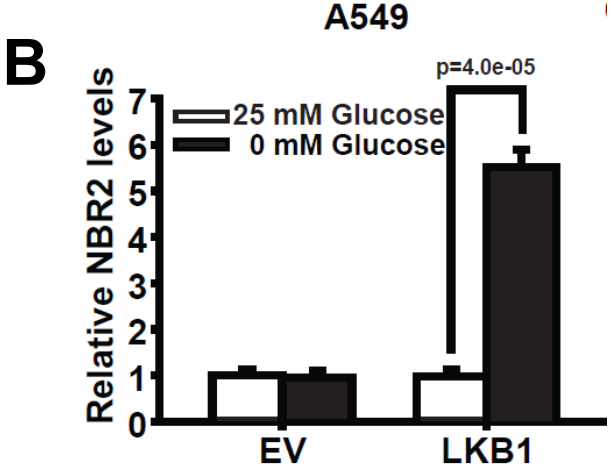
NBR2: long non-coding RNA, non-coding gene

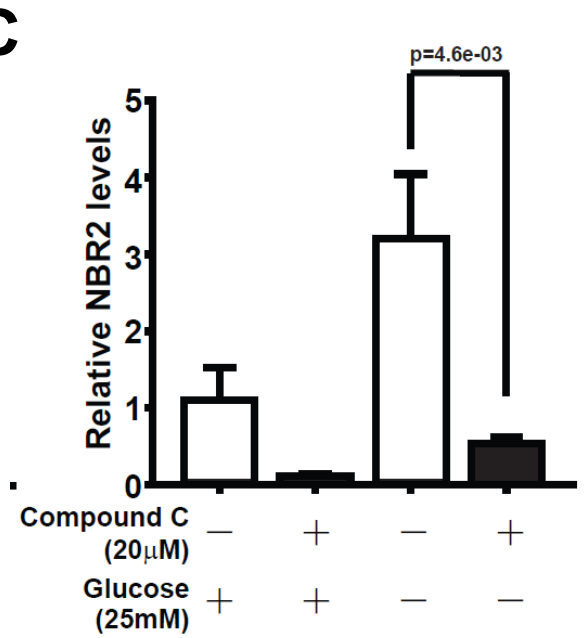
BRCA1P1: BRCA1 pseudogene, non-coding gene

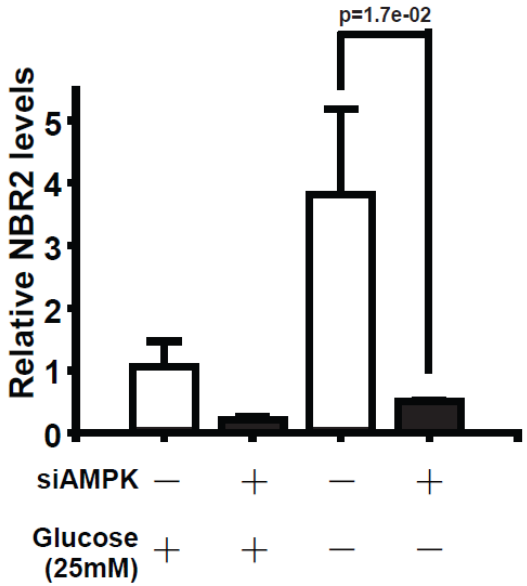
NBR1: protein-coding gene, function as autophagy receptor

LKB1-AMPK-dependent induction of NBR2 by energy stress

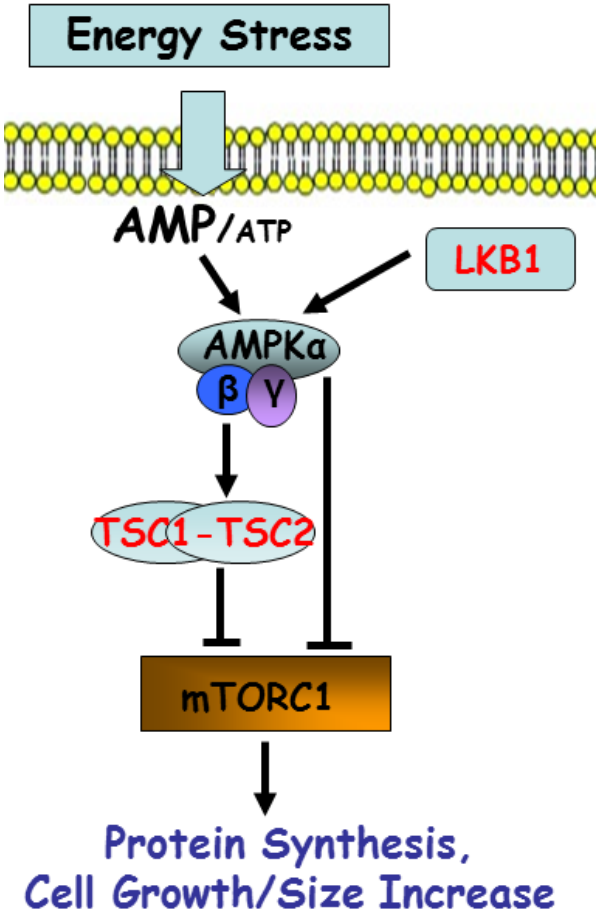


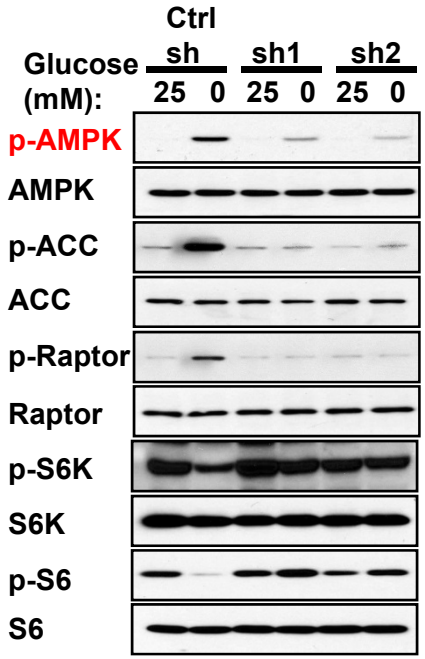






NBR2 depletion attenuates energy stress-induced AMPK activation and mTORC1 inactivation

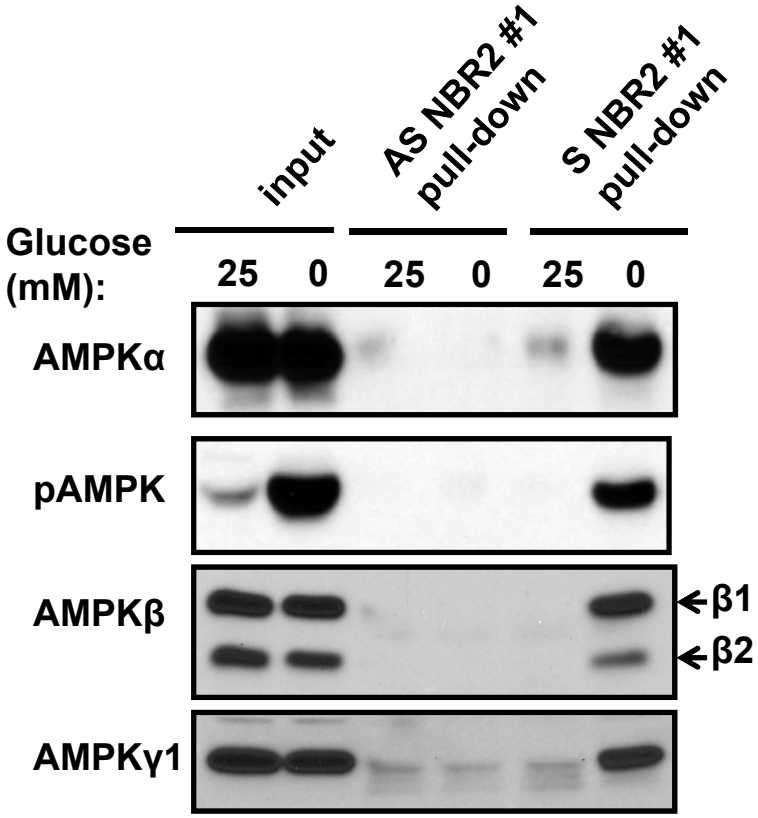




→NBR2 regulates cell proliferation, apoptosis, and autophagy downstream of AMPK under energy stress.

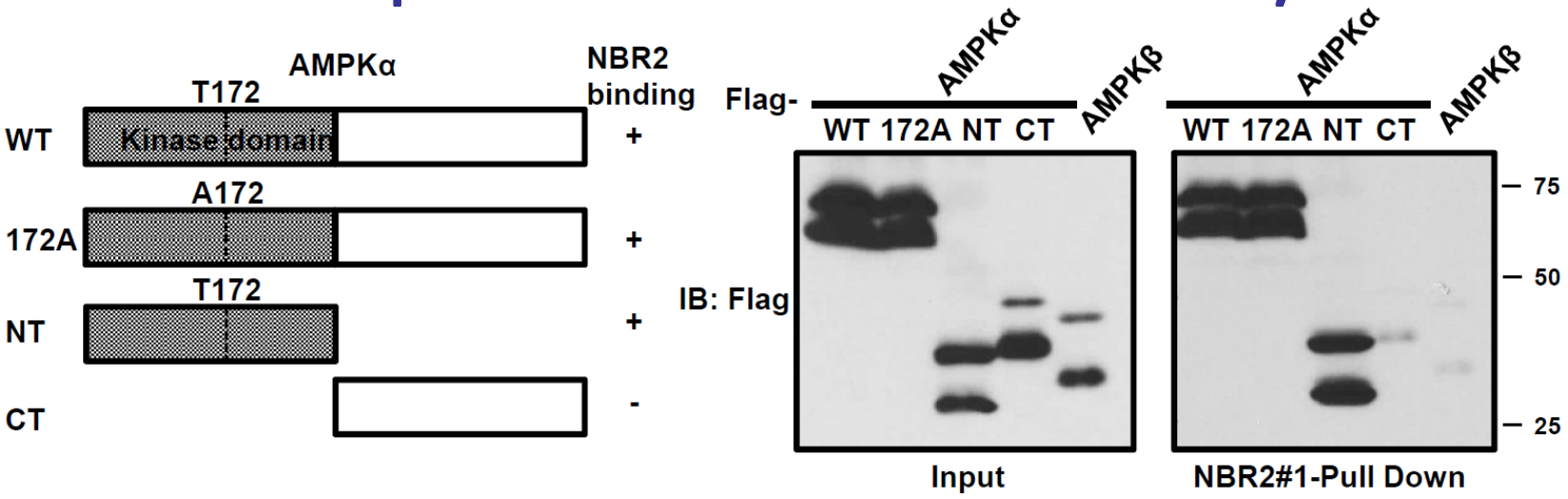
→Overexpression of NBR2 activates AMPK

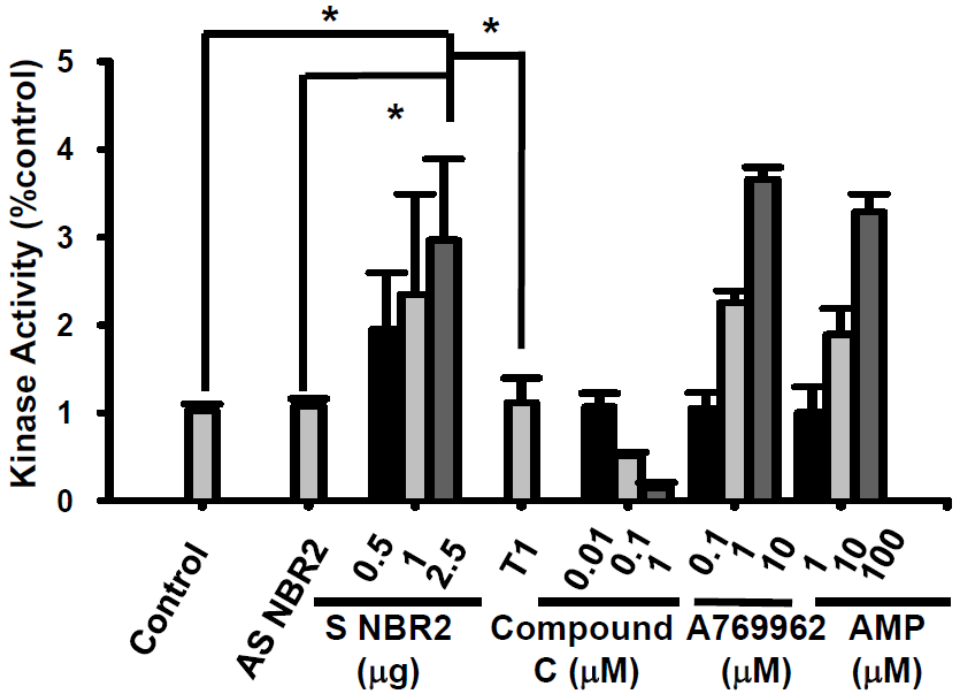
NBR2 interacts with AMPKα



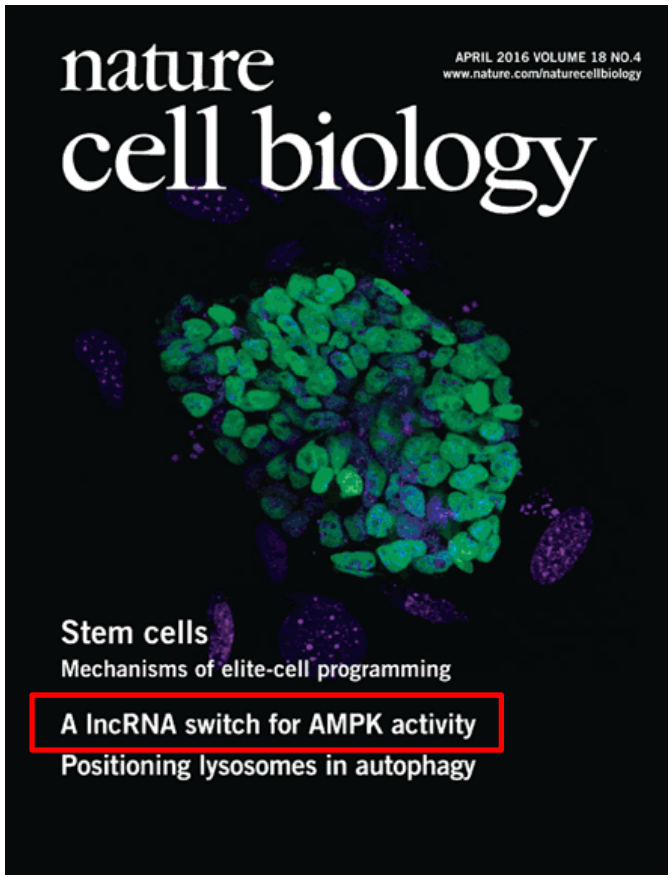
(Using biotinylated RNA, precipitated with streptavidin beads)

NBR2 promotes AMPK kinase activity

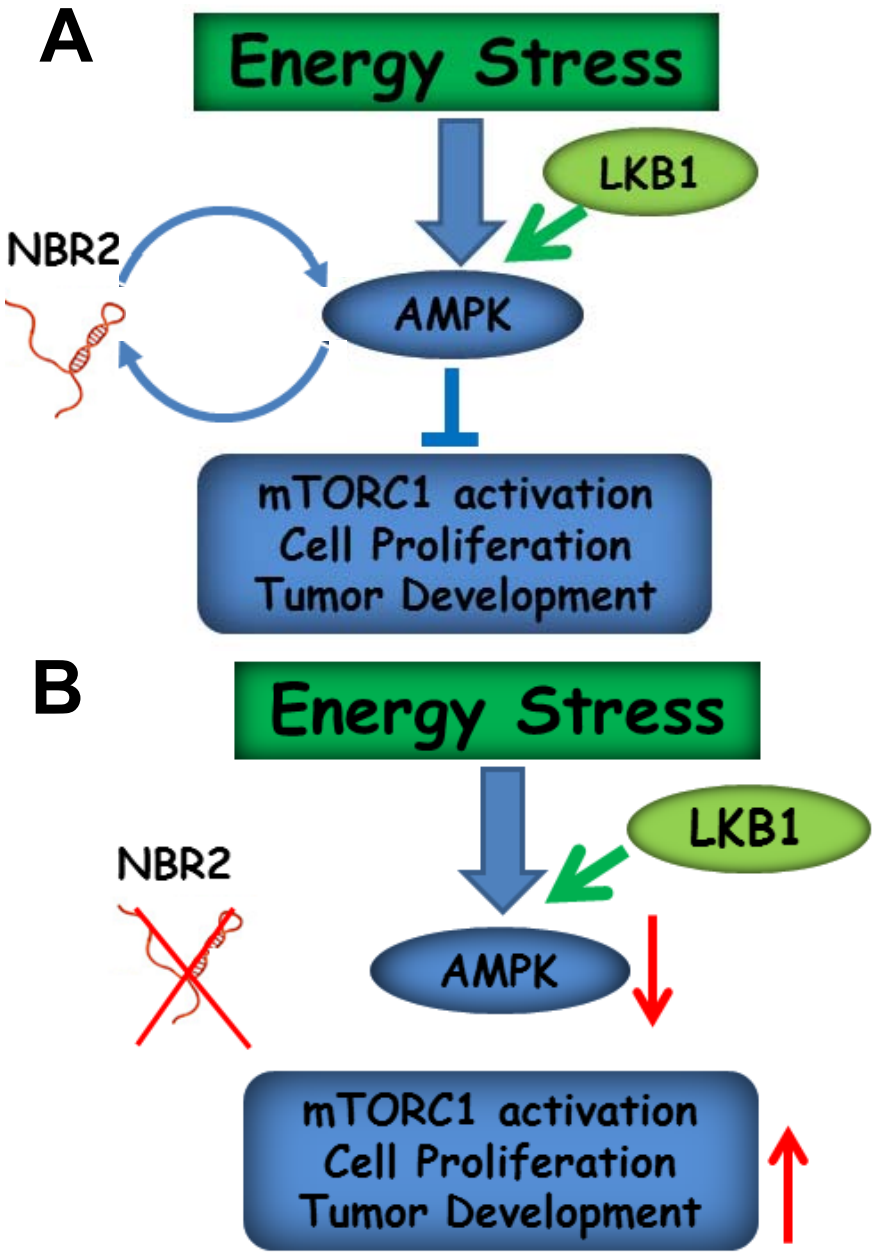




NBR2: A lncRNA switch for AMPK activation



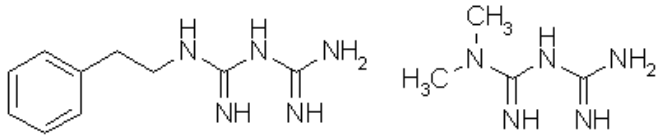
(Liu X, et al, Gan B, *Nature Cell Biology*, 2016)



Biguanides (Metformin/Phenformin) as anti-cancer drugs

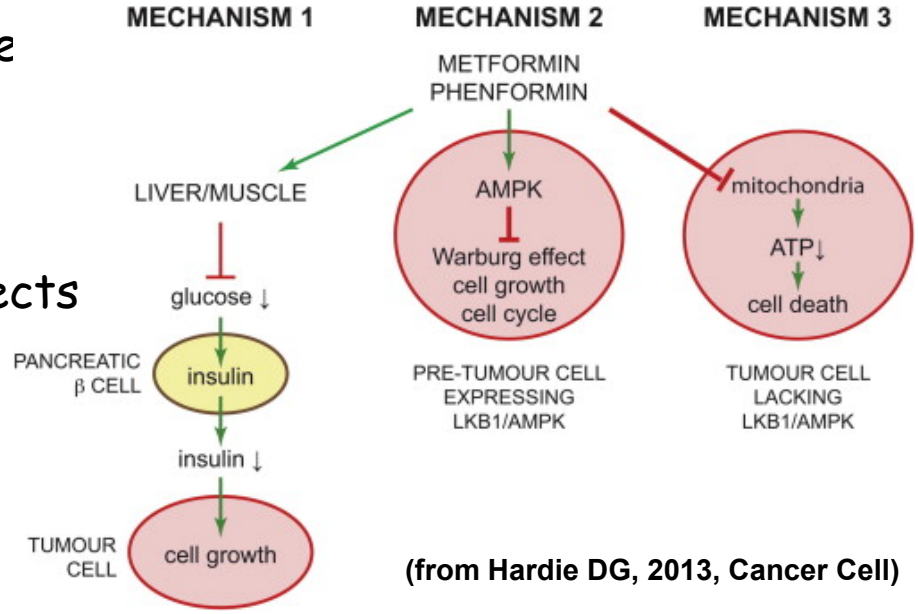
- **Metformin** was originally developed from natural compounds found in the plant known as French lilac.

- **Biguanides (Metformin/Phenformin)** are inhibitors of mitochondrial respiratory chain complex I, and can decrease blood glucose levels. Metformin is most widely used drug to treat diabetes.



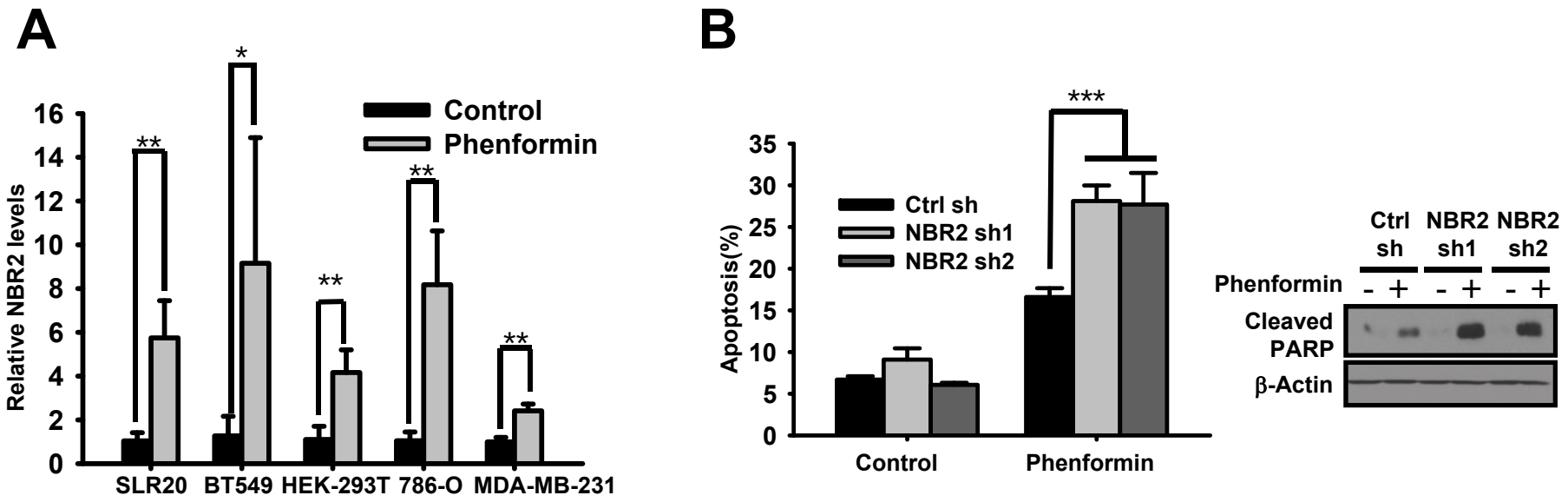
- Retrospective analyses, clinical trials and many functional studies support the beneficial effect of biguanides in cance prevention and treatment.

- At least three mechanisms have been proposed to explain the antitumor effects of biguanides.

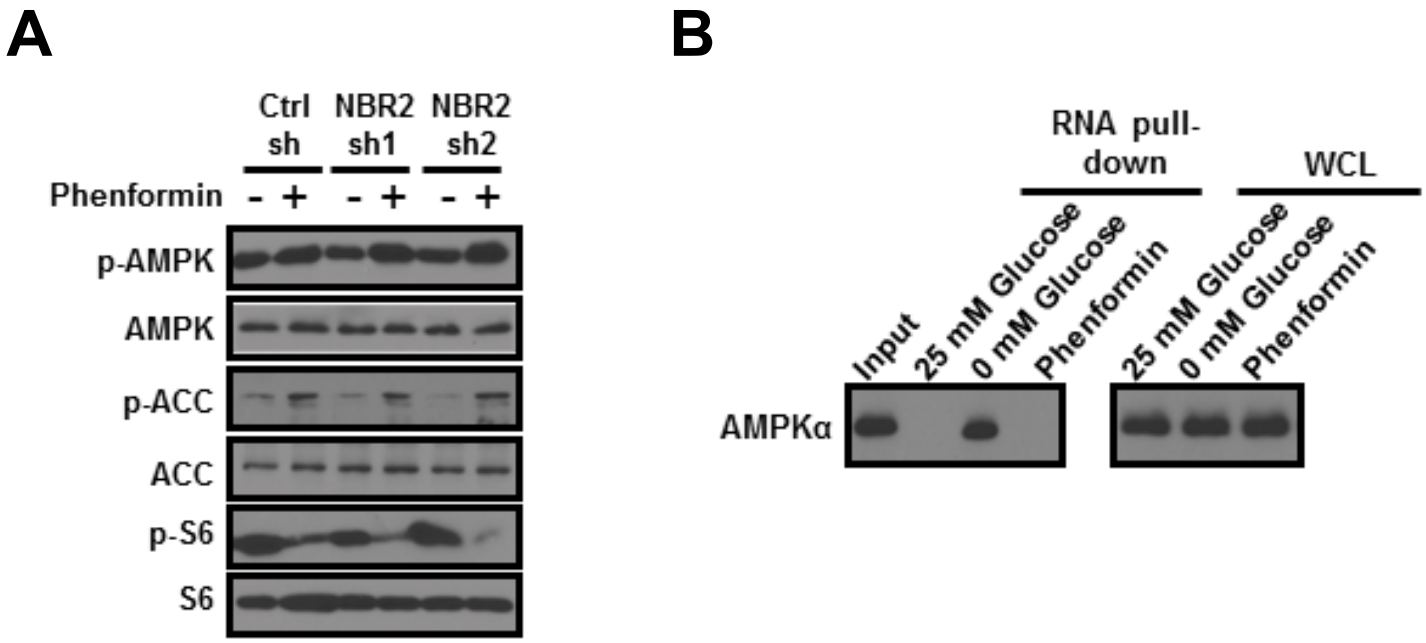


(from Hardie DG, 2013, Cancer Cell)

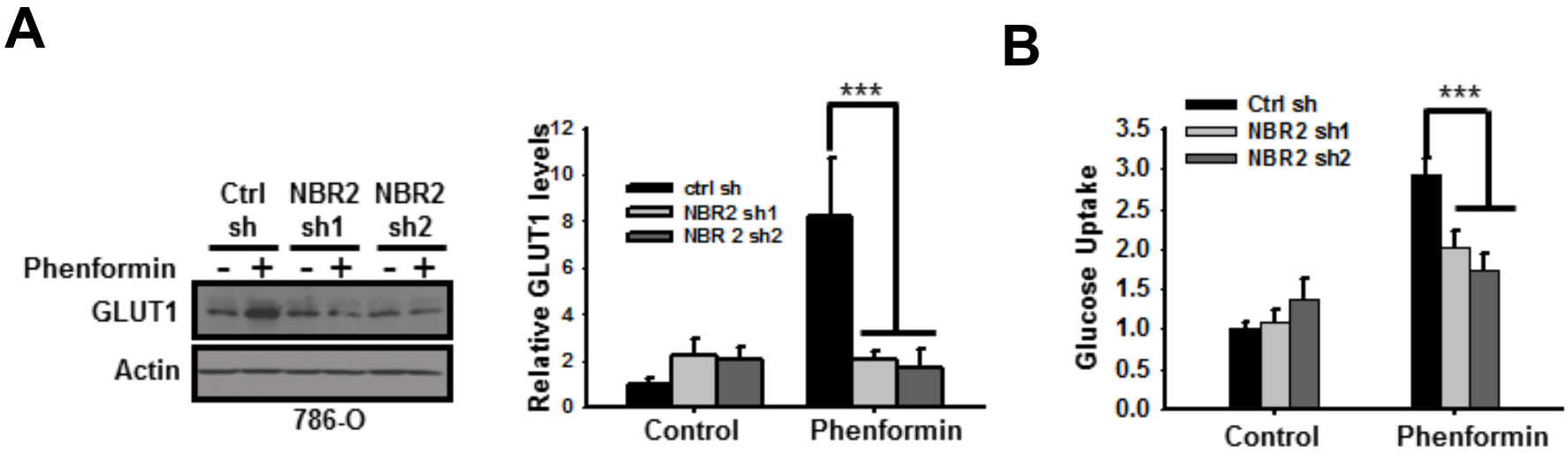
Biguanides induce NBR2 expression and NBR2 regulates cancer cell sensitivity to biguanides



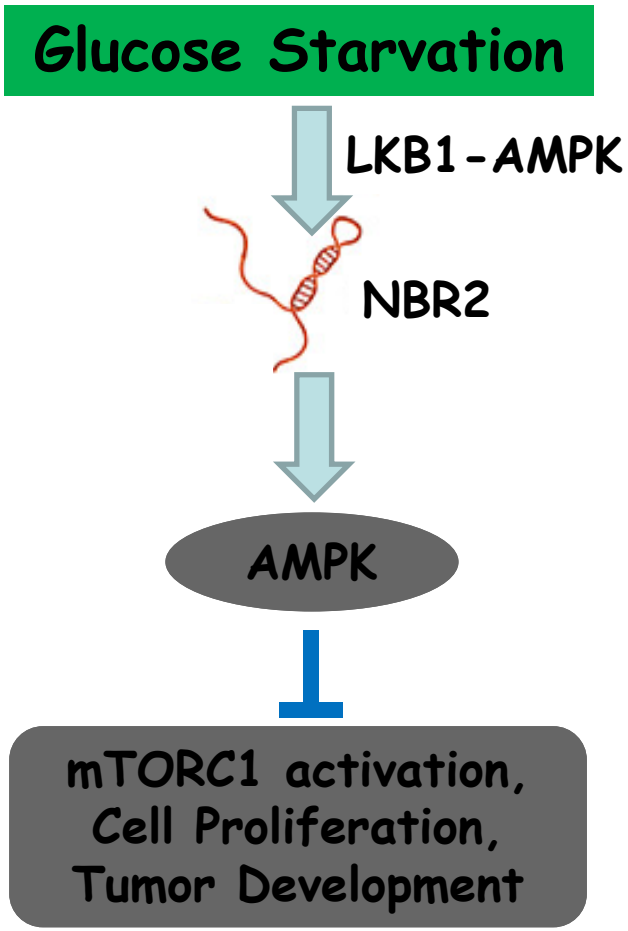
NBR2 does not regulate biguanide-induced AMPK activation



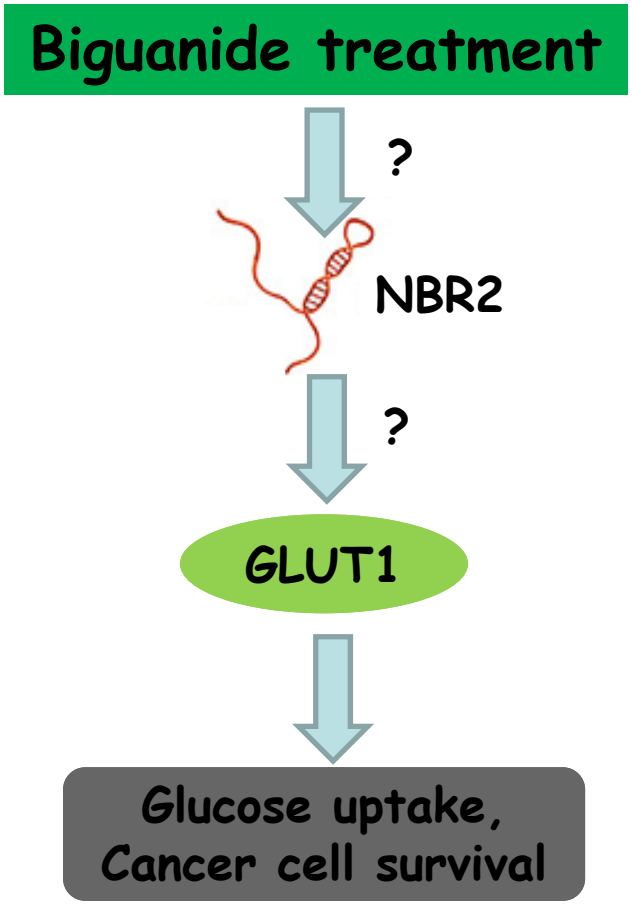
NBR2 regulates biguanide-induced GLUT1 expression and glucose uptake



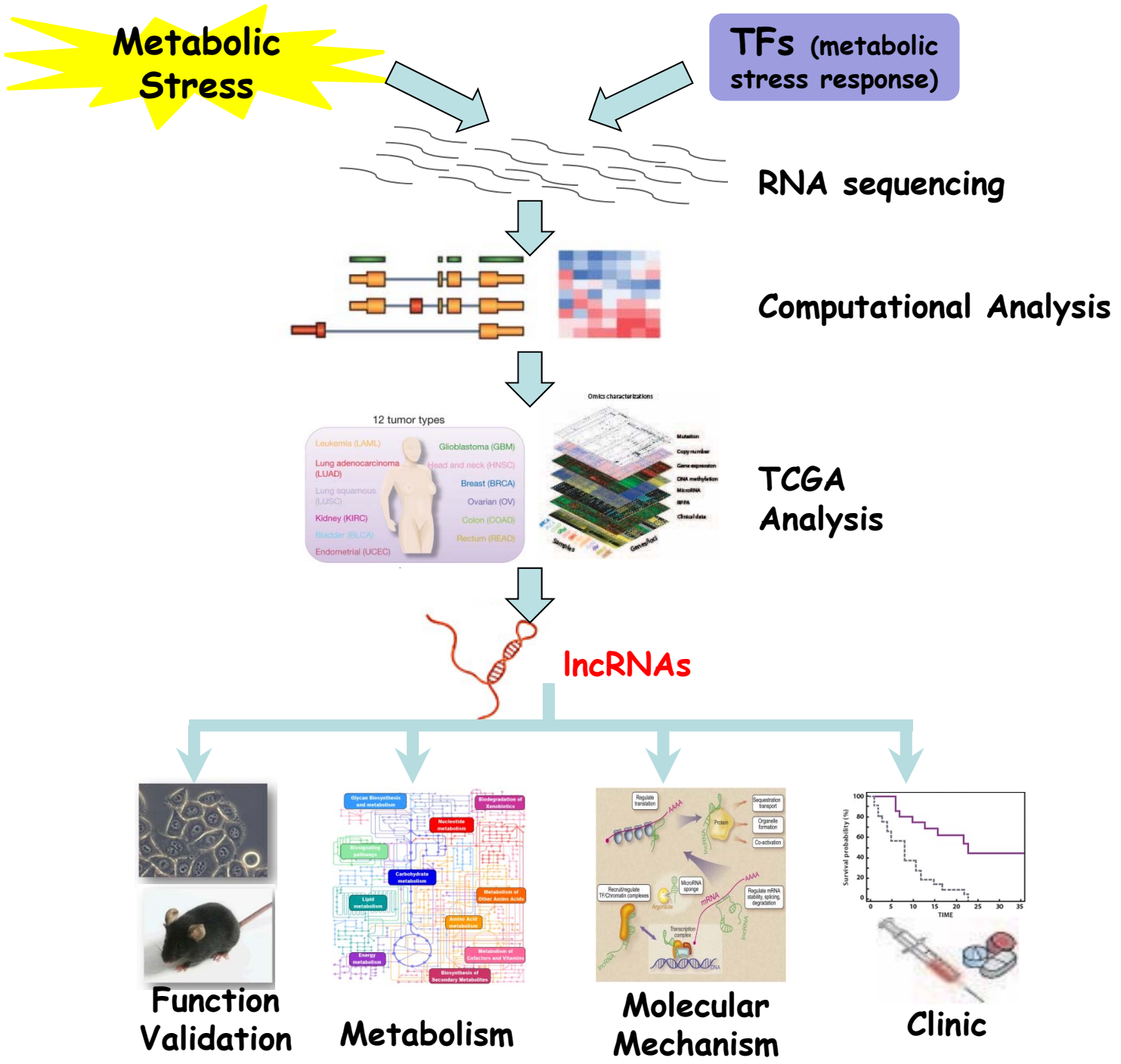
Differential effects of NBR2 under glucose starvation and biguanide treatment



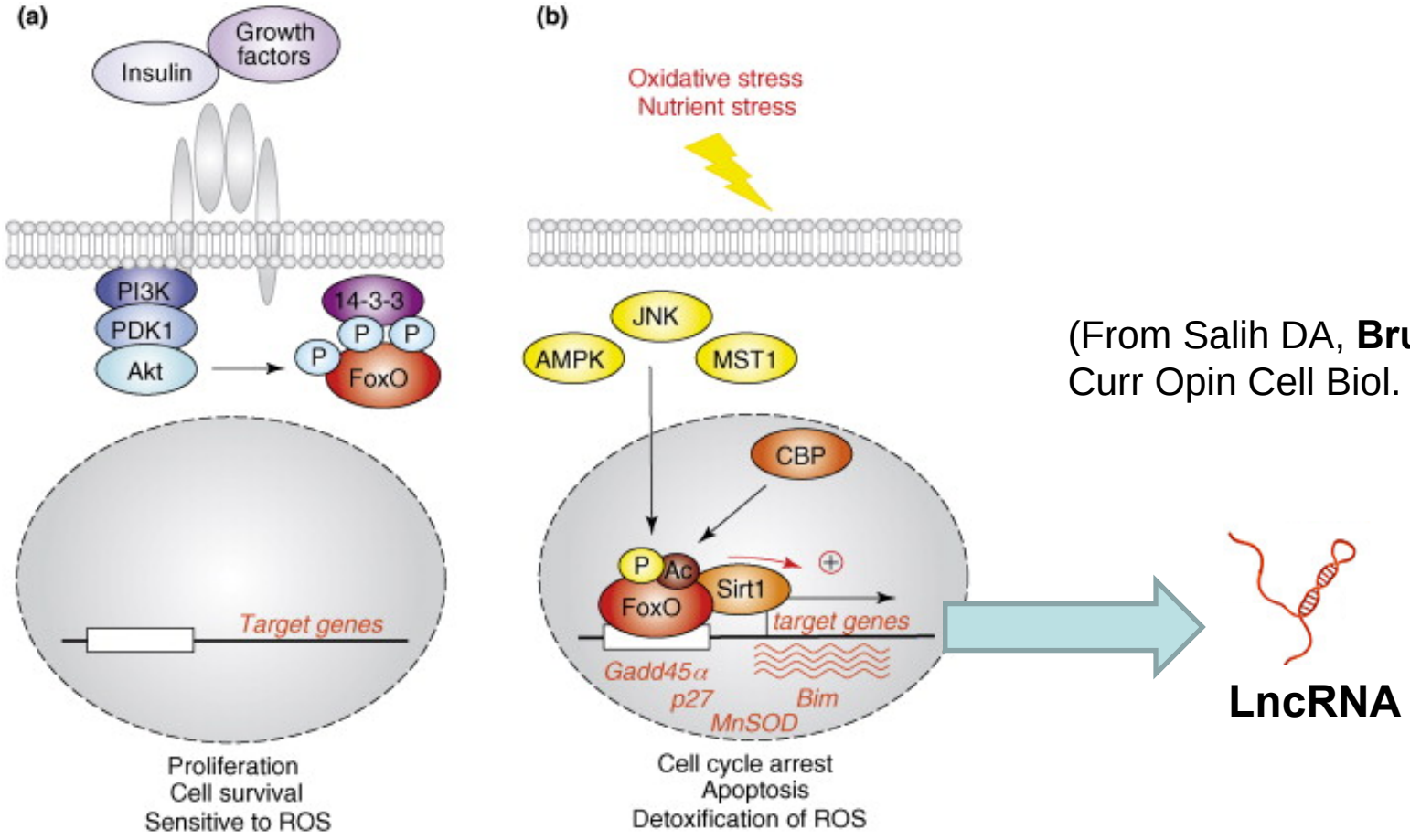
(Liu X, et al, Gan B, *Nature Cell Biology*, 2016)



(Liu X, Gan B, *Cell Cycle*, 2016)


Metabolic Stress
TFs (metabolic stress response)
RNA sequencing
Computational Analysis
12 tumor types
Leukemia (LAML)
Lung adenocarcinoma (LUAD)
Lung squamous (LUSC)
Kidney (KIRC)
Bladder (BLCA)
Endometrial (UCEC)
Glioblastoma (GBM)
Head and neck (HNSC)
Breast (BRCA)
Ovarian (OV)
Colon (COAD)
Rectum (READ)
Omics characterizations
TCGA Analysis
lncRNAs
Function Validation
Metabolism
Molecular Mechanism
Clinic

FoxO transcription factors: at the crossroad of cancer and metabolism



(From Salih DA, **Brunet A**, Curr Opin Cell Biol. 2008)

Our previous studies showed FoxOs play critical roles in mediating energy stress response, drug resistance, and tumor suppression in renal cancer (**Gan B**, et al, ***Cancer Cell***, 2010; Lin A, et al, **Gan B**, ***Oncogene***, 2013; Lin, et al, **Gan B**, ***Cancer Research***, 2014; Dai F, et al, **Gan B**, ***PNAS***, 2017).

Identification of FoxO-induced lincRNAs

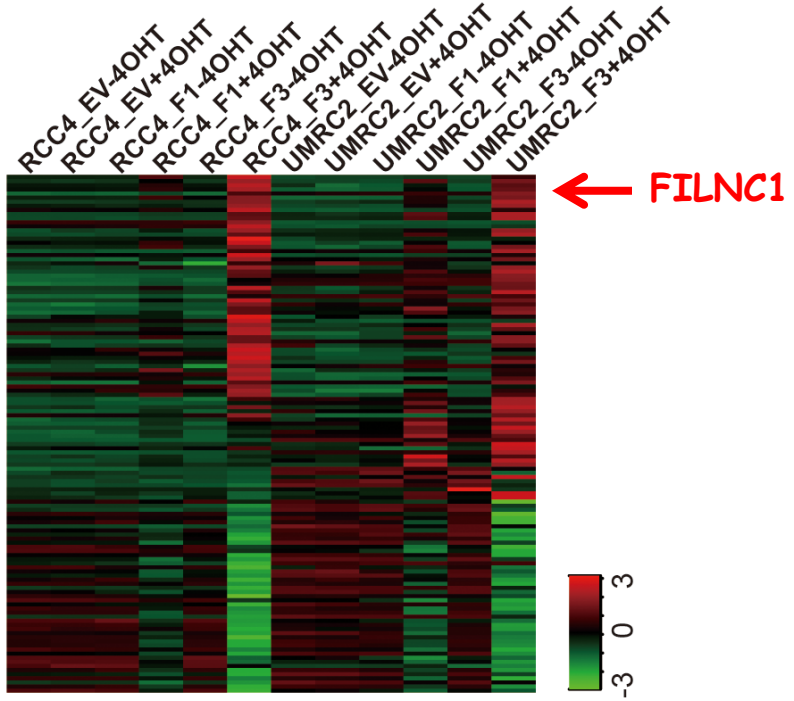
FoxO(TA)ERT2
RCC cells

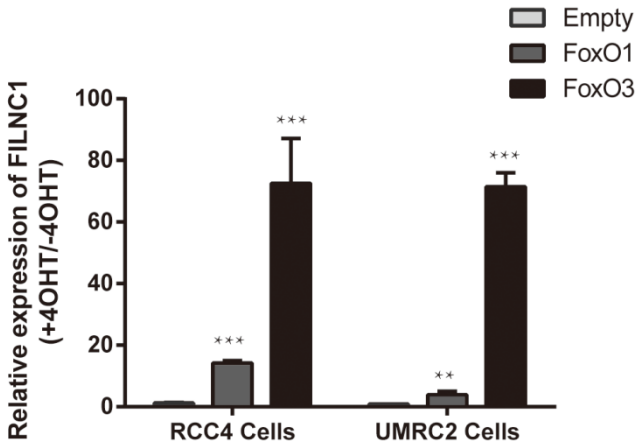
4OHT 12 hr treatment

\- / +

RNA sequencing

Analysis focusing on lincRNAs





TCGA datasets

Validation

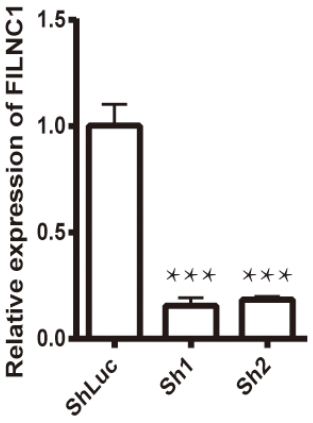
FILNC1 (FoxO-induced long noncoding RNA #1)

→FILNC1 is a FoxO target.

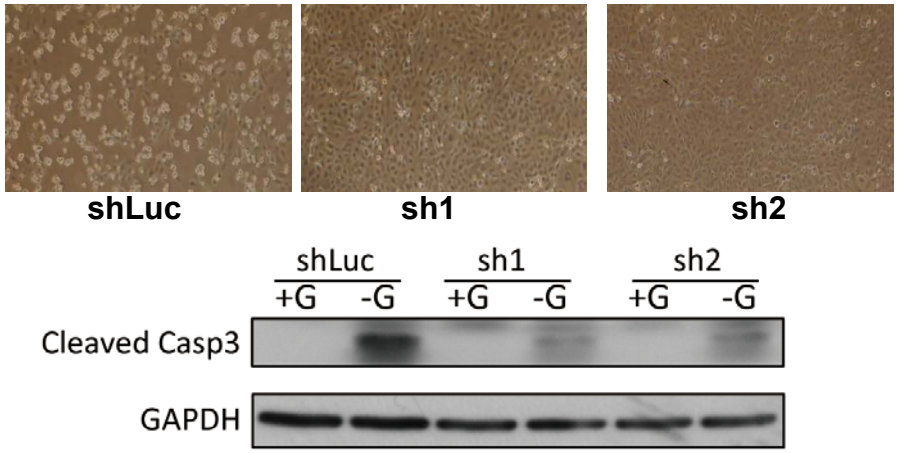
→FILNC1 is induced by energy stress in a FoxO-dependent manner

FILNC1 deficiency inhibits energy stress-induced apoptosis and promotes renal tumor development

A

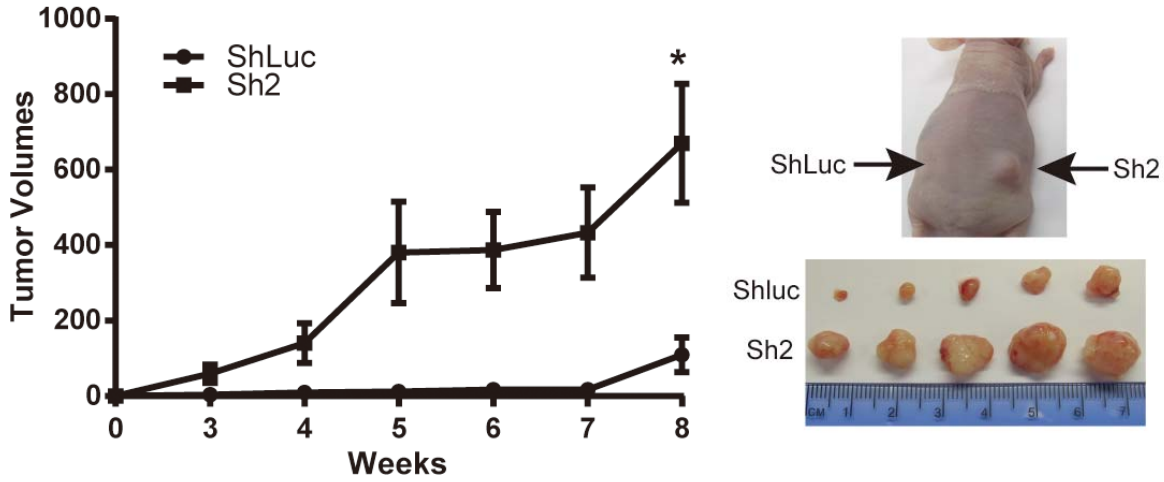


B



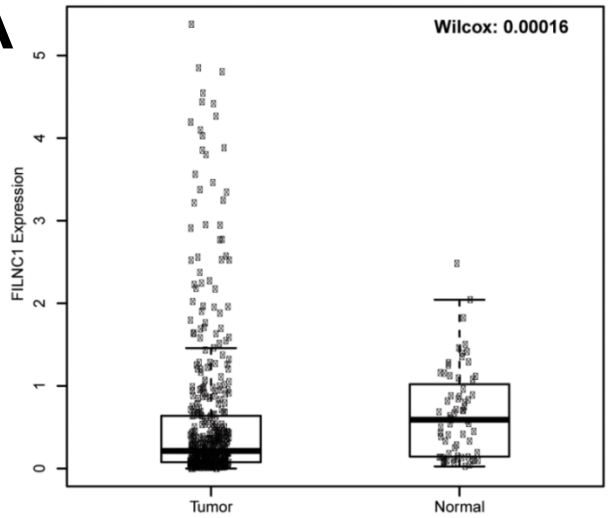
→FILNC1 KD does not affect cell cycle.

C



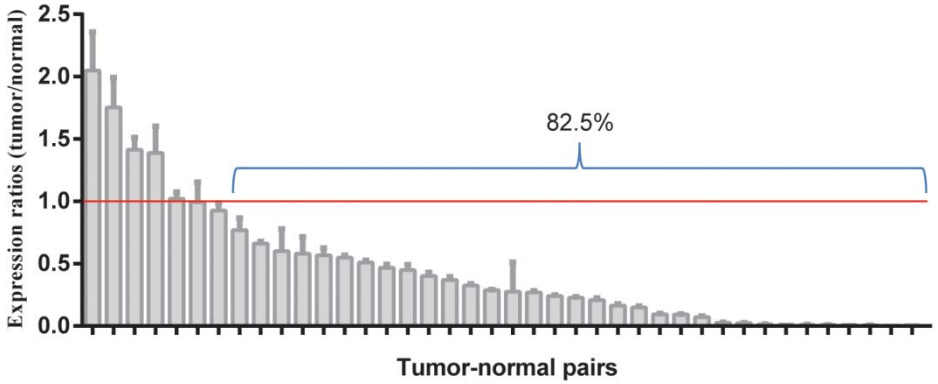
FILNC1 is down-regulated and its low expression correlates with poor clinic outcome in renal cancers

A



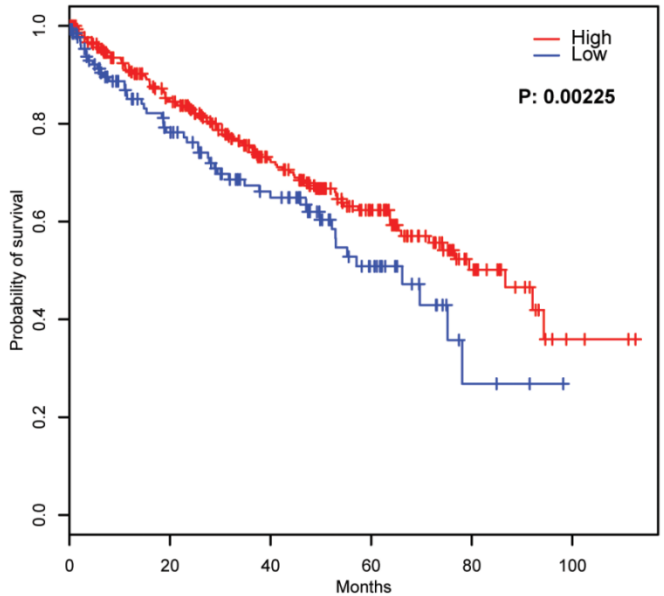
TCGA analysis

B



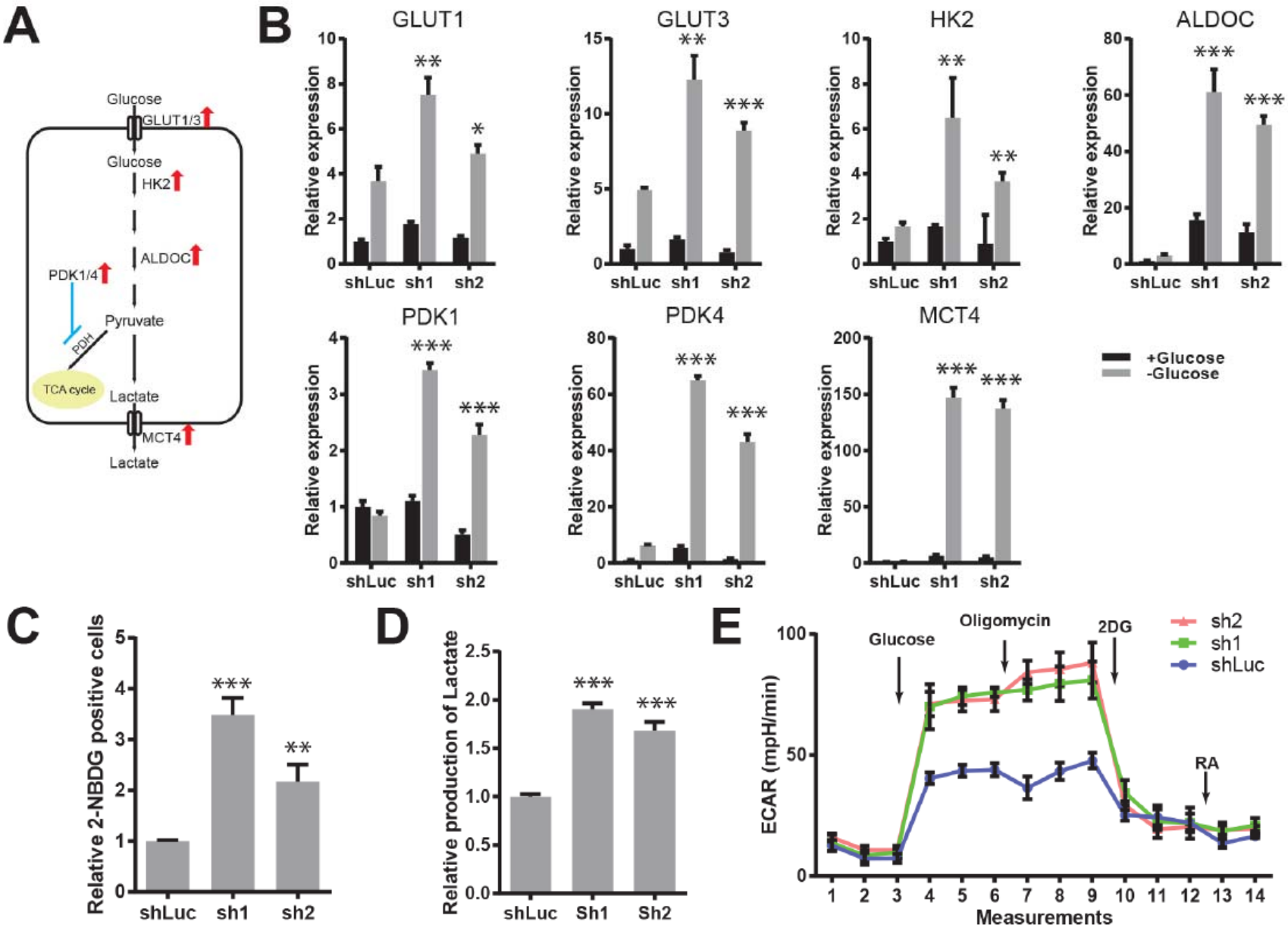
Real-time PCR validation

C

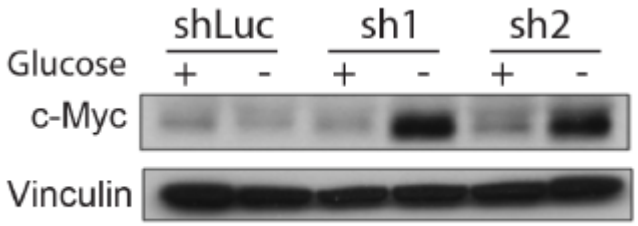


Clinical outcome analysis

FILNC1 deficiency promotes glucose uptake and lactate production



FILNC1 deficiency increases Myc protein level



→FILNC1 KD does not affect Myc mRNA level.

→Myc largely mediates the biological effects afforded by *FILNC1* deficiency under energy stress

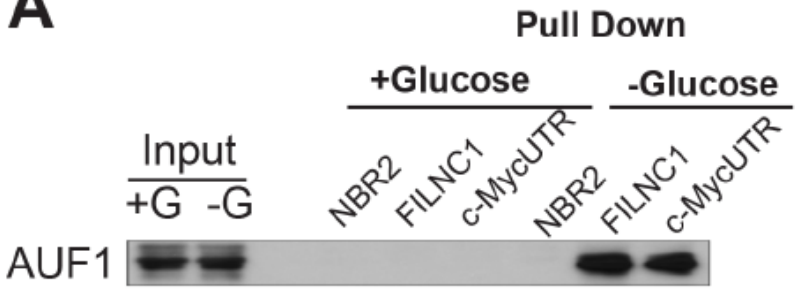
FILNC1 interacts with AUF1 under energy stress and sequesters AUF1 from binding to Myc mRNA

Mass spectrometry for FILNC1

	Beads	Antisense	Sense
IGF2BP1	0	0	1
AUF1	0	1	3
SART3	0	0	5

AUF1 is an (A+U)-rich elements (AREs)-binding protein, and can binds to AREs within 3′ untranslated region (UTR) of *Myc* mRNA and promotes *Myc* translation without affecting *Myc* mRNA level.

A



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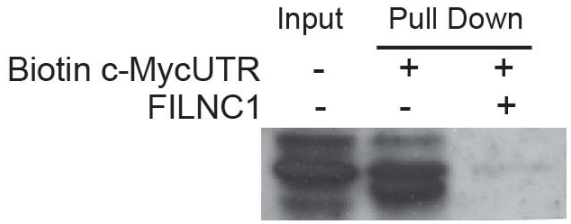
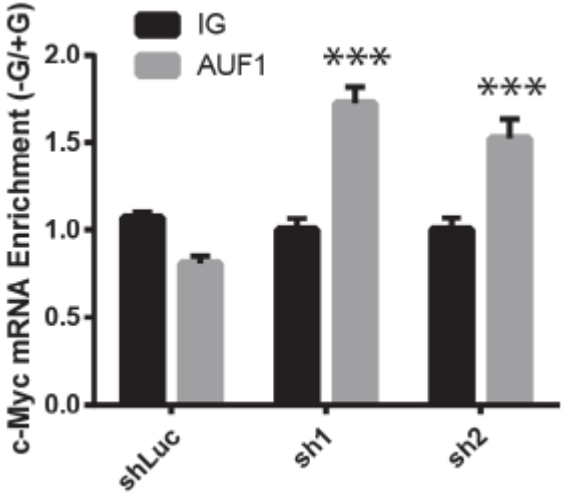
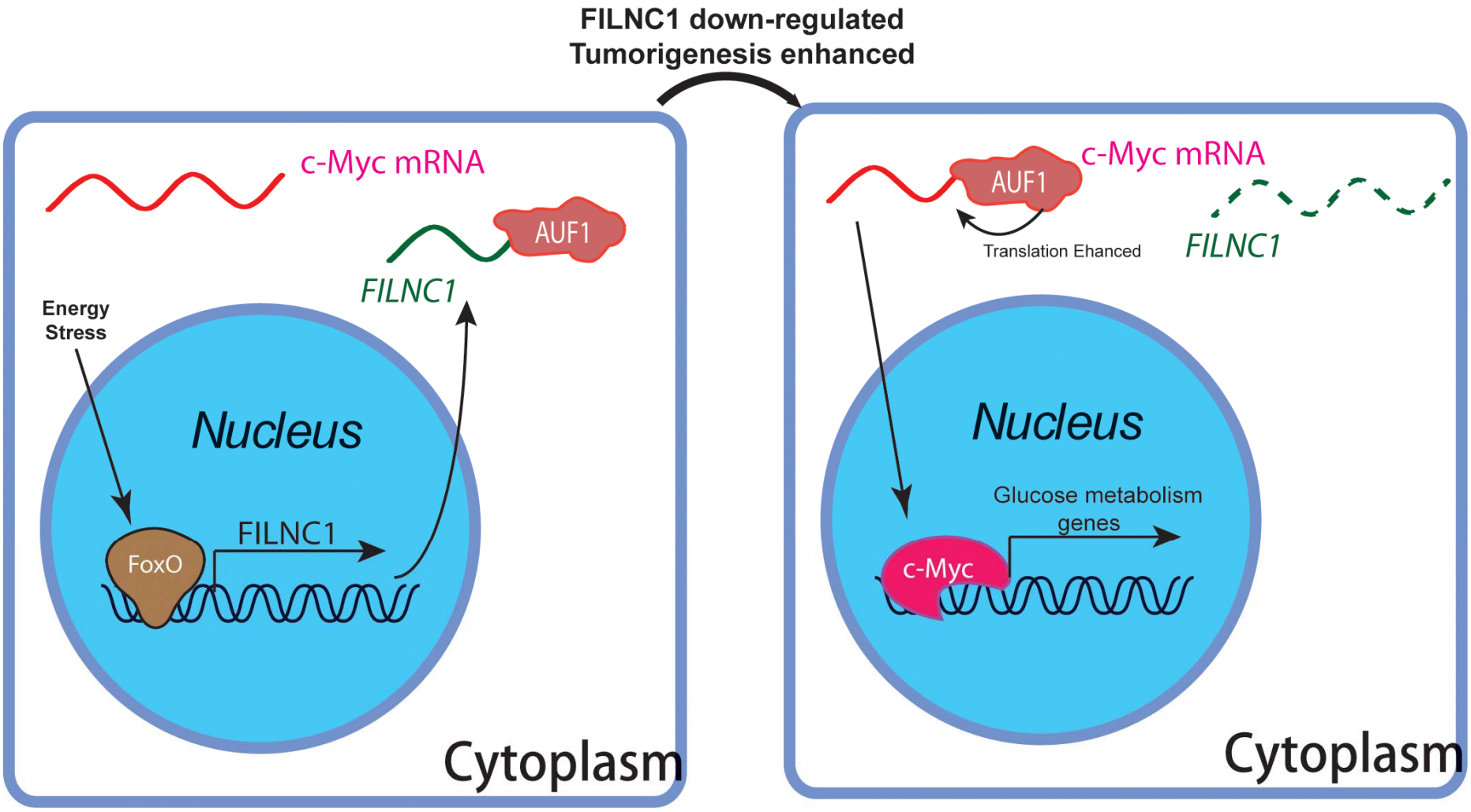


C

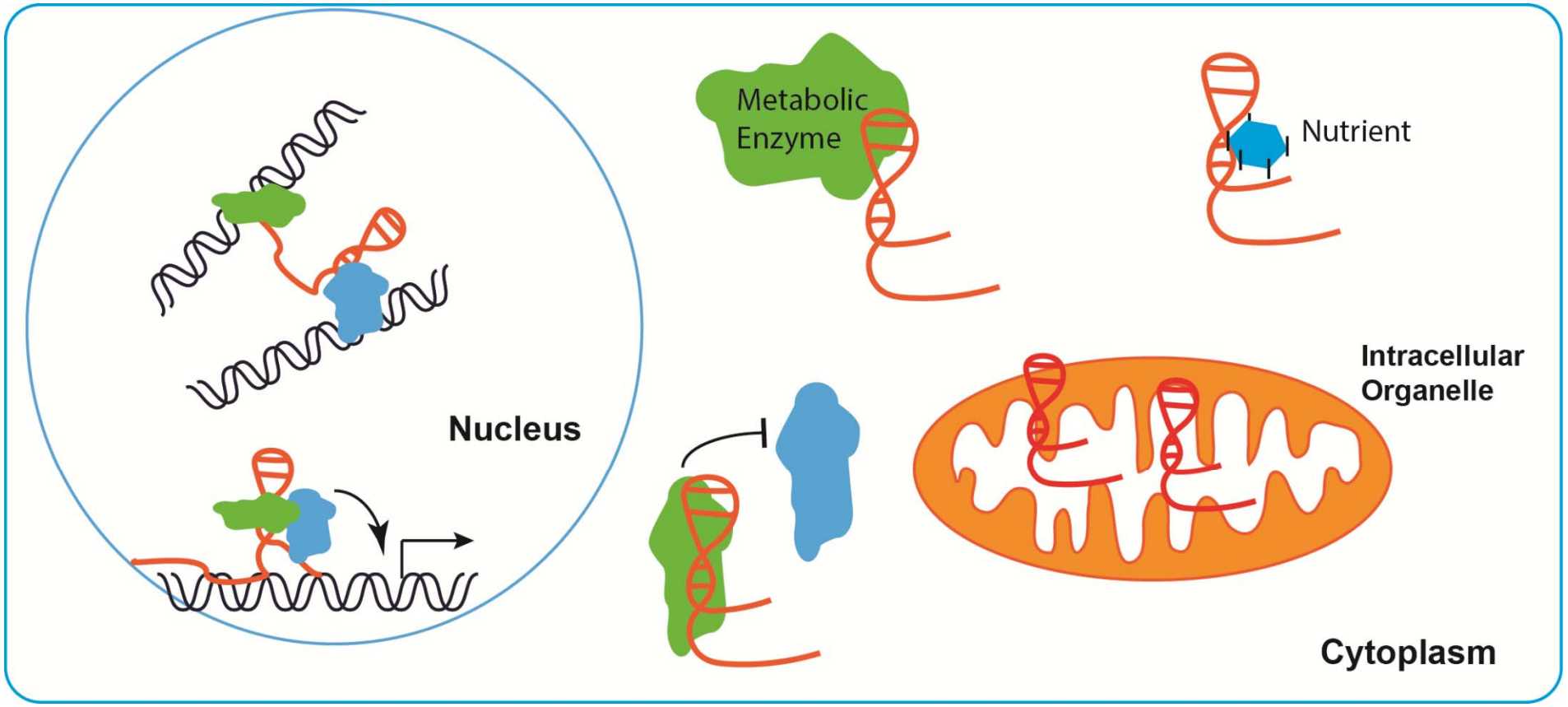


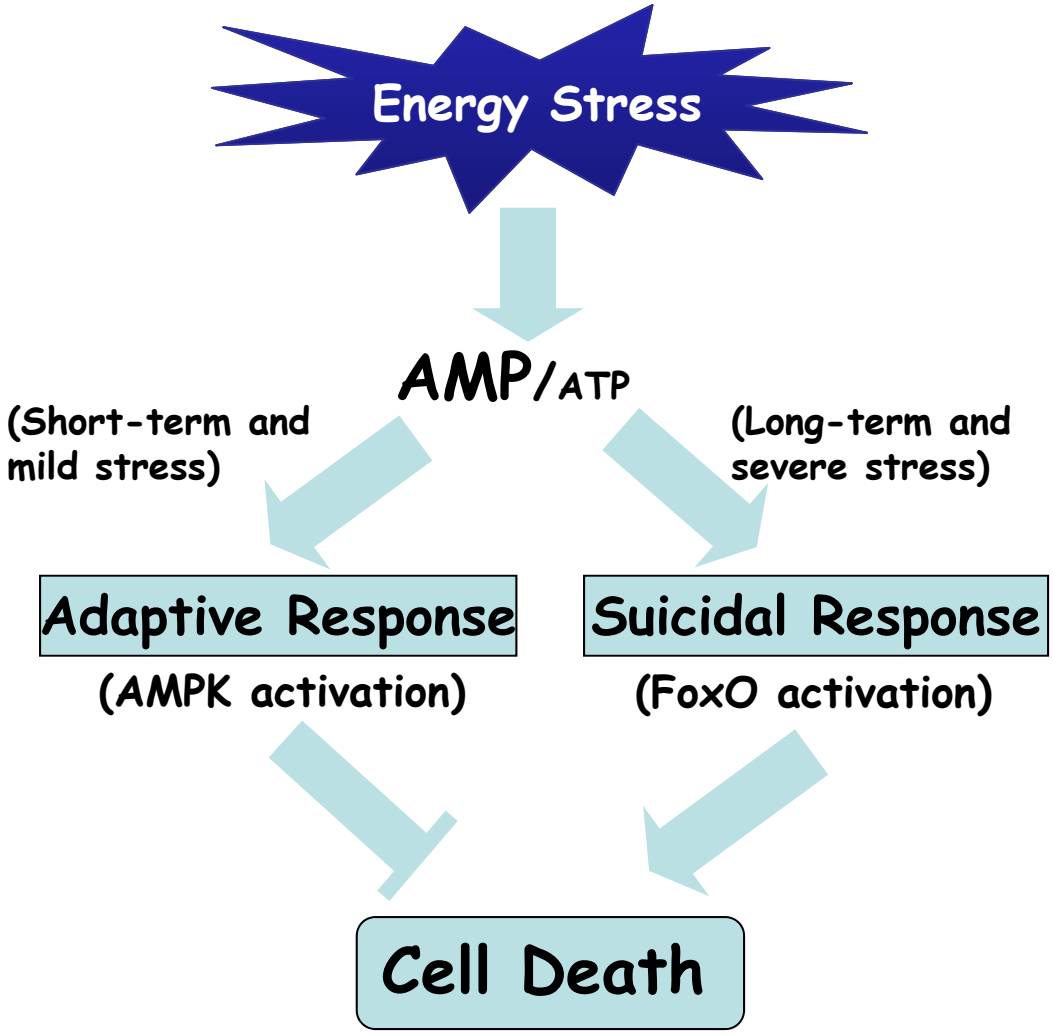
Energy stress-induced lncRNA FILNC1 inhibits Myc-mediated energy metabolism and renal tumor suppression



(Xiao Z, et al, Gan B, *Nature Communications*, 2017)

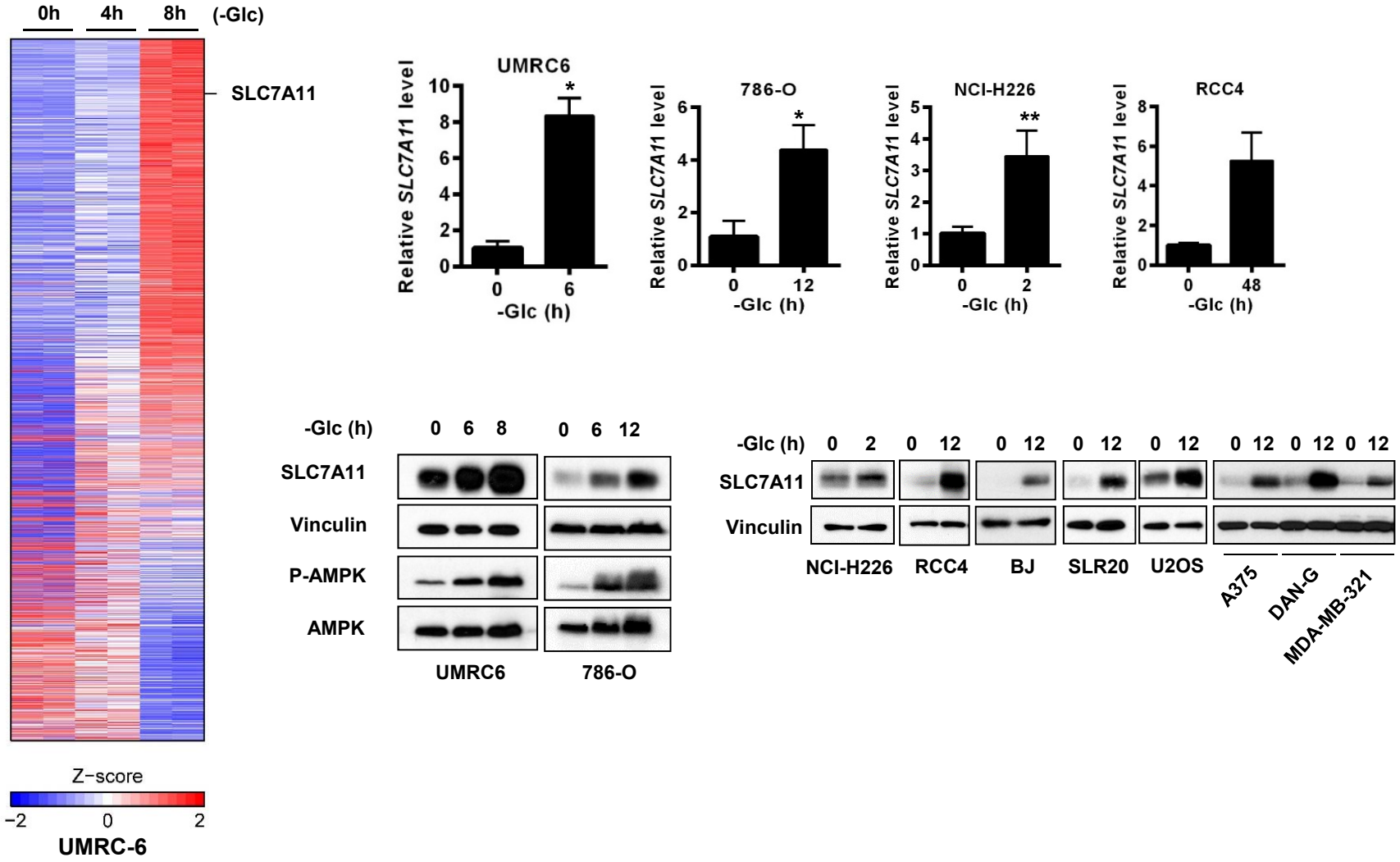
Potential function of LncRNAs in cancer metabolism

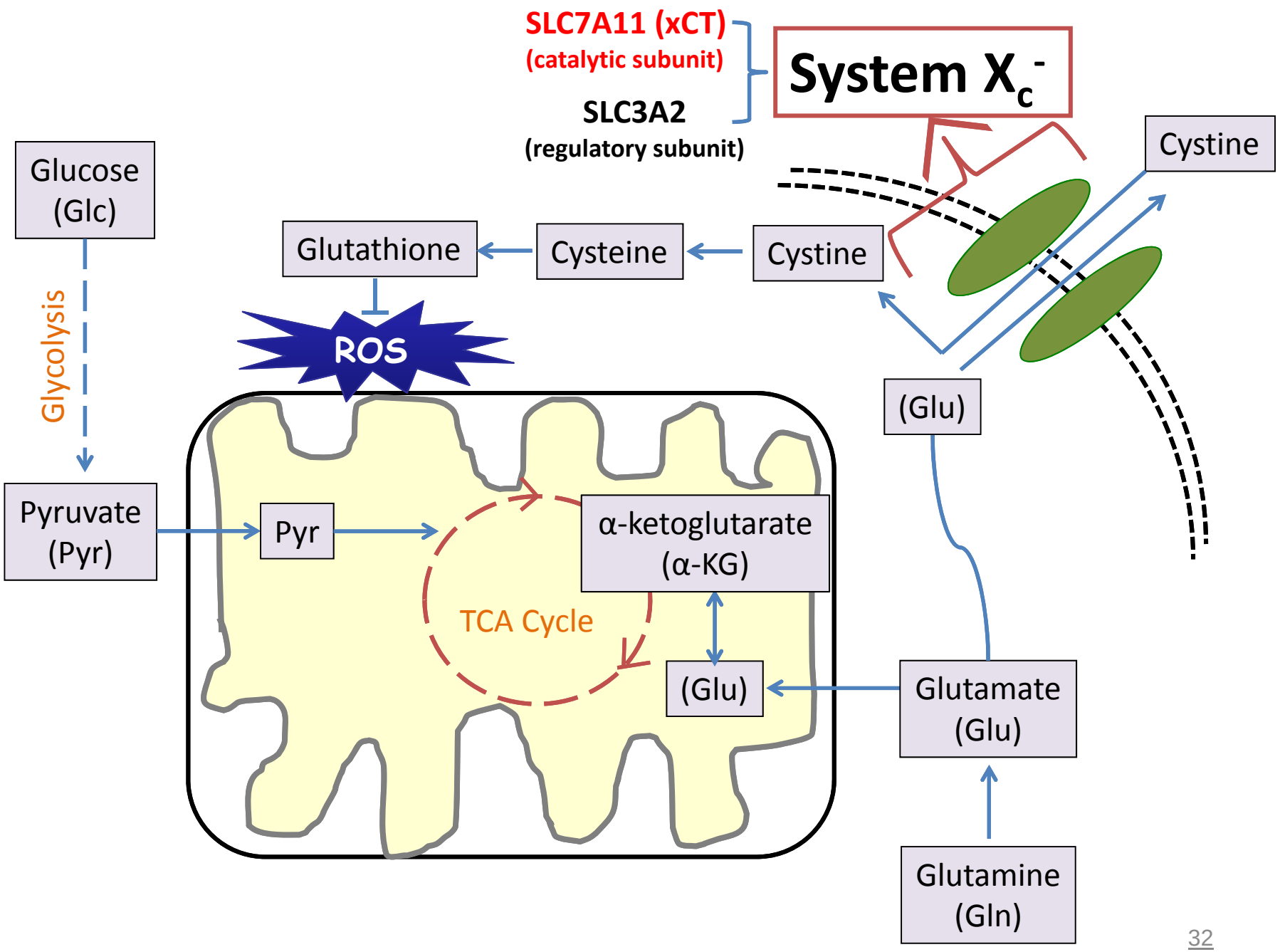




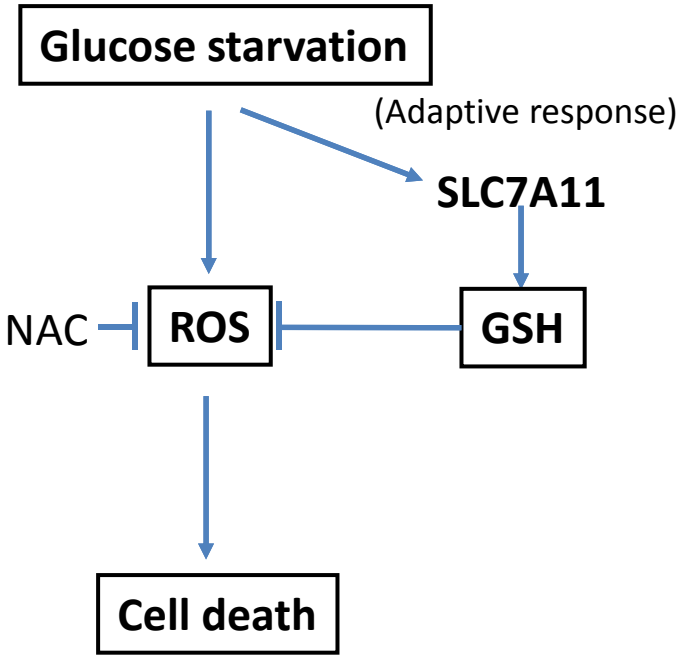
(Gan et al, *Cancer Cell*, 2010;
Lin et al, *Oncogene*, 2013;
Lin et al, *Cancer Research*, 2014;
Liu X, et al, *Nature Cell Biology*, 2016;
Dai et al, *PNAS*, 2017;
Xiao Z, et al, *Nature Communications*, 2017)

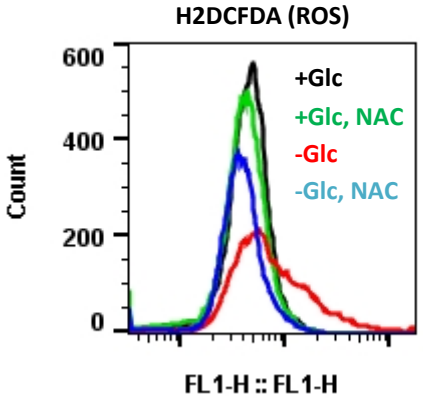
Glucose starvation induces the expression of SLC7A11

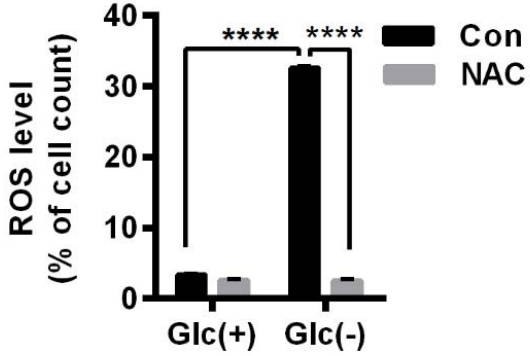


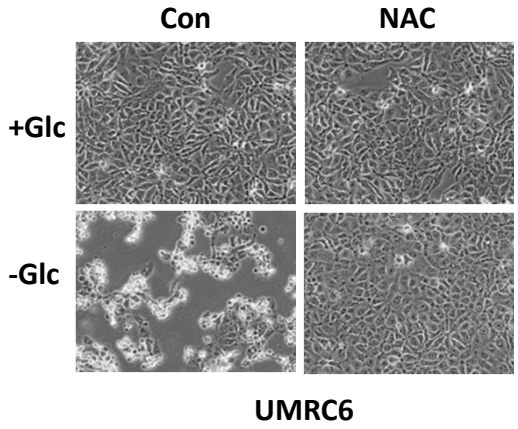

SLC7A11 (xCT)
(catalytic subunit)
SLC3A2
(regulatory subunit)
System X_c^-
Cystine
Glucose (Glc)
Glutathione
Cysteine
Cystine
Glycolysis
ROS
(Glu)
Pyruvate (Pyr)
Pyr
α-ketoglutarate (α-KG)
TCA Cycle
(Glu)
Glutamate (Glu)
Glutamine (Gln)

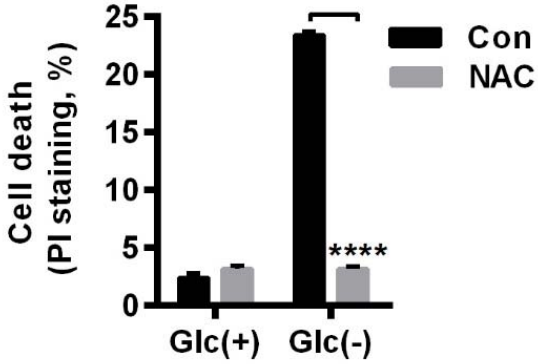
Hypothesis: glucose starvation-induced SLC7A11 serves as an adaptive response to promote survival under metabolic stress





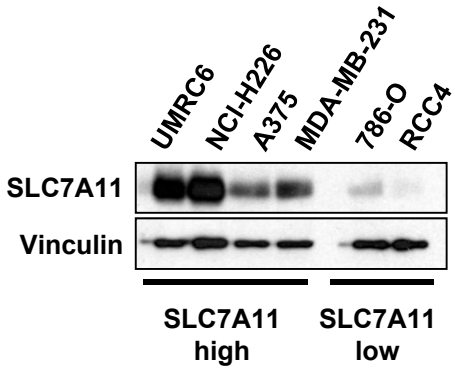


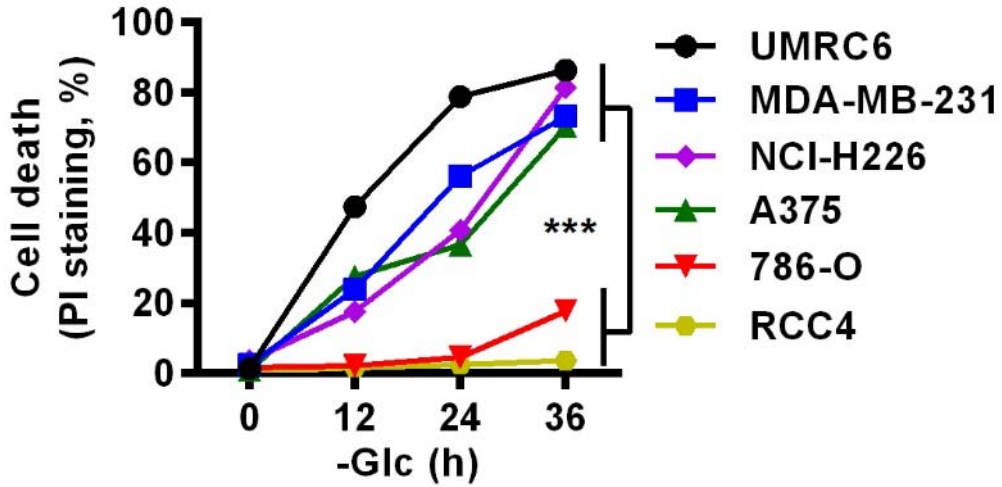




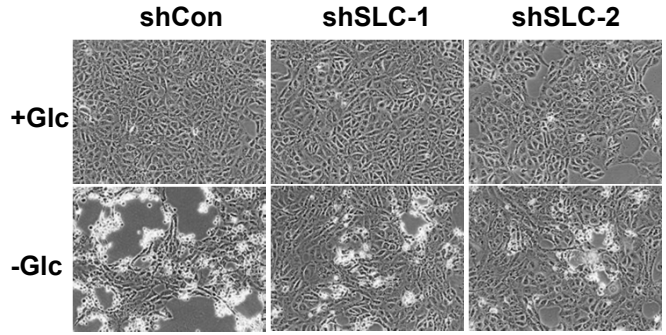
(NAC: N-acetylcysteine)

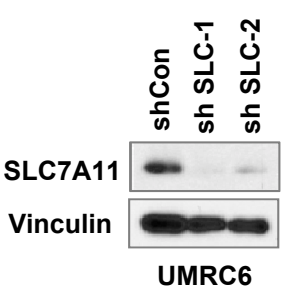
High SLC7A11 expression correlates with increased sensitivity to glucose starvation-induced cell death in cancer cells

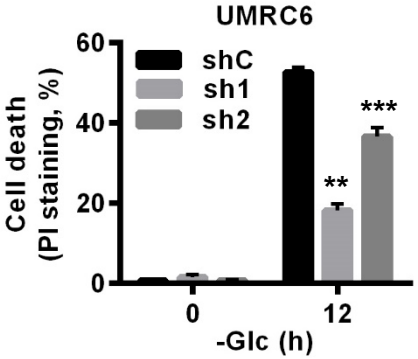


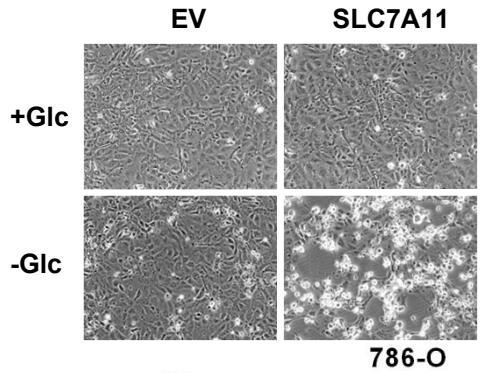


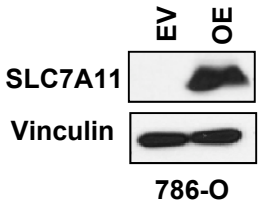
SLC7A11 sensitizes cancer cell to glucose starvation-induced cell death

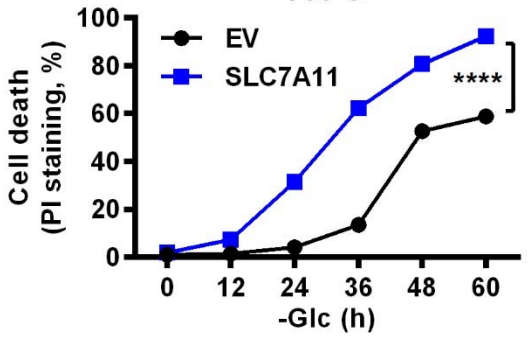


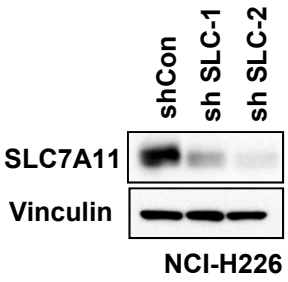


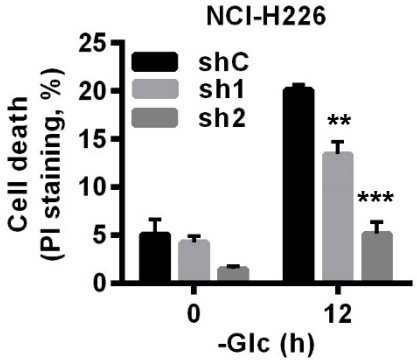


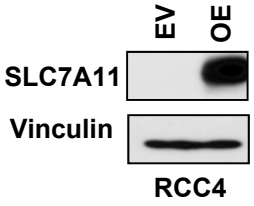


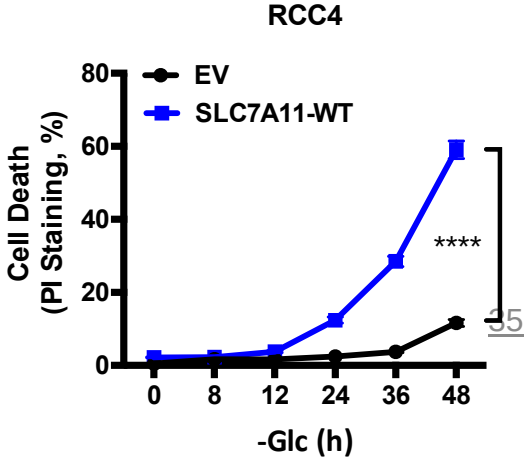






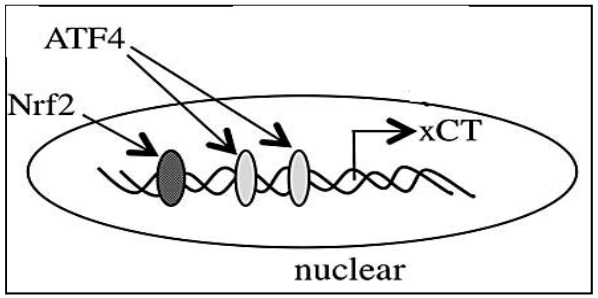


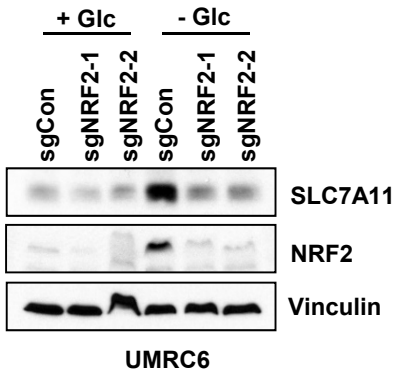


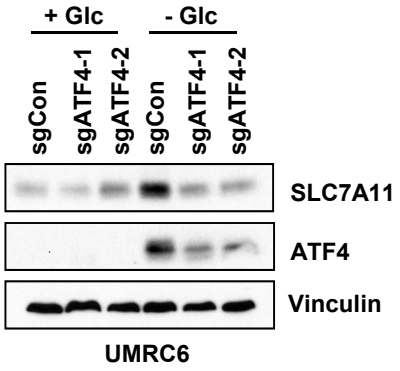


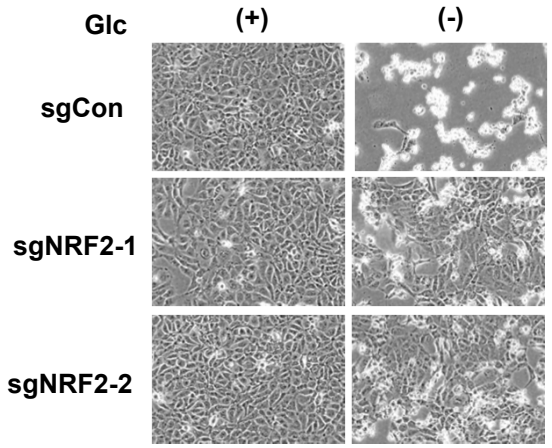
→Pharmacological inhibition of SLC7A11 by sulfasalazine has similar effect.

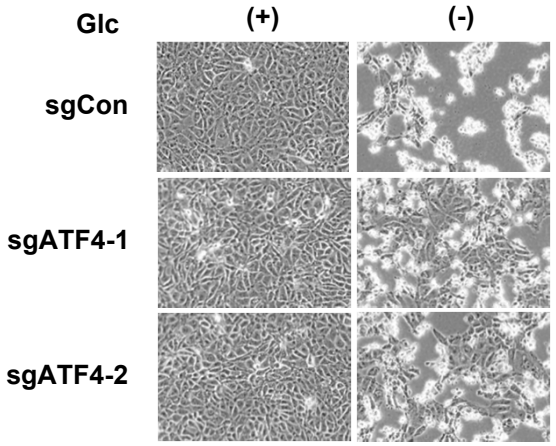
ATF4 and NRF2 promotes glucose starvation-induced cell death through SLC7A11

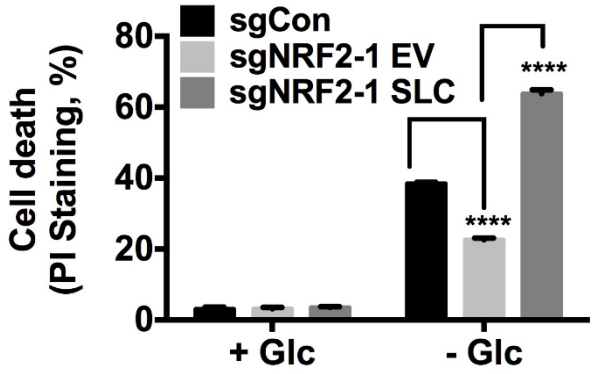


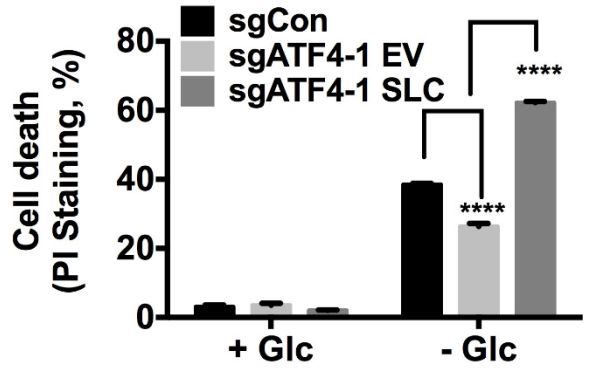




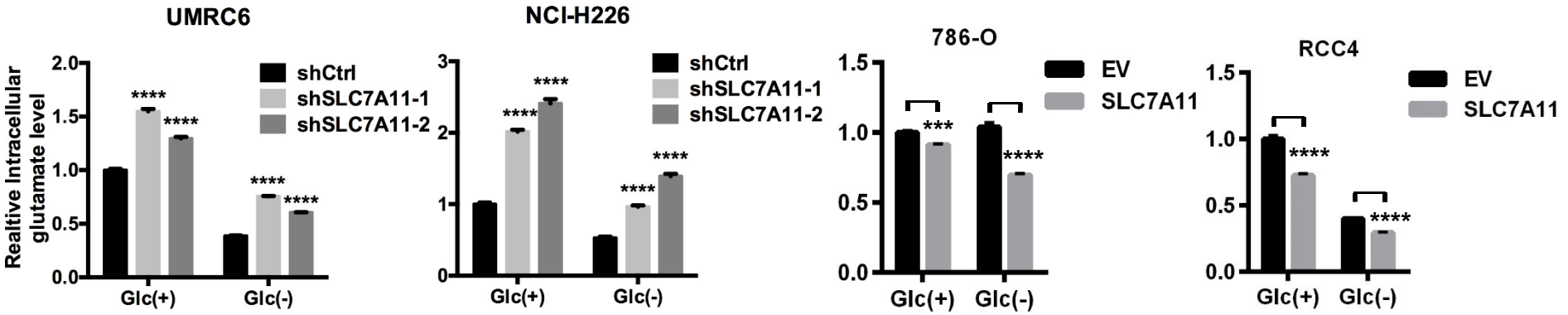


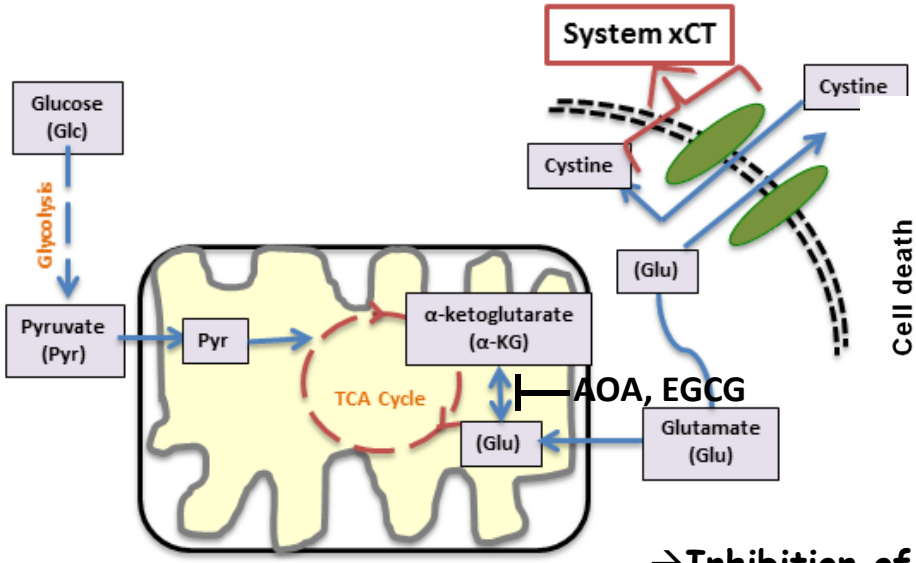


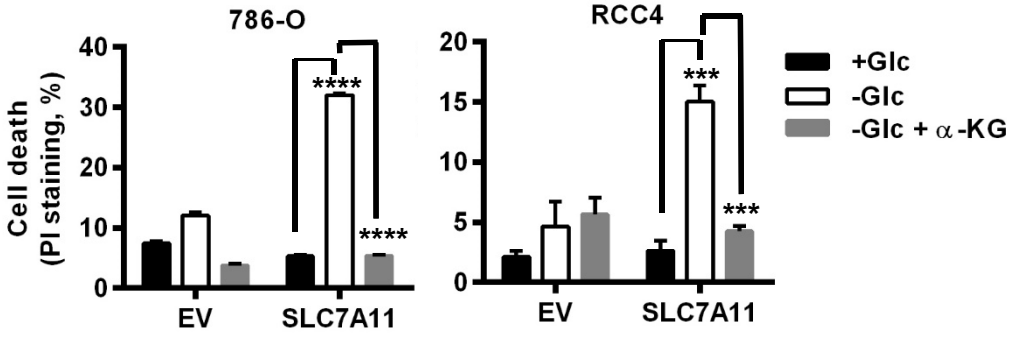




SLC7A11 regulation of glutamate efflux underlies SLC7A11-mediated increased sensitivity to glucose starvation

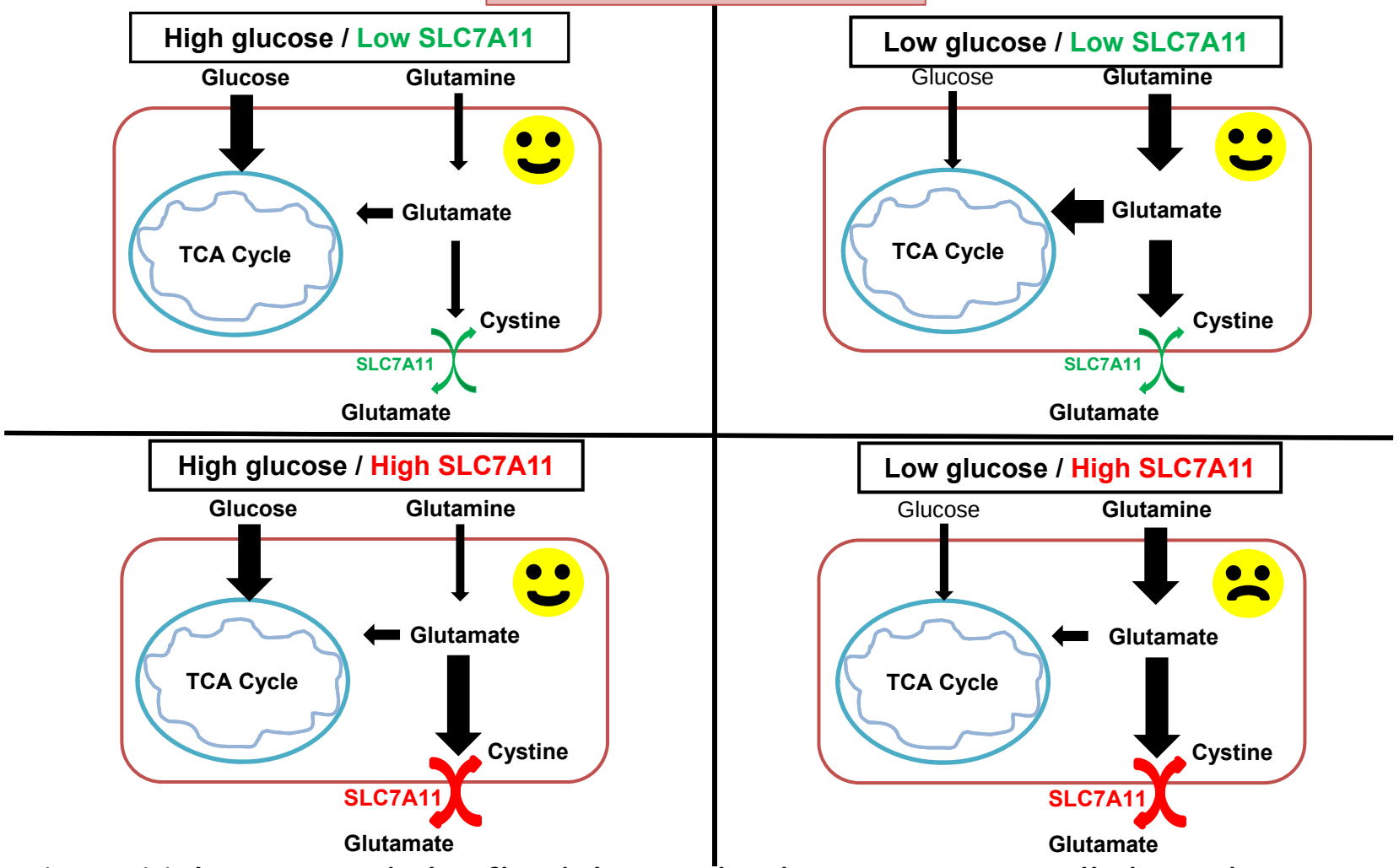






→Inhibition of glutamate conversion to aKG by AOA or EGCG restores glucose dependency in SLC7A11-deficient cells.

Model



→SLC7A11 limits metabolic flexibility and enhances cancer cell dependency on glucose by exporting glutamate.

→Suggest to use glycolysis inhibitors to target the metabolic vulnerability in tumors with high SLC7A11 expression (such as Keap1 or NRF2 mutant tumors).

(Koppula P, Zhang Y, et al, Gan B, 2017, JBC)

Research Topic:

Energy Sensing and Metabolism

Cancer

Research Questions:

1.How normal/cancer cells sense energy availability?

2.How cancer cells adapt to survive and grow under energy stress?

3.How to translate our understanding of energy metabolism in cancer into novel cancer therapeutics?

Presentation Outline:

→**Regulation of energy sensor AMPK by lncRNA NBR2.** (Liu X, et al, NCB, 2016; Liu X, et al, Cell Cycle, 2016)

→**Energy stress-induced lncRNA FLINC1 regulates energy metabolism and tumor suppression.** (Xiao Z, et al, Nature Communications, 2017)

→**Glutamate/cystine antiporter SLC7A11 regulates glucose dependency in cancer cells.** (Koppula, JBC, 2017)

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- Hyemin Lee
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- Junjie Chen
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- Hui-kuan Lin
- Deepak Nagrath
- Wei Li

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