When Flies Get Fat:

How a Tiny Insect Reveals Universal Secrets of Obesity

朱培雯 姜思梅 梁子健

2025-03-27

Outline

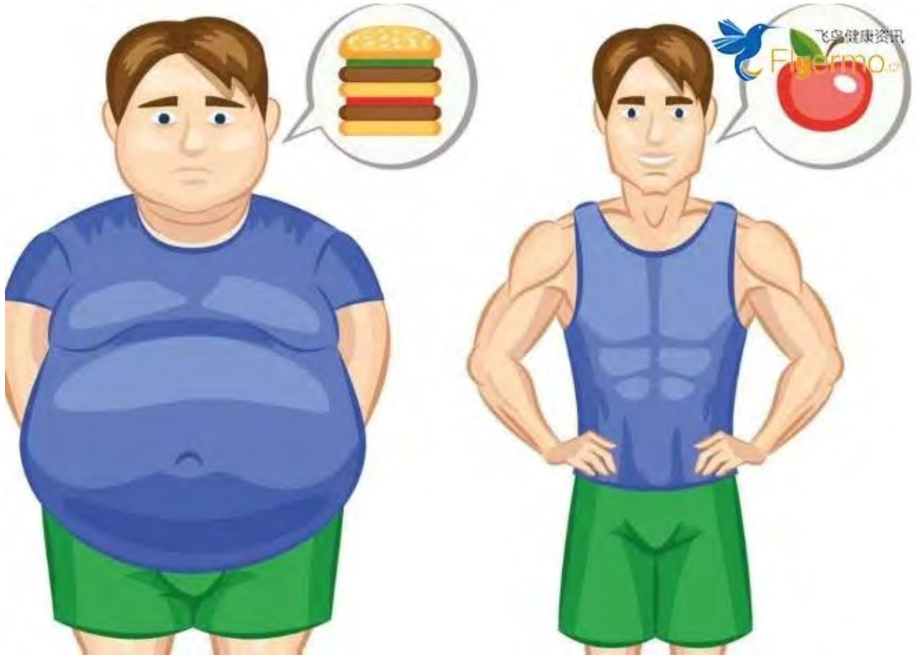
- The Causes and Underlying Mechanisms of Obesity – 朱培雯
- The Behavioral and Physiological Effects of Obesity – 姜思梅
- The Intrinsic Relation Between Exercise and Obesity – 梁子健
- Discussion

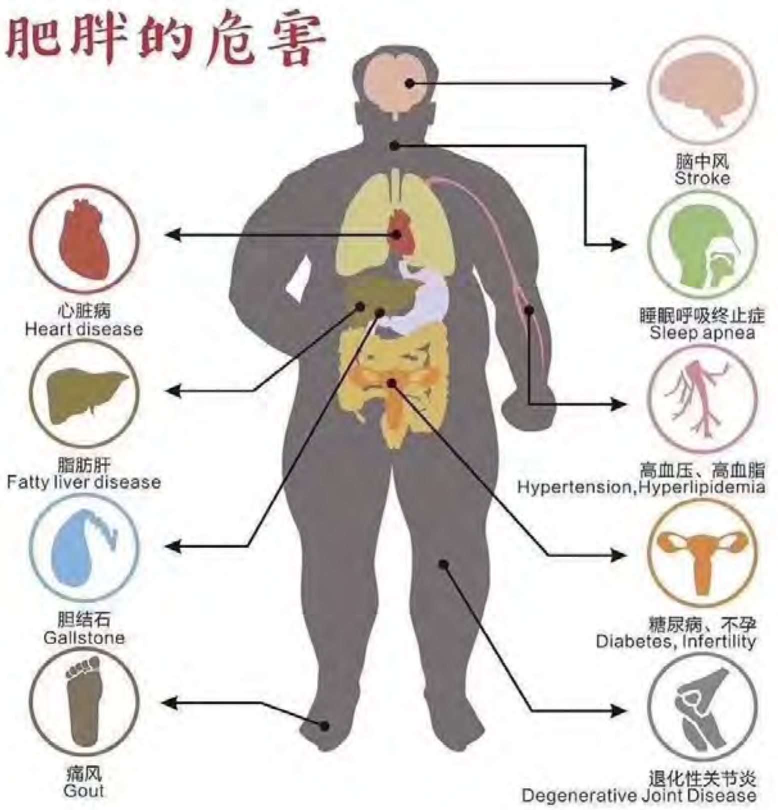
The Causes and Underlying Mechanisms of Obesity

朱培雯

2025-03-27

“一白遮百丑，一胖毁所有”



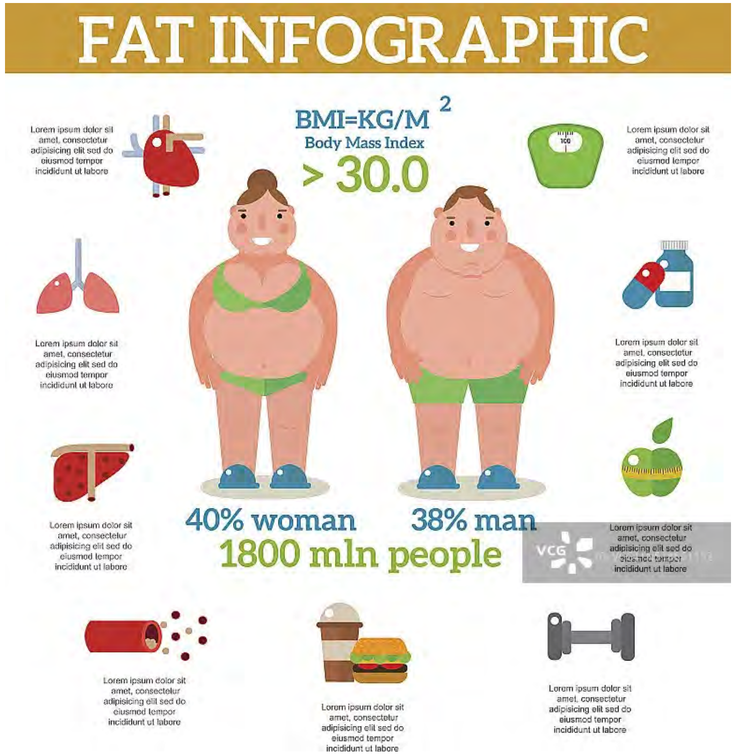

肥胖的危害
脑中风
Stroke
心脏病
Heart disease
睡眠呼吸终止症
Sleep apnea
脂肪肝
Fatty liver disease
高血压、高血脂
Hypertension,Hyperlipidemia
胆结石
Gallstone
糖尿病、不孕
Diabetes, Infertility
痛风
Gout
退化性关节炎
Degenerative Joint Disease

WHO definitions of overweight and obesity in adults

体重指数（BMI）：体重(kg)/身高²(m²)

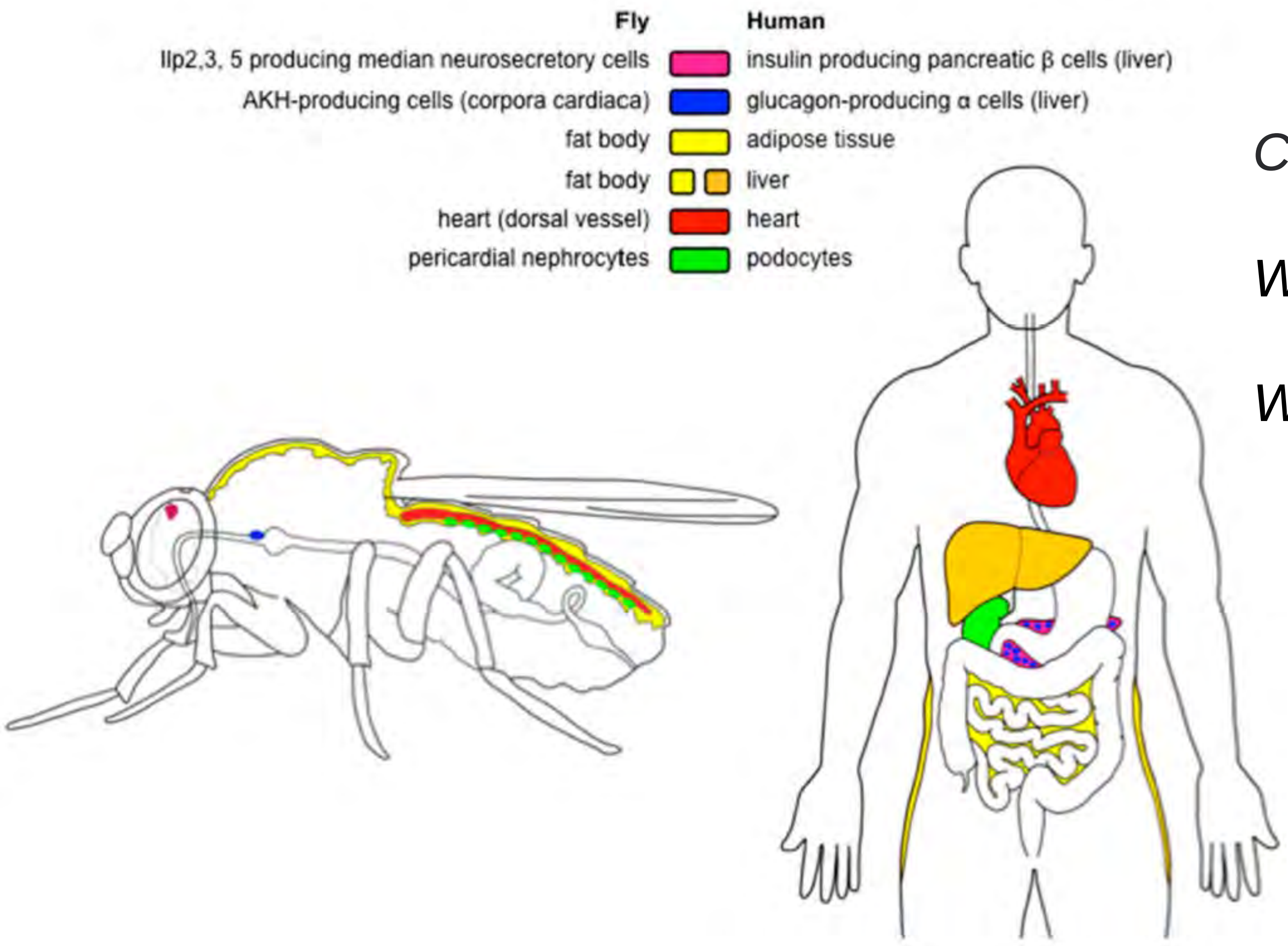
超重：体重指数大于或等于25

肥胖：体重指数大于或等于30



	2020	2025	2030	2035
Adults with overweight (BMI ≥25 to 30 kg/m²)	1.39bn	1.52bn	1.65bn	1.77bn
Adults with obesity (BMI ≥30 kg/m²)	0.81bn	1.01bn	1.25bn	1.53bn
Adults with overweight or obesity as a proportion of all adults globally	42%	46%	50%	54%

Drosophila as a model to study obesity



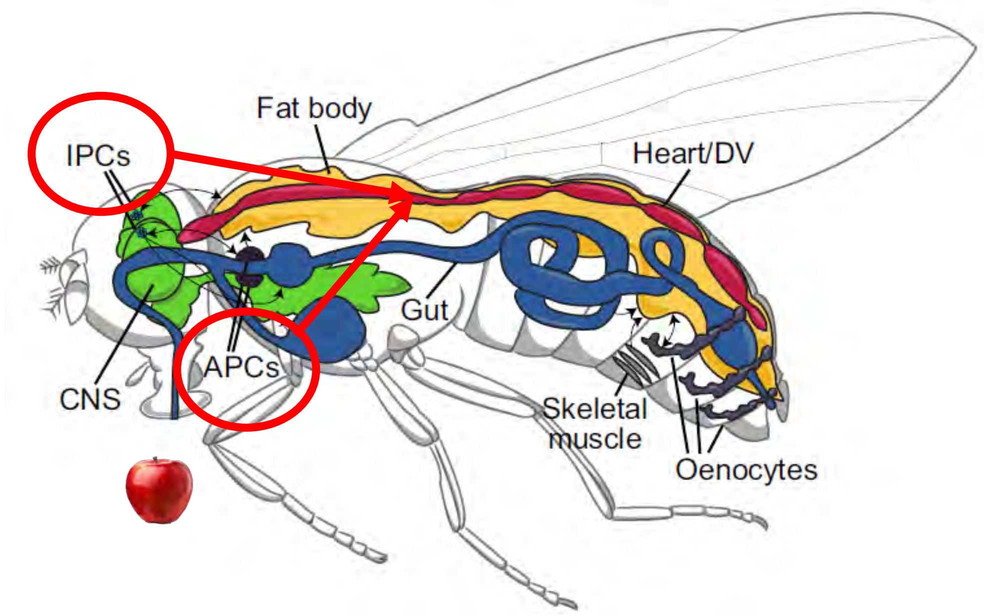
Can fruit flies really be used to study human obesity?

What are the causes of obesity in Drosophila?

What is the induction mechanism of obesity?

(Martina Gáliková, et al.
Int J Mol Sci, 2018)

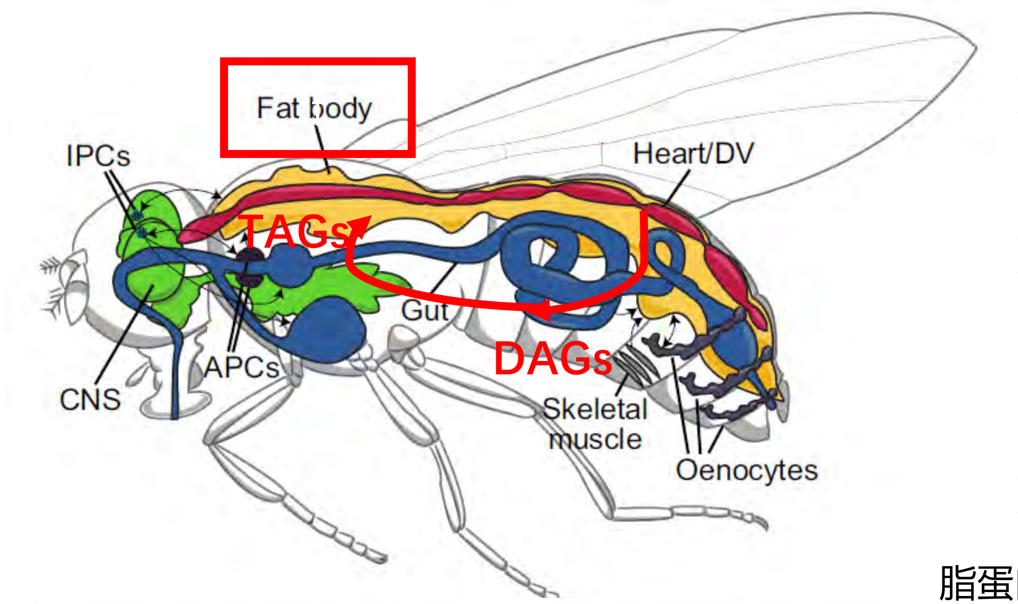
Systems physiology regulating obesity in *Drosophila*

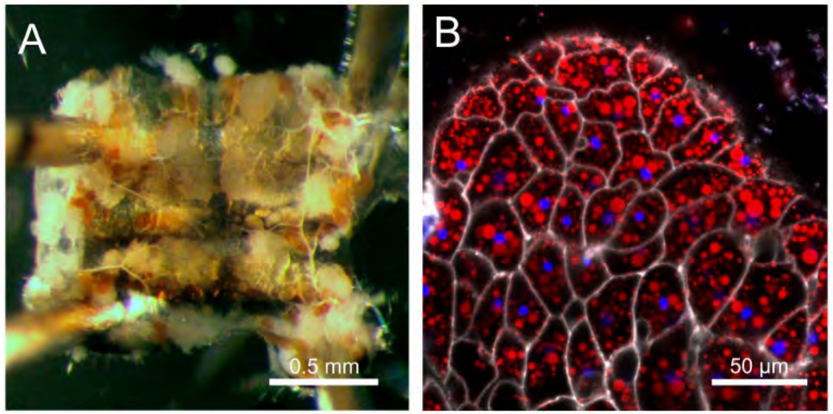


- When food enters through the foregut and is digested and absorbed along the gut……
- Akh-producing cells (APCs) of the corpora cardiaca line the foregut and secrete **Akh**, which serves as the fly's glucagon, to activate feeding and storage energy mobilization.
- Counteracting Akh are the **insulin-like peptides (Ilps)**, which are secreted by a different group of neuroendocrine Ilp-producing cells (IPCs) that lie in the anterior of the central nervous system (CNS).
- These two neurosecretory cells extend axons, which synapse on the heart to release their hormones to enhance efficient metabolic exchange via the fly blood.

(Laura Palanker Musselman, et al. J Exp Biol, 2018)

Systems physiology regulating obesity in *Drosophila*



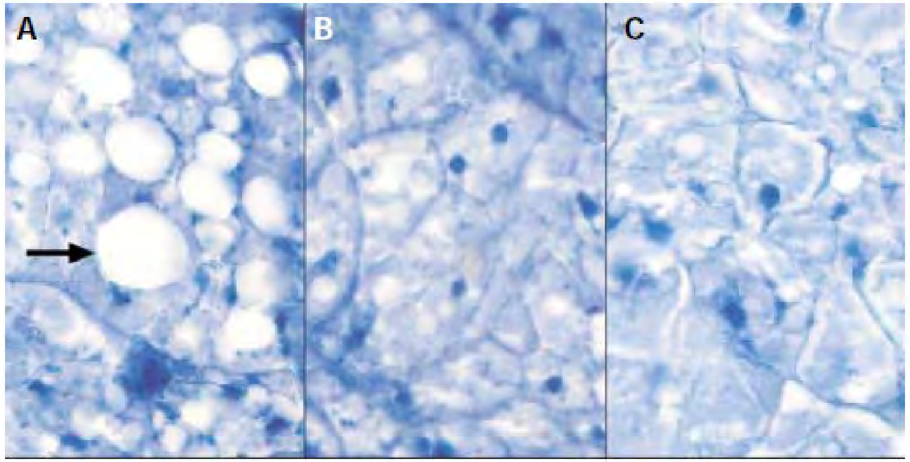


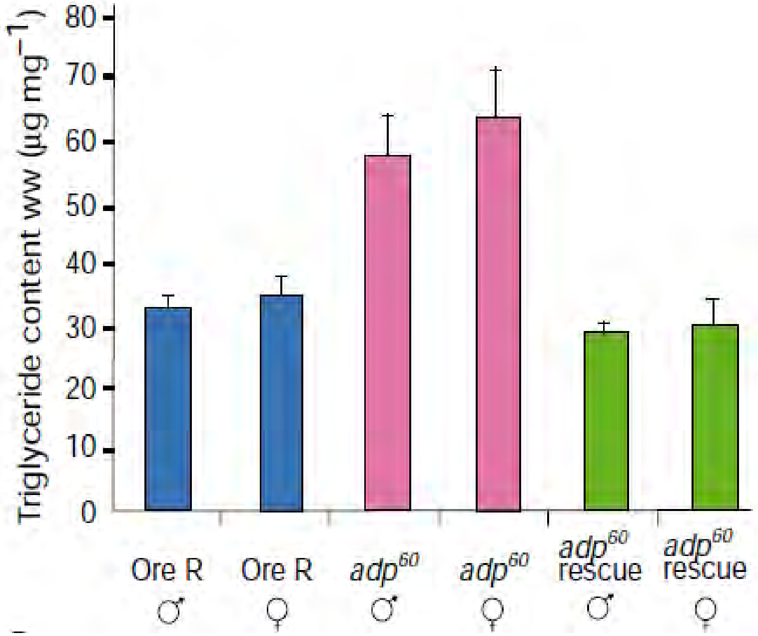
(Laura Palanker Musselman, et al. J Exp Biol, 2018)

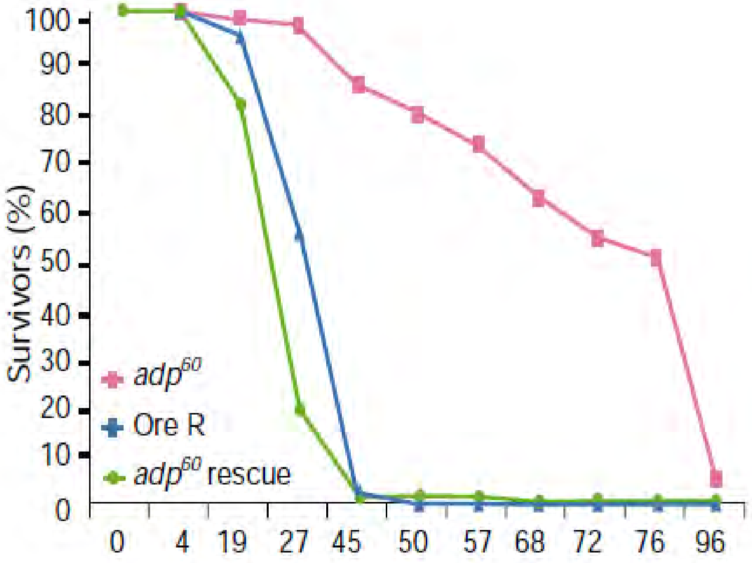
(Martina Gáliková, et al. Int J Mol Sci, 2018)

- Fat bodies express **Ilp** and **Akh** receptors and store fat when nutrients are plentiful.
- The fat body consists of polyploid, sometimes multinucleate cells, which store lipids in specialized organelles **called lipid droplets**
- Absorbed dietary lipids are trafficked from the gut by 脂蛋白 lipophorins in the fly blood as **diacylglycerides (DAGs)** and are stored in lipid droplets as **triacylglycerides (TAGs)**.

Obesity can be studied in invertebrates by using Drosophila genetics

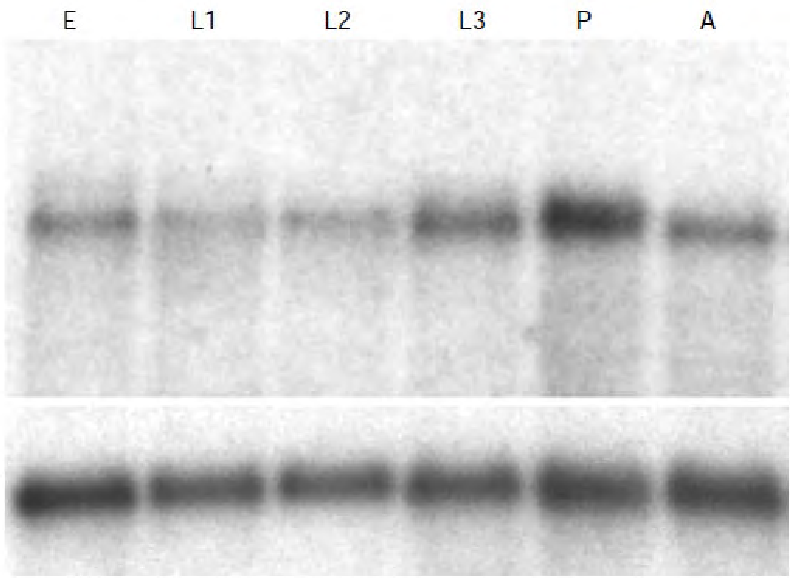


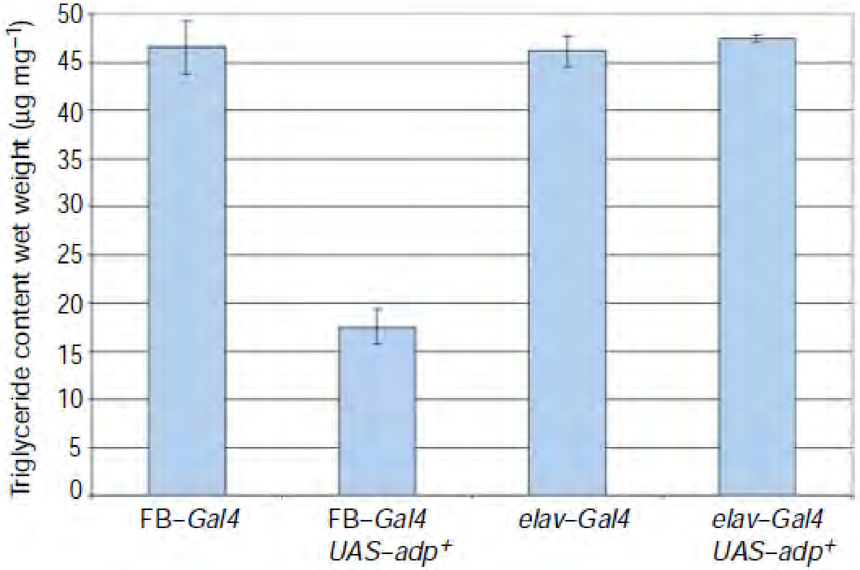


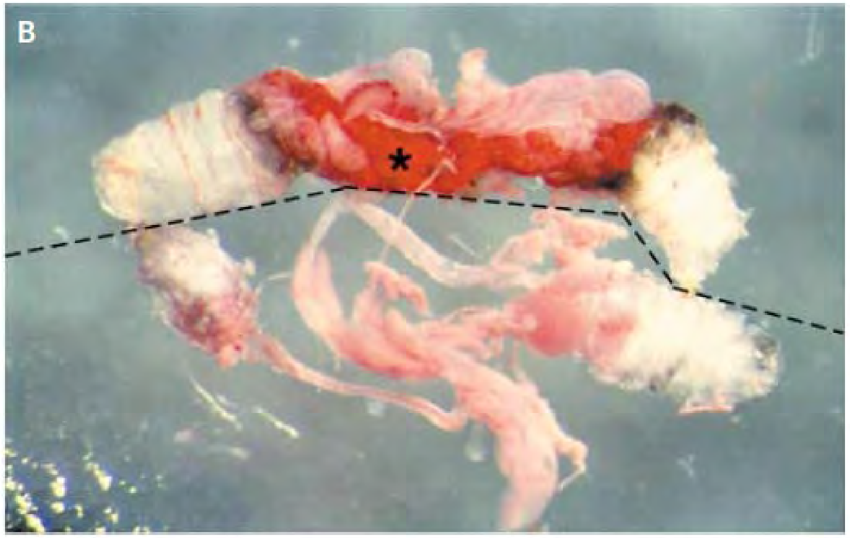


(Thomas Häder, et al. EMBO Rep, 2003)

Obesity can be studied in invertebrates by using Drosophila genetics

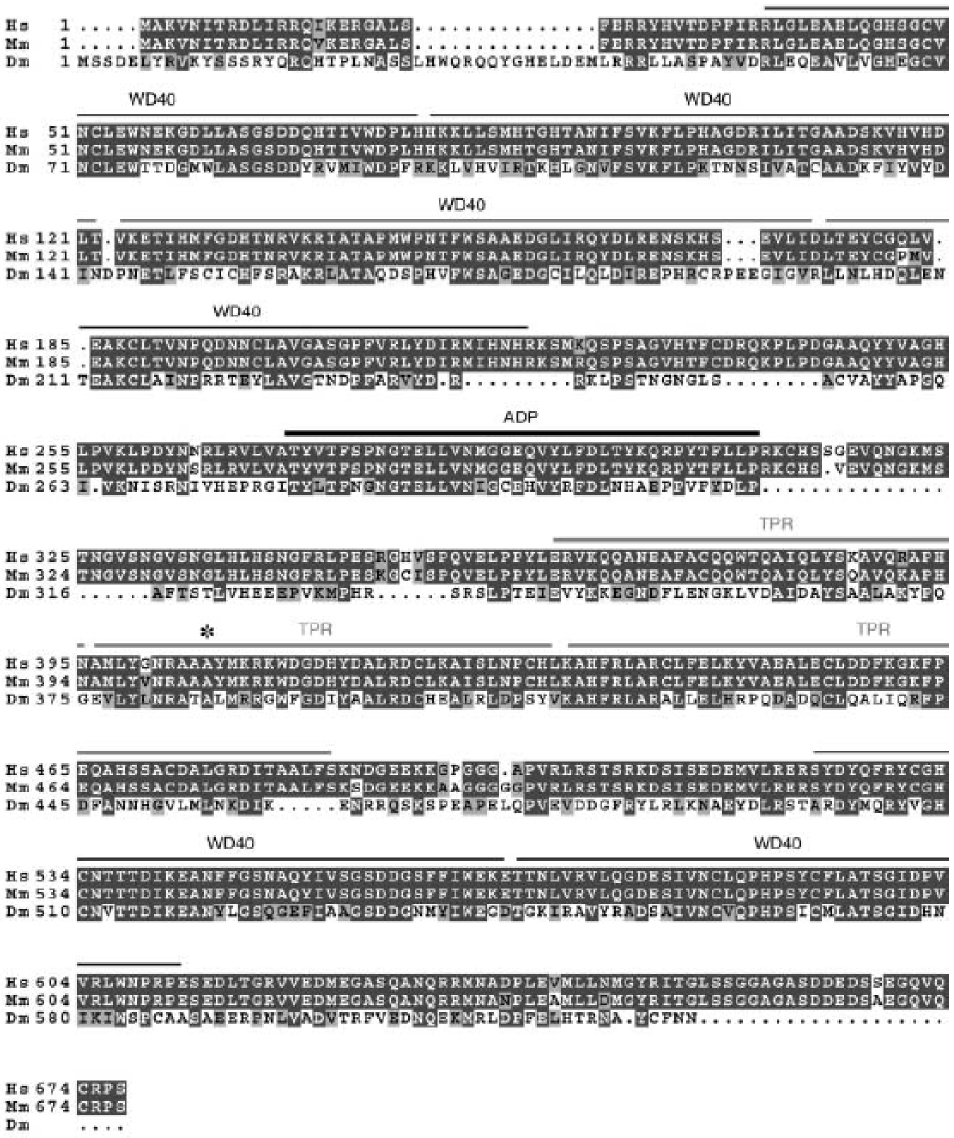


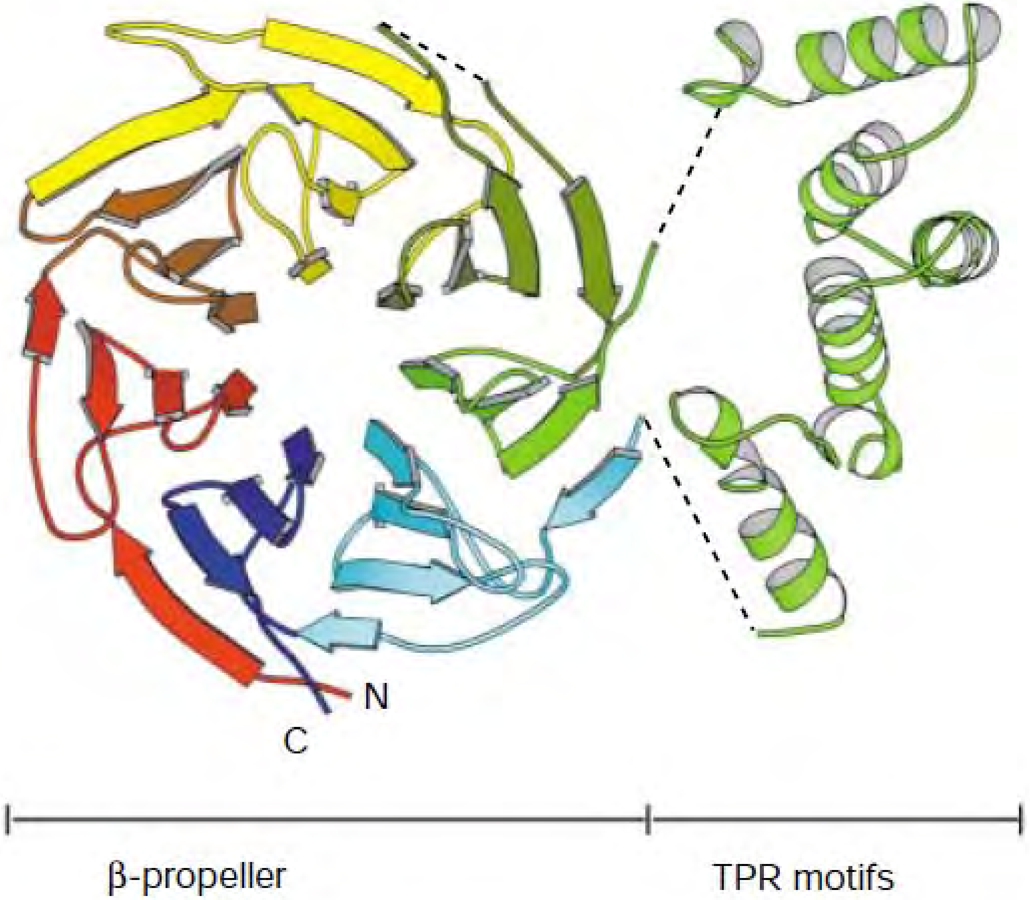




(Thomas Häder, et al. EMBO Rep, 2003)

Obesity can be studied in invertebrates by using Drosophila genetics

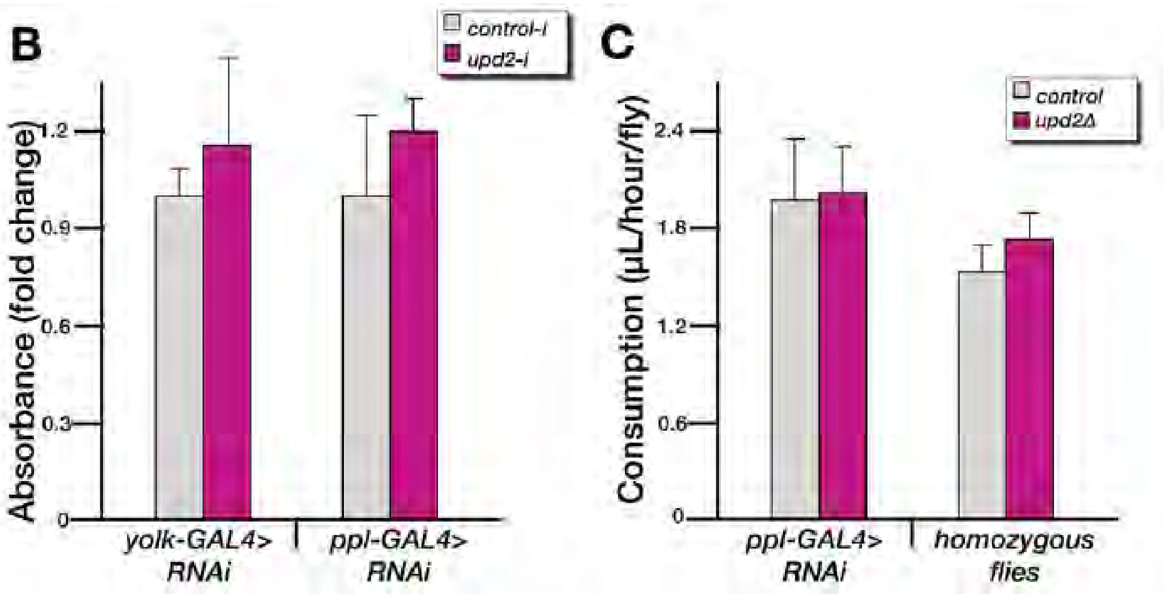




(Thomas Häder, et al. EMBO Rep, 2003)

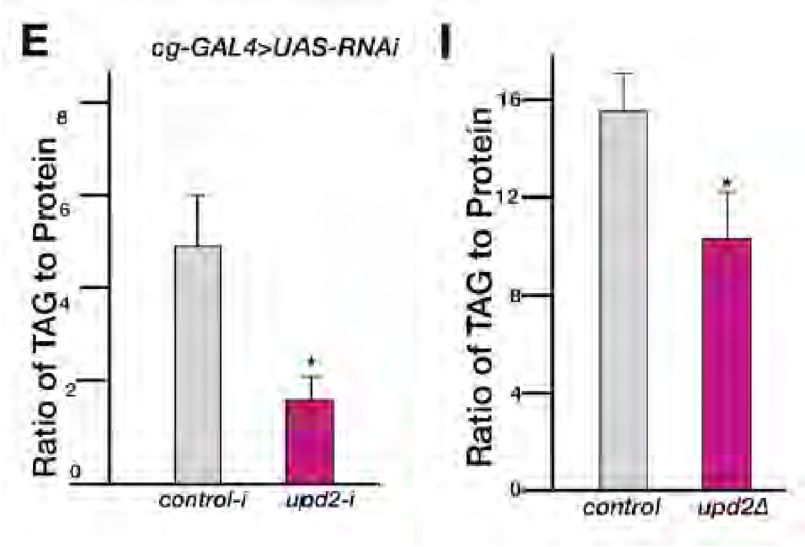
Upd2 expression in the fat body signals the fed state

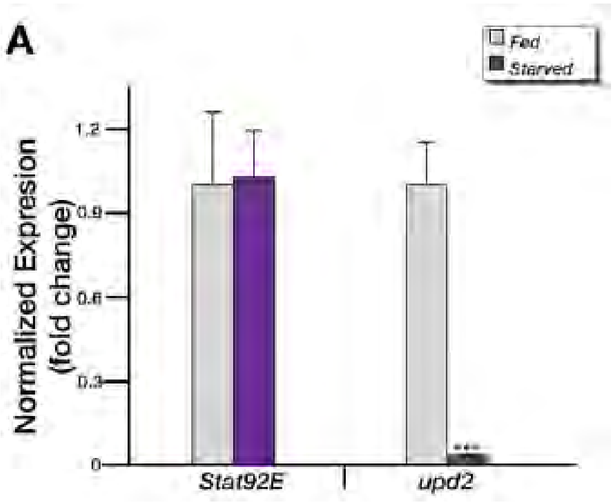
Leptin 人类瘦素

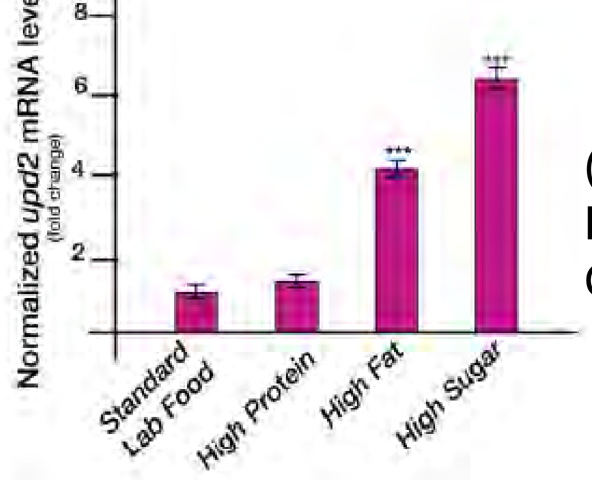


TAG in larvae

TAG in Adult





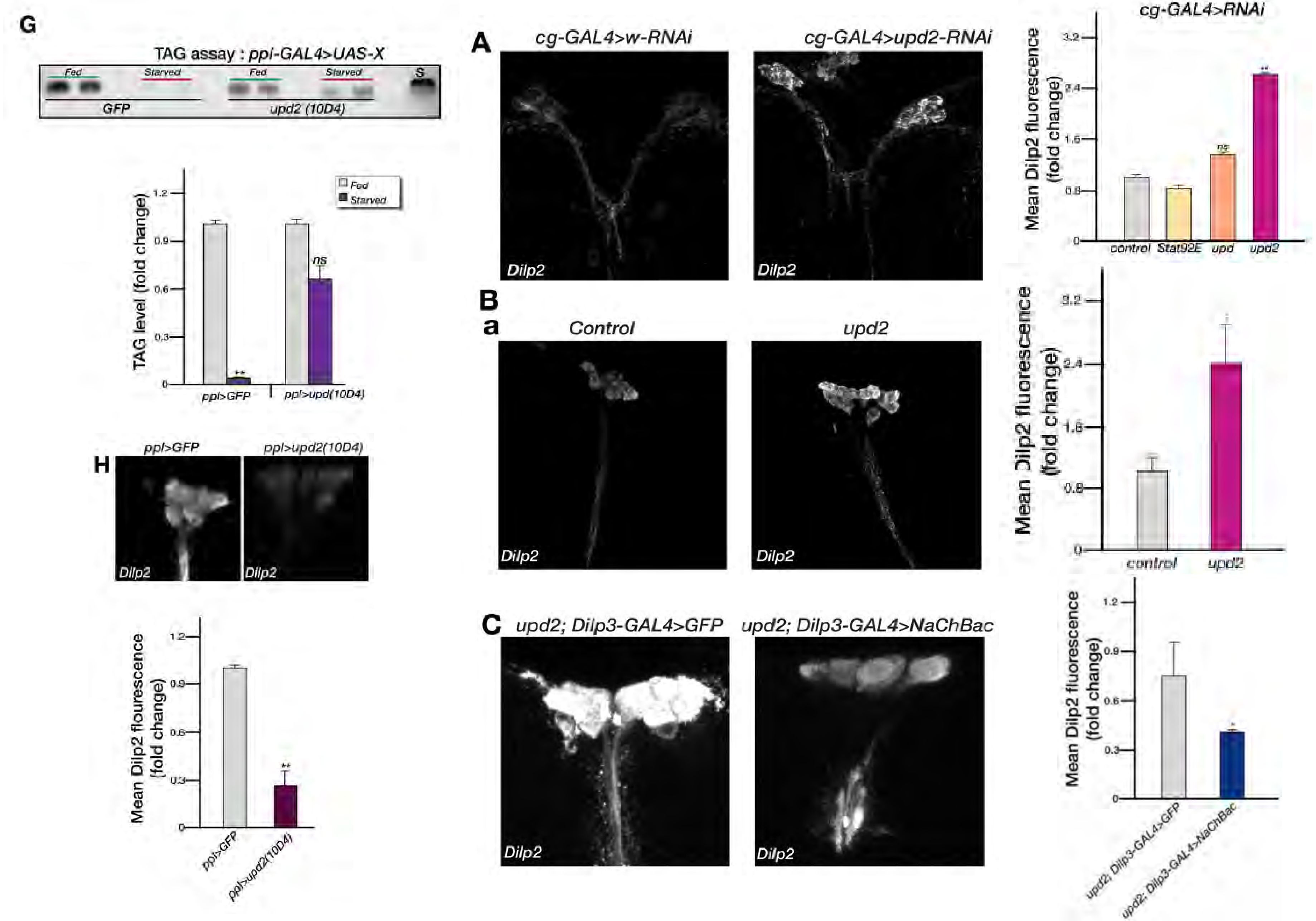


Unpaired 2 （Upd2）是一种与I型

FB在喂养状态下产生的一种分泌因

(Akhila Rajan, et al, Cell, 2012)

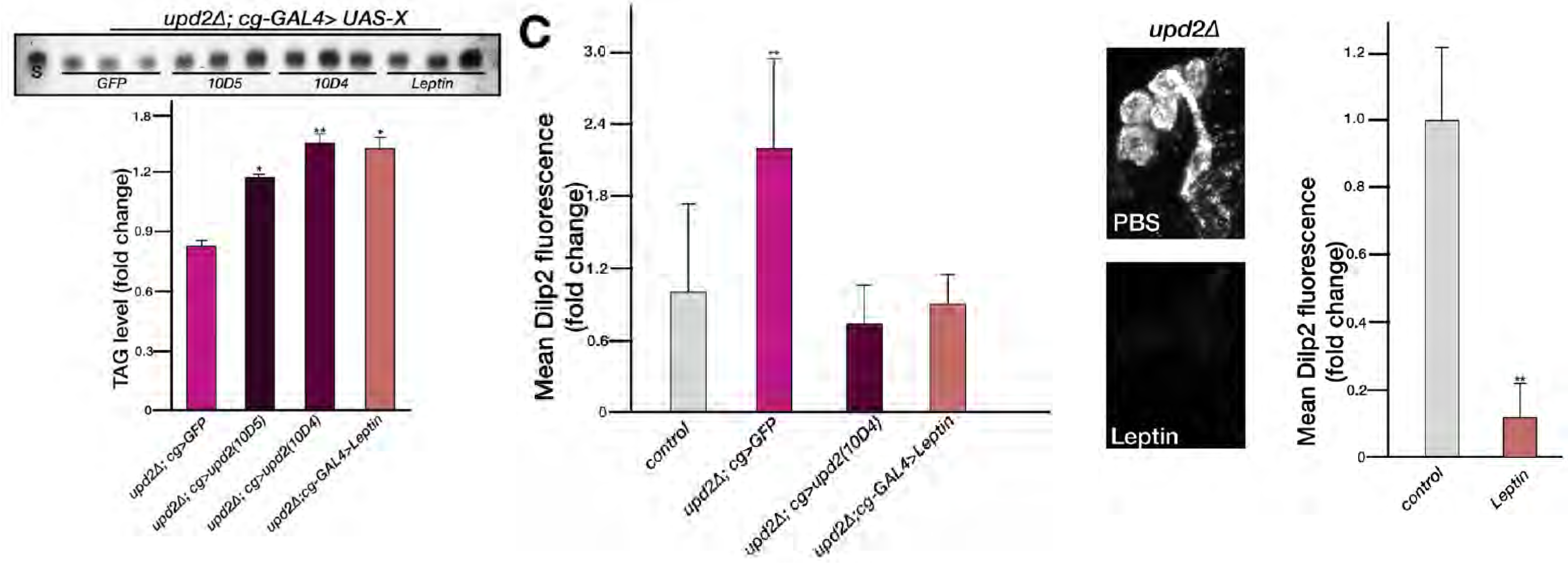
Upd2 remotely controls Dilp accumulation in the IPCs



在没有 upd2 的情况下，TAG 水平的降低，类似于胰岛素信号的减少，表明 Upd2 的主要作用是远程控制 IPCs 分泌 Dilps 以响应营养摄入。

(Akhila Rajan, et al, Cell, 2012)

Human Leptin can rescue the Upd2Δ



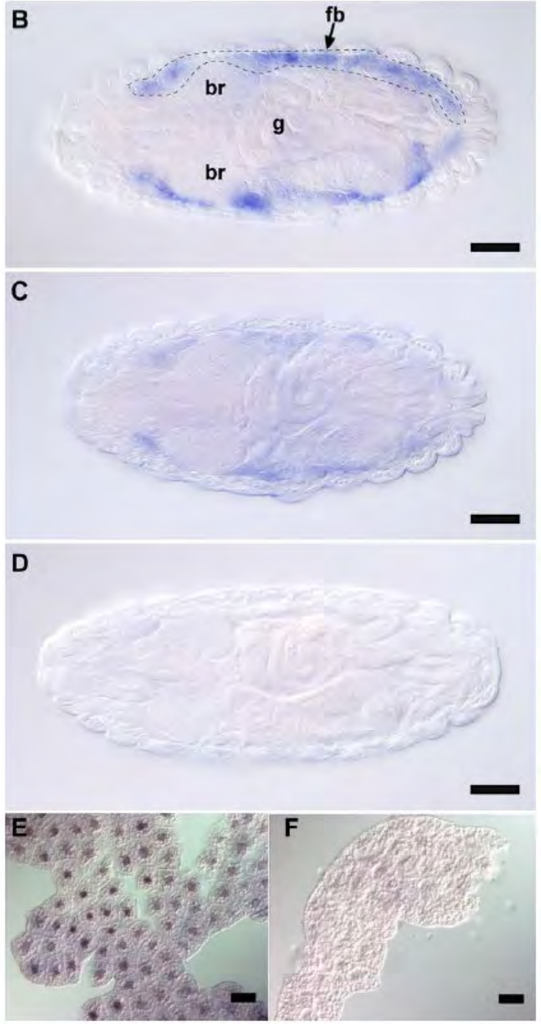
(Akhila Rajan, et al, Cell, 2012)

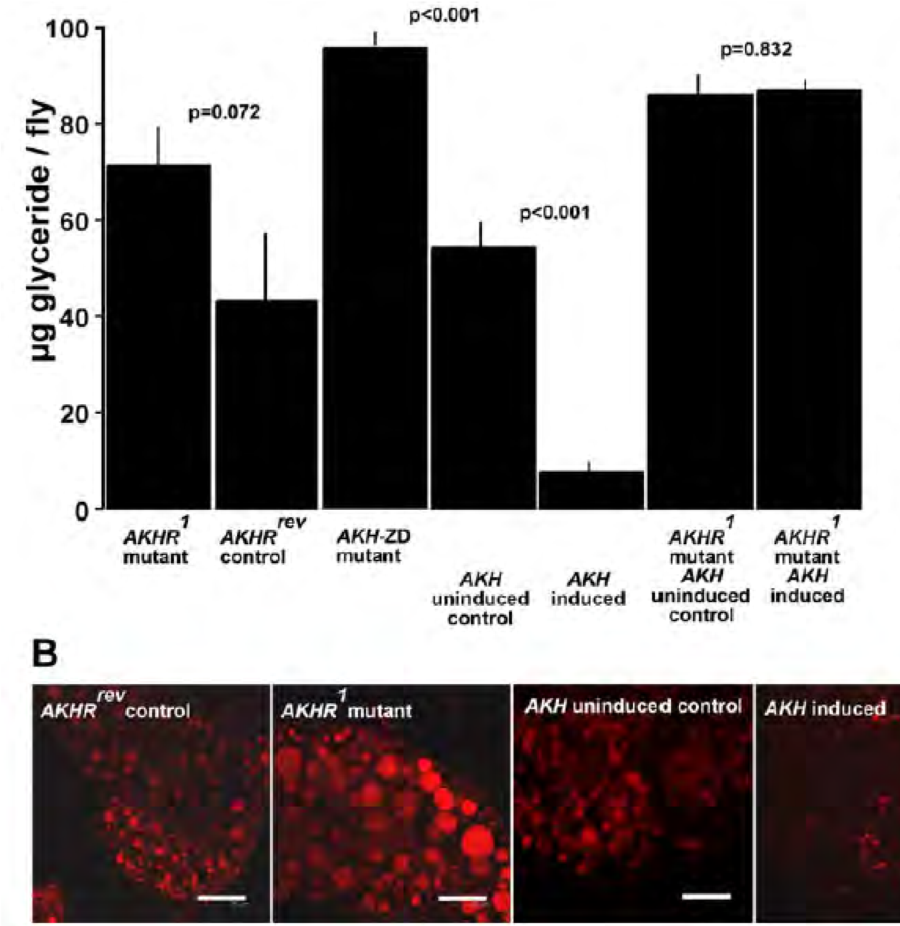
Conclusion：

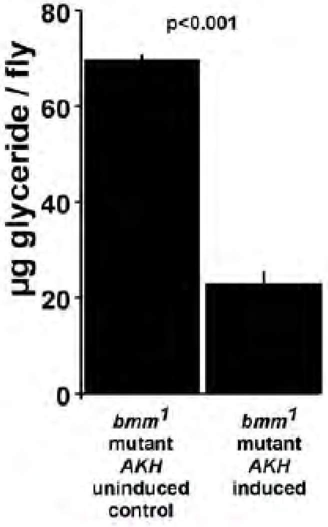
1. The human homologous gene *adp* was identified in *Drosophila* obesity studies. Loss of *adp* activity promotes increased fat storage.
2. Like *leptin* in vertebrates, *Upd2 in Drosophila* is a nutrient sensor, responsible for regulating energy intake and expenditure and controlling appetite. When Upd2 reaches the brain, it regulates insulin secretion, telling flies to store nutrients and promote fat storage.

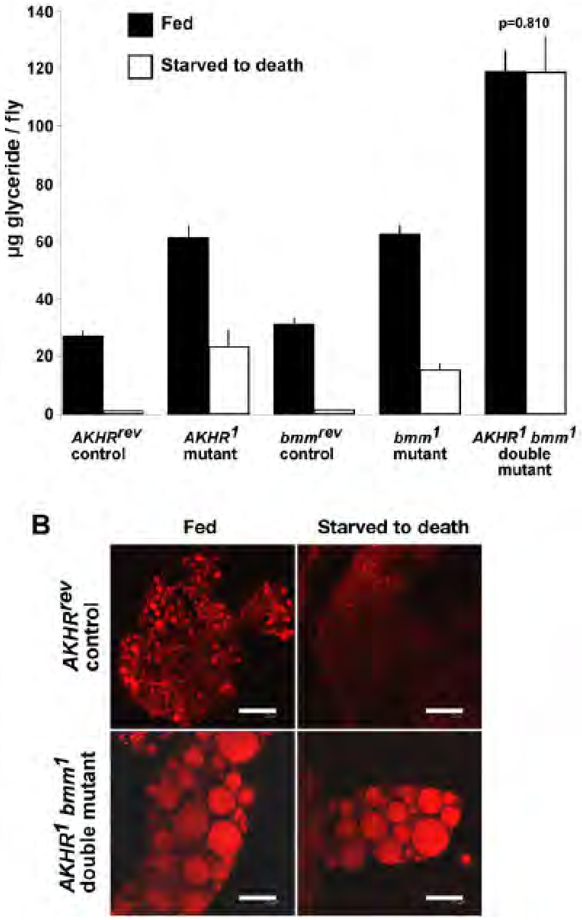
AKH-Dependent Storage Fat Mobilization Strictly Depends on AKHR, but Not on *brummer* Lipase Function

AKH-ZD mutant： the proapoptotic gene *reaper*



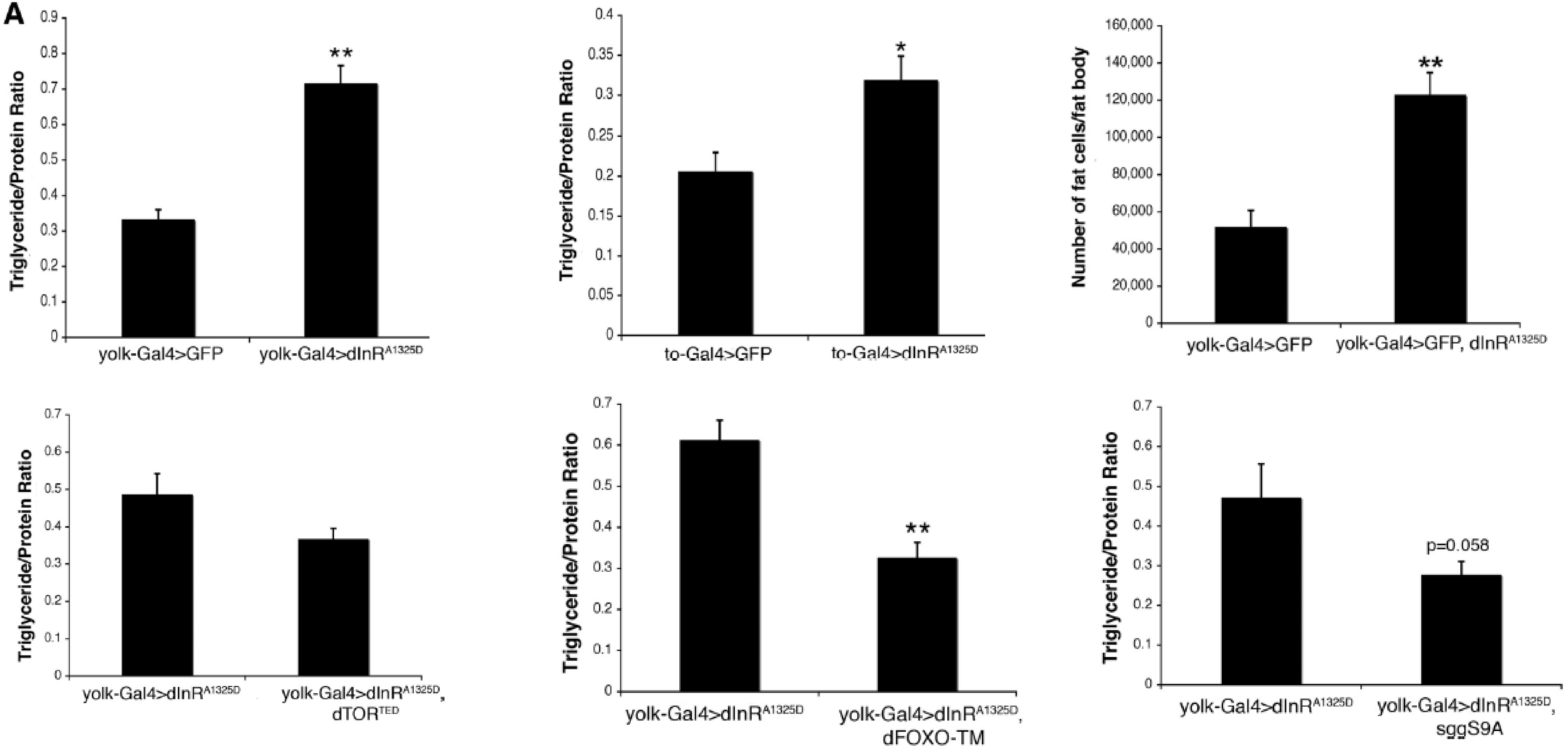






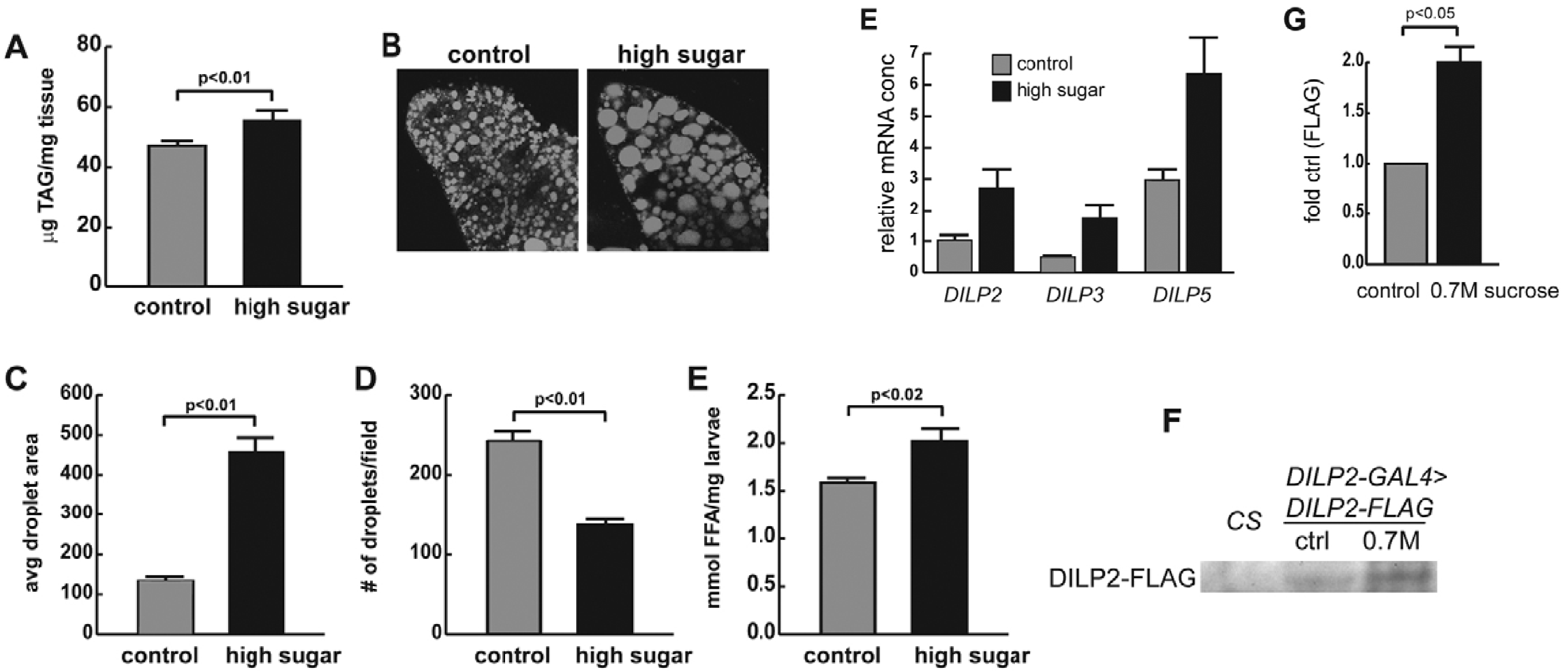
(Sebastian, et al. PLoS Biol, 2007)

Activating insulin signaling in the Drosophila fat body promotes triglyceride storage



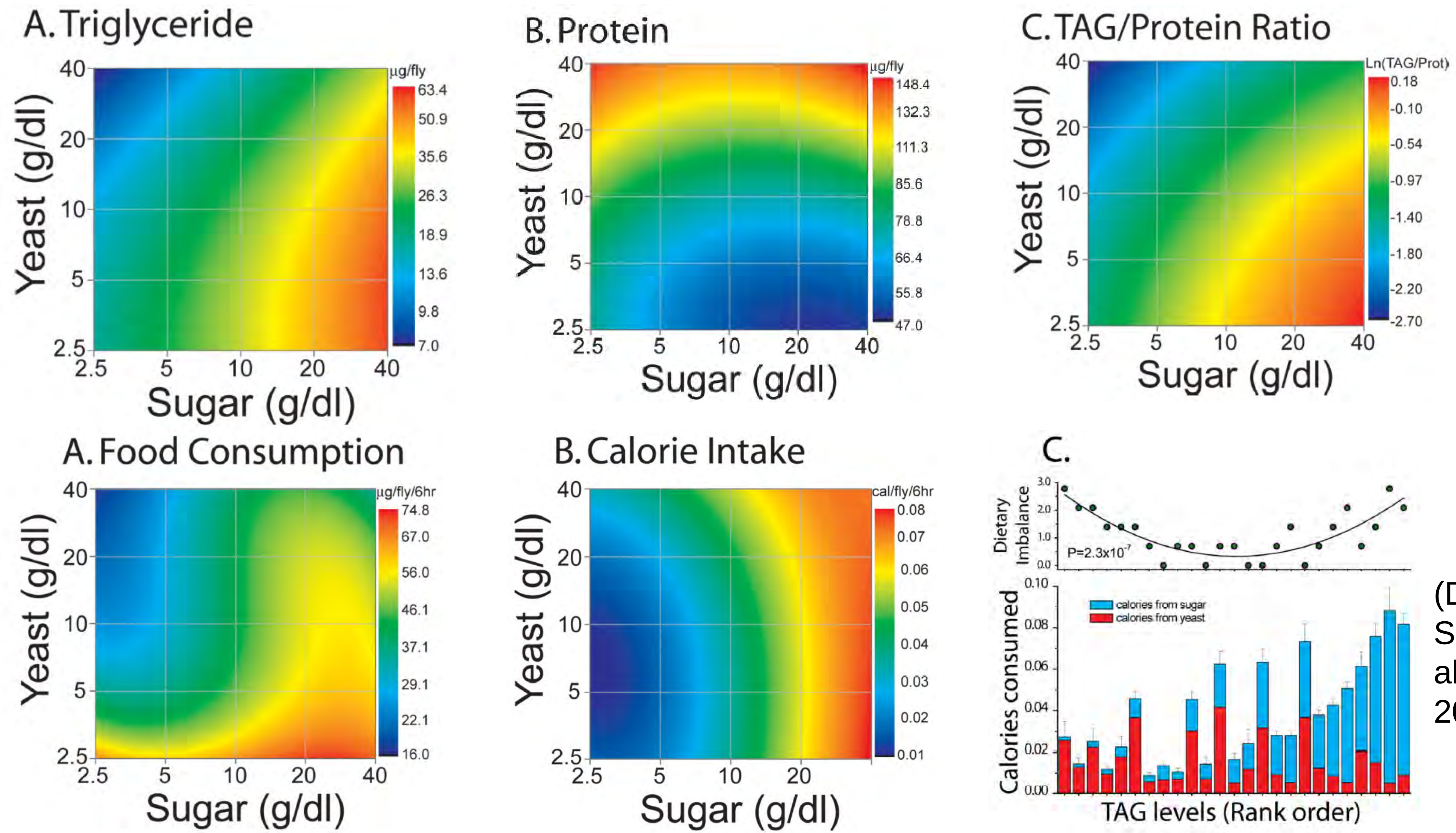
(Justin R., et al, MOLECULAR AND CELLULAR BIOLOGY, 2003)

A high-sugar diet produces obesity and insulin resistance in wild-type Drosophila



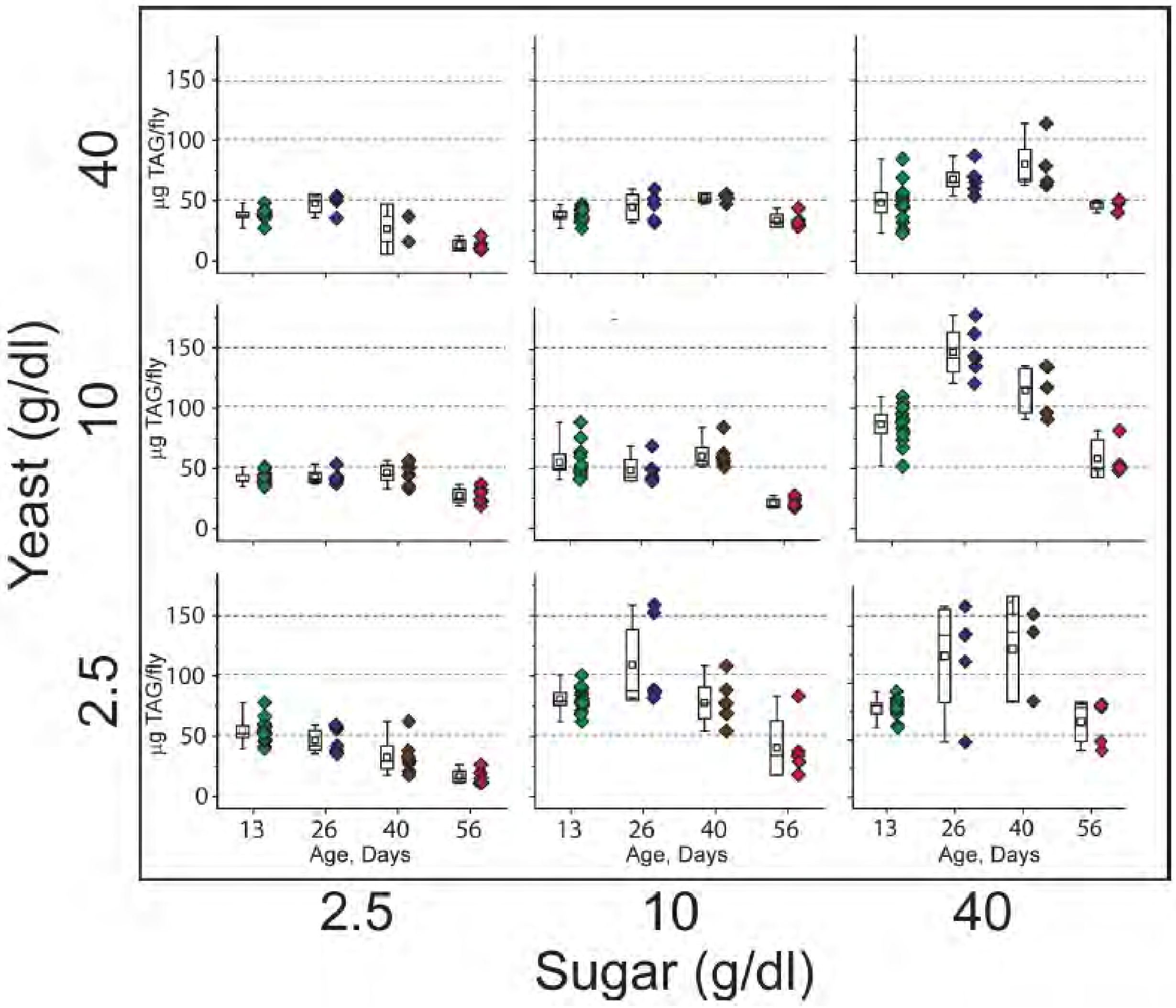
(Ryan T Birse, et al. Cell Metab, 2011)

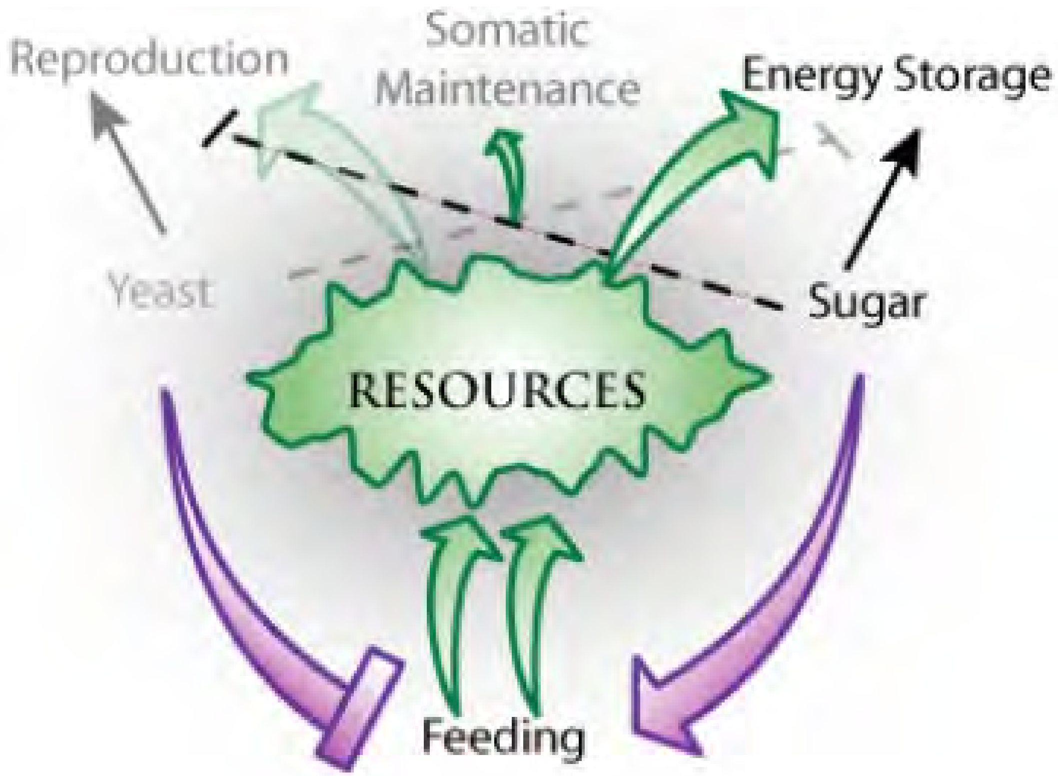
Drosophila obesity are strongly affected by diet composition.



(Danielle A Skorupa, et al. Aging Cell, 2008)

Excess dietary sugar, promoted obesity, which was magnified during aging

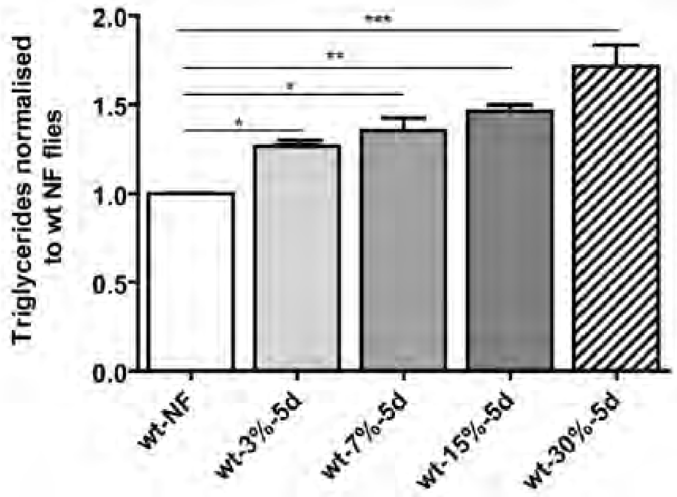


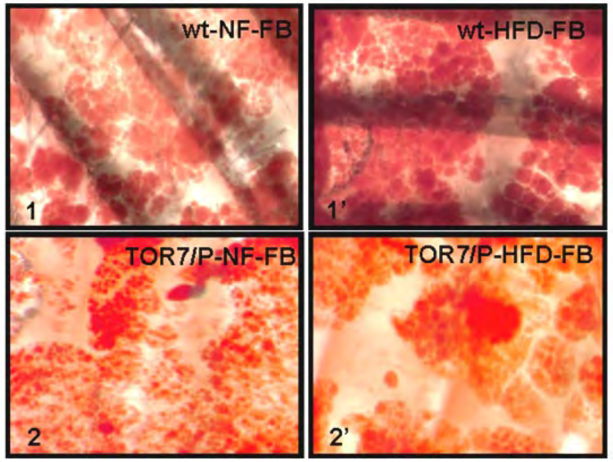


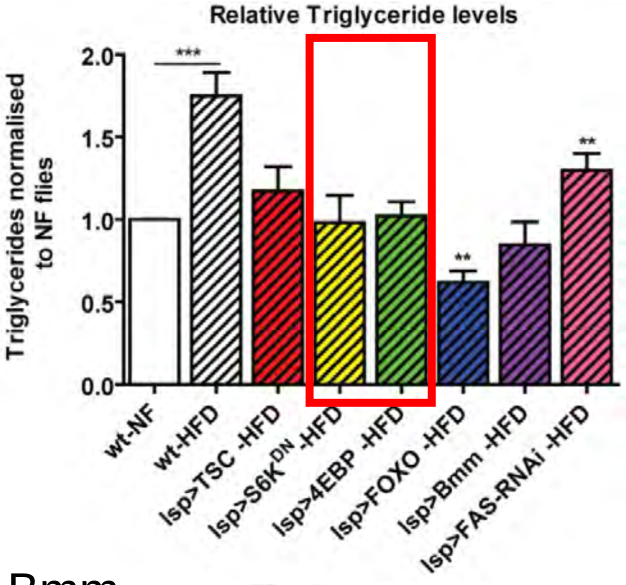
(Danielle A Skorupa, et al. Aging Cell, 2008)

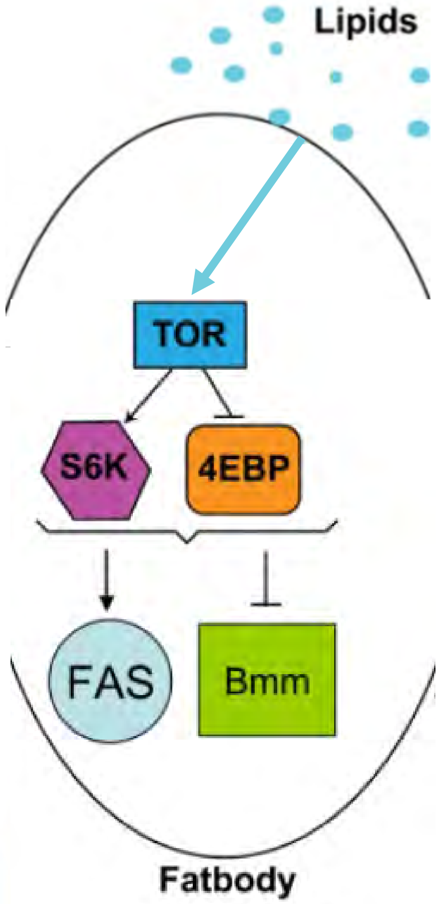
High fat diet-induced obesity is regulated by the TOR pathway in Drosophila

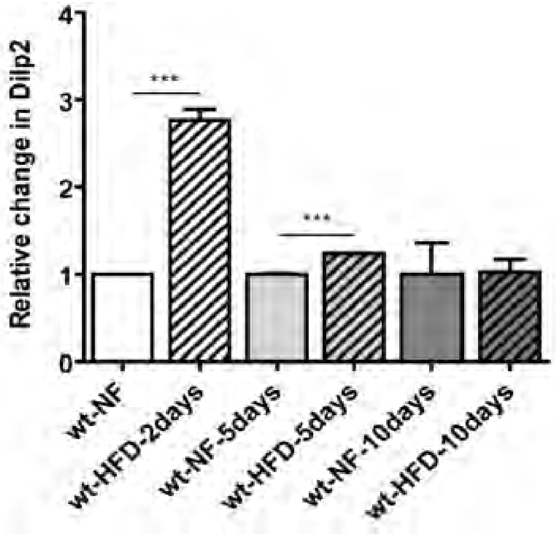
global inhibition of TOR translational effectors (eIf4E and S6K) by 4EBP or dominant-negative S6K overexpression (S6KDN)











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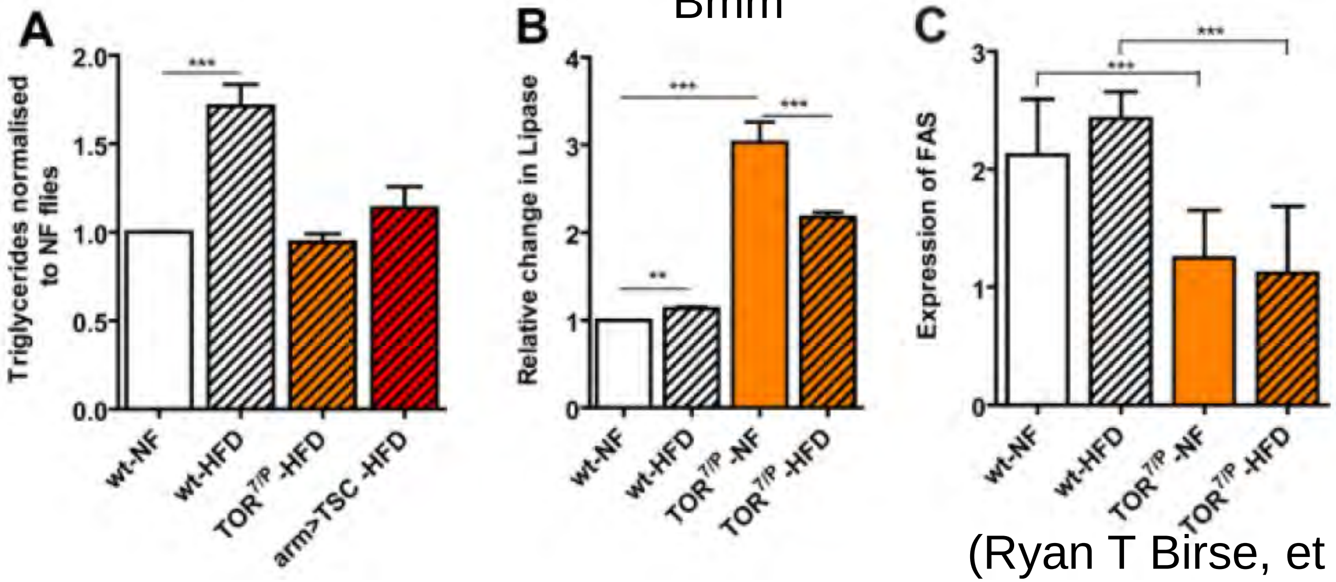
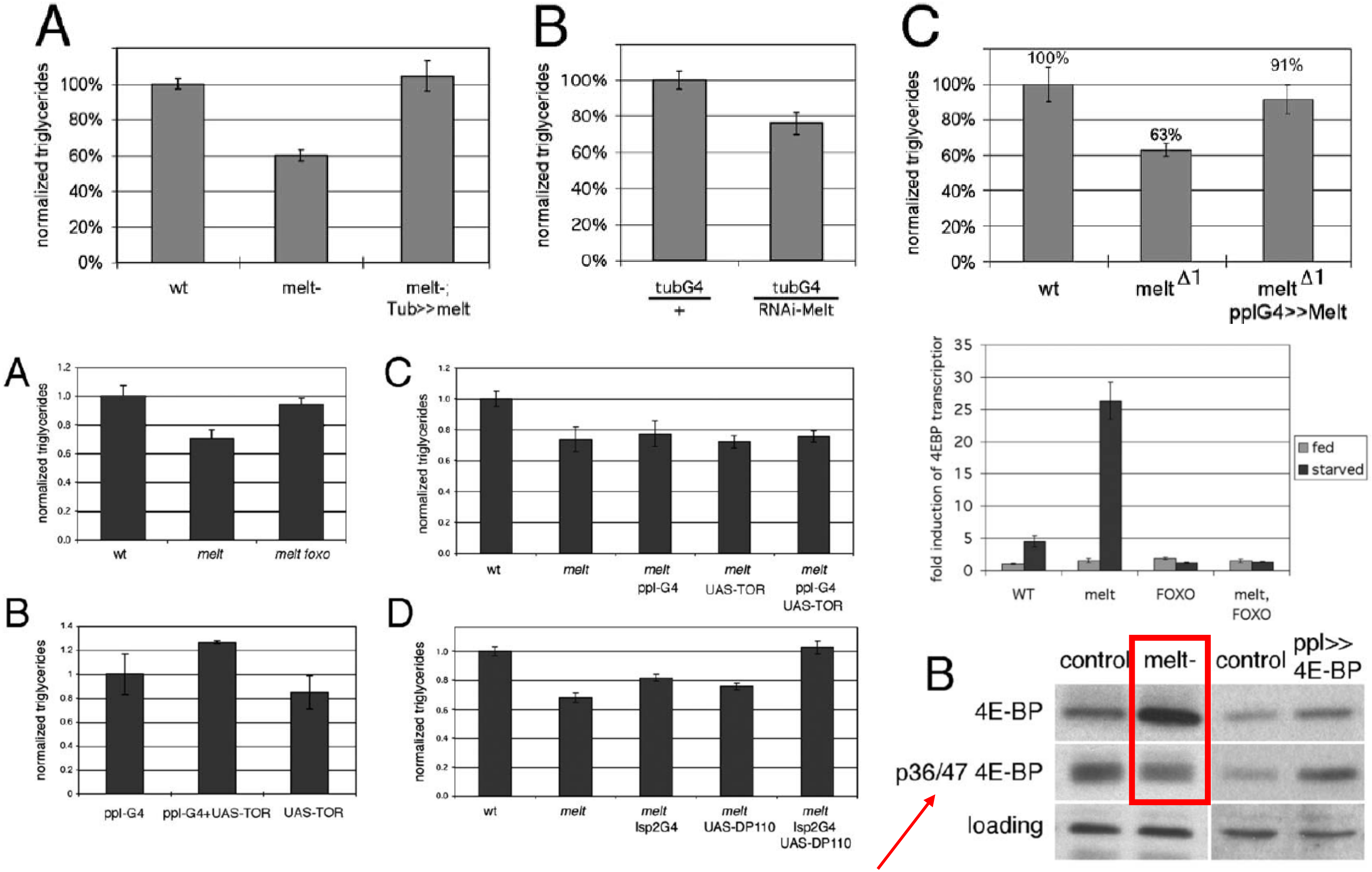
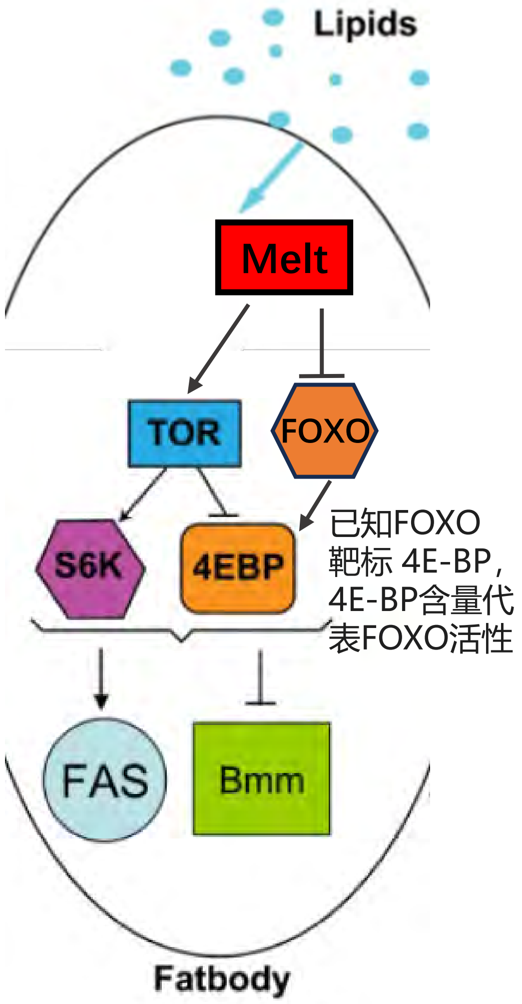


(Ryan T Birse, et al. Cell Metab, 2011)

Drosophila Melted Modulates FOXO and TOR Activity

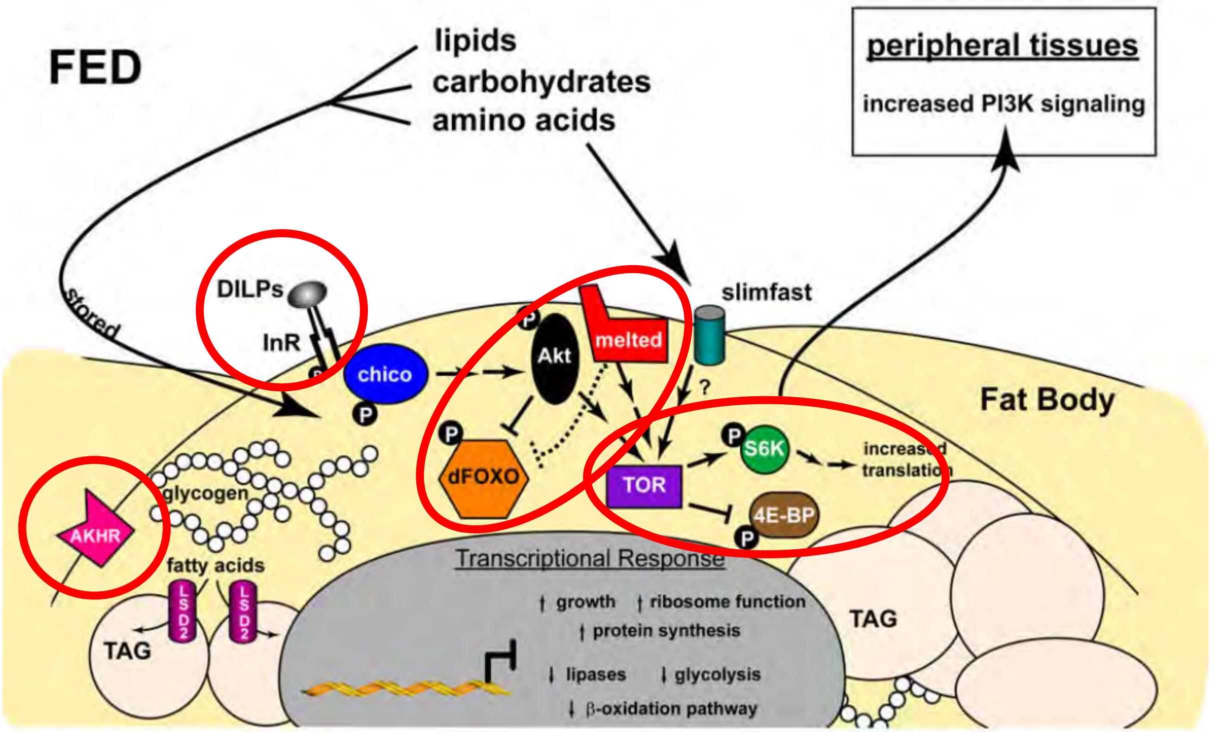




果蝇 4E-BP 在 36/47 位的磷酸化取决于 TOR 活性

(Aurelio A. Teleman, et al. Developmental Cell, 2005)

Summary



(Keith D. Baker, et al. Cell Metab, 2005)

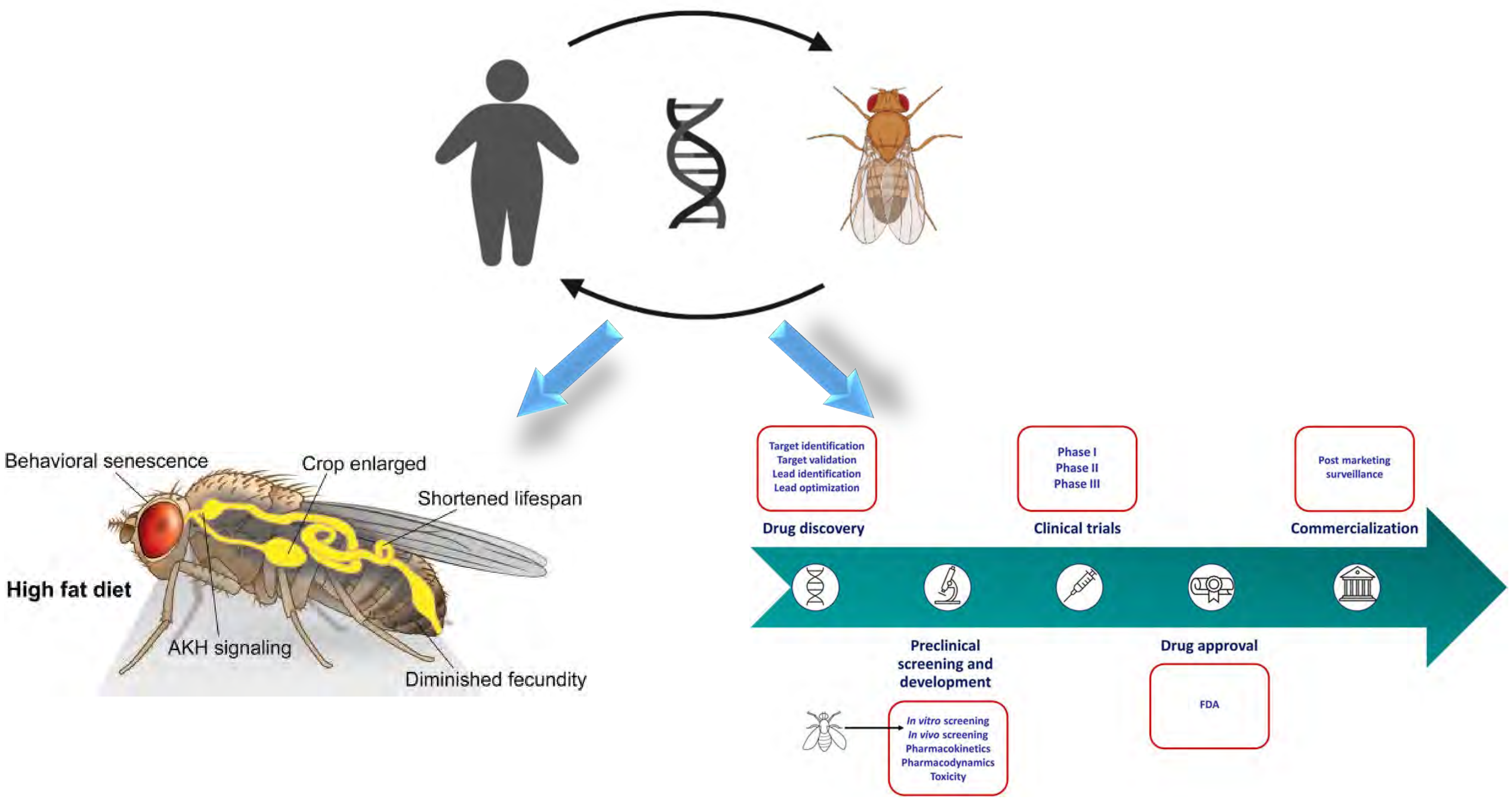
1. Fruit flies could be a new model for obesity research, the human homologous gene adp and the molecule similar to leptin, Upd2. Loss of adp and Upd2 activities promote increased fat storage.
2. AKH and ilp pathways are key pathways for studying obesity, The Ilp pathway dominates fat synthesis; The Akh pathway regulates lipolysis.
3. The increase of Dilp2 level induced by high-sugar diet will promote the intake and storage of sugar by adipose cells and accelerate the accumulation of fat.
4. High fat diet-induced obesity is regulated by the TOR pathway in Drosophila. Its downstream target S6K promotes fat synthesis, and 4EBP affects cell growth and fat metabolism.
5. The transcription factor FOXO is located downstream of the insulin receptor and suppresses adipocyte number. The Melt gene inhibits FOXO activity

Thanks！

Behavioral and physiological effects of obesity

姜思梅

2025.3.27

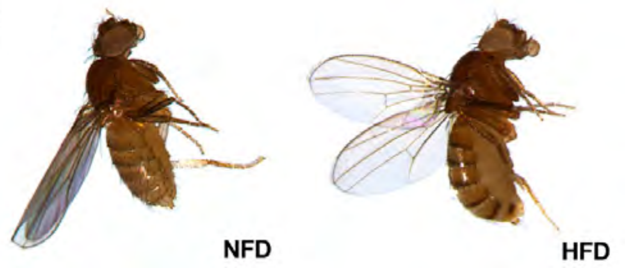


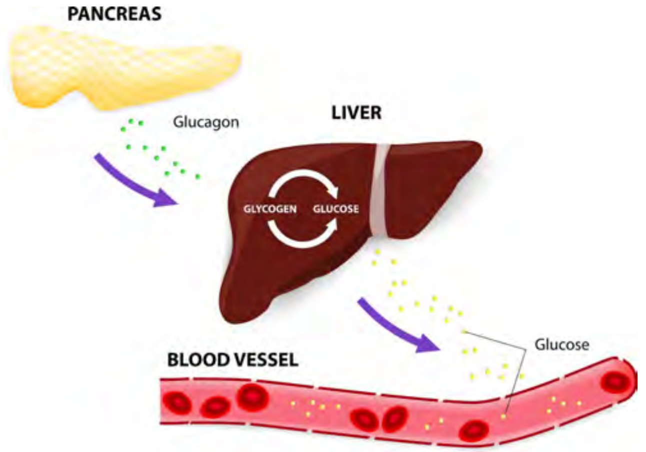
1. The physiological and metabolic effects of obesity
2. How does obesity affect behavior?
3. How does obesity affect lifespan and reproduction?

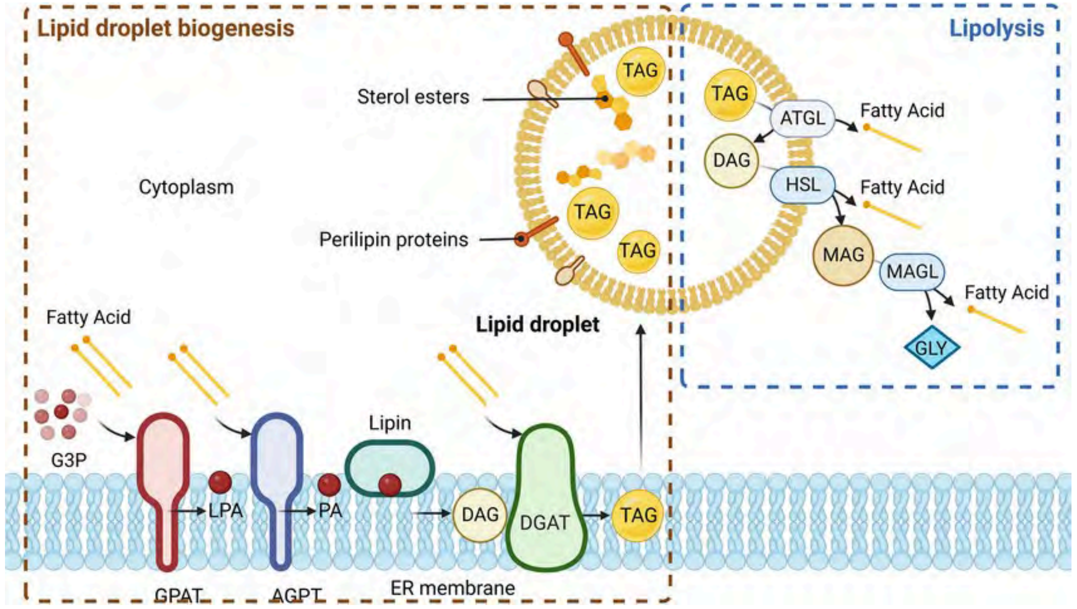
The physiological and metabolic effects of obesity

Physiological indicators for evaluating obesity models:

- Body weight ↑
- Glycogen content ↑
- Haemolymph sugar level (glucose, trehalose) ↑
- Triacylglycerols (TAGs) content ↑
- Fat body lipid droplet (LD) size, number and morphology ↑
- Oxidative stress
- Lipid peroxidation
- Insulin resistance (IR) → type II diabetes
- ……



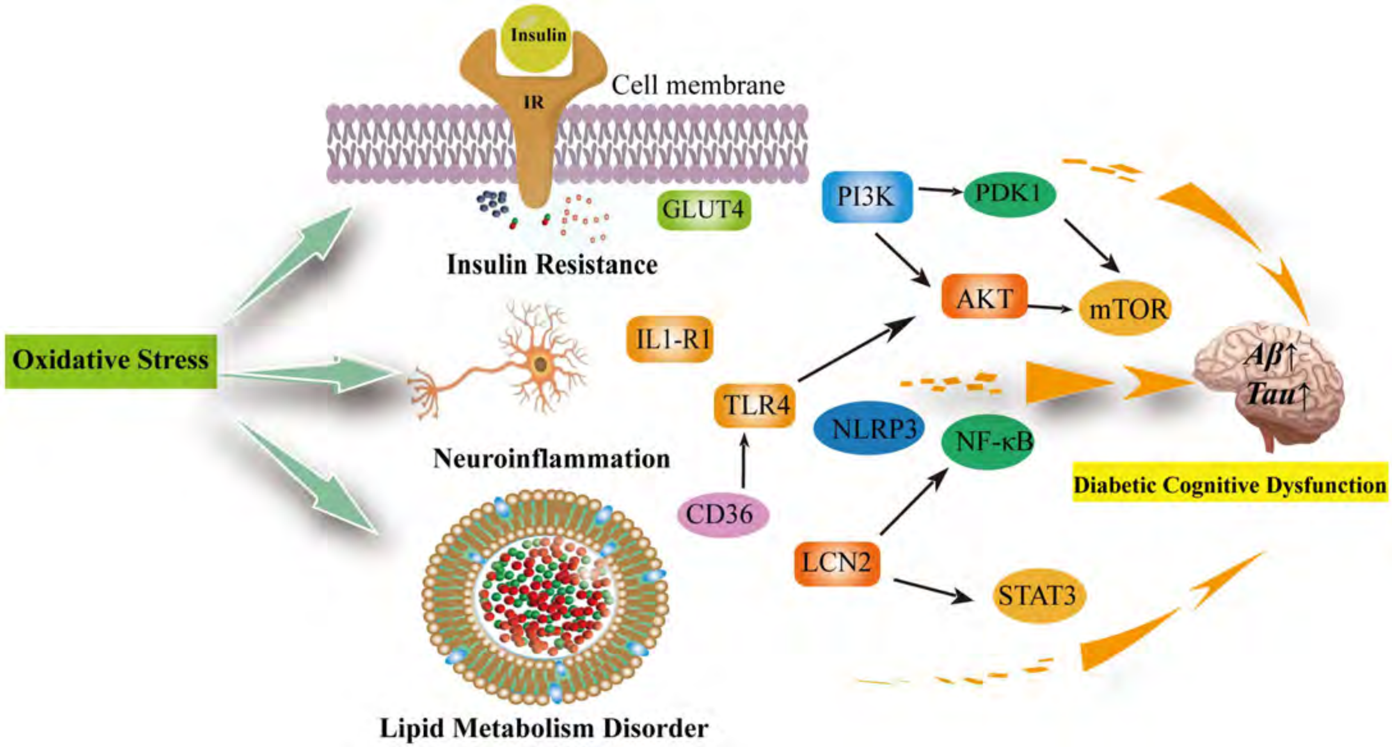


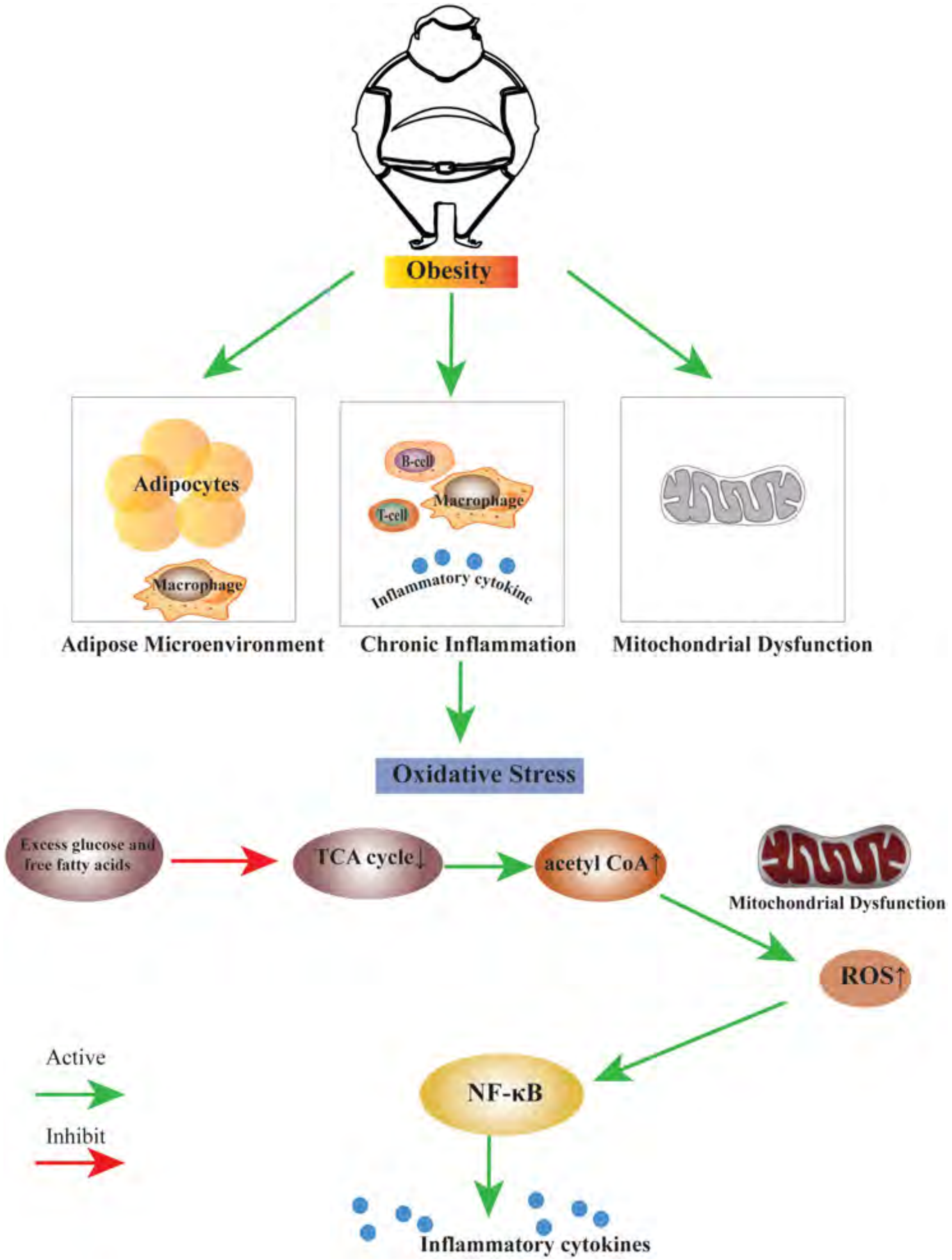


What is oxidative stress (OS)?

In 1985, “oxidative stress” was introduced as a concept in redox biology and medicine. It is defined as “an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage”.

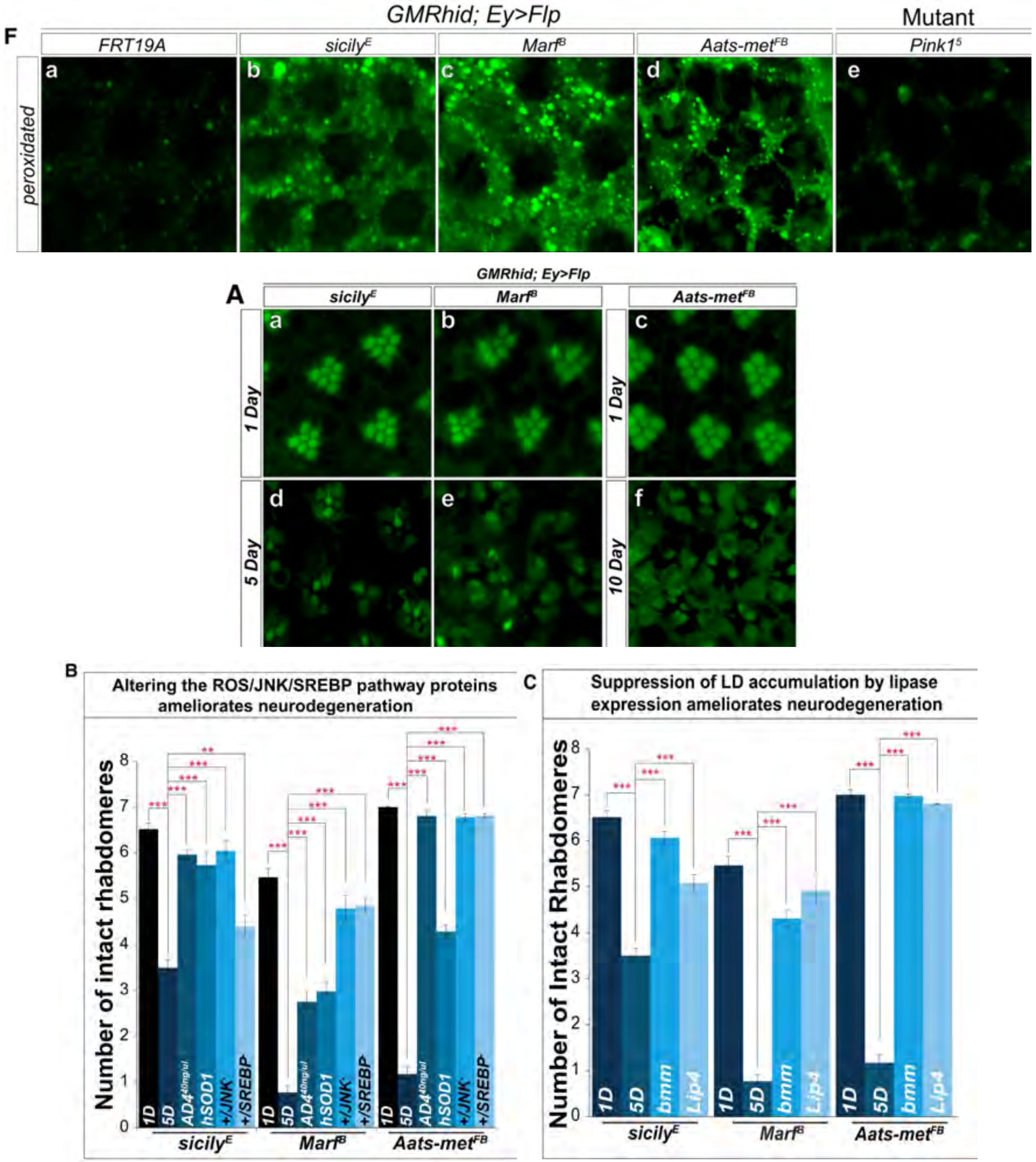
Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the antioxidant defense.

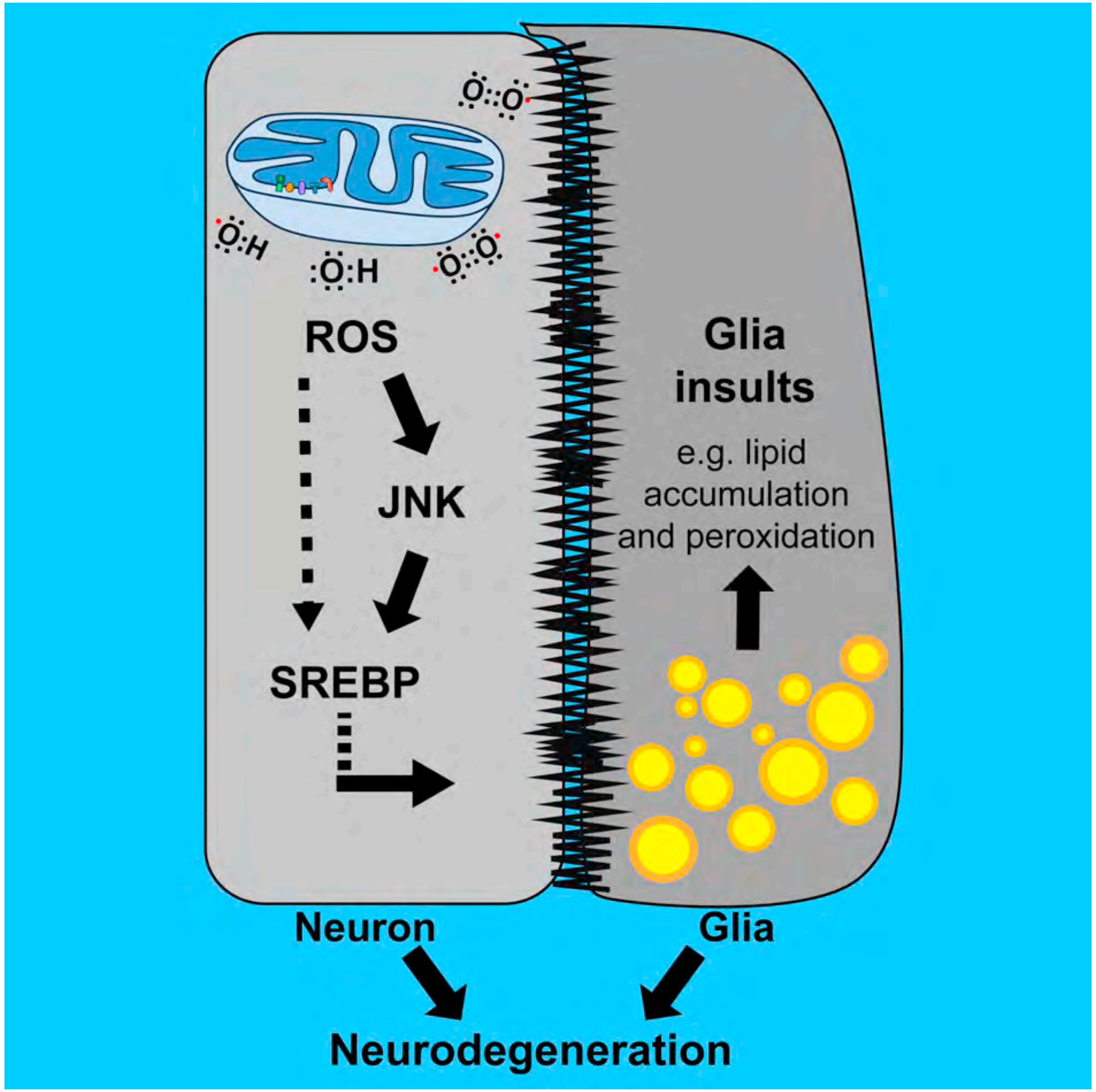




Li HM, et al. *Frontiers in Endocrinology*. 2023

Glial lipid droplets and ROS induced by mitochondrial defects promote neurodegeneration





Liu L, et al. *Cell*. 2015

What is insulin resistance (IR) ?

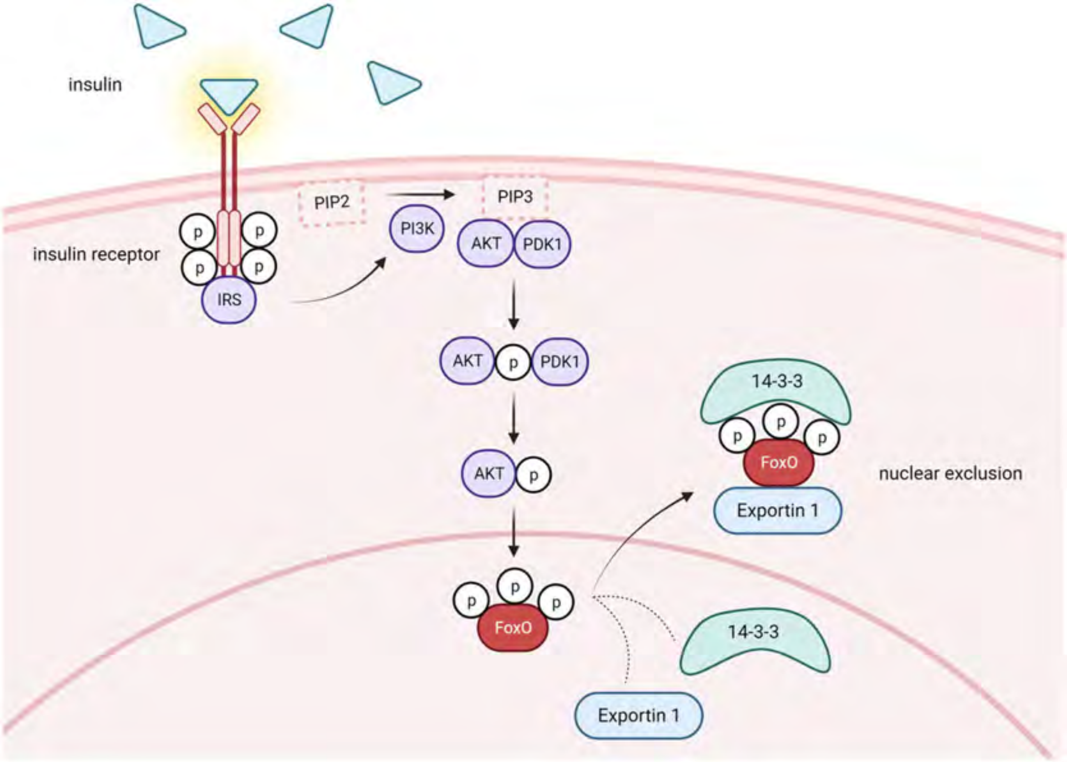
Insulin resistance refers to the body's reduced sensitivity to insulin, resulting in insulin can not efficiently promote glucose entry into the cells, which in turn causes an increase in blood glucose.

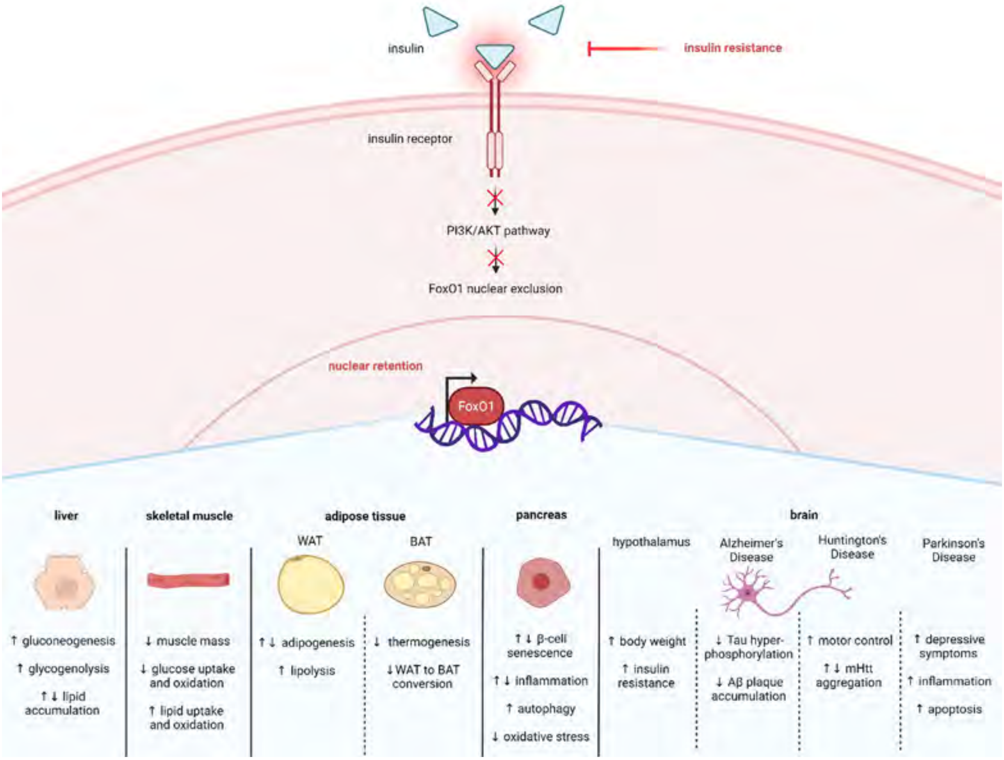
To maintain normal blood sugar levels, pancreatic β cells need to secrete more insulin, which can lead to hyperinsulinemia (高胰岛素血症).

Insulin resistance is one of the pathogenesis of type 2 diabetes mellitus (T2DM).

Indicators to monitor insulin sensitivity：

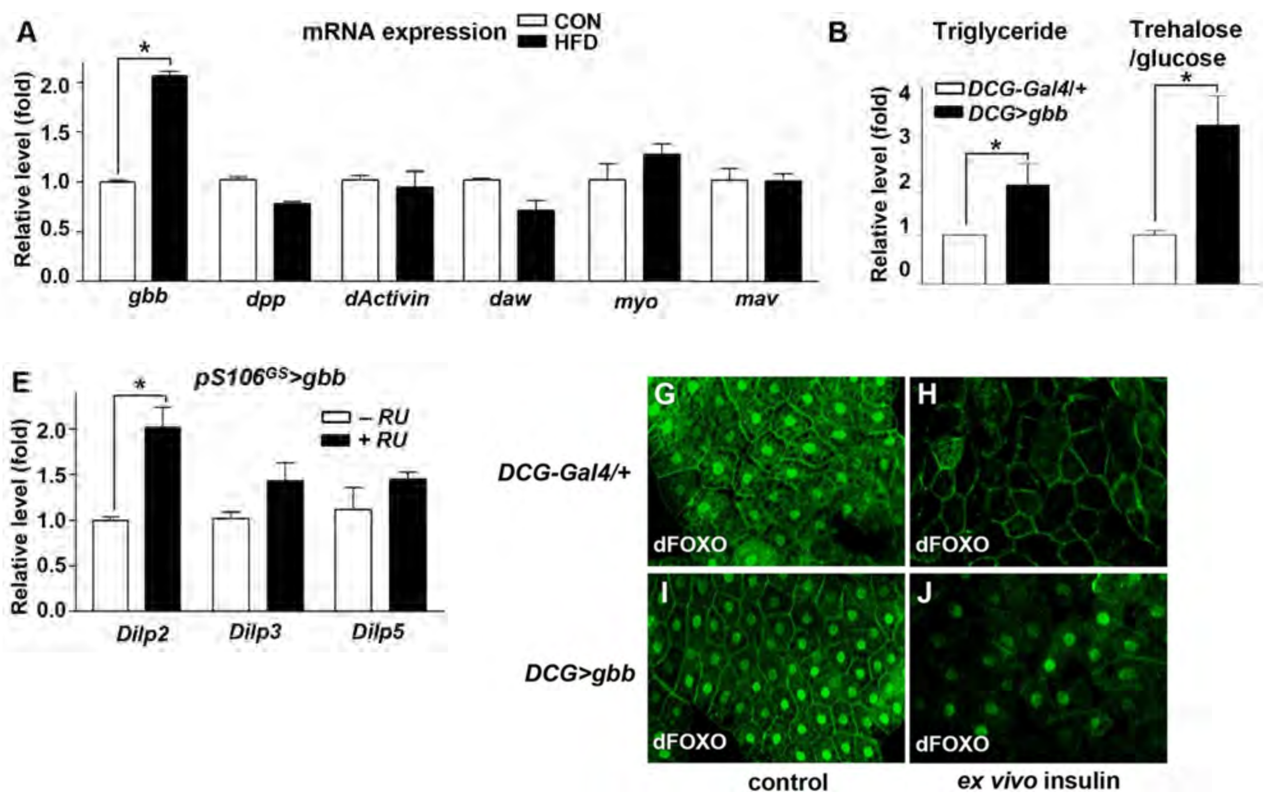
AKT phosphorylation level (p-AKT)、nuclear localization of FOXO

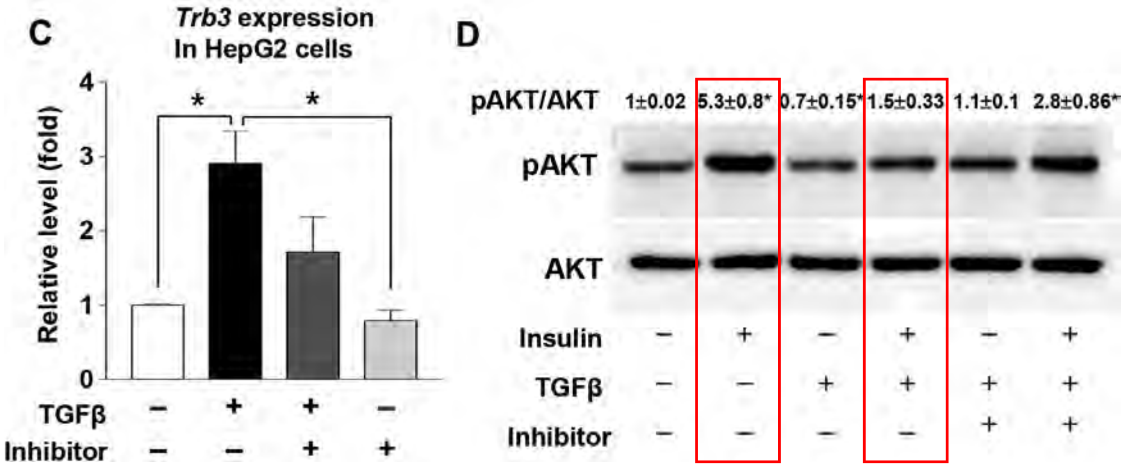


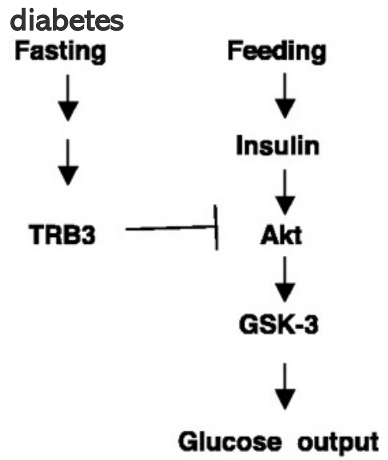


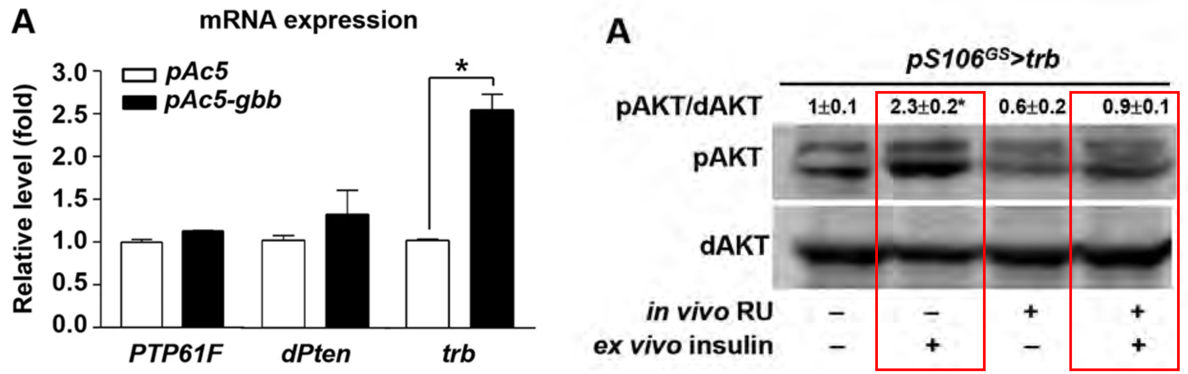
Teaney NA, et al. *Frontiers in Endocrinology*. 2023

High fat diet-induced TGF-β/Gbb signaling provokes insulin resistance through the *tribbles* expression









glass bottom boat (gbb)：哺乳动物转化生长因子-β (*TGF-β*)的果蝇同源物

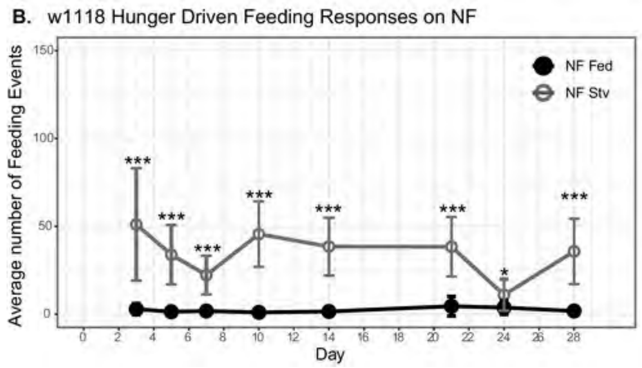
Tribbles：胰岛素信号传导负调节因子，是Gbb信号通路的下游靶基因

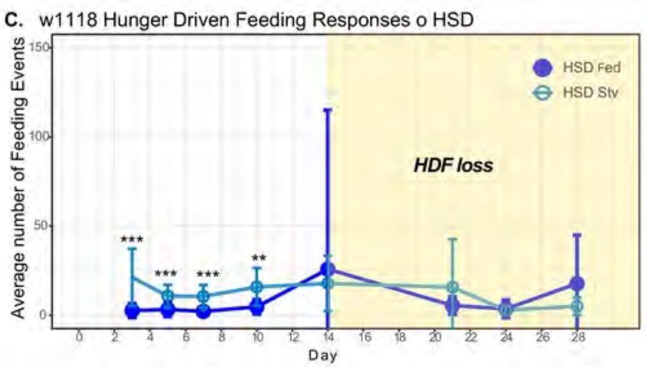
Hong SH, et al. *Scientific Reports*. 2016

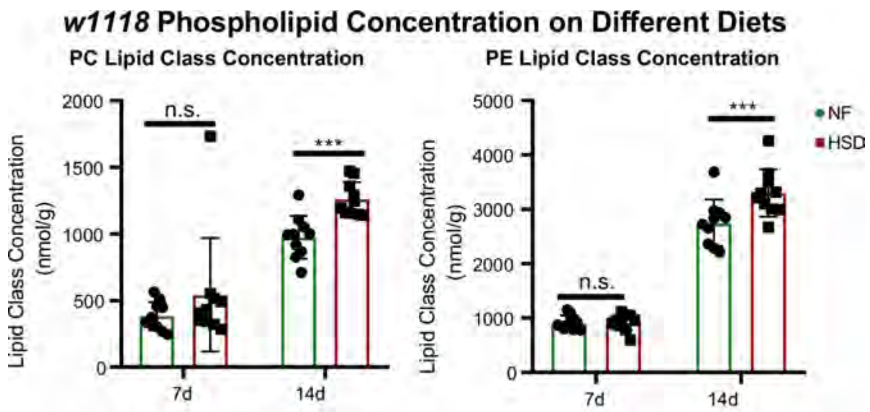
Du KY, et al. *Science*. 2003

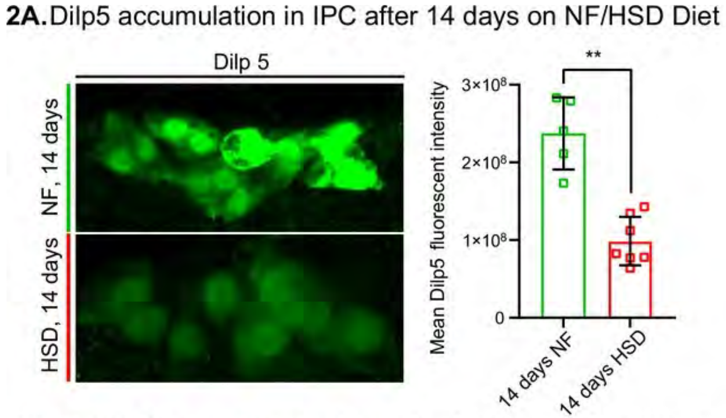
The behavioral effects of obesity

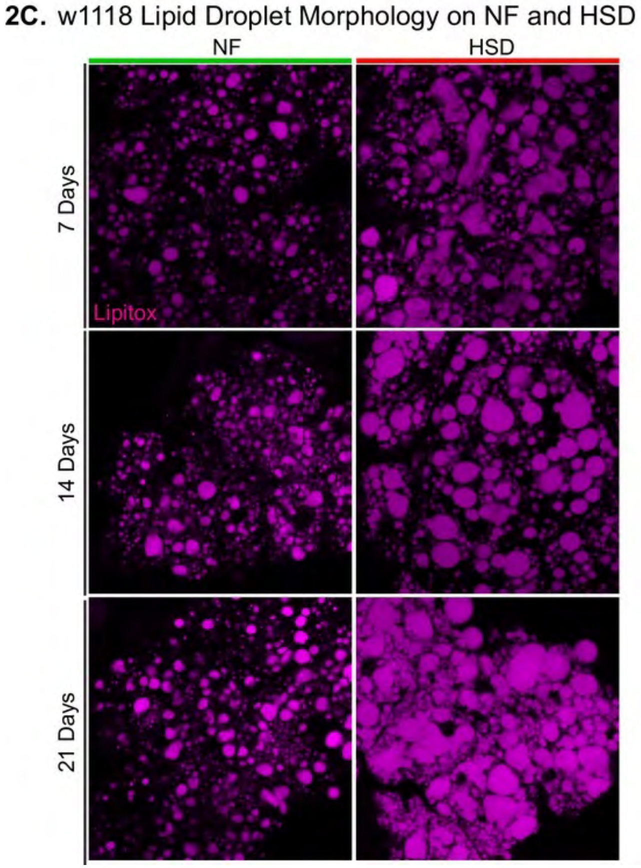
High-sugar diet induces phospholipid imbalance, which leads to the loss of hunger-driven feeding (HDF)

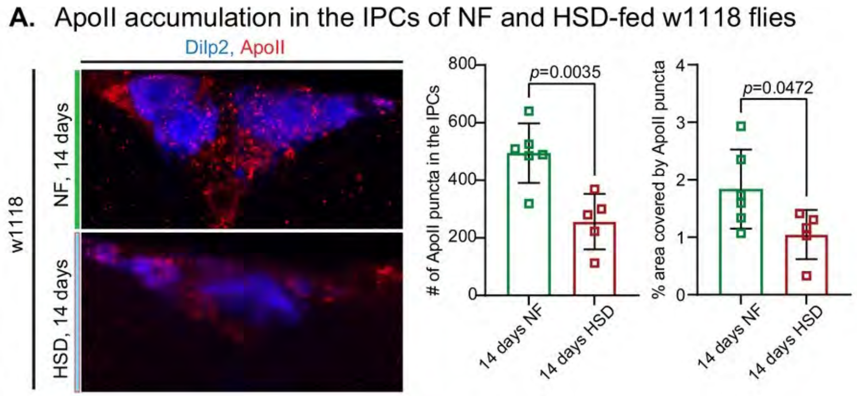


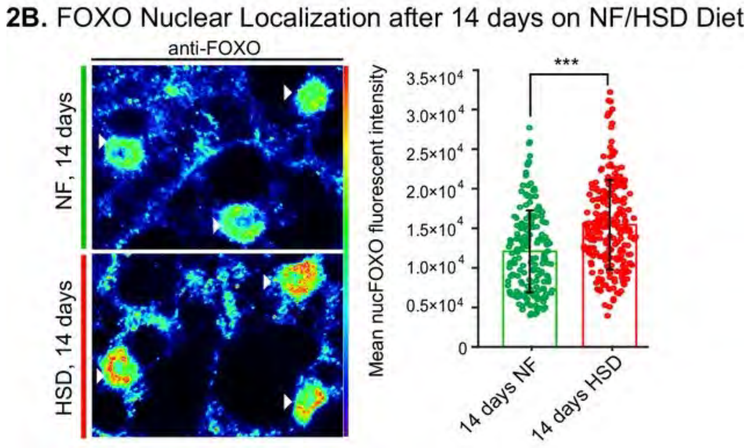








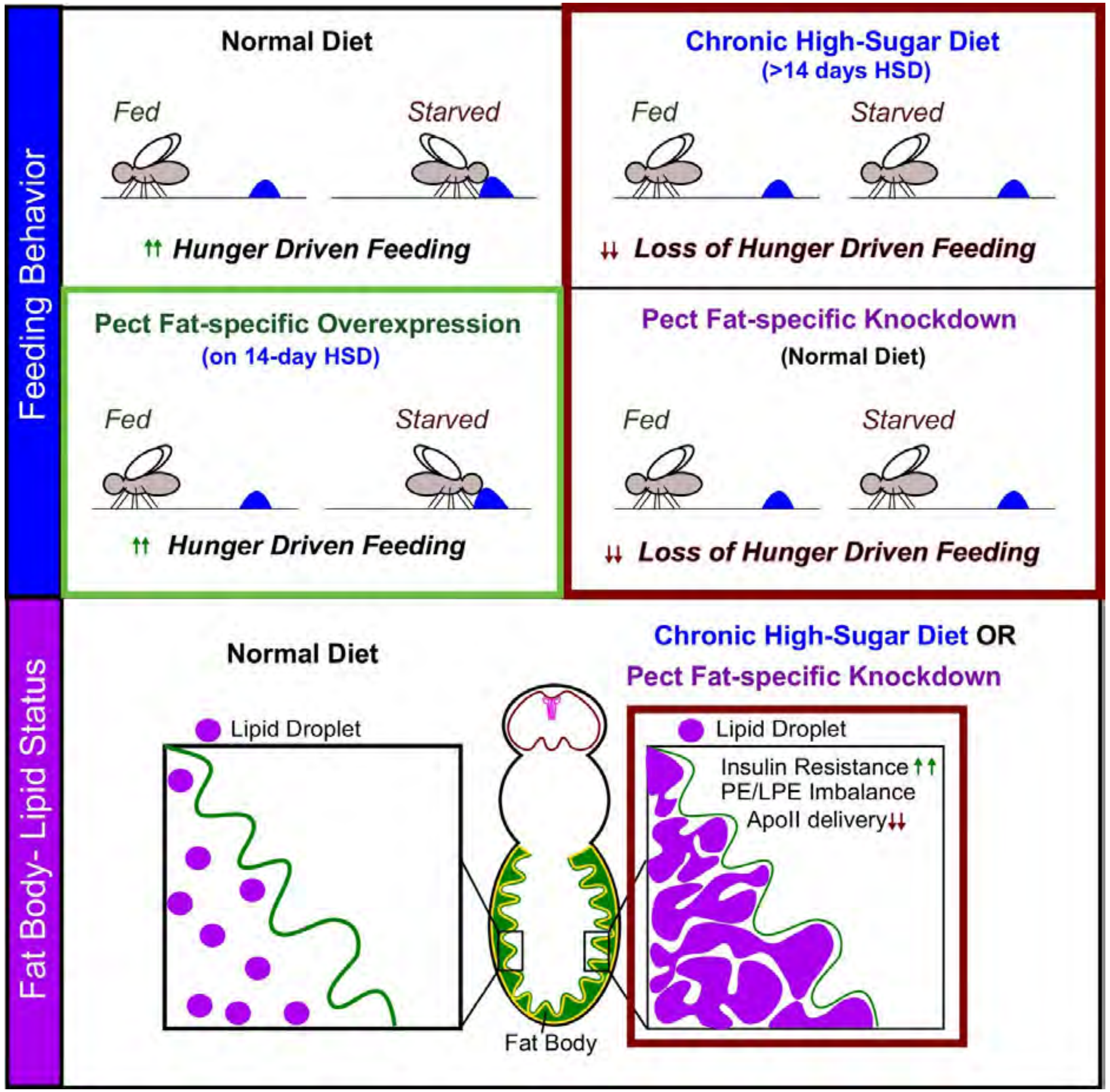




PC：卵磷脂/磷脂酰胆碱
PE：磷脂酰乙醇胺
ApoII：载脂蛋白，将PE从脂肪输送到大脑

Kelly KP, et al. *Elife*. 2022

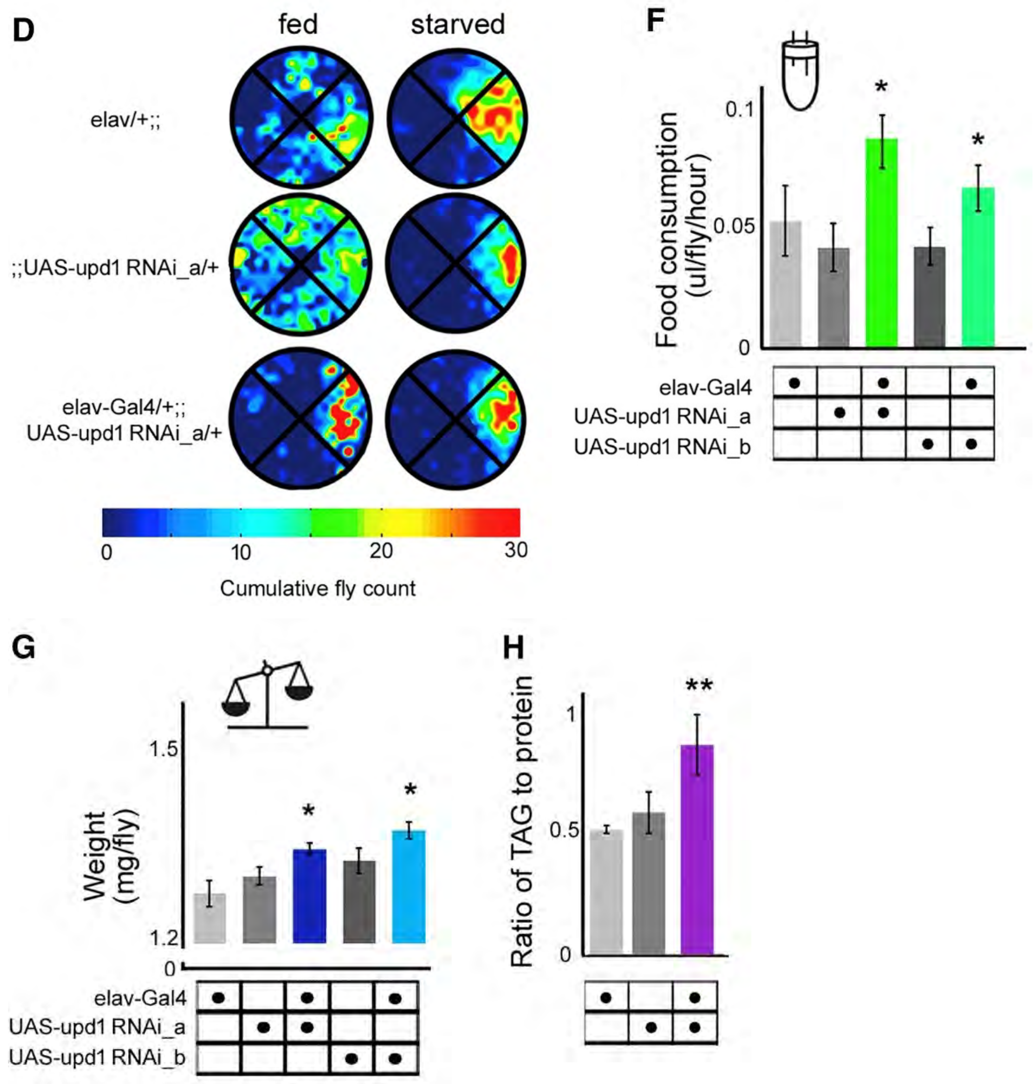
High-sugar diet induces phospholipid imbalance, which leads to the loss of hunger-driven feeding (HDF)

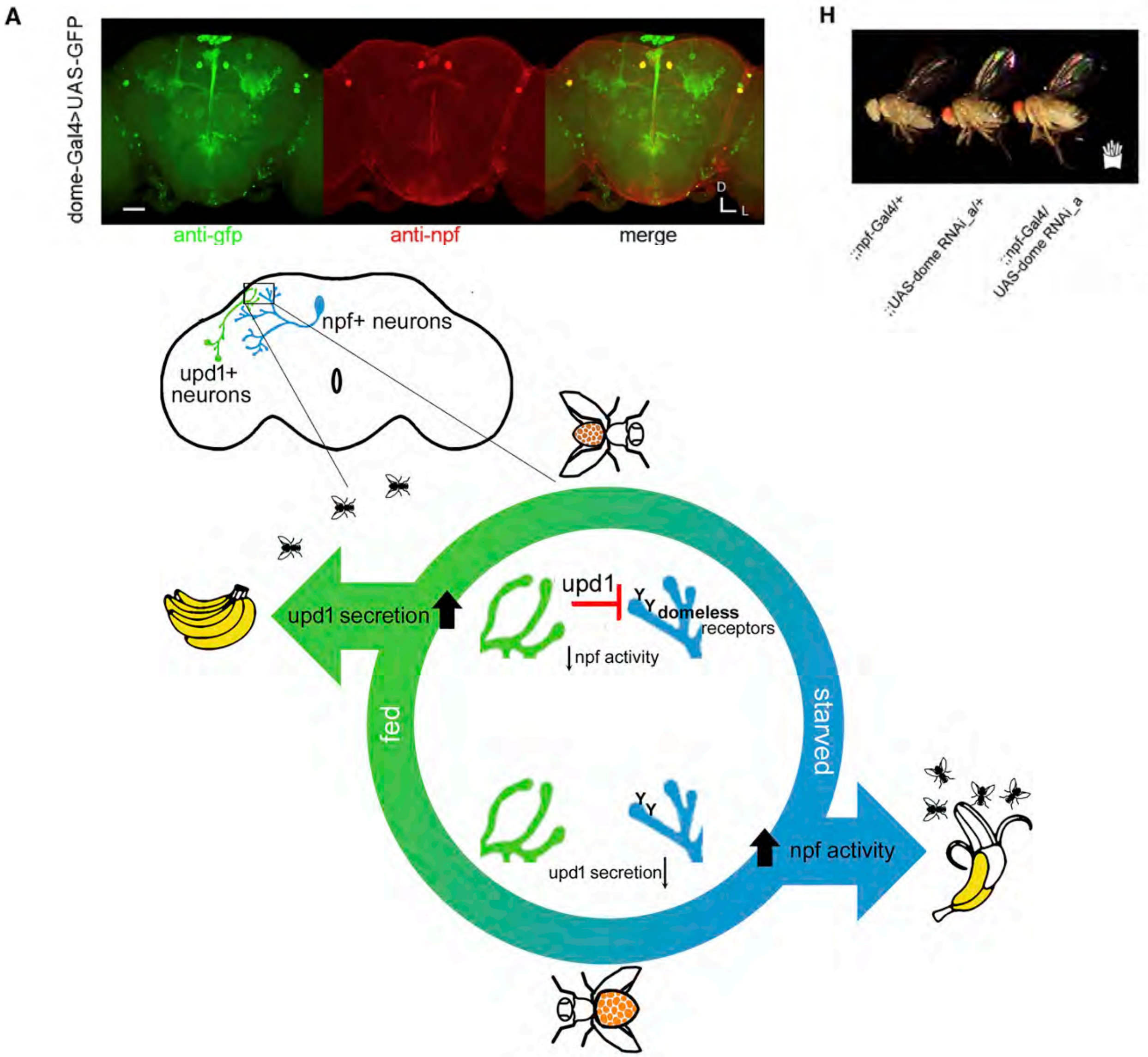


Pect：磷脂酰乙醇胺（PE）合成酶

Kelly KP, et al. *Elife*. 2022

UPD1-NPF neural circuit modulate obesity-linked behaviors in drosophila



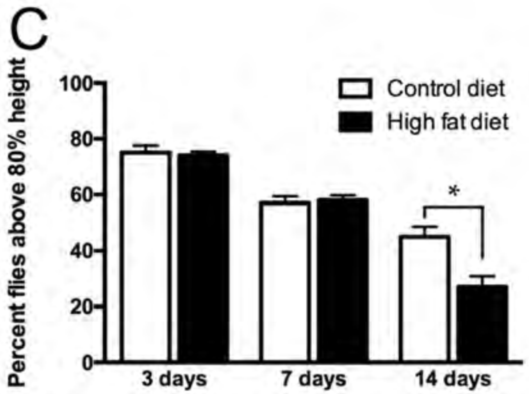


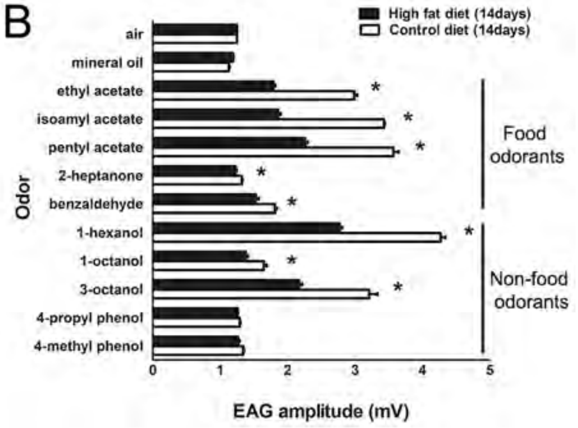
UPD1：“饱腹感激素”瘦素在果蝇中的类似物

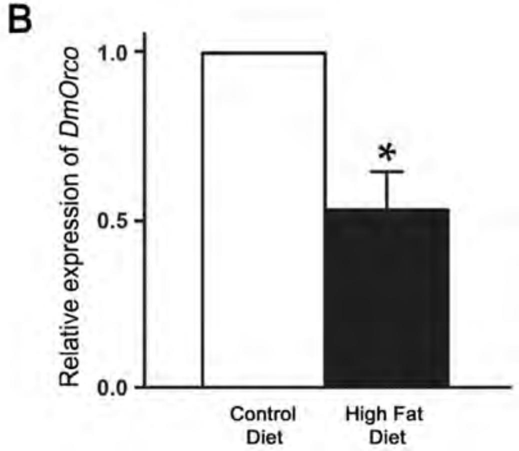
NPF：哺乳动物促食欲神经肽 Y(NPY)在果蝇中的类似物

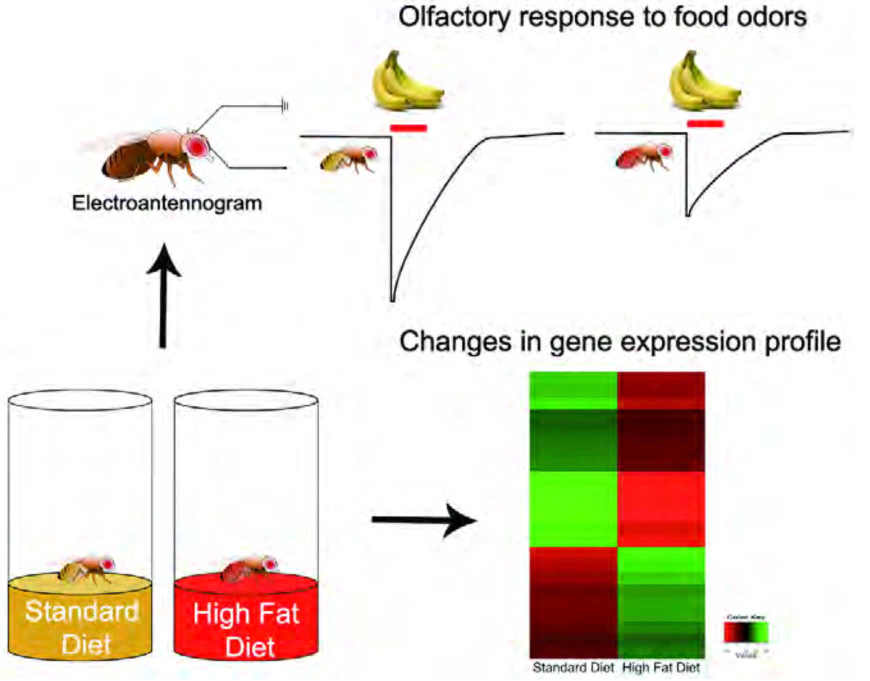
Beshel J, et al. *Cell Metabolism*. 2017

The effects of high fat/sugar diet on sensory system sensitivity in drosophila

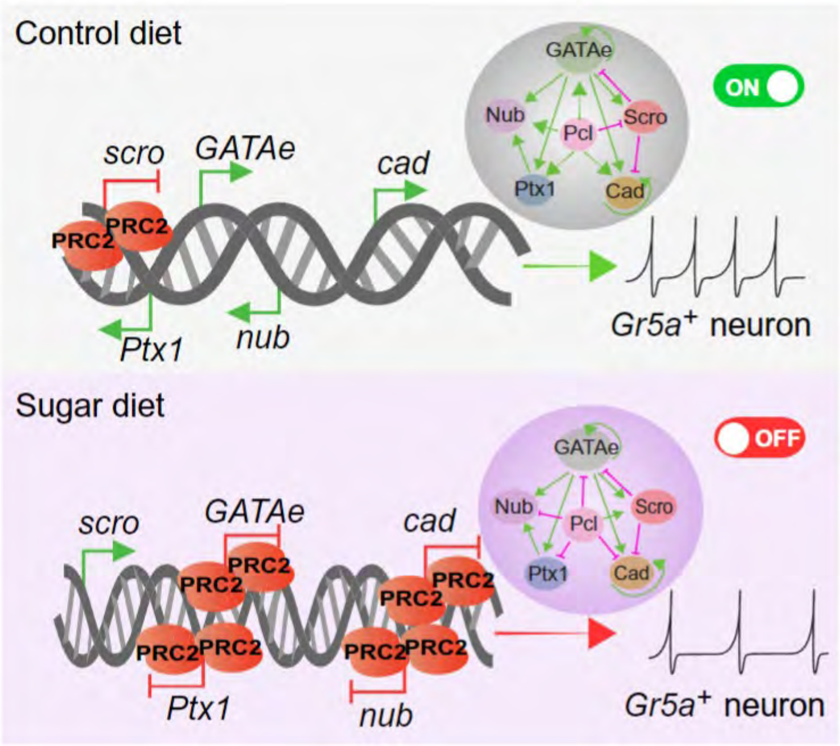






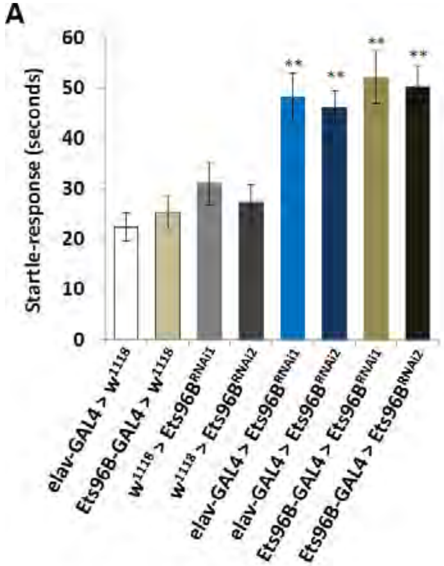


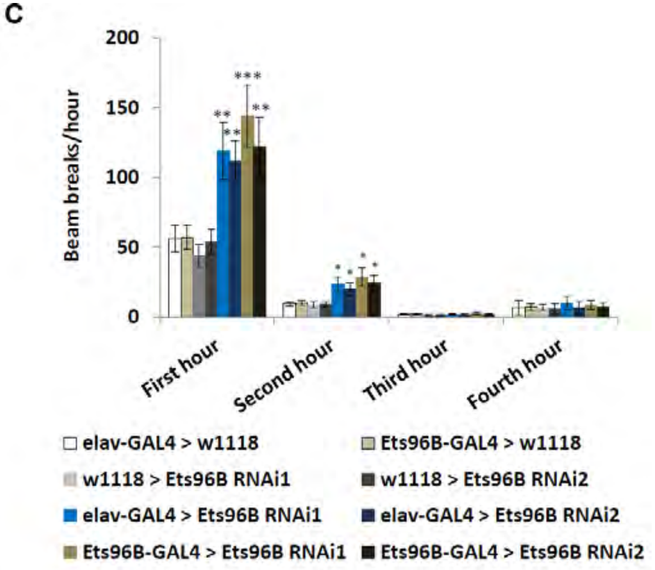
Olfactory receptor genes
Odorant-binding protein genes

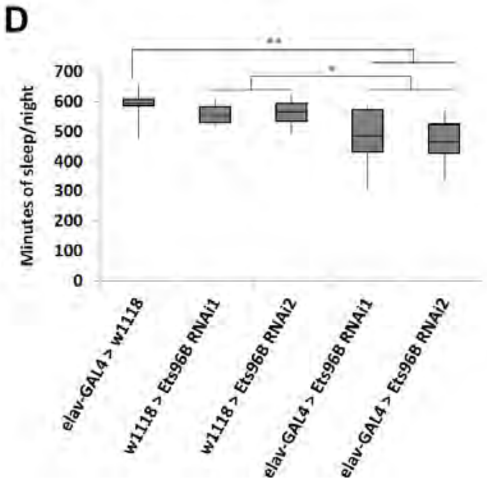


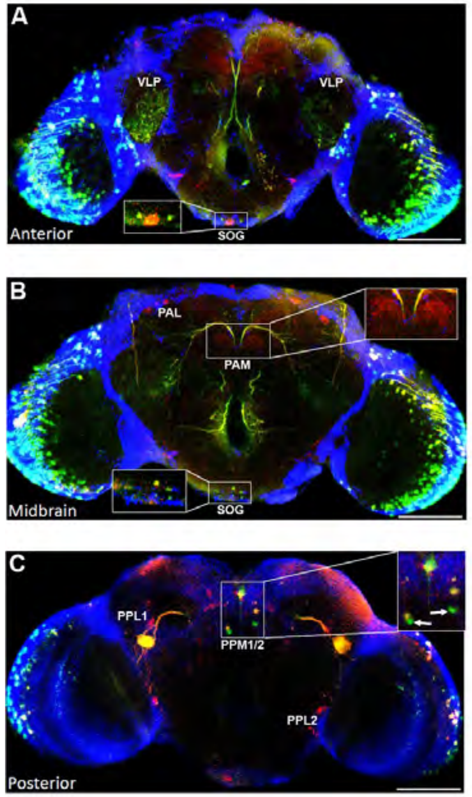
Jung J, et al. *International Journal of Molecular Sciences*. 2018
Vaziri A, et al. *Science Advances*. 2020

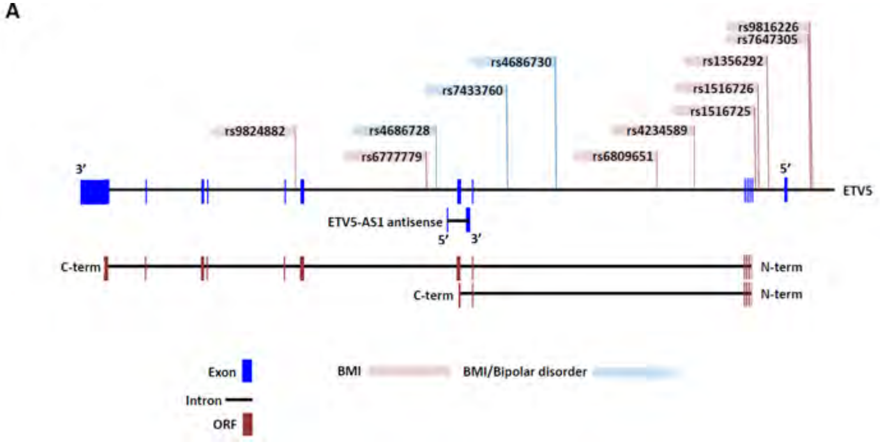
The drosophila *Ets96B*: molecular link between obesity and bipolar disorder











Ets96B：肥胖相关基因ETV5在果蝇中的同源基因，可调节与肥胖和双相情感障碍（BD）相关的细胞系统。

Williams MJ, et al. *Plos Genetics*. 2016

How does obesity affect lifespan and reproduction?

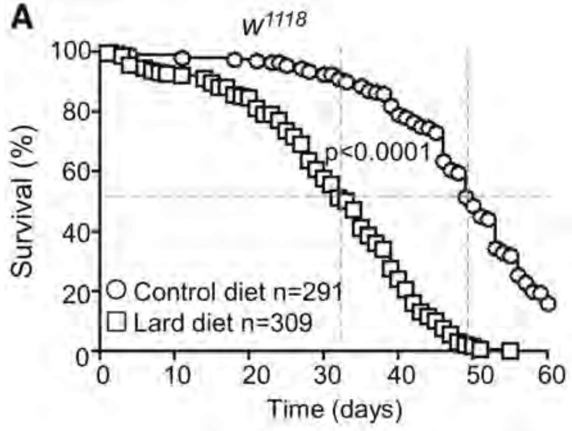
- **lifespan**

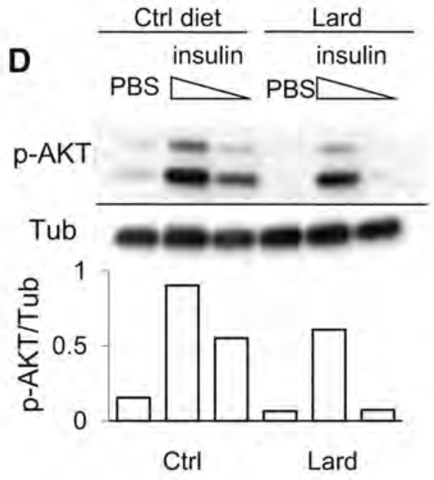
Table 2
Summarizing of literature data on diet-induced obesity and oxidative stress in *D. melanogaster*.

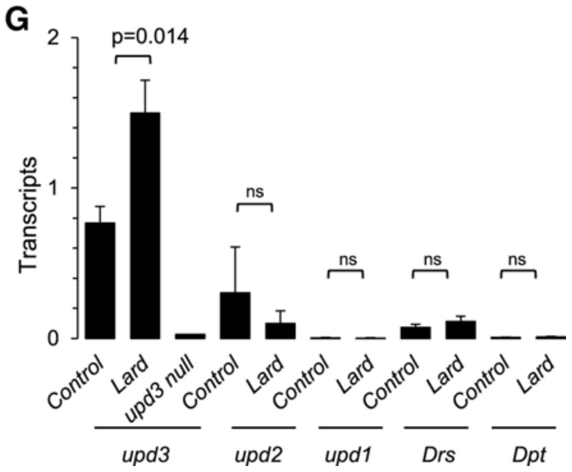
Diet type	Phenotype and metabolic characteristics	References
High glucose diet	Delayed pupation, increased larvae mortality, shortened lifespan. Displayed an obese-like phenotype in adults: increased fly body mass and decreased percentage of water in the body, high body triacylglycerols, glucose, trehalose, and glycogen levels. No oxidative stress.	Rovenko et al., 2015b
High fructose diet	Delayed pupation, increased larvae mortality, shortened lifespan. Displayed an obese-like phenotype in adults: increased fly body mass, higher levels of triacylglycerols, trehalose and glycogen, but unaffected level of circulating glucose. No oxidative stress.	Rovenko et al., 2015b; Stanhope, 2016
High sucrose diet	Delayed pupation and increased pupa mortality, shortened lifespan. Displayed an obese-like phenotype in adults: enhanced levels of lipids and glycogen, increased dry body mass, decreased water content, hyperglycemia and insulin resistance, increased levels of circulating dILPs in hemolymph.	Musselman et al., 2011; Pasco and Léopold, 2012; Morris et al., 2012; Buescher et al., 2013; Rovenko et al., 2015a; Zhang et al., 2017; Hemphill et al., 2017
High starch diet	Delayed pupation, increased larvae mortality, shortened lifespan. Displayed an obese-like phenotype in adults: decreased water content, increased triacylglycerol levels, but no change in body mass of insects or level of circulating glucose.	Abrat et al., 2018
High glucose and fructose diets	Increased intensity of oxidative stress in adults.	Lushchak et al., 2011
High-saturated fat diet (coconut oil)	Reduced survival and lifespan. Displayed an obese-like phenotype in adults: increased circulating glucose levels and body triacylglycerol content, increased insulin-like peptide resistance, enhanced rate of lipid peroxidation, cardiac lipid accumulation and reduced cardiac contractility. Increased intensity of oxidative stress in adults.	Birse et al., 2010; Heinrichsen et al., 2014; Diop and Bodmer, 2015; Trindade de Paula et al., 2016; Hong et al., 2016 Hemphill et al., 2017

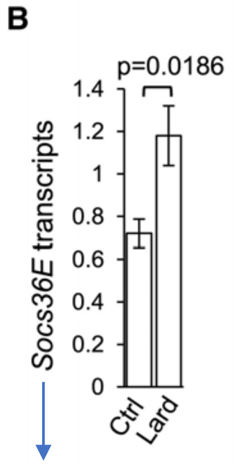
Bayliak MM, et al. *Comp Biochem Physiol A Mol Integr Physiol*. 2019

Macrophage-derived *upd3* cytokine causes impaired glucose homeostasis and reduced lifespan in drosophila fed a lipid-rich diet

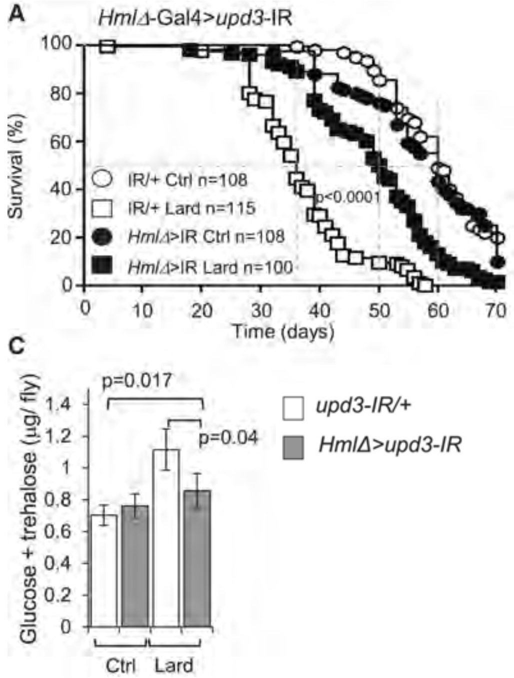


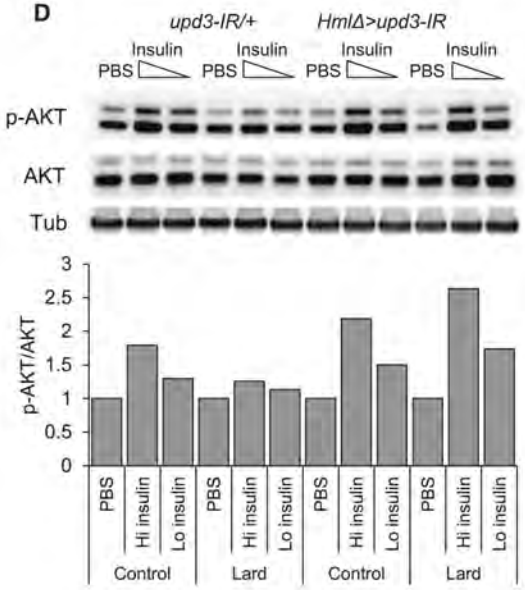


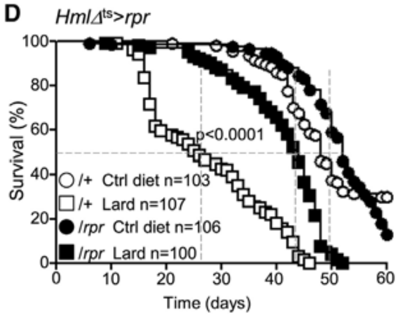


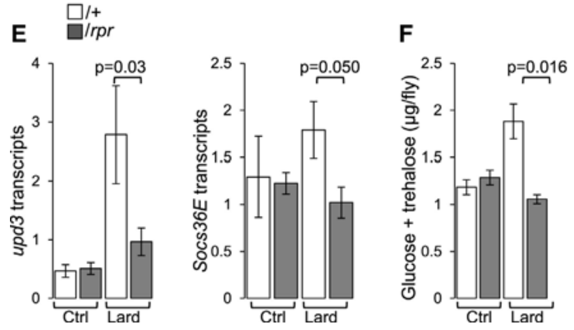


JAK-STAT target gene



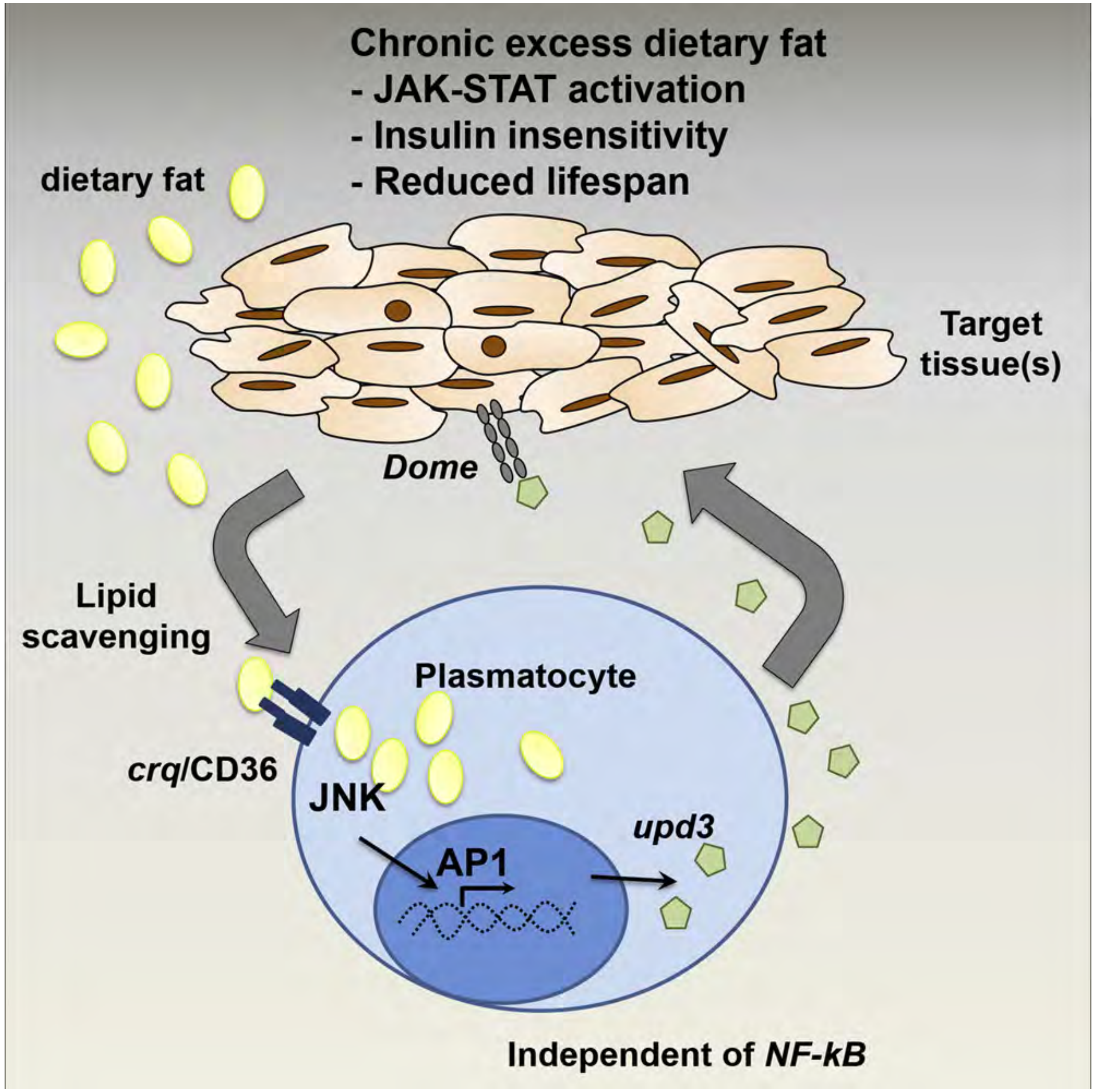






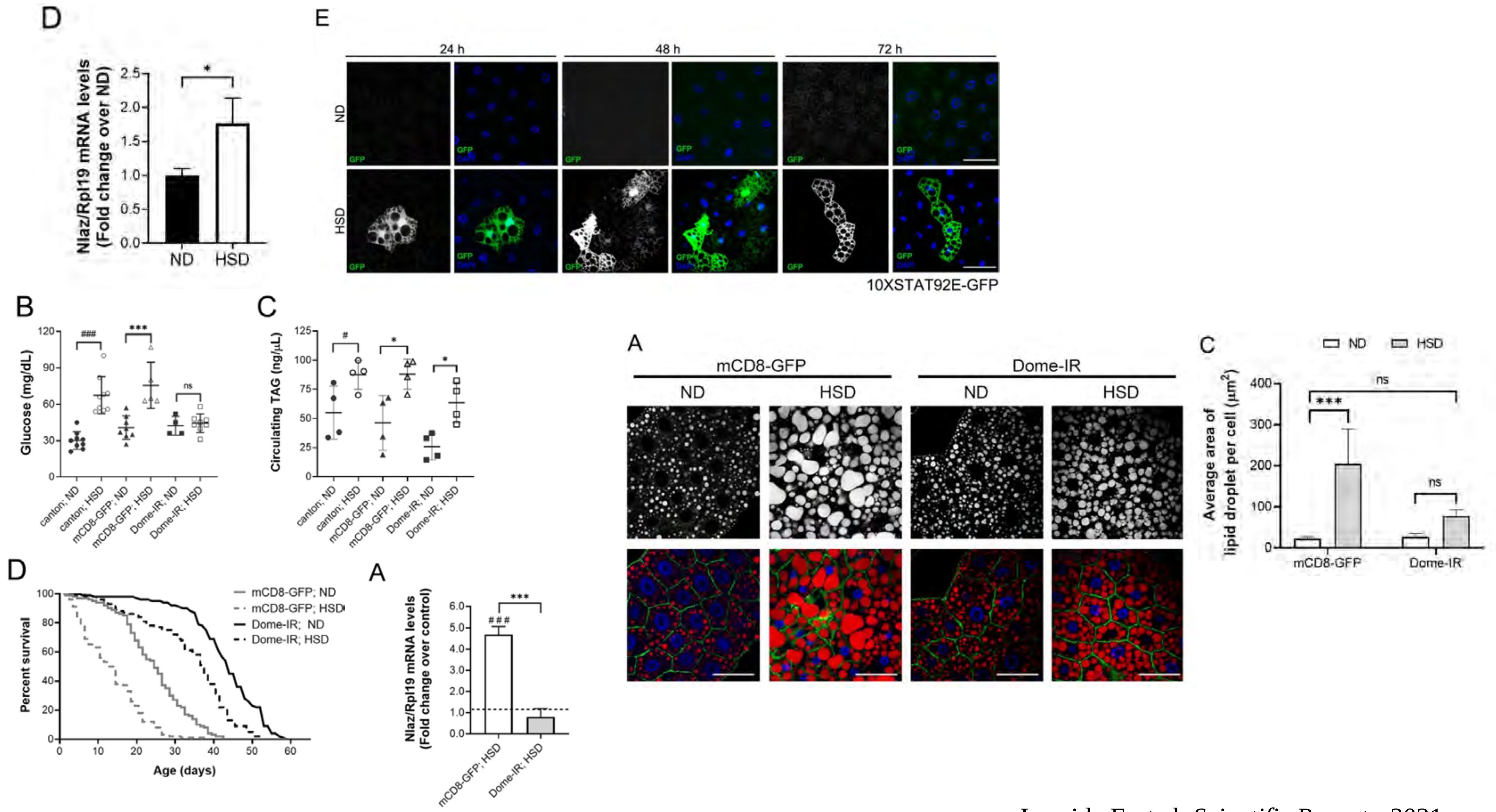
Woodcock KJ, et al. *Immunity*. 2015

Macrophage-derived *upd3* cytokine causes impaired glucose homeostasis and reduced lifespan in drosophila fed a lipid-rich diet



Woodcock KJ, et al. *Immunity*. 2015

Domeless receptor loss in fat body tissue reverts insulin resistance induced by a high-sugar diet and increased the lifespan of larvae

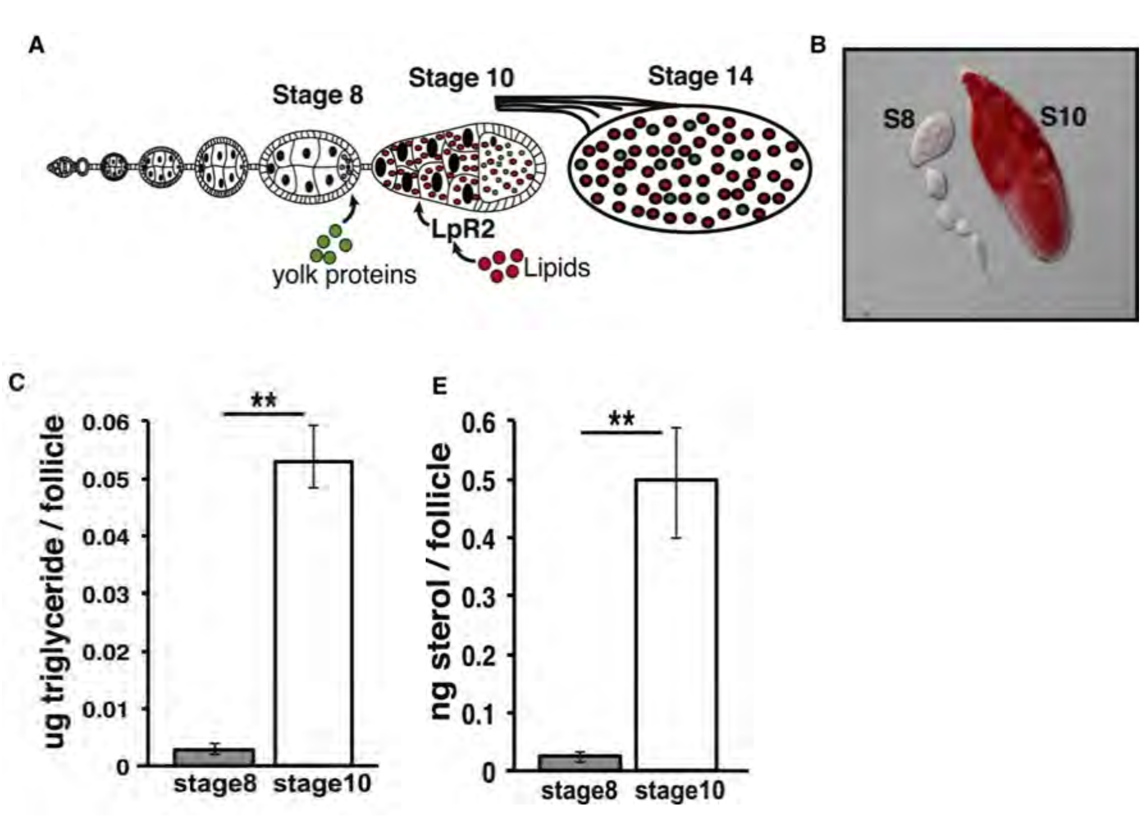


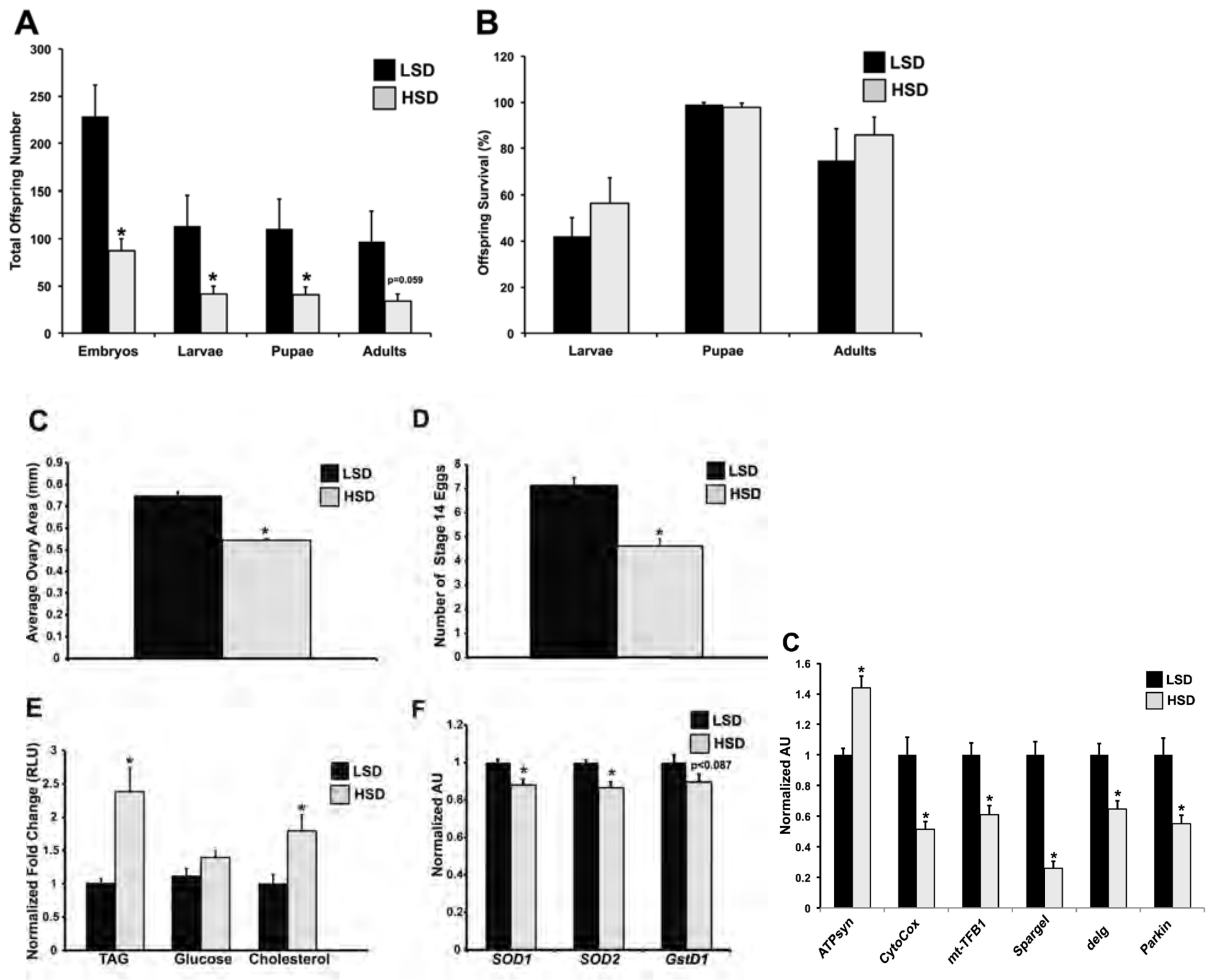
Lourido F, et al. *Scientific Reports*. 2021

Nlaz：编码脂质运载蛋白，调节胰岛素信号通路的活性，被认为是一种 IR 标志物。

- fecundity

Highly obesogenic diets reduce fecundity



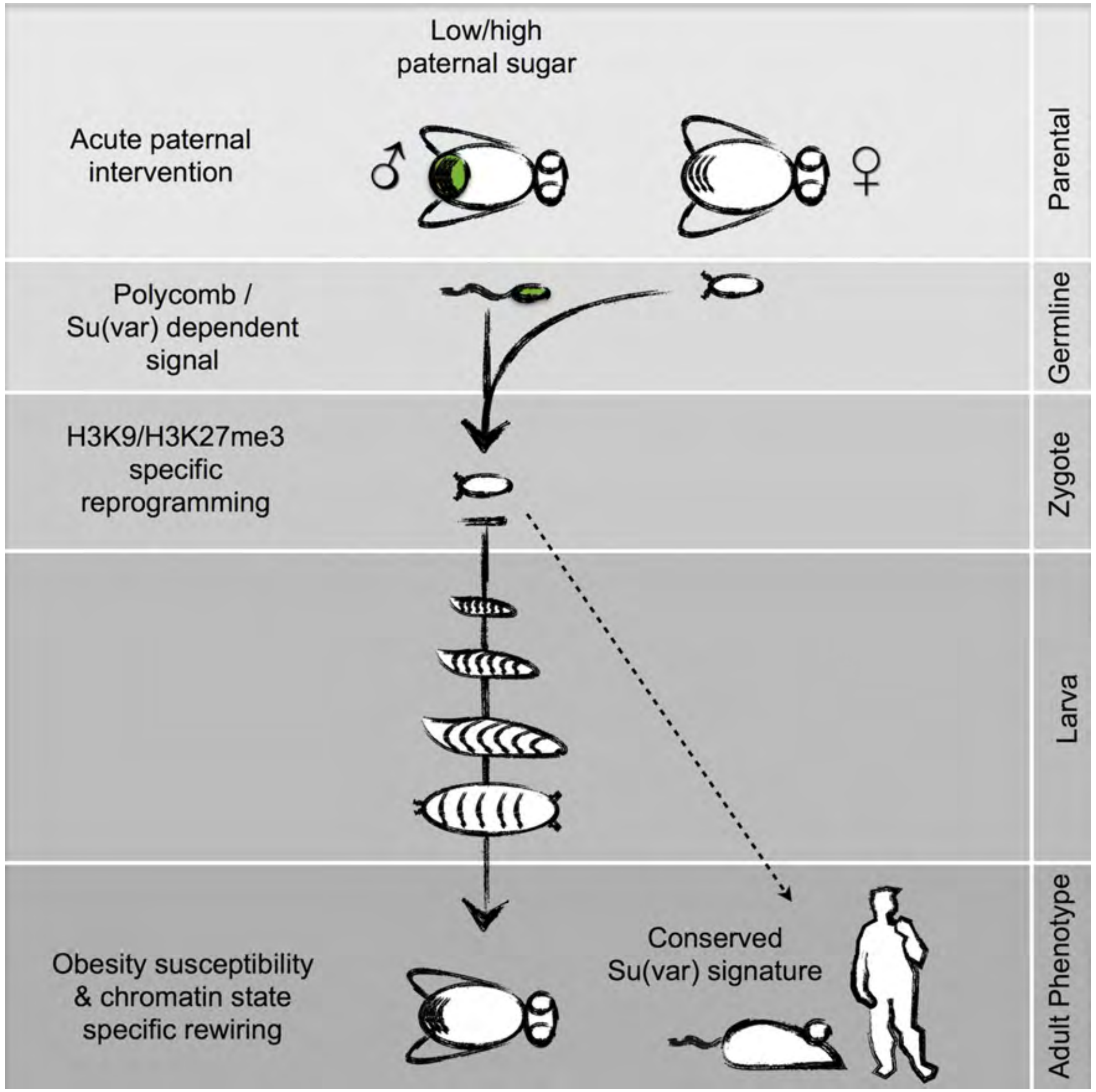


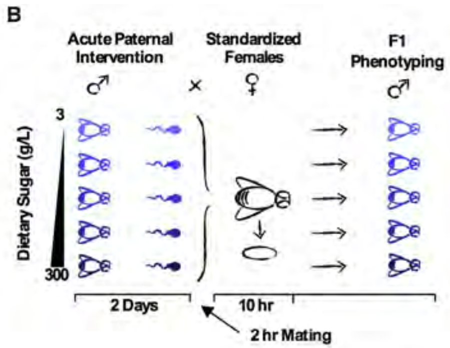
脂质在卵母细胞发育过程中急剧积累，是卵子和胚胎发育早期阶段所必需的。

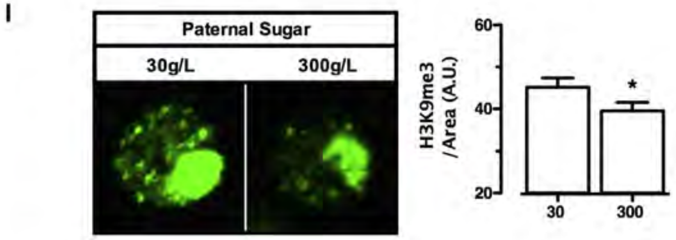
Sieber MH, et al. *Curr Biol*. 2015

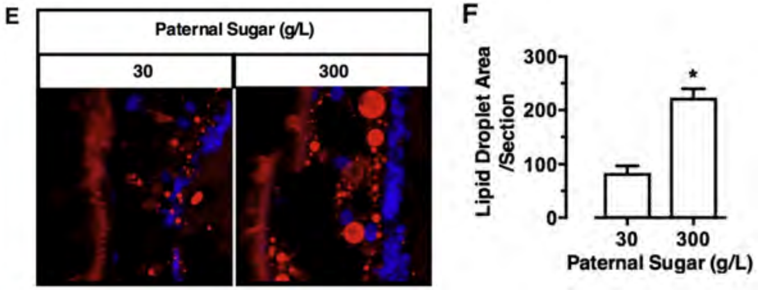
Brookheart RT, et al. *Biochim Biophys Acta Mol Basis Dis*. 2017

Paternal diet changes offspring chromatin state and induces intergenerational obesity









Su(var)： Suppressor of variegation，一类能够抑制位置效应杂色（PEV，Position Effect Variegation）的基因或蛋白质。这些基因或蛋白质通常通过调控染色质结构或表观遗传修饰来影响基因表达。

Öst A, et al. *Cell*. 2014

Summary

- Obesity leads to many physiological and metabolic changes in the body.

  Oxidative stress, Lipid peroxidation, Insulin resistance

- Obesity affects behavioral output through different metabolic pathways or neural circuits.

- Obesity usually results in a shortened life span and reduced fertility of organisms.

- Obesity even induces obesity in offspring through epigenetic inheritance.

Thank you!

The intrinsic relation between exercise and obesity

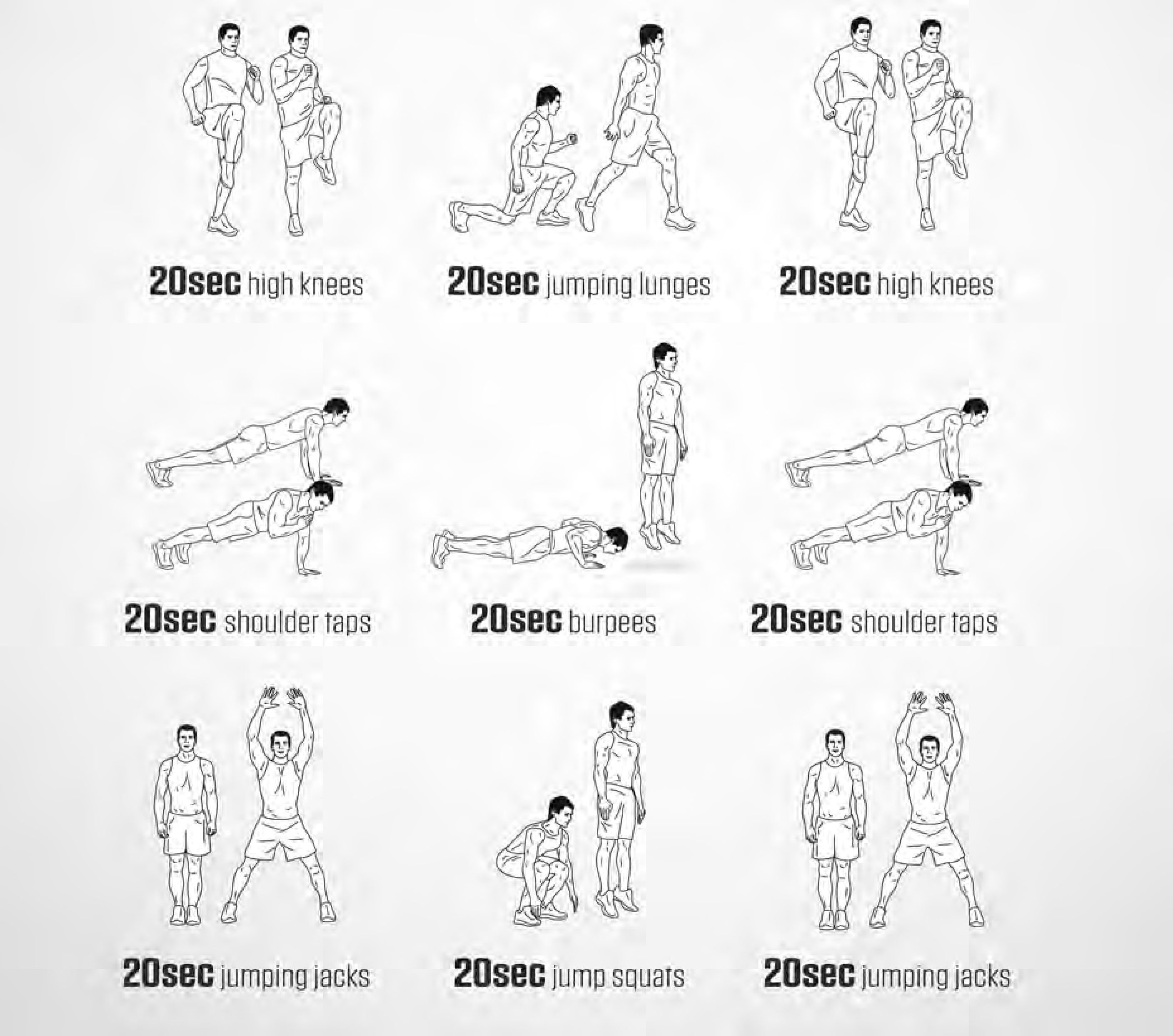
2025-03-27

Joshua Liang

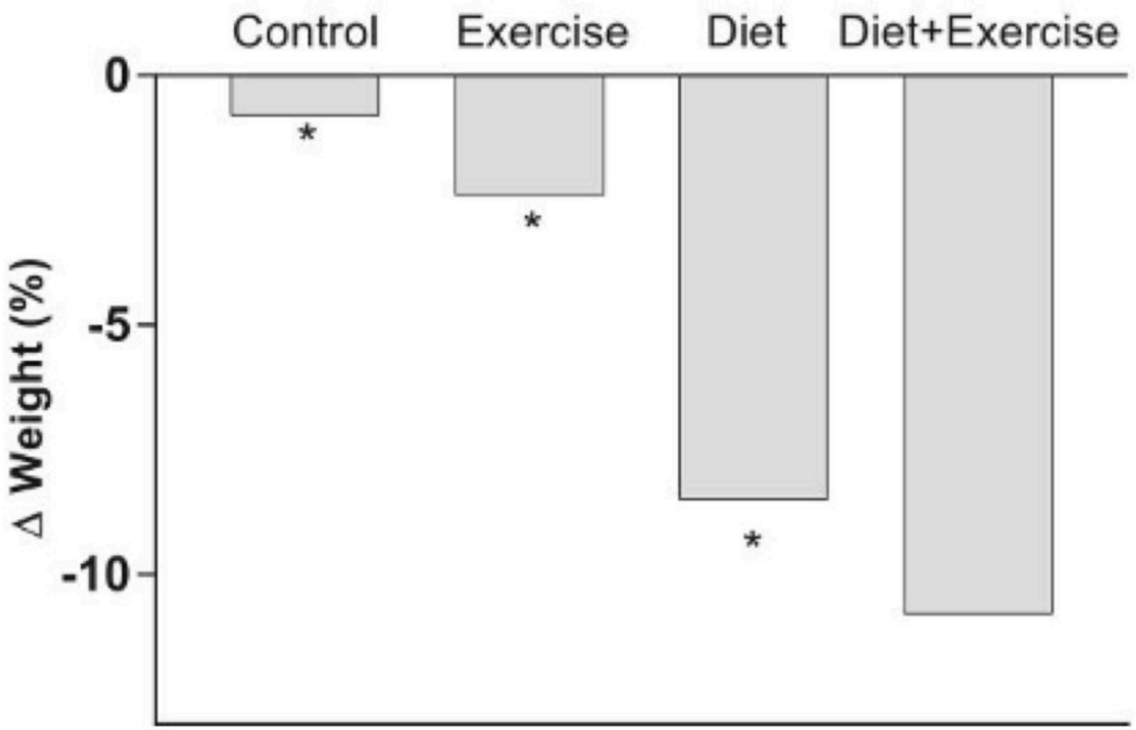
Exercise comes in many forms!

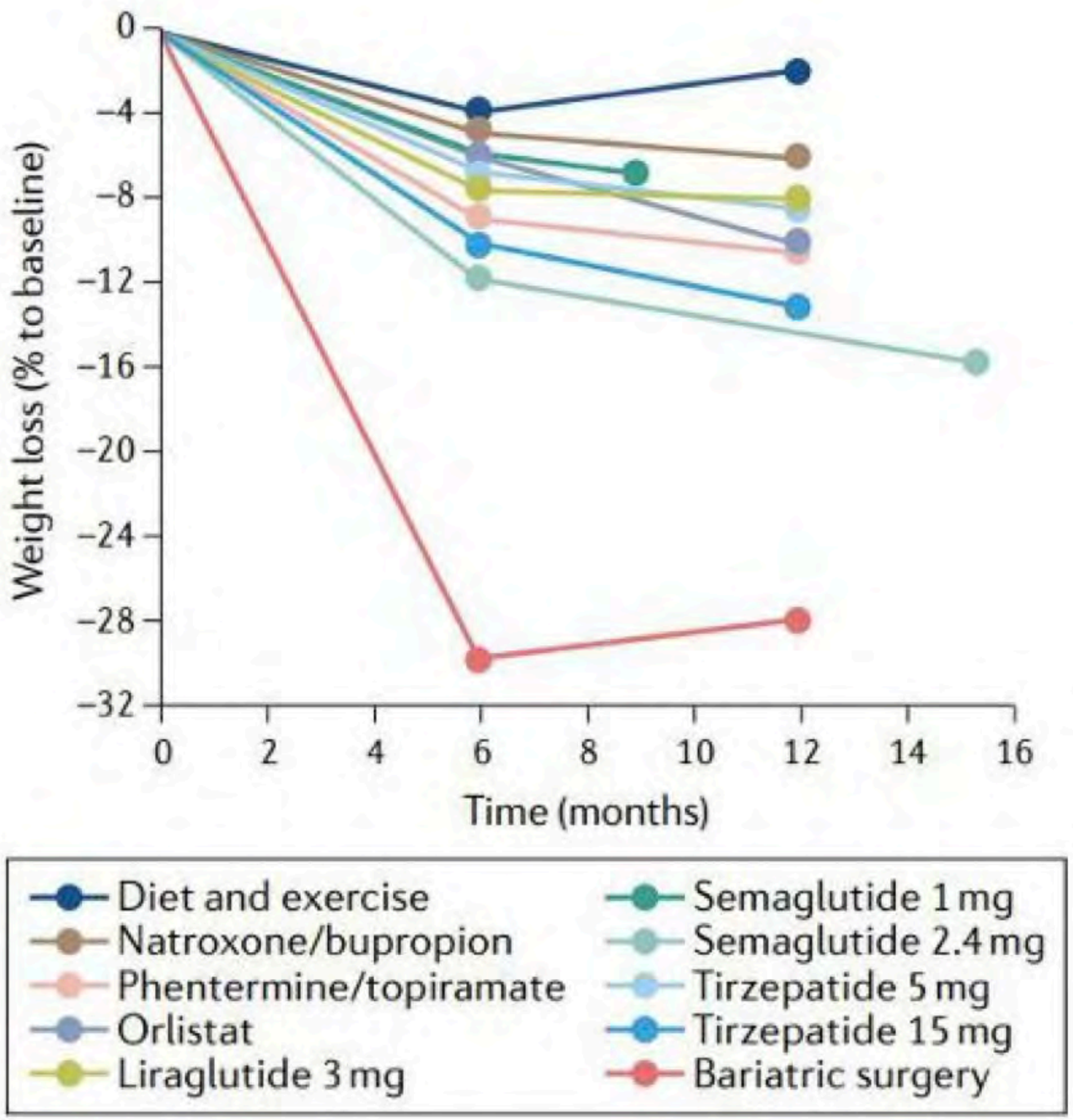
Exercise comes in many forms!

Exercise comes in many forms!



Where Does Exercise Stand Among Obesity Treatments?

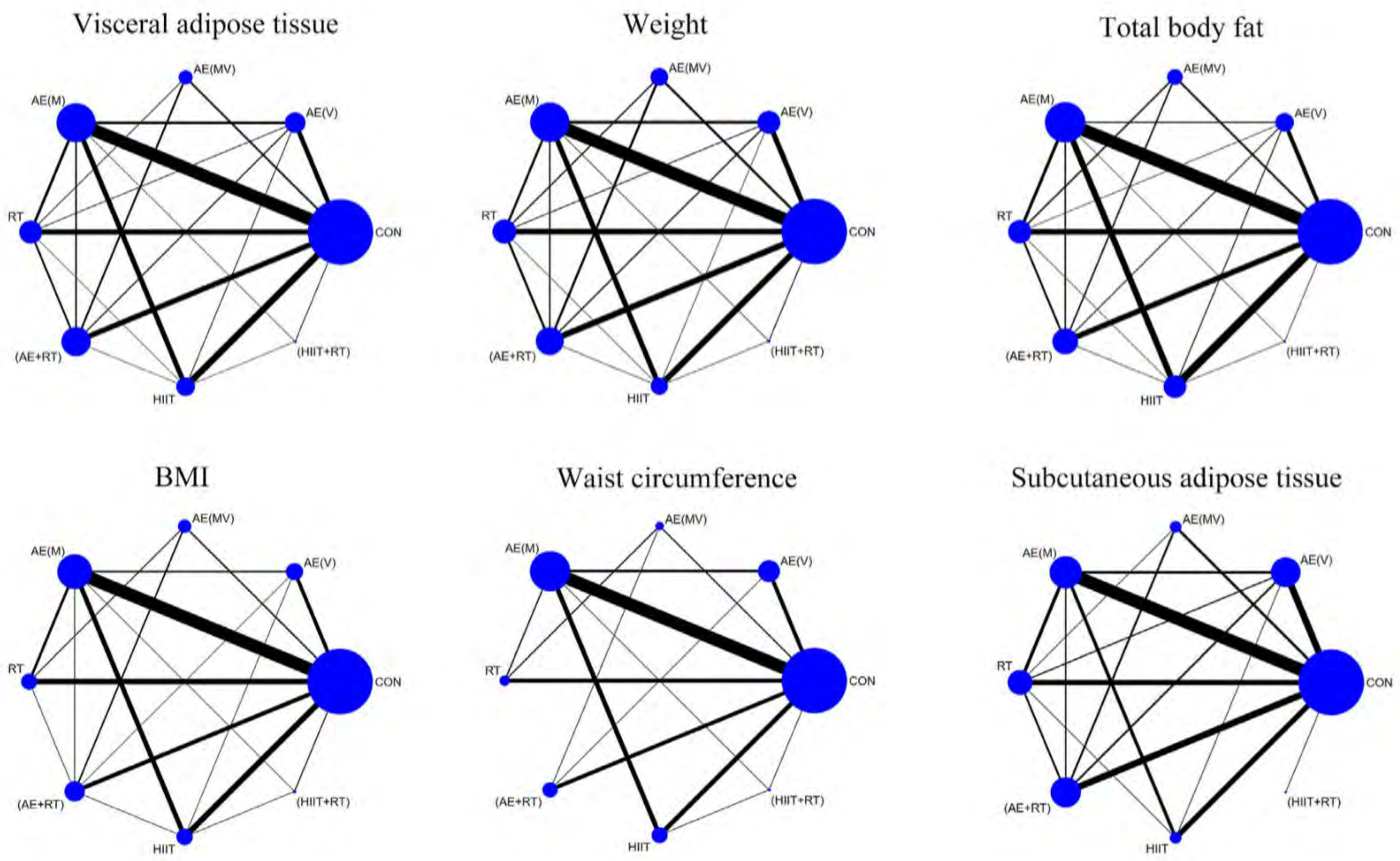




Peri K et al., *BMJ Public Health*, 2024

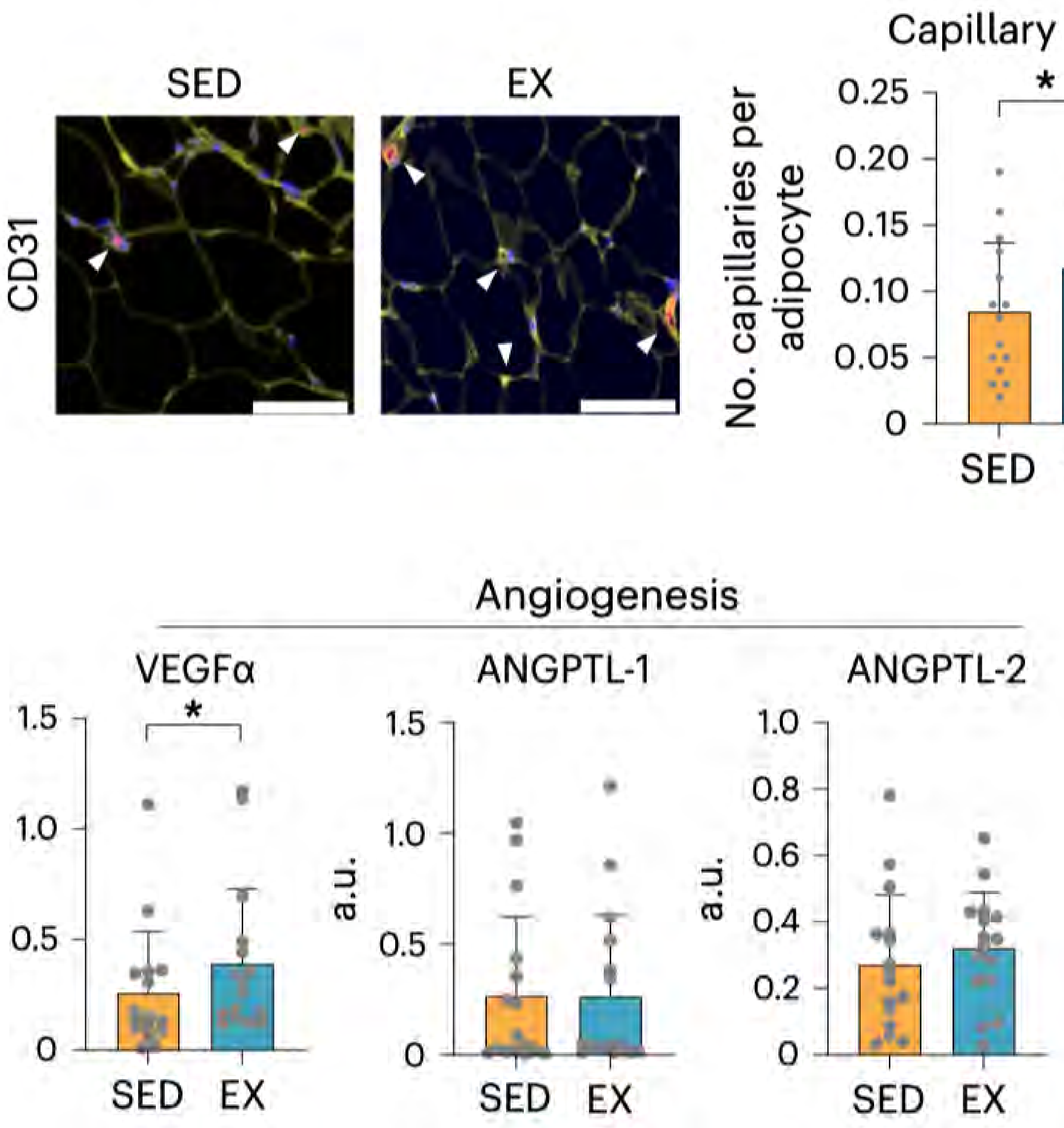
Evidence from 84 RCTs: Not All Exercises Are Equally Effective

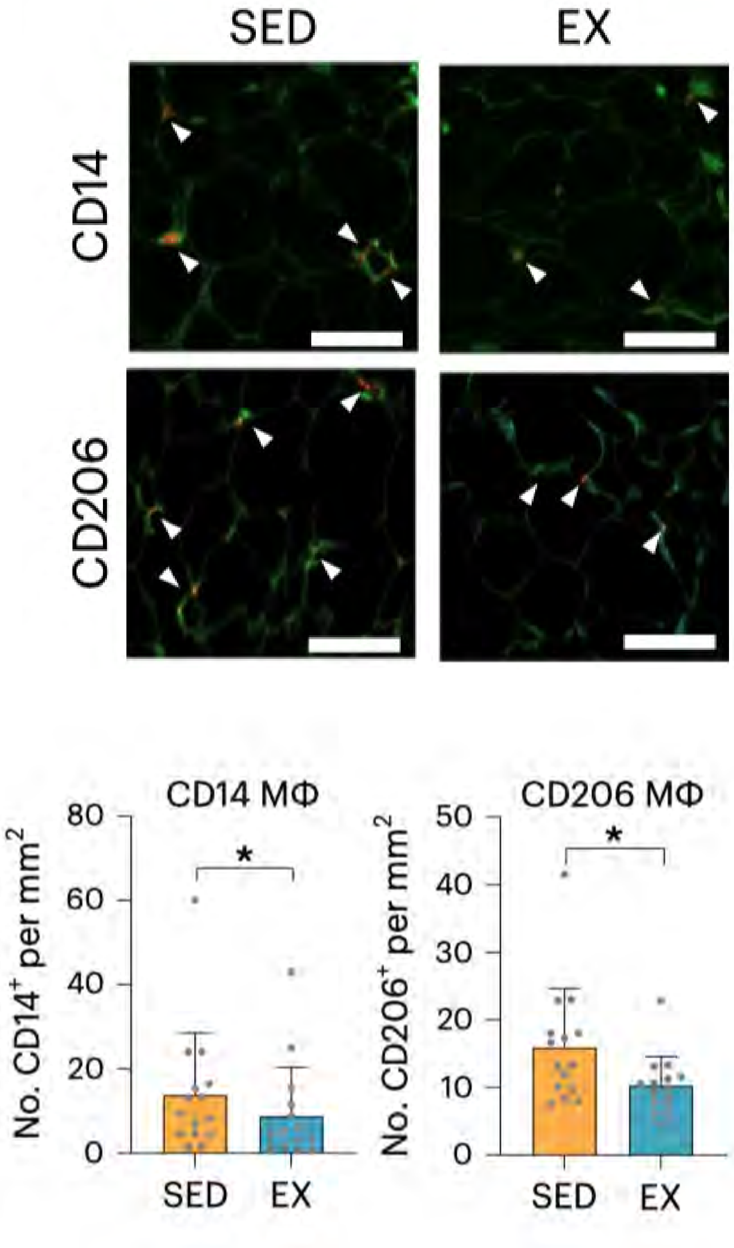
Type	Definition	
CON	No exercise or slight stretching	
AE(V)	Type: Any continuous traditional mode of aerobic training only (e.g., walking, running, cycling, rowing, aerobics, and elliptical exercise).[28]	Intensity: >65% VO_2max or >65% HRR or >75% MHR
AE(MV)		Intensity: Intensity ranges from vigorous to moderate
AE(M)		Intensity: 45%–65% VO_2max or >50%–65% HRR or 65%–75% MHR
RT	Intensity: ≥50% 1RM Type: Any mode of resistance training, including circuit-based programs (e.g., free weights, weights machines, and resistance bands).[28]	
AE + RT	AE combined with RT	
HIIT	Intensity: >65% VO_2max or >65% HRR or >75% MHR in the high-intensity periods Type. Exercise training involves repeated short-to-long bouts of rather high-intensity exercise interspersed with recovery periods, including interval sprint training.[29,30]	
HIIT + RT	HIIT combined with RT	



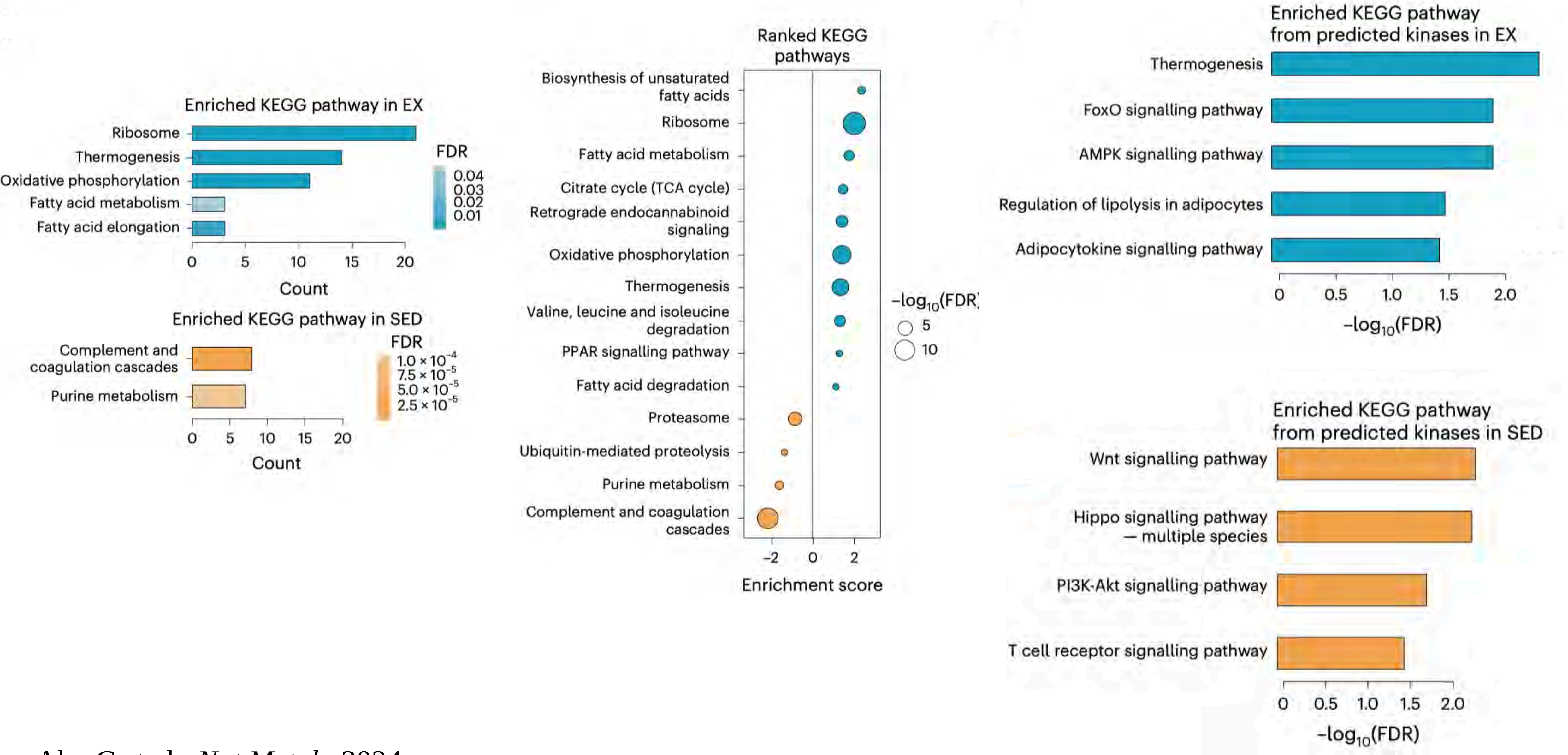
Chen X et al., *Obes Rev*, 2024

Exercise Remodels Subcutaneous Fat: From Capillaries to the Proteome



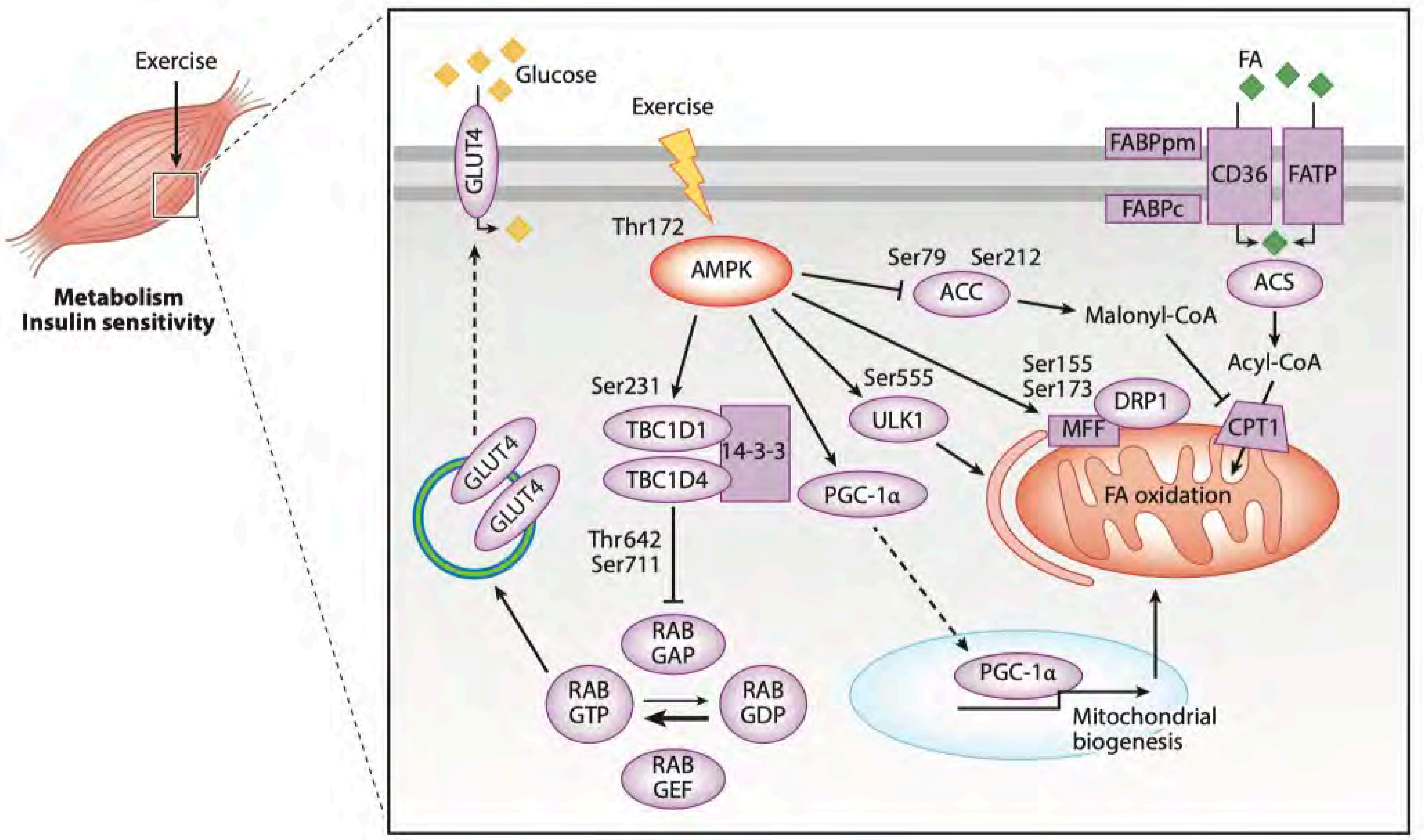


Ahn C et al., *Nat Metab*, 2024



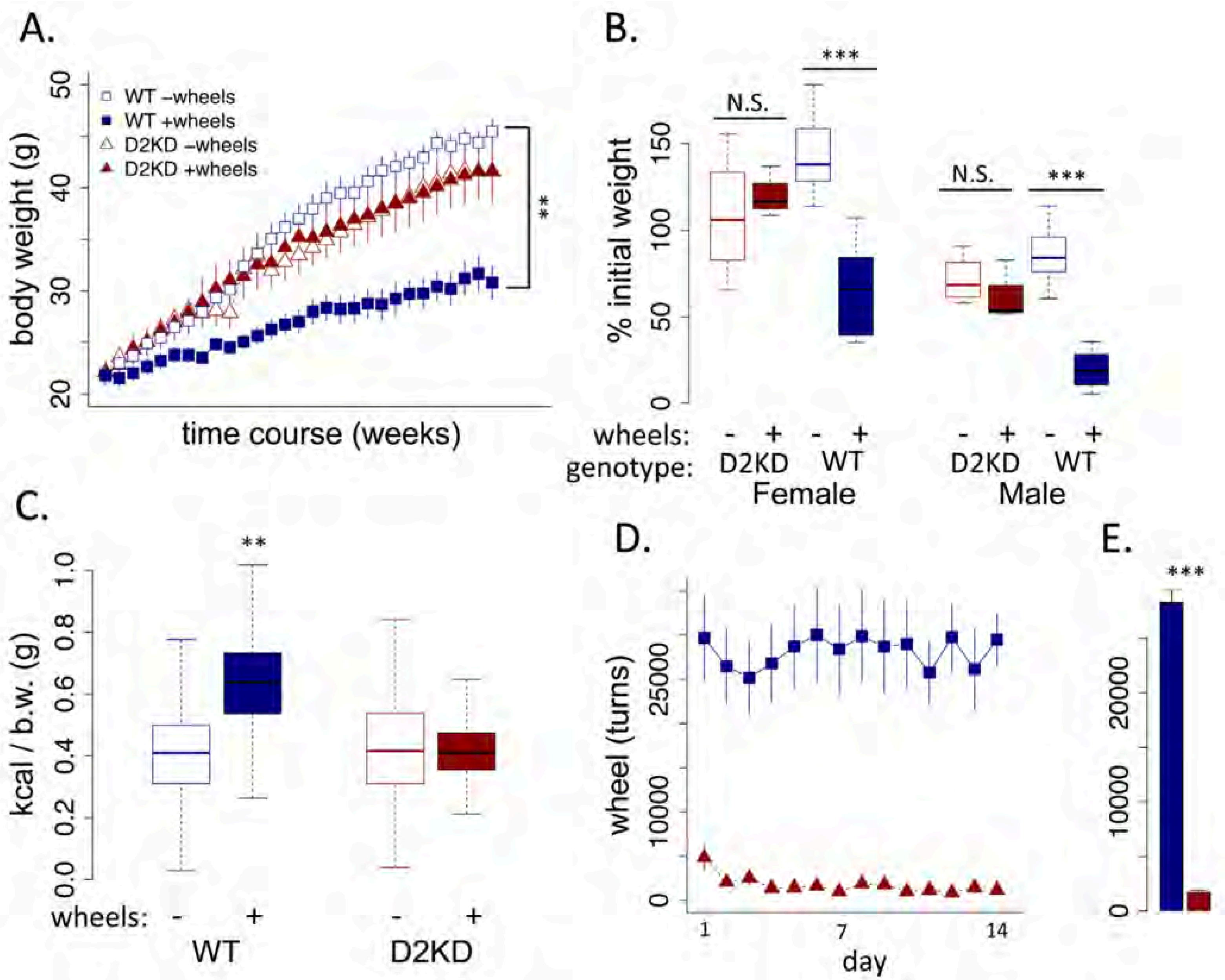
Ahn C et al., *Nat Metab*, 2024

AMPK Integrates Exercise Signals to Regulate Glucose and Lipid Metabolism



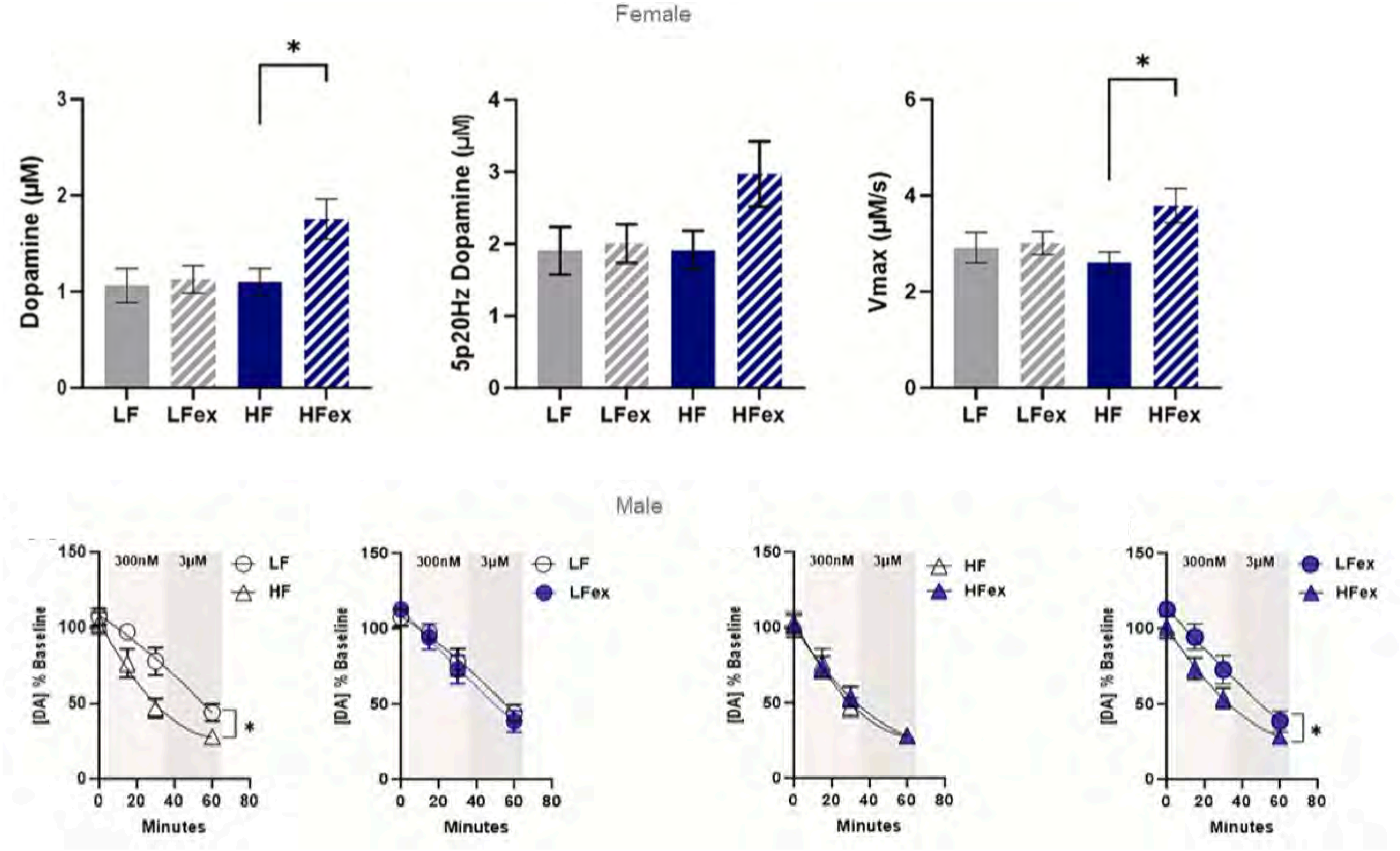
Spaulding HR et al., *Annu Rev Physiol*, 2022

Less Motivation to Move: How D2R Deficiency Increases Obesity Risk



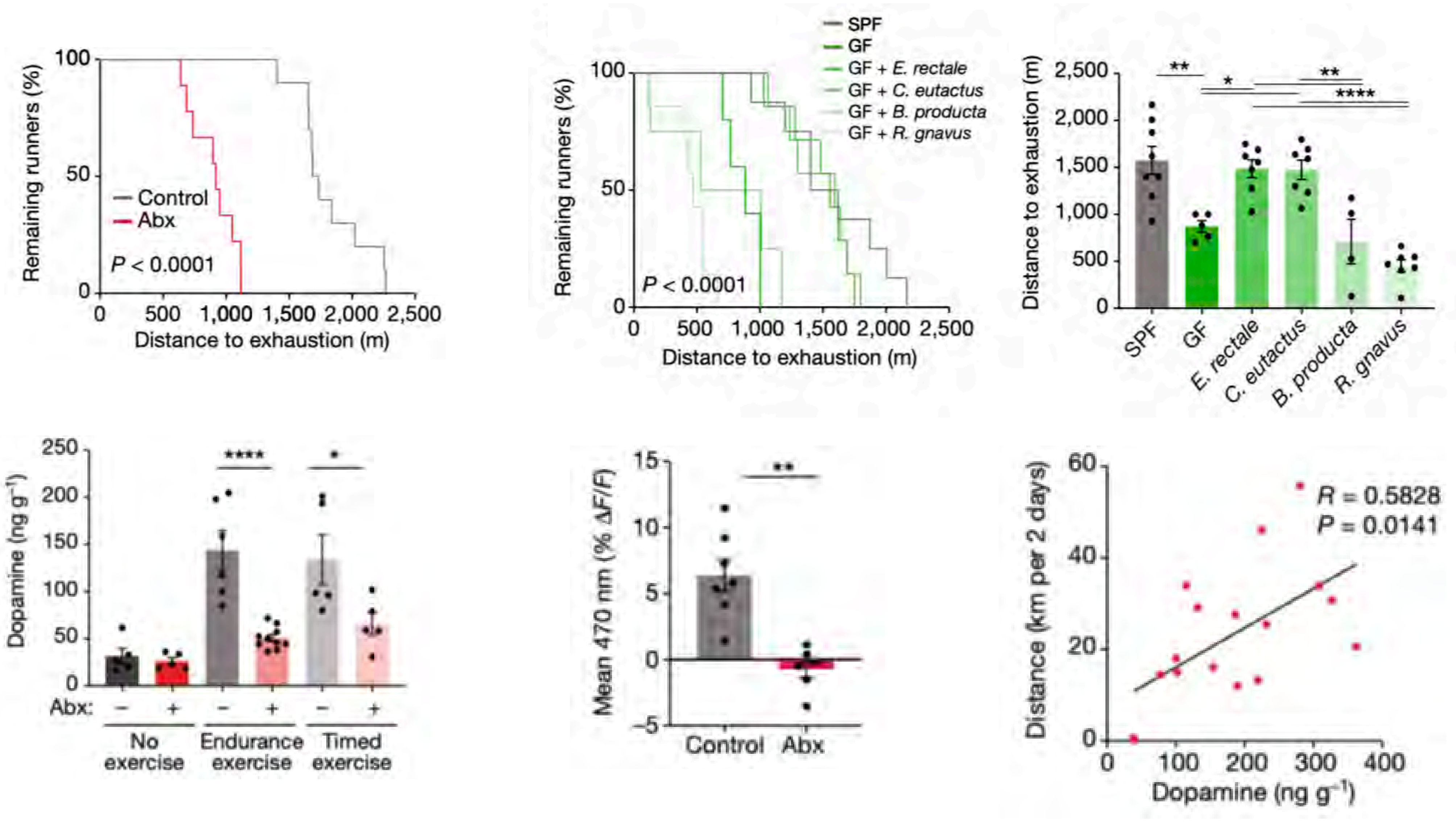
Beeler JA et al., *Biol Psychiatry*, 2016

Exercise Restores Dopamine Function in Obese Females and Enhances Reward Sensitivity

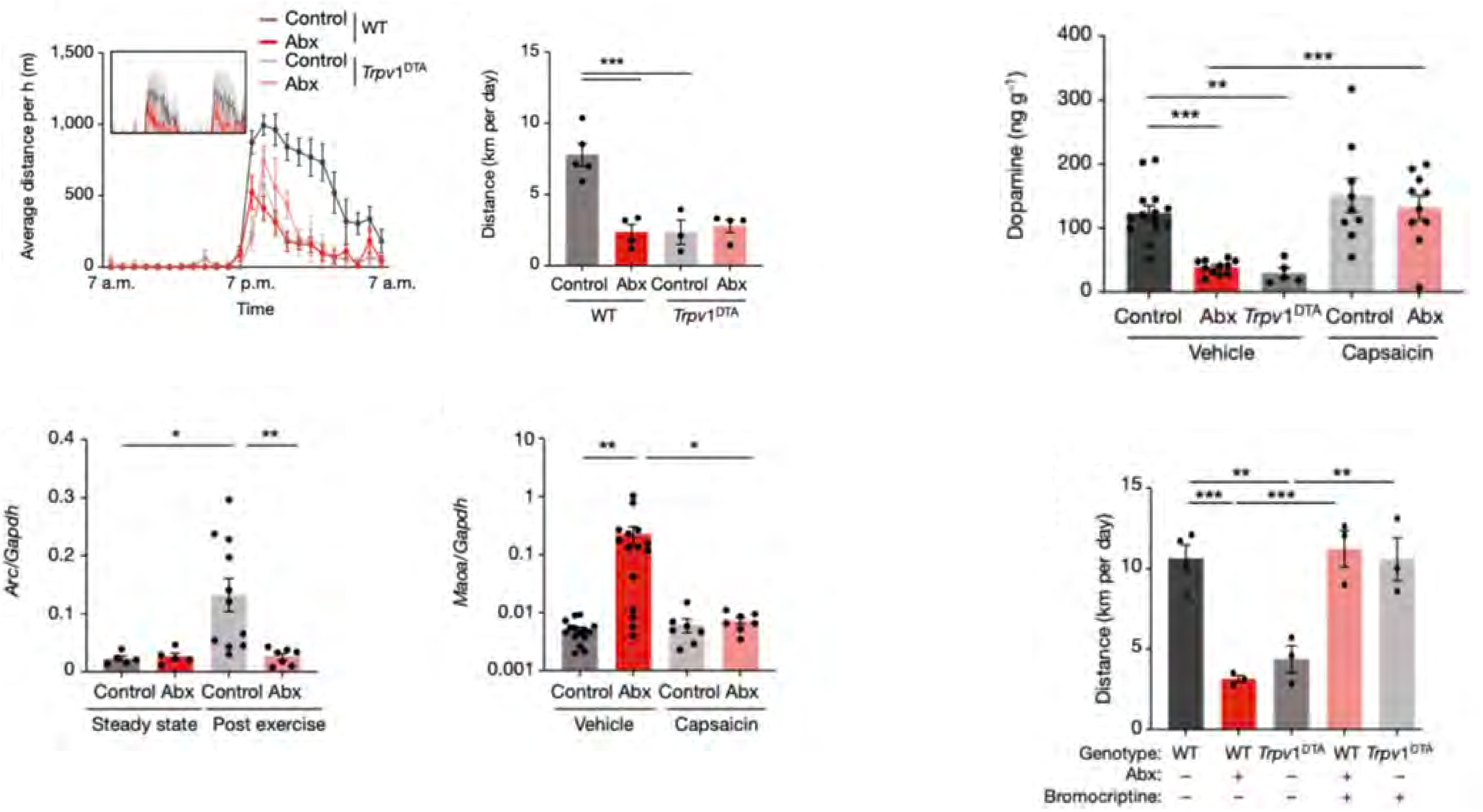


Emmons HA et al., *Neuroscience*, 2024

Microbiota–Dopamine–Exercise Motivation Axis

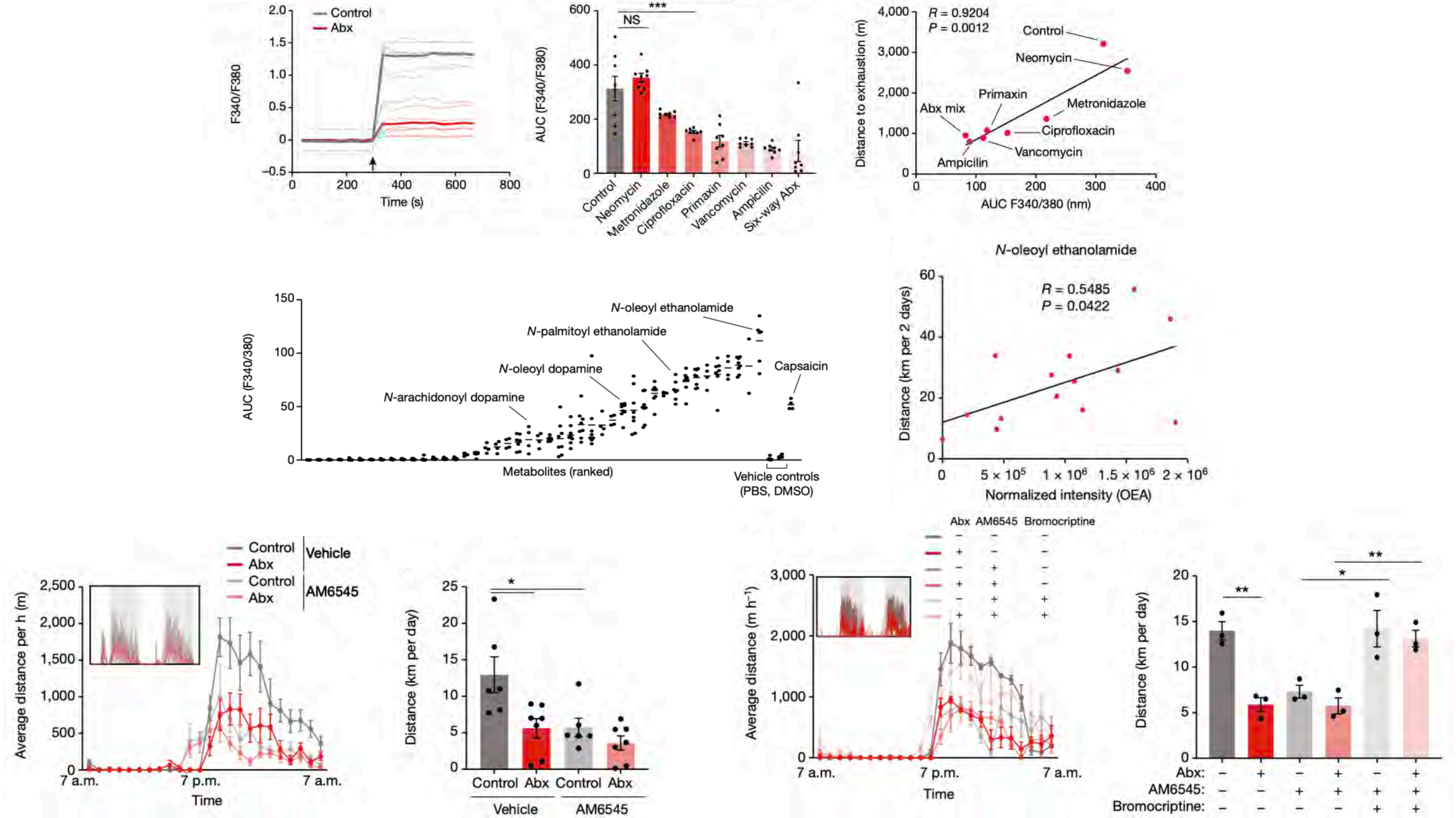


Dohnalová L et al., *Nature*, 2022

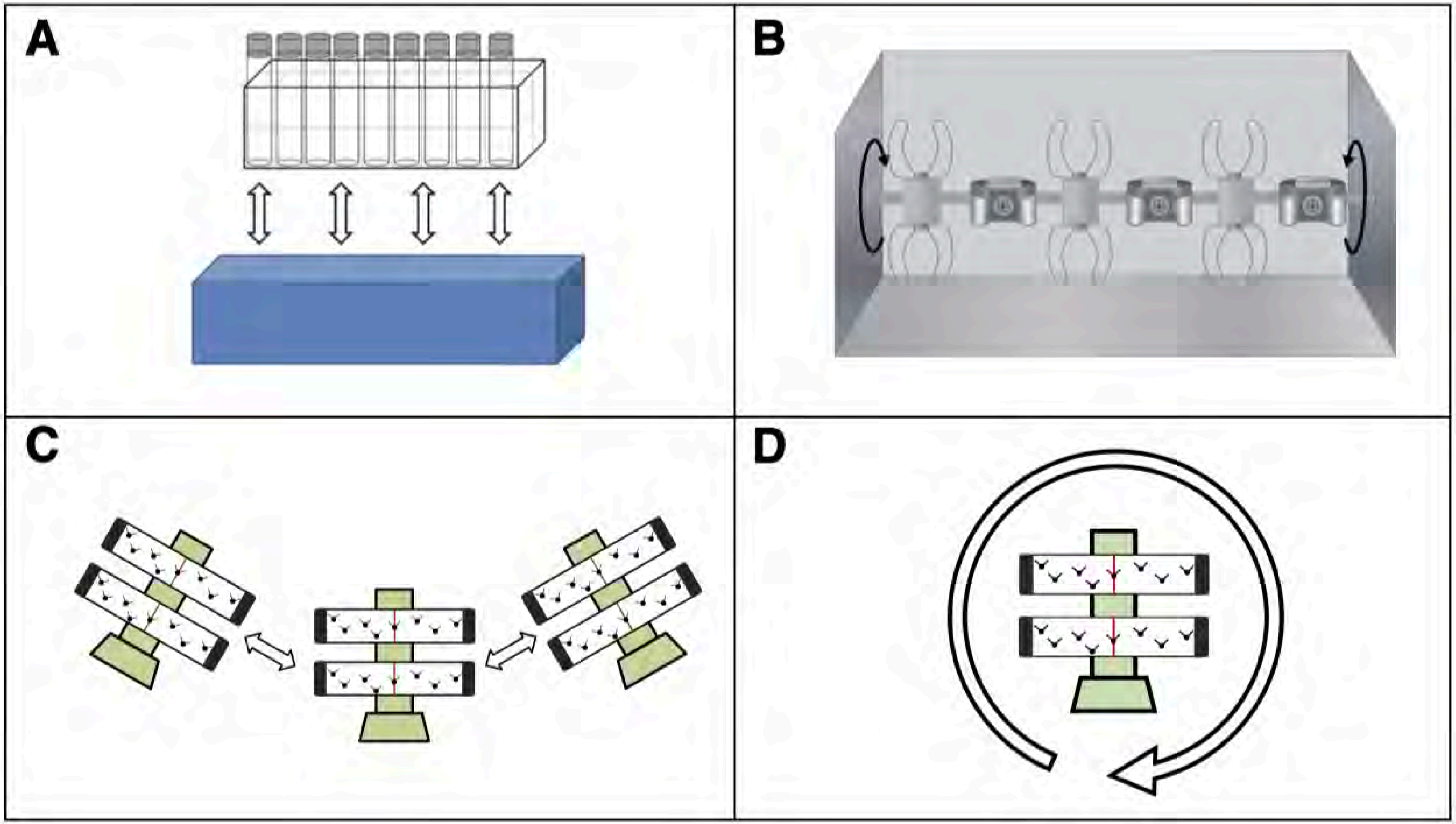


Dohnalová L et al., *Nature*, 2022

Dohnalová L et al., *Nature*, 2022

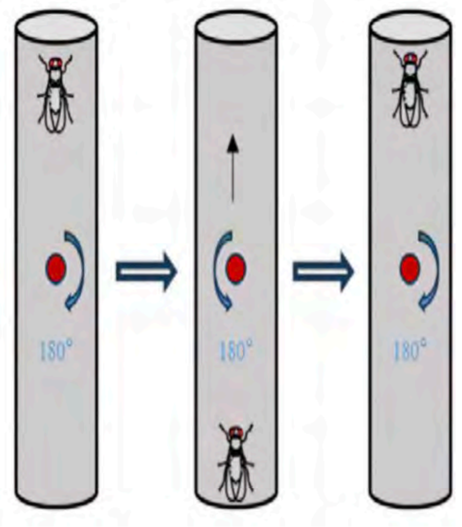


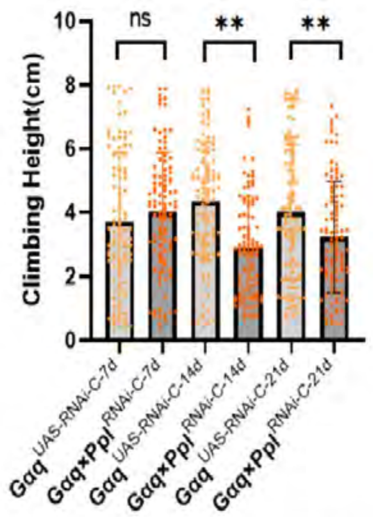
Drosophila as a model system for exercise research

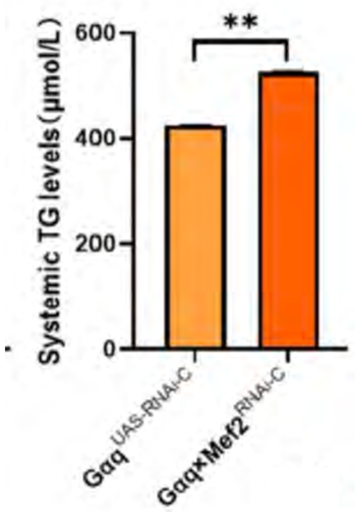


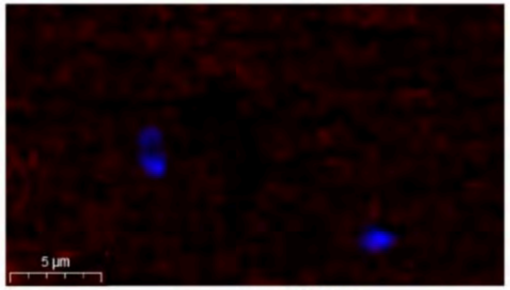
Watanabe LP et al., *J Appl Physiol*, 2019

Endurance Exercise Rescues Obesity and Muscle Dysfunction in Drosophila Gαq-RNAi Models

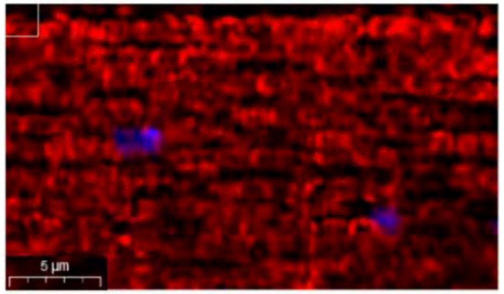




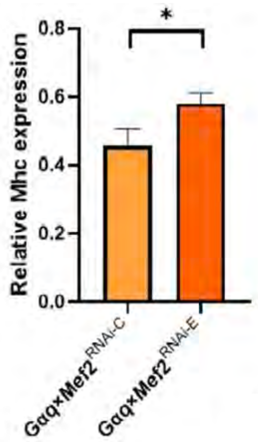


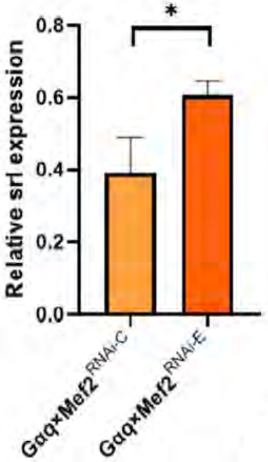


Gαq×Mef2 RNAi-C



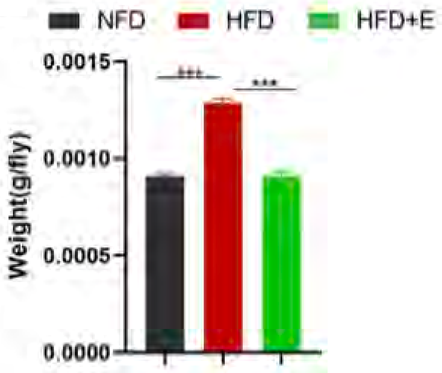
Gαq×Mef2 RNAi-E

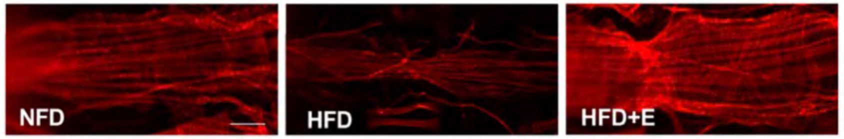


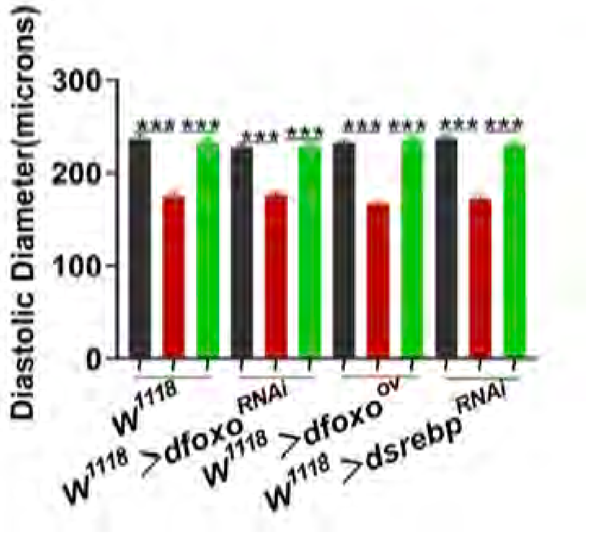


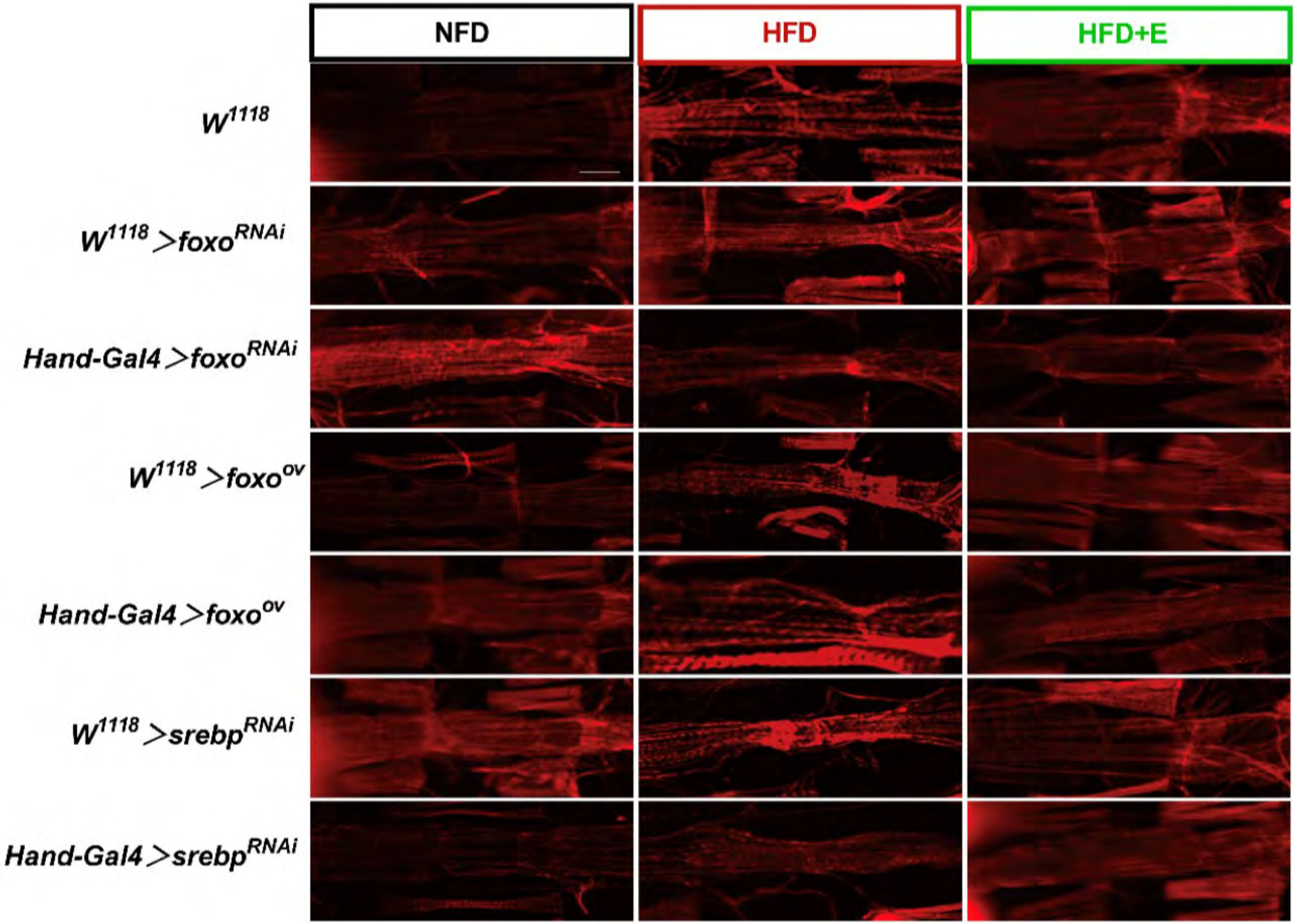
Yin XY et al., *Sci Rep*, 2024

Endurance Exercise Mitigates Obesity and Heart Dysfunction via FOXO/SREBP in *Drosophila*









Yan H et al., *Int J Mol Sci*, 2023

My Personal Fat Loss Plan

- **Training Routine:**
Resistance + cardio 4–5 times/week
Muay Thai training twice/week

- **Diet Strategy:**
<100g carbs/day
Protein >1.5g/kg body weight
Supplement with vitamins, coenzyme Q10, zinc, magnesium, etc.

- **Lifestyle:**
Proper rest
Reduce fat and refined carbohydrate intake

Take-home message

- **Exercise as a Molecular Intervention:** Exercise is not just behavior — it acts on molecular pathways to reverse obesity-related metabolic and neural impairments.

- **Sex, Genetics, and Microbiota Matter:** The benefits of exercise are modulated by sex, genetic background, and gut microbiota, shaping inter-individual variability in outcomes.

- **Drosophila as a Powerful Model:** With genetic tools and scalable exercise systems, Drosophila enables mechanistic studies linking exercise to metabolism, muscle, and neural function.