Préparation du PAIR Cancer-Obésité

Synthèse de l'atelier
Groupe Mécanismes physiopathologiques

Groupe de travail présidé par Marc Billaud
(Centre de Recherche en Cancérologie de Lyon)

Groupe de travail

Mécanismes physiopathologiques et moléculaires

Participants : Robert Barouki, Marc Billaud, Florence Caldefie-Chezet, Vanessa Cottet, Laurent Le Cam, Gilles Mithieux, Catherine Muller, Fabrice Pierre, Pierre Senesse, Jean-Ehrland Ricci, Charlotte Vaysse

Trois grands axes de recherche

I. Conséquences systémiques de l'obésité sur l'oncogenèse

II. Effets de l'obésité sur les mécanismes tumoraux

III. Recherche clinique : biomarqueurs et thérapies

How obesity influences the p53 pathway and carcinogenesis ????

Laurent Le Cam

(Montpellier Cancer Center, FRANCE)

Inserm
Institut national de la santé et de la recherche médicale

ICM
Institut régional du Cancer Montpellier

BioCampus Montpellier

MONTPELLIER CANCER

I. Conséquences systémiques de l'obésité sur l'oncogenèse

Question 1 : Inventorier l'ensemble des altérations inflammatoires, sécrétoires et métaboliques du tissu adipeux associé au développement tumoral.

Question 2 : Mieux comprendre le continuum entre surcharge pondérale, stéatohépatite non alcoolique (NASH) et obésités, ainsi que les mécanismes physiopathologiques et moléculaires liant ces différentes situations cliniques au cancer.

Question 3 : Comment les processus de dysbioses intestinales associés à l'obésité peuvent-ils exercer un effet pro-tumoral ? Favorisent-ils les processus invasifs et la formation de tumeurs secondaires ?

Question 4 : Par quels mécanismes certains facteurs environnementaux péri- et pré-conceptionnels, dont les déséquilibres nutritionnels, associés à l'obésité peuvent promouvoir la formation de cancers à l'âge adulte ? Sont-ils aussi associés au développement de tumeurs pédiatriques ?

Question 5 : Impact de l'obésité chez des patients ayant une prédisposition héréditaire au cancer ? A l'inverse, les personnes ayant une prédisposition à l'obésité (hérédité monogénique ou polygénique) ont-elles un risque accru de développer des cancers ? Via quels processus moléculaires?

p53: a canonical « gate keeper » tumor suppressor

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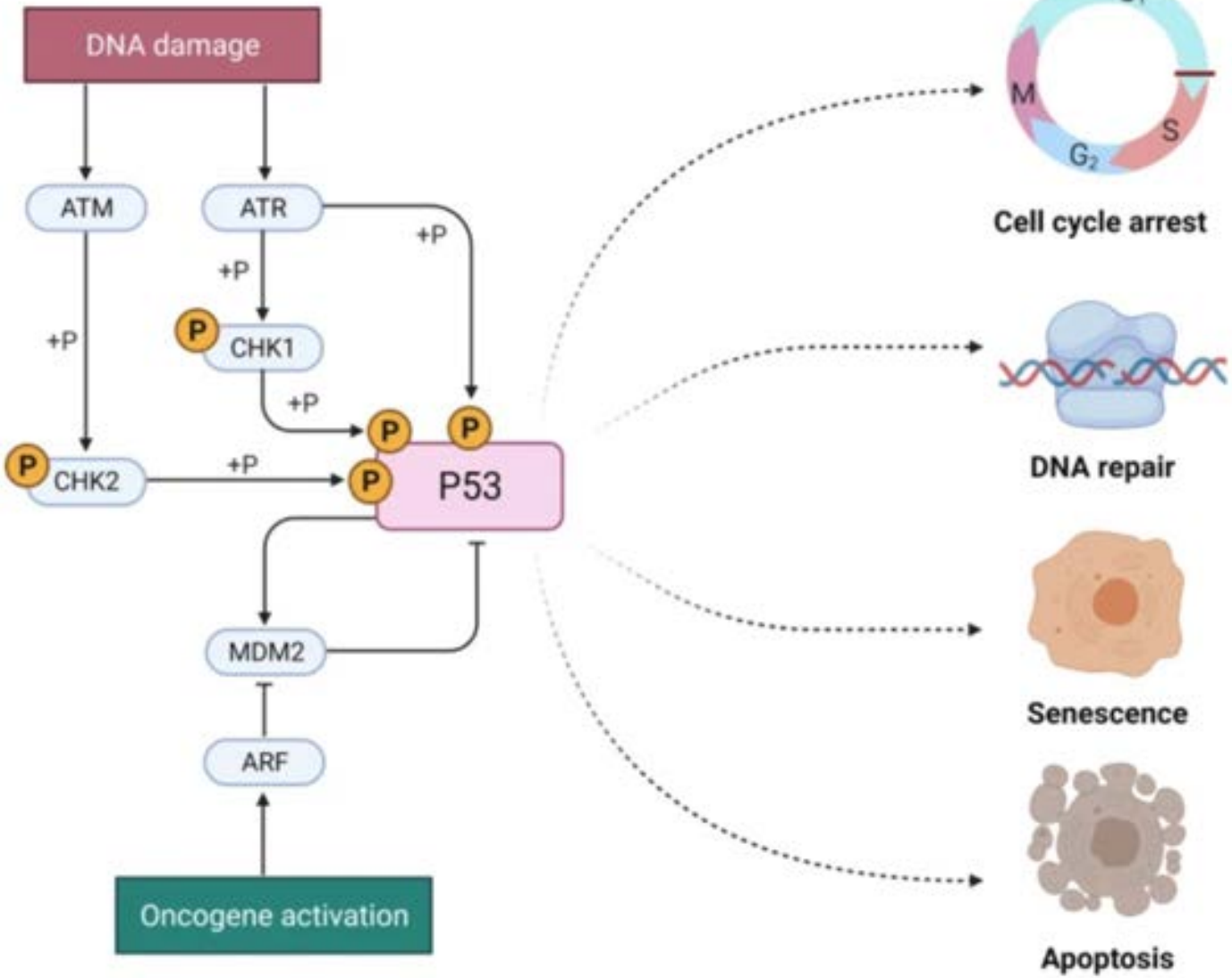
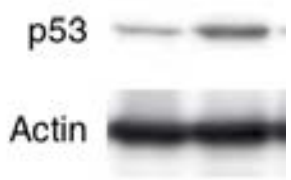


From Marei et al. Cancer Cell Int. 2021

p53: a nutrient sensor and « gate keeper » of metabolic homeostasis

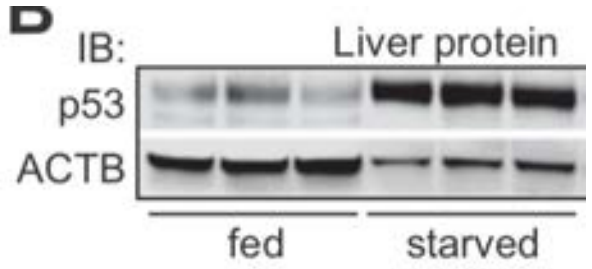
Excess of nutrients



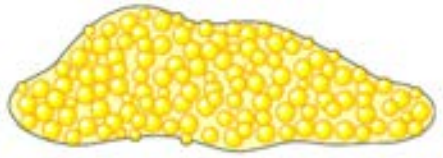
Chow HFD

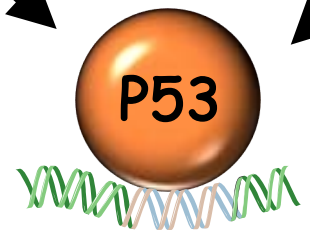
From Minamino et al., Nat Med 2009

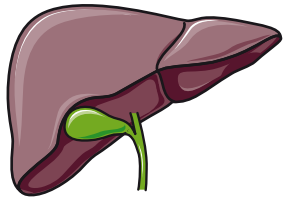
Nutrient starvation



From Prokesch et al., FASEB 2017







Lipid storage

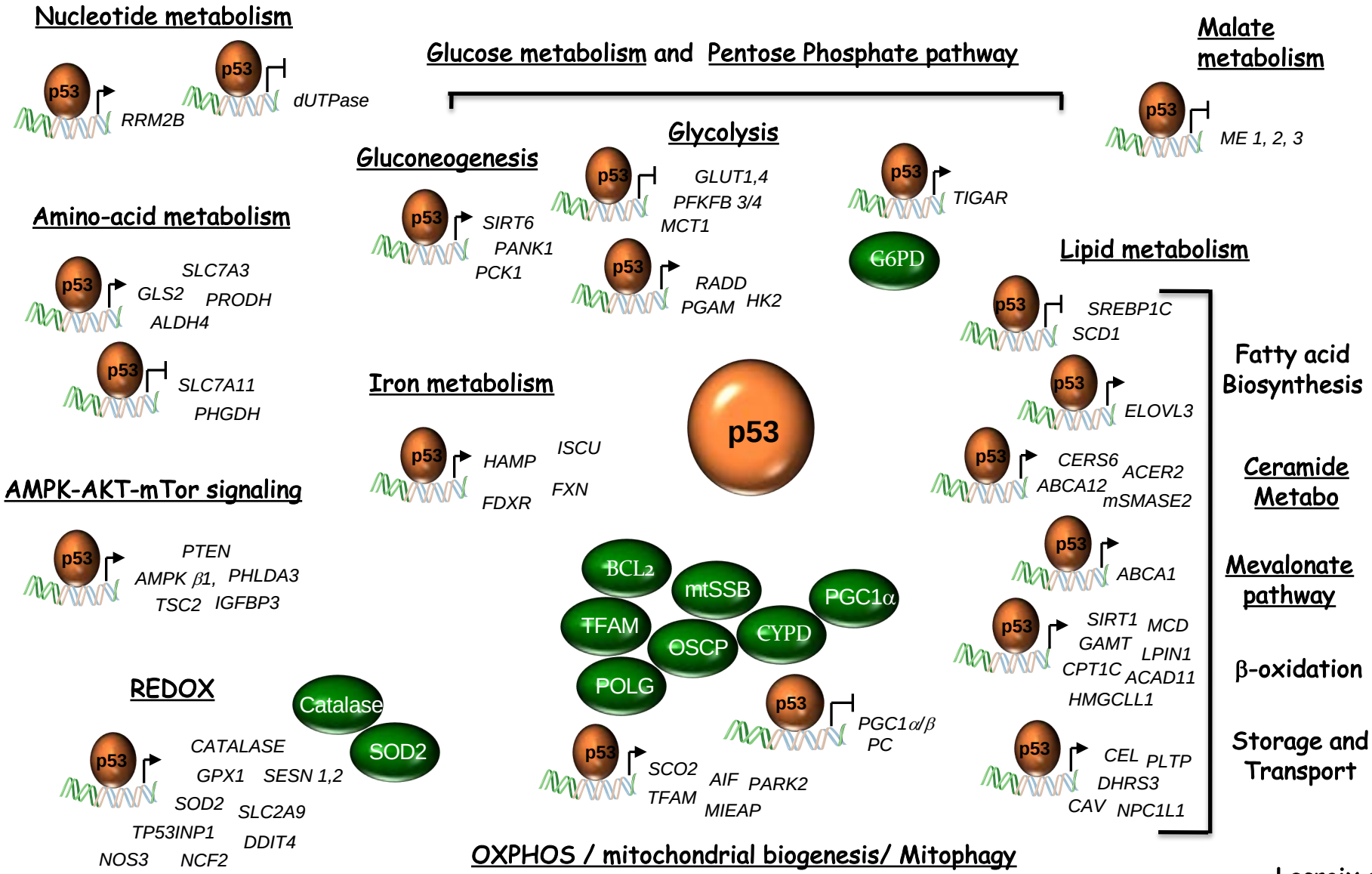
Lipid metabolism

Amino acid metabolism

Glucose homeostasis

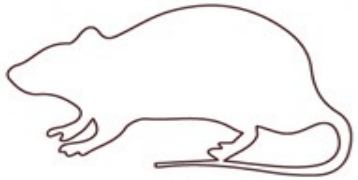
Inflammation

p53 controls multiple metabolic pathways

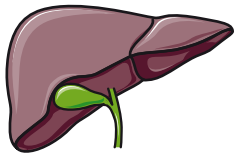
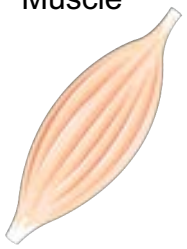


Lacroix et al., Mol Met 2019

Deregulation of p53 metabolic functions in mammals



Rodents

P53 metabolic functions	Tissue	Disease
- energy expenditure - FA synthesis - FA storage - Mitochondrial respiration	Adipose tissue 	Obesity
- insulin secretion - Mitochondrial respiration	Pancreas 	
- amino-acid catabolism - Gluconeogenesis - FAO - Mitochondrial respiration - Glucose utilisation - anti-oxidant defenses - Insulin signaling - Cholesterol metabolism - Ureagenesis	Liver 	Diabetes Liver disease Steatosis NASH
- Mitochondrial Biogenesis - Mitochondrial respiration - ATP production - ROS production - FAO - PPP - Glucose utilisation	Muscle 	Cardiovascular diseases

Humans

Lacroix et al., Mol Met 2019

II. Effets de l'obésité sur les mécanismes tumoraux

Question 1 : Comment l'obésité agit-elle sur les différentes étapes du processus tumoral (initiation, invasion, métastases)? Quels sont les mécanismes moléculaires (génétiques/épigénétiques/métaboliques) et cellulaires impliqués à chacune de ces étapes?

Question 2: L'obésité modifie-t-elle la plasticité des cellules cancéreuses dont les phénomènes de transdifférenciation et de transitions épithélio-mésenchymateuses ? Influe-t-elle sur les propriétés d'auto-renouvellement des cellules souches cancéreuses (CSC) et sur les processus de dédifférenciation/reprogrammation de cellules tumorales en CSC ?

Question 3 : Effets de l'obésité sur le dialogue entre les composants du microenvironnement tumoral (adipocytes, CAF, cellules endothéliales, infiltrat immunitaire, cellules du système nerveux autonome) et les cellules cancéreuses ?

mutant p53 controls many aspects of tumor progression

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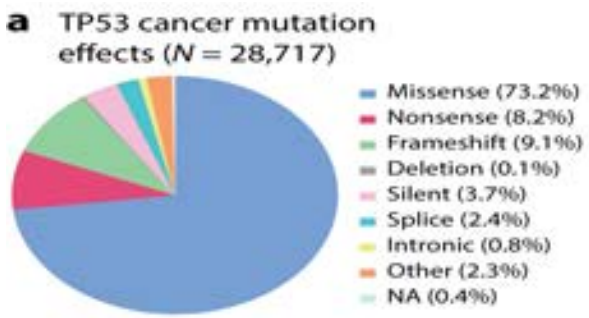
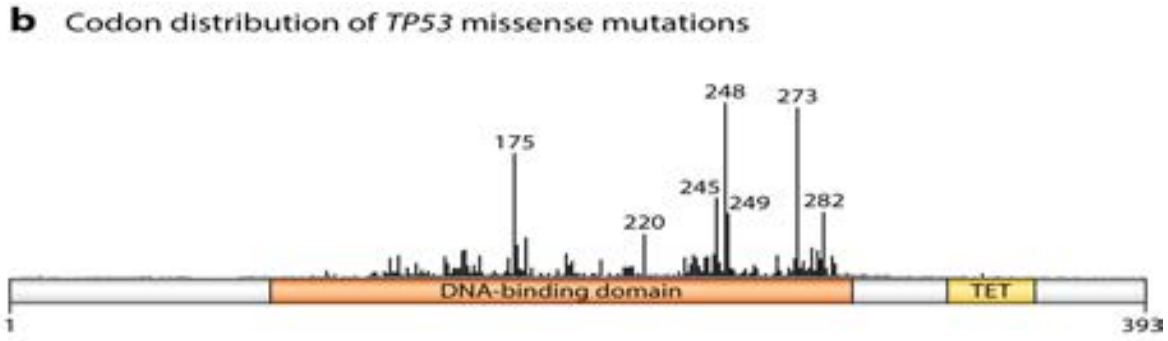
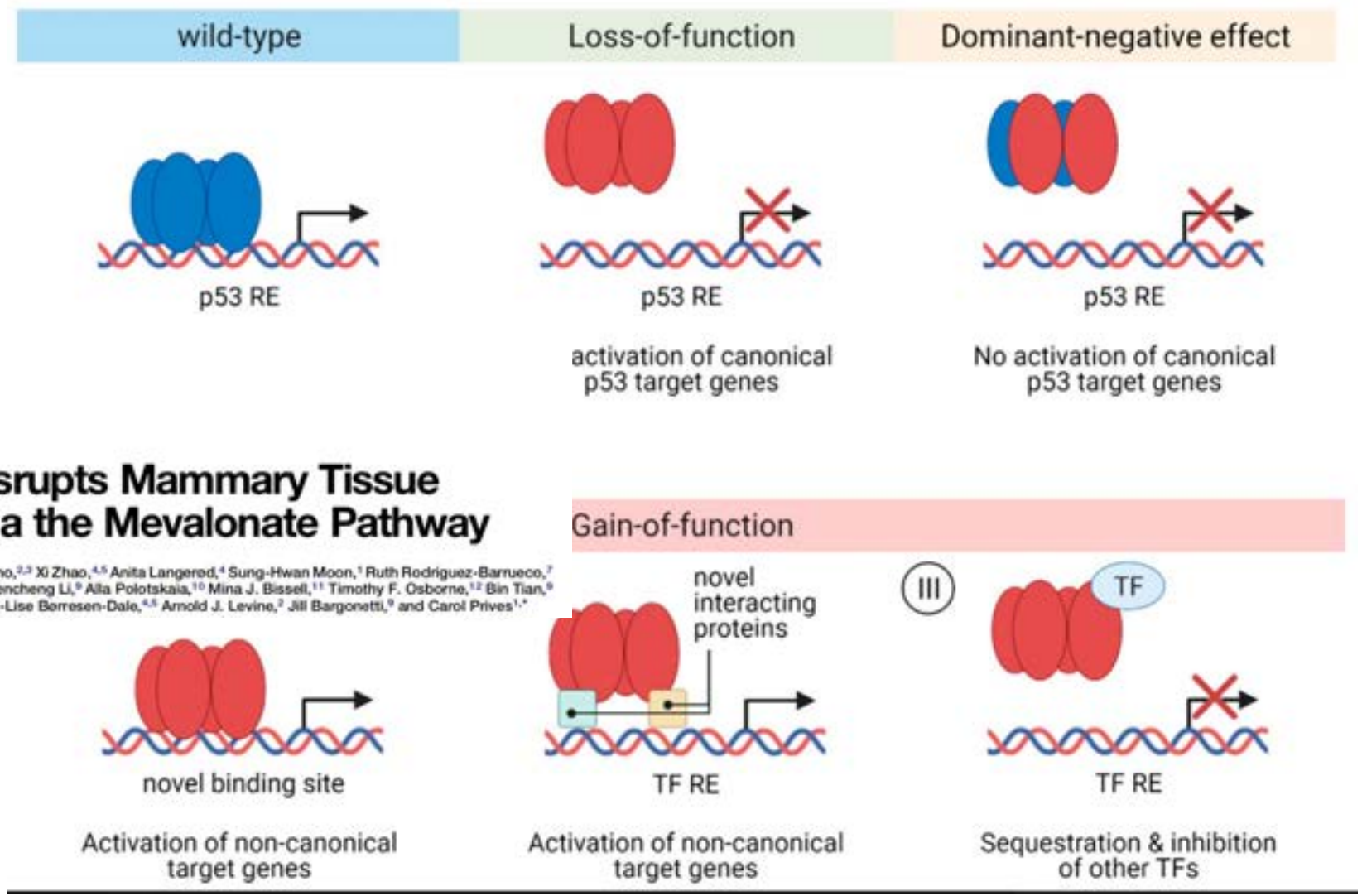




mutant p53 controls many aspects of tumor progression



Cell

Mutant p53 Disrupts Mammary Tissue Architecture via the Mevalonate Pathway

William A. Freed-Pastor,[1] Hideaki Mizuno,[2,3] Xi Zhao,[4,5] Anita Langerød,[4] Sung-Hwan Moon,[1] Ruth Rodriguez-Barrueco,[7] Anthony Barsotti,[1] Agustin Chicas,[8] Wencheng Li,[9] Alla Polotskaia,[10] Mina J. Bissell,[11] Timothy F. Osborne,[12] Bin Tian,[9] Scott W. Lowe,[8] Jose M. Silva,[6,7] Anne-Lise Børresen-Dale,[4,5] Arnold J. Levine,[2] Jill Bargonetti,[9] and Carol Prives[1,*]

mutant p53 controls many aspects of tumor progression

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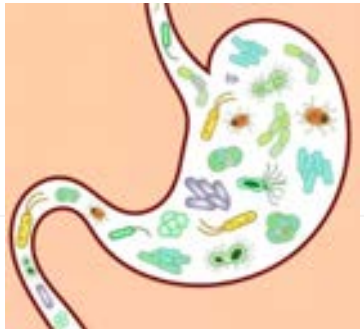
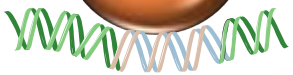
microbiome



Tumor ecosystem

Mut P53

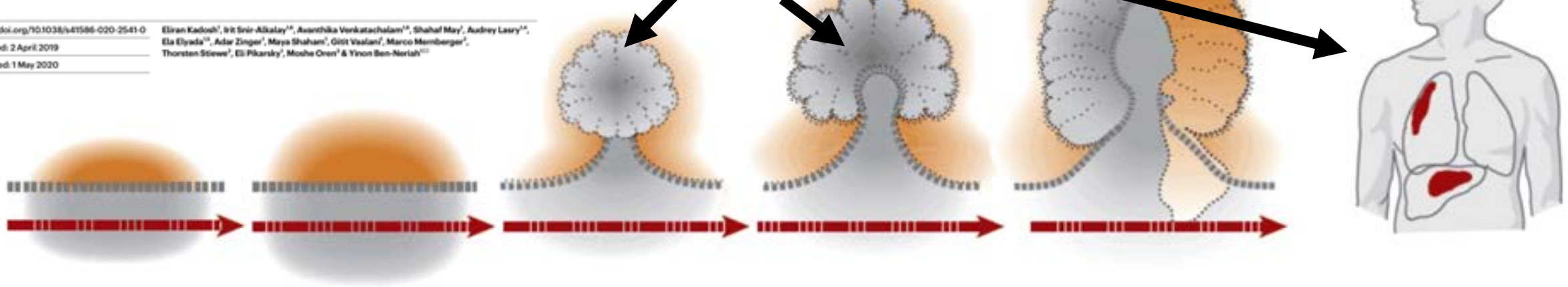


Article

The gut microbiome switches mutant p53 from tumour-suppressive to oncogenic

https://doi.org/10.1038/s41586-020-2541-0
Received: 2 April 2019
Accepted: 1 May 2020

Eliran Kadosh[1], Irit Snir-Alkalay[1,5], Avanthika Venkatachalam[1,5], Shahaf May[1], Audrey Lasry[1,5], Ela Elyada[1,5], Adar Zinger[1], Maya Shahaf[1], Gitit Vaalani[1], Marco Mernberger[2], Thorsten Stiewe[2], Eli Pikarsky[1], Moshe Oren[3] & Yinon Ben-Neriah[1,4]



Normal epithelium → Hyperproliferative epithelium/ dysplastic crypts → Small adenoma → Large adenoma → Carcinoma → Metastases

III. Recherche clinique : biomarqueurs et thérapies

Question 1 : L'indice de masse corporelle (IMC) est classiquement utilisé pour identifier le surpoids et l'obésité, mais cet indicateur ne prend pas en compte la topographie de la répartition de la masse graisseuse, viscérale ou périphérique. L'IMC n'intègre pas non plus, par définition, d'informations sur l'état inflammatoire chronique et/ou le syndrome métabolique associé à l'obésité. Il existe en effet des patients obèses (sujet MHO/metabolic healthy obese) sans syndrome métabolique. L'utilisation de nouveaux biomarqueurs liant l'obésité à l'initiation et la progression tumorale est donc nécessaire.

Question 2 : Quel est l'impact de l'obésité sur la résistance thérapeutique : radiothérapie des cancers, chimiothérapies standards, traitements ciblés et immunothérapie ?

Question 3 : Quels mécanismes sont mis en jeu dans la sarcopénie chez les sujets obèses pouvant influencer les complications de la prise en charge du cancer et le pronostic sur la survie ?

Obesity, therapeutic efficacy and side effects

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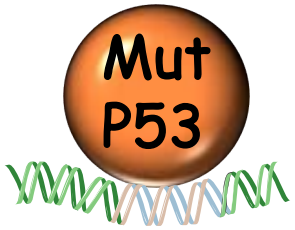
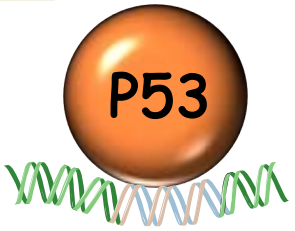


Therapeutic window

Biomarkers



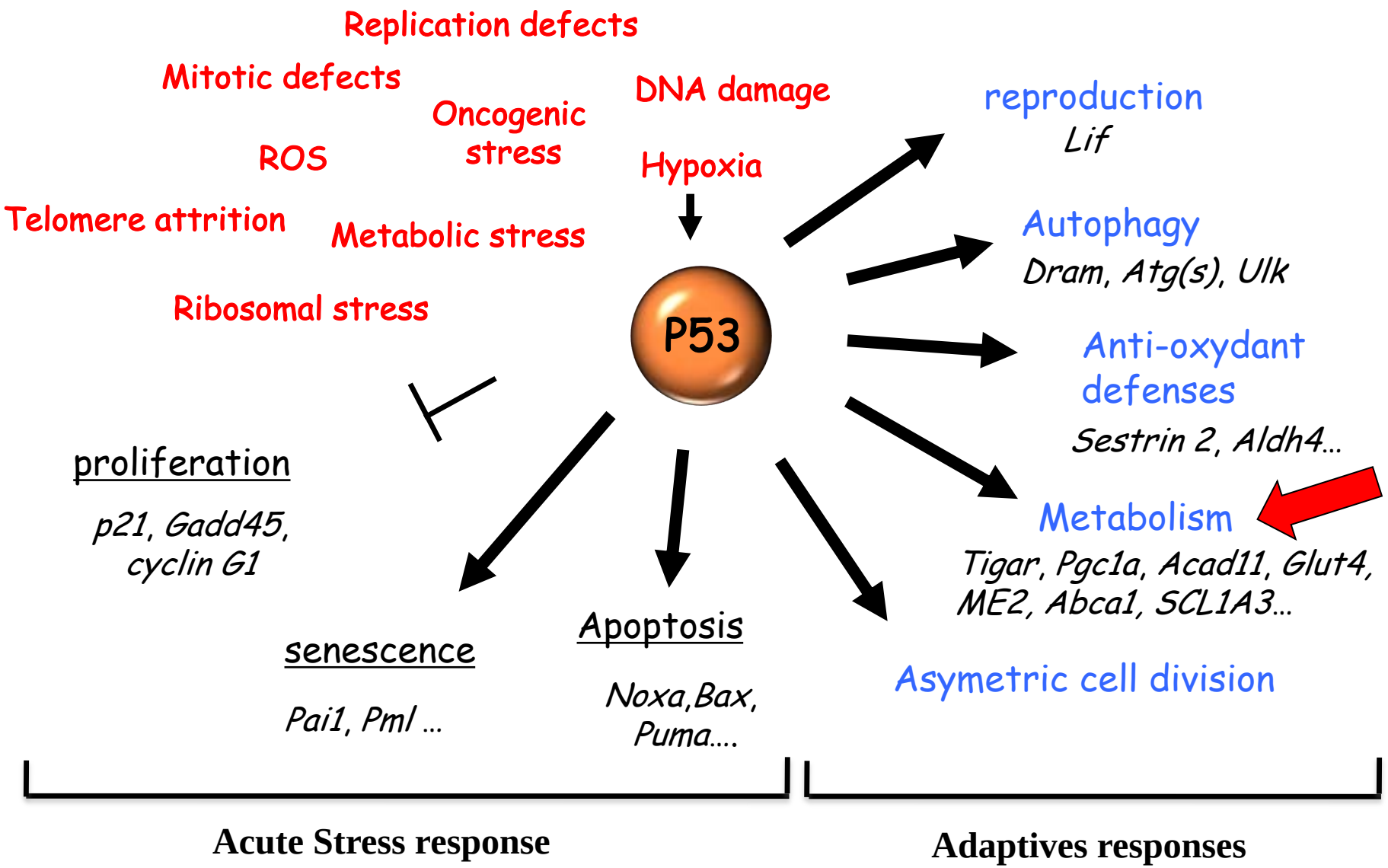
Biodisponibility

Drug metabolism

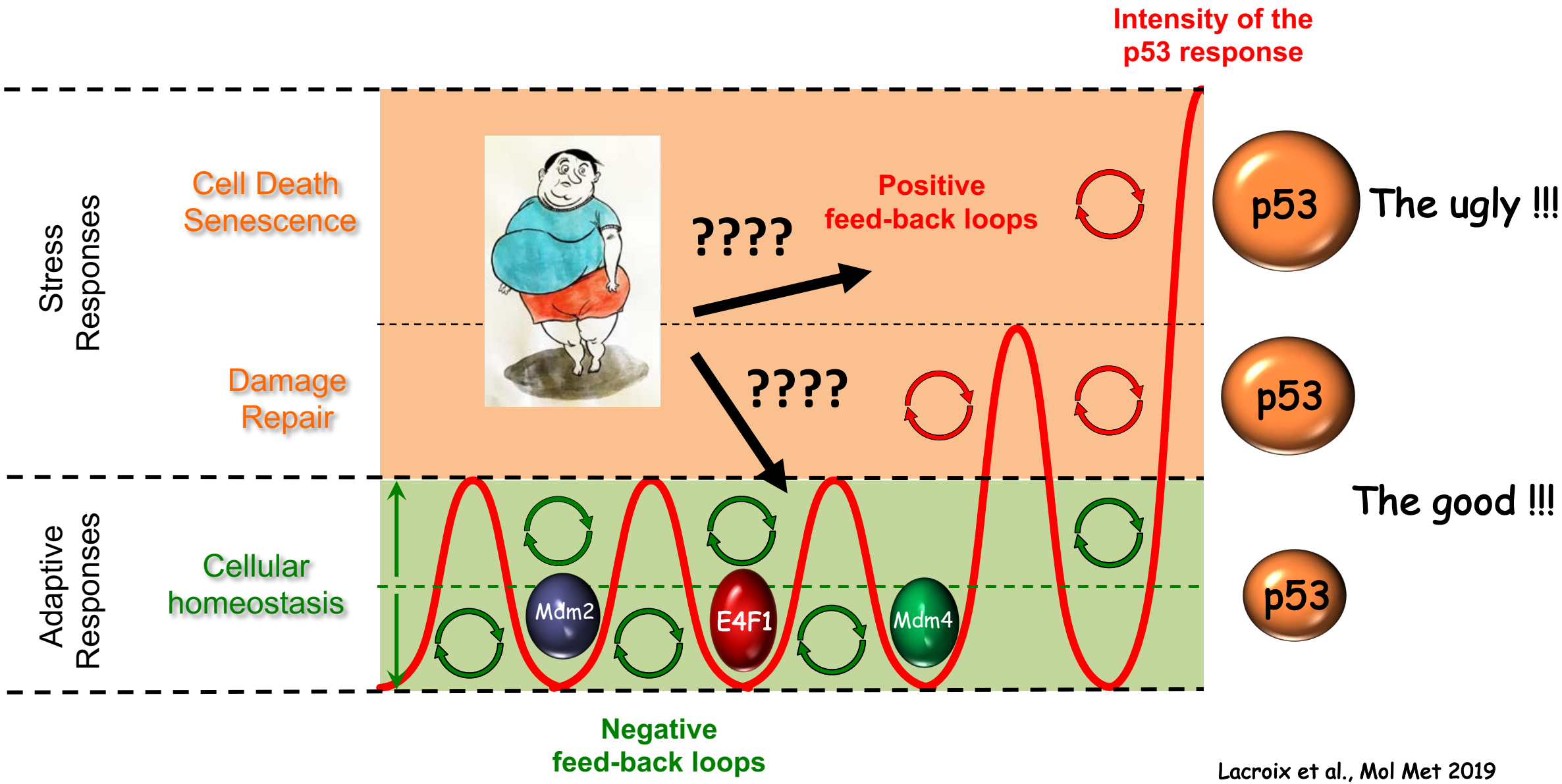
Off-targets

side effects

p53: a canonical « gate keeper » tumor suppressor also involved in adaptive responses

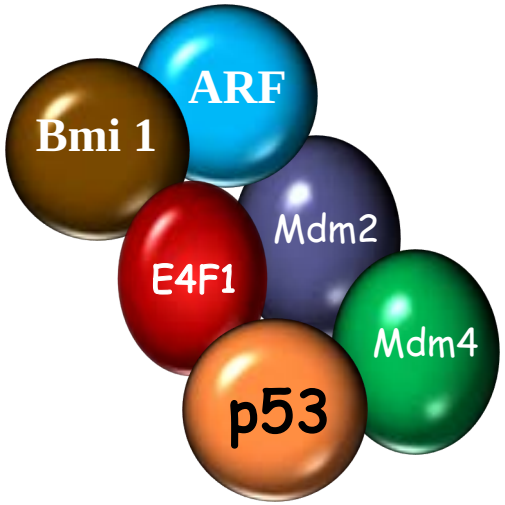


The p53 pathway maintains metabolic homeostasis



Lacroix et al., Mol Met 2019

The p53 pathway and metabolism



Bmi1 oncogene

ARF tumor suppressor

MDM2/MDM4 oncogenes

p53 tumor suppressor

METABOLISM

Senescence

tumorigenesis

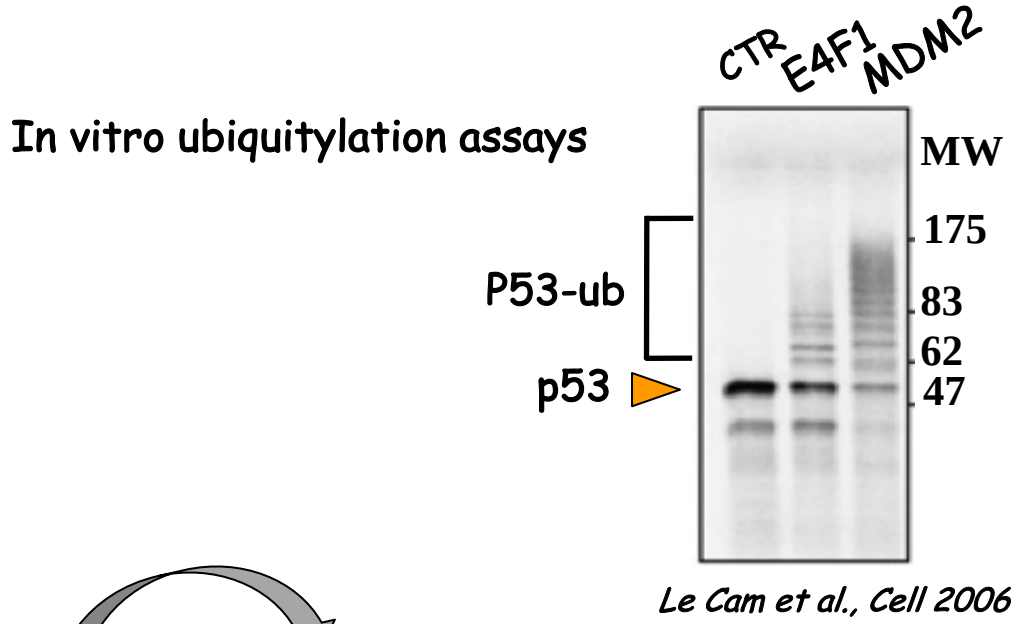
Obesity/T2D

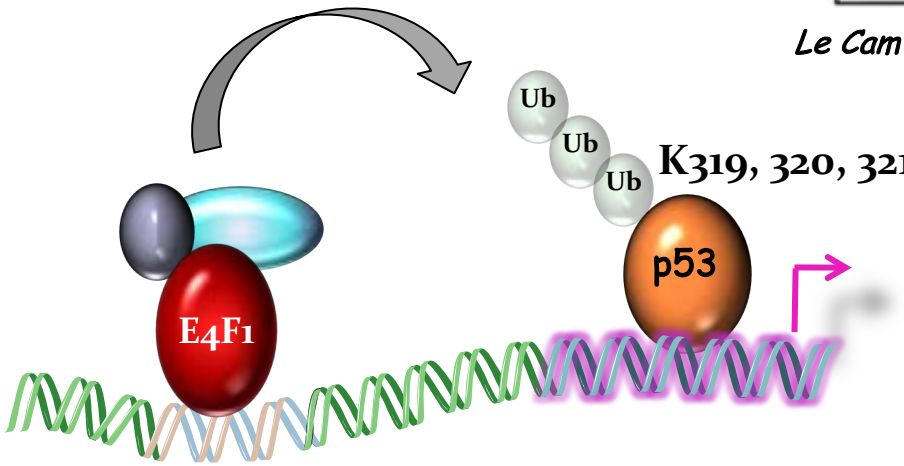
NASH

CNS

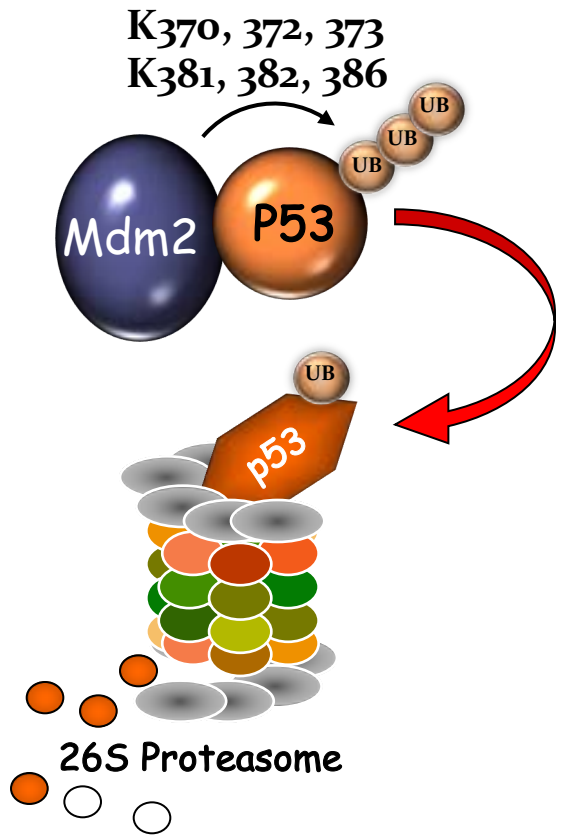
muscular endurance

MDM2 and E4F1: 2 important regulators of the p53 pathway



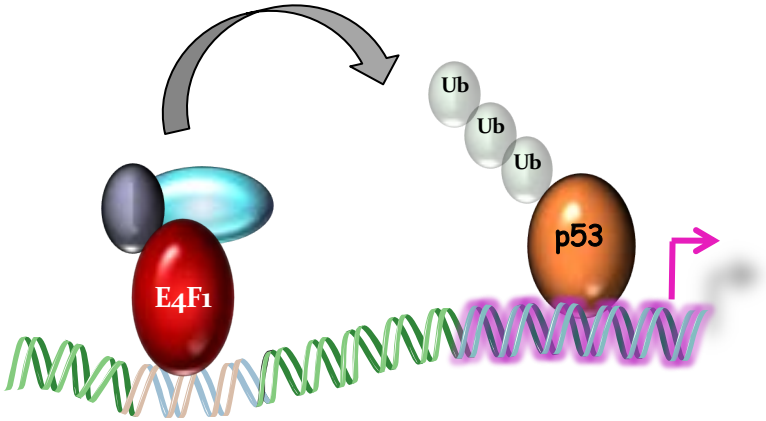


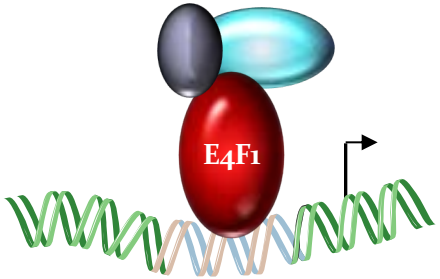
Transcriptional regulation



Protein degradation and localization

MDM2 and E4F1 are multifunctional proteins



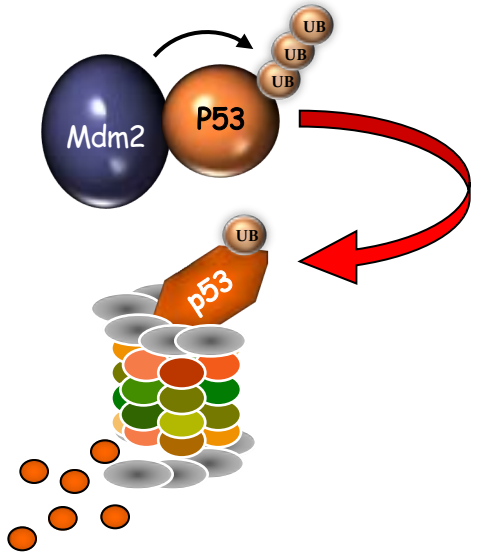


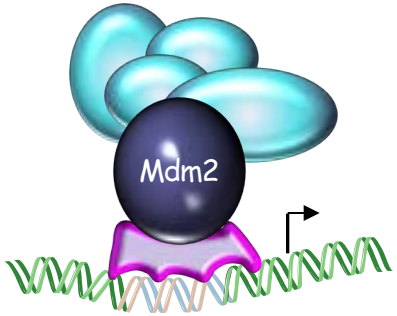
Pyruvate metabolism

Lacroix et al., PNAS 2016

Goguet-Rubio et al., PNAS 2016

Lacroix, Linares et al., Nat Comms 2021





serine metabolism

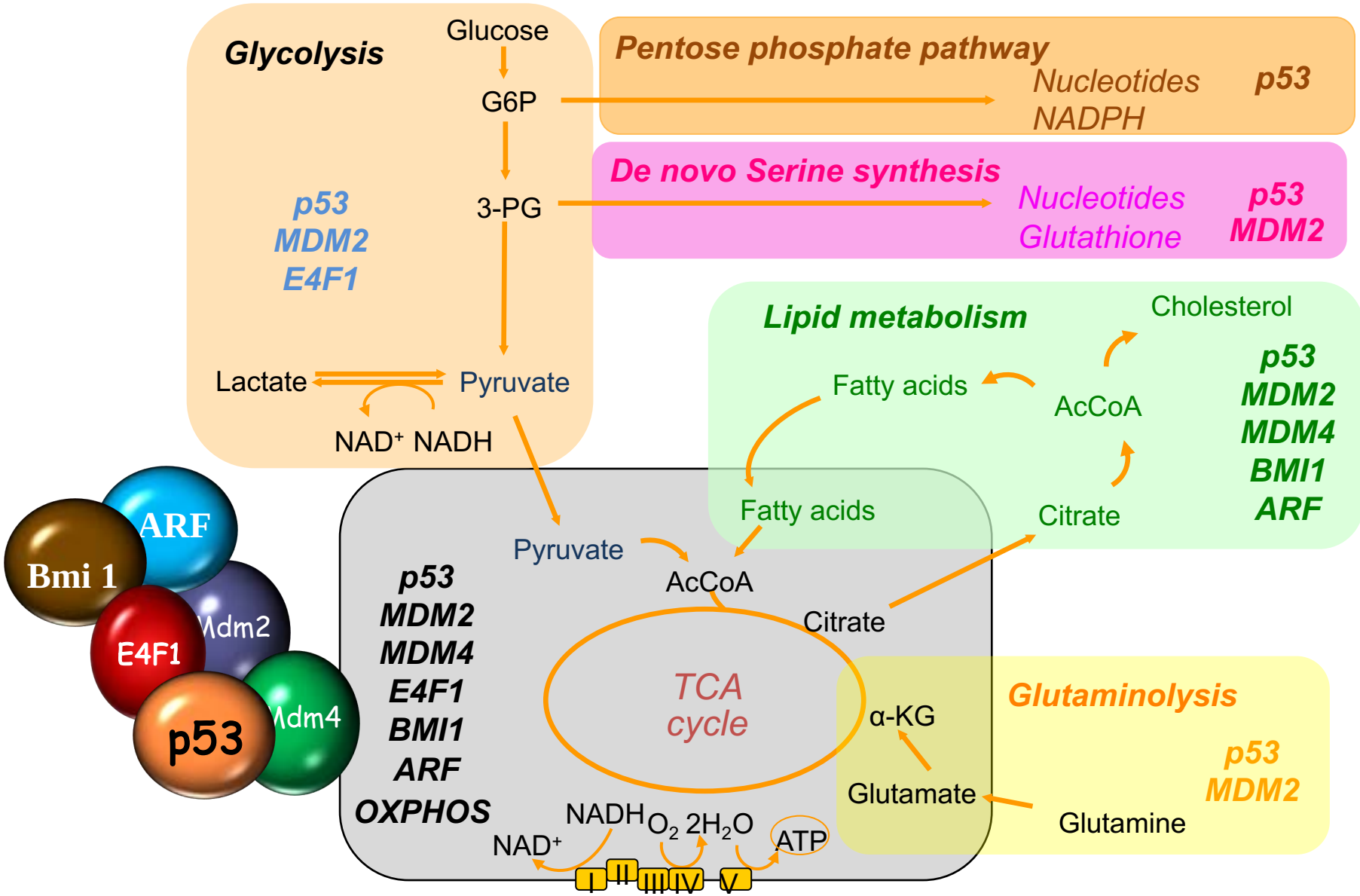
Mito respiration

Riscal et al., Mol Cell 2016

Arena et al., Mol Cell 2018

Cissé et al., Sc. Transl Med 2020

How are these p53-associated metabolic networks coordinated?



Computational modeling of p53-associated metabolic networks


C. De Blasio (Post-doc)


O. Villafraz (Post-doc)


PF. Roux (Post-doc)

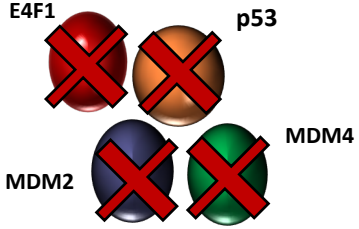

P. Rodriguez-Mier (Post-doc)


N. Poupin (CRCN)

Collabs:
- **F. Jourdan (INRA, Toulouse)**
- **JC Portais / F. Bellvert / H. Kulyk / L. Peyriga (Metatoul)**
- **P. Hainaut (IAB, Grenoble)**
- **U. Hibner / D. Grégoire**
- **C. Hirtz (IRMB, Montpellier)**
- **Infrastructure nationale MetaboHub**

STEP 1 — Generation of cellular models

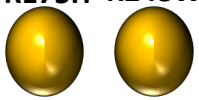
conditional cKOs / cKI Mefs for key components of the p53 pathway



single, double, triple cKO

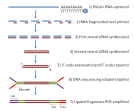
Mutant-p53

R175H R248W

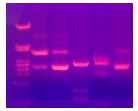


STEP 2 — Profiling (OMICs data)

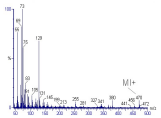
Transcriptomic (RNA seq)



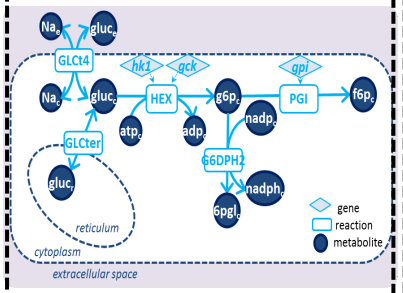
Proteomic (MS)

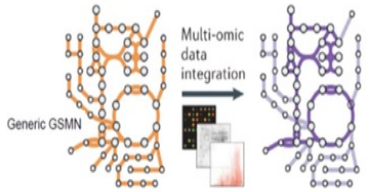


ExoMetabolomic (NMR & MS)



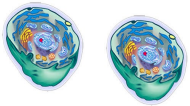
STEP 3 — Computational modeling

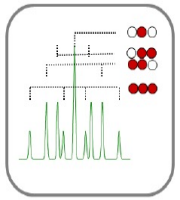




STEP 4 — Model refinement & validations

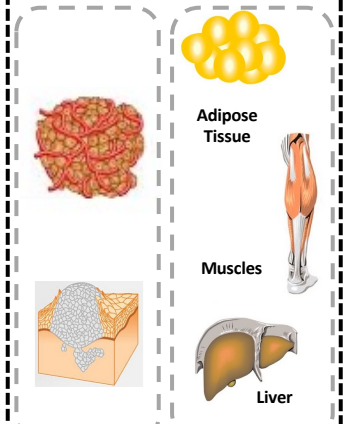
ONGOING





Stable Isotope tracing experiments (^{13}C,^{15}N subsrates)

STEP 5 — Therapeutic strategies & biomarkers



Cancers

Metabolic disorders

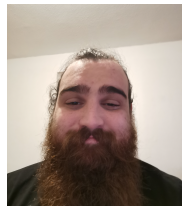
Analysis of p53-associated metabolic functions in vivo

NASH, OBESITY, T2D, CANCER

C. De Blasio
(Post-doc)

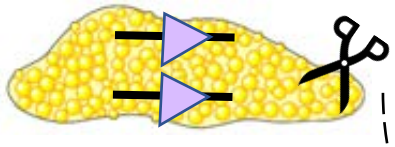
M. Lacroix
(CRCN INSERM)

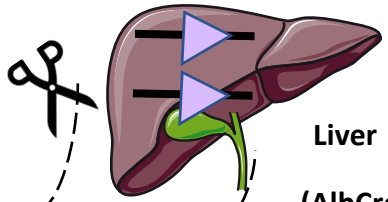
A. Lahalle
(PhD, 2nd year)



D. Laurent
(M1 student)

Adipose tissue
(AdipoCreER; UCP1CreER)





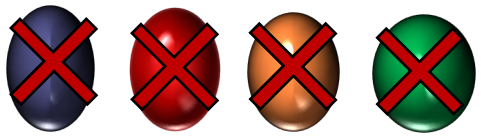
Liver

(AlbCre)

***E4f1* flox, *Mdm2* flox, *p53* flox, *Mdm4* flox**

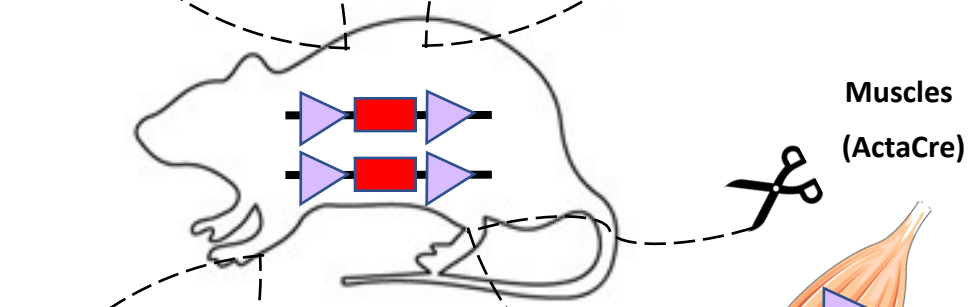
Single, double, Triple cKO

MDM2 **E4F1** **p53** **MDM4**



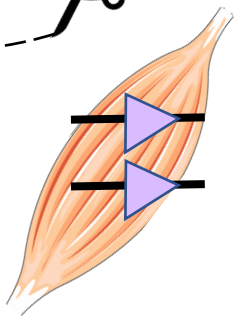
p53 hot-spot mutants

R172H **R248W**



Muscles

(ActaCre)



Whole body
(ROSACreER)

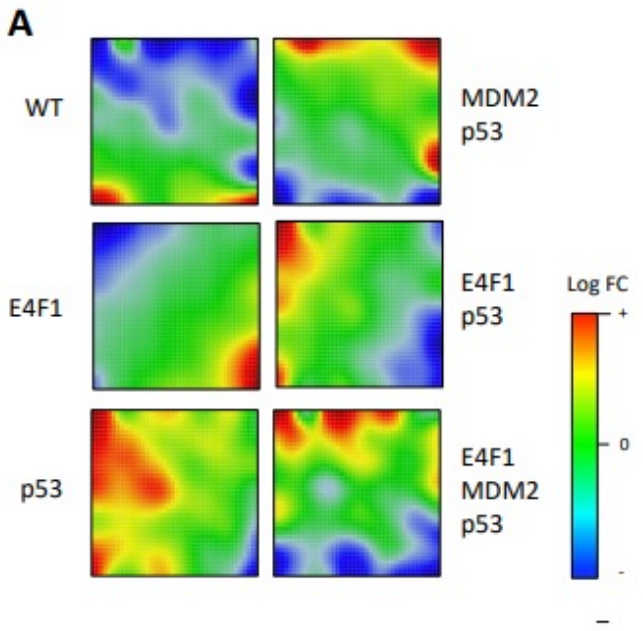
C. Talignani
(AI, Univ)

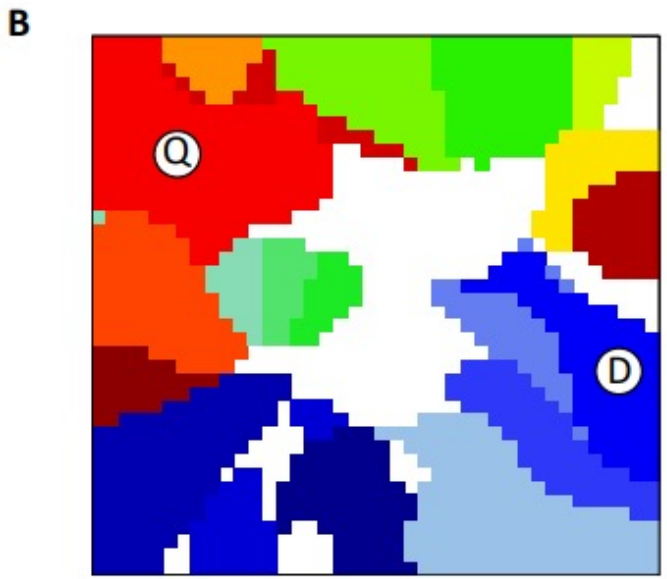
PF. Roux
(Post-doc)

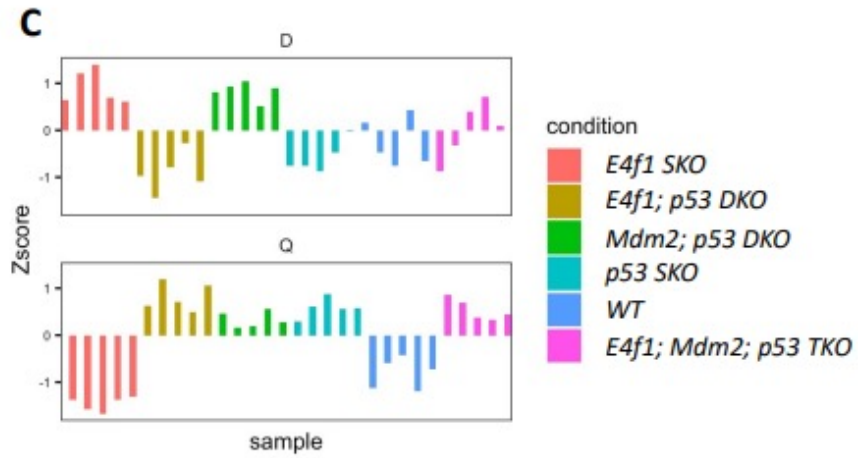
Computational modeling of p53-associated metabolic networks

Self organizing maps

PF. Roux
(Post-doc)





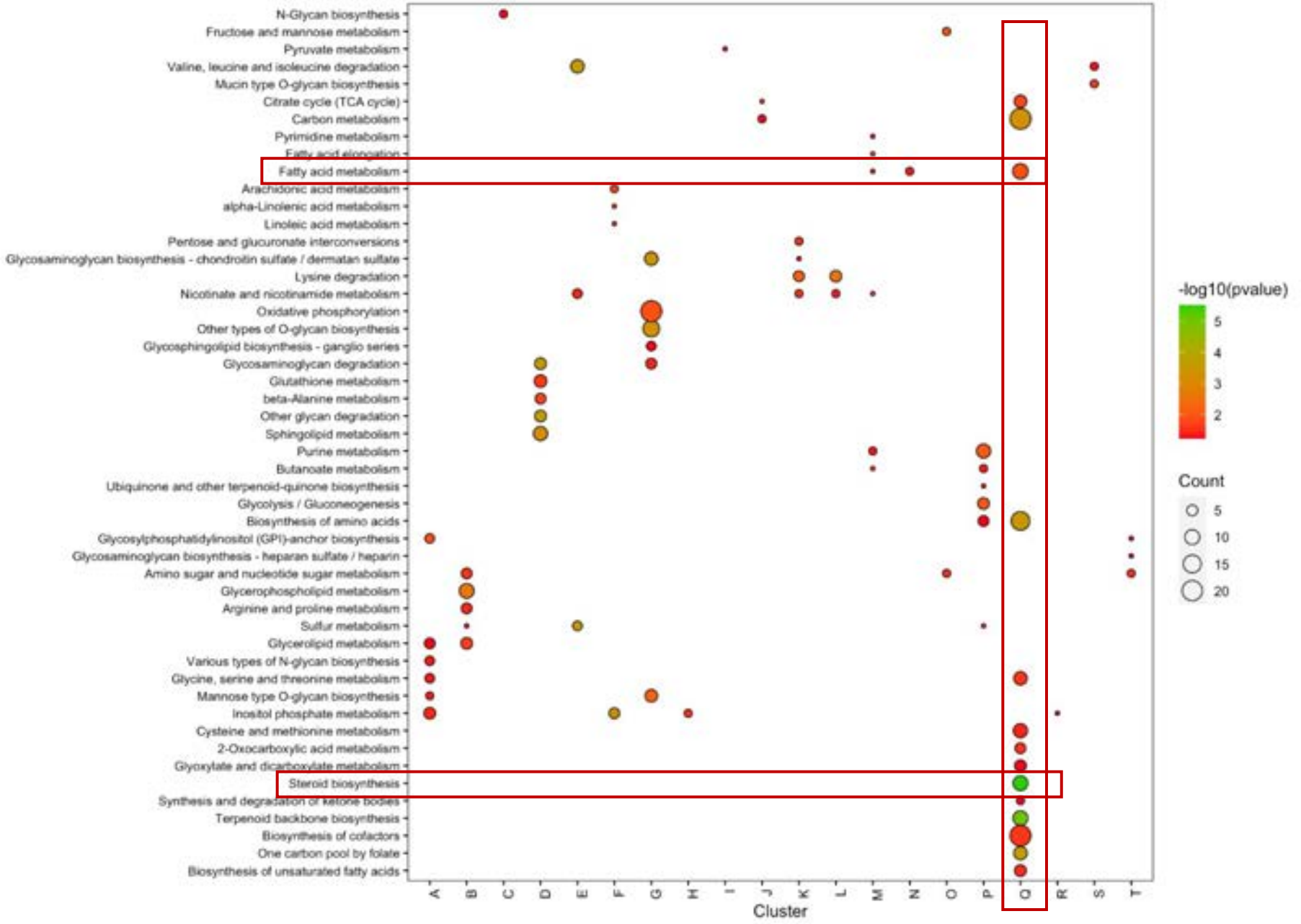


Antagonistic effects

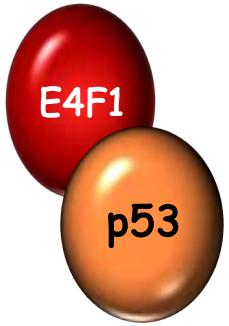
Synergistic effects

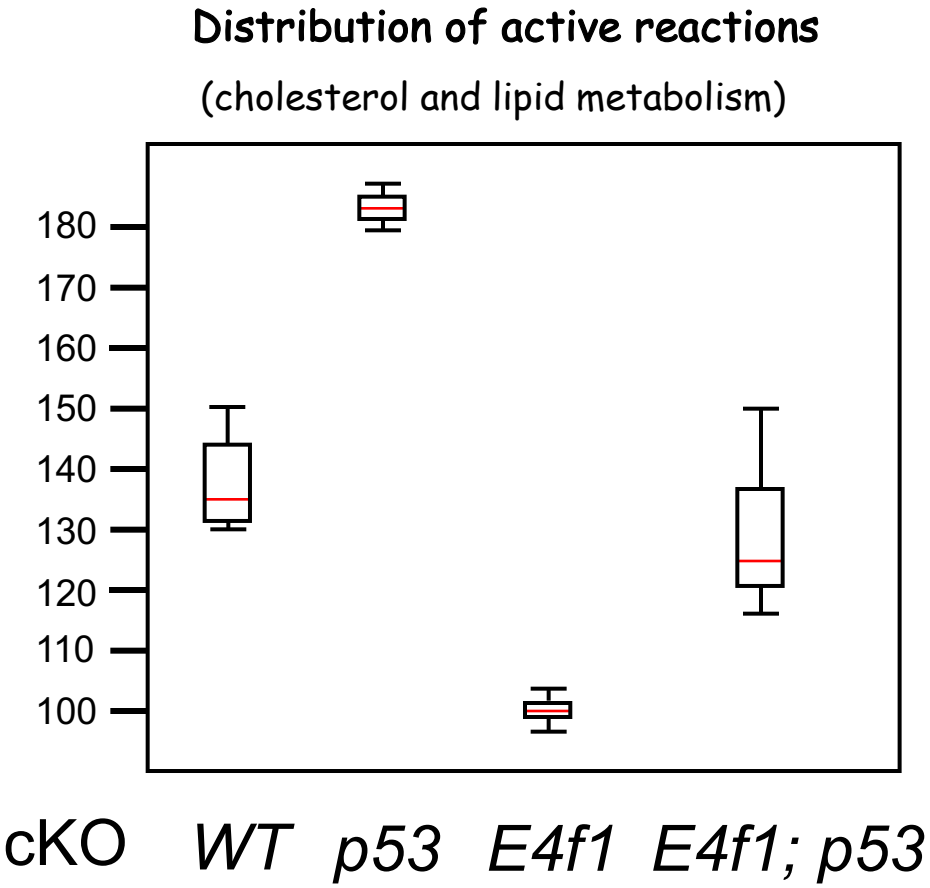
Epistatic effects

OVER-REPRESENTATION MAPS (RNA-seq)



Genome scale metabolic networks





P. Rodriguez-Mier
(Post-doc)

N. Poupin
(CRCN)

Collab: F. Jourdan
(INRAe-Toxalim, Toulouse)

E4F1 and p53 display antagonistic activities in lipid metabolism

E4F1 cKO mice are lipodystrophic

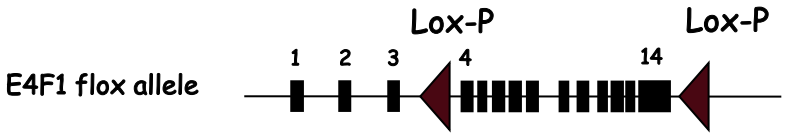
Lacroix, Linares et al., Nat Comms 2021


M. Lacroix

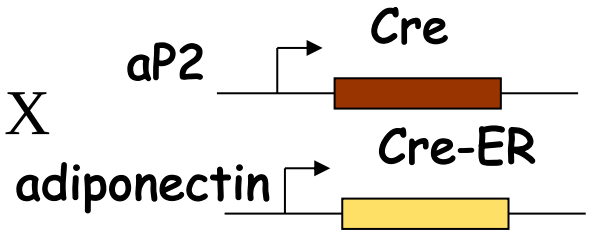

L. Linares

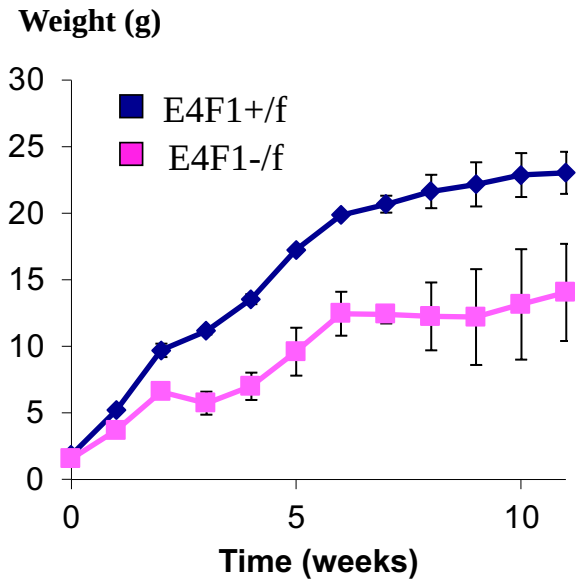

C. Fau

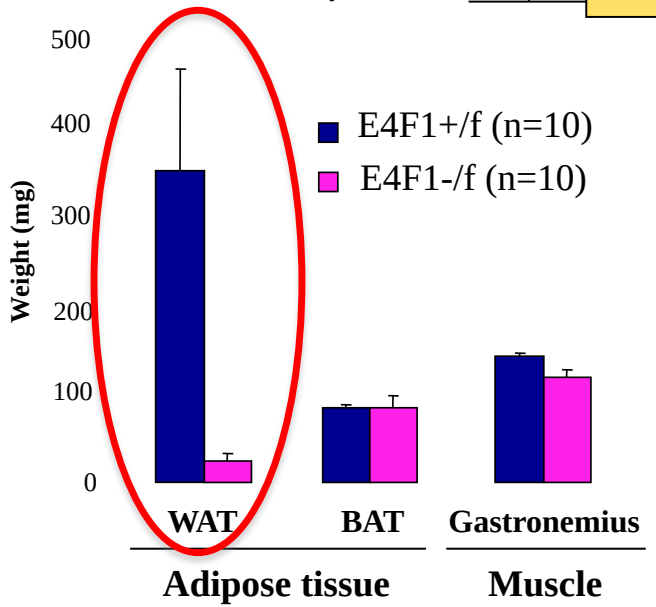
E4F1 adipose-tissue specific KO



X



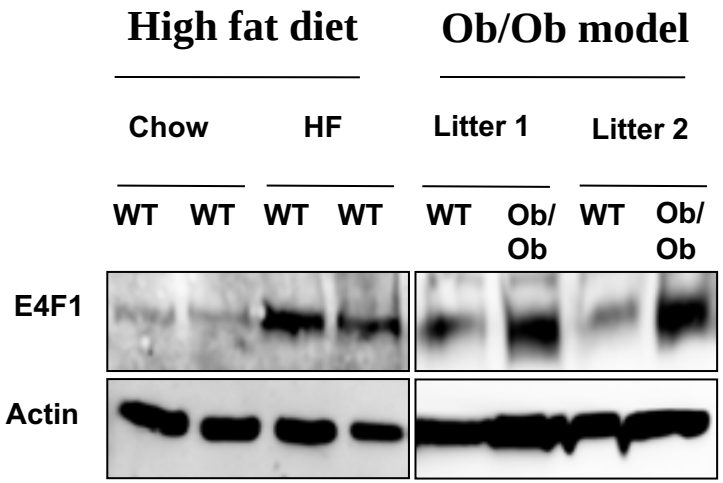




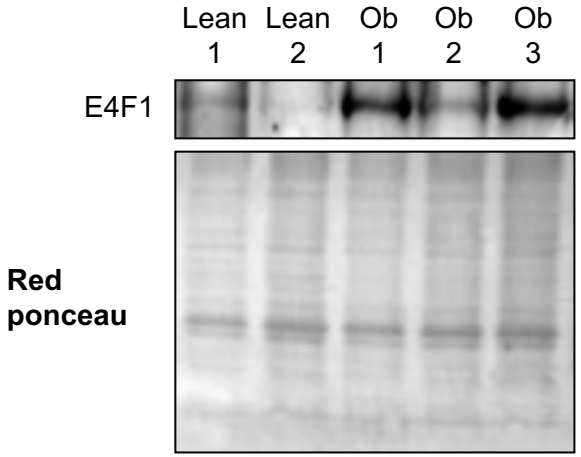
Gonadal fat depot

E4F1 and obesity

E4F1 expression increases during obesity



murine adipose tissue



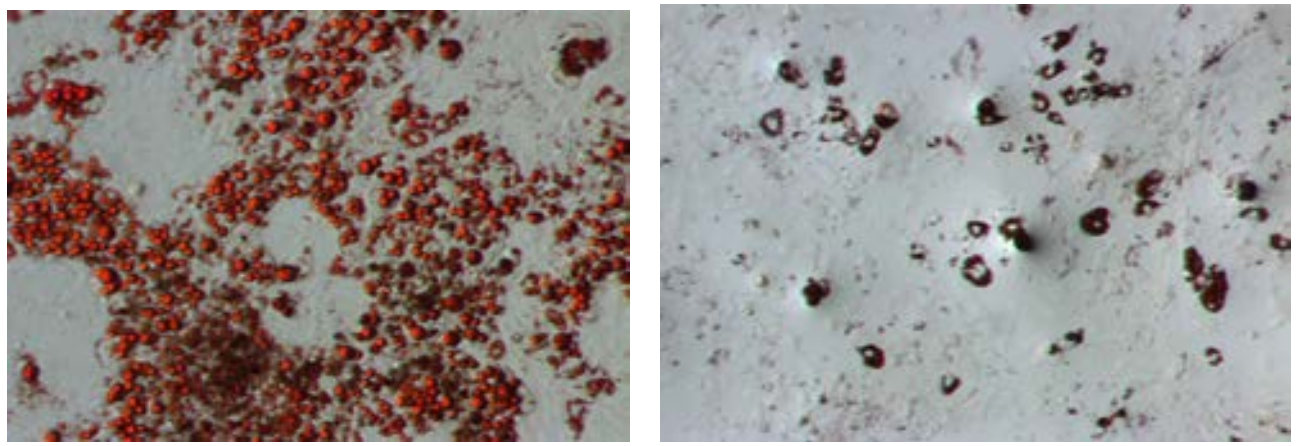
Human samples (visceral fat)

Adipocyte differentiation in E4F1 cKO MEFs and preadipocytes

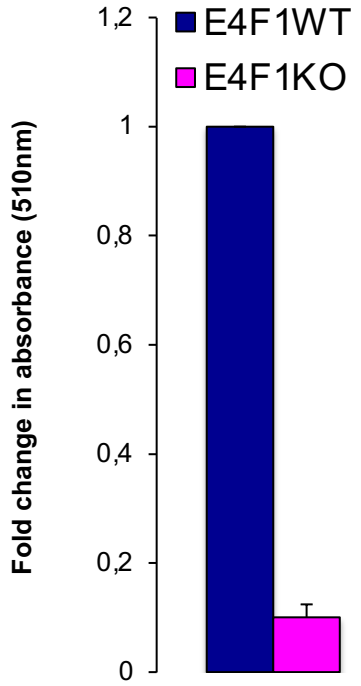
in vitro adipocyte differentiation

E4f1 WT (day 10)

E4f1 KO (day 10)



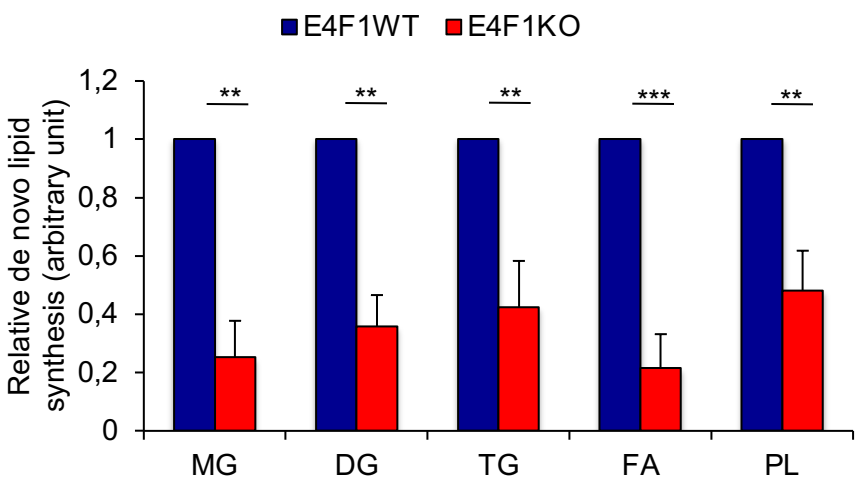
O-Red Oil staining



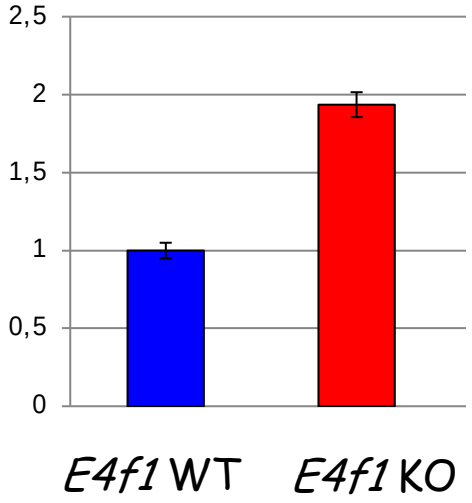
Adipocyte differentiation in *E4f1* cKO MEFs

E4f1 KO cells exhibit:

decreased lipid synthesis and **increased fatty acid oxidation**

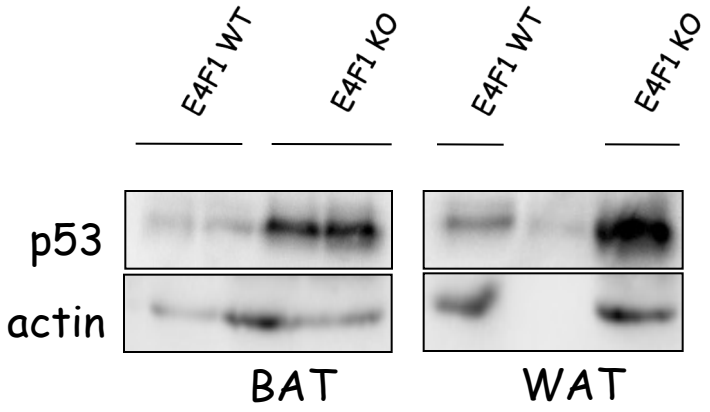


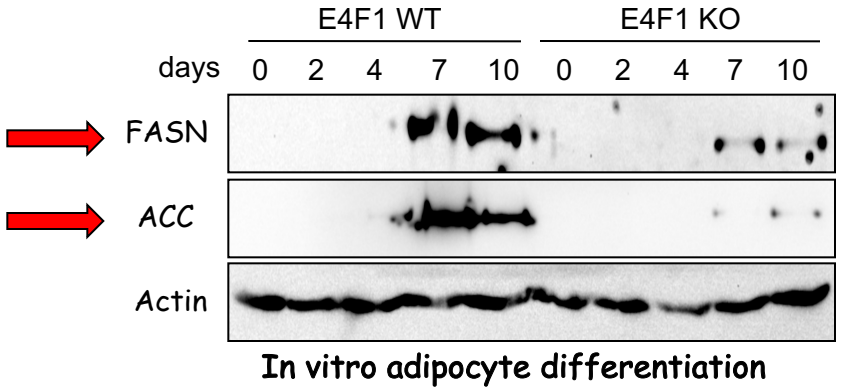
De novo lipid synthesis
(^{14}C-acetate incorporation)



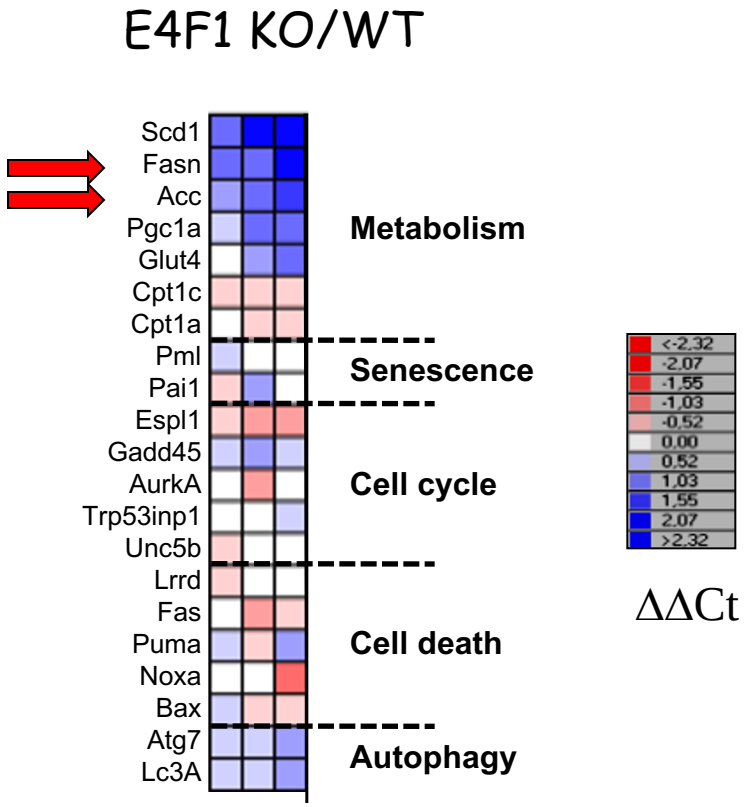
Fatty acid β-oxidation
(^{3}H-labelled palmitate)

p53 is induced upon E4F1 inactivation in WAT and BAT

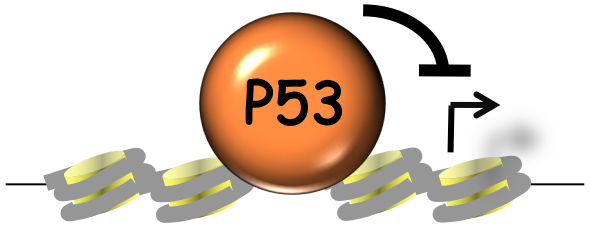




In vitro adipocyte differentiation



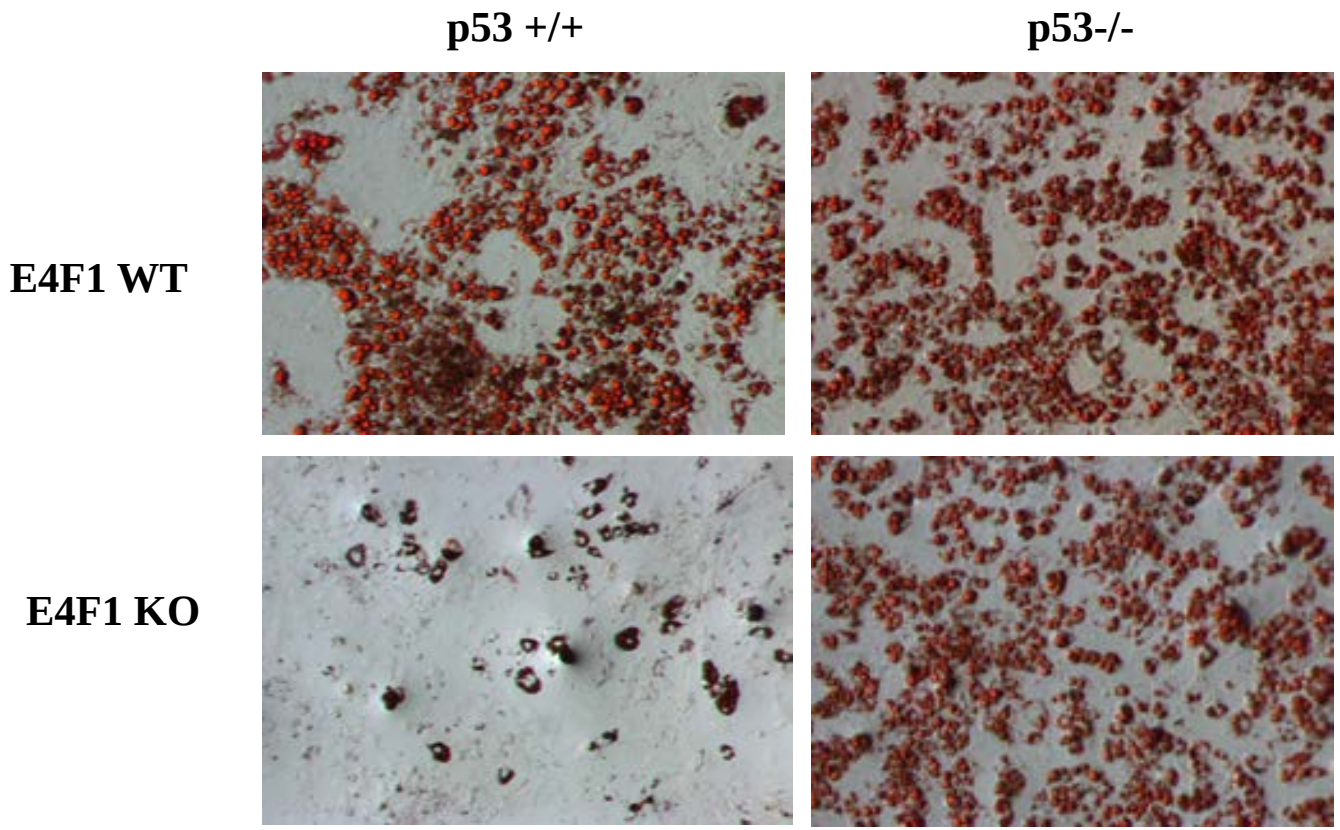
Microfluidic based RT-qPCR



Scd1, Fasn, Acc, Pgc1a, Glut4

p53 inactivation rescues E4F1 KO adipose tissue defects

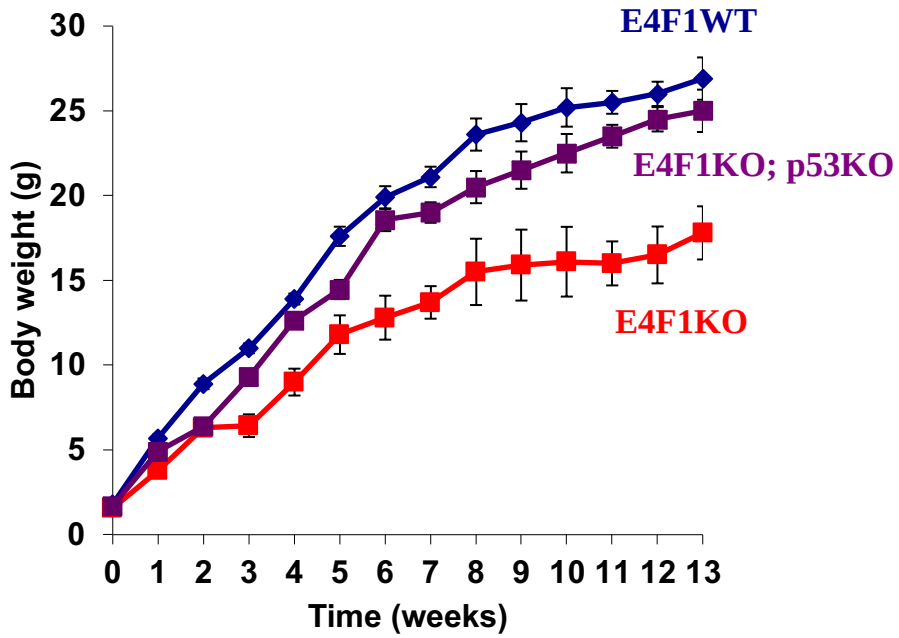
in vitro adipocyte differentiation



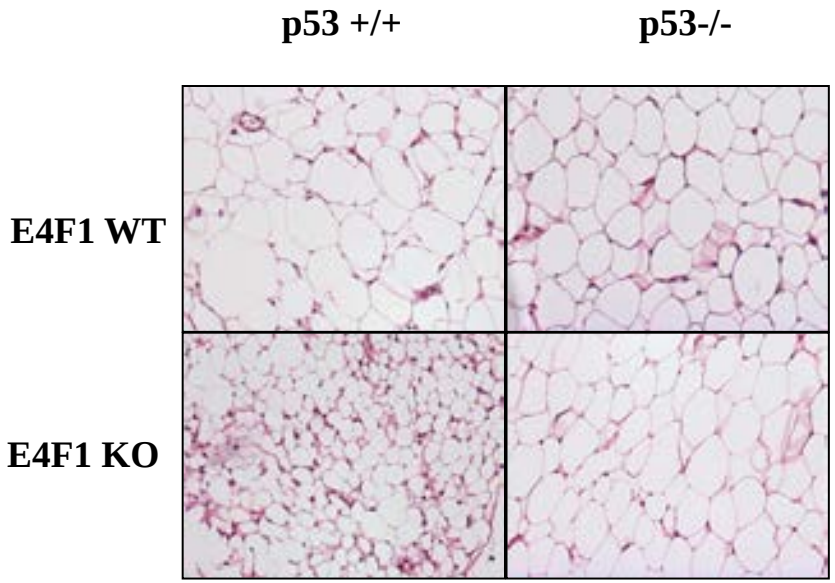
O-Red Oil staining

p53 inactivation rescues E4F1 KO adipose tissue defects

A.

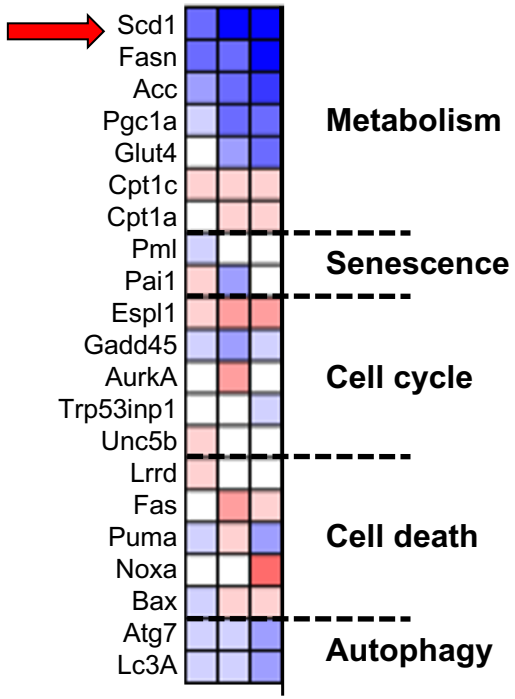


B.

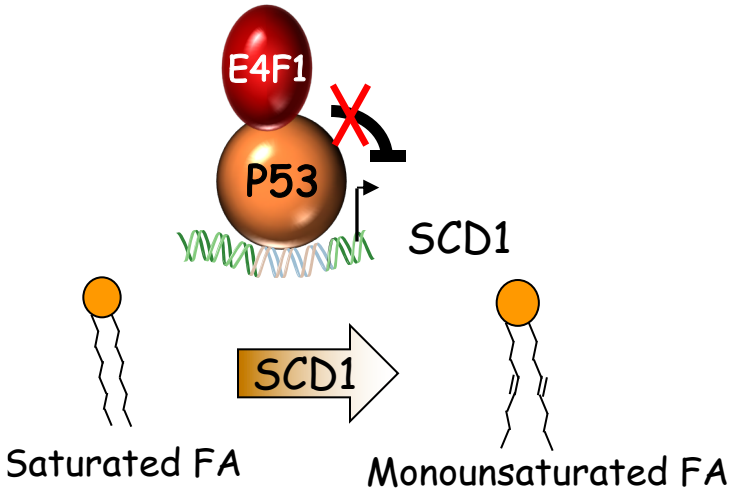


Role of the E4F1-p53-SCD1 axis in adipose tissue function

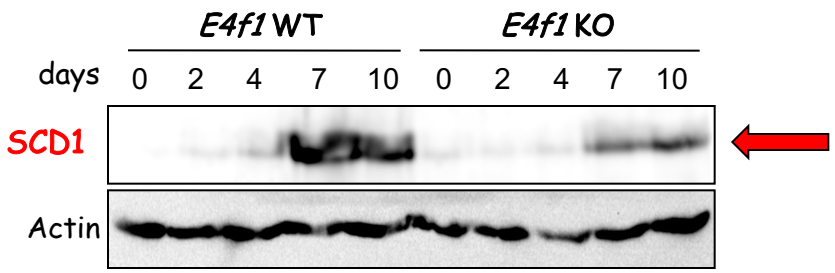
E4F1 KO/WT
(mRNA levels)



RT-qPCR

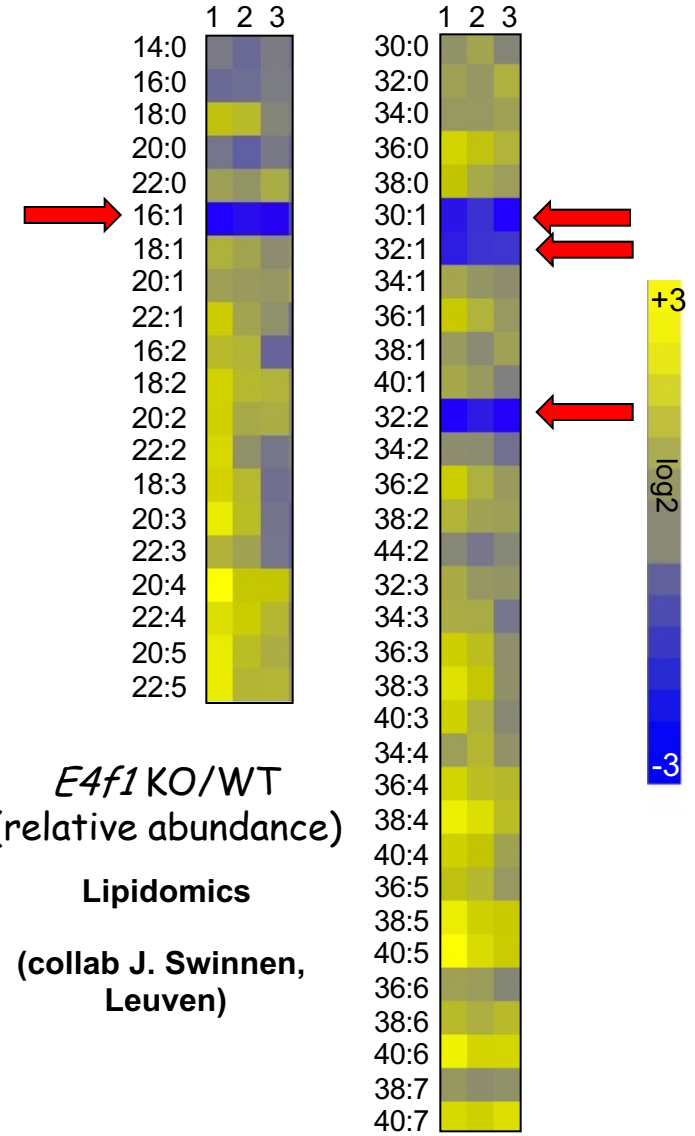


In vitro adipocyte differentiation



Immunoblot

Phosphatidylcholine

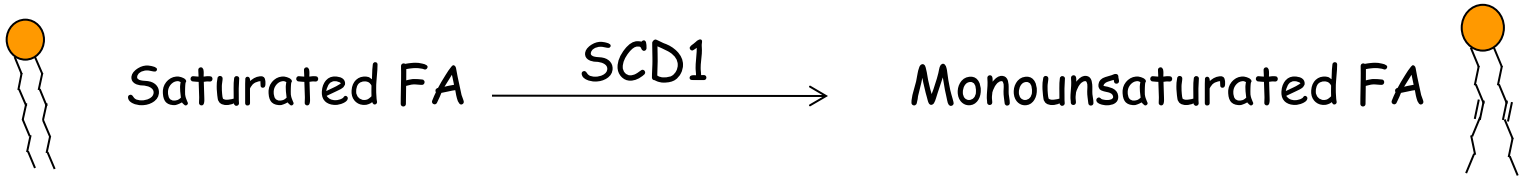


E4f1 KO/WT
(relative abundance)

Lipidomics

(collab J. Swinnen, Leuven)

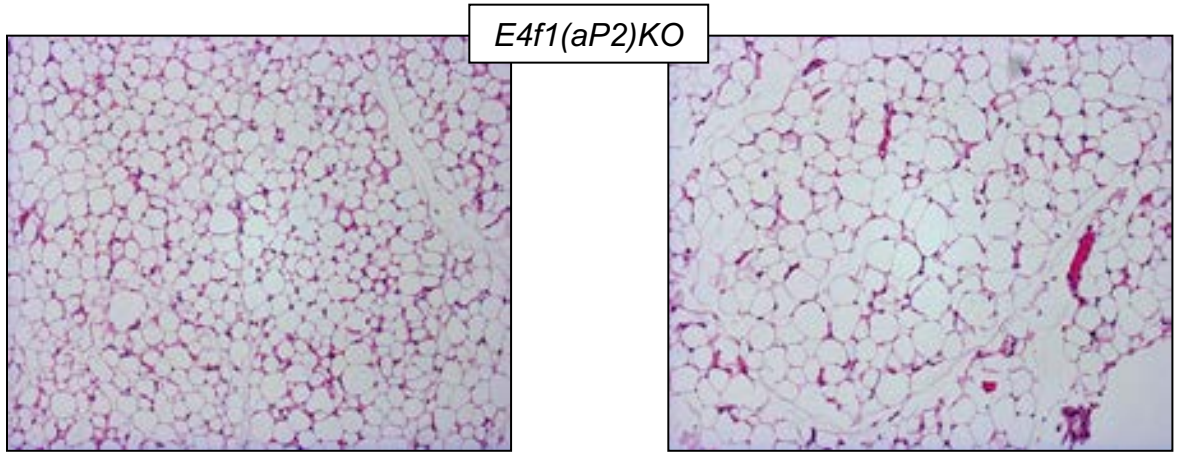
Monounsaturated FAs rescue E4F1 KO WAT defects



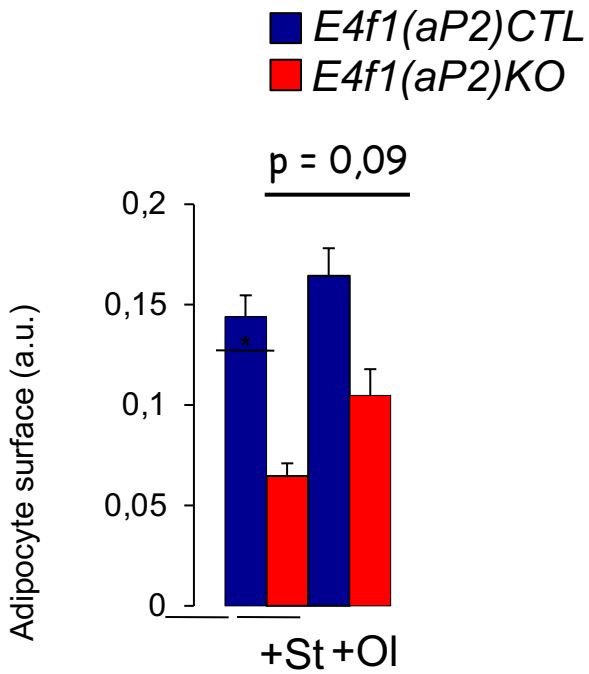
Normal diet

+ stearate (C:18:0)

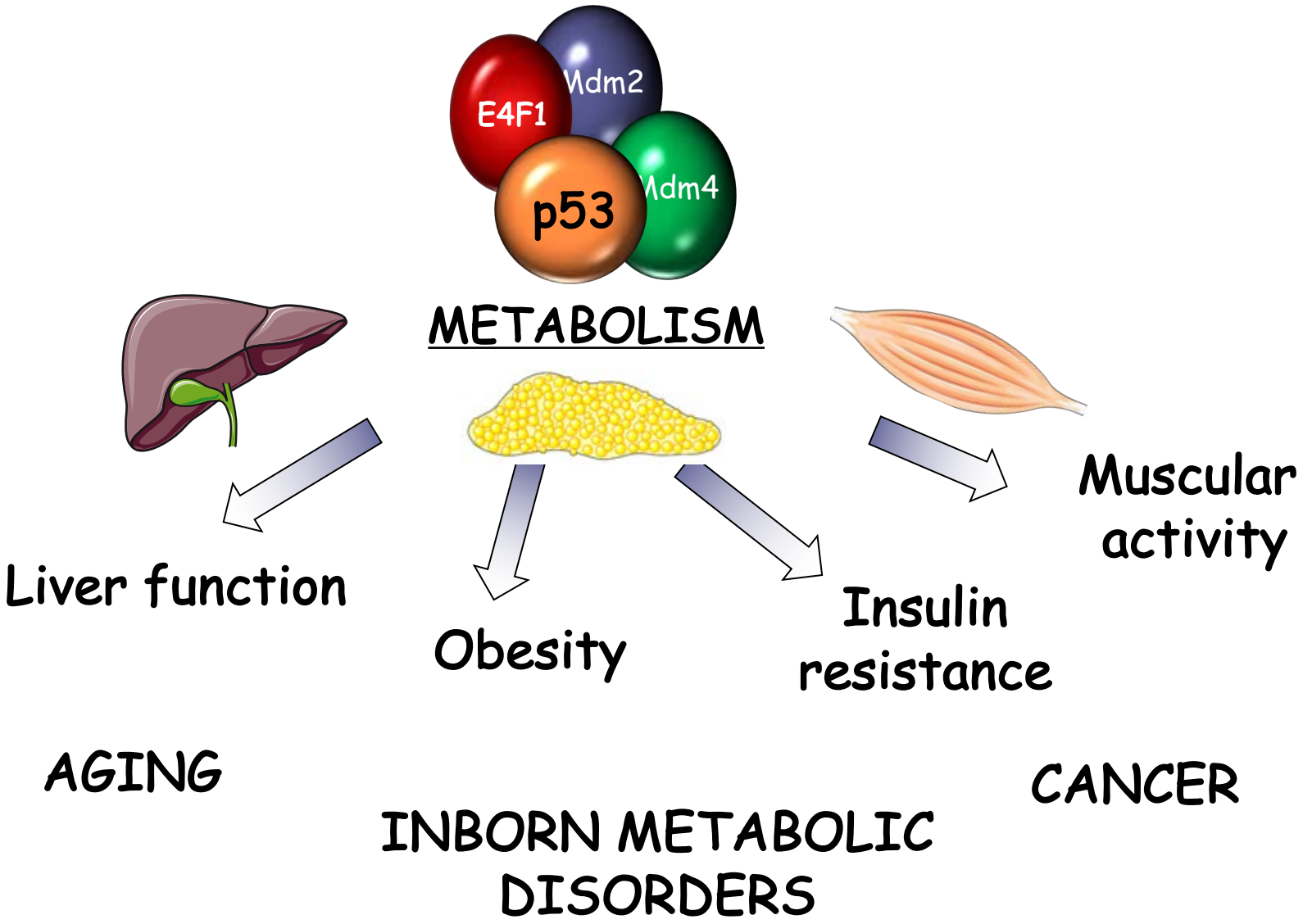
+ oleate (C18:1)

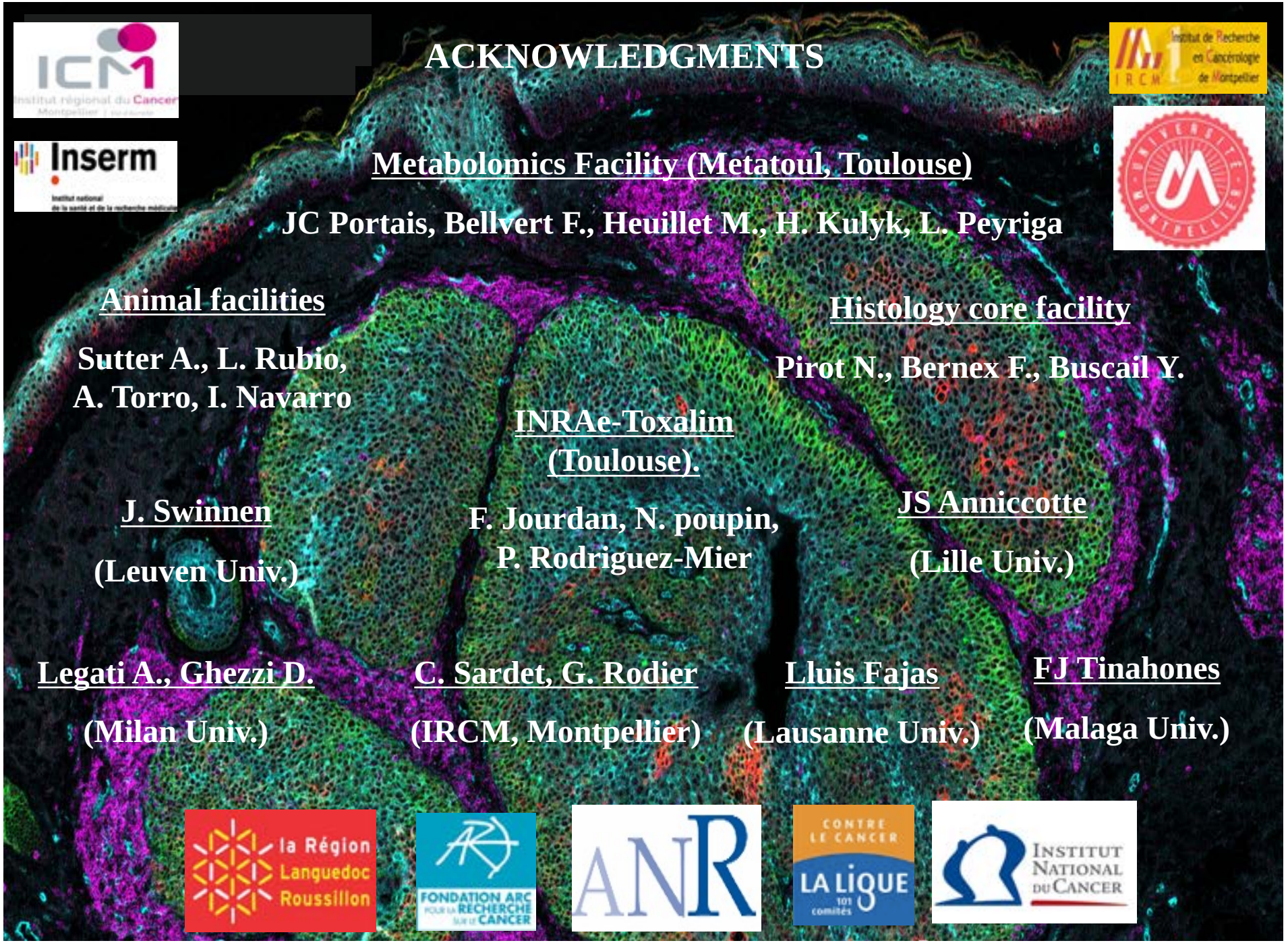


(3 weeks)



CONCLUSIONS





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Sutter A., L. Rubio,
A. Torro, I. Navarro

Histology core facility

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INRAe-Toxalim (Toulouse).

F. Jourdan, N. poupin,
P. Rodriguez-Mier

J. Swinnen

(Leuven Univ.)

JS Anniccotte

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Legati A., Ghezzi D.

(Milan Univ.)

C. Sardet, G. Rodier

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Lluis Fajas

(Lausanne Univ.)

FJ Tinahones

(Malaga Univ.)