Cancer cell metabolism: The Warburg effect revisited

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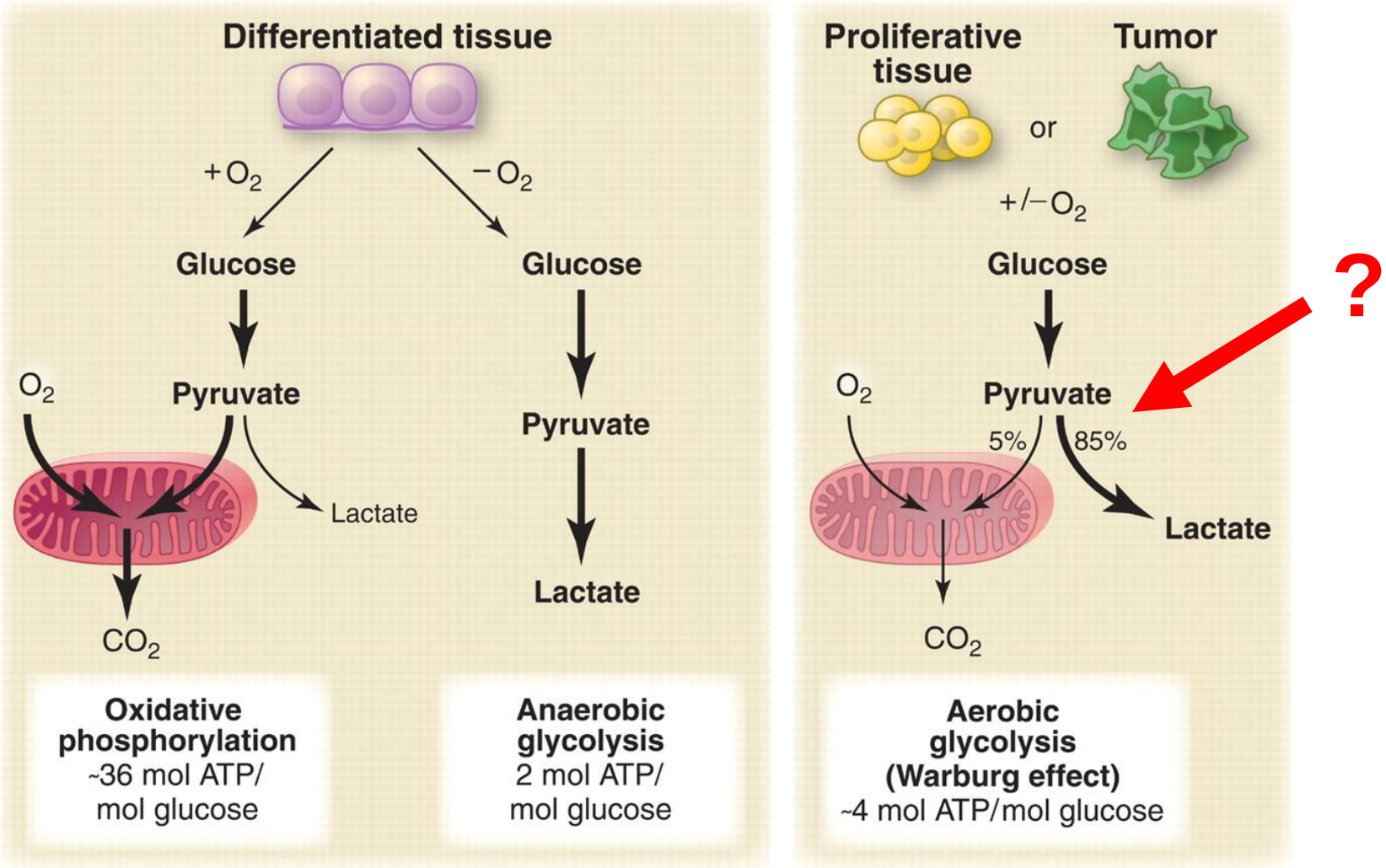
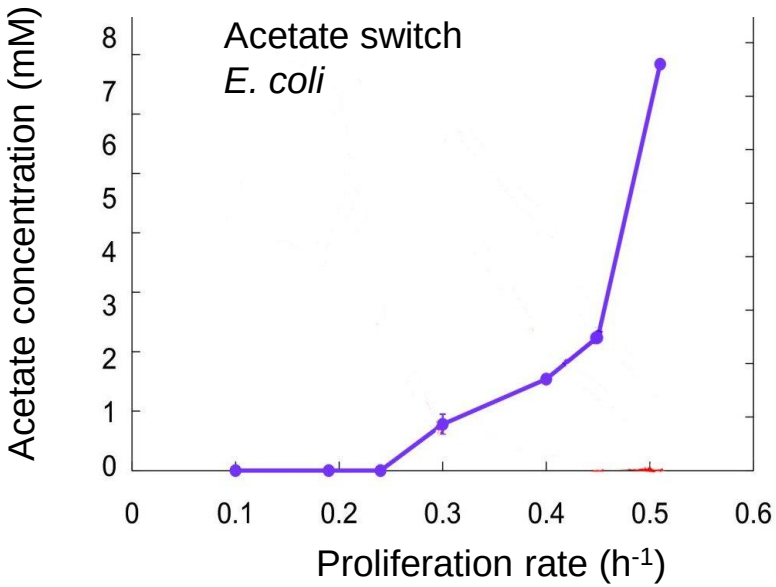
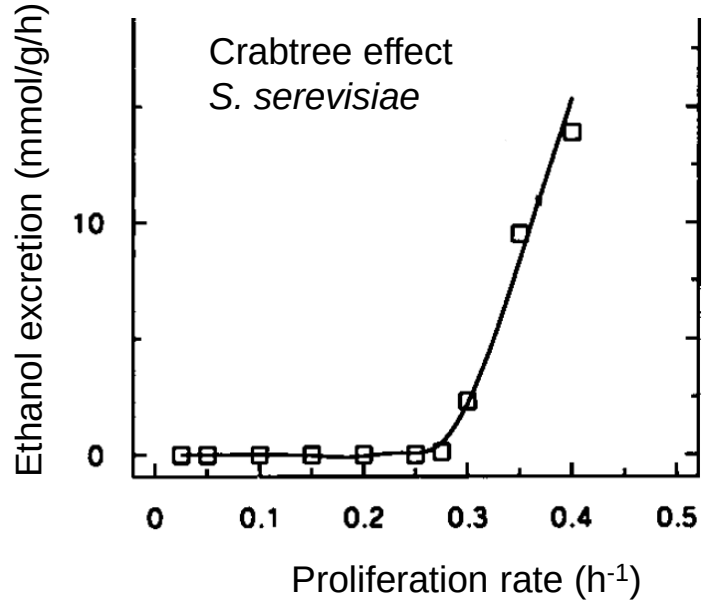
Metabolic states in mammalian cells

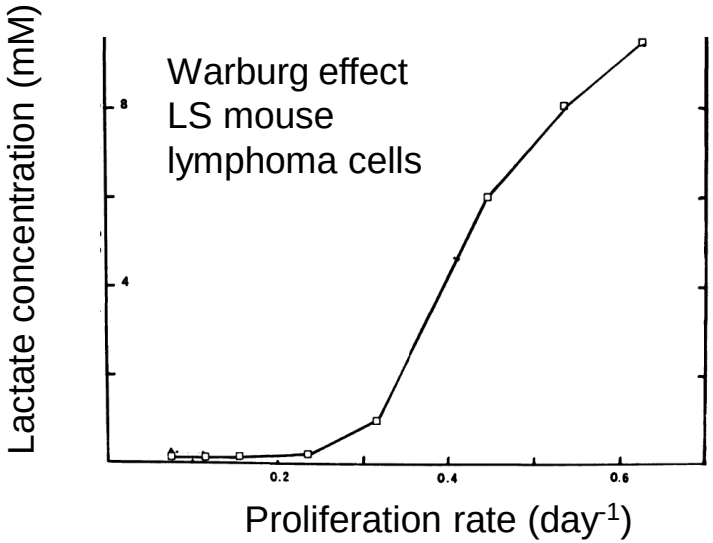


Vander Heiden, Cantley & Thompson (2009) Science 324:1029-1033

Aerobic glycolysis is a general phenomenon, and it is a threshold phenomenon



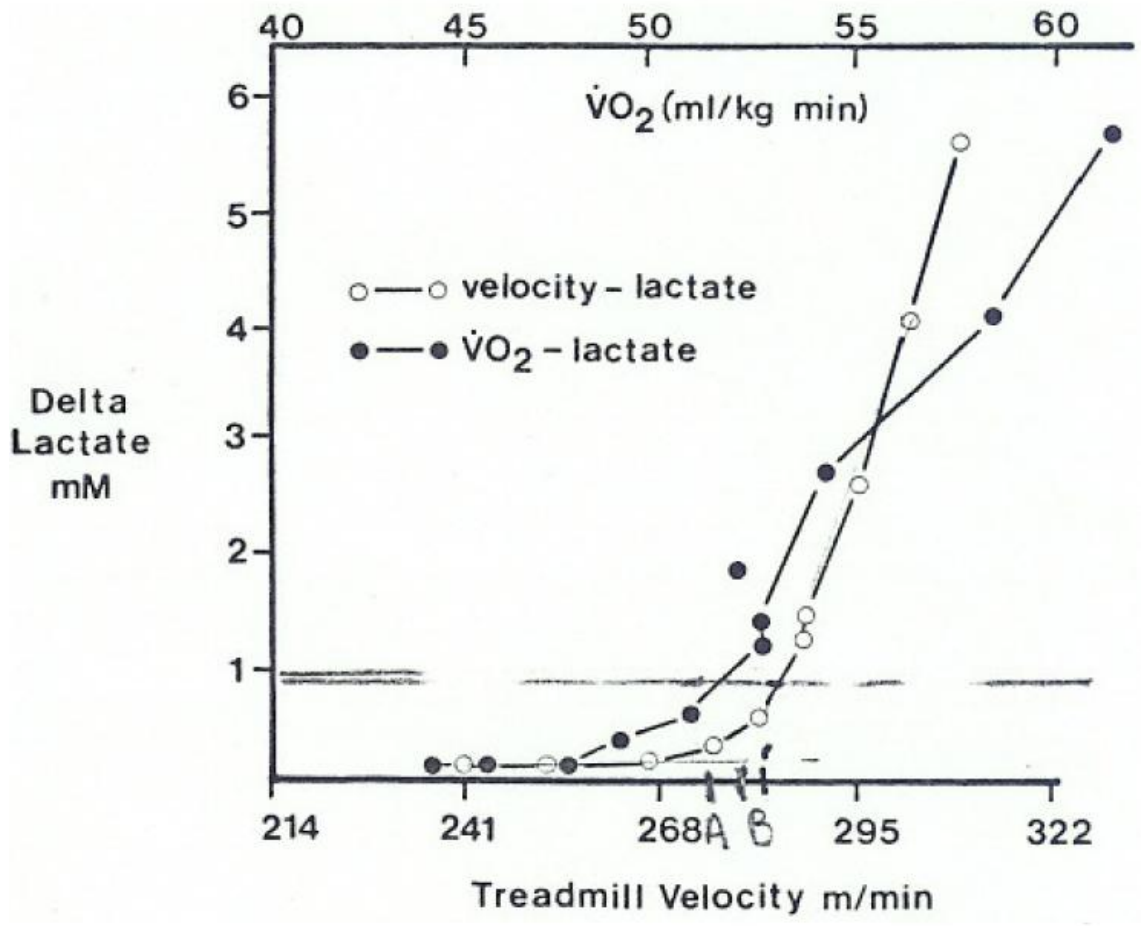




All cultures are under aerobic conditions

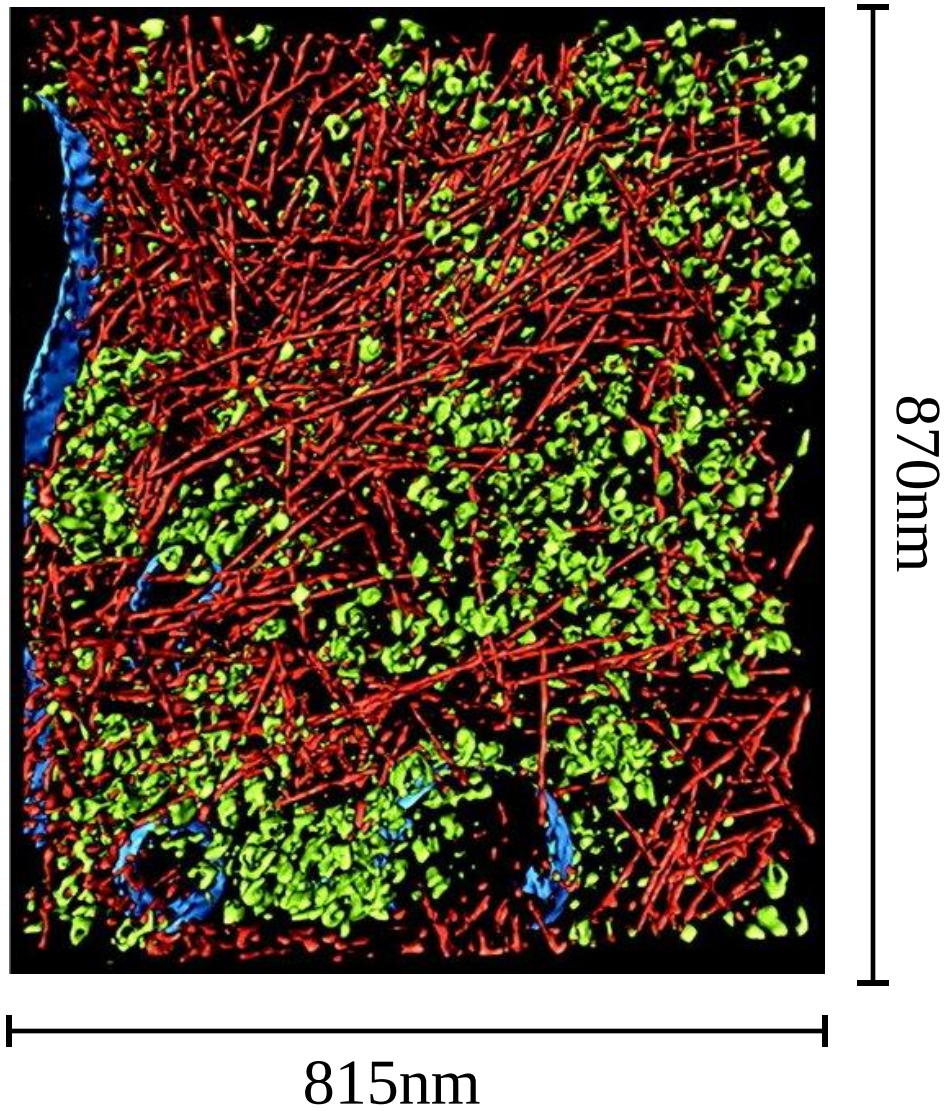
E. coli: Valgepea *et al* (2010)
BMC Syst Biol 4:166
S. serevisiae: Van Hoek *et al* (1998)
Appl Env Microbiol 64:4226-4233
LS mouse cells: Sinclair (1974)
In Vitro 10:295-305

Aerobic glycolysis in non-proliferating cells



Farrell et al (1979) Plasma lactate accumulation and distance running performance. Medicine and Science in Sports 11:338-344

Molecular crowding



Actin filaments

Ribosomes

Membranes

Electron tomography image of *Dictyostelium discoideum* (social amoeba)

Madalia *et al* (2002)
Science 298:1209-1213

Crowding coefficient

Relative cell volume fraction occupied by the enzyme (pathway enzymes) per unit of reaction (pathway) rate

$$a = \phi / f = vE / kE = v / k$$

ϕ	occupied volume fraction
f	reaction rate
E	enzyme concentration
v	enzyme molar volume
k	effective turnover number

Glycolysis vs Oxidative phosphorylation

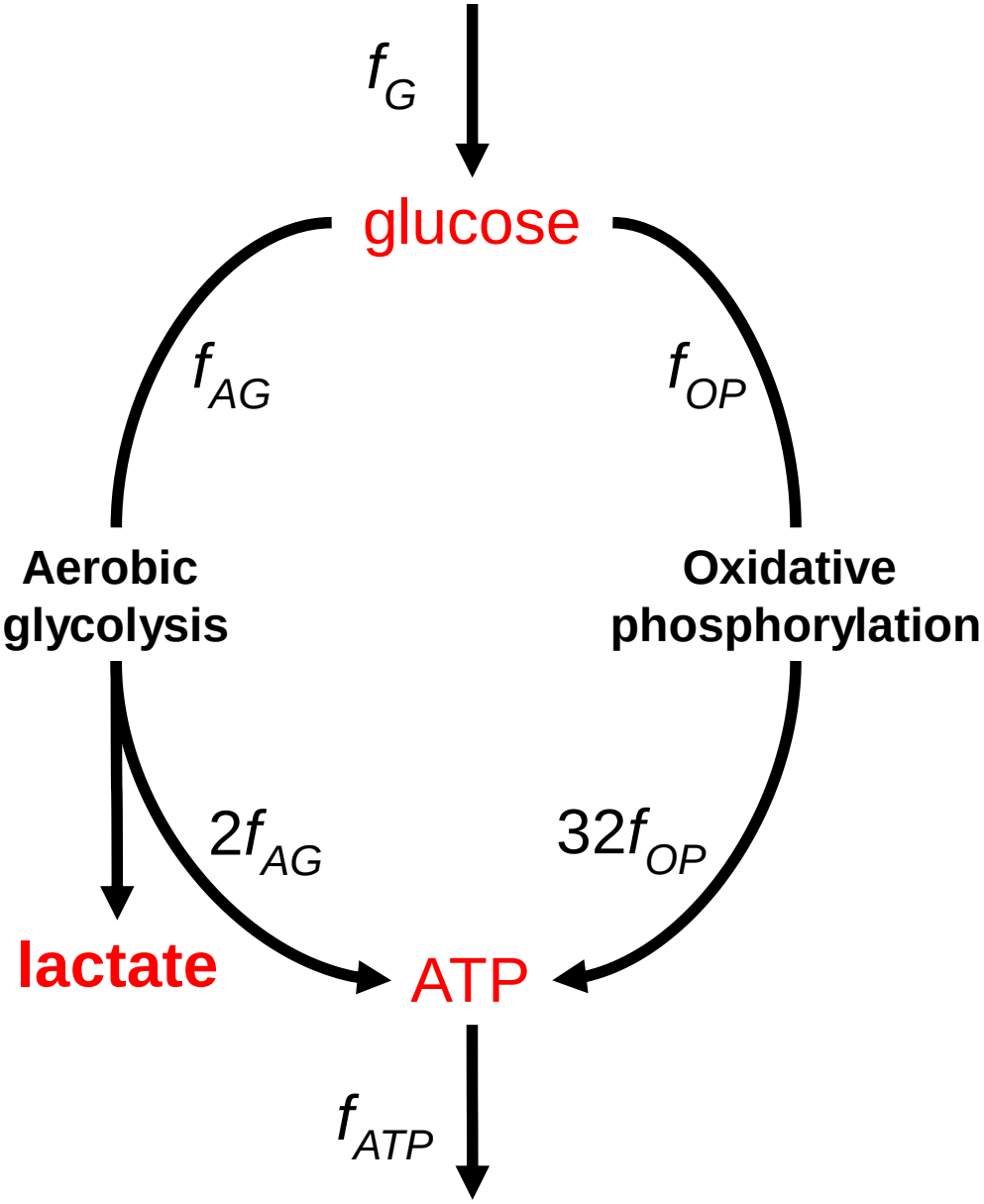
Yield

Glycolysis	Y_G=2 mol ATP / mol glucose
OxPhos	Y_{OP}=32 mol ATP / mol glucose

Crowding coefficient

Glycolysis	a_G~0.0014 / (mM ATP/min)
OxPhos	a_{OP}~0.017 / (mM ATP/min)

Simplified model



Given the ATP demand f_{ATP} and the maximum volume fraction ϕ_0 (about 0.4), what are the values of f_{OP} and f_{AG} that minimize f_G?

Minimize

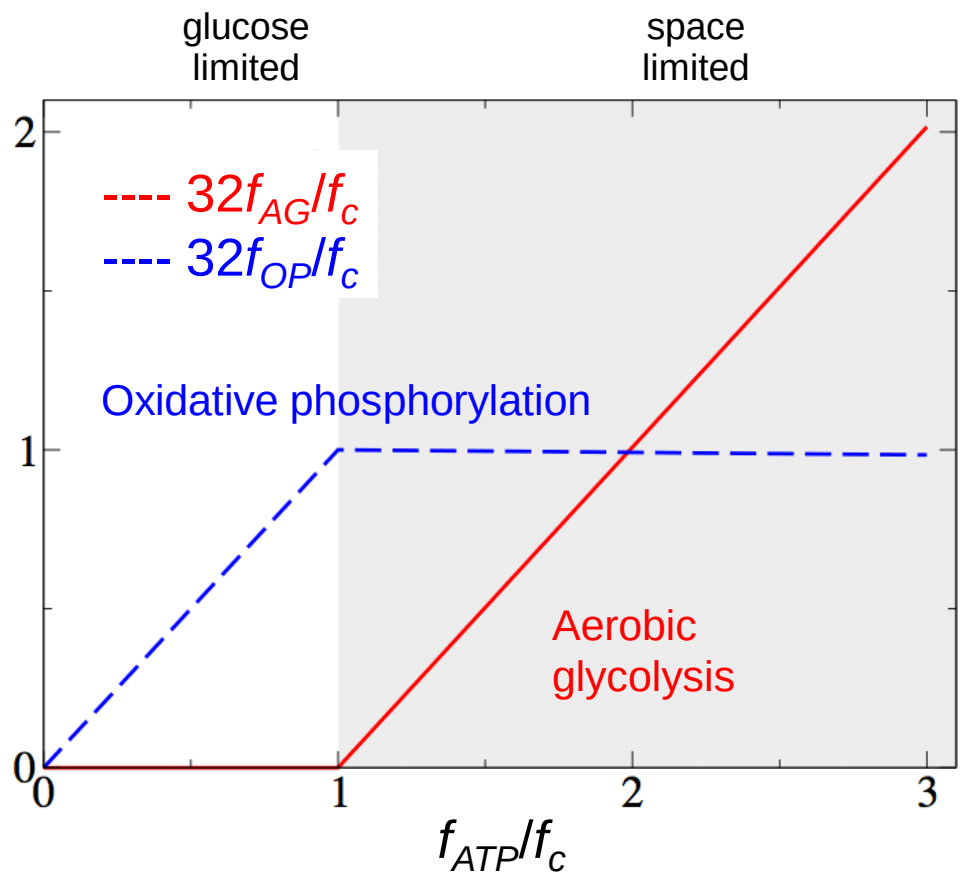
$$f_G = f_{AG} + f_{OP}$$

subject to the constraints

$$2f_{AG} + 32f_{OP} = f_{ATP}$$

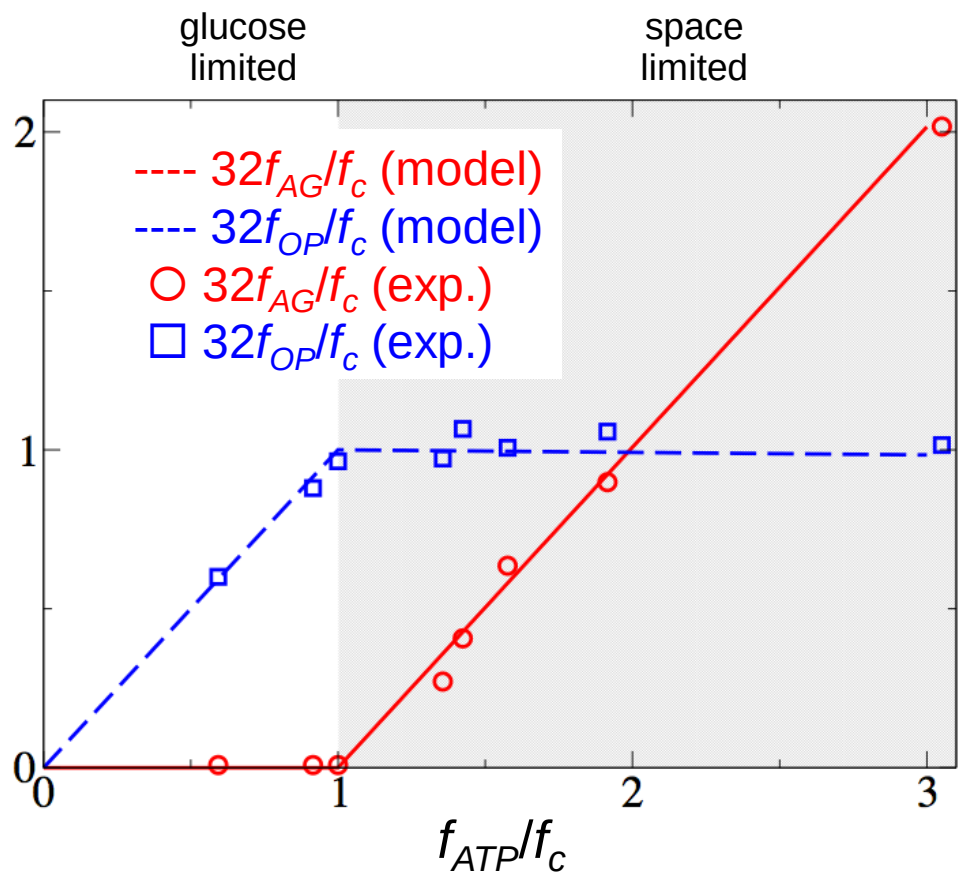
$$a_G 2f_{AG} + a_{OP} 32f_{OP} \square \phi_0$$

Simplified model



$f_c = \phi_0 / a_{OP}$ ~ 24 mM ATP/min

Simplified model



Model

f_c=24 mM/min

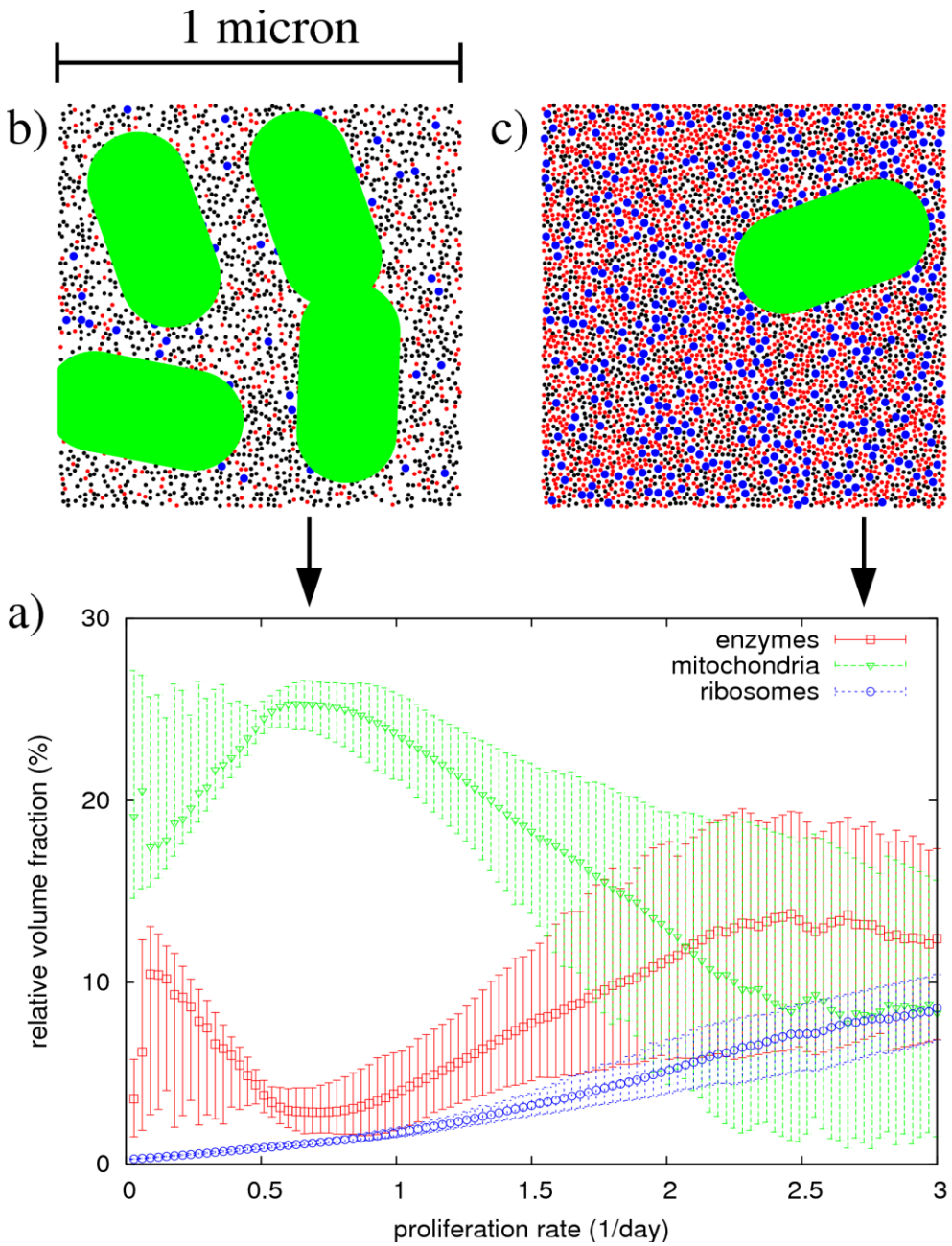
LS mouse cells

f_c=30 mM/min

Experimental data from

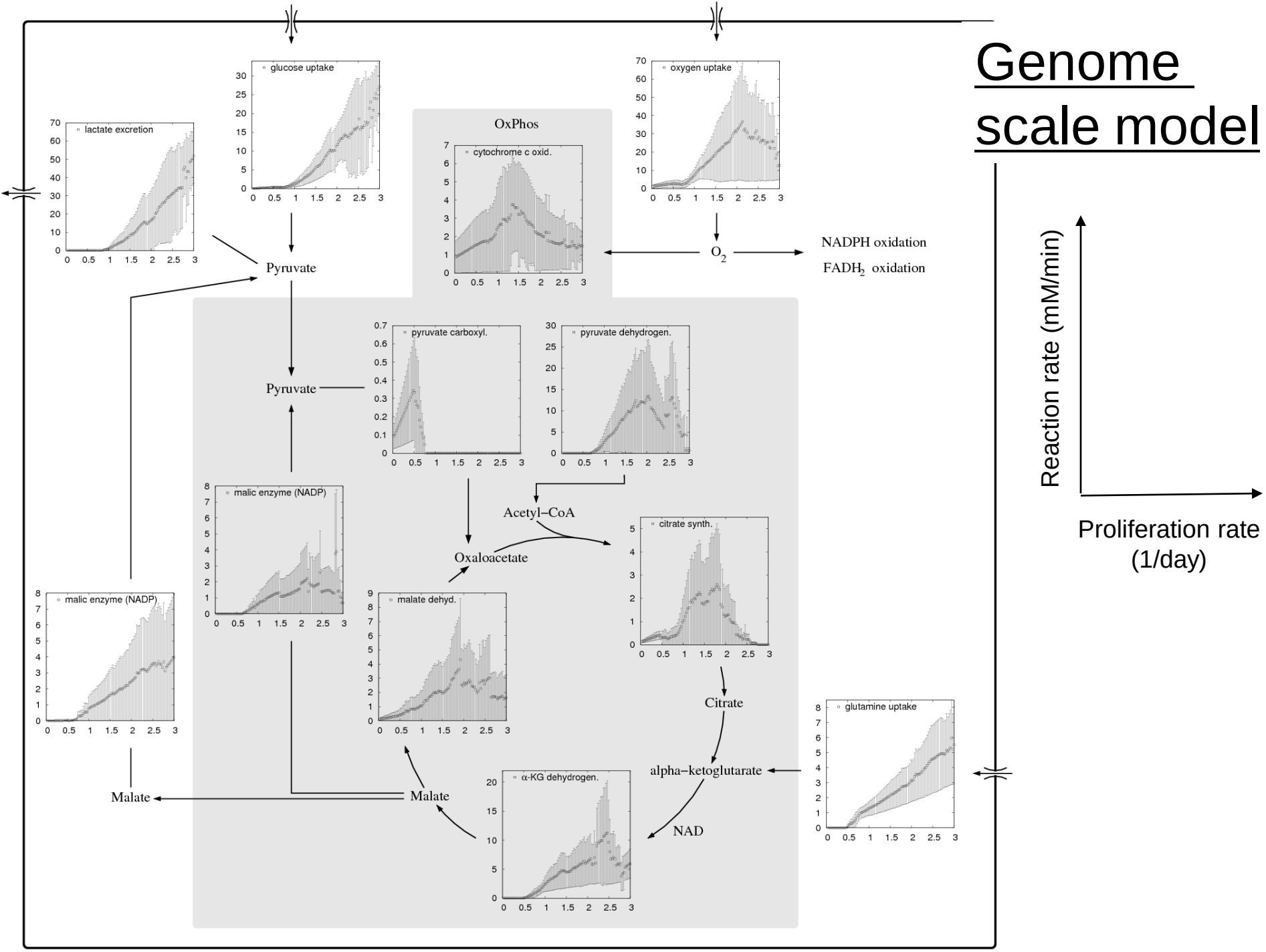
Sinclair R (1974) Response of mammalian cells to controlled growth rates in steady-state continuous culture, In Vitro 10:295-305

Genome scale model

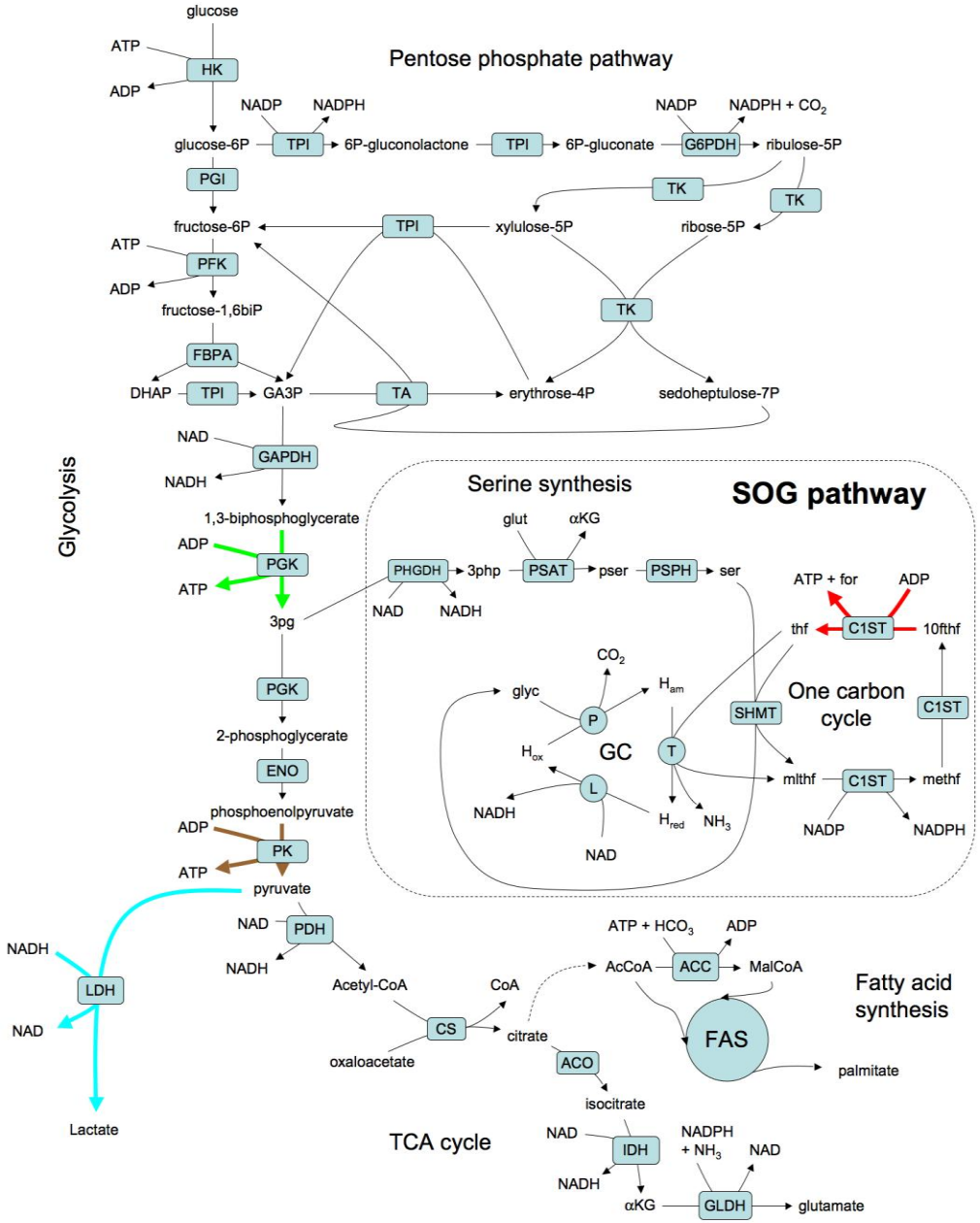


- mitochondria
- ribosomes
- enzymes
- structural proteins

Genome scale model

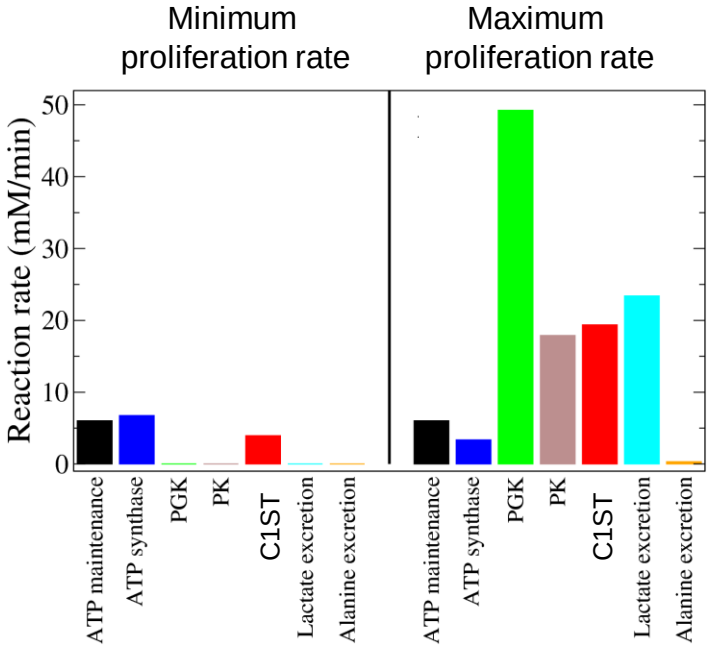


Predicted pathway for ATP production

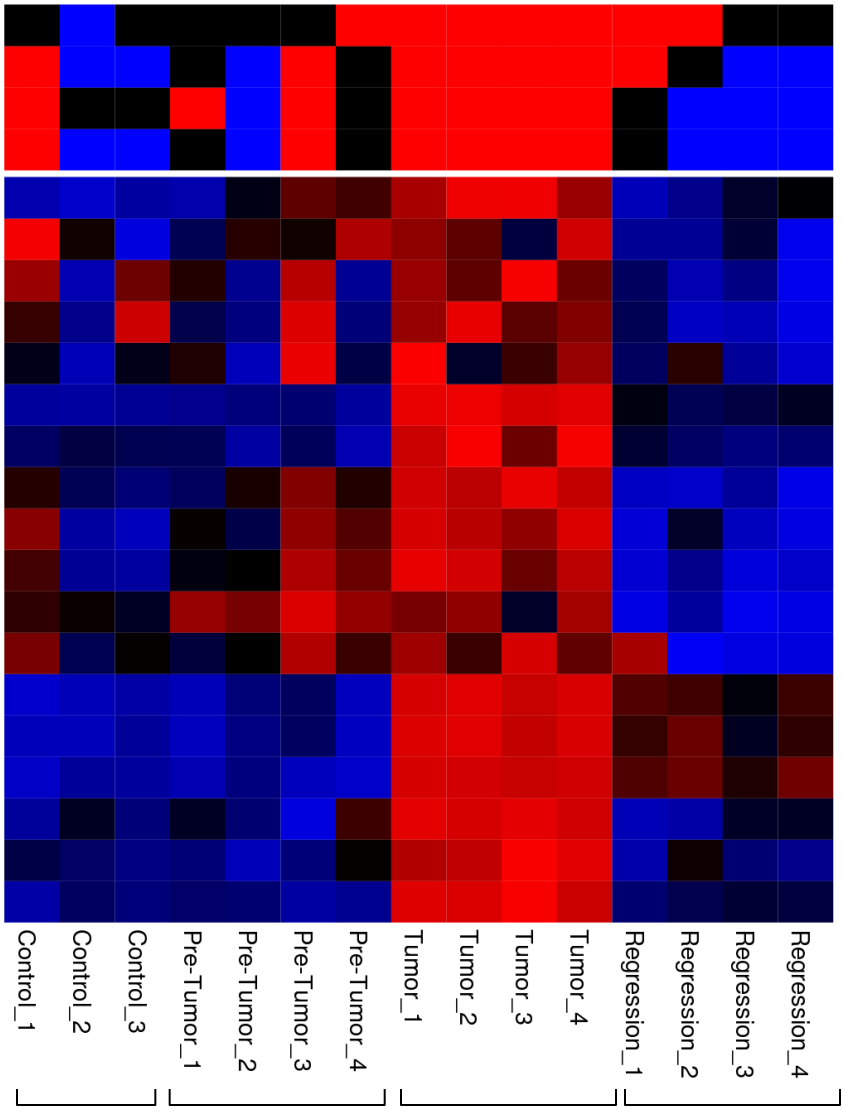


C1ST: C_1-tetrahydrofolate synthase

4 mol ATP / mol glucose



The predicted pathway is driven by Myc



YU_MYC_TARGETS_UP
DANG_MYC_TARGETS_UP
COLLER_MYC_TARGETS_UP
SCHUHMACHER_MYC_TARGETS_UP

Myc targets signatures

GLDC
GCSH
DLD
DLD
DLD

Glycine cleavage system

MTHFD1L
MTHFD2
SHMT2
MTHFD1
MTHFD1
SHMT1
SHMT1

One carbon metabolism

PSPH
PSPH
PSAT1
PHGDH
PHGDH
PHGDH

Serine biosynthesis

Normal

4-5 weeks after Myc induction

8-10 weeks after Myc induction

3 days after Myc inactivation

Based on data from Hu et al 2011