Control of Tumor Metabolism by Rb

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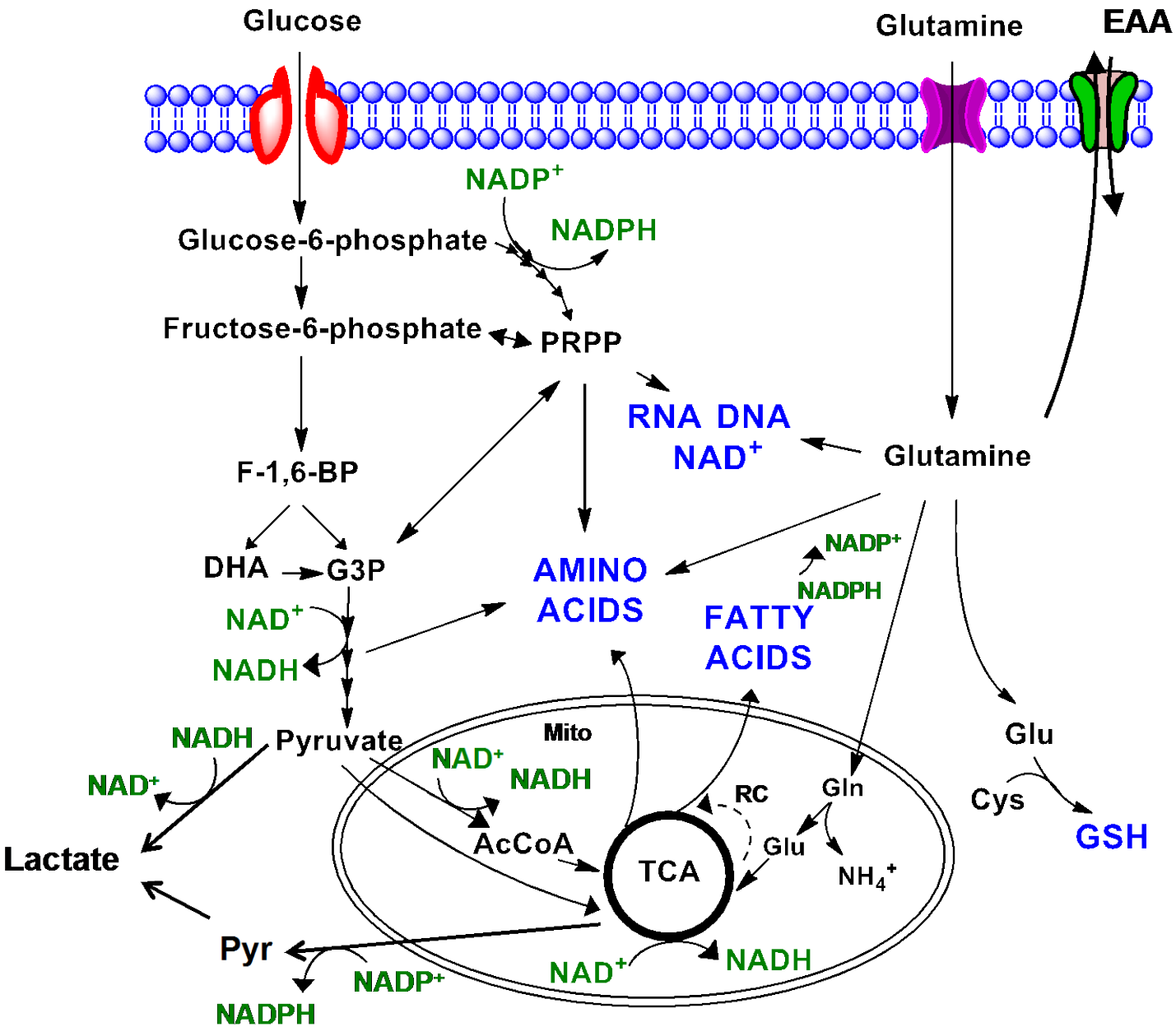
University of Louisville

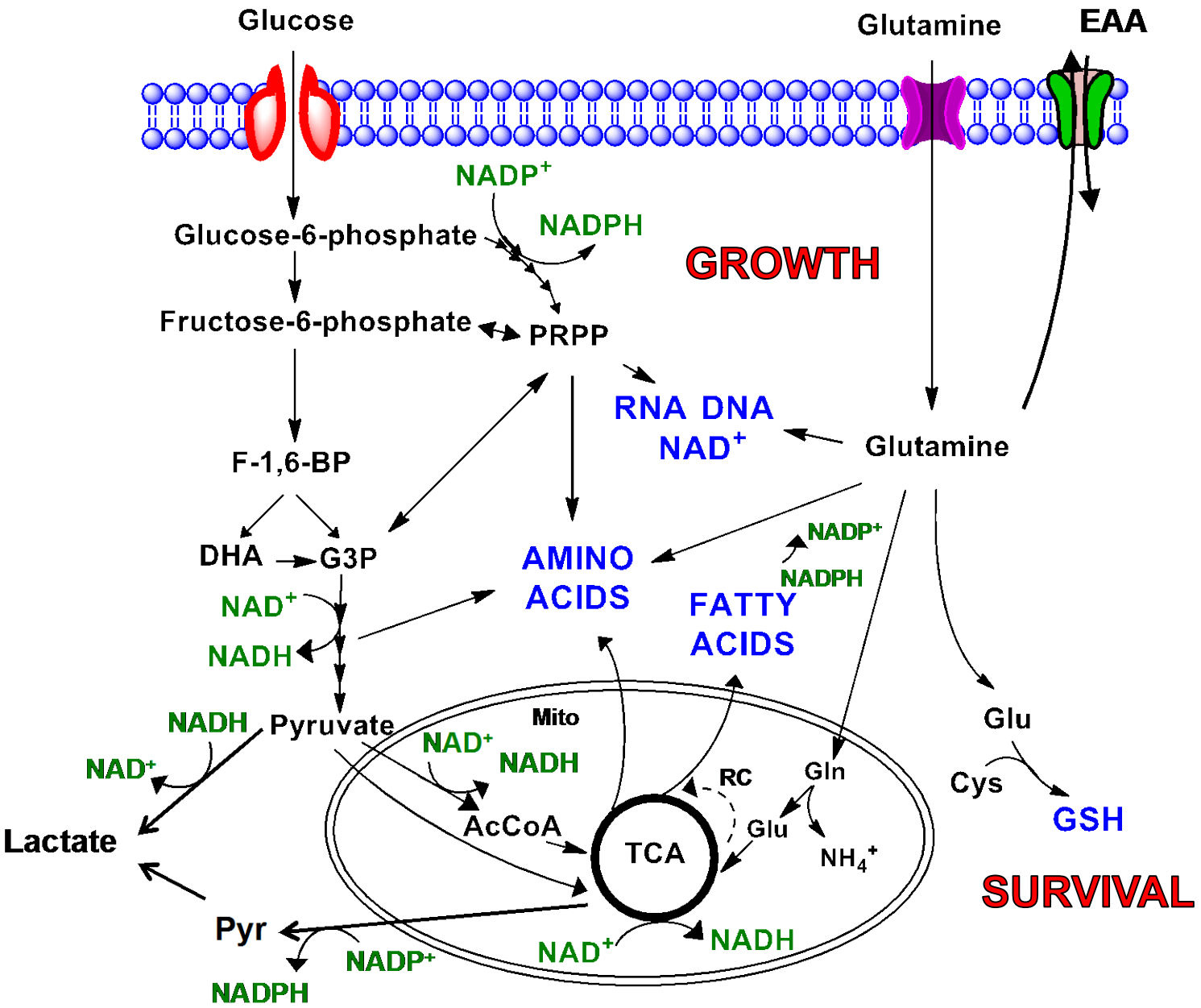
2017 UK Metabolism Symposium
August 5

James Graham Brown
Cancer Center

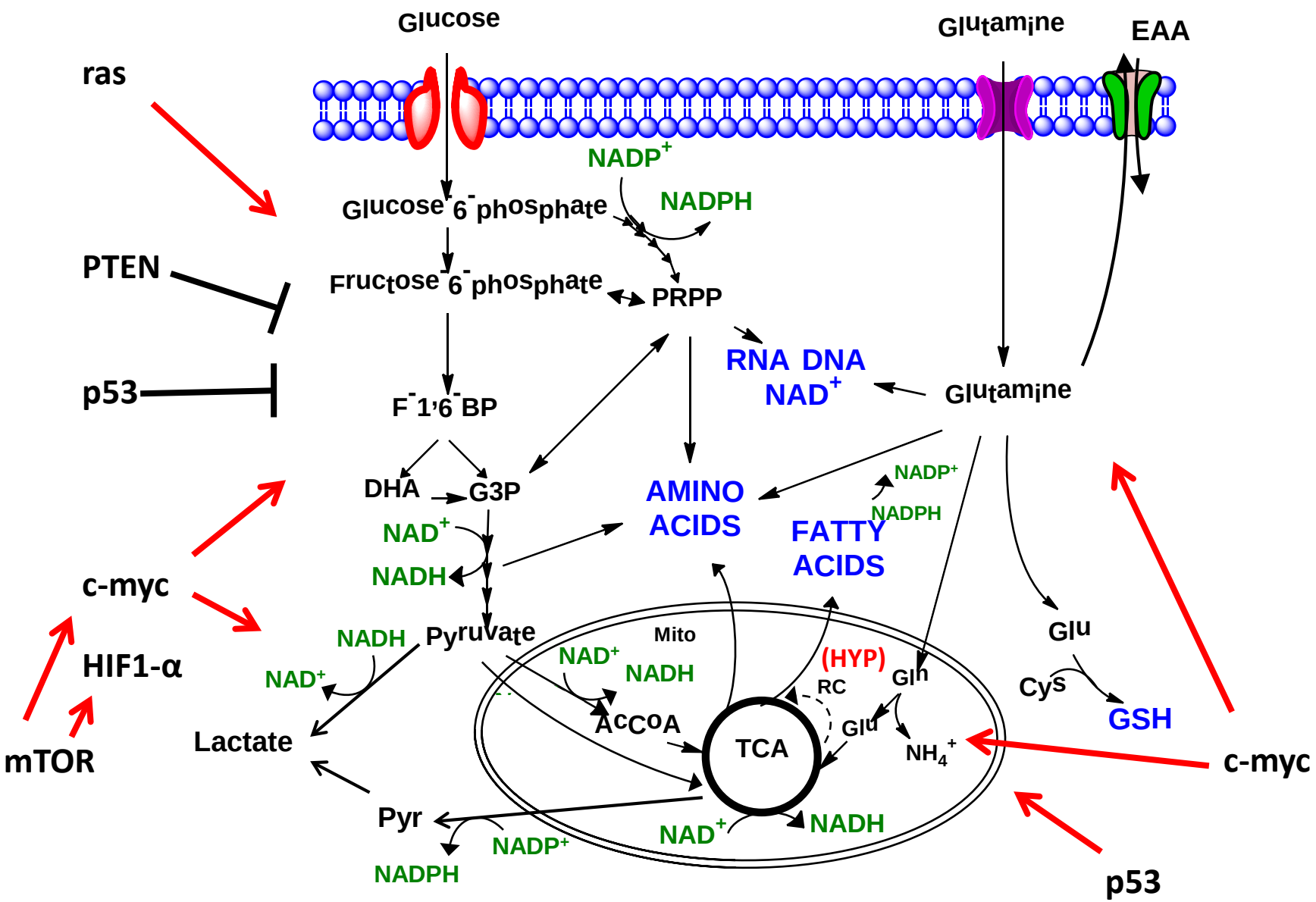
Interplay within Intermediary Metabolism



Interplay within Intermediary Metabolism



Oncogenic Regulation of Glucose and Glutamine Metabolism



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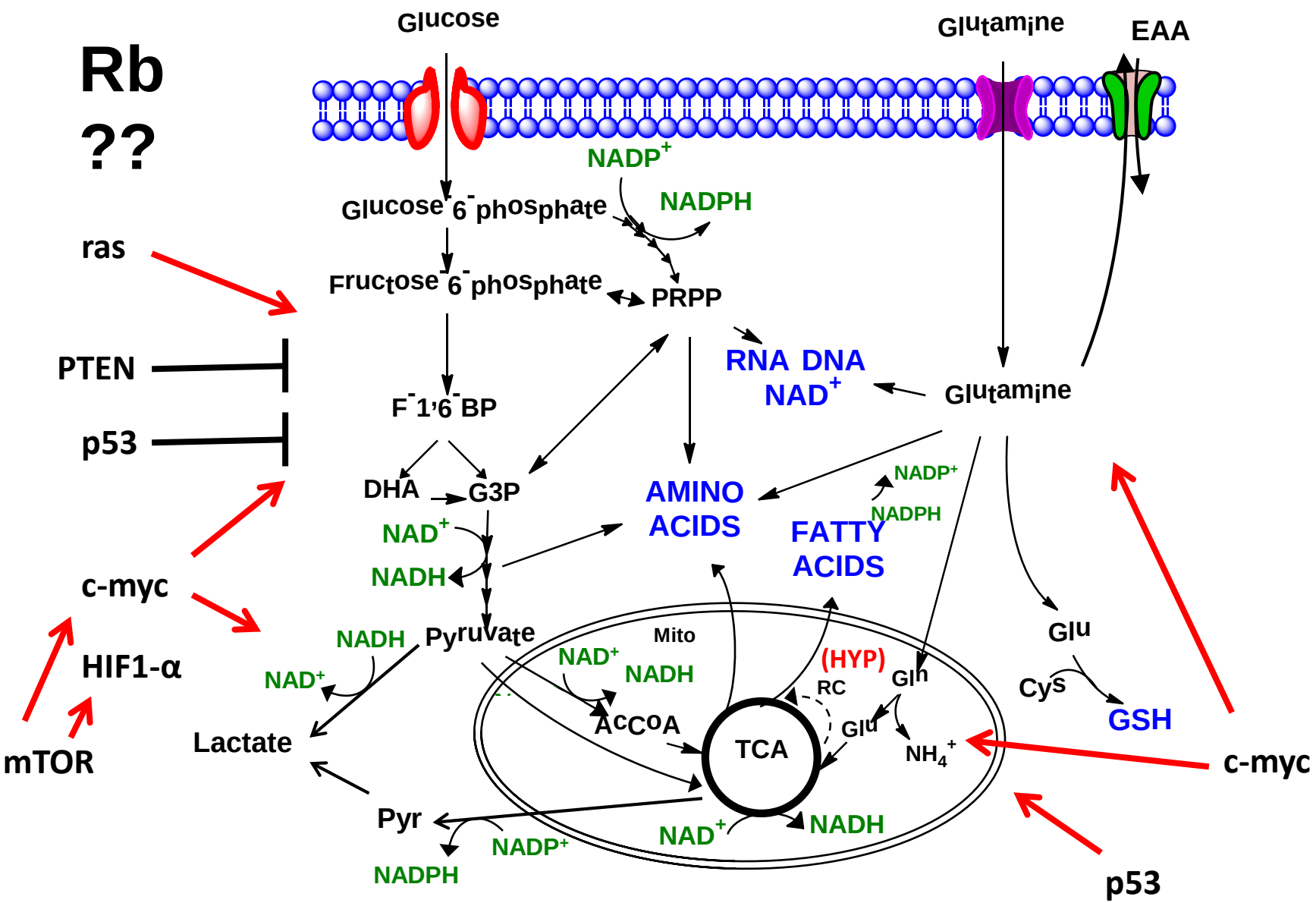
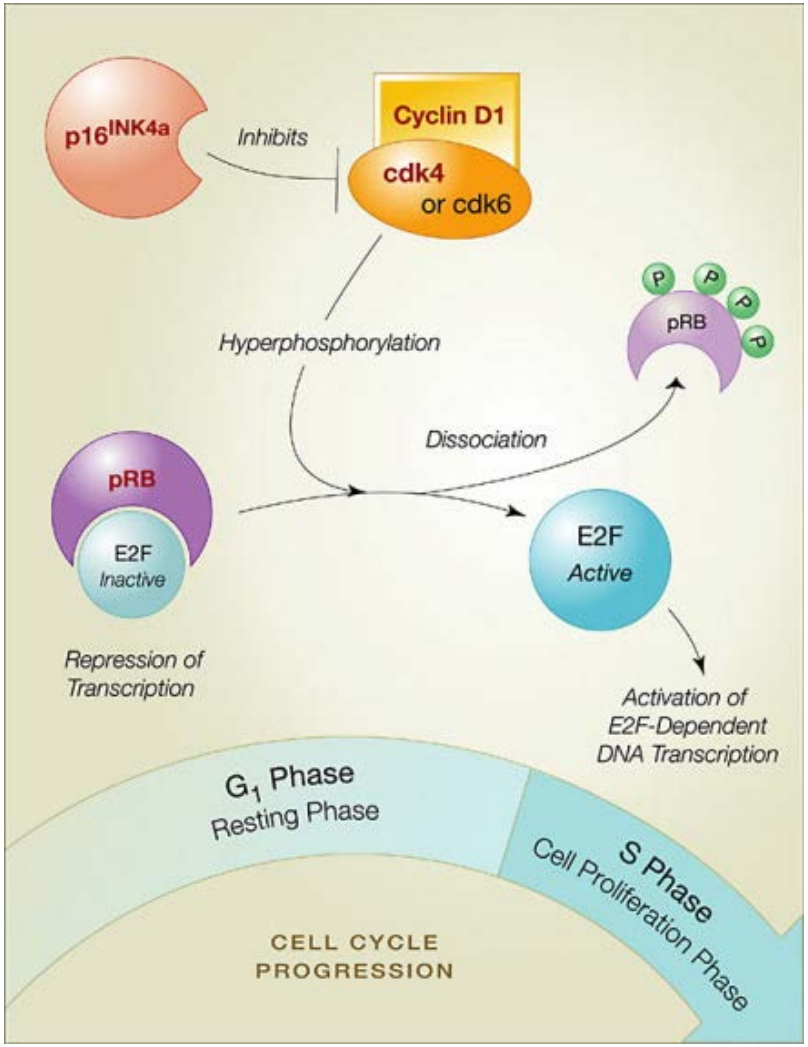
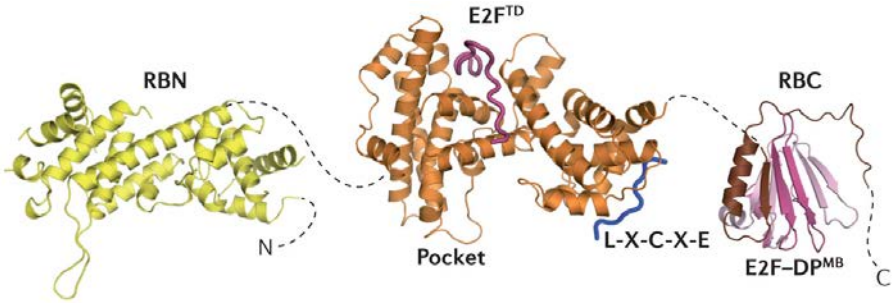


Retinoblastoma Protein and Cancer



Curr Opin Cell Biol, 14(6) 684–691



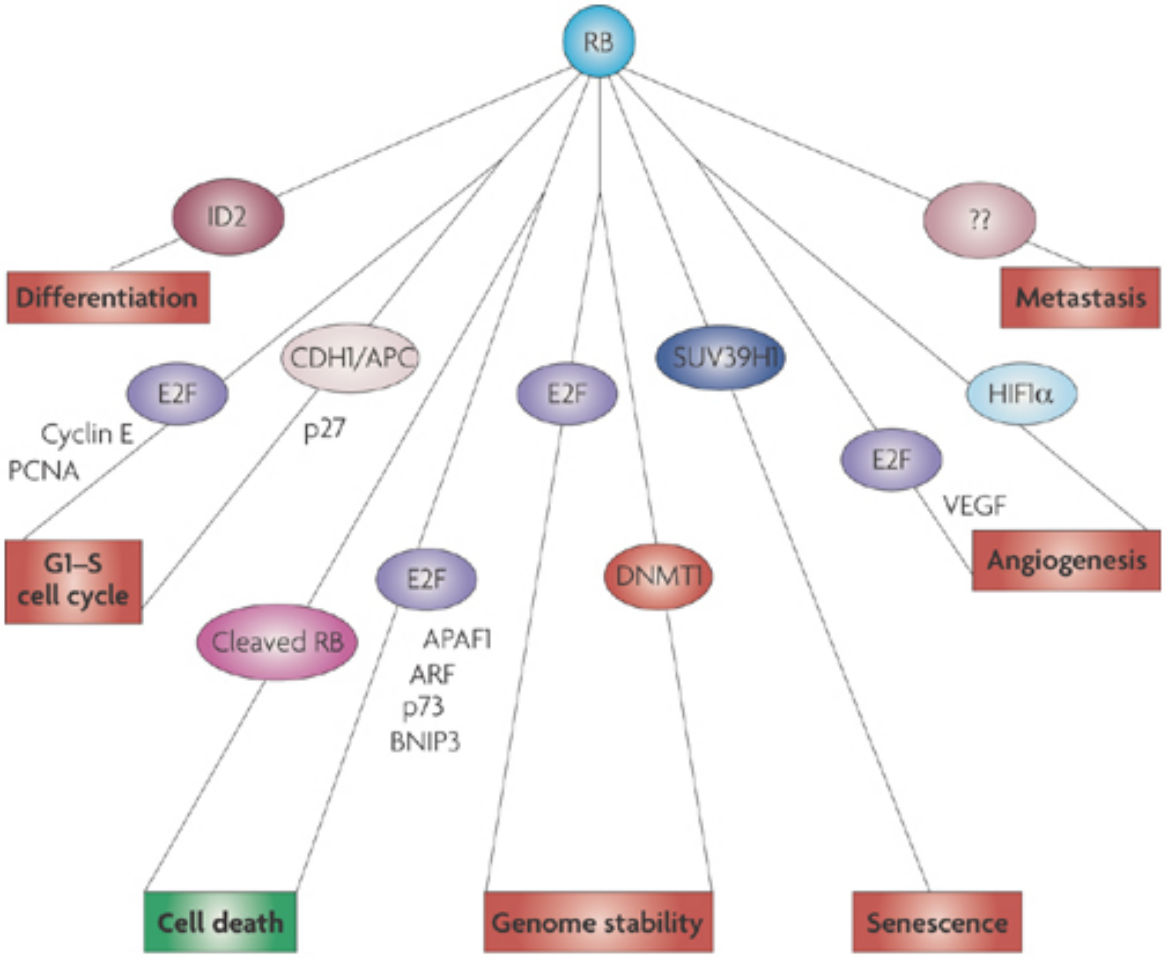
Nature Reviews Molecular Cell Biology 14, 297-306

Cancer type	Loss of p16INK4A	Overexpression of cyclin D1*	Loss of RB	RB activity (indirect)	Refs
SCLC	<10% ND	<10% ND	>90% ND	Not assessed	54,59,196
NSCLC	40–60% indeterminate	40–60% indeterminate	10–20% indeterminate	Poor outcome	31,196–203
Bladder	20–40% poor outcome	20–80% favourable outcome	30-70% poor outcome	Not assessed	199,204–208
Prostate	10–40% indeterminate	0–35% indeterminate	30–60% indeterminate	Poor outcome	31,78,109, 111,144–148, 150, 209–213
Melanoma	40–60% poor outcome	30–60% no influence	10–40% no influence	Not assessed	214–219
Pancreas	40–70% poor outcome	50–70% indeterminate	<5% ND	Not assessed	220–225
Colorectal	30–60% no influence	40–60% no influence	0–20% no influence	Not assessed	203,226–228
Liver	30–70% indeterminate	20–40% indeterminate	20–40% indeterminate	Poor outcome	174,229–237
Breast	20–40% indeterminate	30–70% favourable outcome (ER-positive)	10–30% indeterminate (ER-negative)	Poor outcome	31,104,118, 127,168,174, 229–237

The percent of lesions in each pathway constituent is reflective of reports in the published literature and where possible represents a consensus range. The effect of the lesion in regard to survival is noted. In certain contexts a consensus based on tumours analysed has not been reached (indeterminate). Unless otherwise noted outcome is measured as survival. *Functional RB status was determined by indirect measures in these analyses. ER, oestrogen receptor; ND, not determined; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

Nature Reviews Cancer 8, 714-724

Retinoblastoma Protein and Cancer

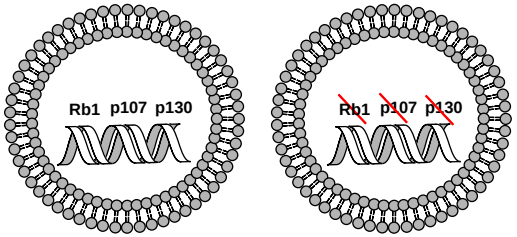


Nature Reviews Cancer 8, 671-682

Can Rb Directly Regulate Metabolism – Coupling Cell Cycle to Macromolecule Availability??

Experimental Model Systems

WT **TKO**

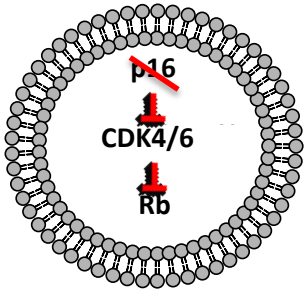


Isogenic MEFs

TKOs are immortal, resistant to G_1 arrest, loss of contact inhibition

Genes & Devel 14: 3037

Human Tumor Cells



A549 (lung)
HCT116 (colorectal)

p16 deletion leads to increased CDK4/6 activity and hyper-p-Rb

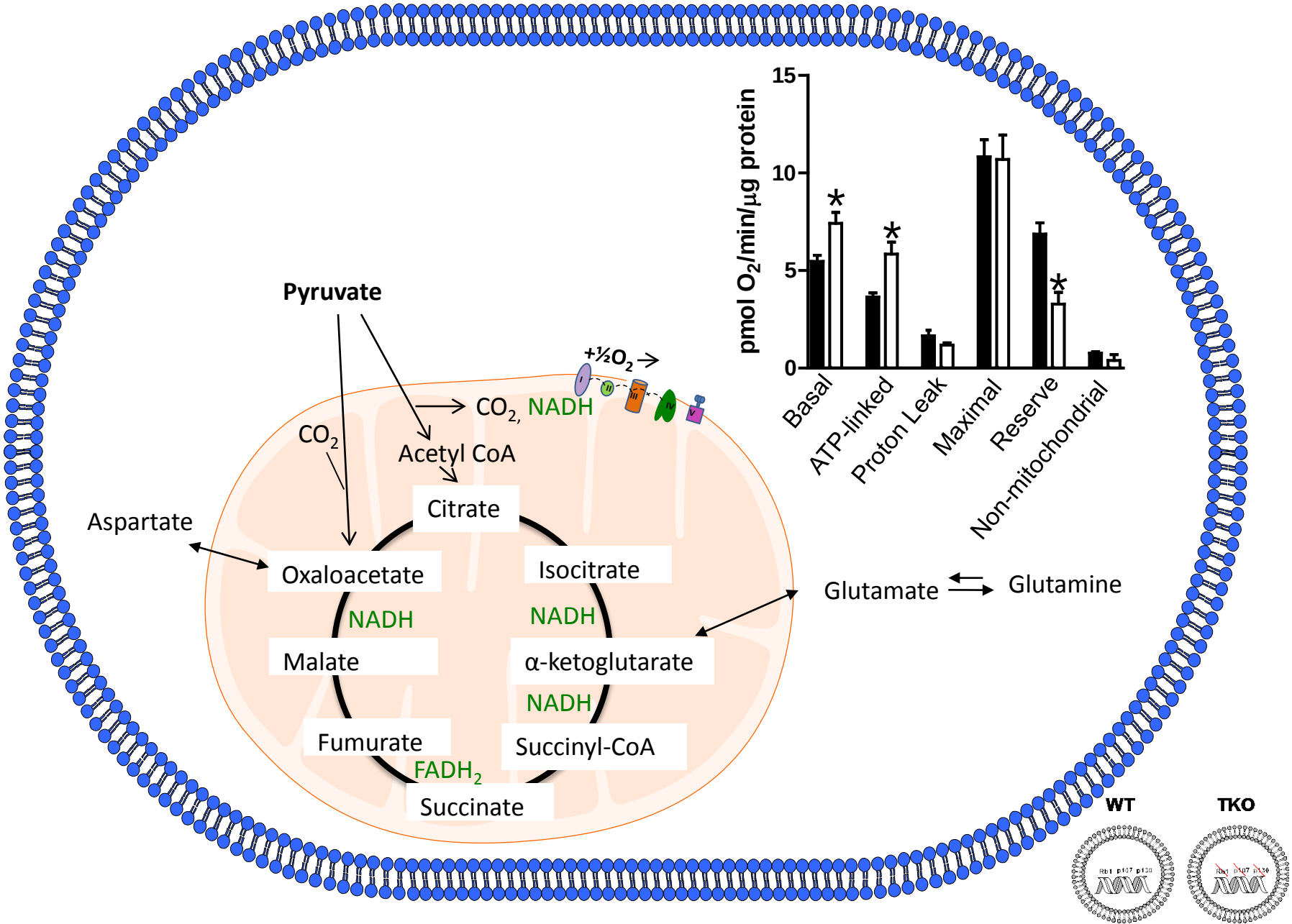
Mouse Lung Tumor Model

Kras^{LSL} / *Rb1*$^{lox/lox}$

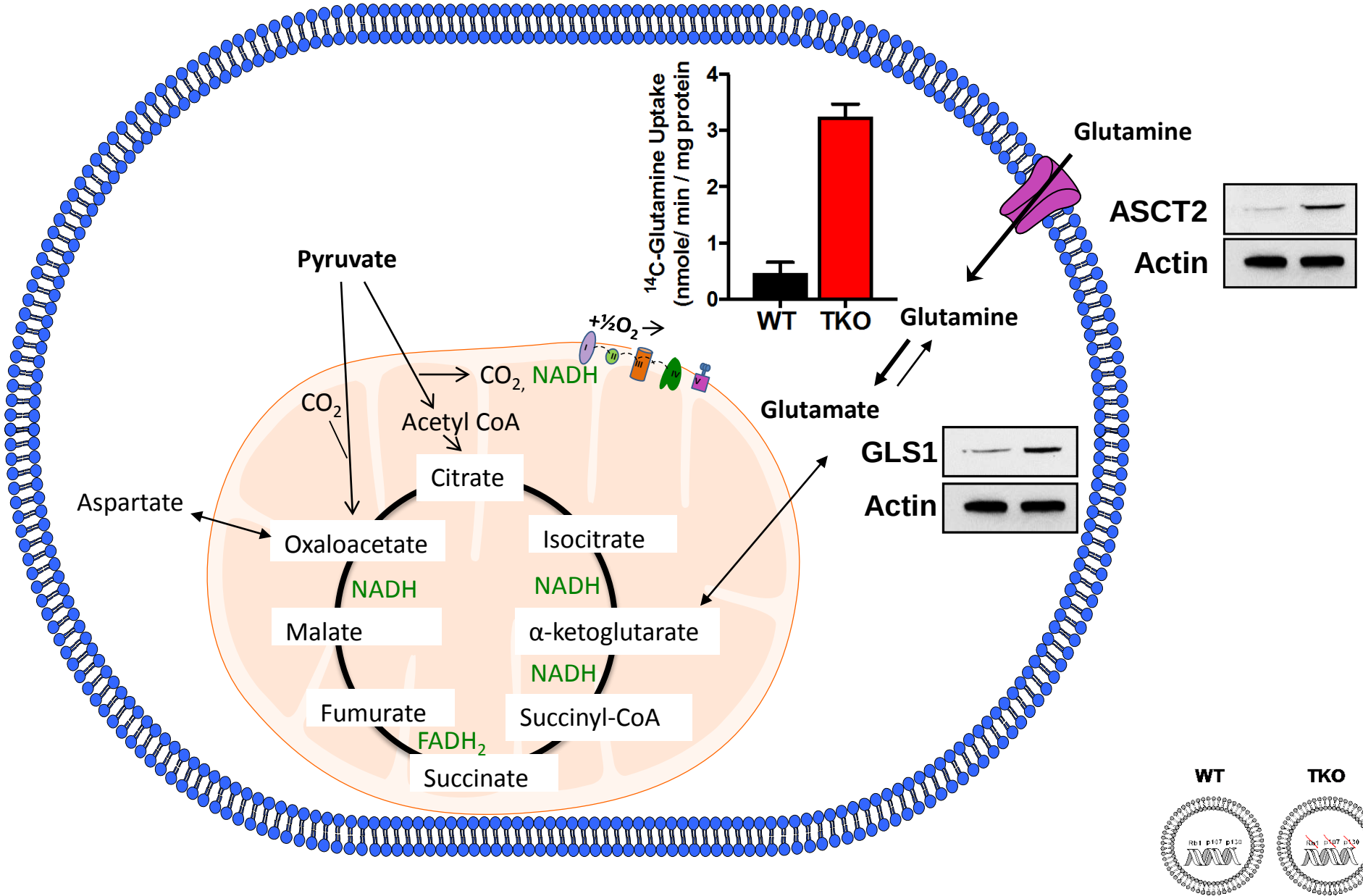
Loss of Rb expression alters lung tumor phenotype

Oncogene 28, 1393–1399

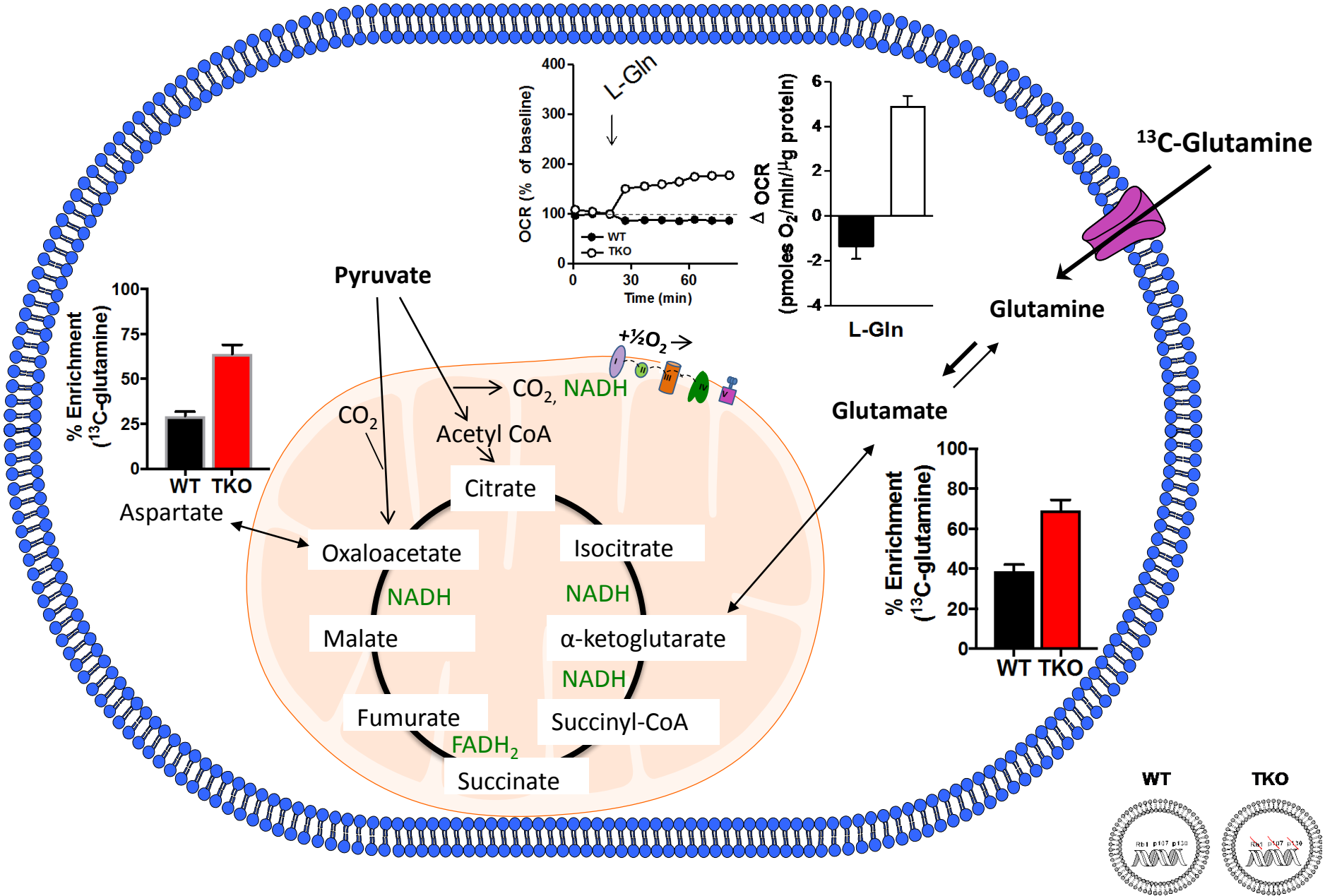
TKO MEFs Exhibit Elevated Oxygen Consumption



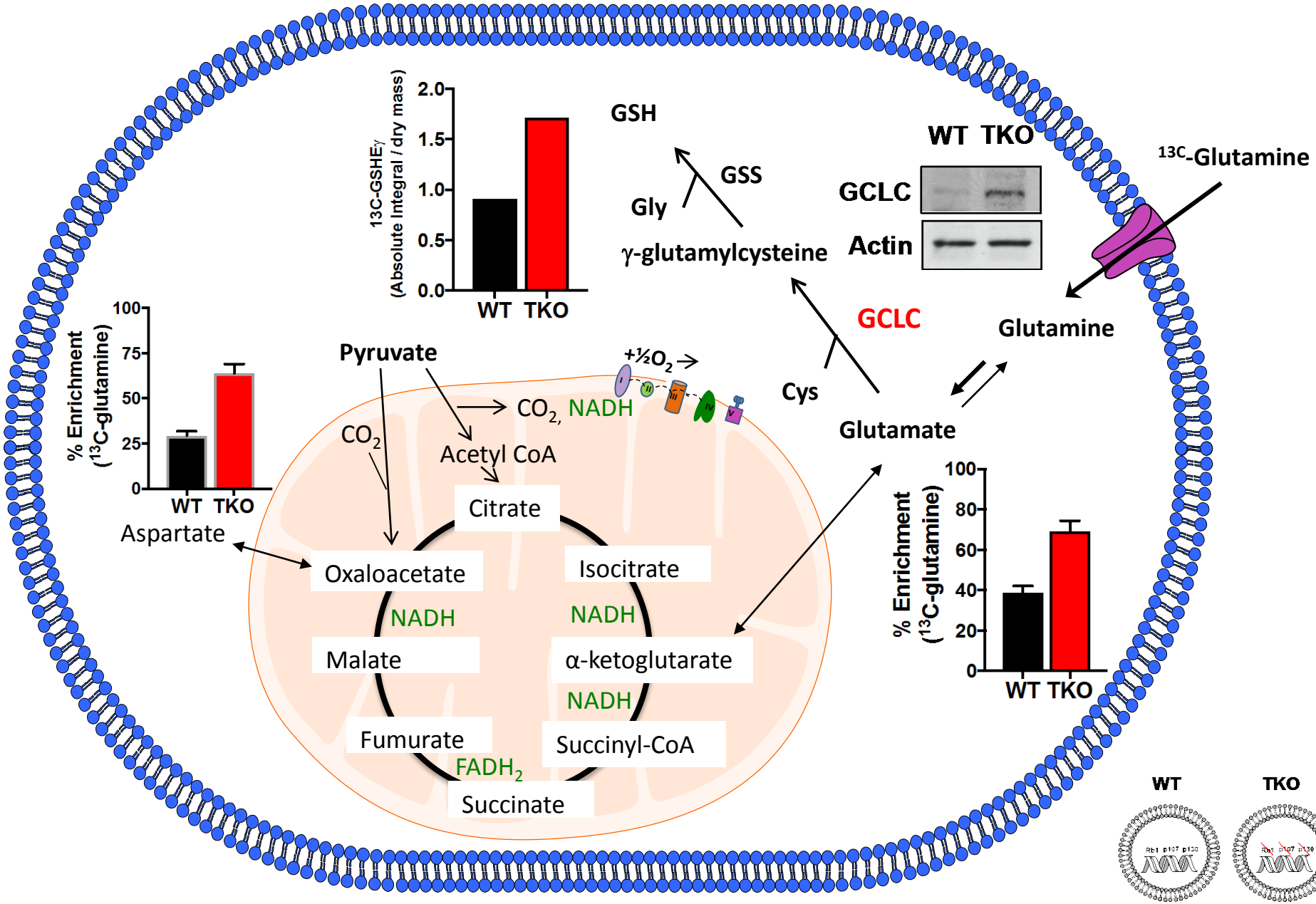
Loss of Rb Increases Glutaminolytic Enzymes and Glutamine Consumption



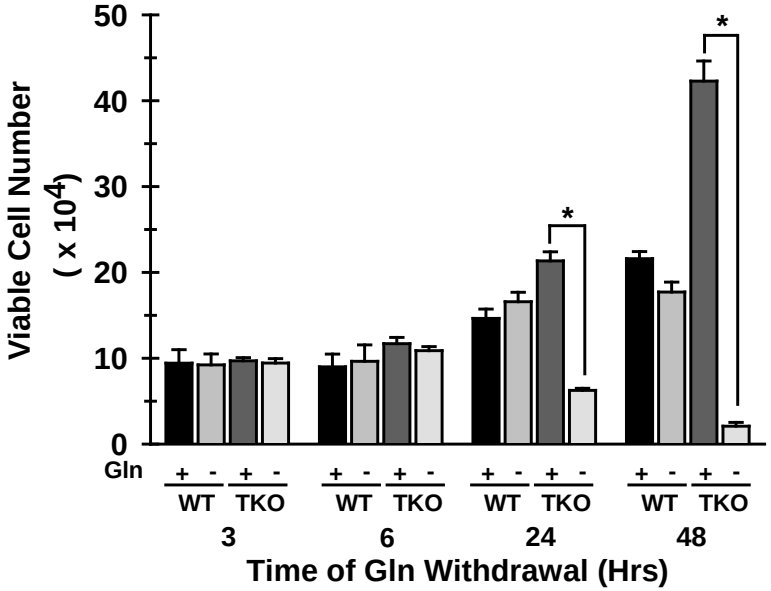
Glutamine Anaplerosis Contributes to Oxygen Consumption in TKO MEFs

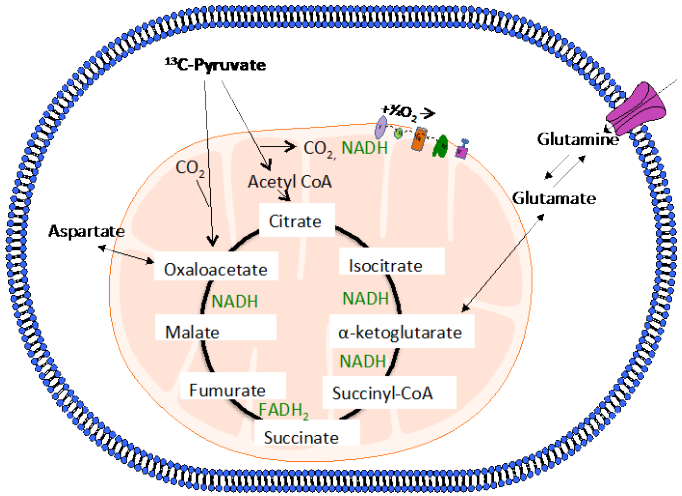


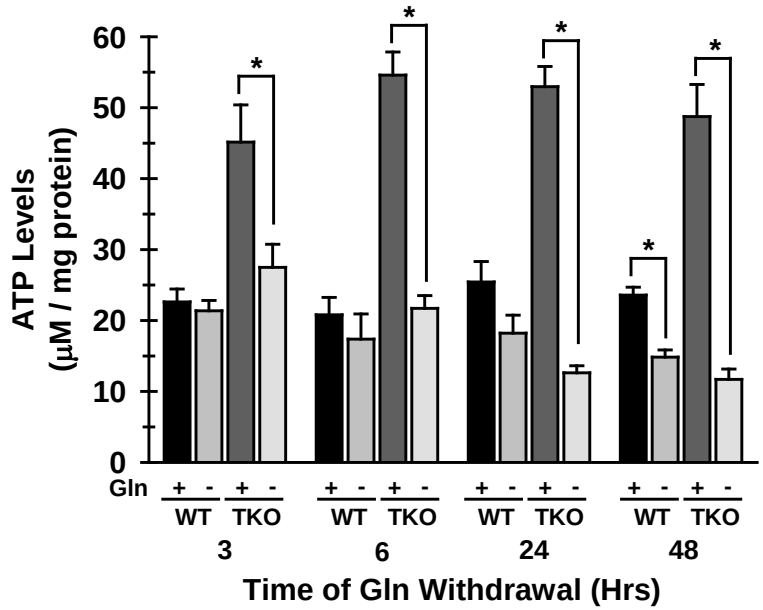
Loss of Rb Function Elevates Glutamine Carbon Incorporation into GSH

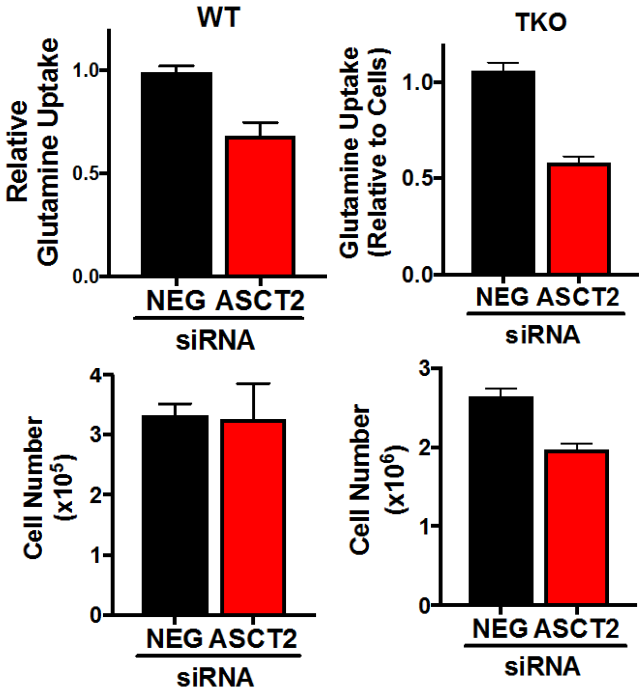


Glutamine Withdrawal or Reduction in Transporter Expression Selectively Affects TKO MEFs

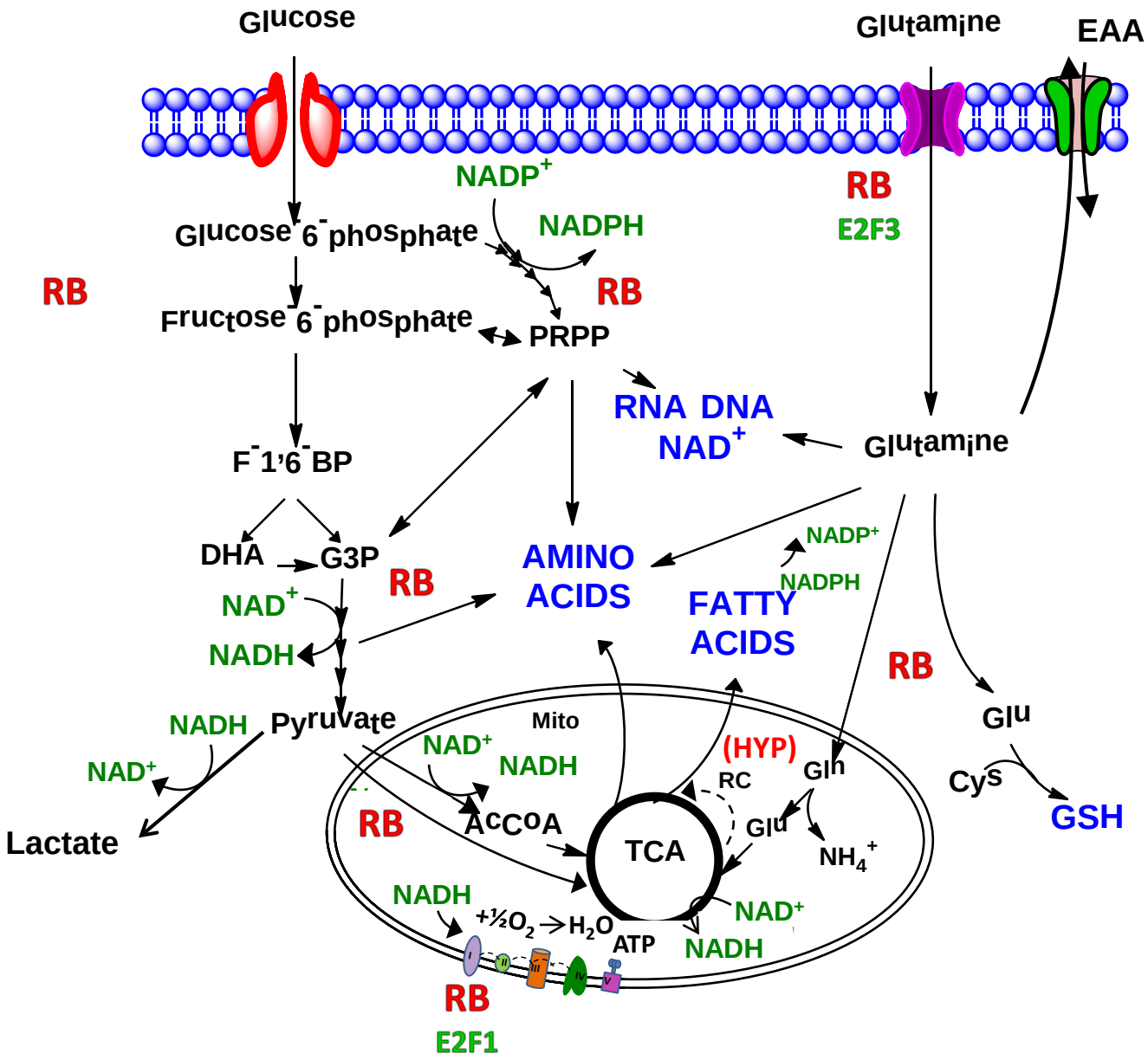








Potential Regulatory Nodes for Rb



Acknowledgements

Clem Lab

Miriam Reynolds
Traci Kruer
Susan Dougherty
Lindsey Reynolds

DOVS- UofL

Doug Dean
Yongqing Liu

RCSIRM

Andrew Lane
Teresa Fan
Rick Higashi

JGBCC NMR

Sam Arumugam

Cardiology

Brad Hill

Center for Regulatory and Environmental Analytical Metabolomics

Xiang Zhang
Biyun Shi
Liqing He

Stanford

Julian Sage
Anne-Flore Zmoos

KLCRP