



# **Cell cycle regulators are crucial mediators of metabolism in normal and in cancer cells**

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## Déclaration de lien d'intérêt

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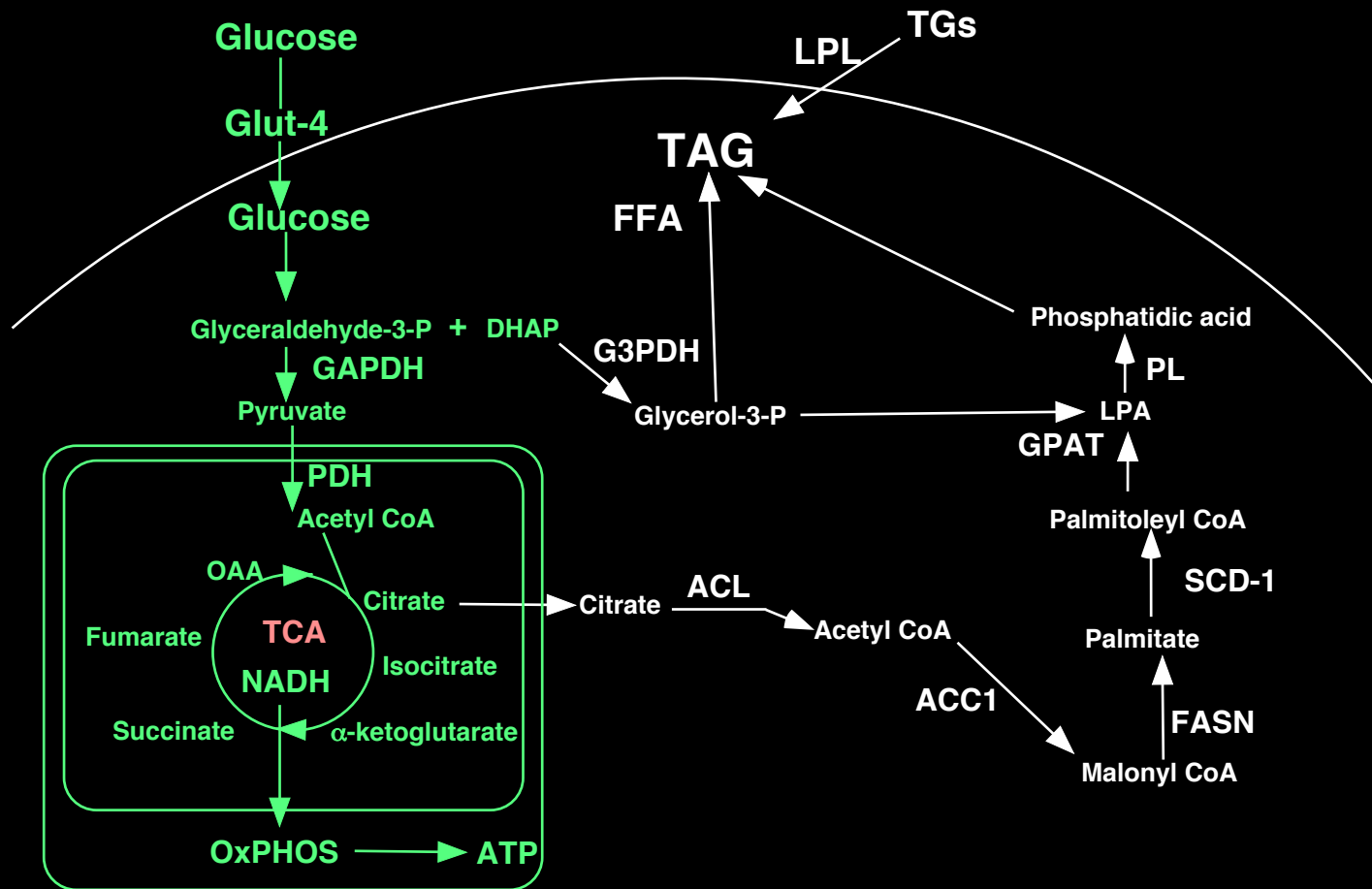
Je n'ai aucune affiliation ou lien financier avec une organisation Commerciale qui constitue un lien d'intérêt avec ma présentation

# **Metabolism**

**From the greek *metabolos*: changes, transformation**

**These are the mechanisms that are used to transform substrates, products, and molecules into energy, which is required to support function or structure of a cell, an organ, or an organism**

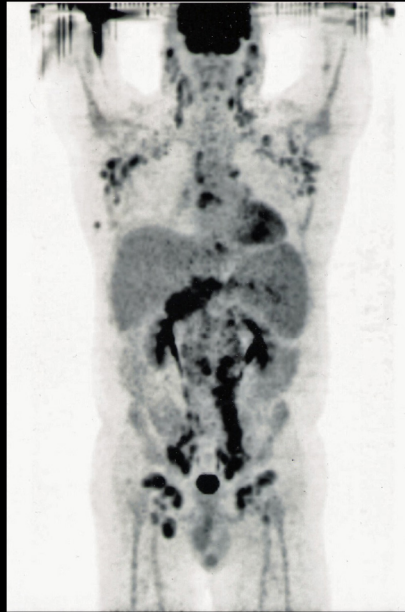
# Oxidative and glycolytic metabolism



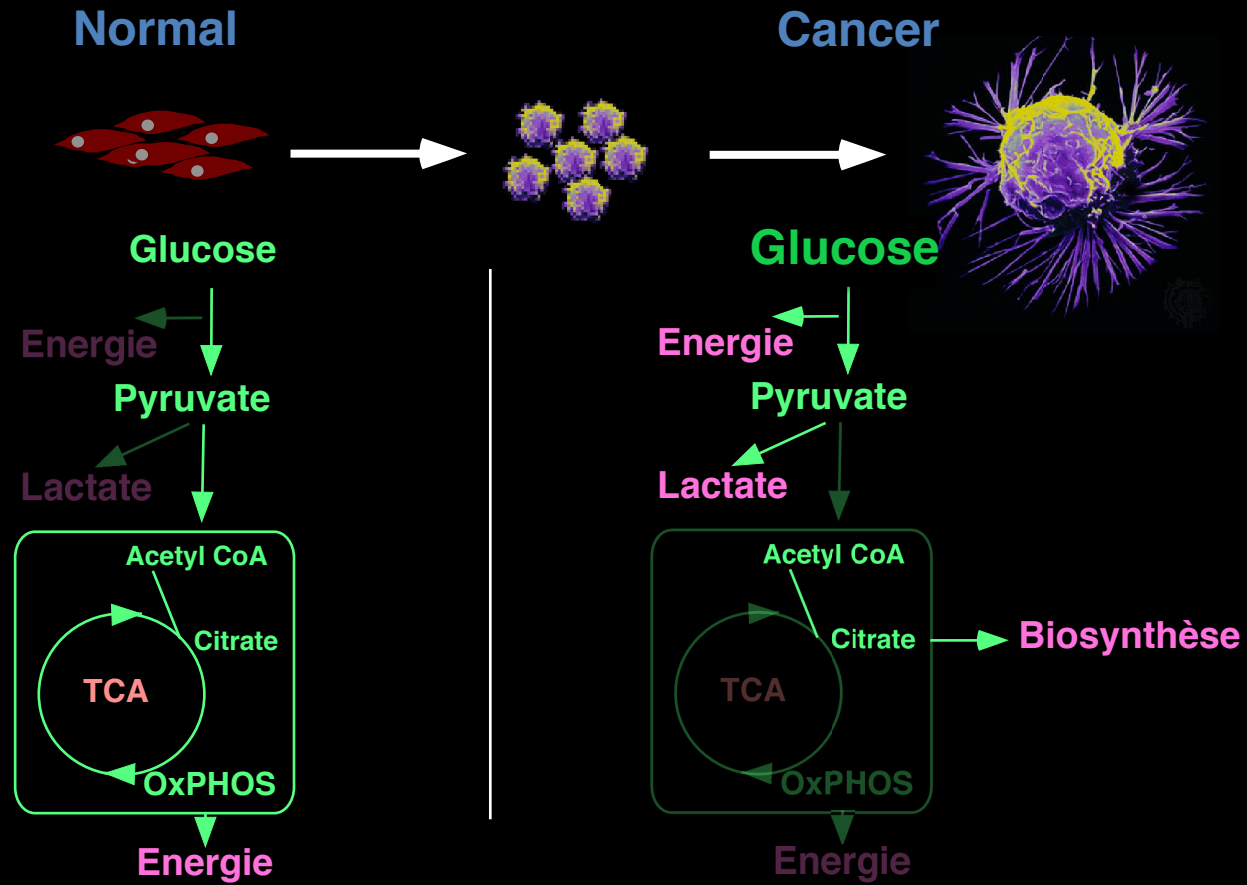
# Cancer cells are addicted to glucose

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PET-scan



# The metabolic switch



**How does it happen ?**

# A dual interdependent role for cell cycle regulators

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Hormones , nutrition, insulin,  
metabolites, growth factors,  
**Oncogenic pathways**

↓  
**Cell cycle regulators**

↙ ↘  
**Metabolic changes**  
lipid synthesis, oxidative, glucose

**Cell cycle**

↘ ↙  
**Cell proliferation**

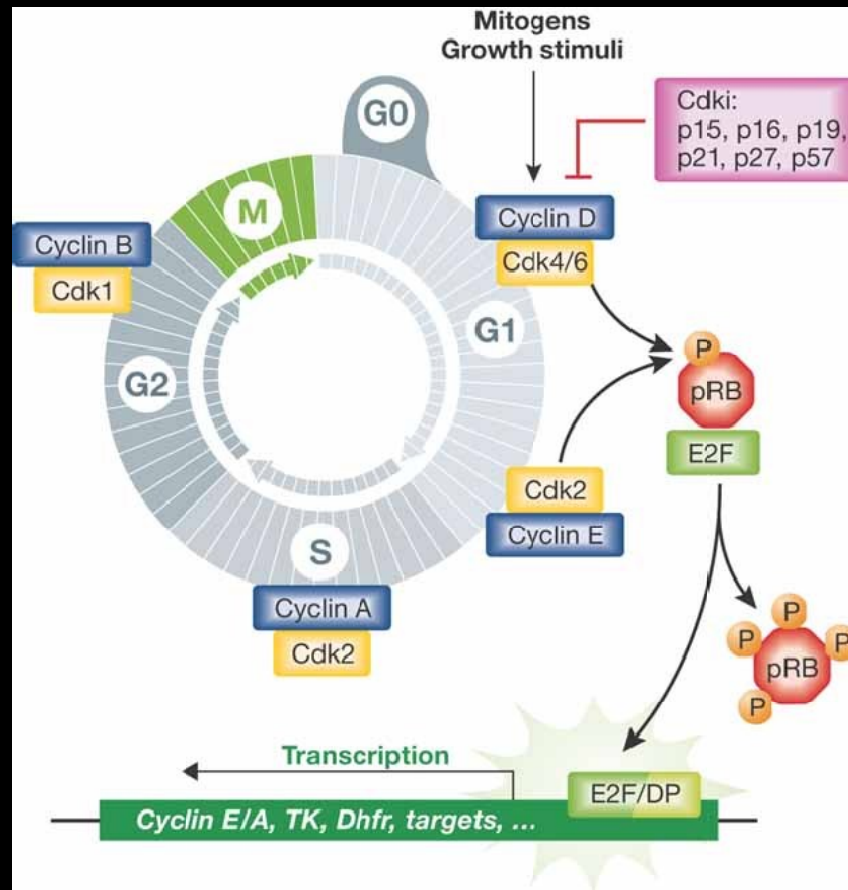
↓  
**Metabolic pathologies**  
(obesity, diabetes)

↓  
**Regeneration, Development,**  
**CANCER**

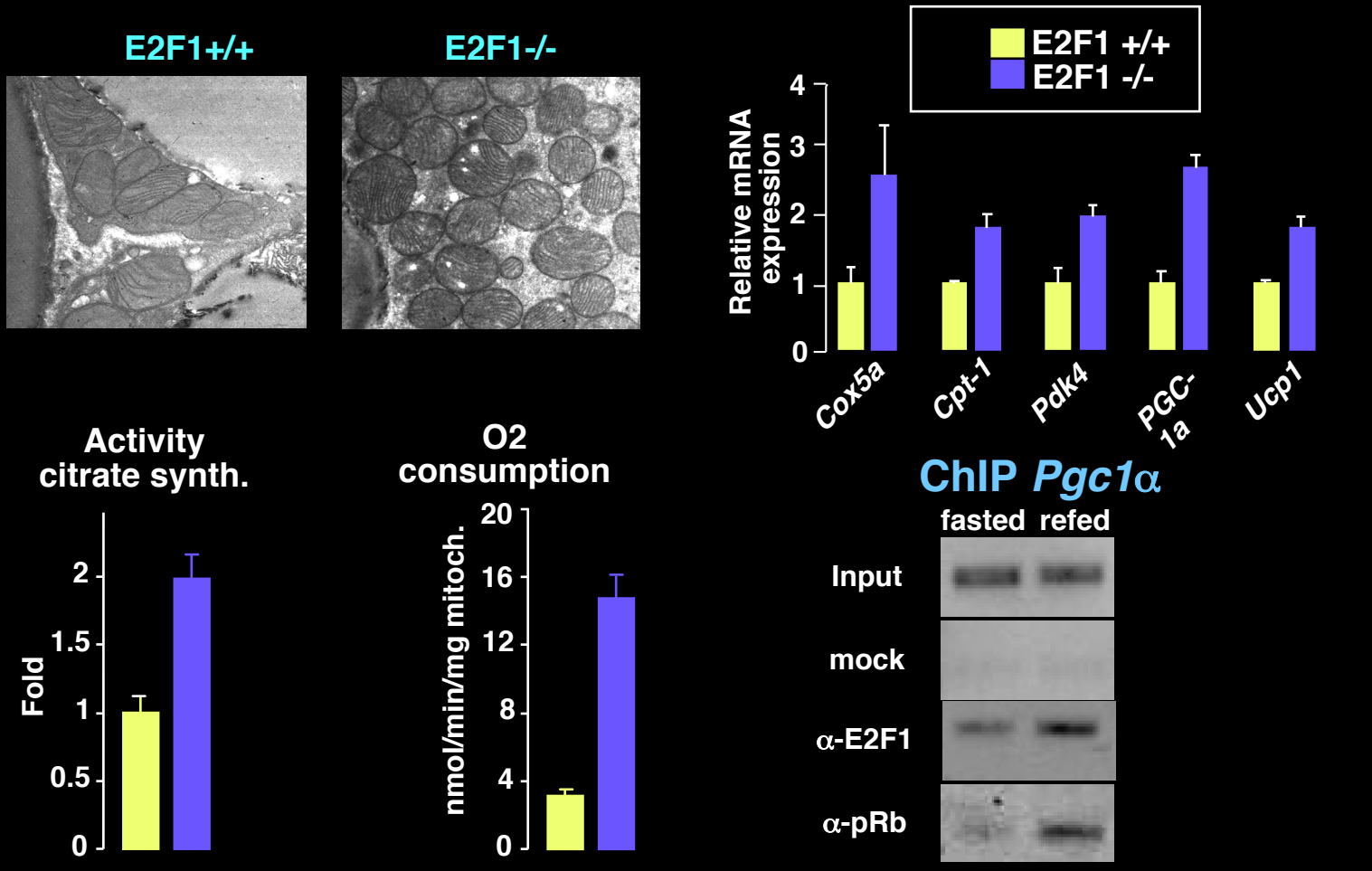
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# The cell cycle

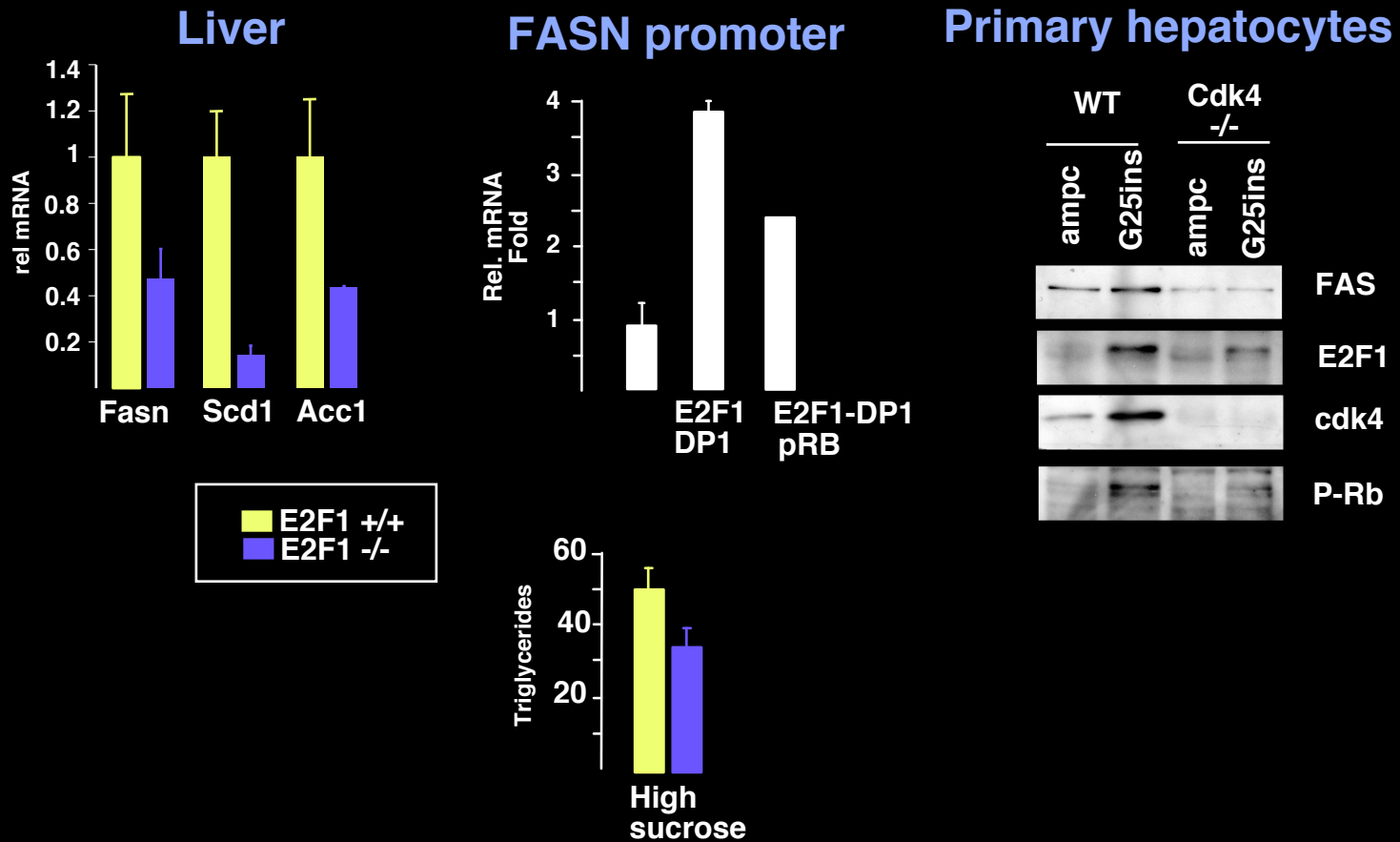


# E2F1 modulates oxidative metabolism



Annicotte et al. 2011 Nat. Cell. Biol.

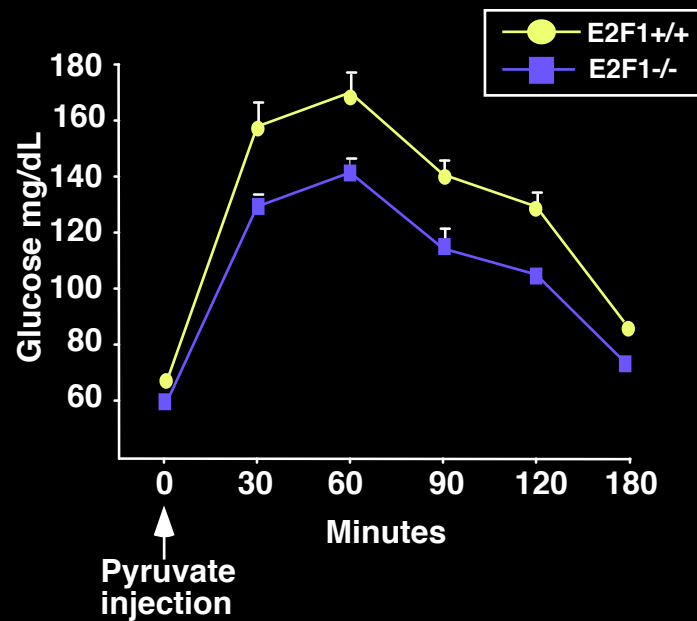
# E2F1 controls lipid synthesis pathways



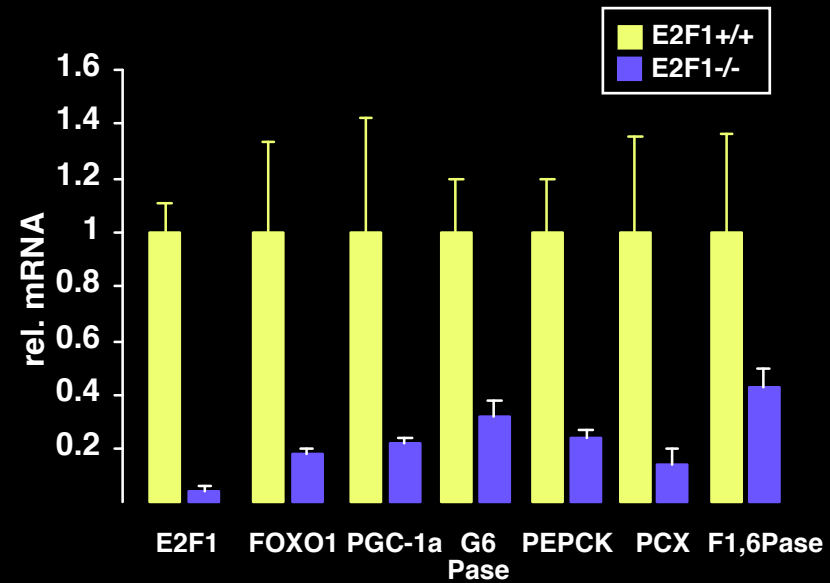
# E2F1 controls glucose production in liver

Pyruvate  $\xrightarrow{\text{Gluconeogenesis}}$  Glucose

## Pyruvate tolerance test



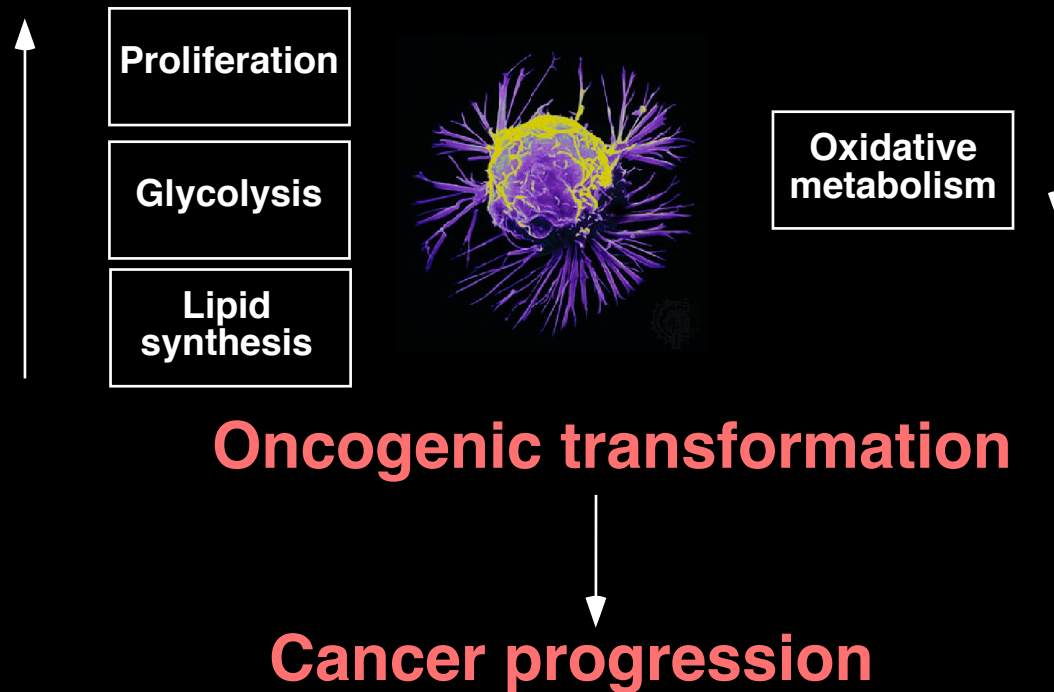
## Gene expression



# E2F1 is a dual regulator of proliferation and metabolism in cancer cells

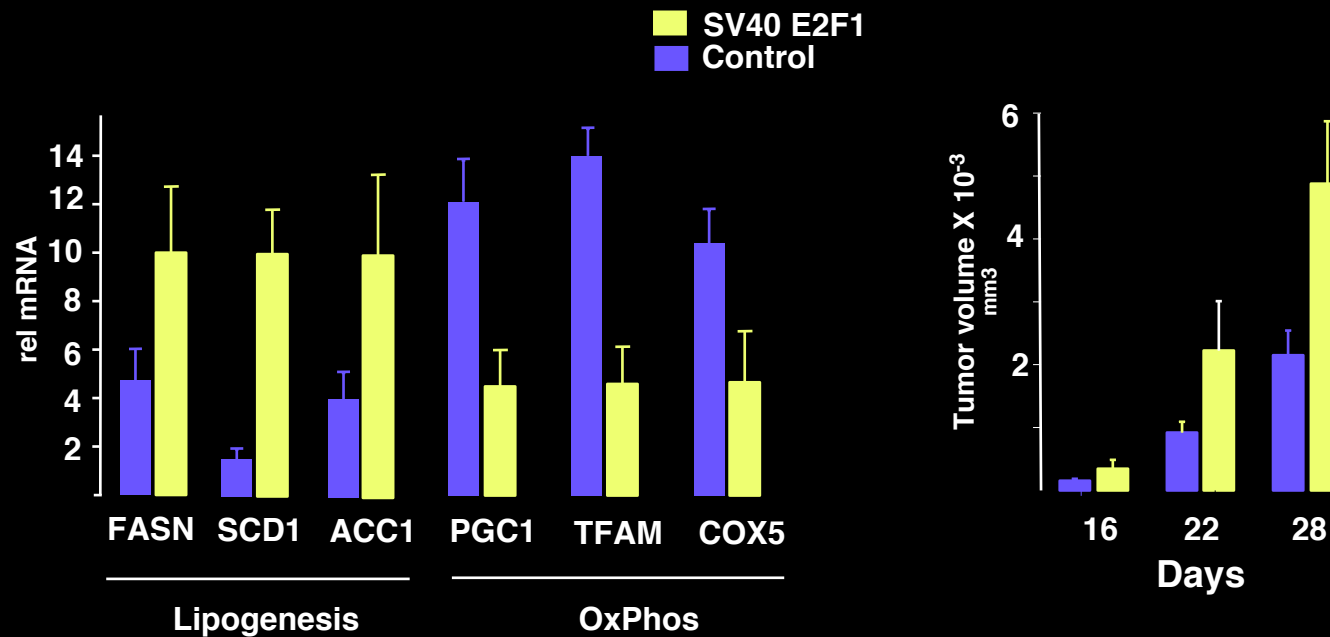
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## E2F1-pRB-cdk4 In cancer cells

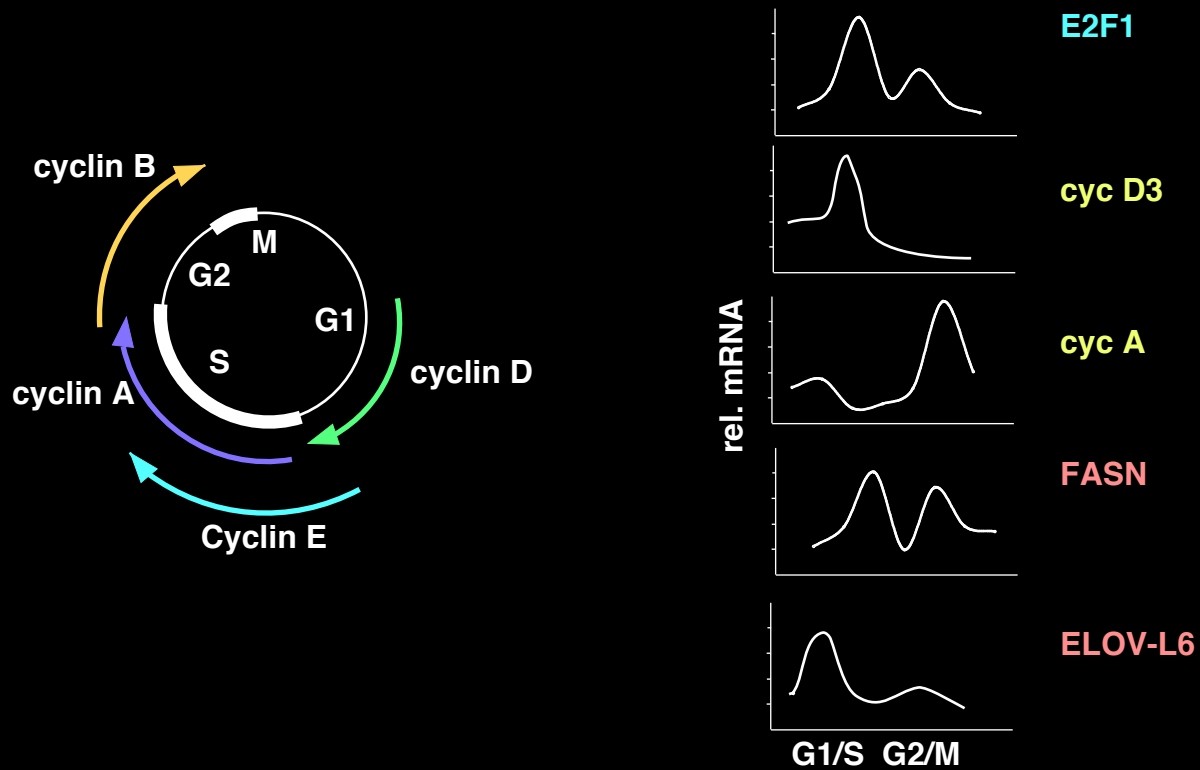


# E2F1 regulates the expression of metabolic genes in transformed cells and in tumors

## MEF Tumors

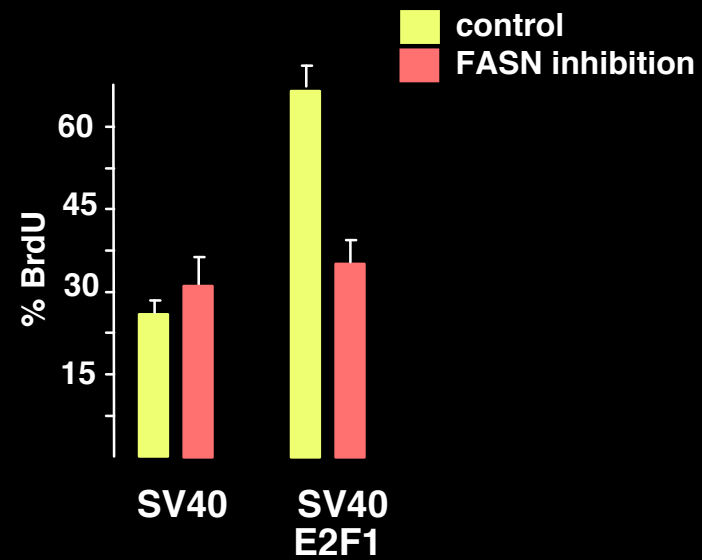


# Lipogenic genes are regulated in an E2F1- and cell cycle-dependent manner



## Inhibition of lipid synthesis abrogates E2F1-mediated transformation

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**How can we use metabolic E2F1-cdk4 targets in cancer cells for therapy ?**

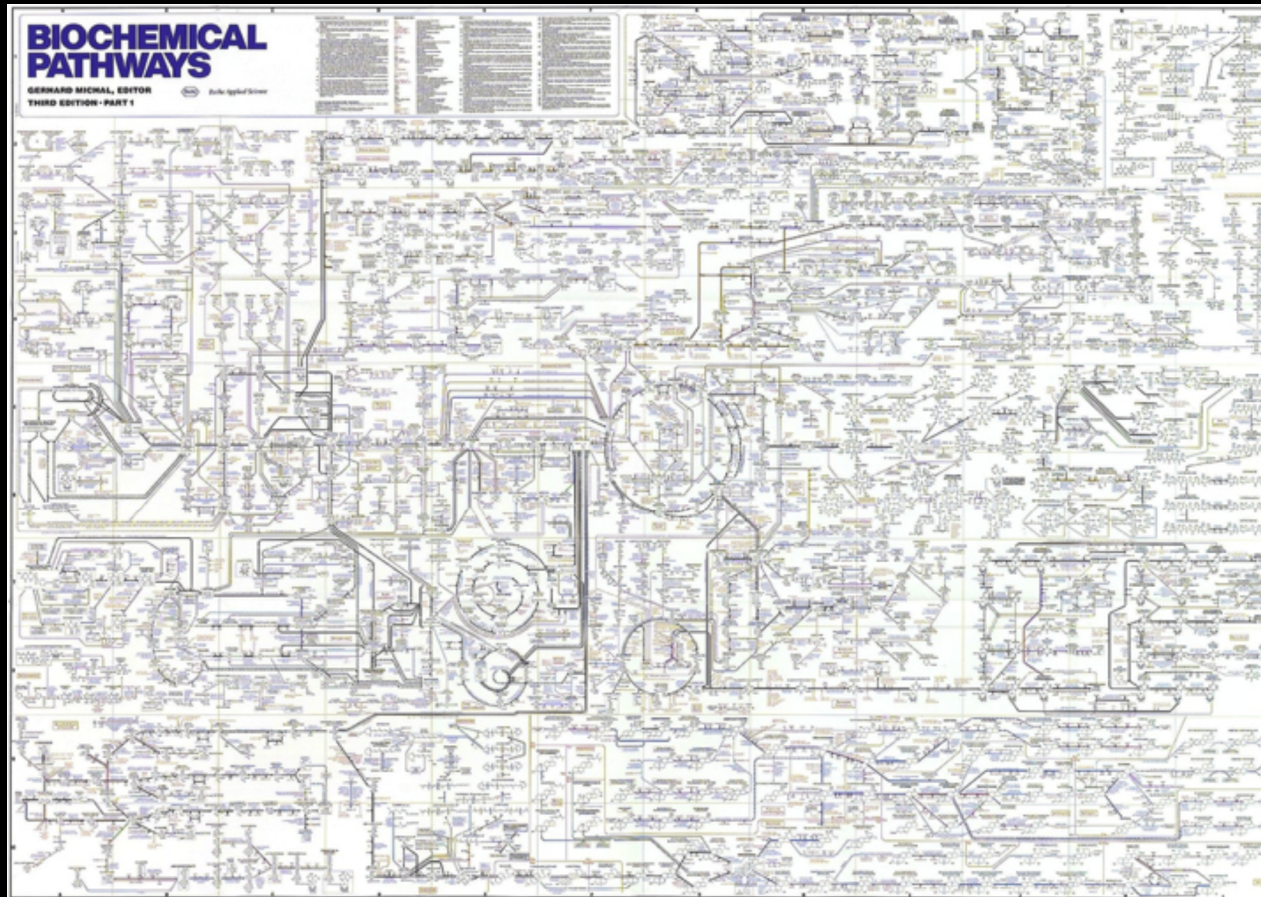
**How to approach it ?**

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# These are city pathways



# These are metabolic pathways

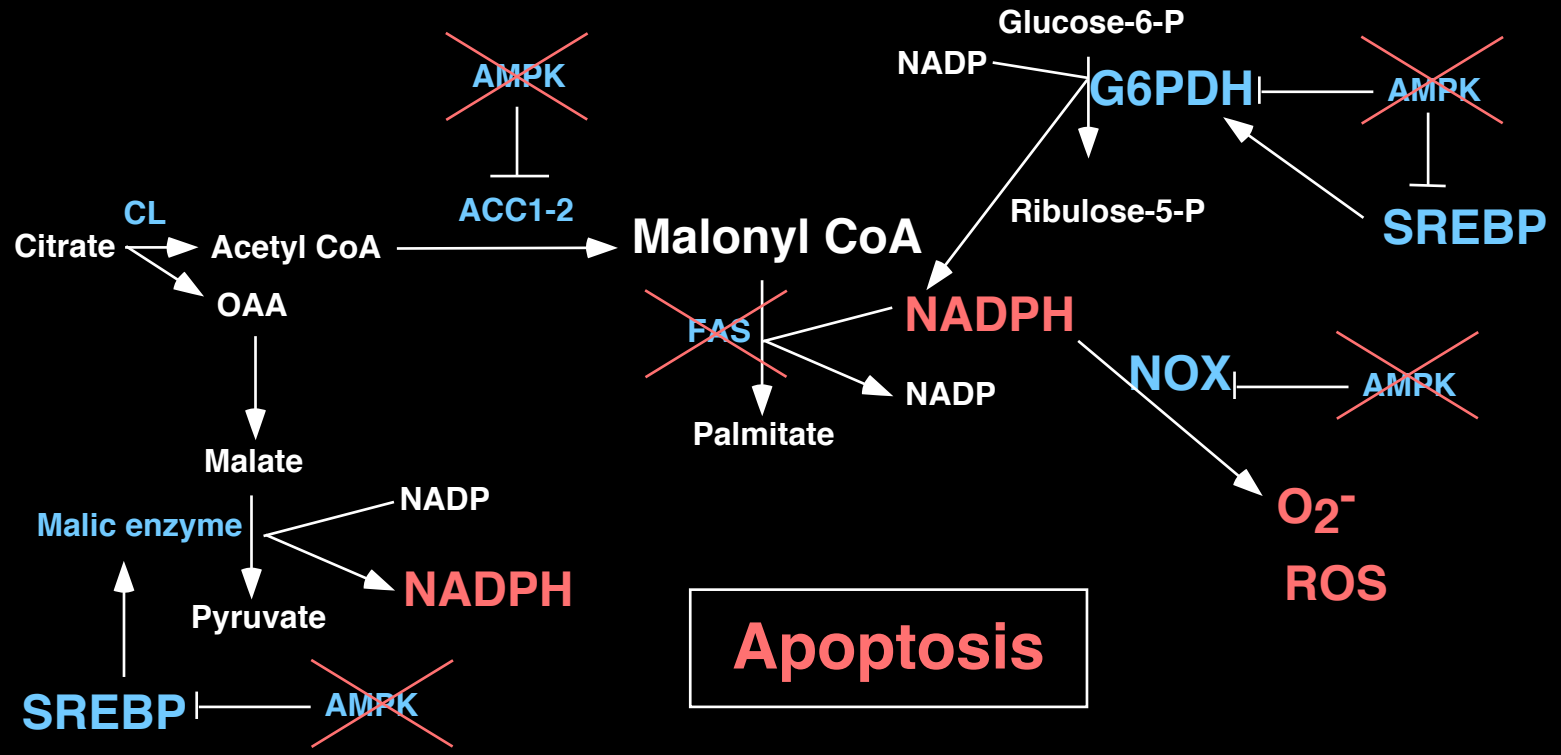


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**Metabolic Bioengineering  
to define new anti-cancer therapies**

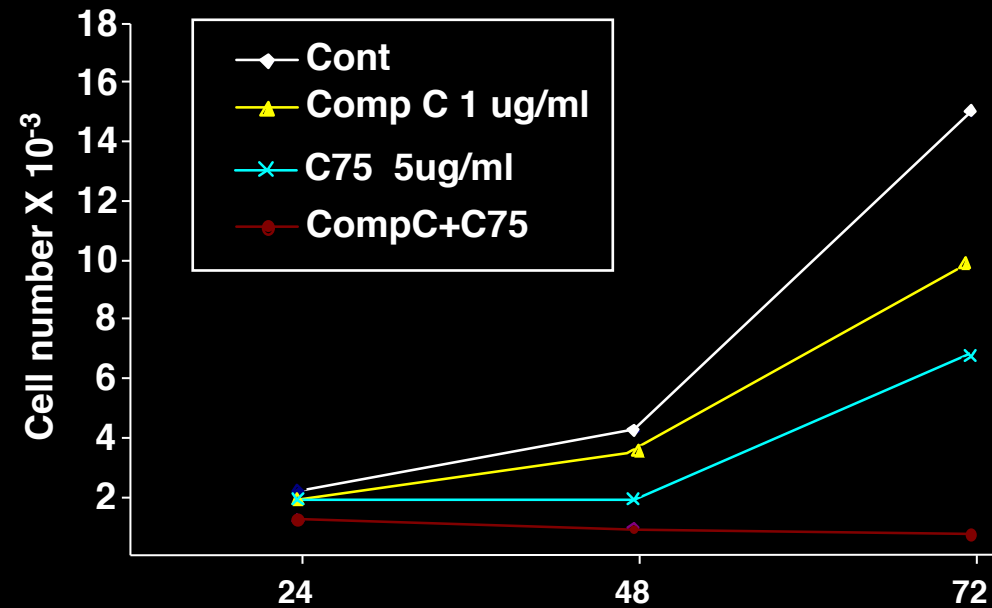
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# NADPH accumulation may increase oxidative stress in cancer cells



# Concomitant inhibition of FASN and AMPK inhibits proliferation of cancer cells

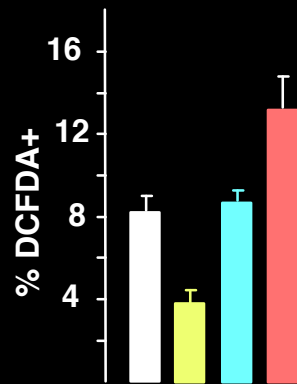
C4.2 cells



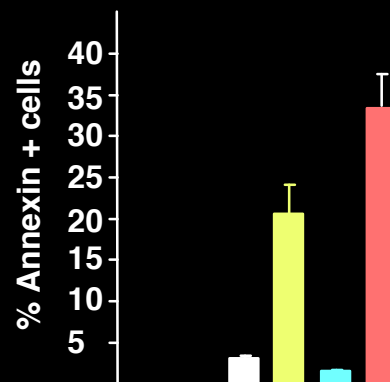
# Dual inhibition of FASN and AMPK increases ROS, apoptosis and inhibits tumor growth in mice

control  
FASN inhibitor  
AMPK inhibitor  
Combination

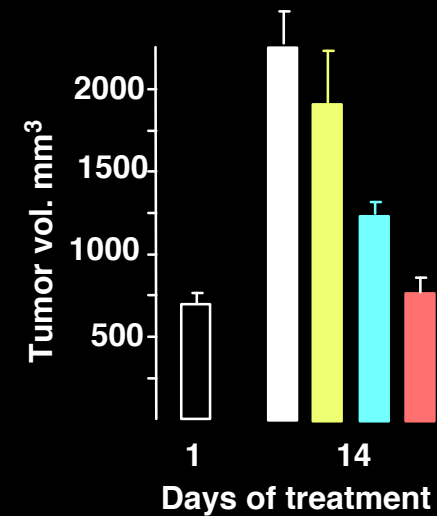
## ROS formation



## Apoptosis



## Tumor growth



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**Warburg proposed (1930s), and we know  
that cancer cells switch their metabolism**

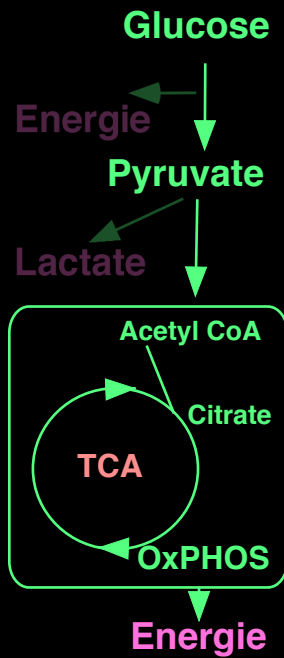
**We propose now that whole organism  
metabolism switch to facilitate  
tumor growth**

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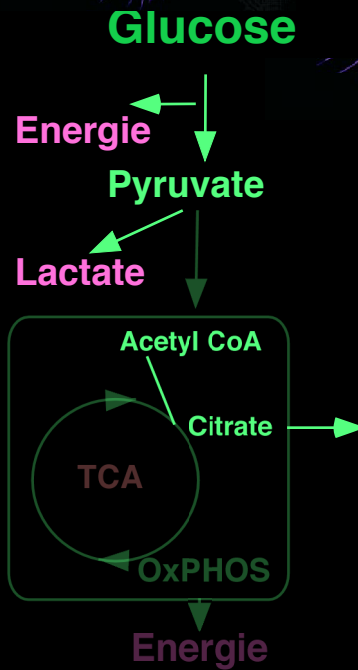
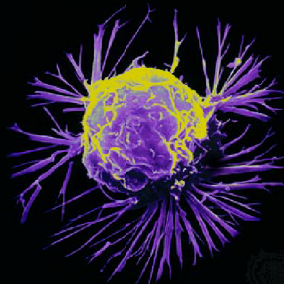


# The cellular metabolic switch

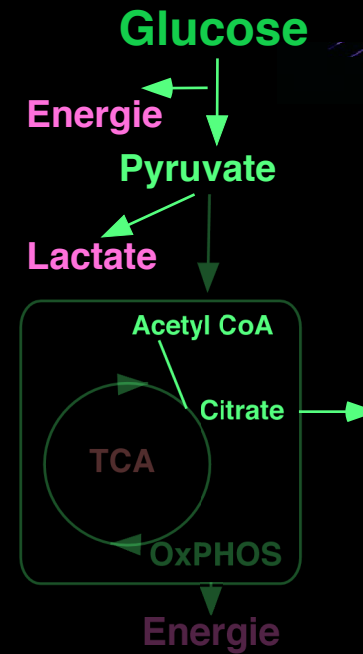
Normal



Cancer

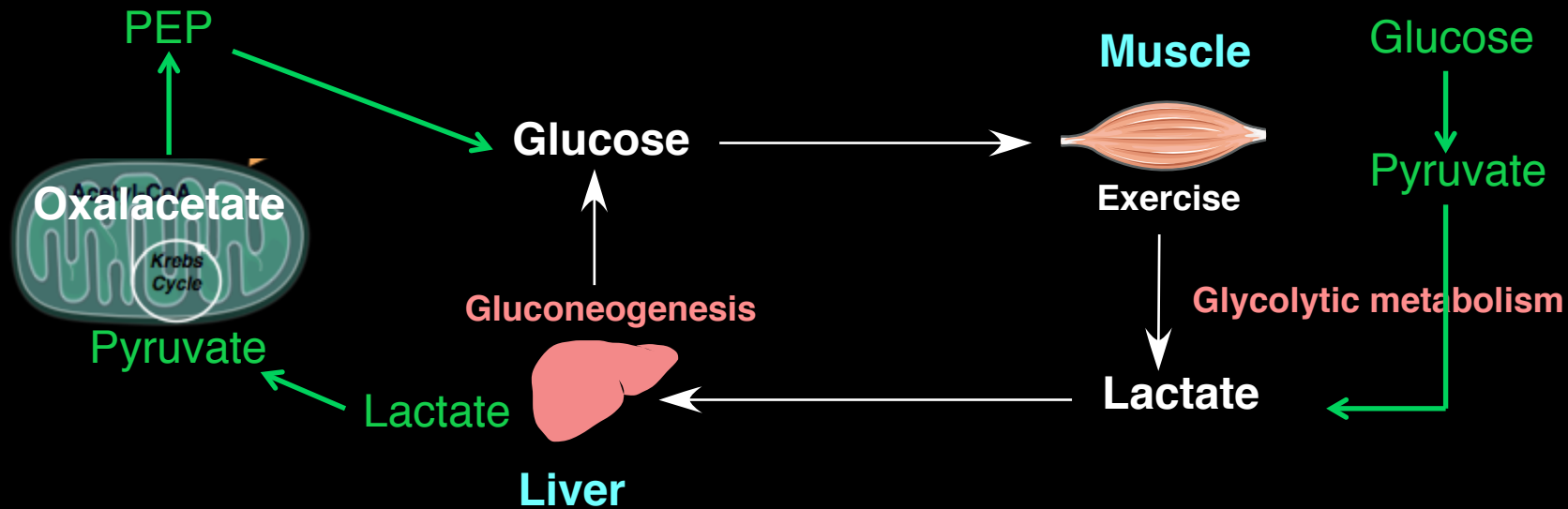


Muscle  
Intense exercise



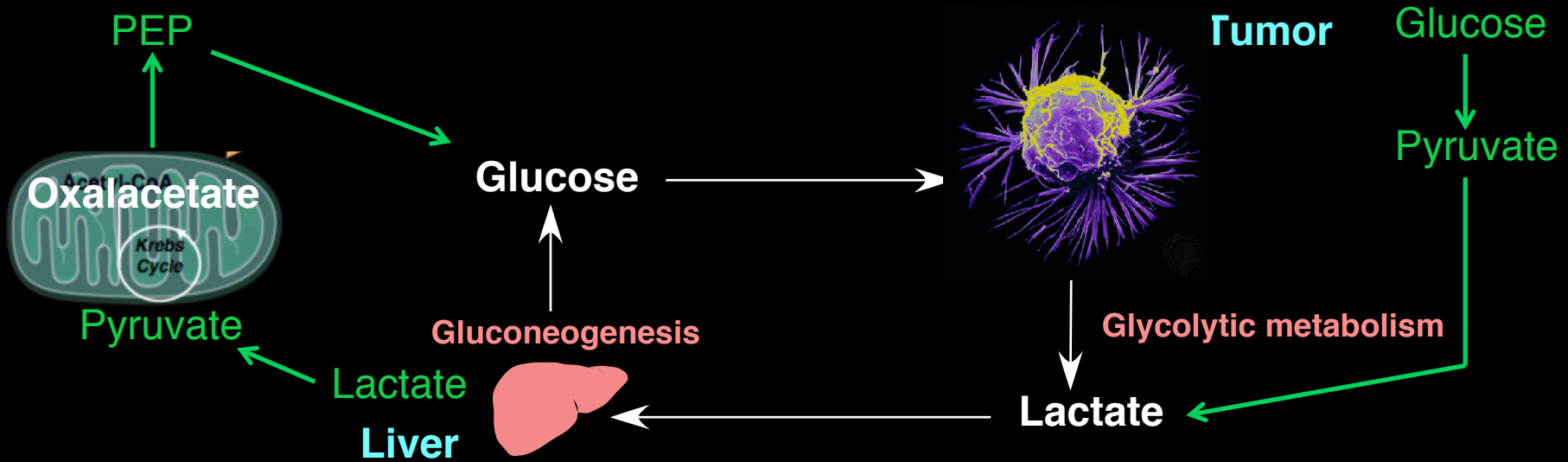
# Metabolic communication is part of normal physiology

## Cori cycle



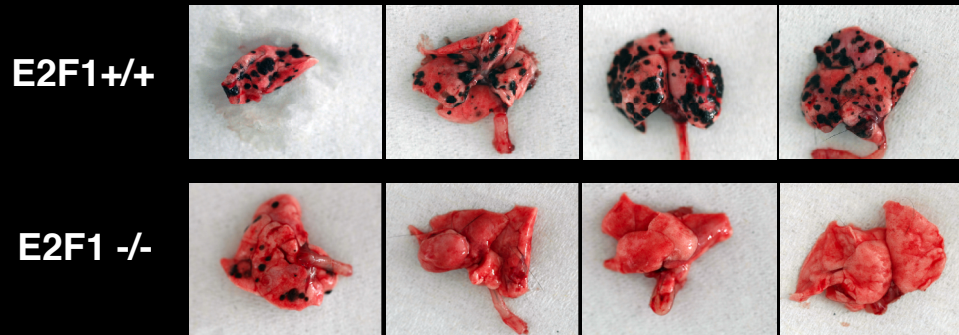
# Metabolic communication is part of cancer physiology

## Cori cycle

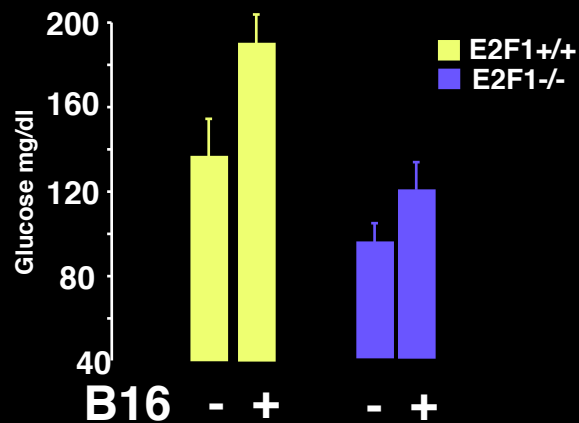


# Deficient gluconeogenesis in E2F1<sup>-/-</sup> mice abrogates tumor growth

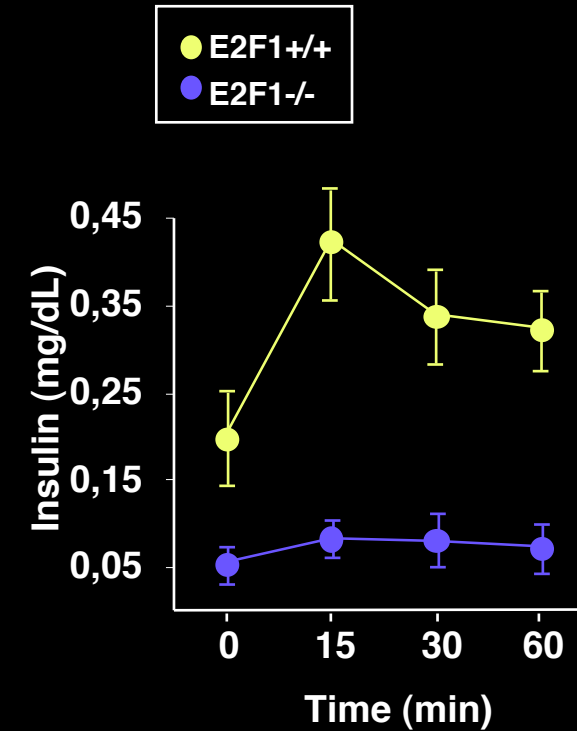
## Lung metastasis



## Gluconeogenesis



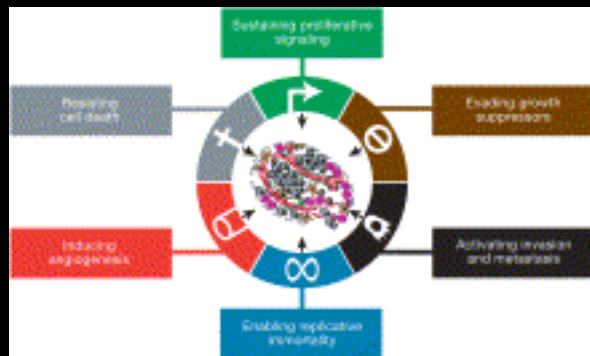
# Glucose restores tumor formation in E2F1<sup>-/-</sup> mice



# Tumors cannot survive without the host

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## Hallmarks of cancer



## Hallmarks of the HOST

Liver, kidney (Glucose)

Immune system (modulation)

Brain (??)

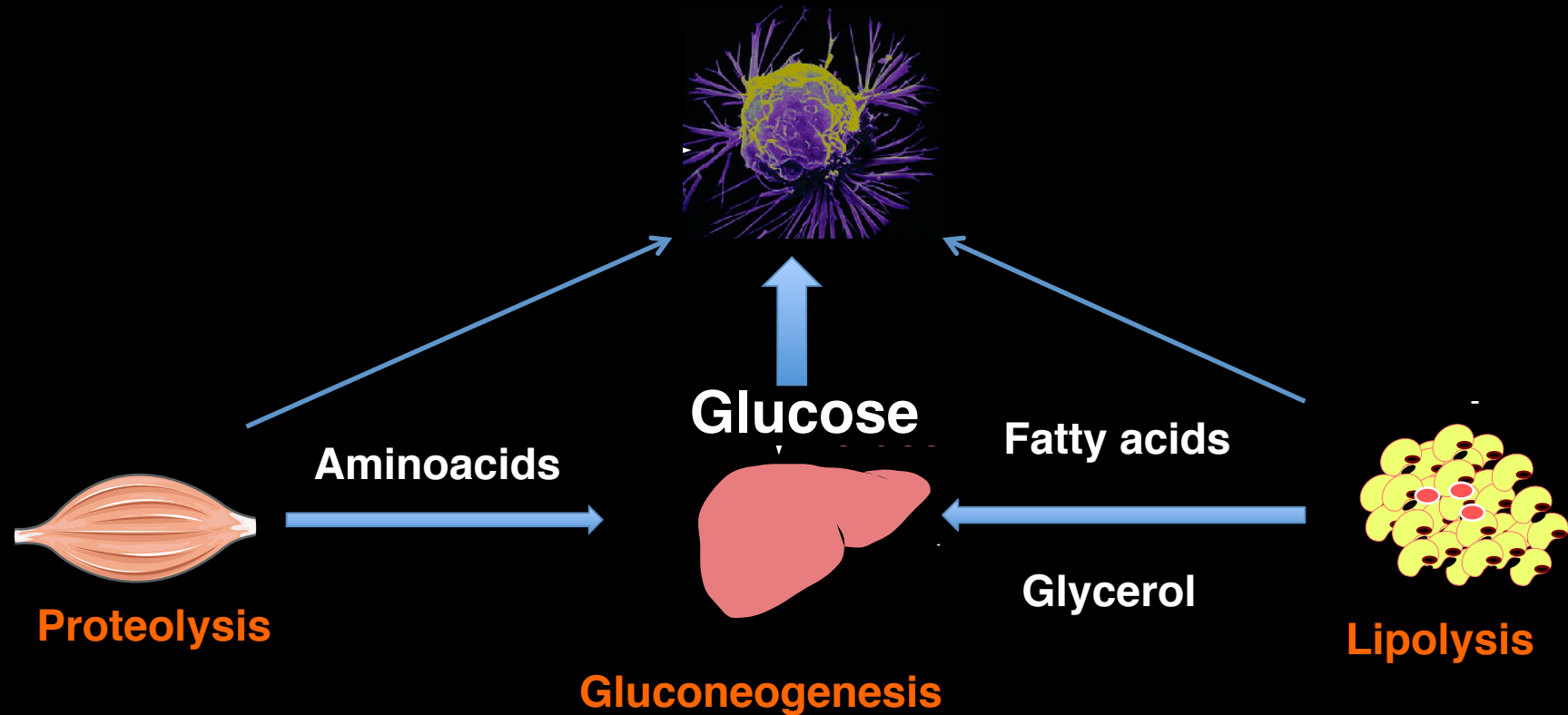
Muscle (proteins)

Adipose tissue (fatty acids)

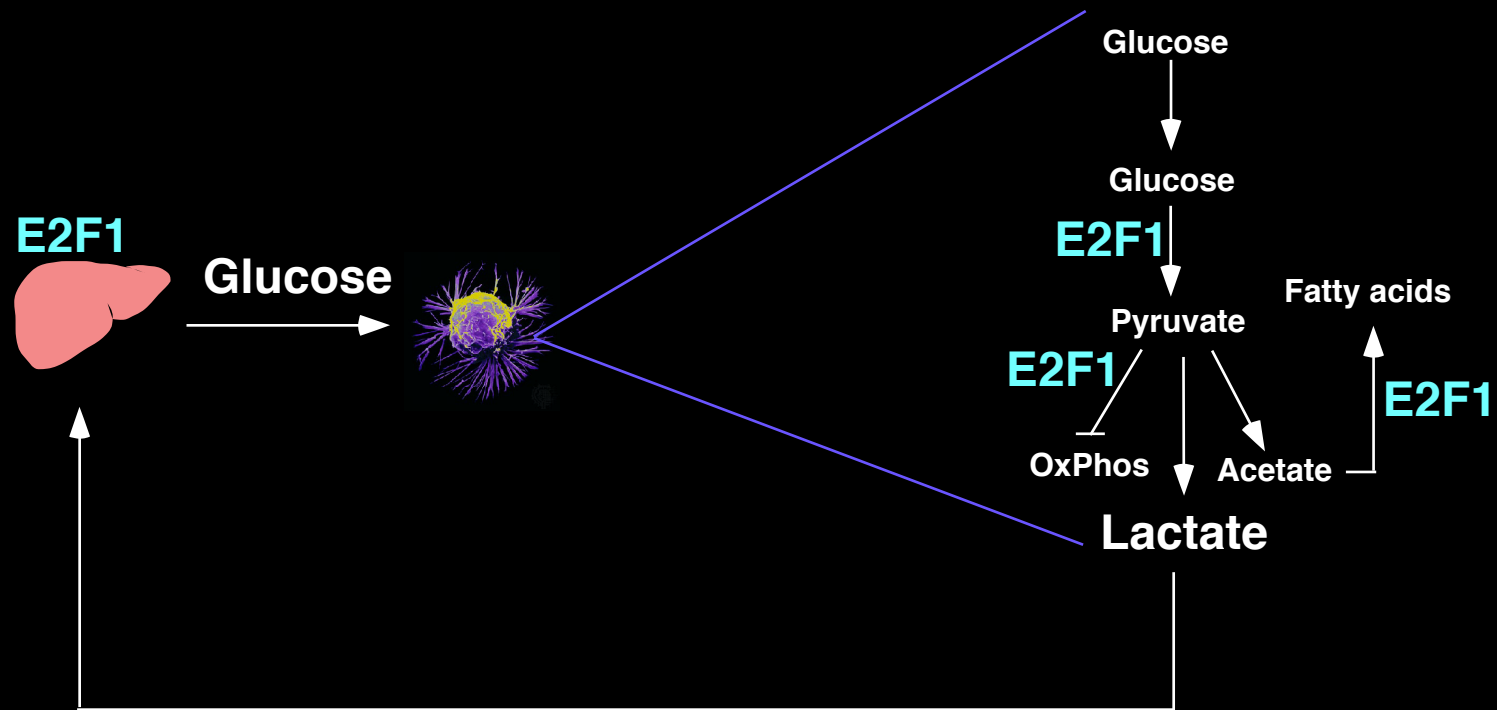
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# Tumors cannot survive without the host: Cachexia as a proof

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# E2F1 contributes to both cell and host metabolic adaptation to cancer





## Collaborators

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**Hospital Clinic de Barcelona**

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**Mariano Barbacid**

**Marcos Malumbres**

**EPF, Lausanne, SW**

**Johan Auwerx**

**Cambridge, UK**

**Toni Vidal-Puig**

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**Laurent Le Cam**

**Victor Ségalen, Bordeaux**

**P. Dubus**

**IGMM, Montpellier**

**Claude Sardet**

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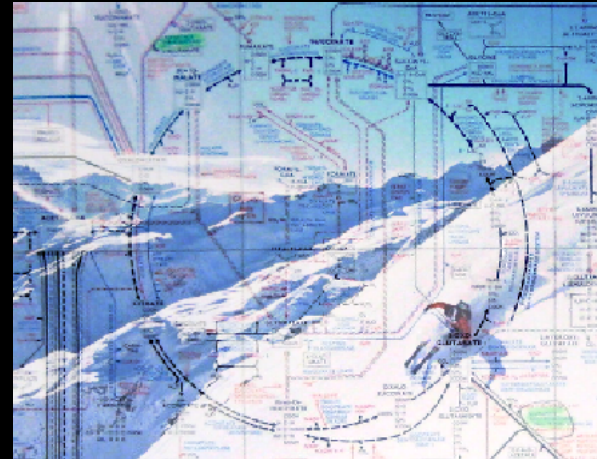
**Sébastien Hure**

**Isabel Lopez-Mejia**

**Albert Giralt Coll**

**Xavier Escote**

**Marine Bruand**



**Jean-Sébastien Annicotte**

**Emilie Blanchet**

**Vanessa Fritz**

**Carine Chavey**

**Ludivine Pradelli**