

ICDM 2018,

October 12th, 2018, Seoul



50 Years of Challenge,
Hope for Diabetes Cure
KDA 50TH ANNIVERSARY

Crosstalk between adipokines and hepatokines
in the maintenance of metabolic homeostasis
and cardiovascular health

Aimin Xu

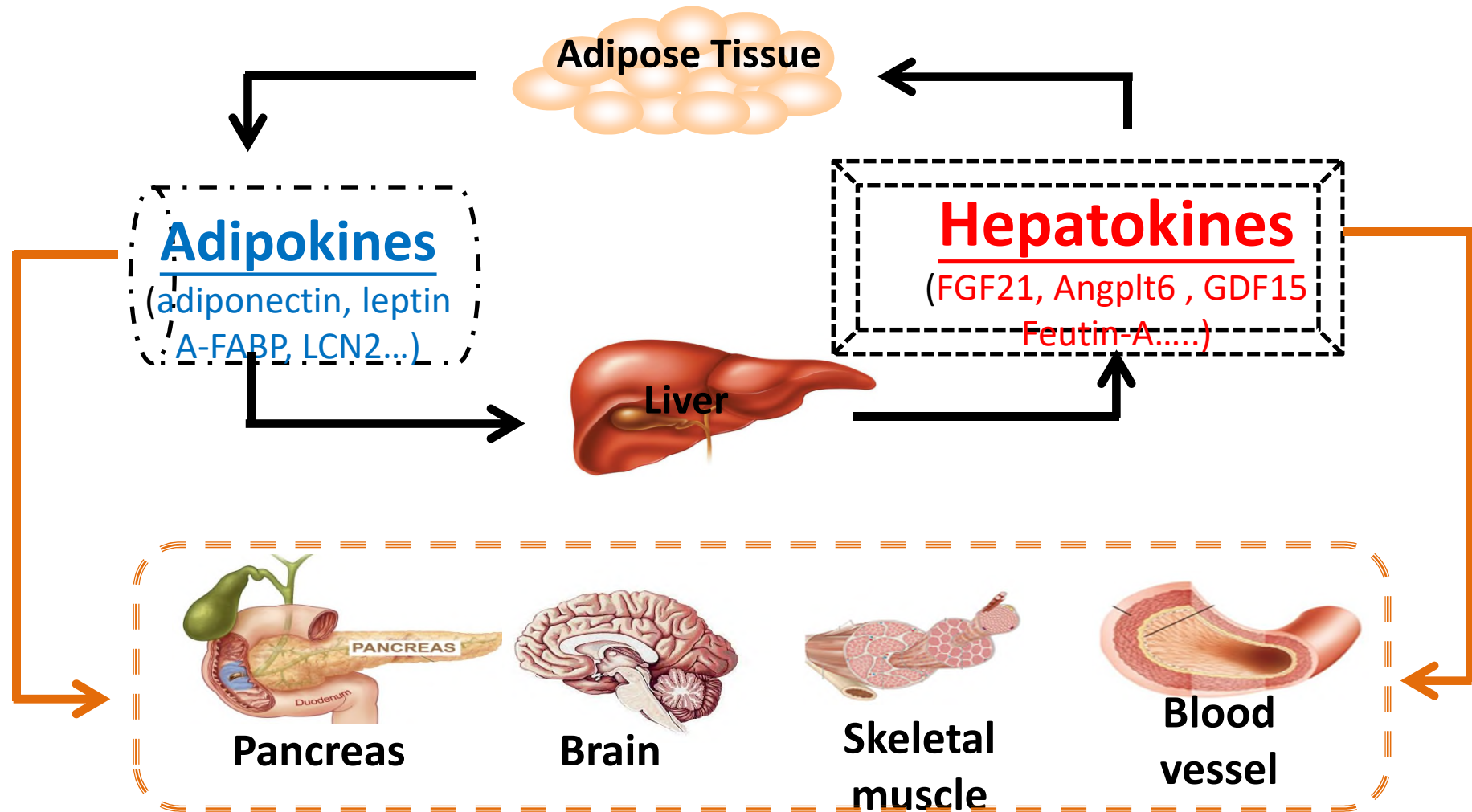
*State Key Laboratory of Pharmaceutical Biotechnology, Dept.
of Medicine & Dept. of Pharmacology and Pharmacy
The University of Hong Kong*

Disclosure statement

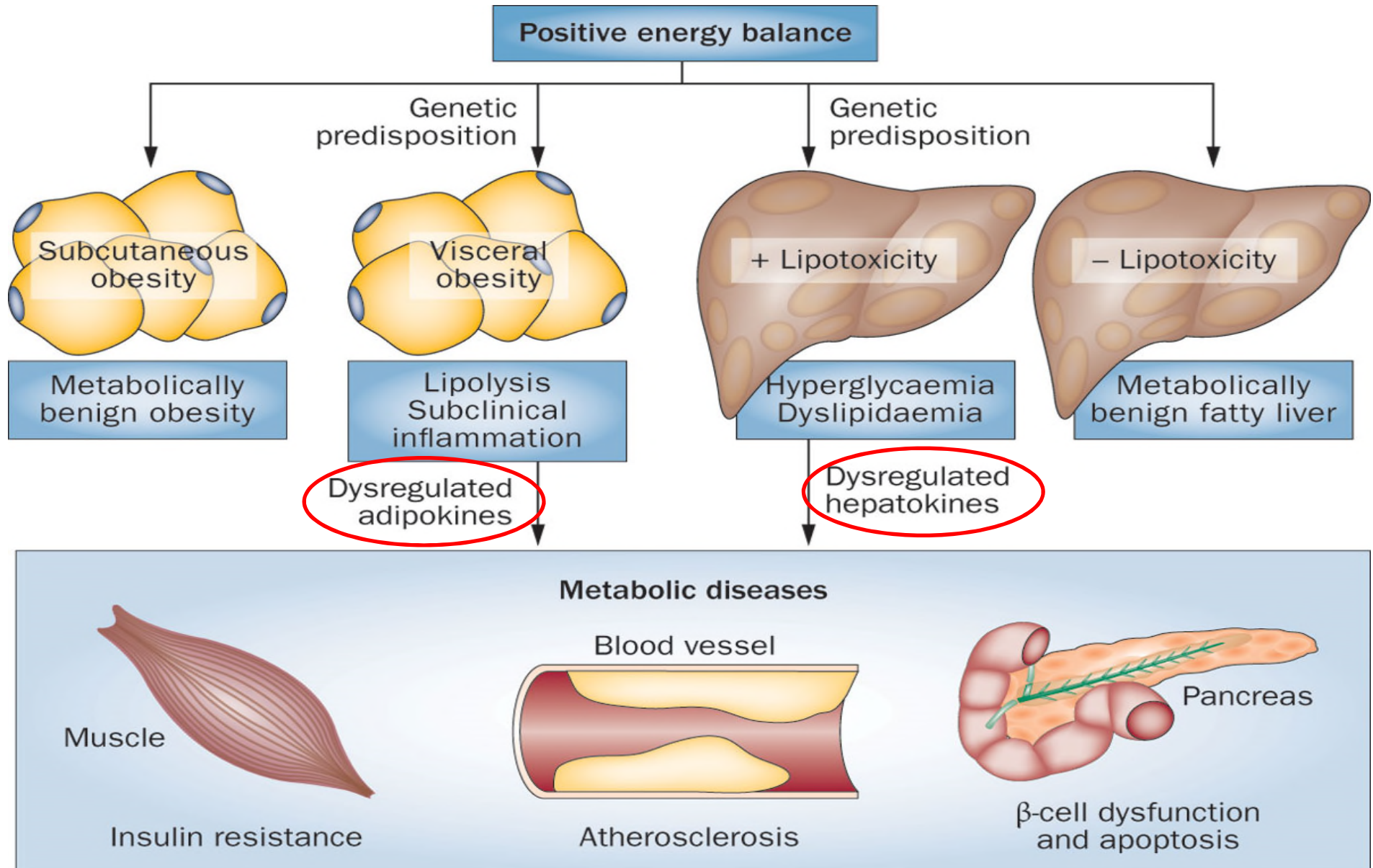
I am a board member of DaAn gene Co (stock number: 300635) and BGI Genomics (stock number: 300676) in China.

This presentation is not related to any business activities with these two companies

Adipokines and hepatokines in controlling multi-organ crosstalk, metabolism and cardiovascular homeostasis



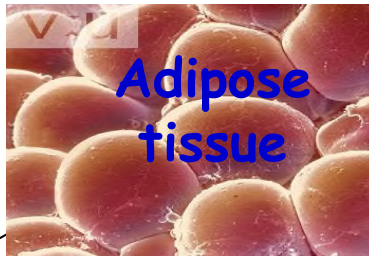
Dysregulated adipokines / hepatokines are key players in obesity-related cardiometabolic diseases



Adipokines/hepatokines identified and characterized in our laboratory

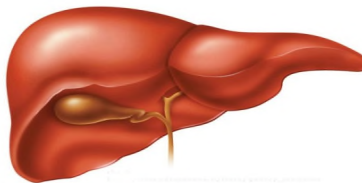
A-FABP

(Xu A, et al, *Clin Chem*, 2006)
(Xu & Tso et al, *Circulation*, 2007)
(Tso & Xu et al, *Diabetes Care*, 2007)
(Yeung D et al, *ATVB*, 2007)
Yeung D et al, *Euro Heart J*, 2008)
Hui X, *JBC*, 2010, *Neurology*, 2011)
Hoo R, *J Hepatology*, 2012,
Lin Z, *Circulation*, 2015
Shu L, *Nature Commun.*, 2017



Lipocalin-2

(Wang Y et al, *Clin Chem*, 2
(Law I, *Diabetes*, 2010)
JBC, 2012; Liu Y, *BJP*, 2012
Song R, *Circulation Research*, 2014
J Hepatology, 2016; *Circulation*, 2016



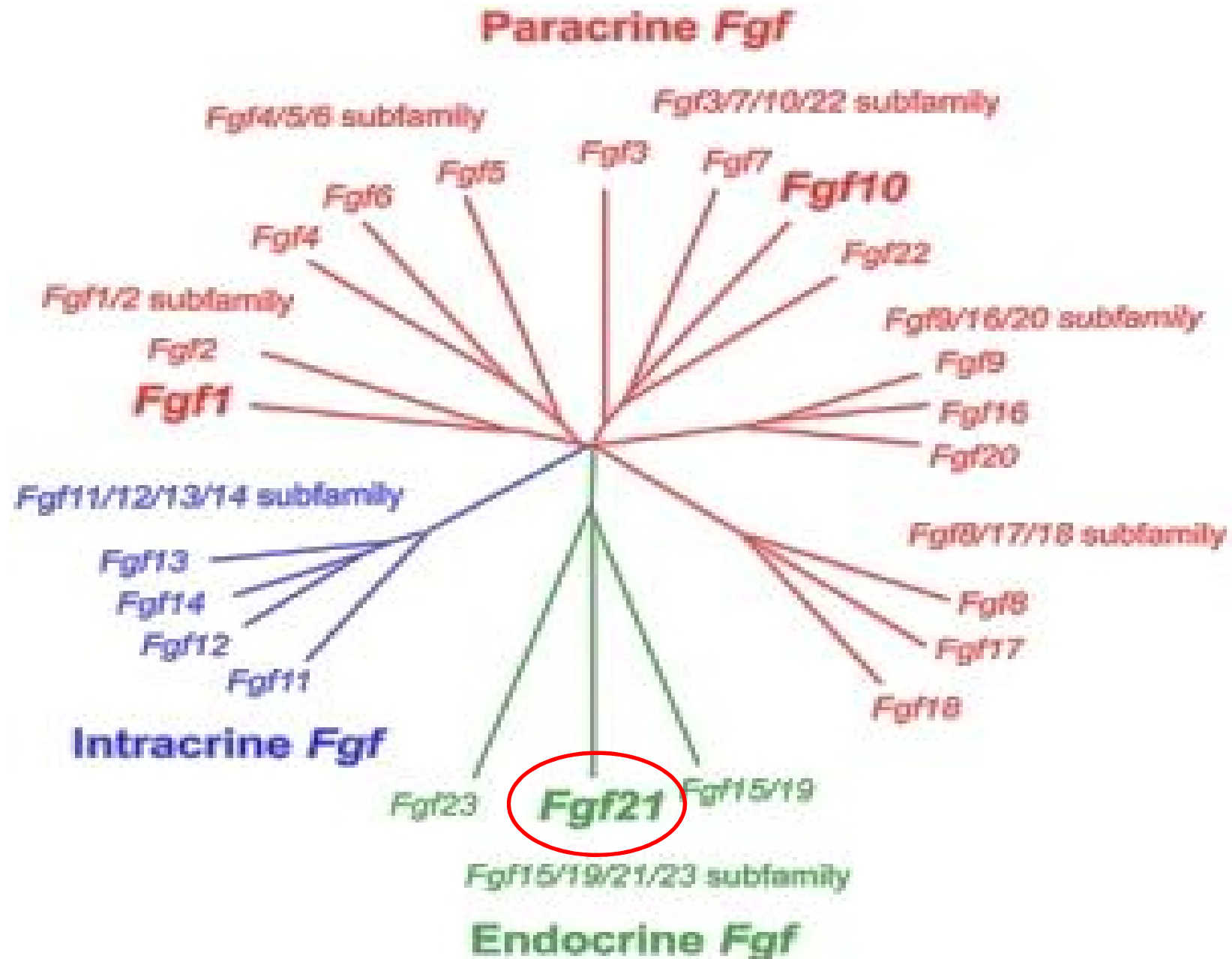
Adiponectin

(Xu A et al, *J. Clin. Invest*, 2003,
Wang et al, *JBC* 2002, 2004, 2005, 2006
Cancer Res, 2006, Chow WS et al, *Hypertension*,
2006; Cheng K et al, *Diabetes*, 2007, Hoo R, et al.
ATVB, 2007, Liu M, *PNAS*, 2008, *Hepatology*, 2008,
Cell Metabolism, 2009, 2011, 2014, 2015 *Diabetes*,
2009, 2010, 2011, 2012, 2011, *PNAS*, 2012,
Circulation, 2013, 2014

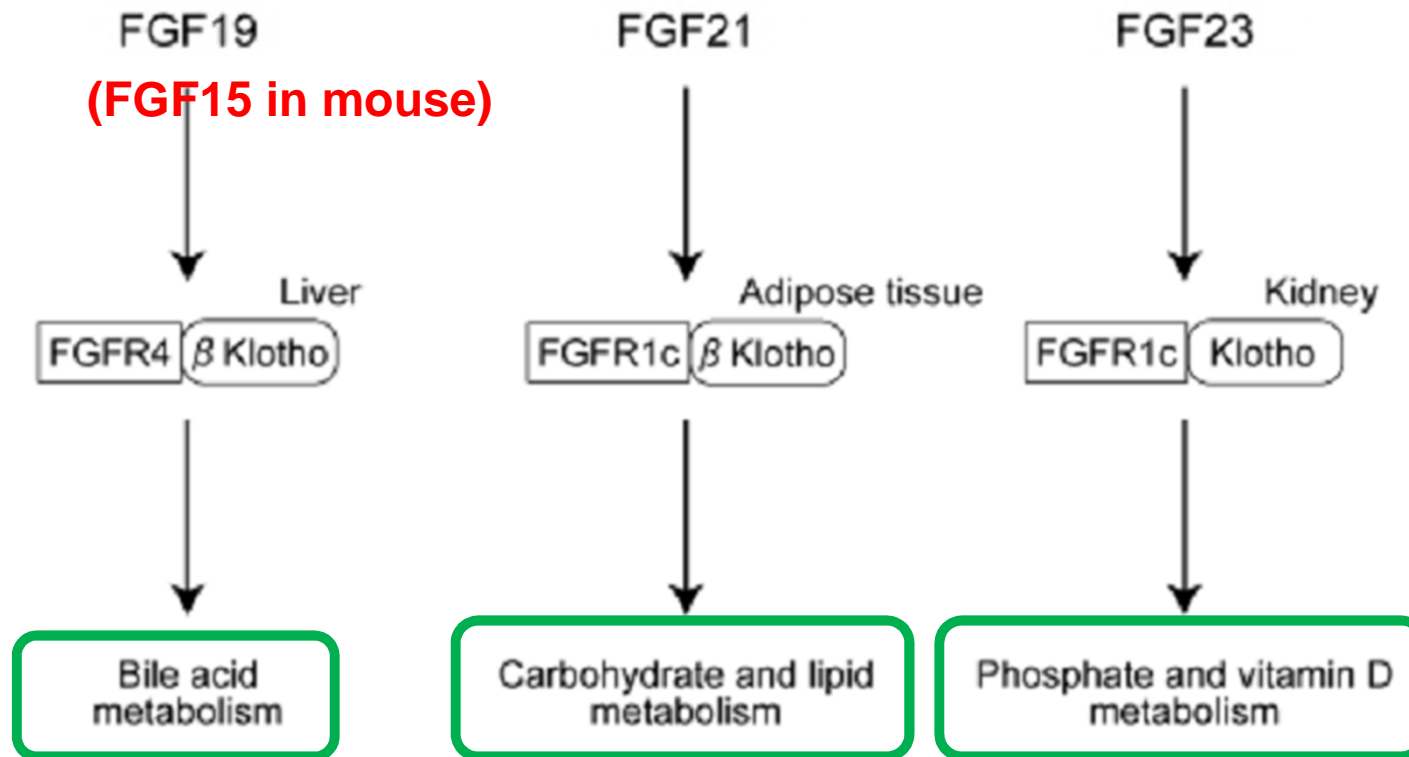
FGF21

Zhang X, *Diabetes*, 2008; *Diabetes*, 2010;
Chen C; *Diabetes Care*, 2011; Yu H, *Clin. Chem.* 2011; Chen W, *JBC*, 2011; Ge X, *JBC*, 2011; Xiang Y, *JECM*, 2011 ; Li H, *Diabetes*, 2012; *J Hepatology*, 2012;
Ong L, *JCEM*, 2012; Lin ZF, *Cell Metabolism*, 2013;
Ye D, *Hepatology*, 2014, Lin Z, *Circulation*, 2015, *Cell Metabolism*, 2017, 2018

FGF21: a member of the endocrine FGF subfamily

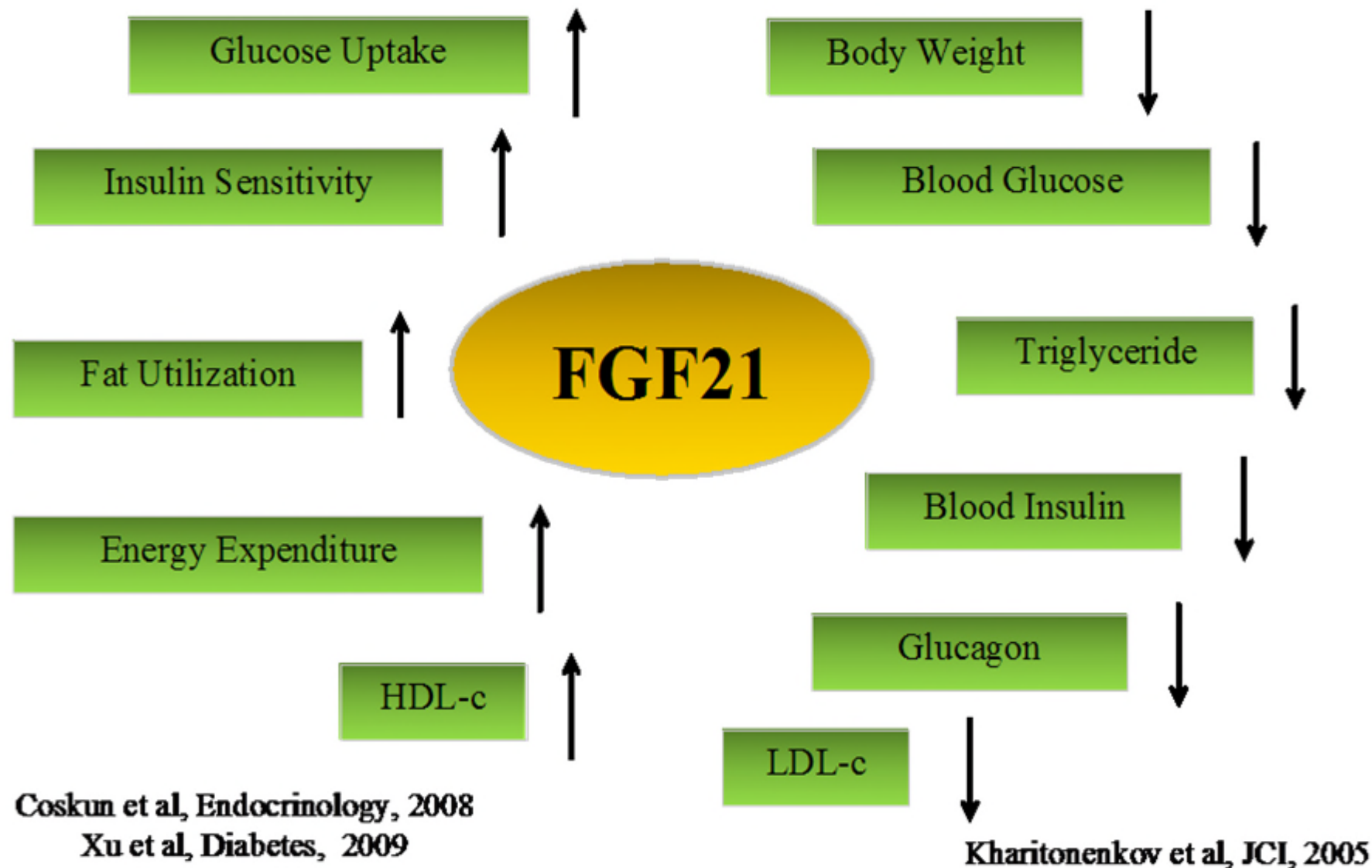


The endocrine members of the FGF family

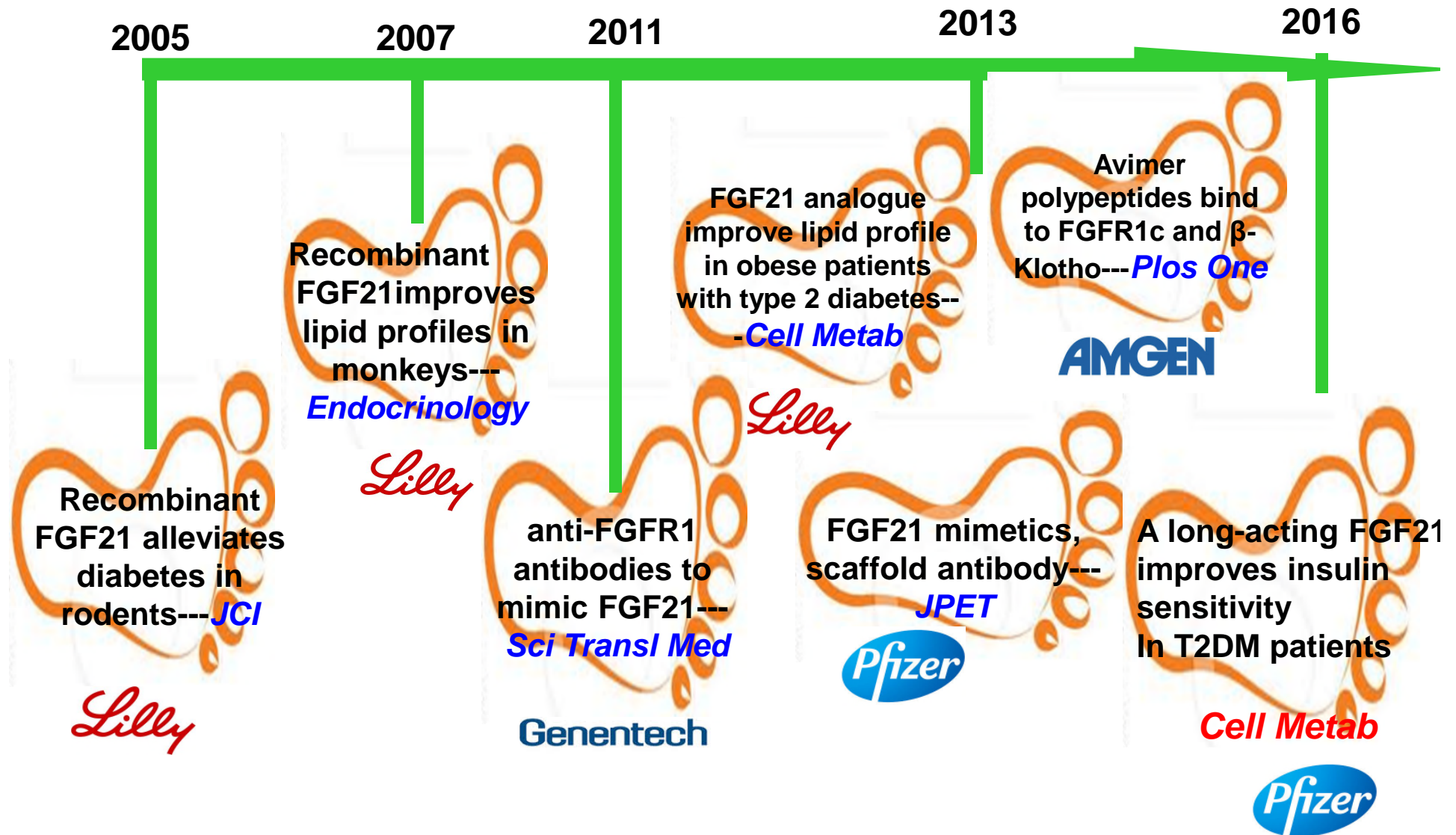


1. do not possess heparin-binding properties,
2. Require β -klotho for binding to the FGF receptors,
3. Exert their metabolic effects in an endocrine manner.

Multiple beneficial effects of recombinant FGF21 in animals

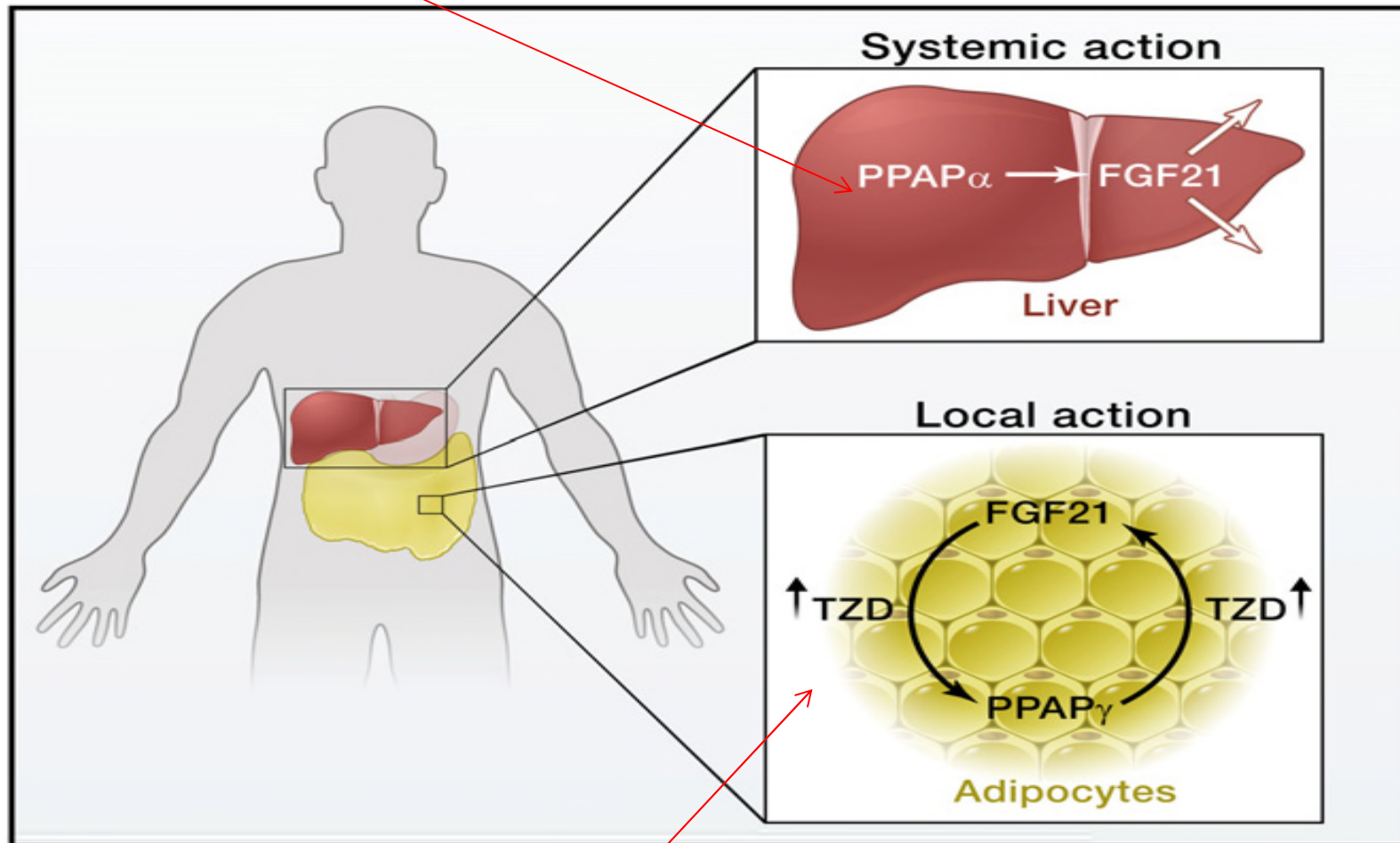


FGF21: an emerging drug for cardiometabolic syndrome



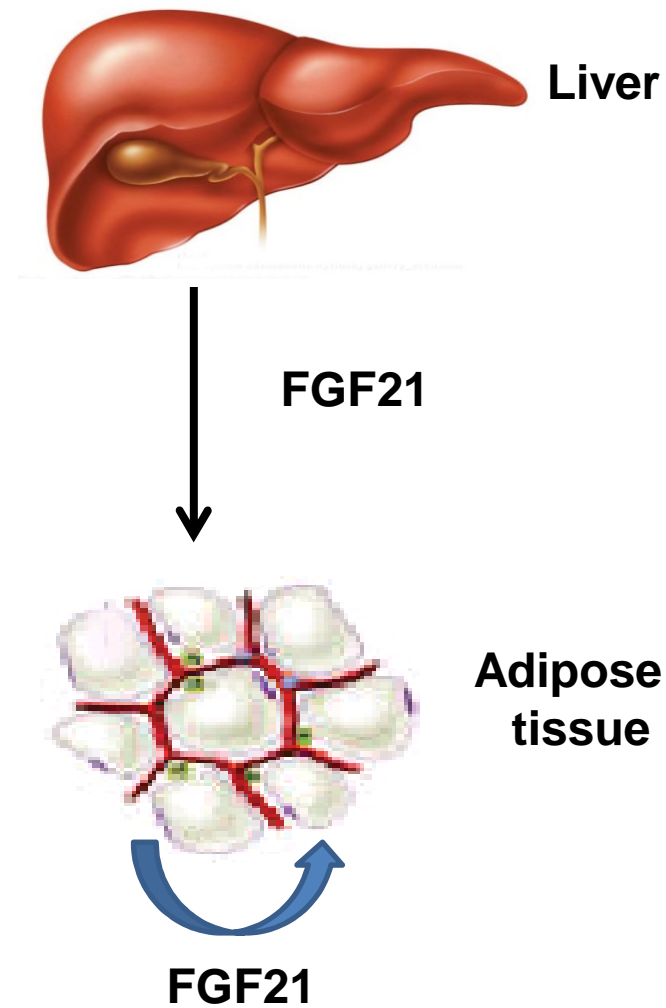
FGF21 is a dual downstream target of both PPAR α and PPAR γ

Fenofibrates (lipid-lowering drug)

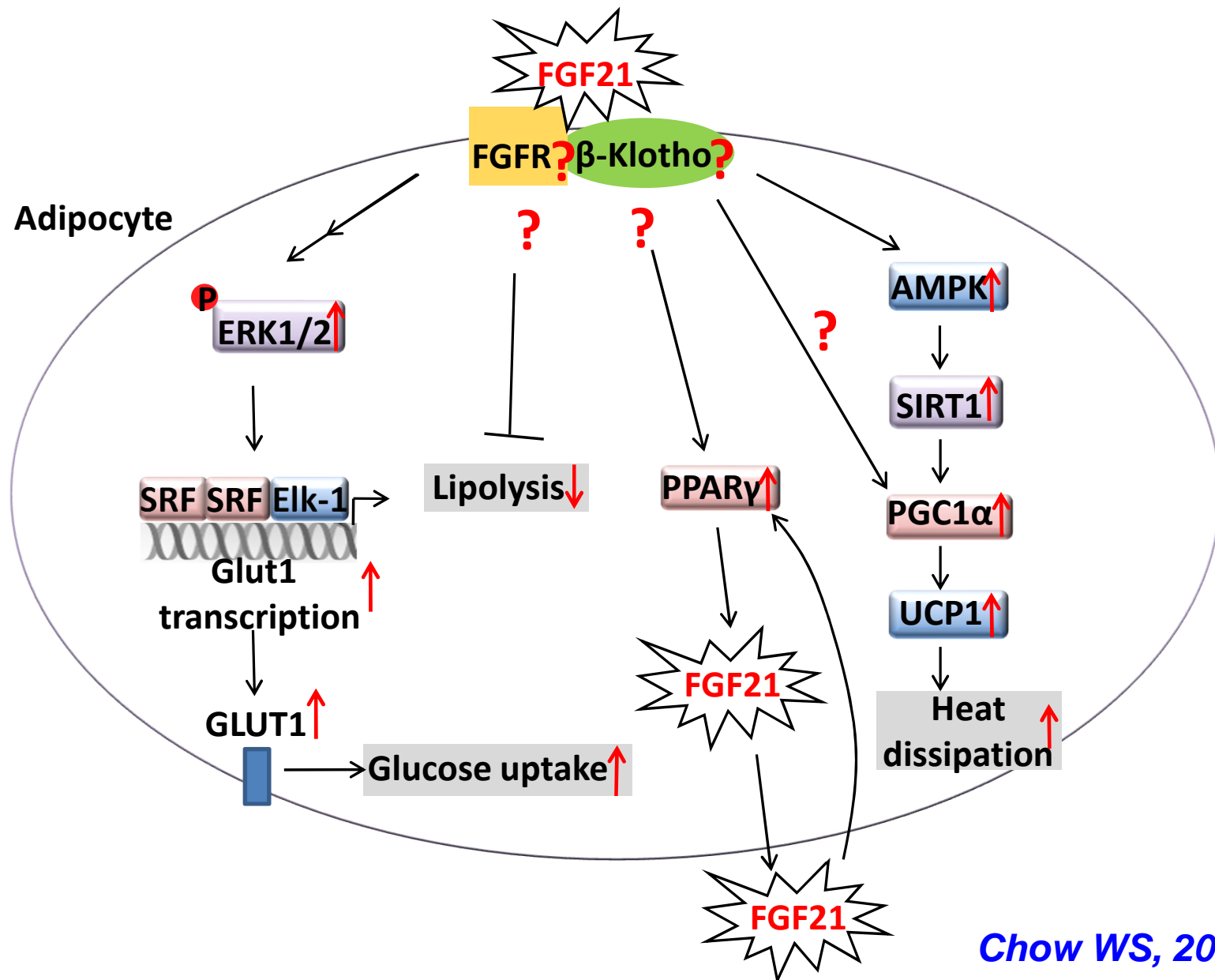


Thiazolidinediones (anti-diabetic drug)

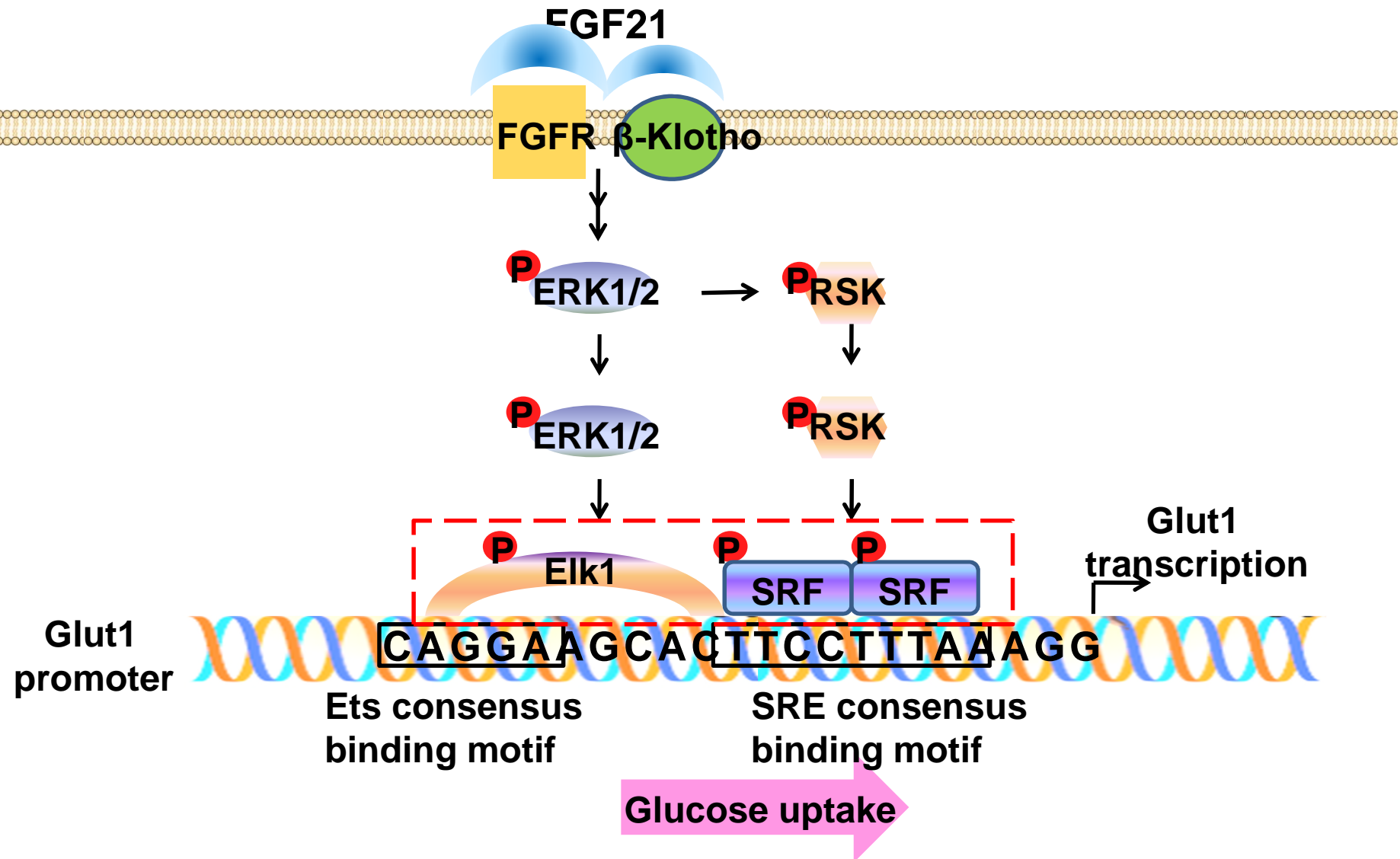
Adipose tissue as a major target of FGF21



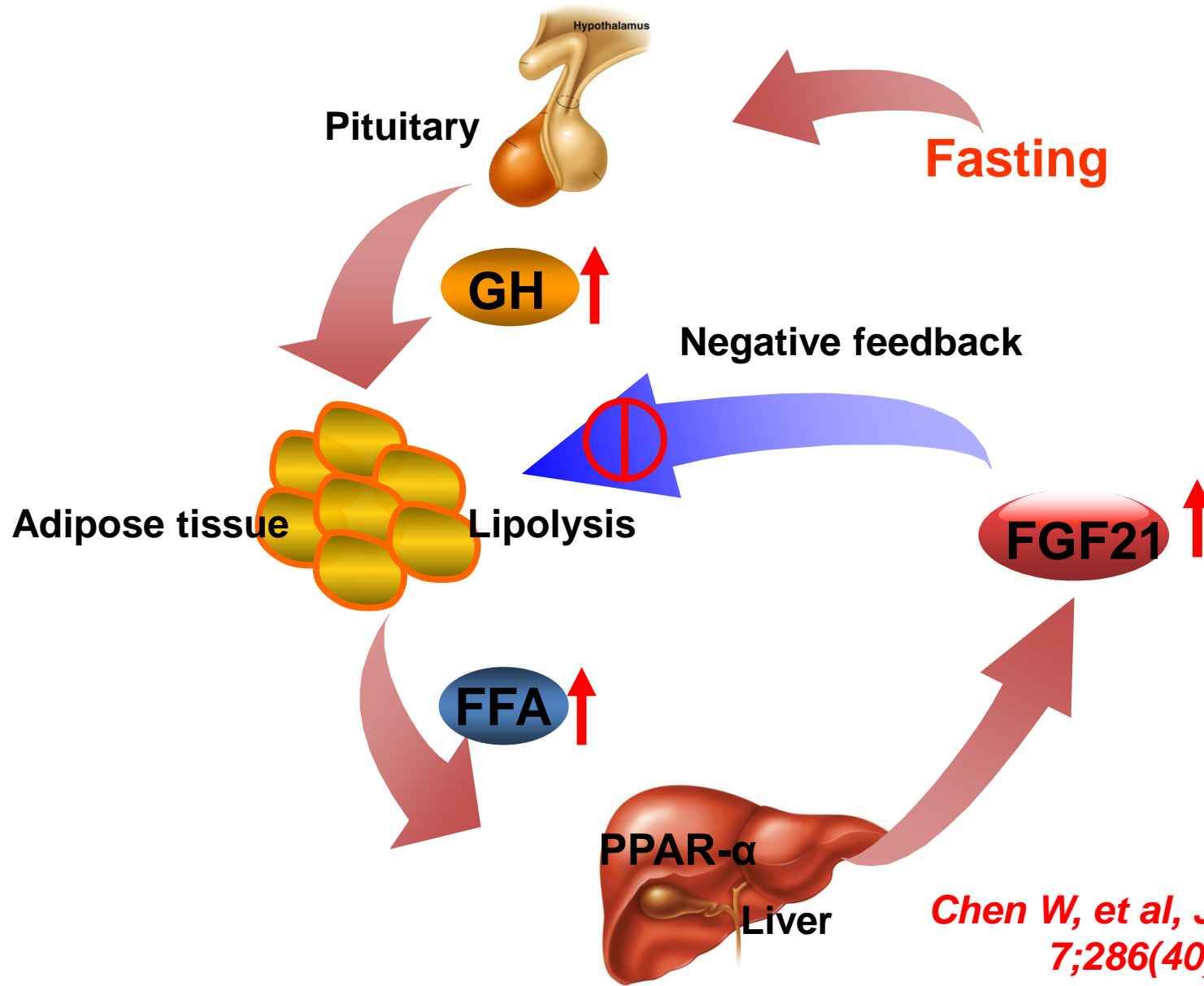
Multiple effects of FGF21 in adipocytes



FGF21 induces glucose uptake by inducing the expression of GLUT1 in adipocytes (*Ge X, J Biol. Chem. 2011, 286:34533-41*)



FGF21 fine-tunes growth hormone-induced lipolysis in adipocytes



*Chen W, et al, J Biol Chem. 2011
7;286(40):34559-66.*

Adipocytes play an obligatory role in mediating the metabolic actions of FGF21

1. The metabolic benefits of FGF21 are abrogated in mice with adipocyte-specific depletion of FGFR1 or β -klotho (*Ding X, Cell Metab. 2012; Adam A, Molecular metabolism, 2013*).

2. Lipodystrophic mice with little fat are resistant to metabolic actions of FGF21 (*Murielle M, PLoS One, 2013*)

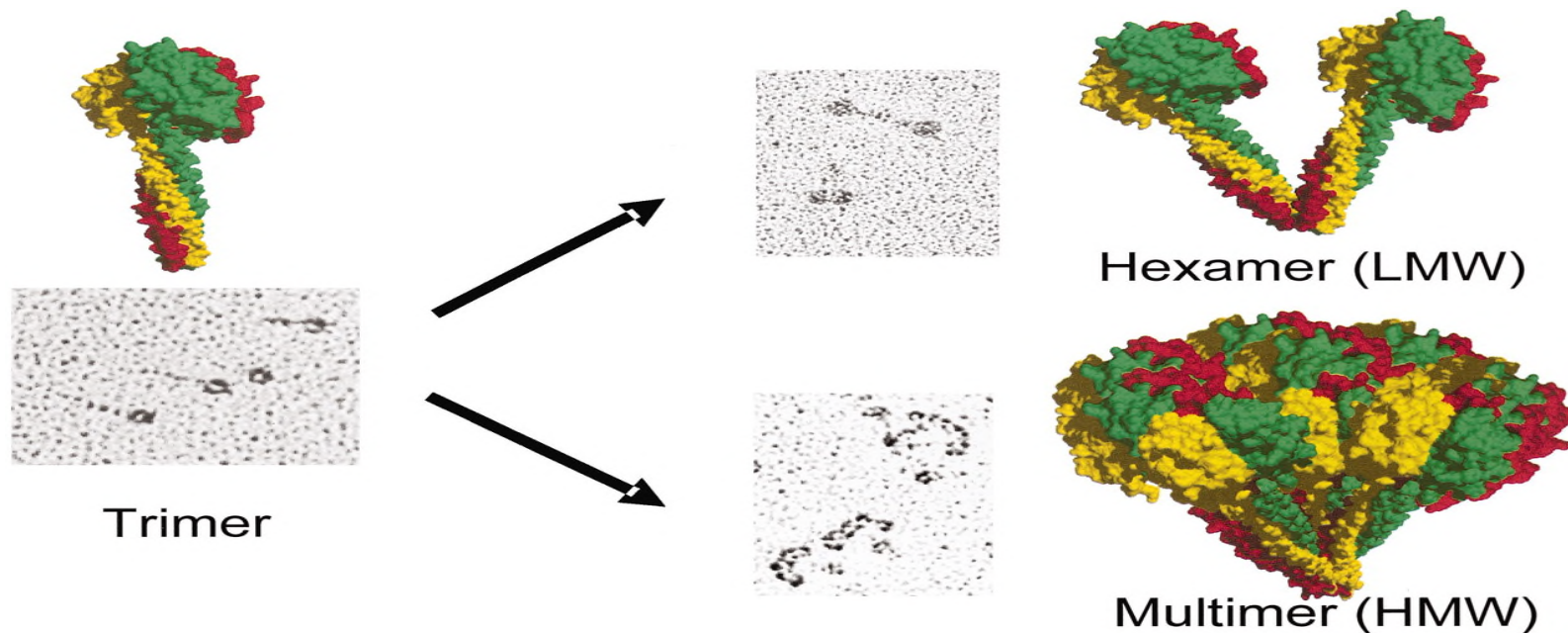
How does FGF21 exert its profound effects on systemic insulin sensitivity and glucose homeostasis via its actions in adipocytes??

Adiponectin as a downstream mediator of FGF21

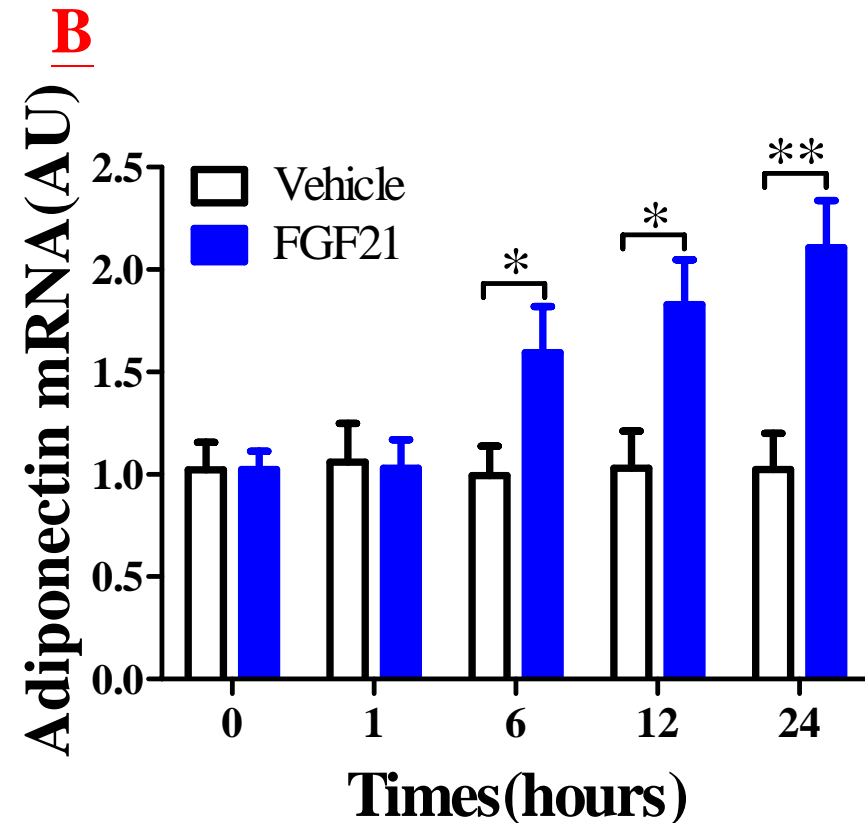
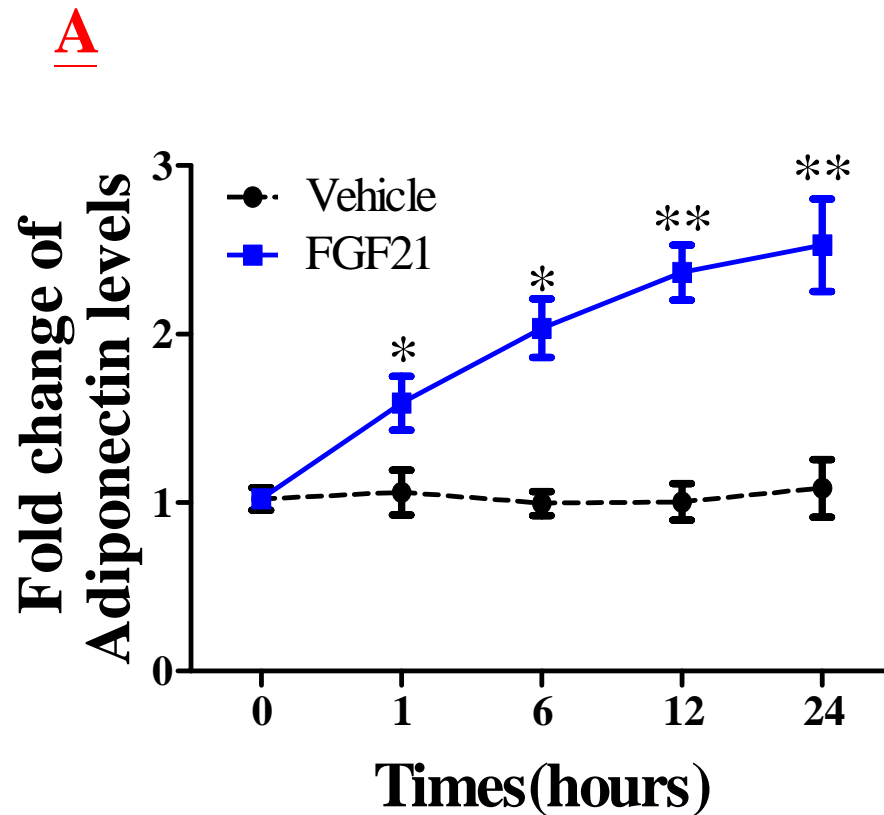


Lin Zhuofeng, Cell Metabolism, 2013; Circulation, 2015

Adiponectin: a major adipokine secreted from adipocytes with insulin-sensitizing, anti-inflammatory properties

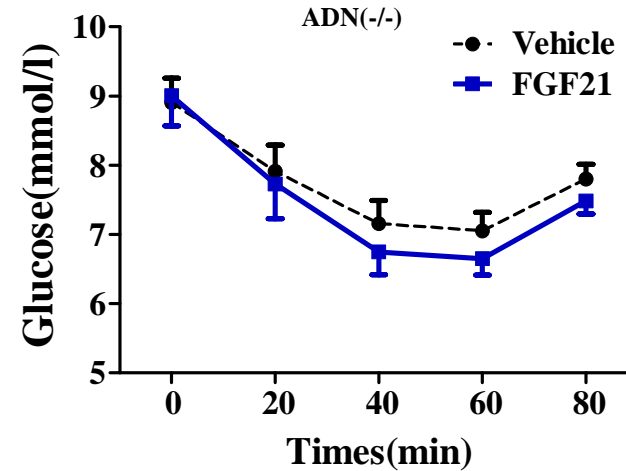
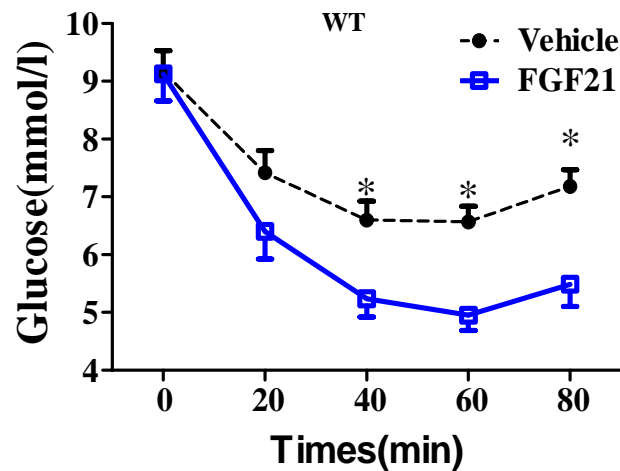
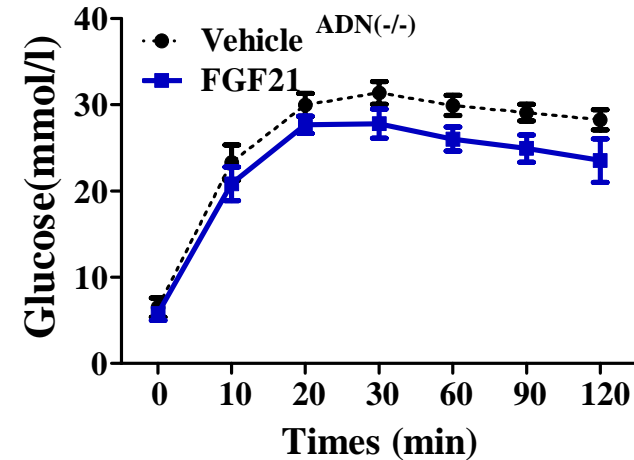
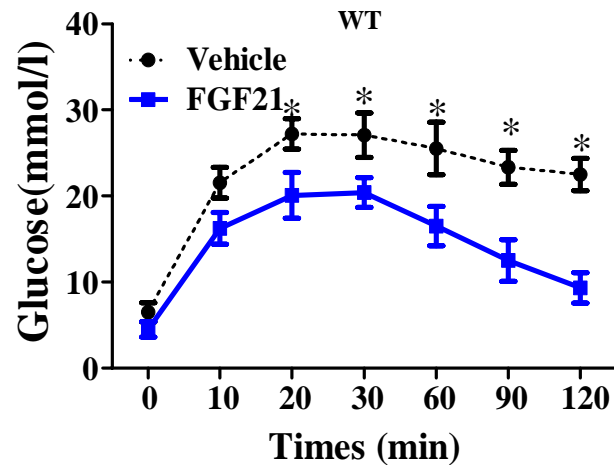


FGF21 induces both expression and secretion of adiponectin in mouse adipocytes

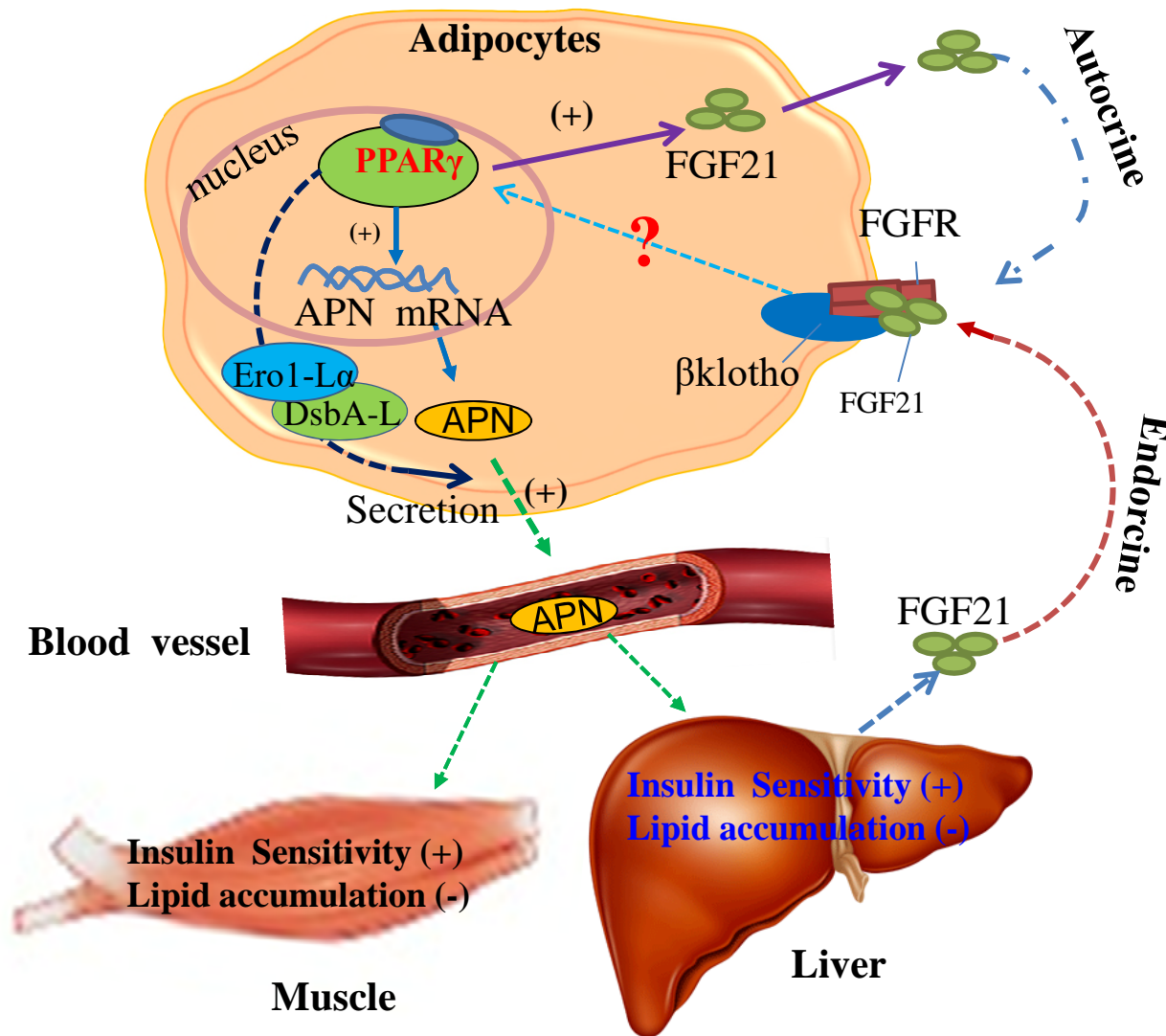


Lin ZF, Cell Metabolism, 2013: 7;17:779-89.

The beneficial Effects of FGF21 on glucose metabolism and insulin sensitivity are impaired in adiponectin KO mice



Adiponectin confers the metabolic actions of FGF21 in the liver and skeletal muscle



Lin ZF, Cell Metabolism, 2013: 7;17:779-89.

An FGF21-Adiponectin-Ceramide Axis Controls Energy Expenditure and Insulin Action in Mice

William L. Holland,¹ Andrew C. Adams,³ Joseph T. Brozinick,³ Hai H. Bui,³ Yukiko Miyauchi,¹ Christine M. Kusminski,¹ Steven M. Bauer,³ Mark Wade,³ Esha Singhal,¹ Christine C. Cheng,³ Katherine Volk,³ Ming-Shang Kuo,³ Ruth Gordillo,¹ Alexei Kharitonov,^{3,*} and Philipp E. Scherer^{1,2,*}

¹Touchstone Diabetes Center, Department of Internal Medicine

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The University of Texas Southwestern Medical Center, Dallas, TX 75390-8549, USA

³Lilly Research Laboratories, Division of Eli Lilly and Company, Indianapolis, Indiana, USA

*Correspondence: a.kharch@lilly.com (A.K.), philipp.scherer@utsouthwestern.edu (P.E.S.)

<http://dx.doi.org/10.1016/j.cmet.2013.03.019>

NEWS & VIEWS

METABOLISM

Adiponectin—a mediator of specific metabolic actions of FGF21

Regina Goetz

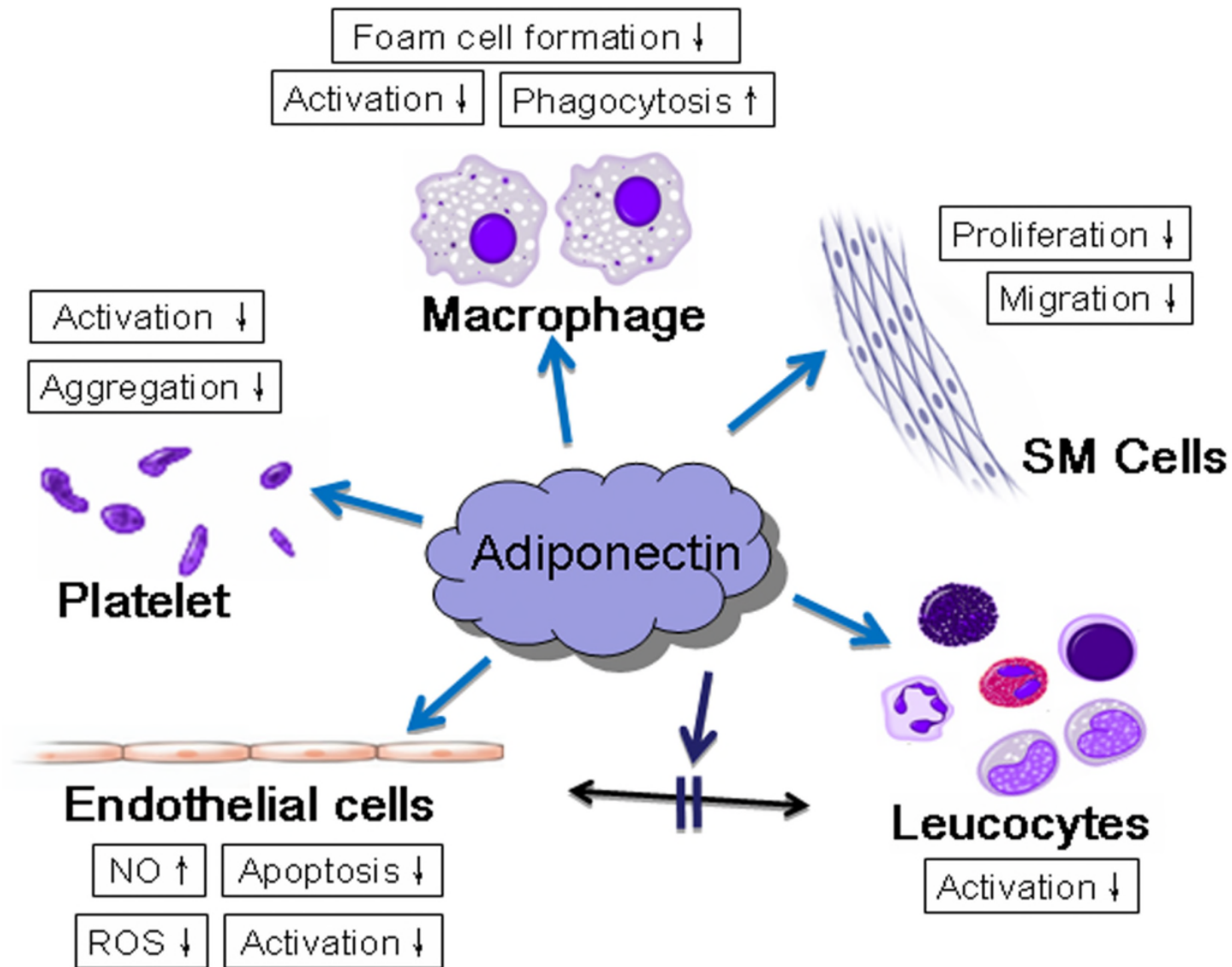
Adiponectin and fibroblast growth factor 21 (FGF21) regulate glucose and lipid metabolism in similar ways and are both critically involved in the antidiabetic effects of thiazolidinedione drugs. Studies in mice now shed light on how adiponectin and FGF21 are functionally linked, which has intriguing implications for the therapeutic potential of these hormones.

Goetz, R. *Nat. Rev. Endocrinol.* advance online publication 16 July 2013; doi:10.1038/nrendo.2013.146

that is, adiponectin does not seem to regulate FGF21 secretion, at least not under physiological conditions.² This conclusion is suggested by the finding that the knock-out of adiponectin has no effect on serum FGF21 concentrations in mice in the fed or the fasted state.²

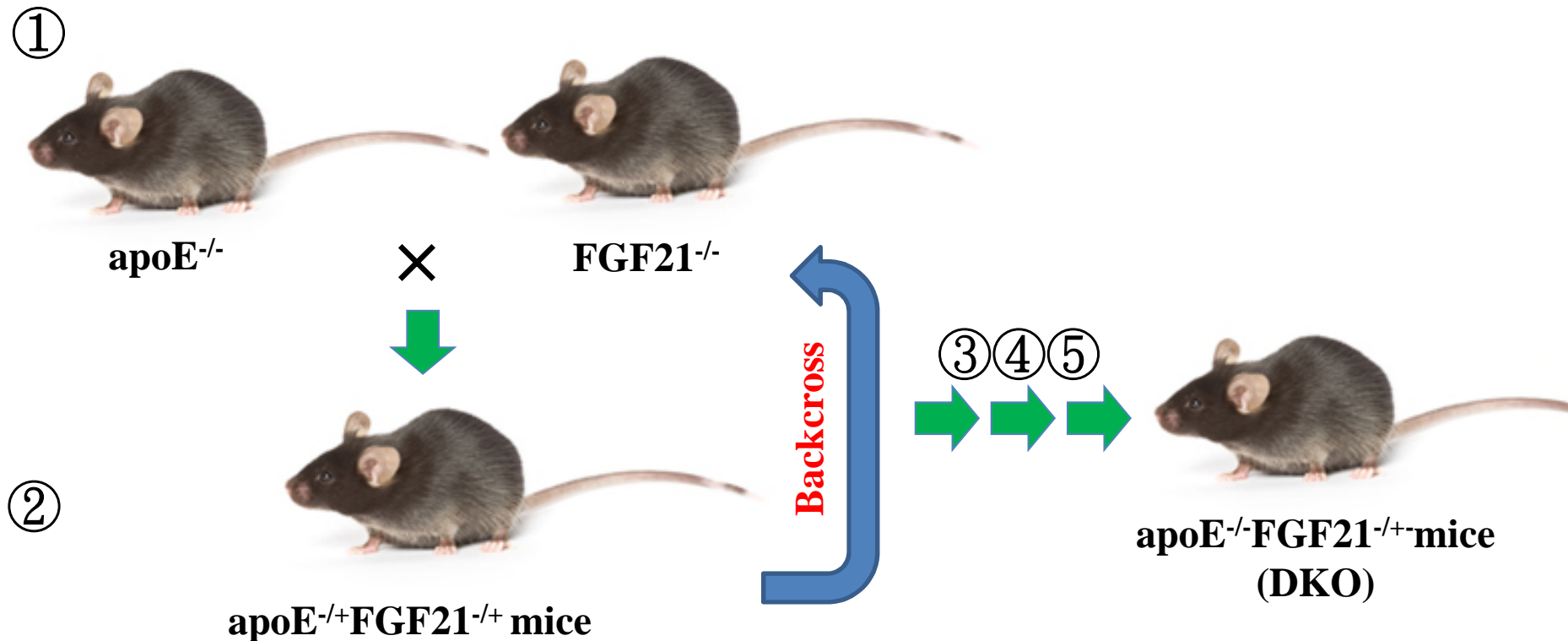
FGF21 positively regulates adiponectin secretion; therefore, the next question to answer was whether adiponectin mediates the metabolic effects of FGF21 in the fed state. A related question that is intriguing from a drug discovery point of view, but was not adequately addressed in the

Adiponectin exerts its vasculoprotective activities through multiple mechanisms



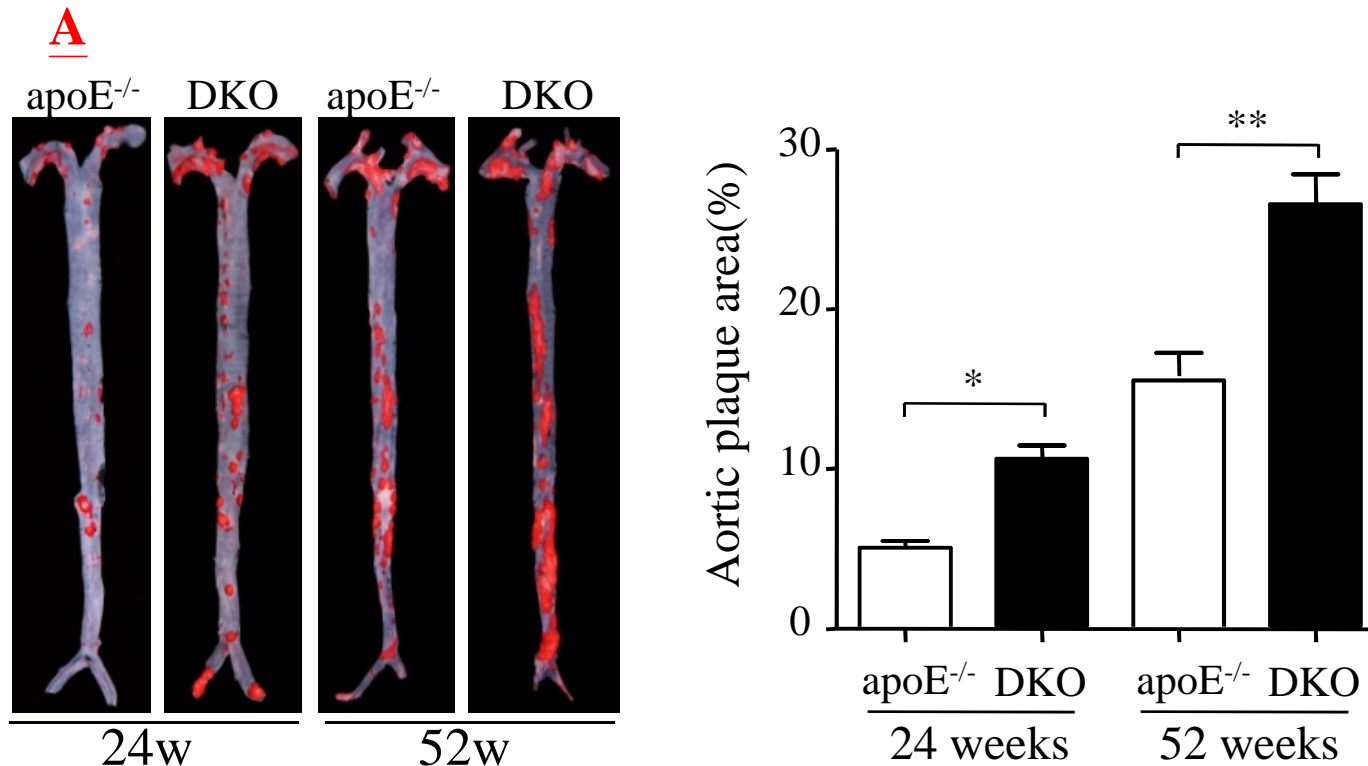
Zhu W, Clinical Science, 2008; Xu A & Vanhoutte PM, AJP, 2012

Does FGF21 play a protective role against atherosclerosis?



**apoE and FGF21 double
knockout mice(DKO)**

ApoE^{-/-} mice with FGF21 deficiency exhibit exacerbated atherosclerosis

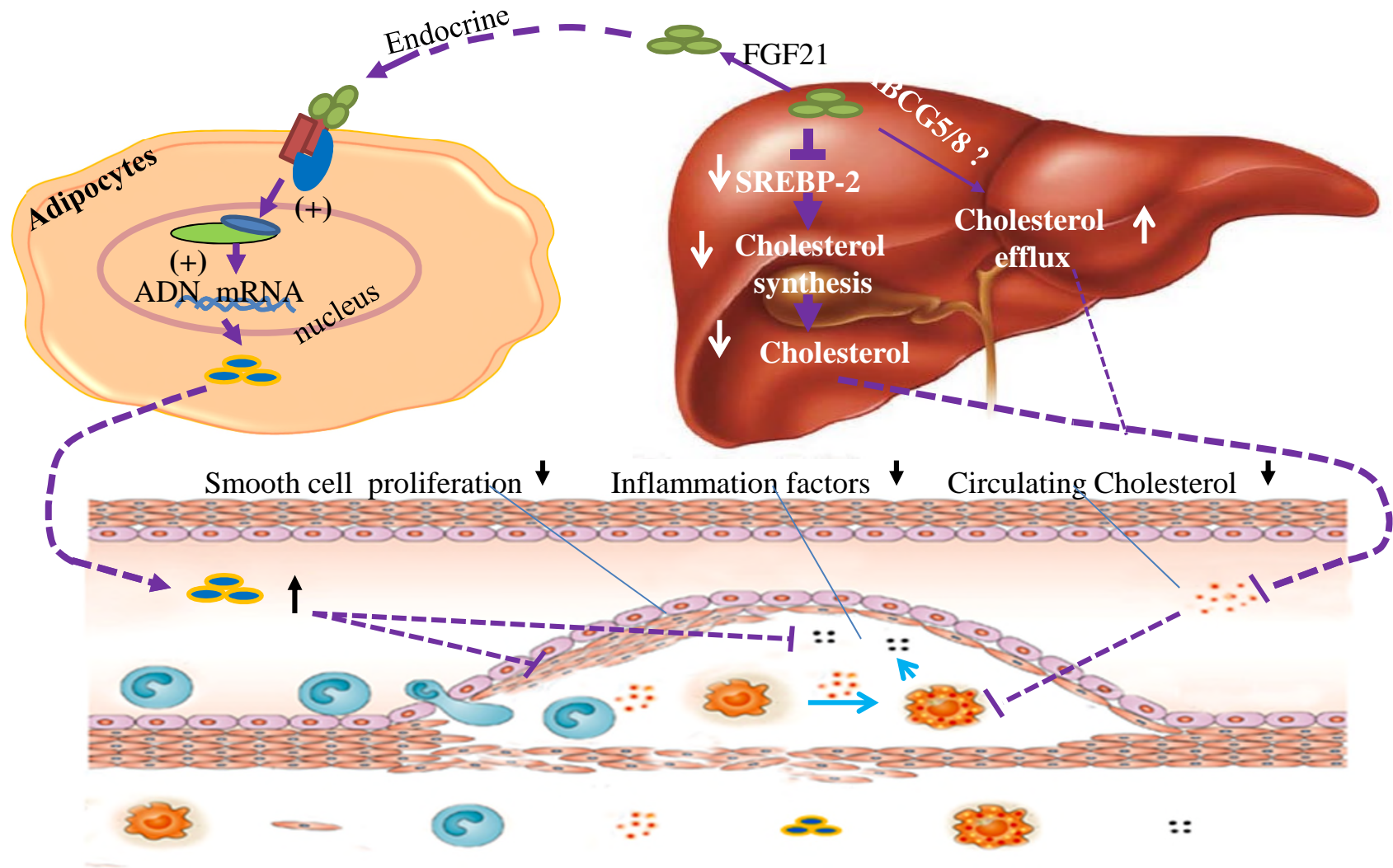


En face staining of entire aortas of 24- and 52-week-old mice with Oil red O.

*, $p < 0.05$; **, $p < 0.01$.

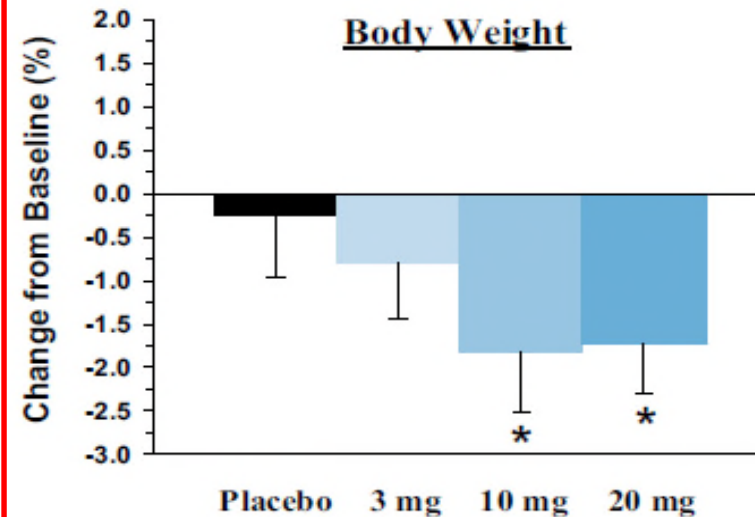
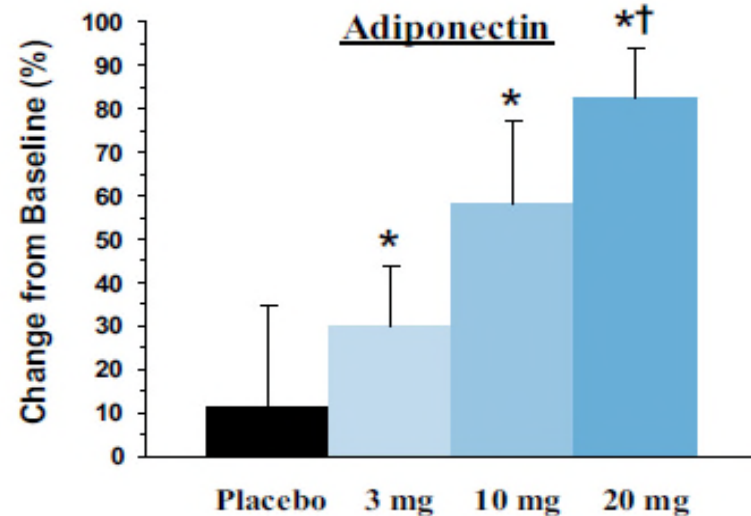
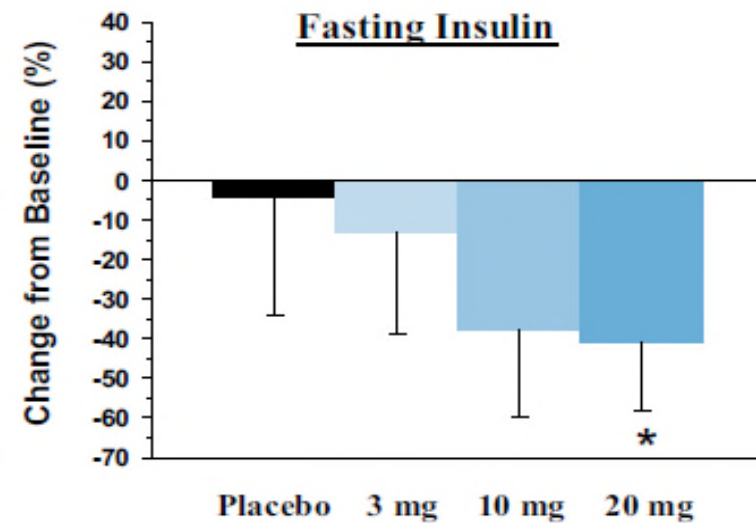
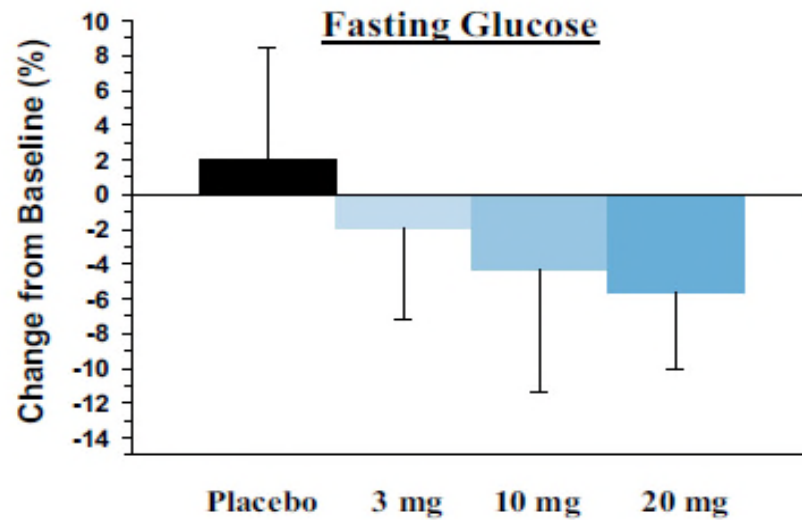
Lin Z, Circulation, 2015

FGF21 suppresses atherosclerosis via induction of adiponectin (ADN) and suppression of Srebp-2

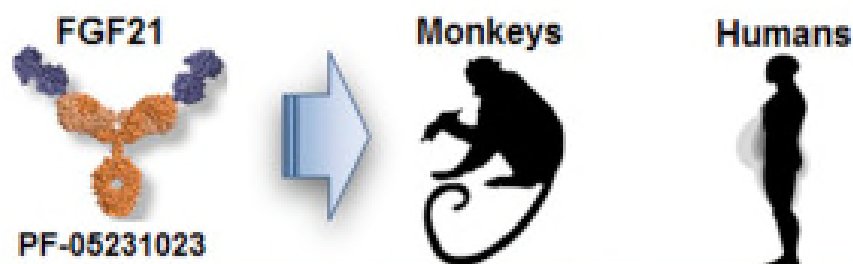


Lin Z, Circulation , 2015

The FGF21 analog LY2405319 markedly increases plasma adiponectin concentrations in T2D patients

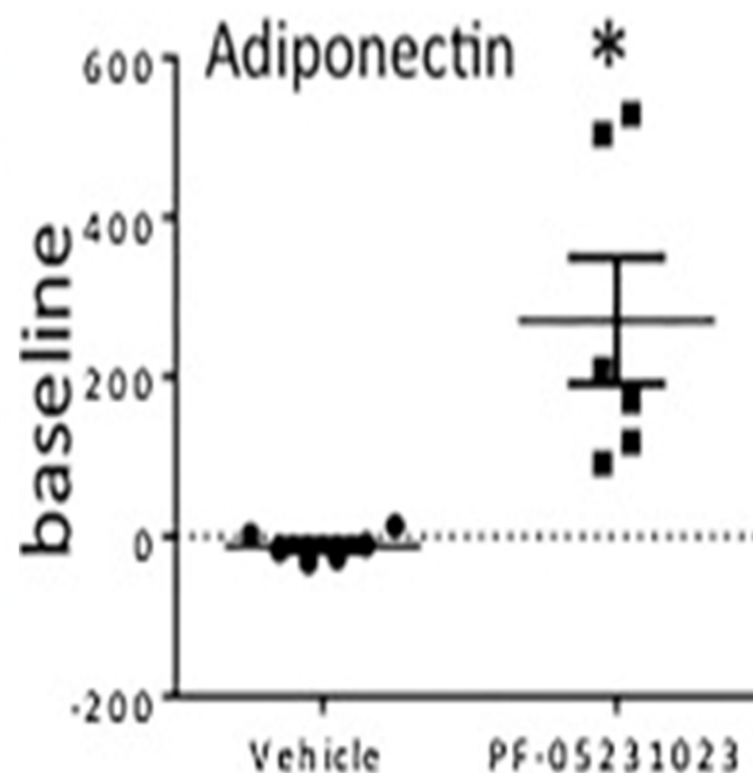


A Long-Acting FGF21 Molecule, PF-05231023, Decreases Body Weight and Improves Lipid Profile in Non-human Primates and Type 2 Diabetic Subjects, Cell Metab. 2016 Mar 8;23(3):427-40



Recent clinical trial by Pfizer

Metabolic Endpoints		
Glucose/Insulin	↔	↔
Body weight	↓	↓
Food intake	↓	?
Browning of WAT	↔	?
Triglycerides	↓	↓
Adiponectin	↑	↑
IGF1	?	↑
Bone Biomarkers		
Mineral content	↔	?
Resorption (CTX)	?	↑
Formation (BSAP, Osteocalcin, P1NP)	?	↓

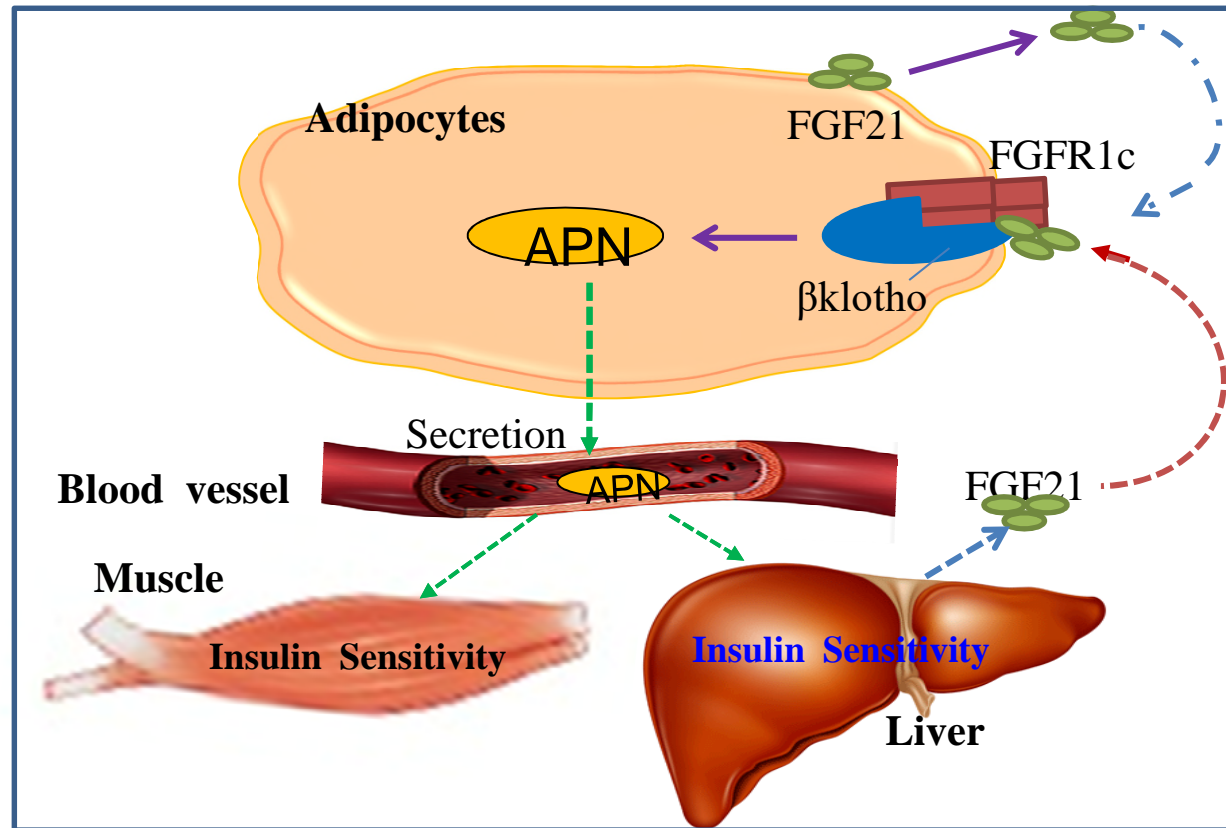


The FGF21-adiponectin axis: a promising therapy against obesity-related cardio-metabolic diseases

FGF21



ADN



↓ Insulin resistance

↓ Glucose

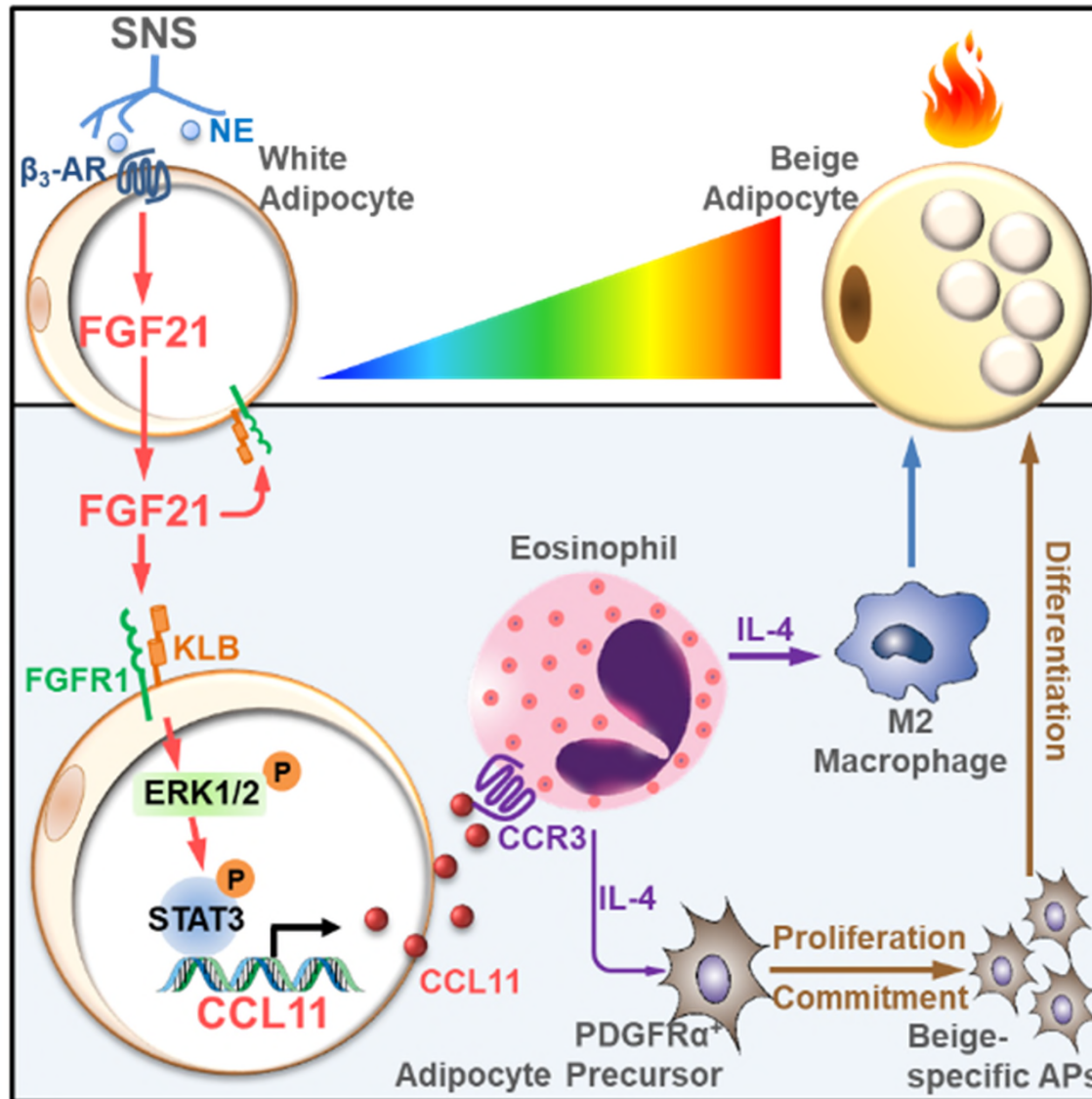
↓ Hypertriglyceridemia

↓ LDL-cholesterol

↑ HDL-cholesterol

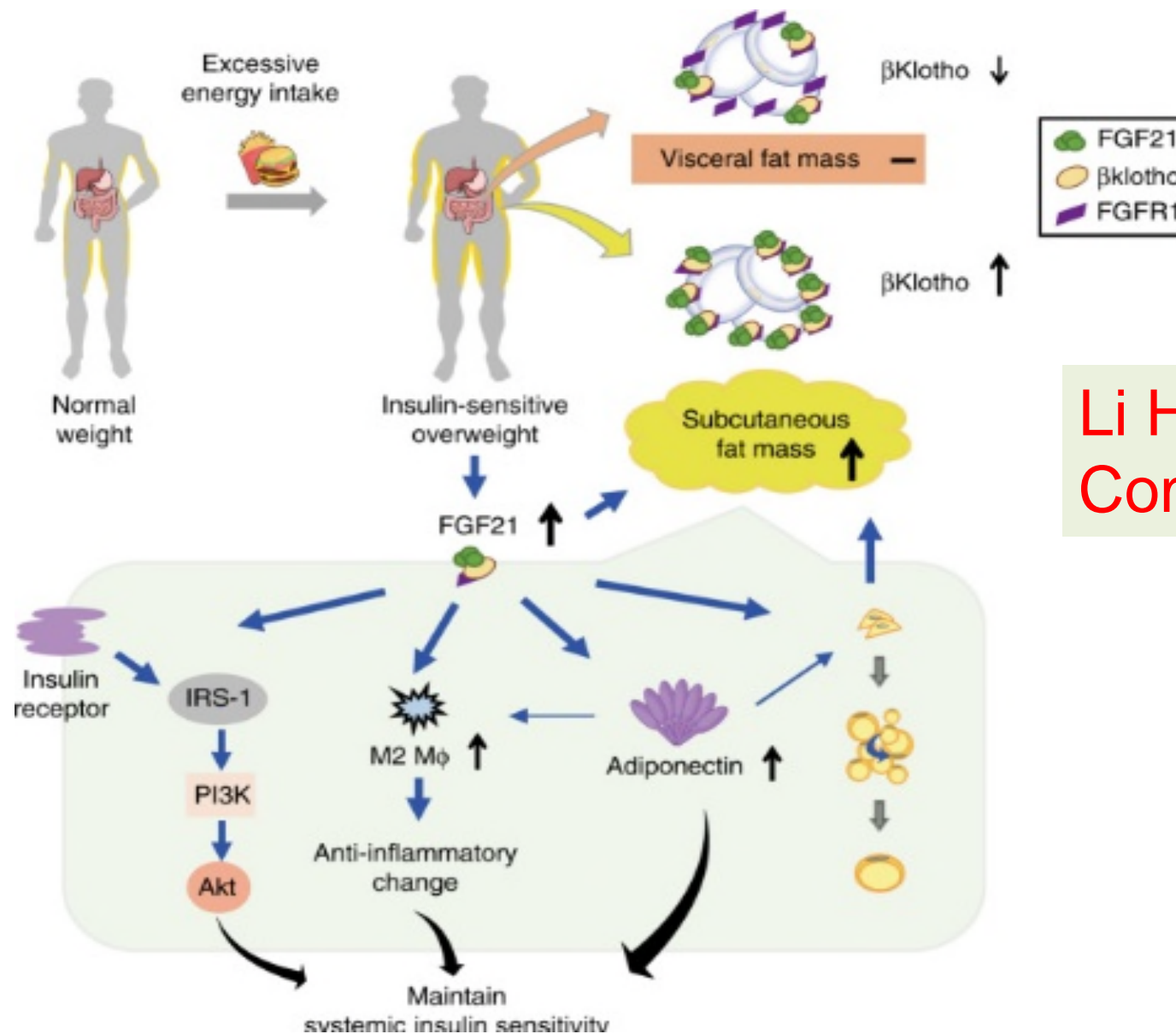
↓ Atherosclerosis

FGF21 acts in an autocrine manner to promote beiging of white adipose tissue



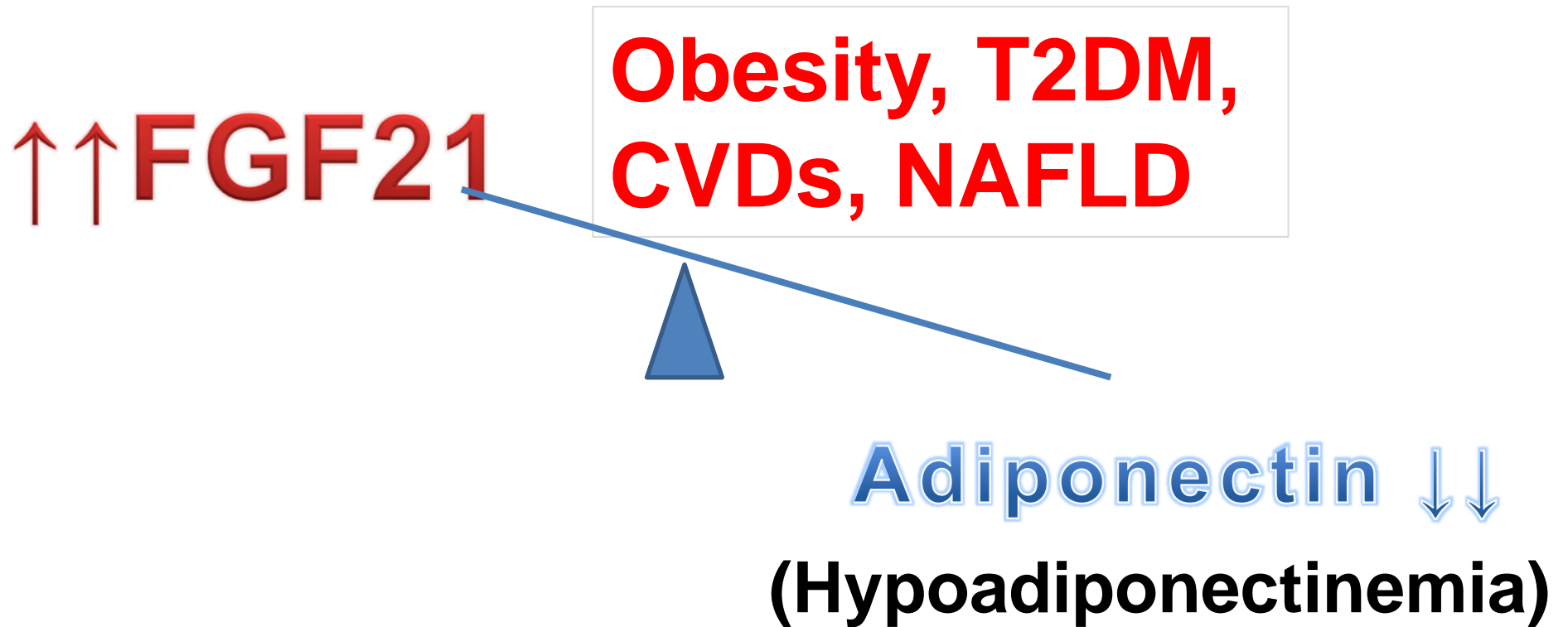
Huang & Zhong et al, Cell Metab. 2017 26(3):493-508

FGF21 increases insulin sensitivity through specific expansion of subcutaneous adipose tissues

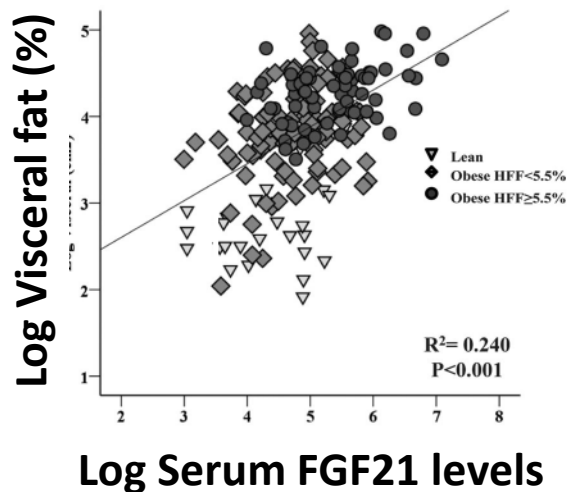
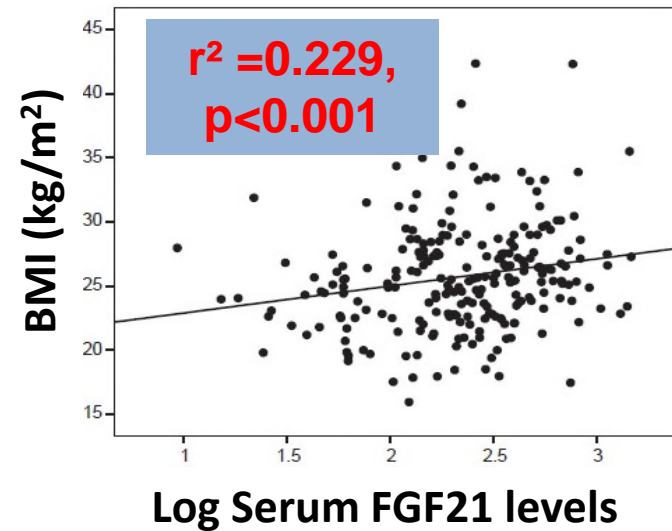
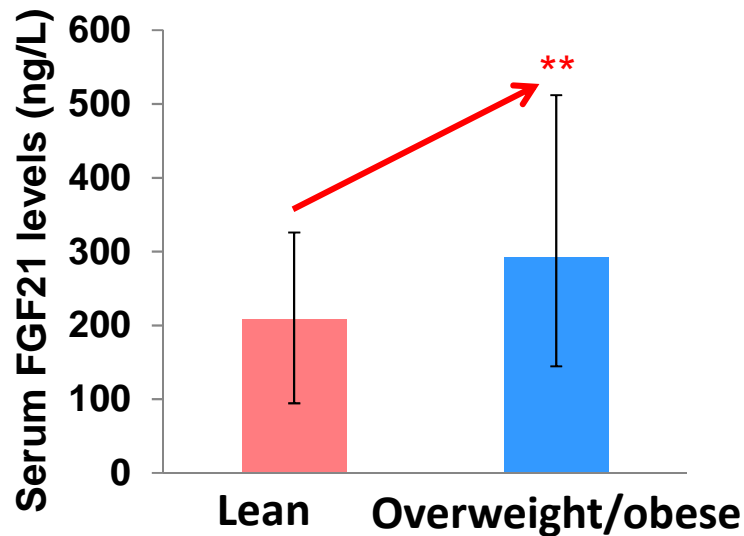


Li Huating, Nat. Commun. 2018

Discordant changes of FGF21 and adiponectin in obesity-related syndrome



Serum FGF21 levels are significantly elevated in overweight/obese subjects

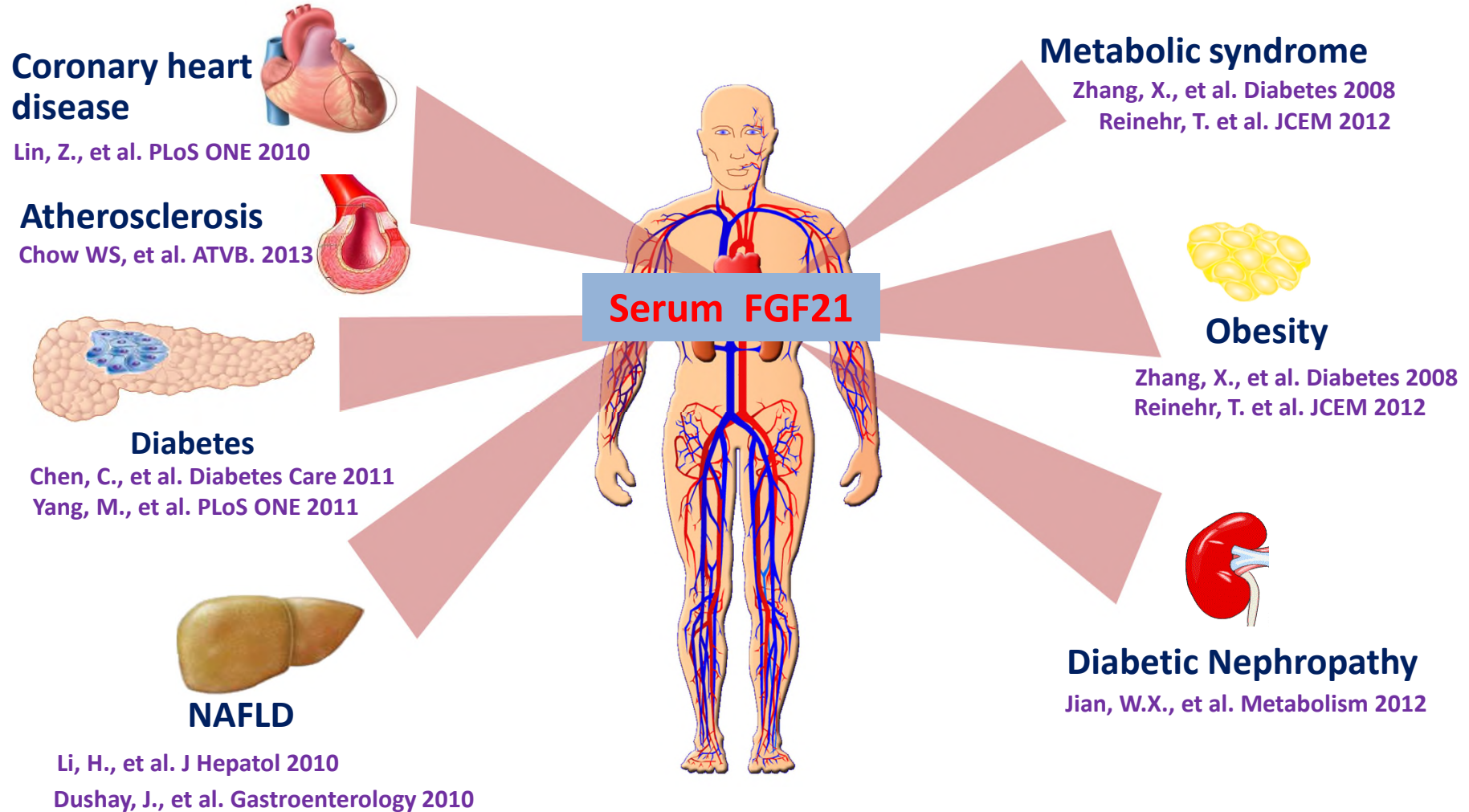


N=217

Zhang, X., et al. Diabetes 2008

Giannini C et al., J Clin Endocrinol Metab. 2013

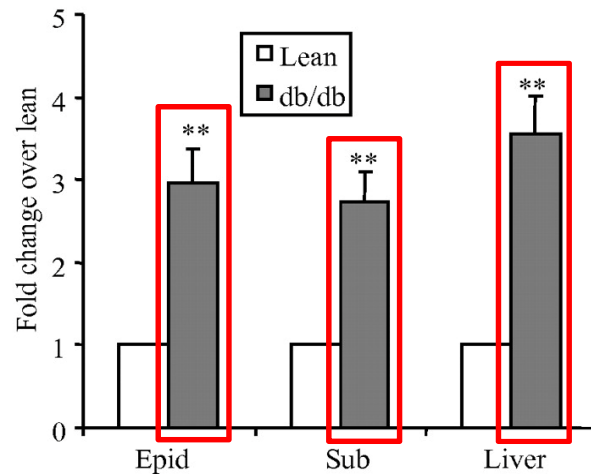
Elevated circulating FGF21 is associated with a cluster of obesity-related complications



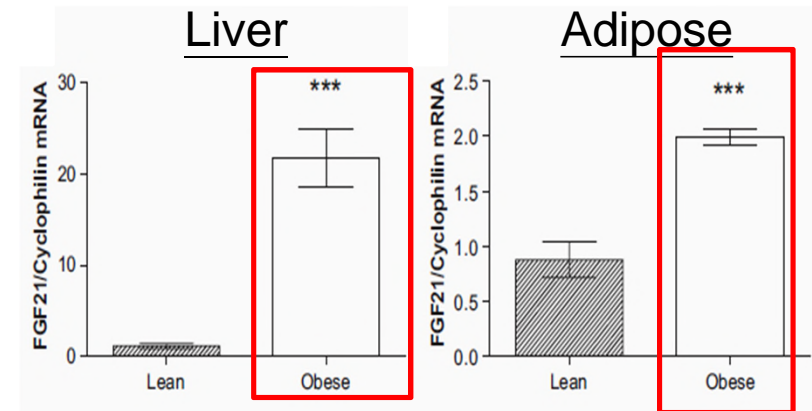
Elevated FGF21 production in obese animals

Tissue

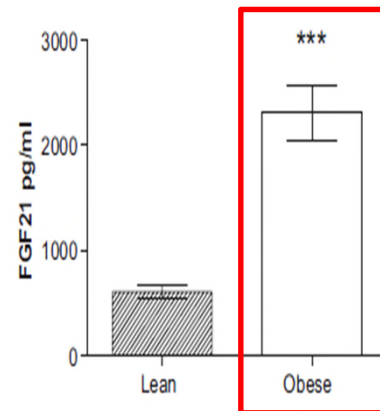
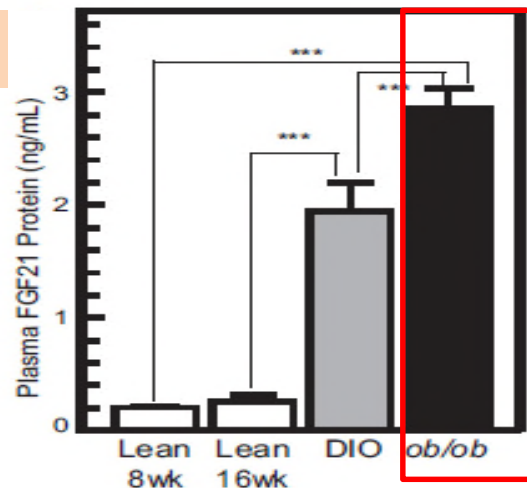
Genetic-induced obesity



Diet-induced obesity

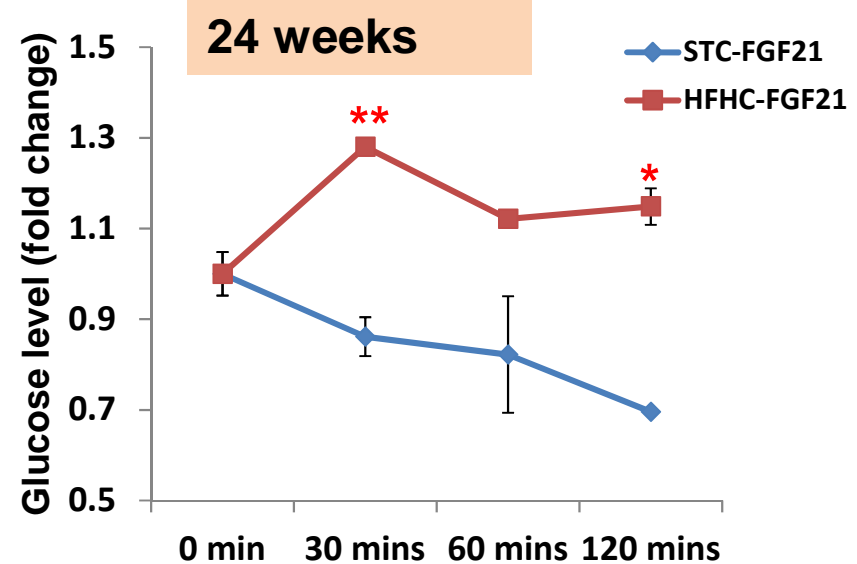
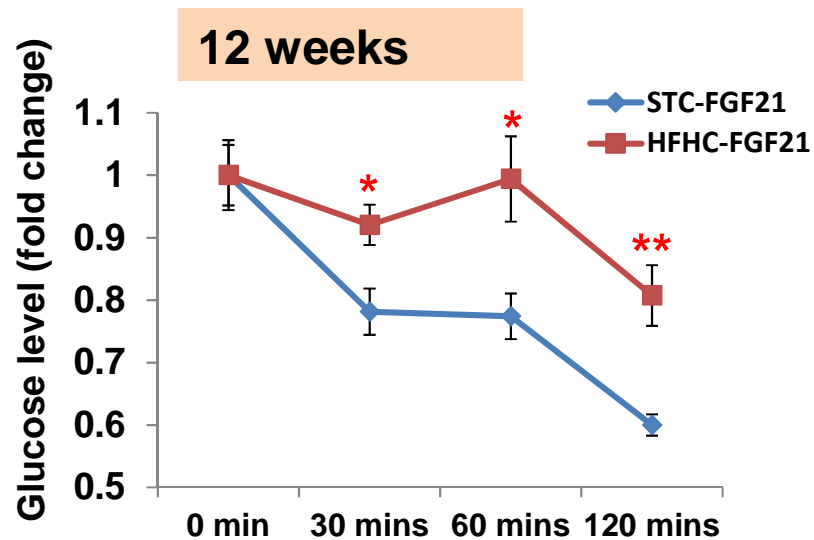
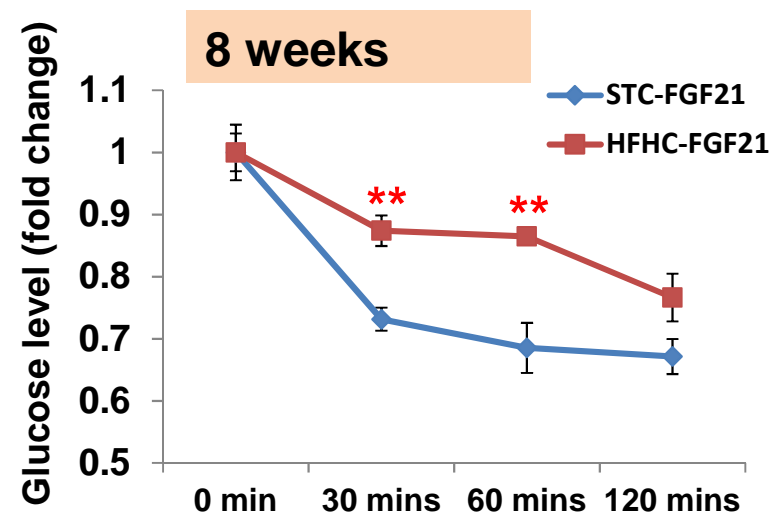
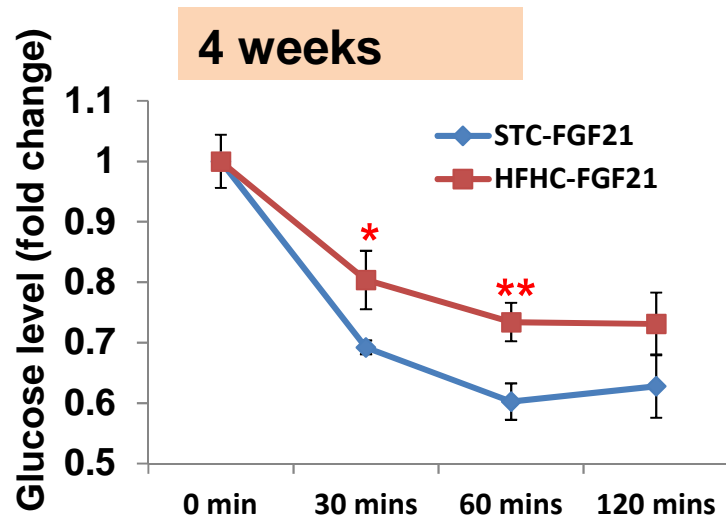


Serum

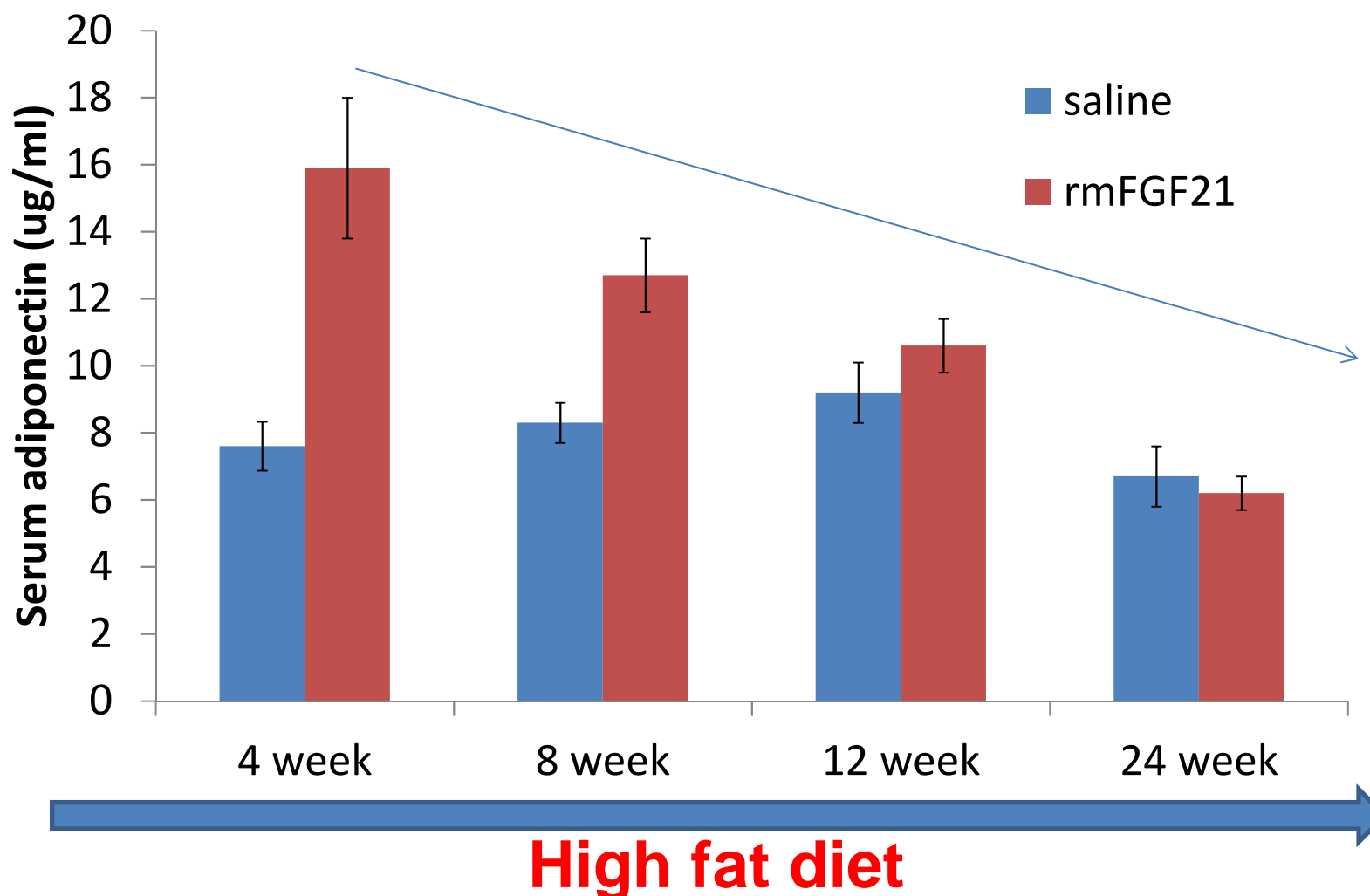


**FGF21
Resistance
??**

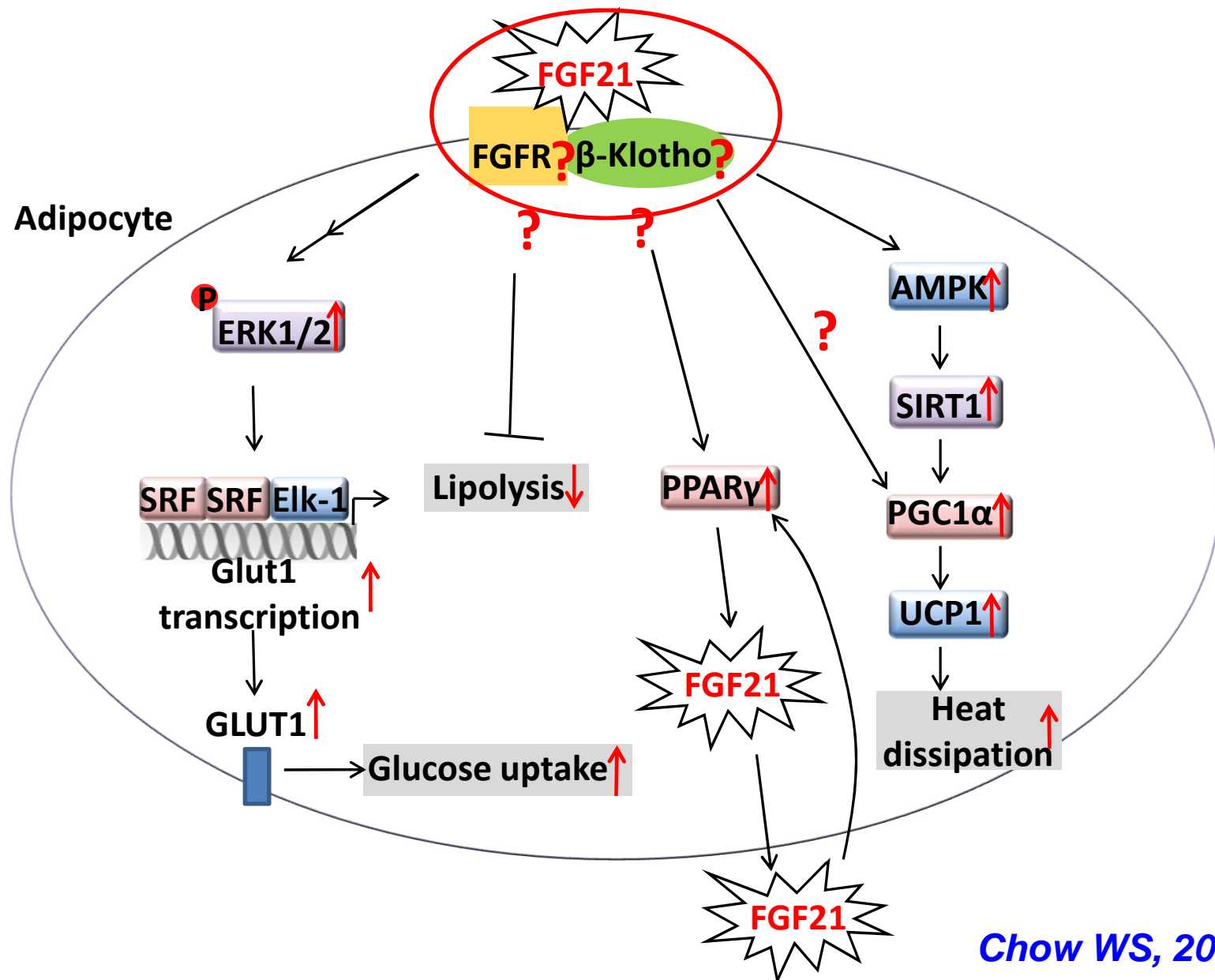
The glucose-lowering effects of FGF21 are progressively decreased in diet-induced obese mice



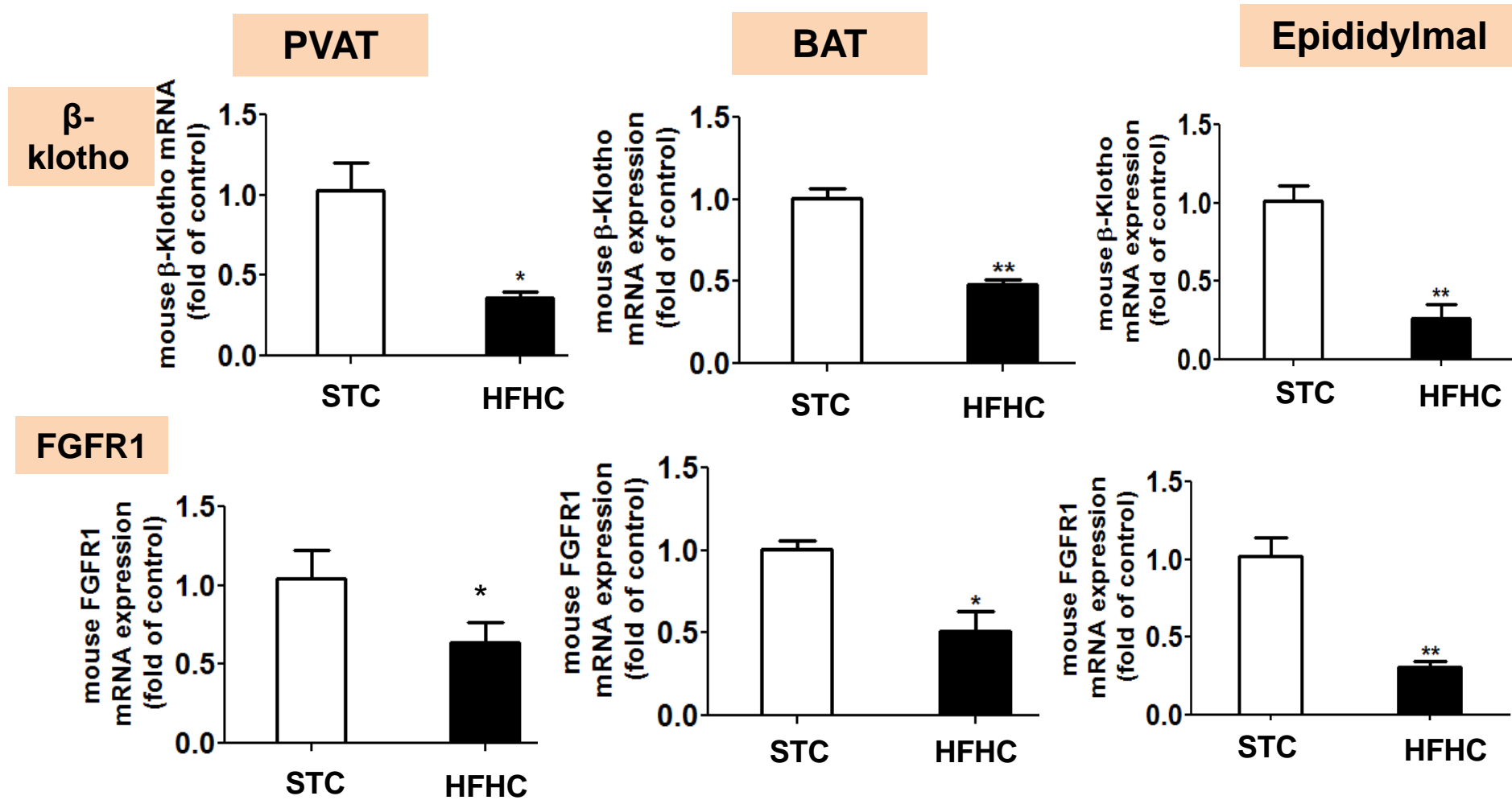
The ability of recombinant FGF21 (rmFGF21) to increase circulating adiponectin is progressively impaired in diet-induced obesity



Mechanisms of FGF21 resistance?

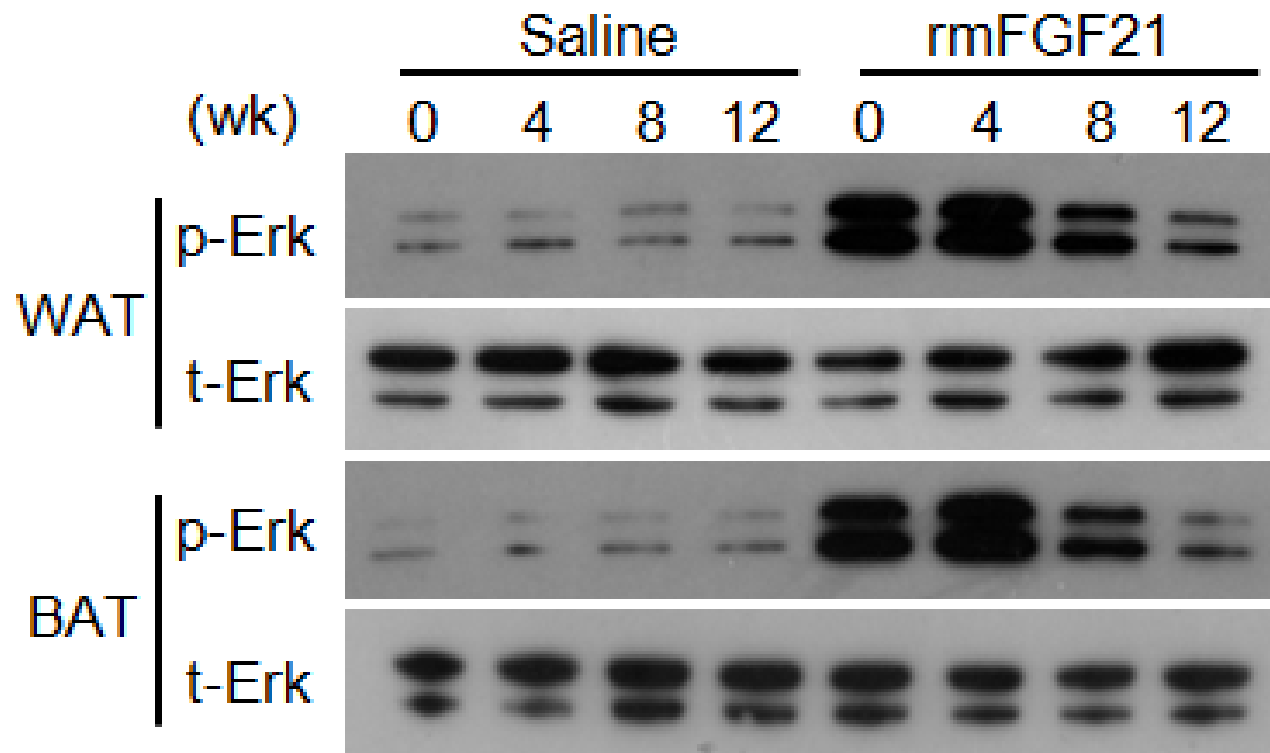


A marked down-regulation of β -klotho and FGFR1 in different fat depots in obese mice

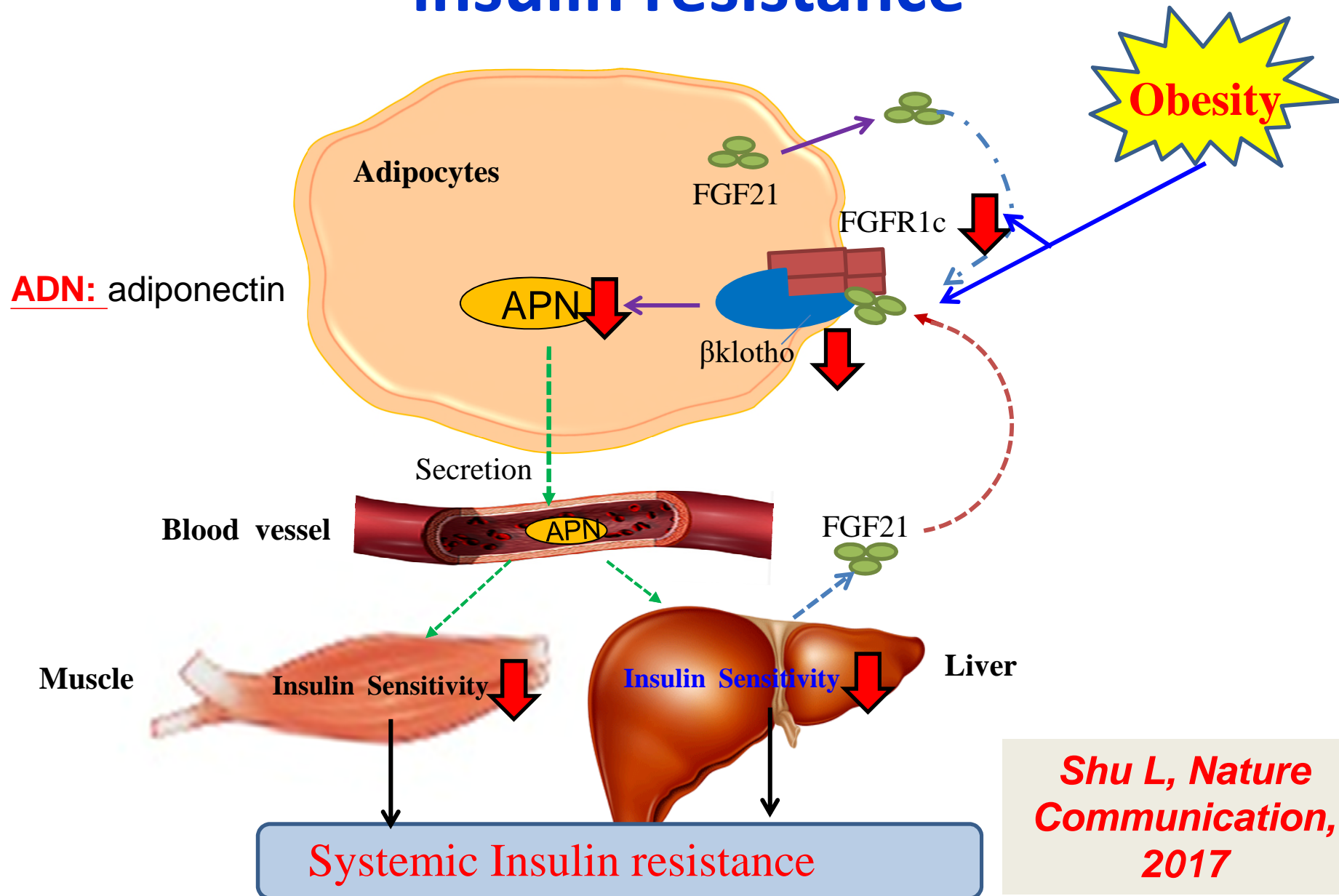


HFHC: High fat high cholesterol diet

Dietary obesity is associated with FGF21 resistance in adipose tissues



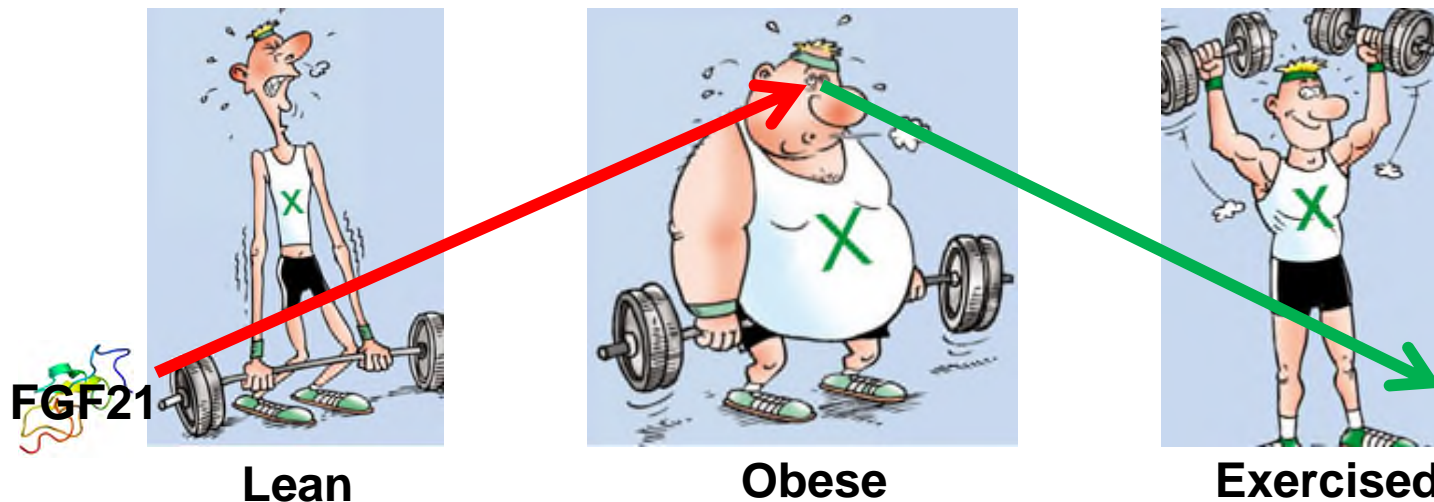
FGF21 resistance as a cause of systemic insulin resistance



FGF21 is an exercise responsive factor

Obese subjects

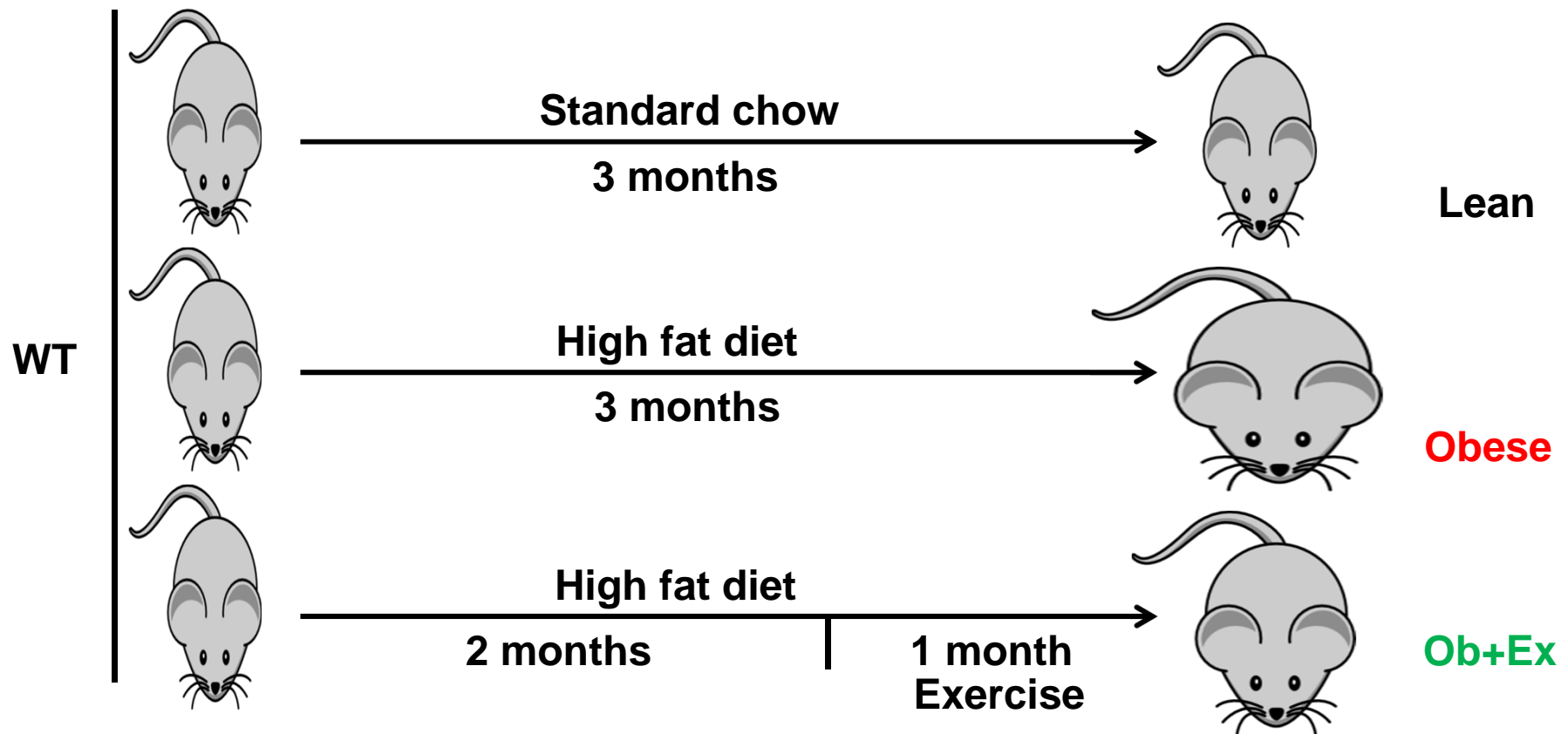
- ✓ 3-month combined aerobic and resistance exercise programme **reduced** plasma FGF21 levels in **obese** women. (Sae et al., *Clinical Endocrinology*, 2011)
- ✓ 9-month voluntary running significantly **lowered** serum FGF21 levels in **obese** rats. (Justin et al., *Appl. Physiol. Nutr. Metab.*, 2012)
- ✓ A 5-week endurance exercise program that comprised of three cycle ergometer sessions/ week **reduces** serum FGF21 levels in **elderly men**. (Taniguchi et al., *J Clin Endocrinol Metab*, 2015)



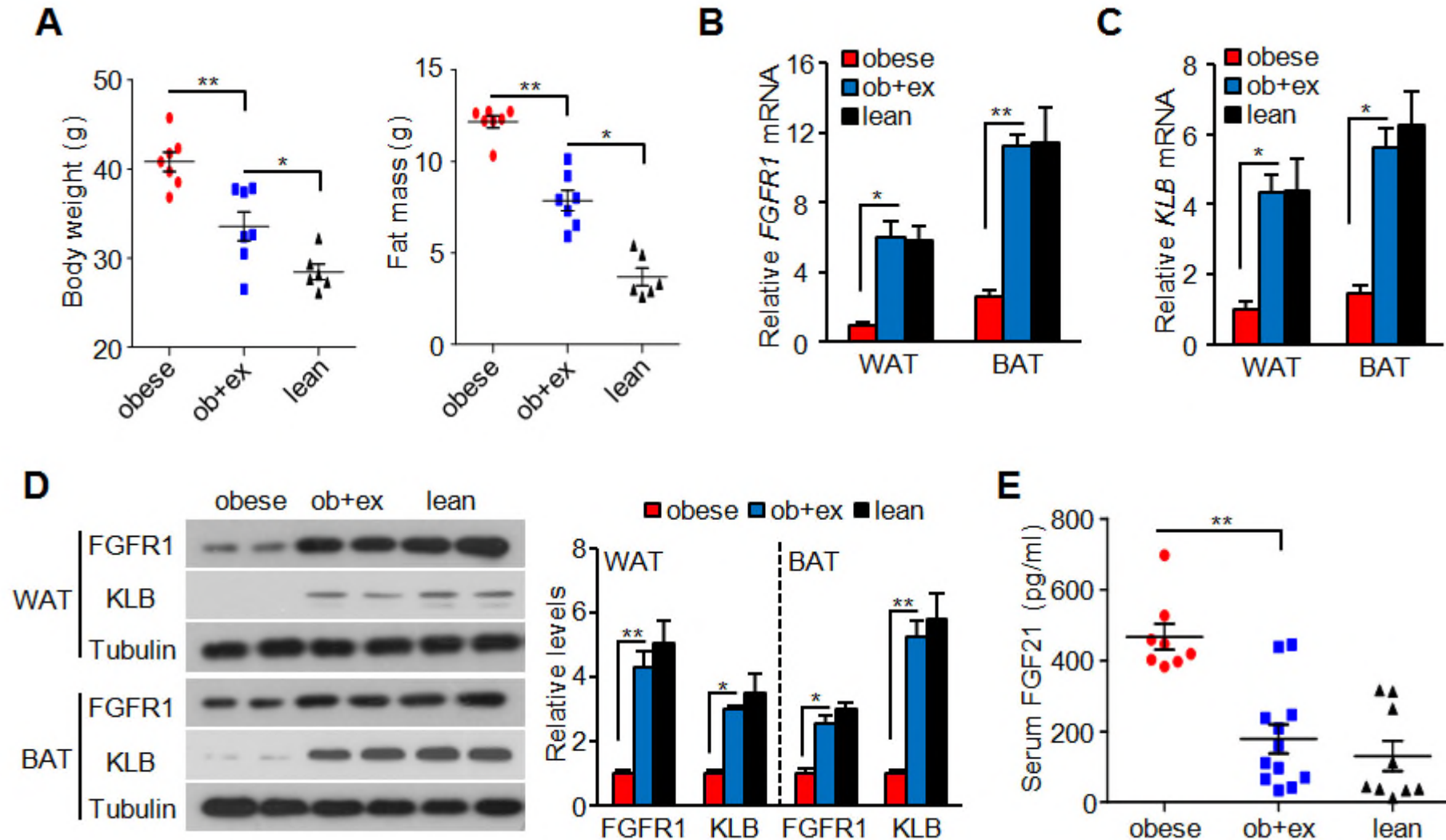
Can exercise reverse obesity-induced FGF21 resistance in mice?



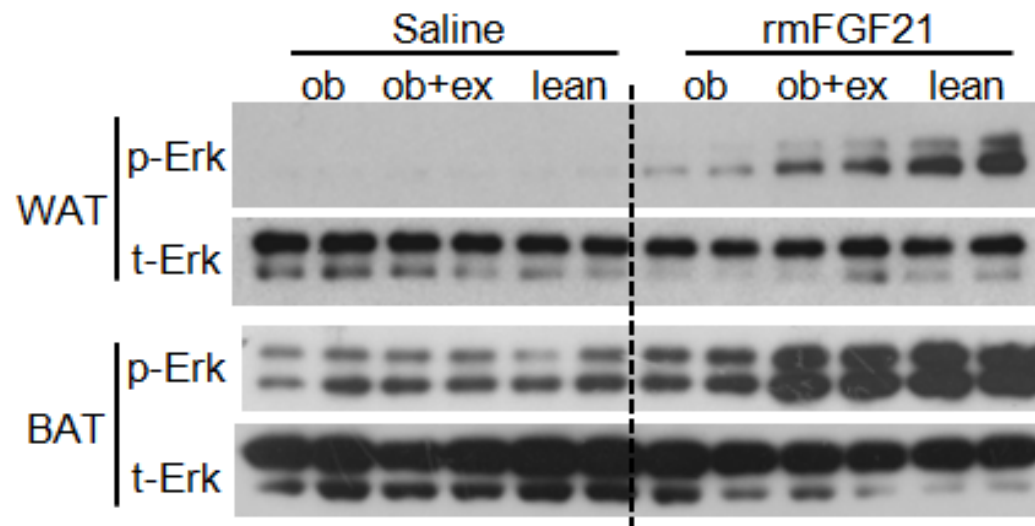
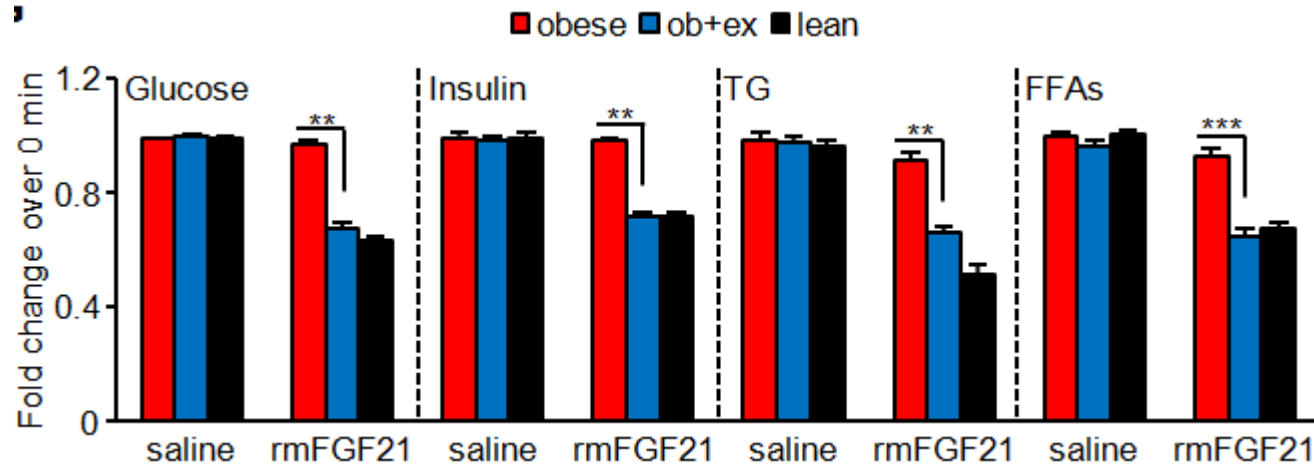
Peter Geng



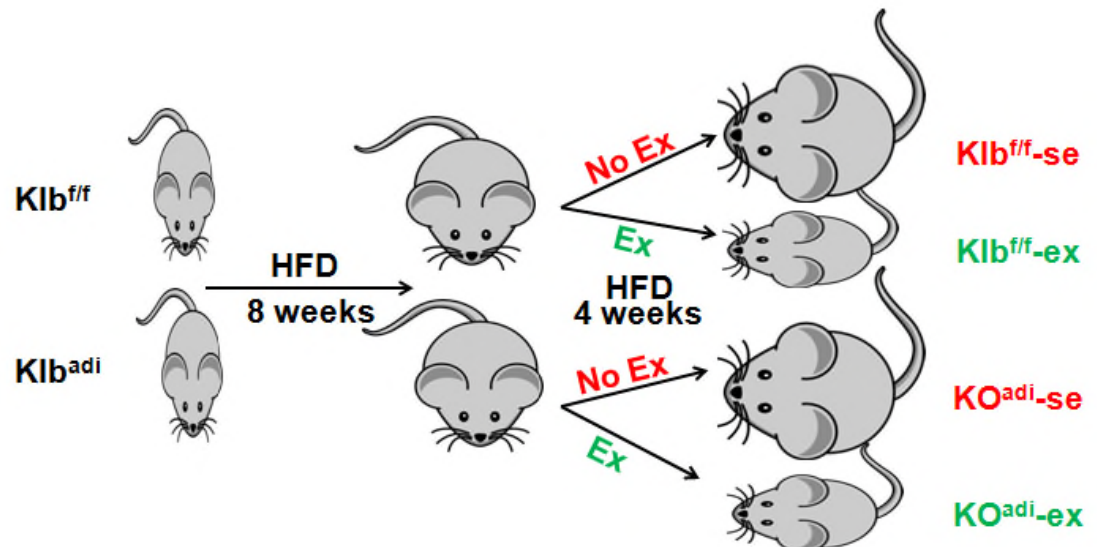
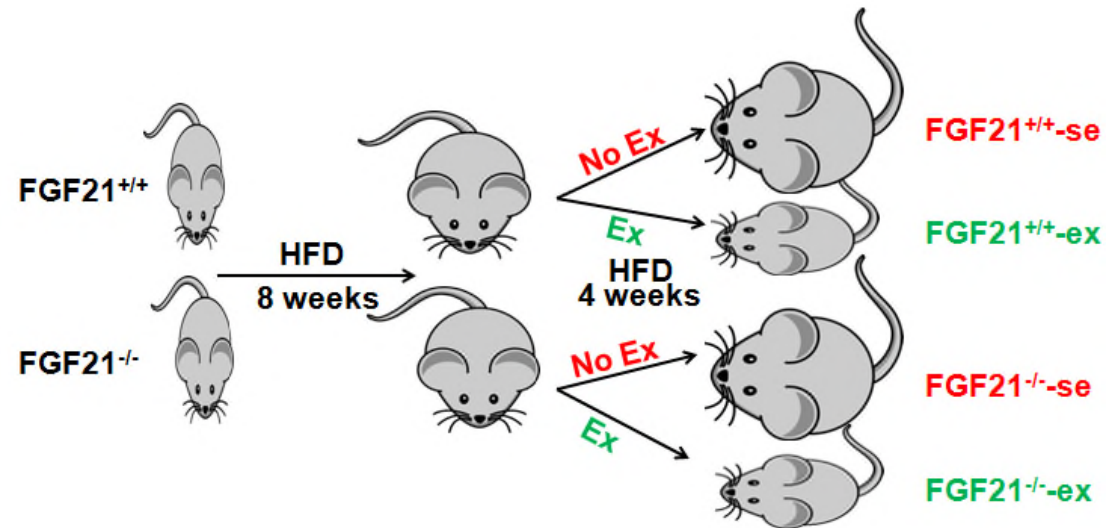
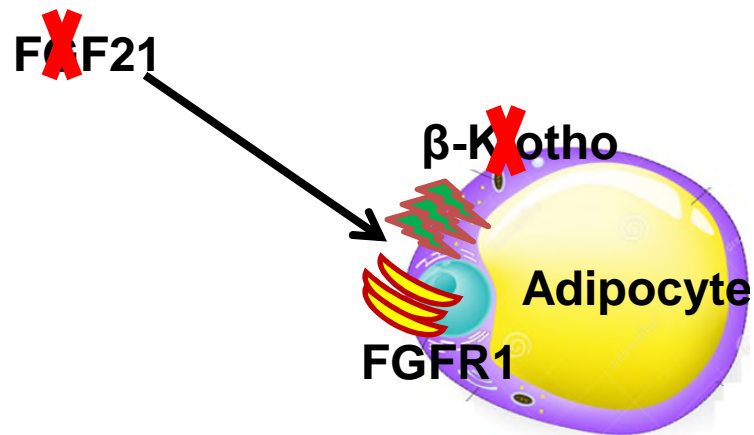
Chronic exercise reverses obesity-induced downregulation of the FGF21 receptor complexes in adipose tissues



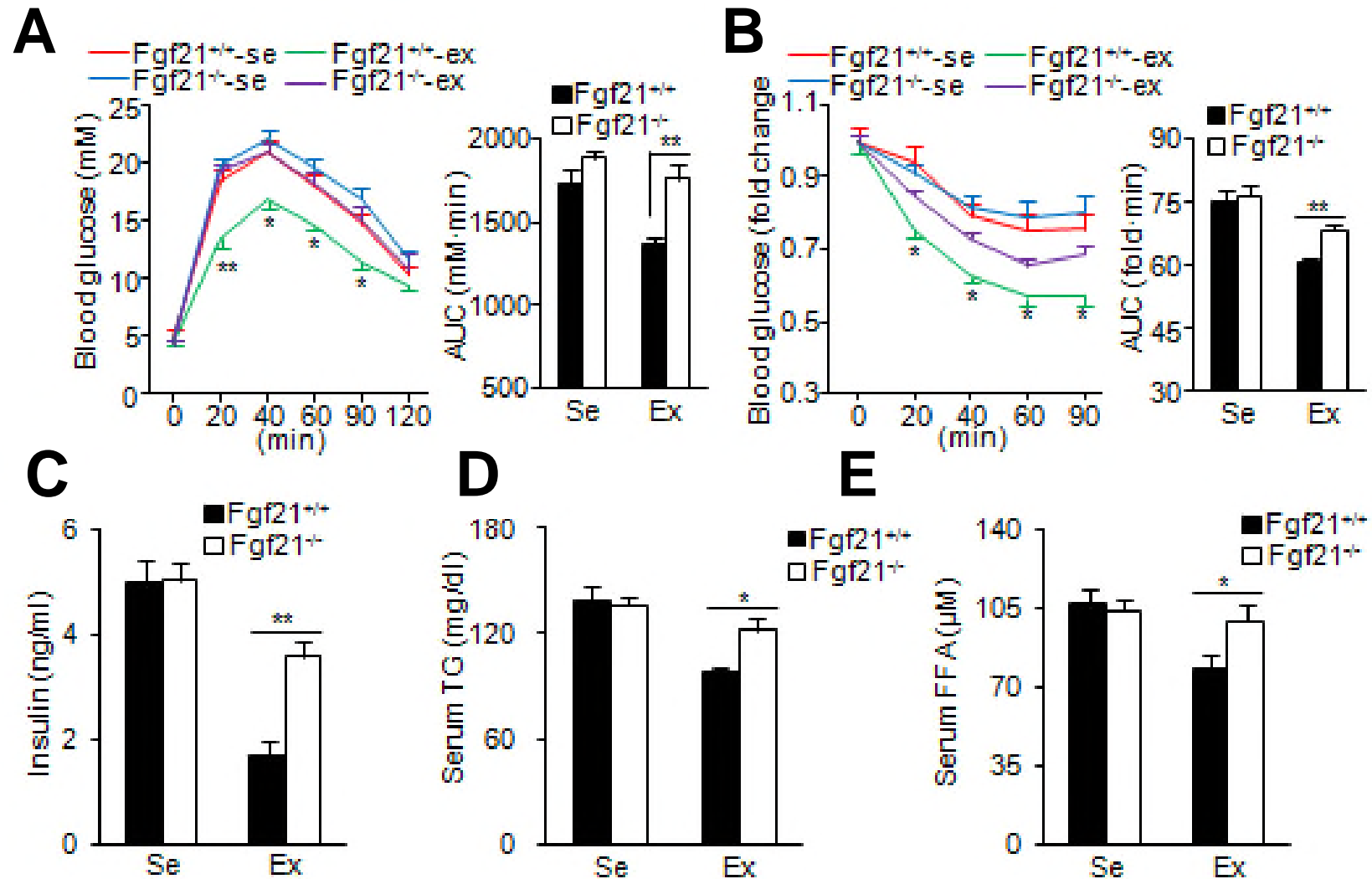
Chronic exercise restores FGF21 sensitivity in obese mice



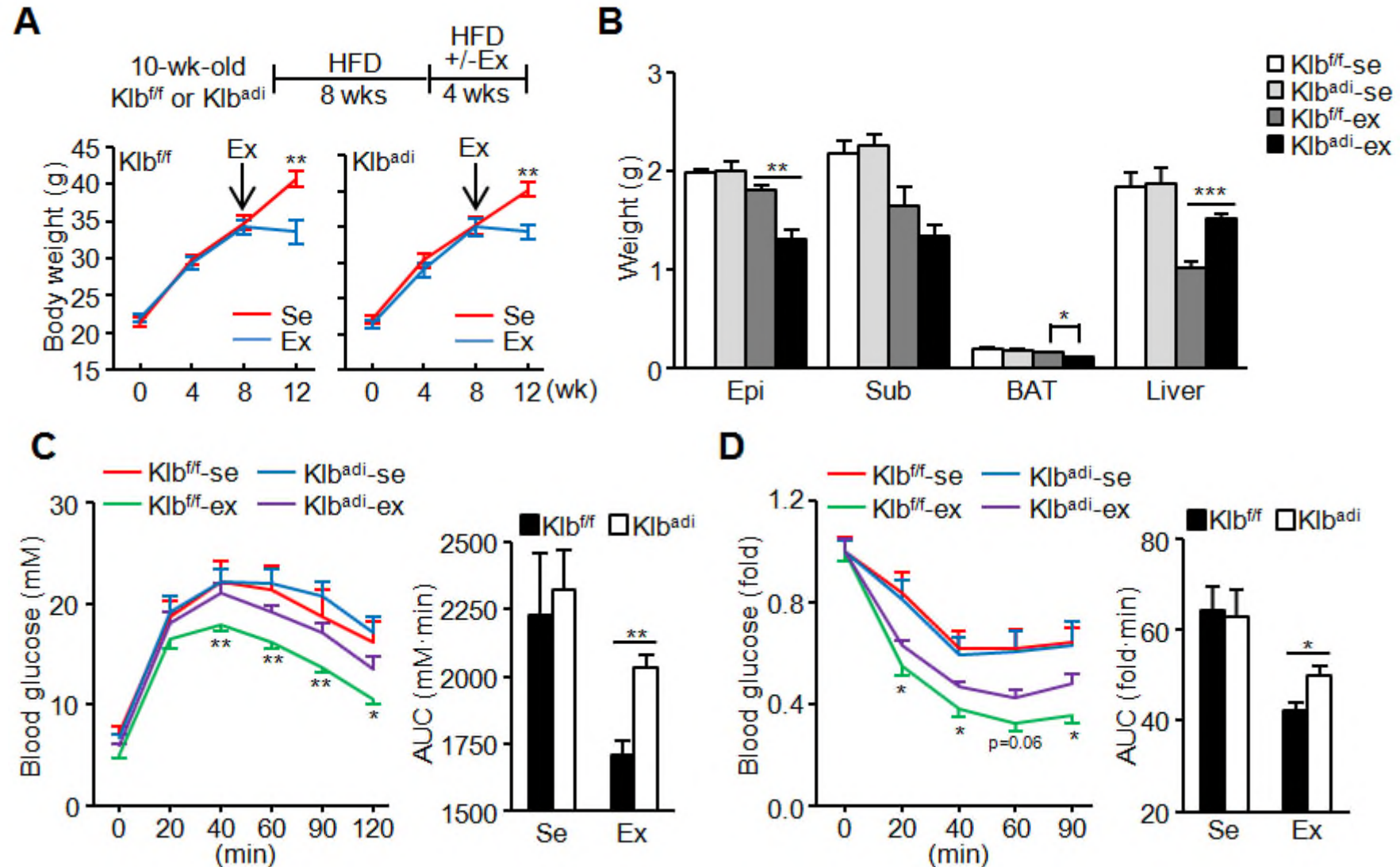
Q: Whether adipose actions of FGF21 is required for mediating the metabolic benefits of exercise?



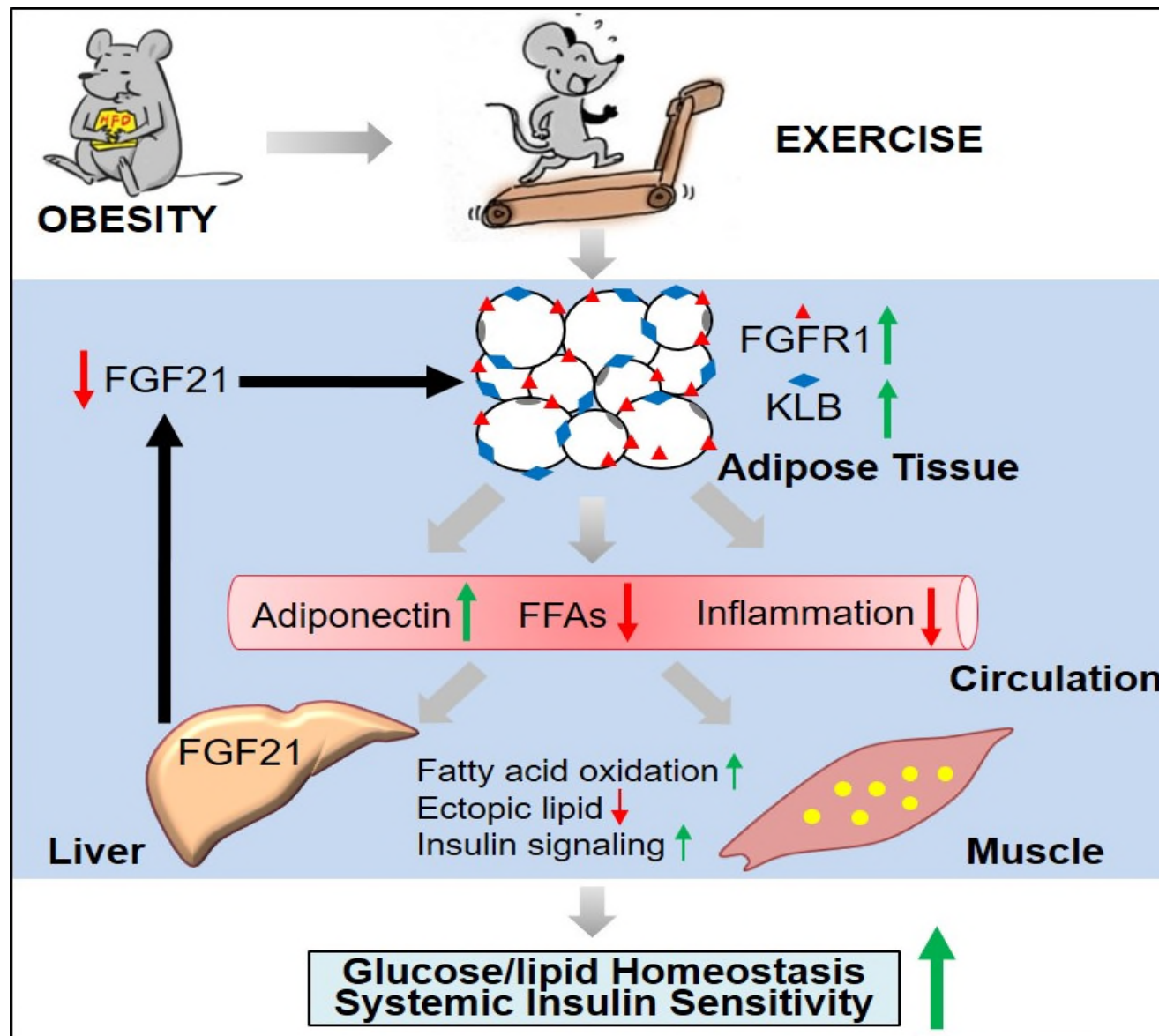
Global FGF21 KO mice exhibit no metabolic improvement in response to exercise



Adipocyte-KLB-specific KO mice refractory to the metabolic benefits of exercise

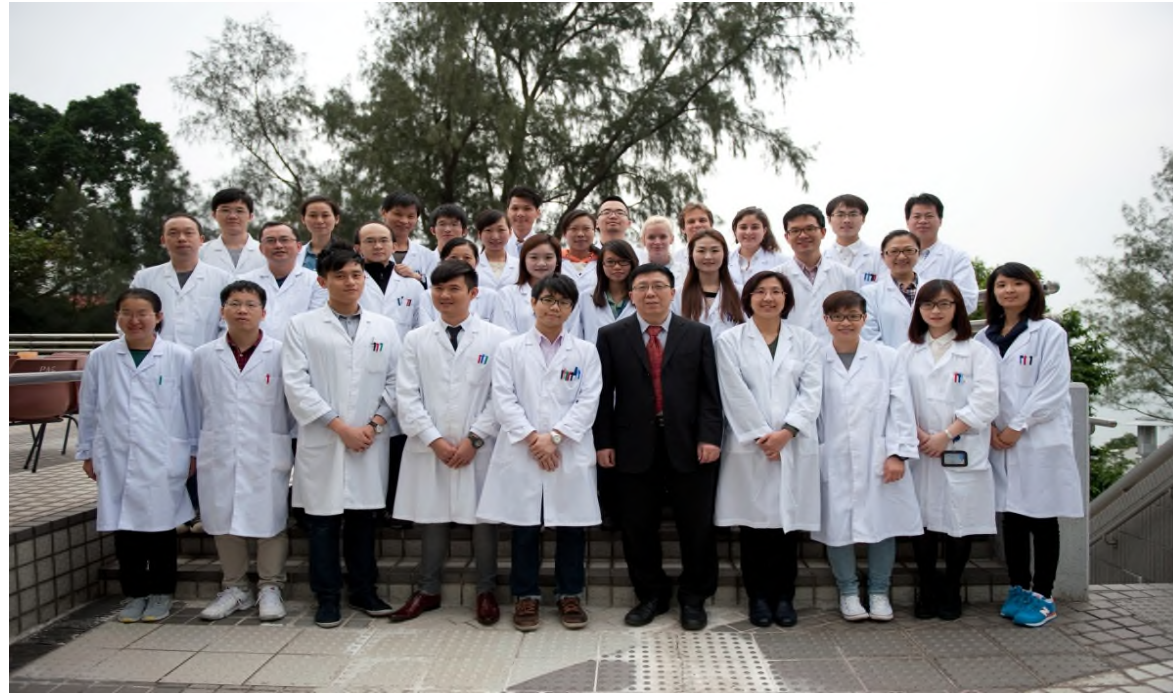


FGF21 signaling in adipose tissues mediates the metabolic benefits of exercise by coordinating inter-organ crosstalk



Acknowledgement

HKU
team



Kyoto University

*Prof. Nobuyuki Itoh
Dr. Yuhei Hotta*

**Shanghai Diabetes Center, Jiao
Tong University**

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Thank you!

