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FGF21 Resistance in Adipose Tissues as a Cause of Insulin Resistance

The ICDM 2013 & 5th AASD Scientific Meeting

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Dept of Medicine & Dept of Pharmacology and Pharmacy

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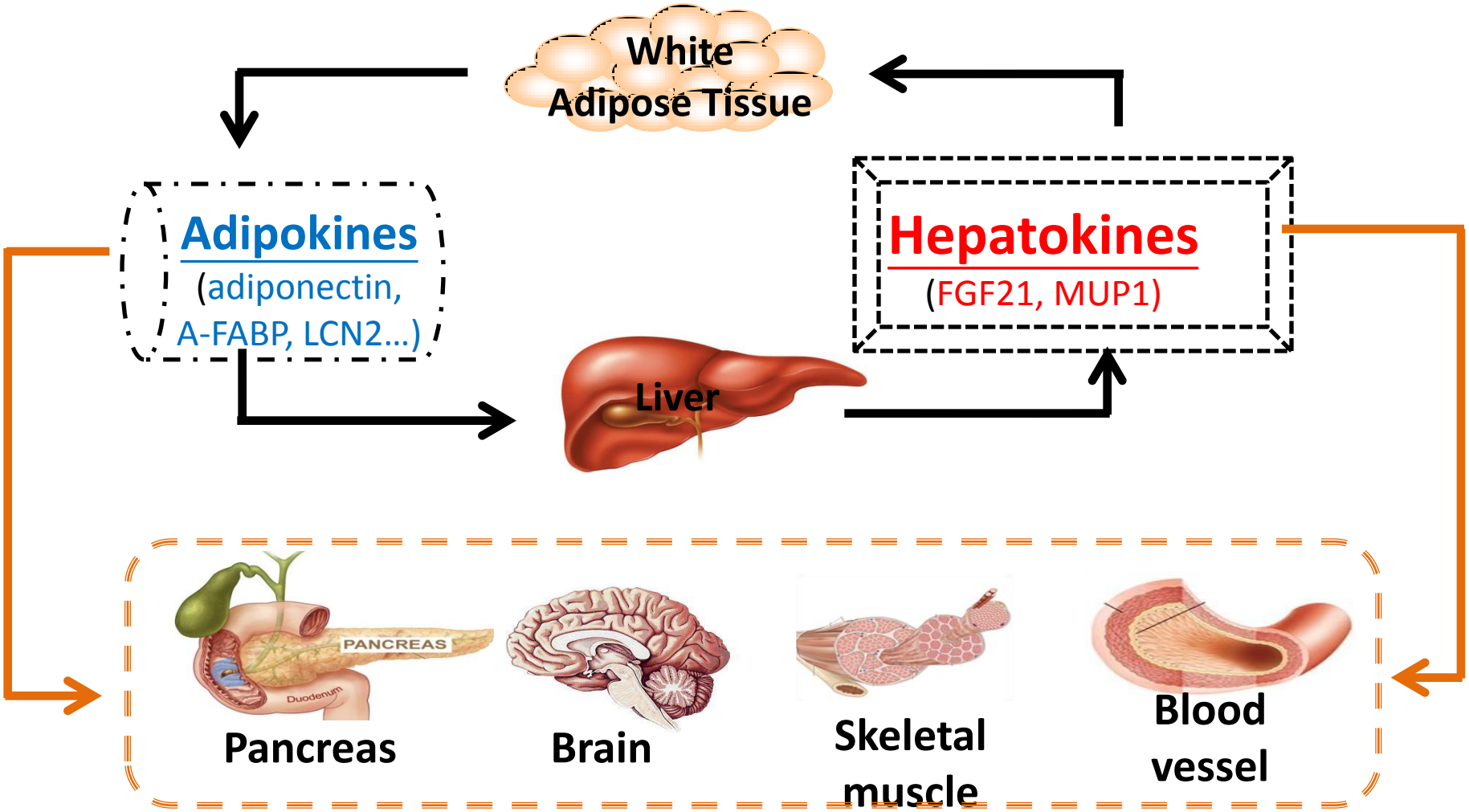
Our research focus: Adipokines and hepatokines in obesity-related cardiometabolic syndrome



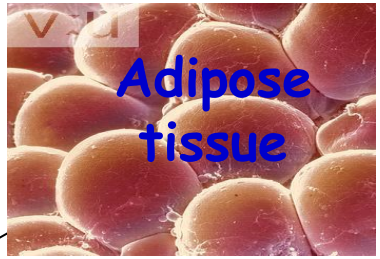
Adipokines characterized in our laboratory

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,

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 Diabetes, 2009, 2010, 2011, 2012, **Cell Metabolism**, 2011, **PNAS**, 2012



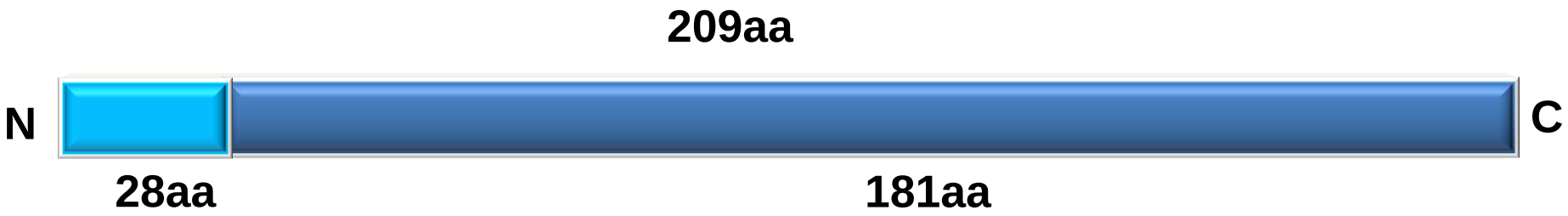
Lipocalin-2

(Wang Y et al, **Clin Chem**, 2007)
(Law I, **Diabetes**, 2010)
JBC, 2012; Liu Y, **BJP**, 2012

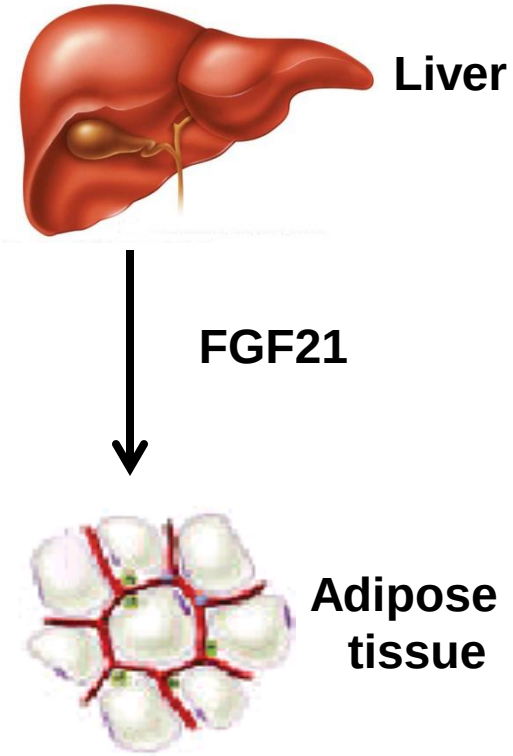
FGF21

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**

FGF21 as a metabolic regulator



- It is secreted mainly from the liver.
- Its major target is adipose tissue.

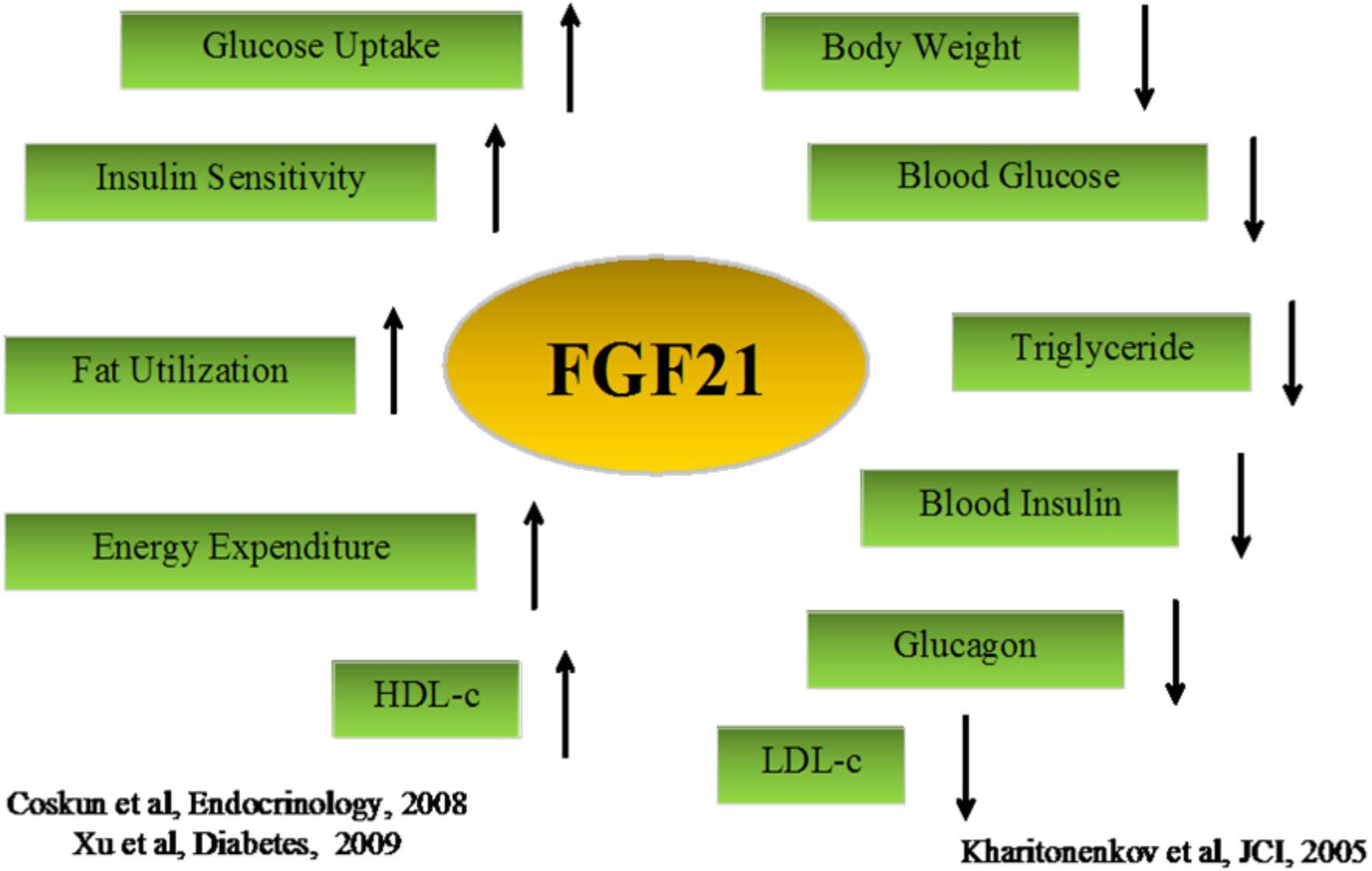


- Administration of recombinant FGF21 acutely decreases blood glucose to a normal level in both rodents and monkeys with diabetes

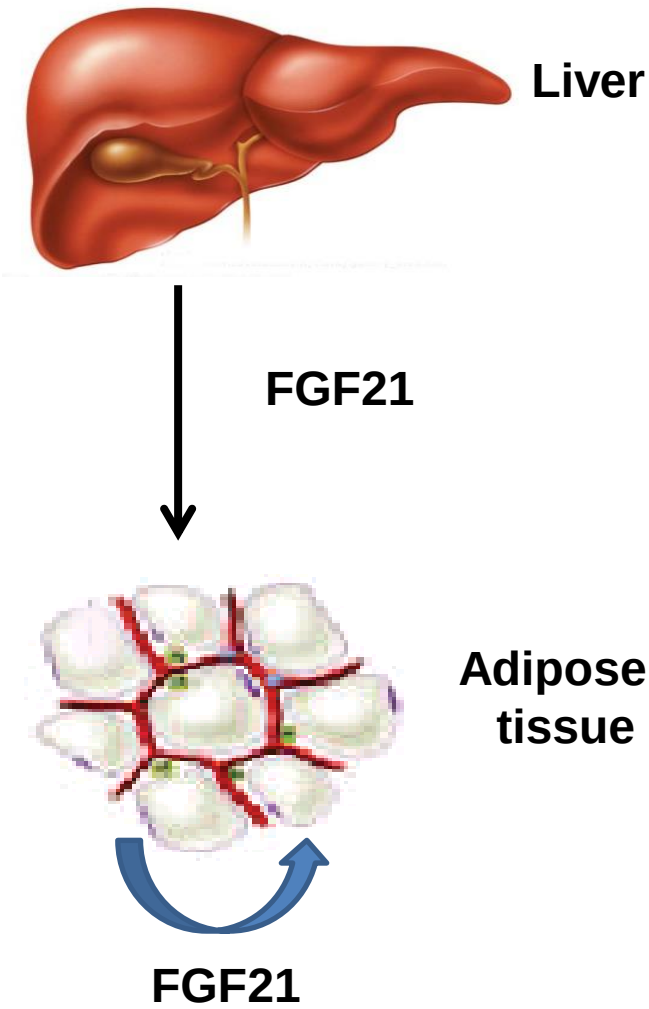
.

- It does not have mitogenic activities.

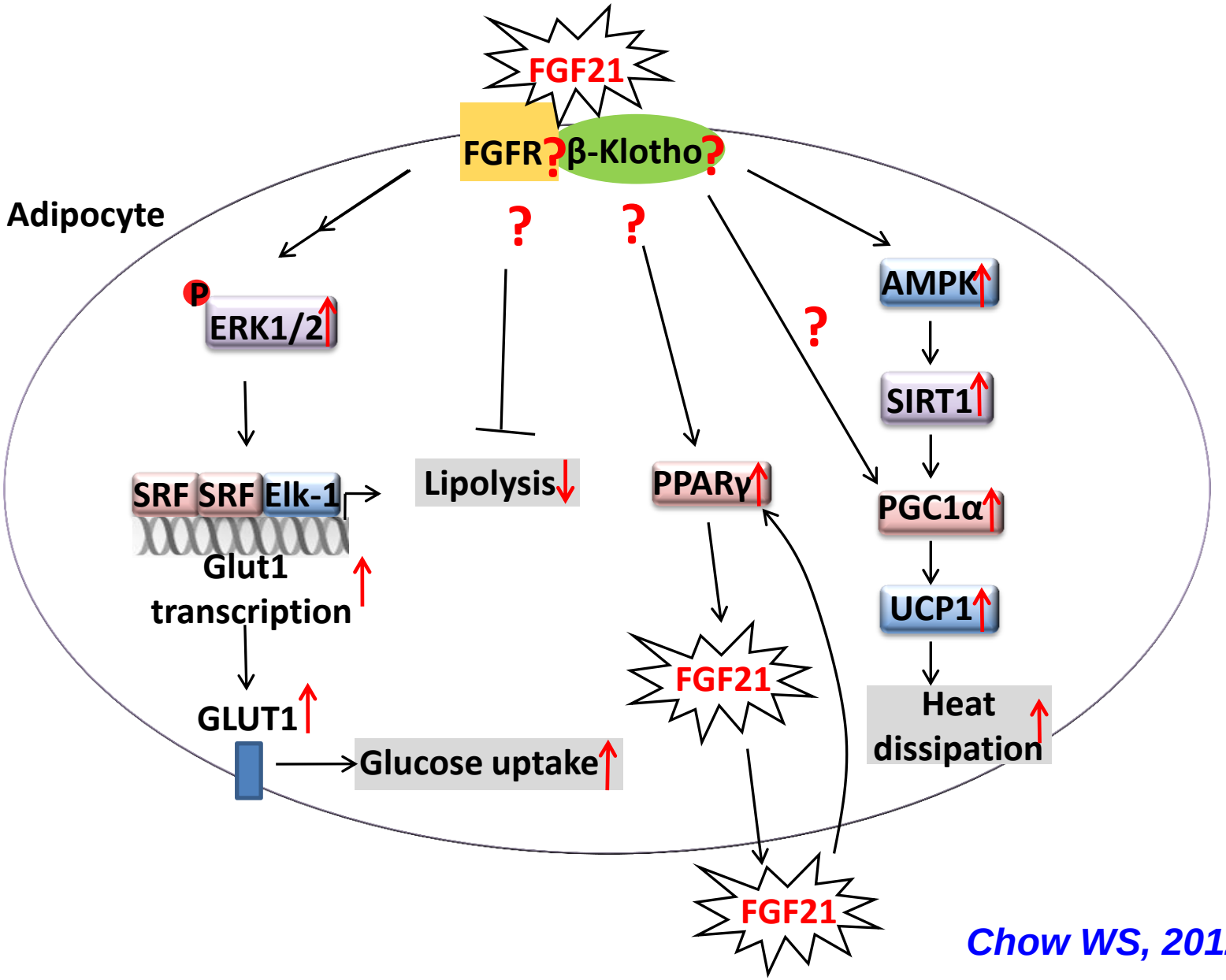
Multiple beneficial effects of recombinant FGF21 in animals



Adipose tissue as a major action site of FGF



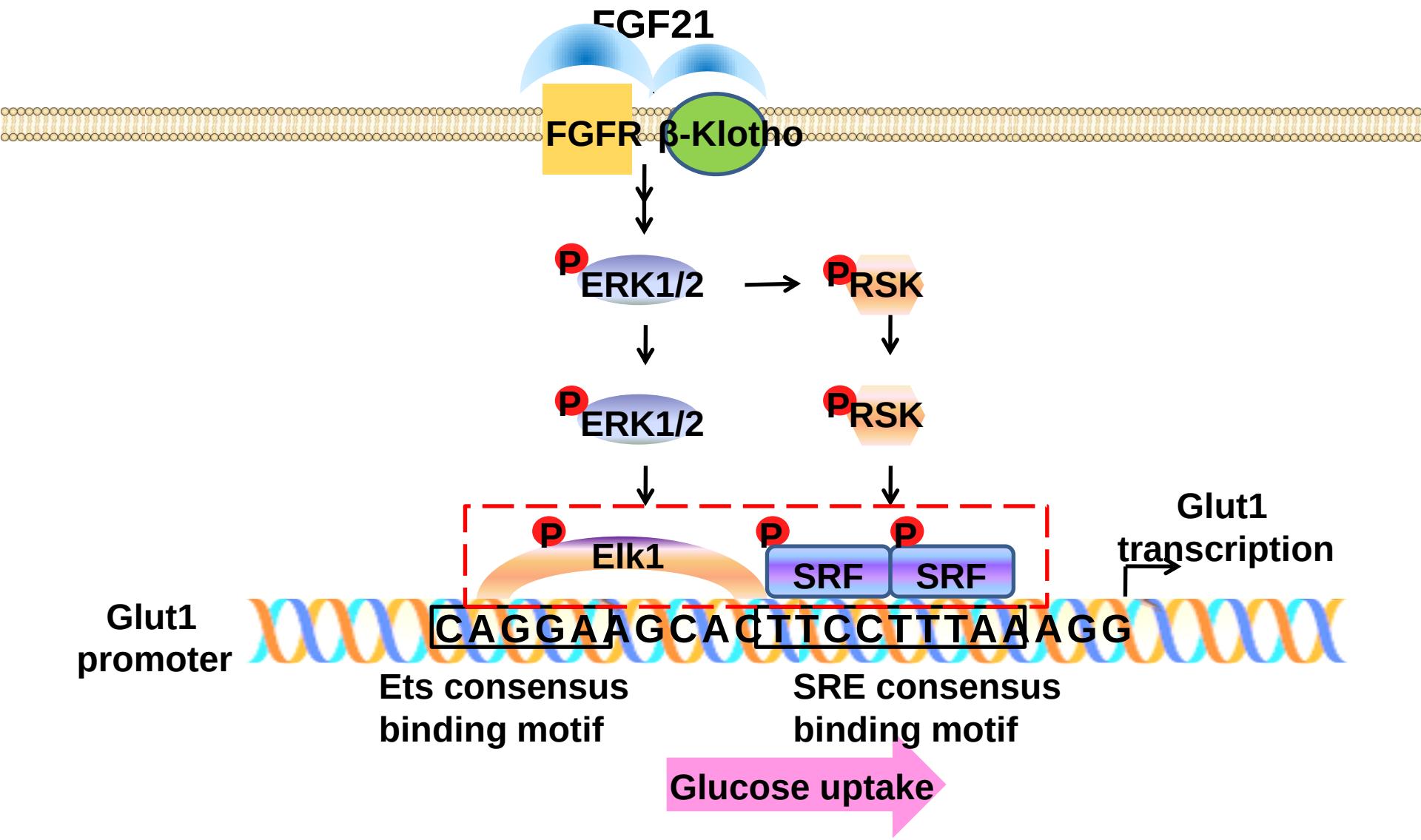
Multiple effects of FGF21 in adipocytes



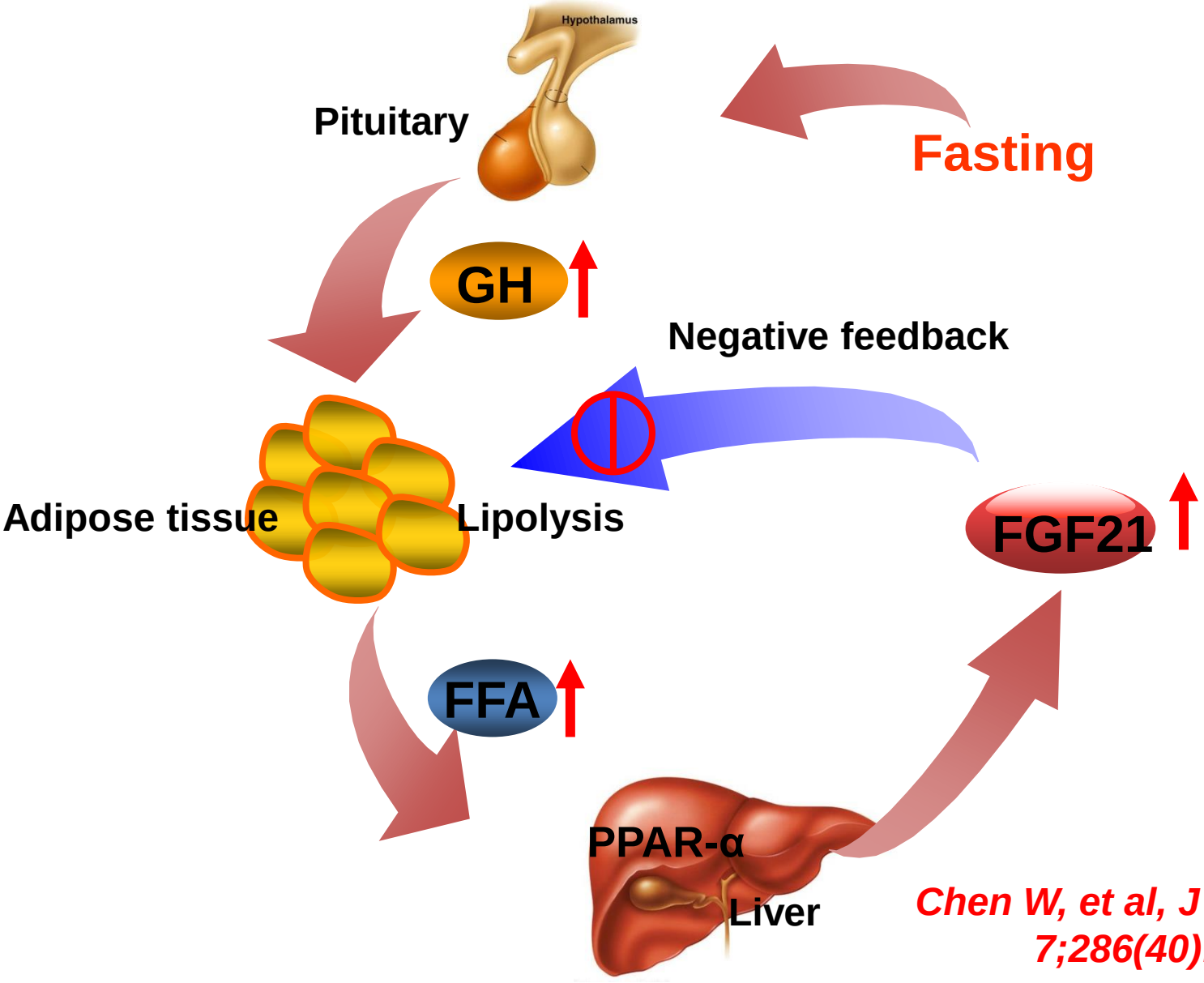
Chow WS, 2012

FGF21 induces glucose uptake by inducing the expression of GLUT1 in adipocytes

(*Ge X, J Biol. Chem. 2011, 286:34533-41*)

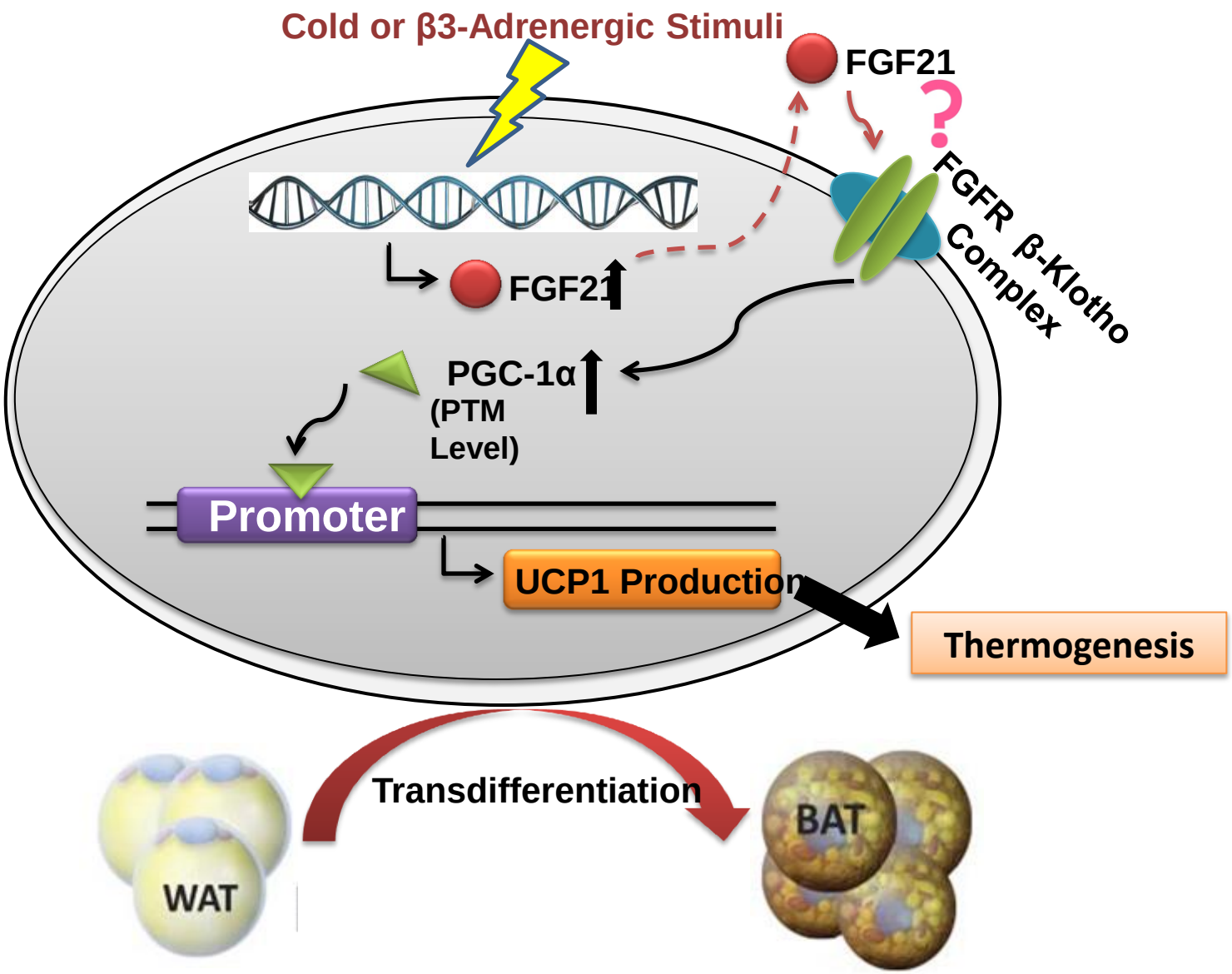


FGF21 fine-tunes growth hormone-induced lipolysis in adipocytes



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

FGF21 Regulates PGC-1α and Browning of White Adipose Tissues



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

Cell Metabolism
Short Article

βKlotho Is Required for Fibroblast Growth Factor 21 Effects on Growth and Metabolism

Xunshan Ding,[1,2] Jamie Boney-Montoya,[1] Bryn M. Owen,[2] Angie L. Bookout,[2,3] Katie Colbert Coate,[2,4] David J. Mangelsdorf,[2,4,*] and Steven A. Kliewer[1,2,*]
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[3]Division of Hypothalamic Research, Department of Internal Medicine
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http://dx.doi.org/10.1016/j.cmet.2012.08.002

SUMMARY

Fibroblast growth factor 21 (FGF21) is a fasting-induced hepatokine that has potent pharmacologic effects in mice, which include improving insulin sensitivity and blunting growth. The single-transmembrane protein βKlotho functions as a coreceptor for FGF21 in vitro. To determine if βKlotho is required for FGF21 action in vivo, we generated whole-body and adipose tissue-selective βKlotho-knockout mice. All of the effects of FGF21 on growth and metabolism were lost in whole-body βKlotho-knockout mice. Selective elimination of βKlotho in adipose tissue blocked the acute insulin-sensitizing effects of FGF21. Taken together, these data demon-

loss (Coskun et al., 2008; Kharitonenkov et al., 2005, 2007; Xu et al., 2009). Thus, FGF21 is a promising drug candidate for treating human metabolic disease.

In vitro studies showed that FGF21 and FGF15/19 act through a cell-surface receptor complex composed of conventional FGF receptors and βKlotho, a single-pass transmembrane protein (Kharitonenkov et al., 2008; Ogawa et al., 2007; Suzuki et al., 2008). FGF21 interacts directly with the extracellular domain of βKlotho in the FGFR/βKlotho complex and activates FGF receptor substrate 2α and ERK1/2 phosphorylation. Whereas the FGFRs are expressed in most tissues, βKlotho expression is restricted to just a few, including liver and both WAT and BAT (Fon Tacer et al., 2010). FGF21 modulates the expression of metabolic genes in each of these tissues (Coskun et al., 2008).

Mice lacking βKlotho in all tissues are viable and fertile (Ito et al., 2005). However, these βKlotho-knockout (KO) mice are

ARTICLE IN PRESS
Brief communication
MOLECULAR METABOLISM

The breadth of FGF21's metabolic actions are governed by FGFR1 in adipose tissue

Andrew C. Adams[1,*], Chaofeng Yang[2,*], Tamer Coskun[1], Christine C. Cheng[1], Ruth E. Gimeno[1], Yongde Luo[2], Alexei Kharitonenkov[1,**]

ABSTRACT

FGF21 is a multifunctional metabolic regulator. The co-factor βKlotho (KLB) allows FGF21 to signal via FGF receptors. Given the widespread nature of FGFR expression and KLB presence in several organs, it remains unclear which tissue/FGFR isoform determine FGF21 action. Here we show that deletion of FGFR1 in fat (FR1KO) leads to a complete ablation of FGF21 stimulated transcriptional activity in this tissue. Furthermore, FR1KO mice showed no FGF21-mediated lowering of plasma glucose, insulin and triglycerides, altered serum levels of adipokines, no increase in energy expenditure, but preserved reductions in serum/liver FFAs as compared to wild type mice. Of importance, the anti-glycaemic actions of FGF19 were fully evident in FR1KO mice implying that FGF19 functions in a FGFR1/adipose independent manner. Taken together, our findings reveal the existence of an adipose FGFR1 driven axis of cross-tissue communication which defines several aspects of FGF21 biology and delineates ons between FGF21 and FGF19.

Adipose tissue; FGFR1; FGF19

OPEN ACCESS Freely available online
PLoS one

FGF21 Promotes Metabolic Homeostasis via White Adipose and Leptin in Mice

Murielle M. Véniant[1], Clarence Hale[1], Joan Helmering[1], Michelle M. Chen[1], Shanaka Stanislaus[1], Jim Busby[1], Steven Vonderfecht[2], Jing Xu[1], David J. Lloyd[1]*
1 Department of Metabolic Disorders, Amgen Inc., Thousand Oaks, California, United States of America, 2 Department of Pathology, Amgen Inc., Thousand Oaks, California, United States of America

Abstract

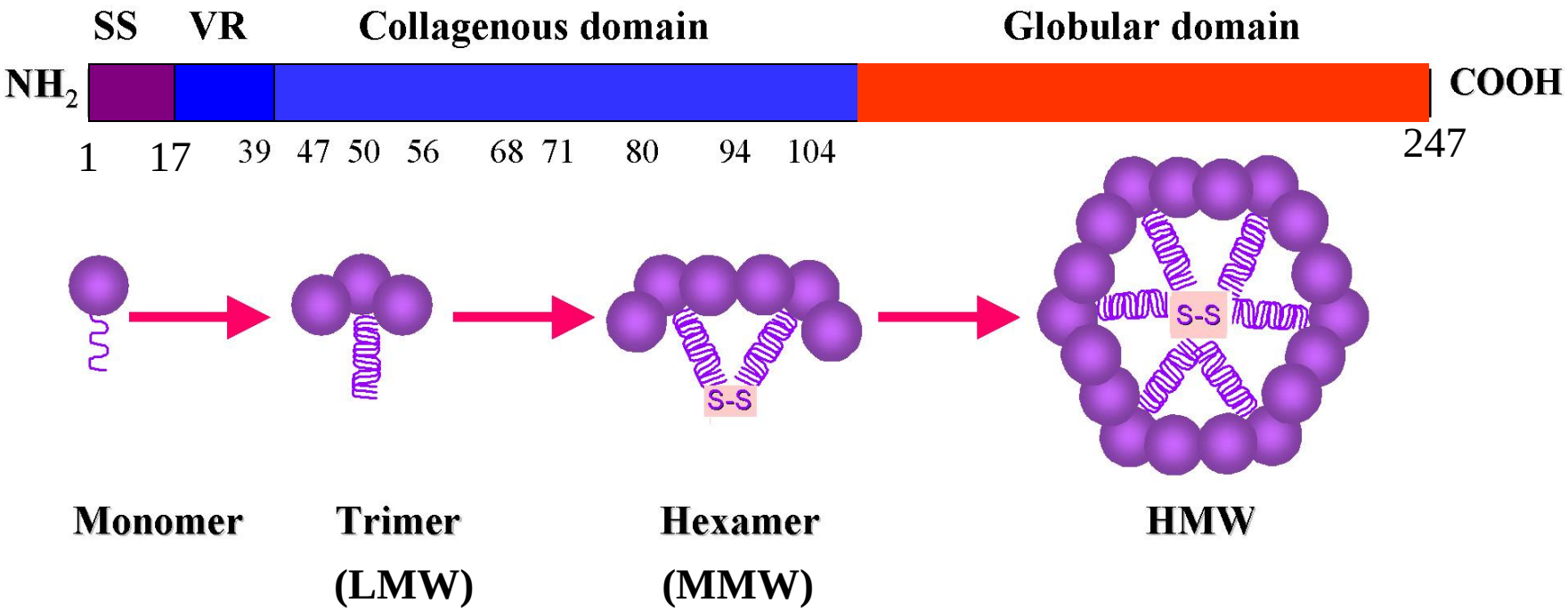
Fibroblast growth factor 21 (FGF21) is a potent metabolic regulator, and pharmacological administration elicits glucose and lipid lowering responses in mammals. To delineate if adipose tissue is the predominant organ responsible for anti-diabetic effects of FGF21, we treated mice with reduced body fat (lipodystrophy mice with adipose specific expression of active sterol regulatory element binding protein 1c; Tg) with recombinant murine FGF21 (rmuFGF21). Unlike wildtype (WT) mice, Tg mice were refractory to the beneficial effects of rmuFGF21 on body weight, adipose mass, plasma insulin and glucose tolerance. To determine if adipose mass was critical for these effects, we transplanted WT white adipose tissue (WAT) into Tg mice and treated the mice with rmuFGF21. After transplantation, FGF21 responsiveness was completely restored in WAT transplanted Tg mice compared to sham Tg mice. Further, leptin treatment alone was sufficient to restore the anti-diabetic effects of rmuFGF21 in Tg mice. Molecular analyses of Tg mice revealed normal adipose expression of *Fgfr1*, *Klb* and an 8-fold over-expression of *Fgf21*. Impaired FGF21-induced signaling indicated that residual adipose tissue of Tg mice was resistant to FGF21, whilst normal FGF21 signaling was observed in Tg livers. Together these data suggest that adipose tissue is required for the triglyceride and glucose, but not the cholesterol lowering efficacy of FGF21, and that leptin and FGF21 exert additive anti-diabetic effects in Tg mice.

1. Cell Metab. 2012 Sep 5;16(3):387-
2. PLoS One. 2012;7(7):e40164.
3. Molecular Metabolism,
   Available online 27 August 2012.

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

Adiponectin as a mediator?

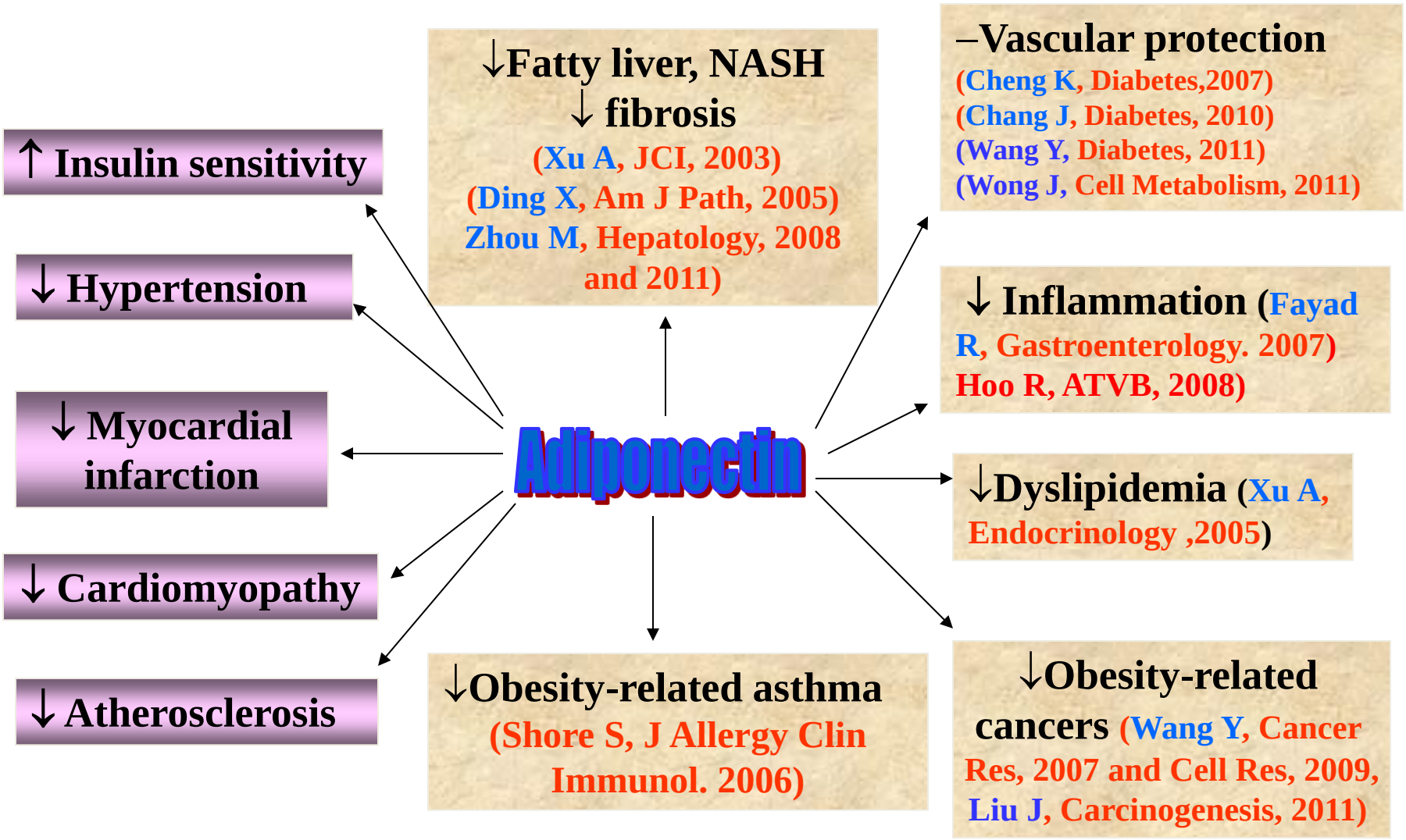
Adiponectin, an insulin sensitizing adipokine predominantly produced from adipocytes



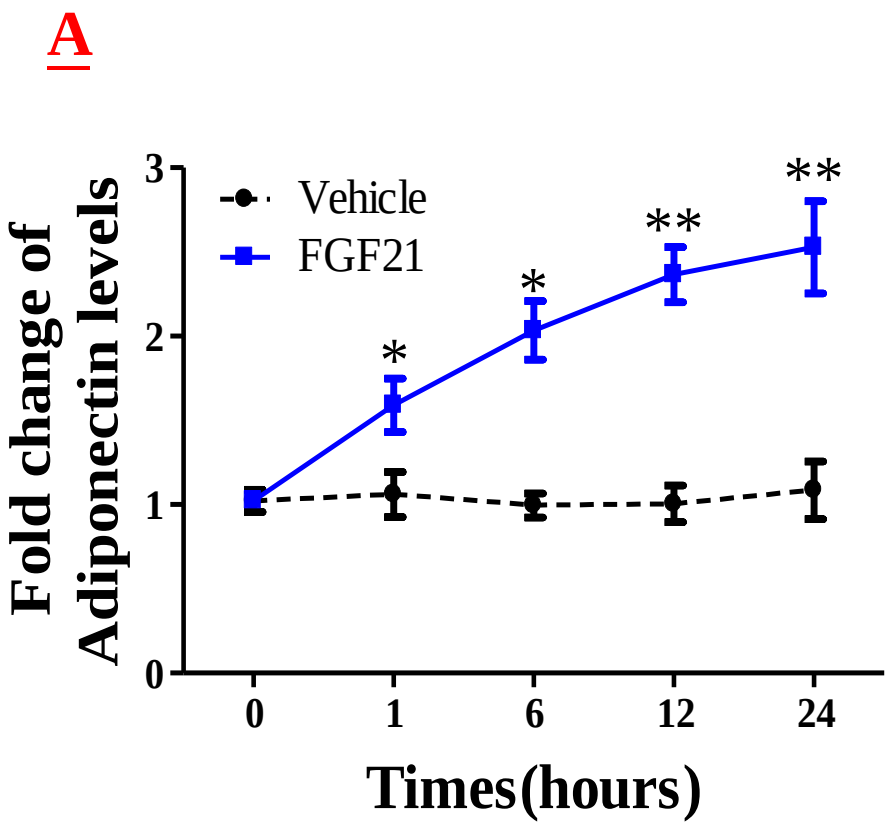
HMW: High molecular weight

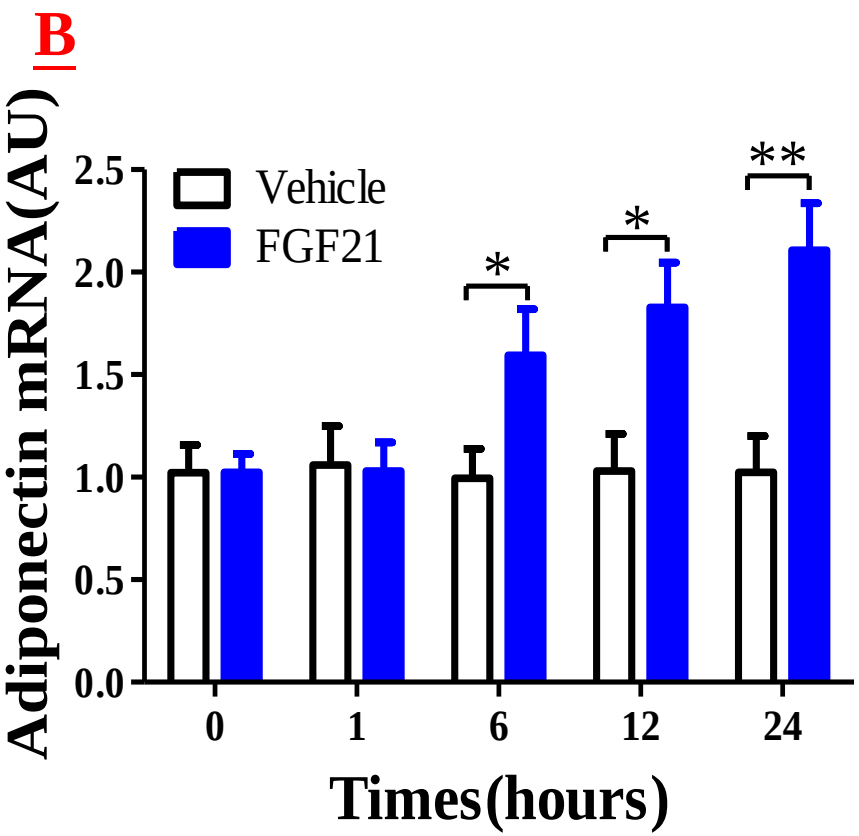
Wang Y et al, JBC, 2002, *JBC, 2004, JBC, 2006, JBC, 2008, Proteomics, 2005, 2006; Richards AA, Mol. Endocrinol, 2010, Wang Y, Biochem J, 2008 (Review), JMB, 2009*

Multiple protective effects of adiponectin against a cluster of obesity-related disorders



FGF21 induces both expression and secretion of adiponectin in mouse adipocytes



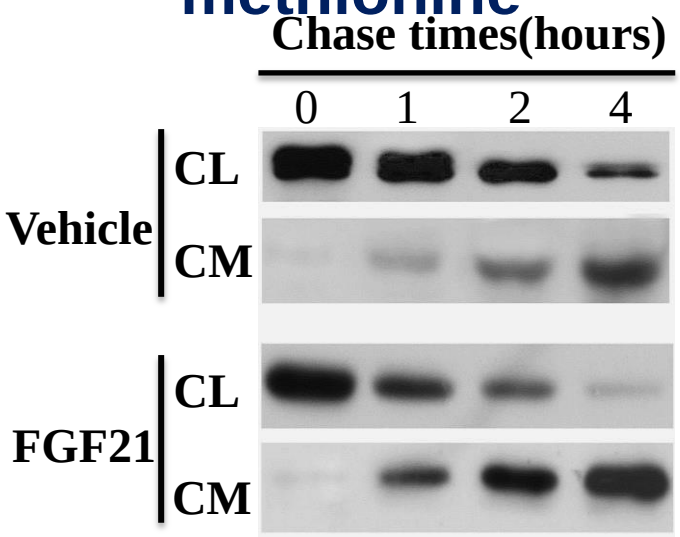


Lin ZF, Cell Metabolism, 2013: 7;17:779-89.

FGF21 enhances adiponectin secretion in mouse adipocytes

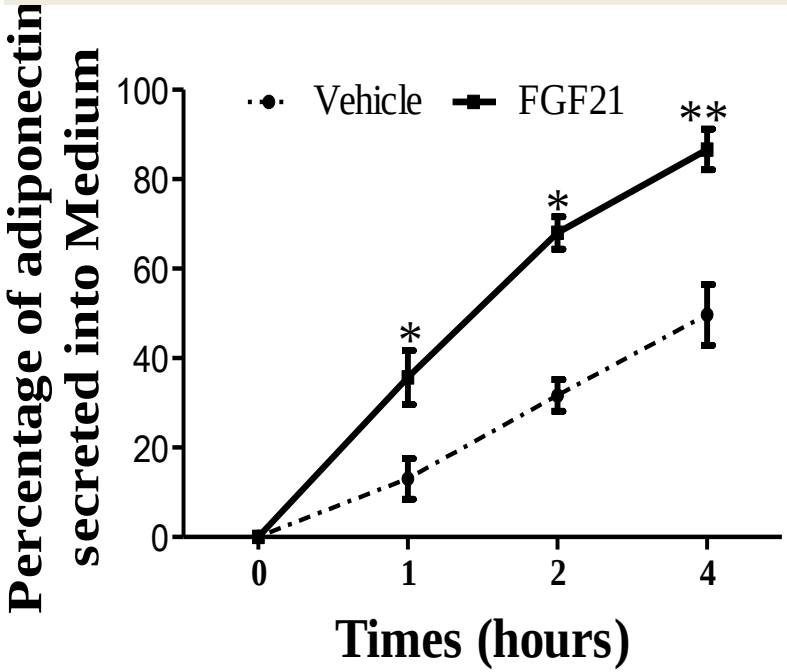
A

Pulse-chase experiment with ^{35}S methionine



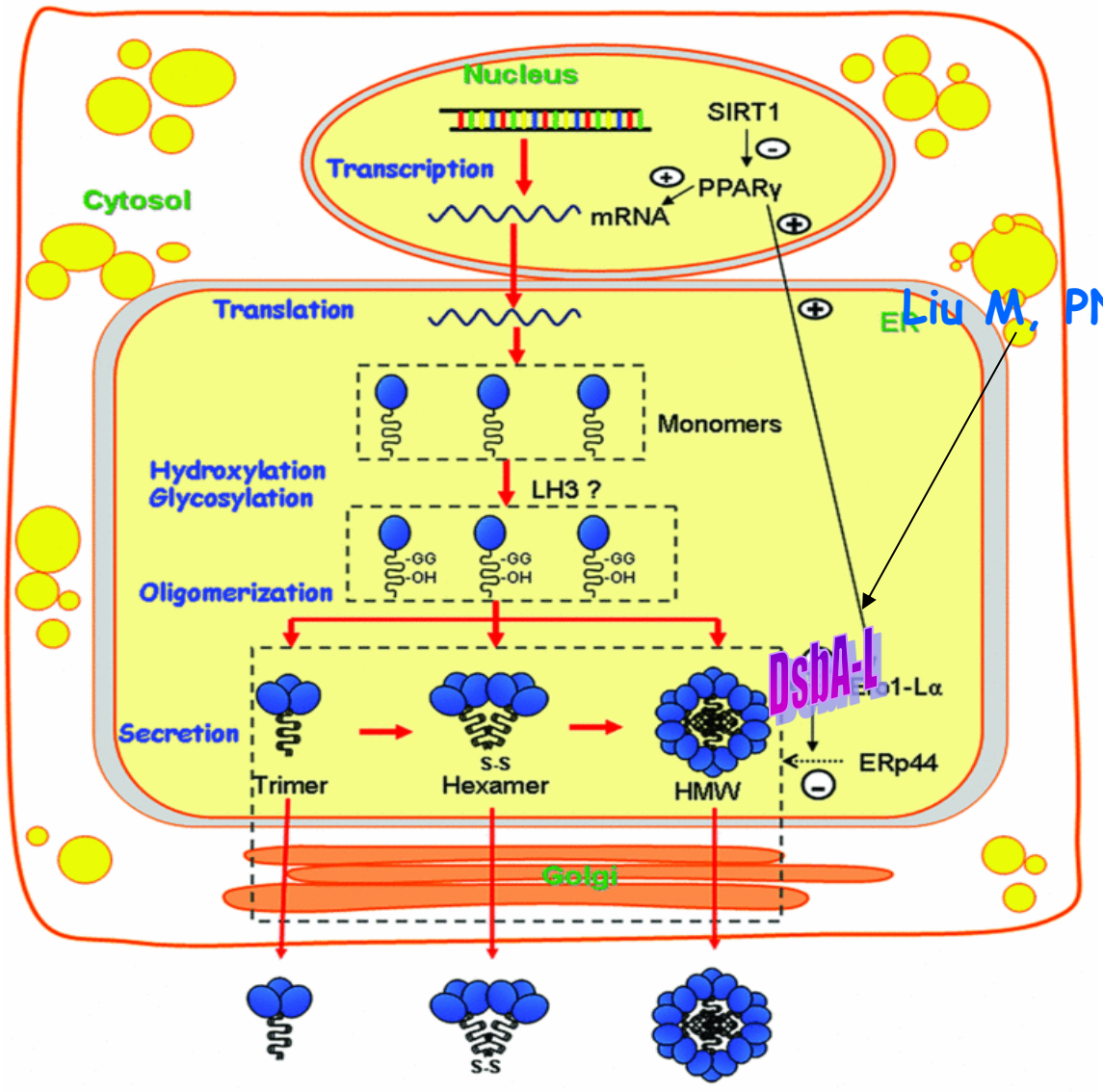
B

Percentage of adiponectin released



CL: Cell lysates; CM: Conditioned medium

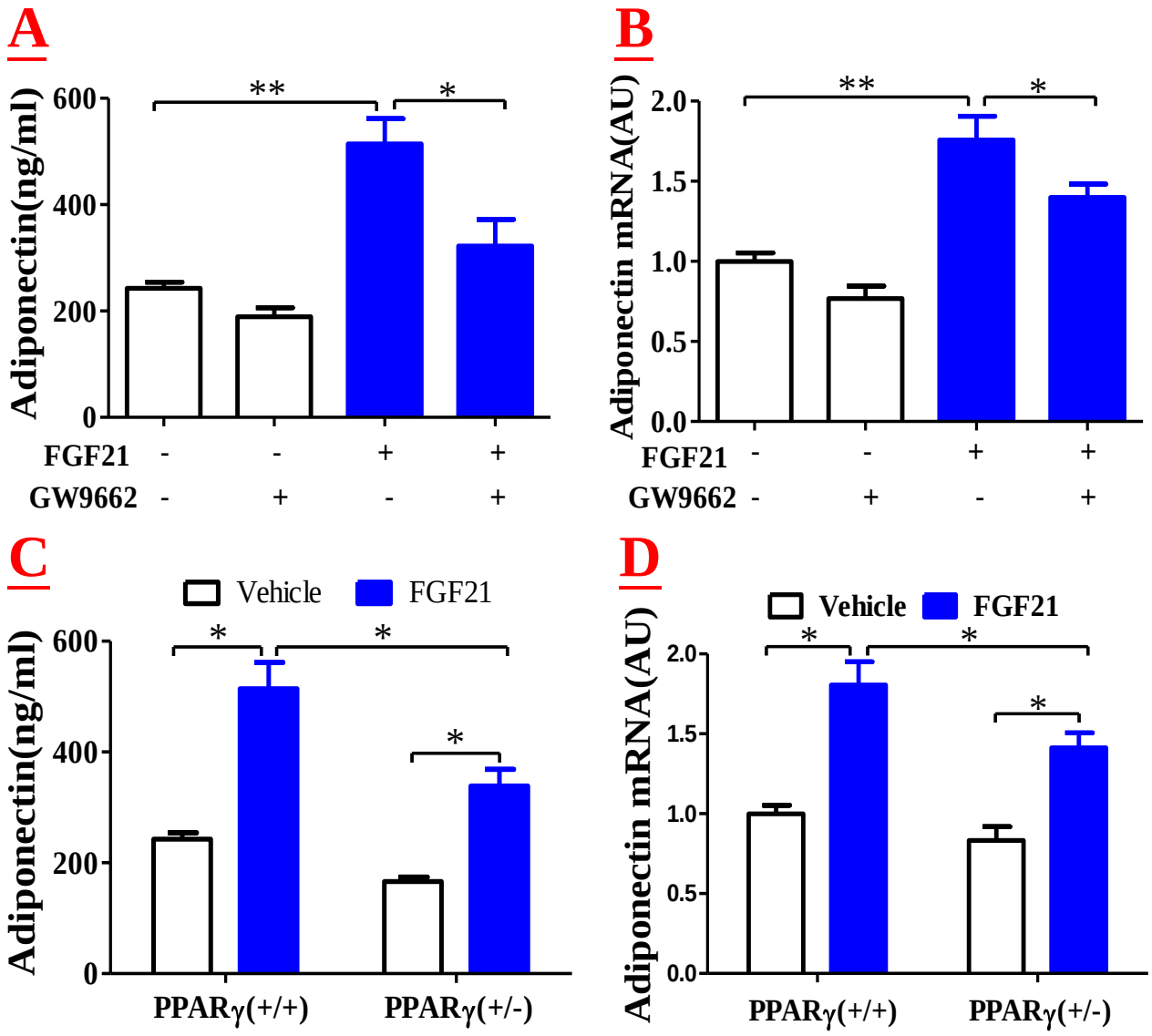
PPARr agonists increase adiponectin expression and secretion



Liu M, PNAS, 2008

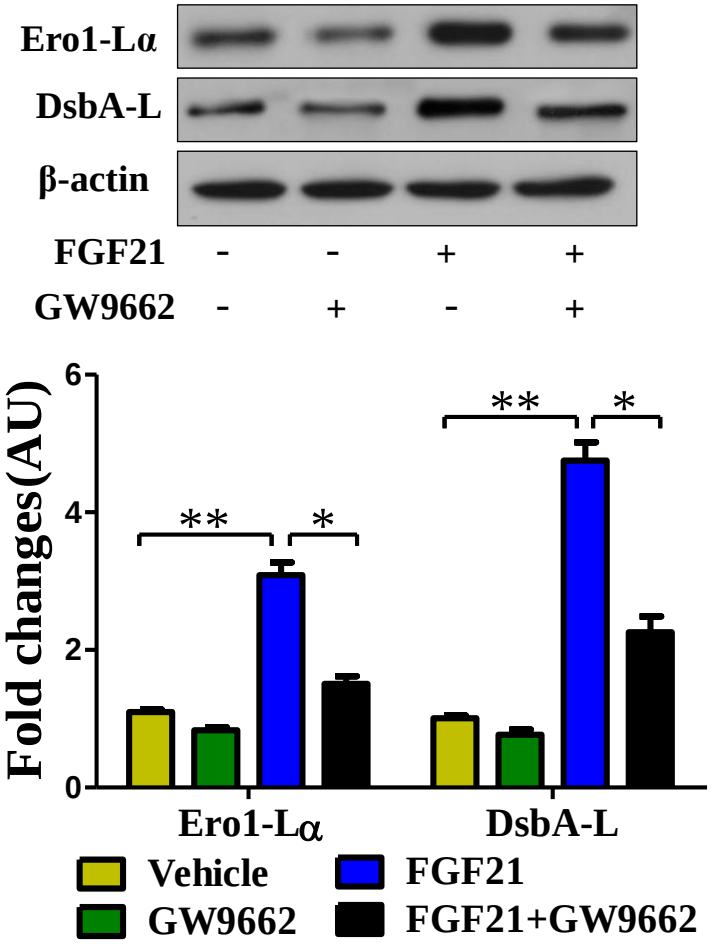
Reviewed by Wang Y, Biochem J, 2008

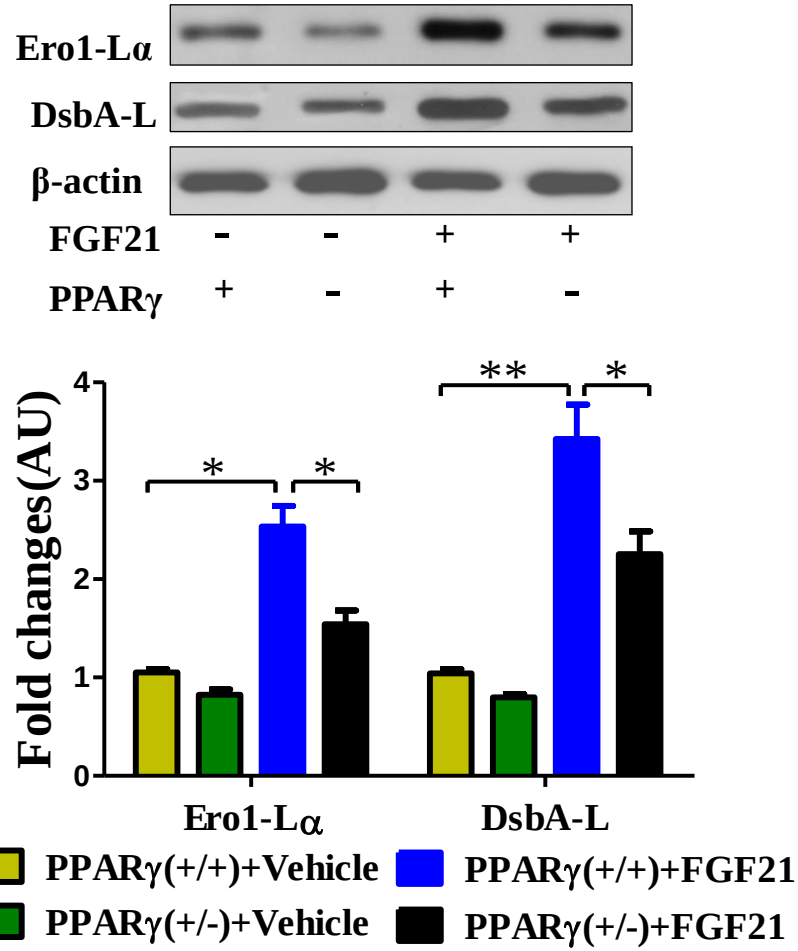
Suppression of PPARγ attenuates FGF21-induced expression and secretion of adiponectin



GW9662: PPARr antagonist

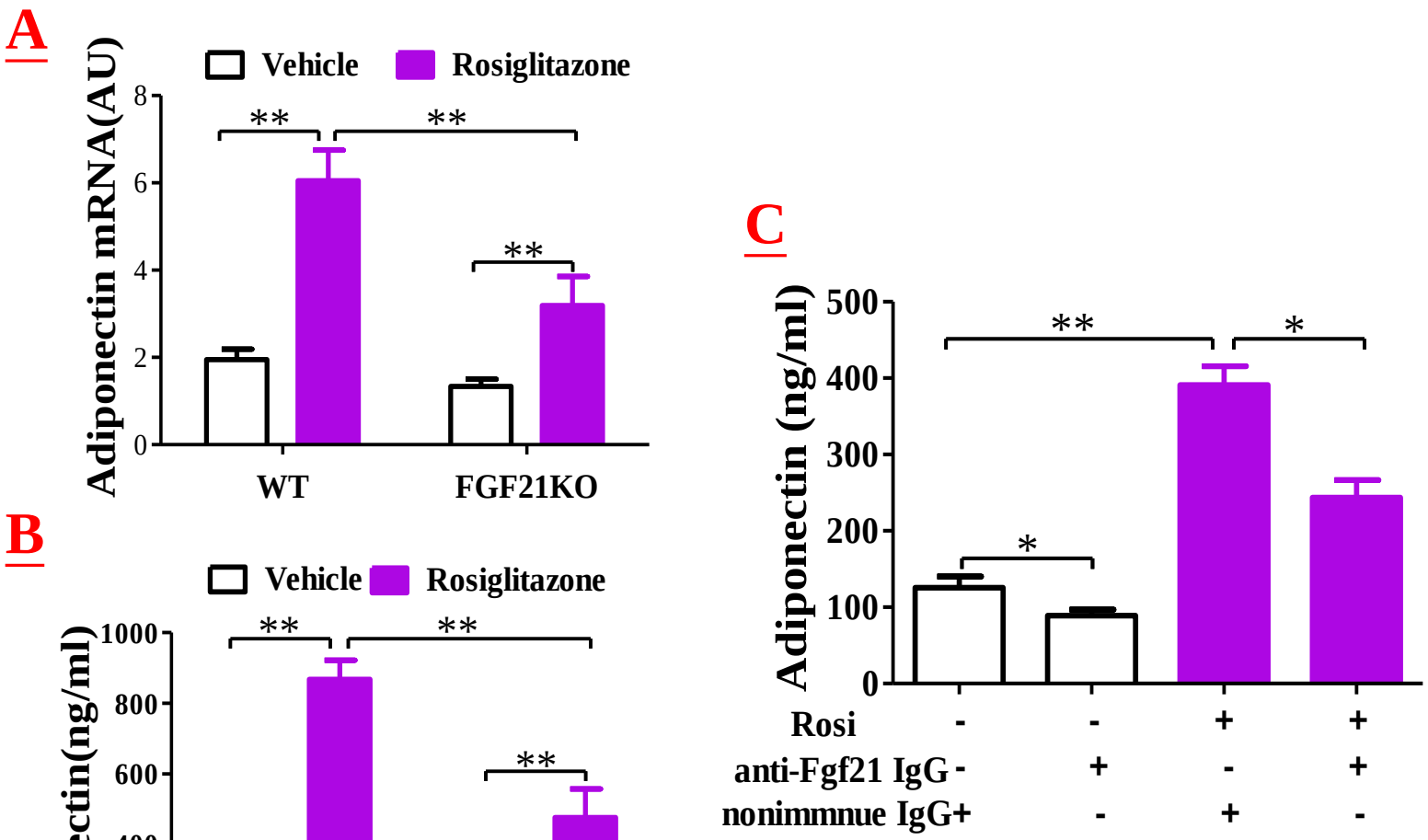
FGF21 induces the expression of molecular chaperones involved in adiponectin secretion





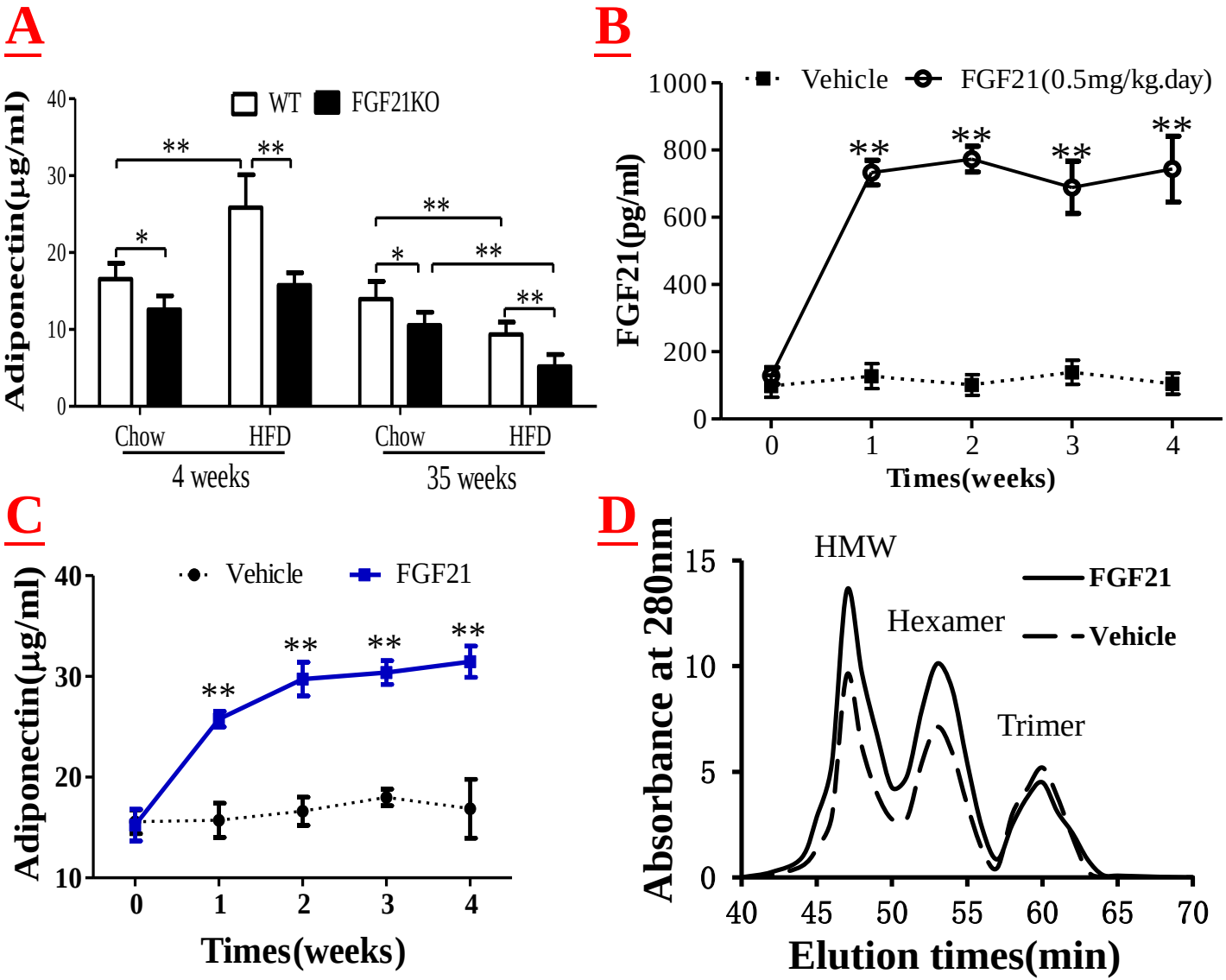
* p<0.05; **p<0.01. n=5-6

FGF21 acts in an autocrine manner to induce adiponectin production in adipocytes

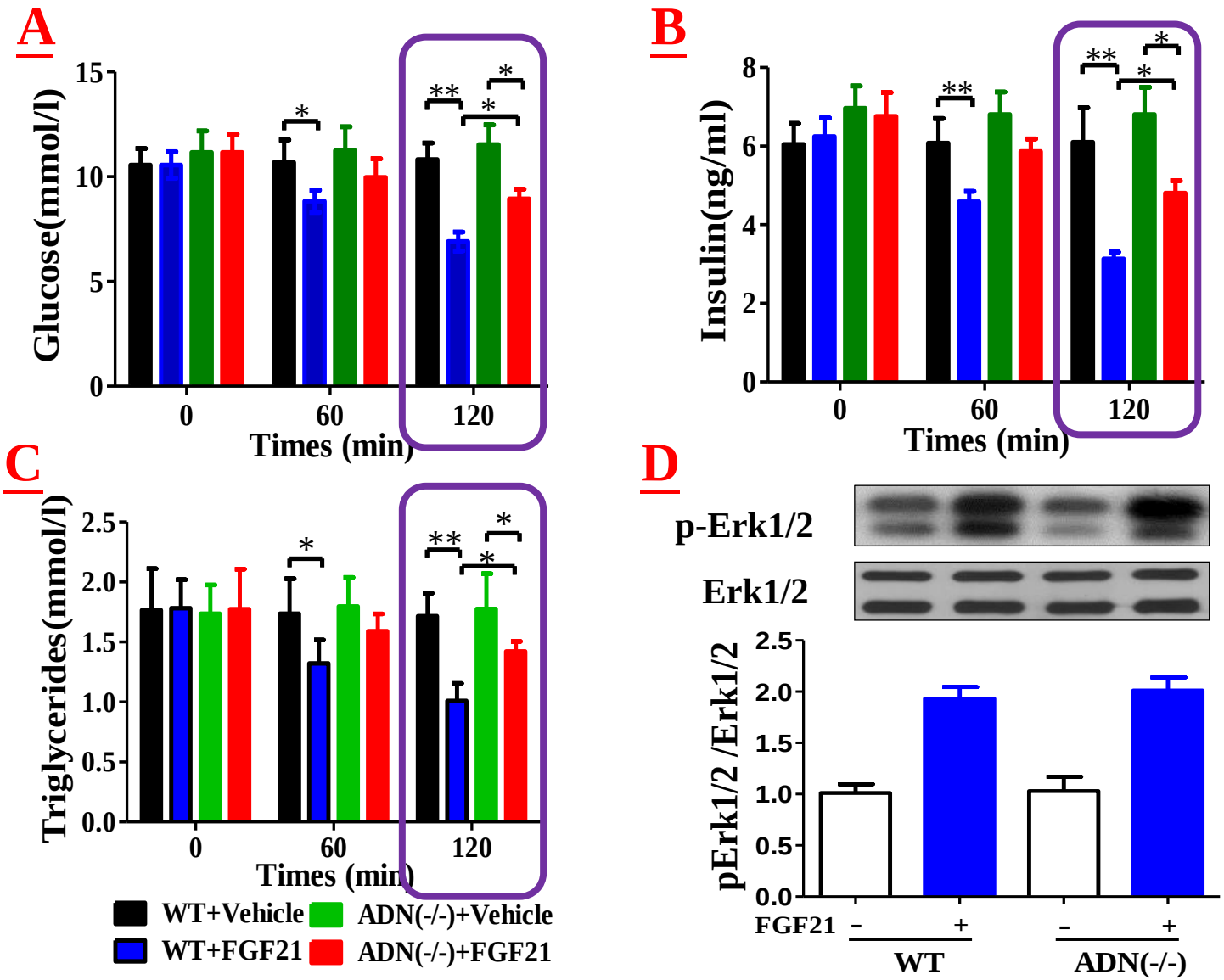


*p<0.05; **p<0.01. n=5 in each grou

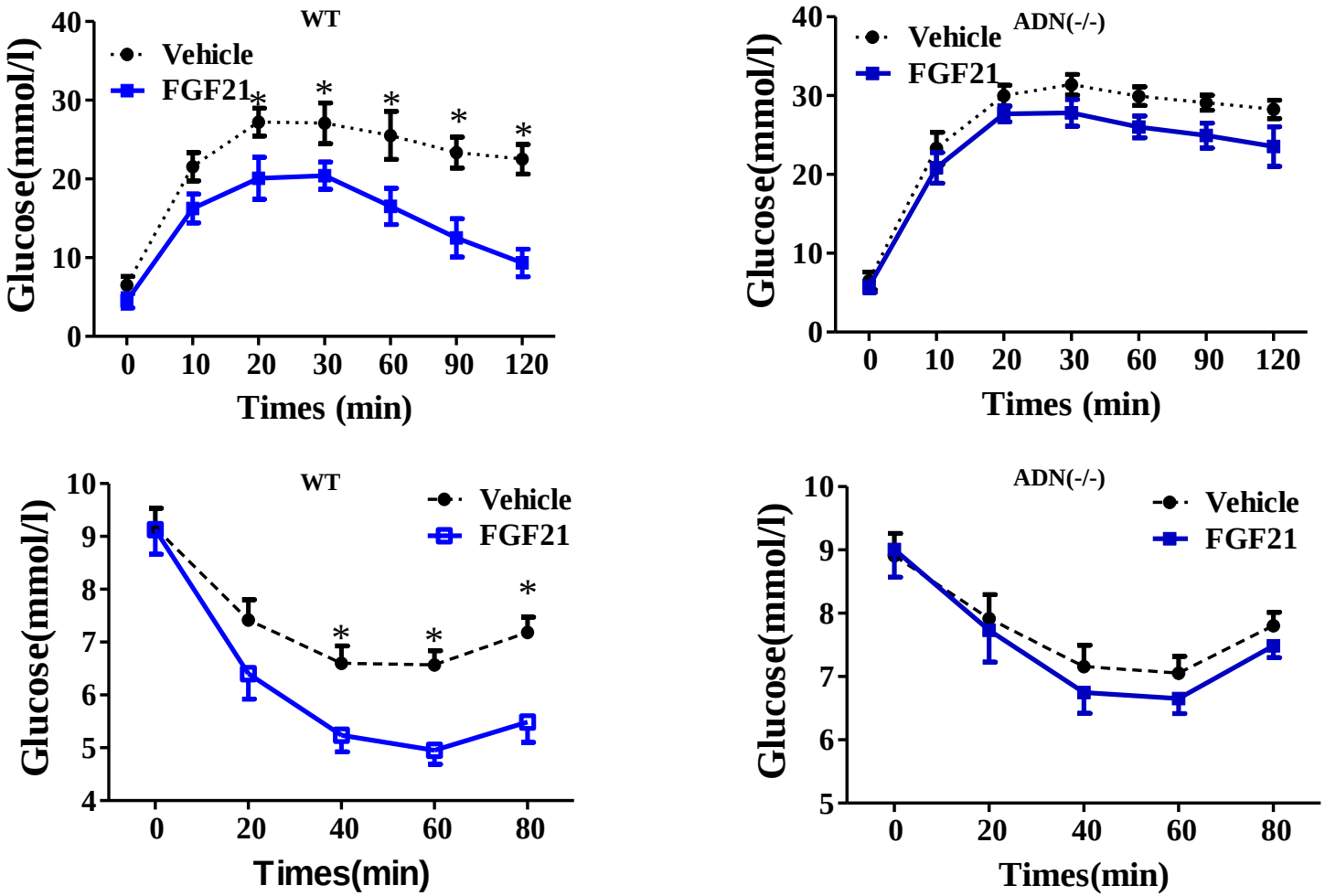
FGF21 induces adiponectin production in mice



The acute metabolic benefits of FGF21 are abrogated in adiponectin-deficient mice with dietary obesity

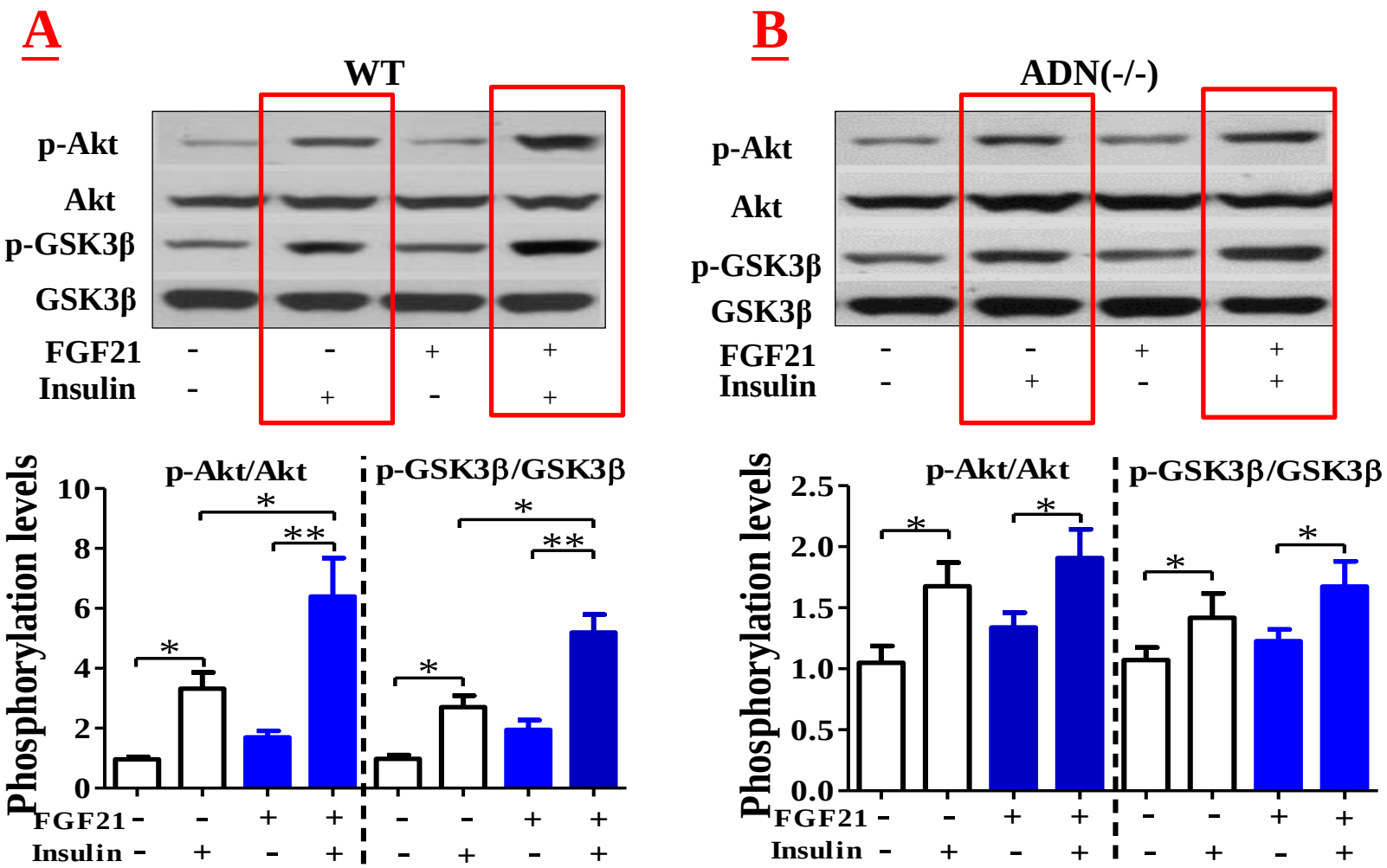


The beneficial Effects of FGF21 on glucose metabolism and insulin sensitivity are impaired in adiponectin KO mice



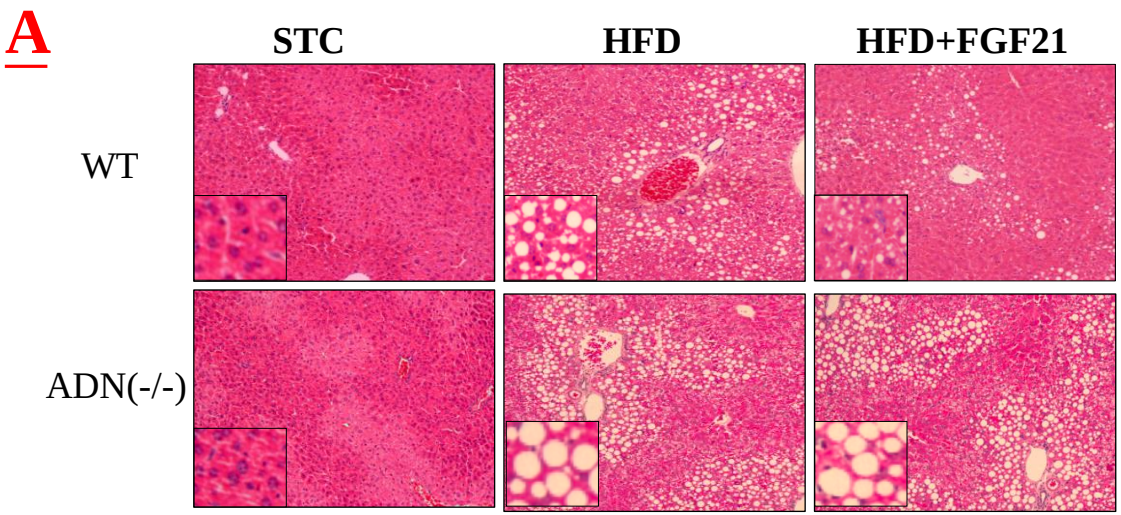
Lin ZF, Cell Metabolism, 2013: 7;17:779-89.

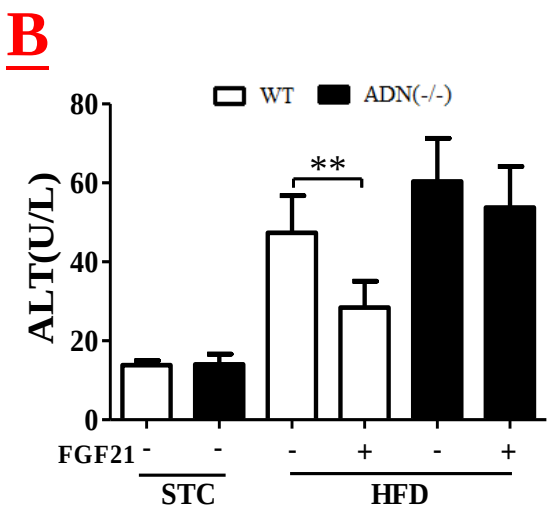
The insulin-sensitizing effects of FGF21 in the liver are mediated by adiponectin

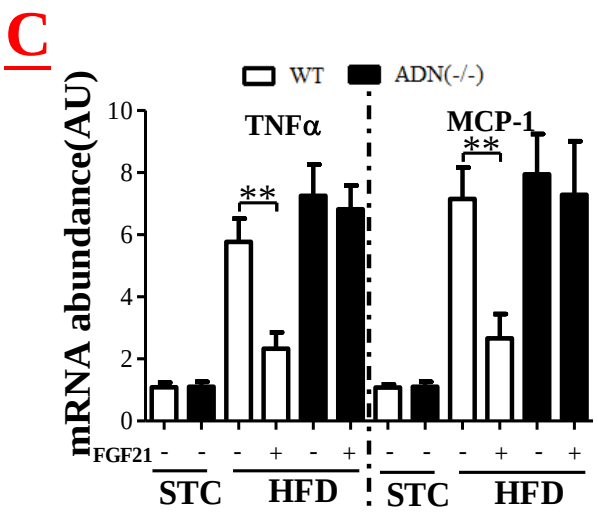


*p<0.05; **p<0.01. n=5 in each group

Adiponectin is required for FGF21-mediated alleviation of fatty liver disease in obese mice

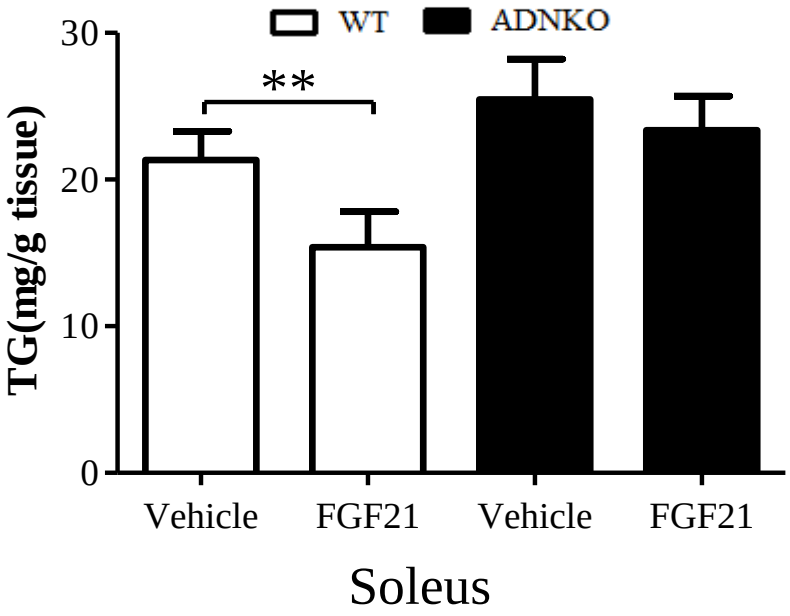


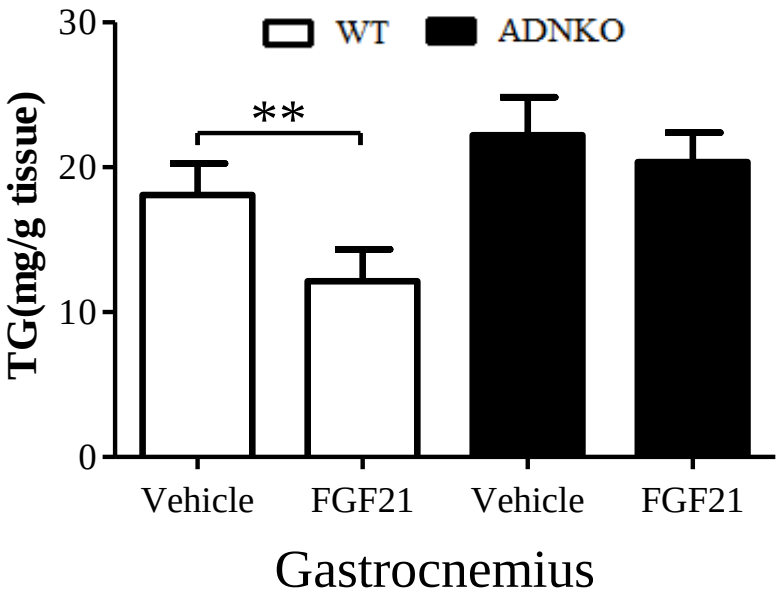




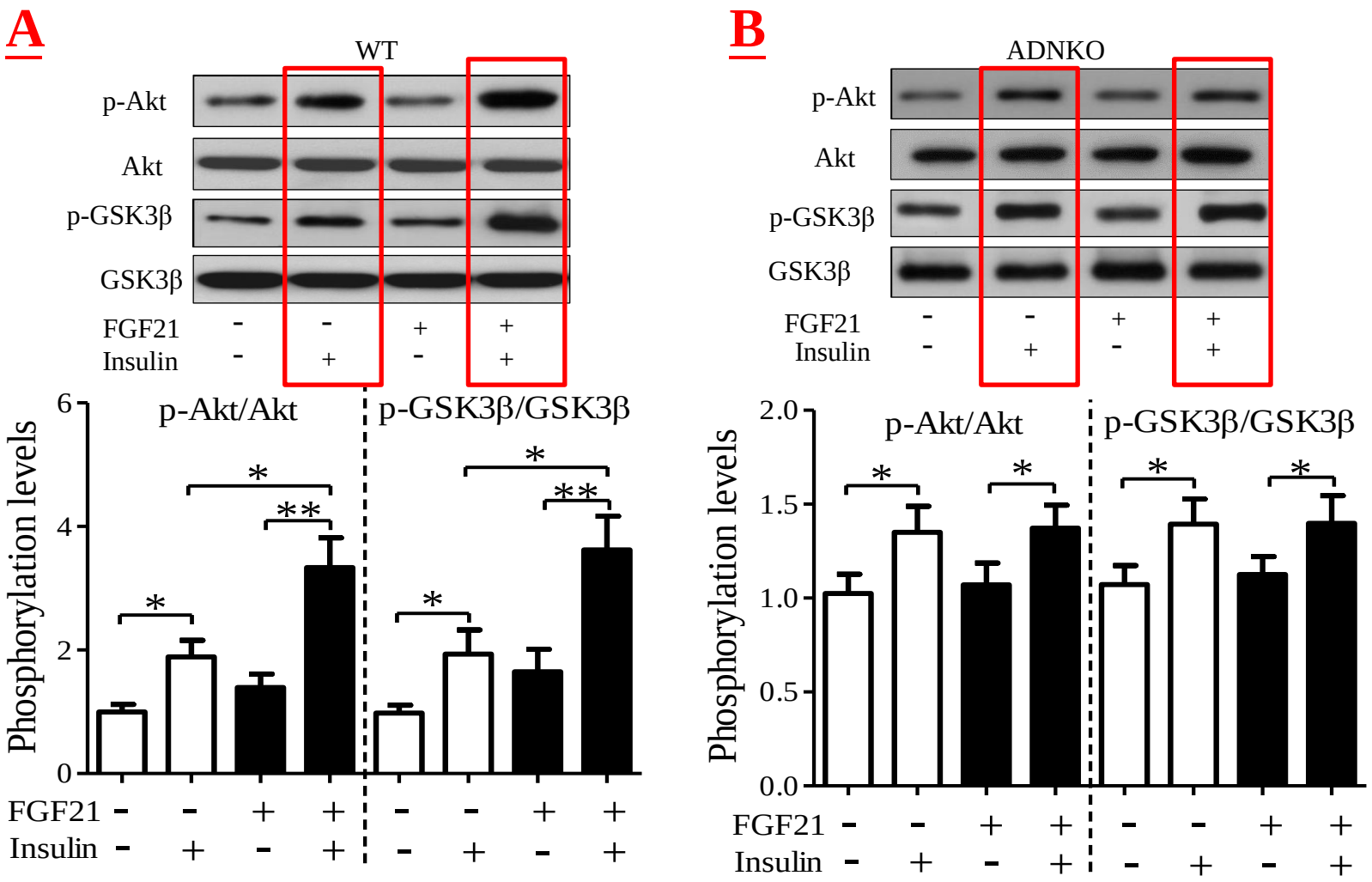
*p<0.05; **p<0.01. n=6 in each group

Adiponectin is obligatory for FGF21-mediated reduction of HFD-induced lipid accumulation in skeletal muscle



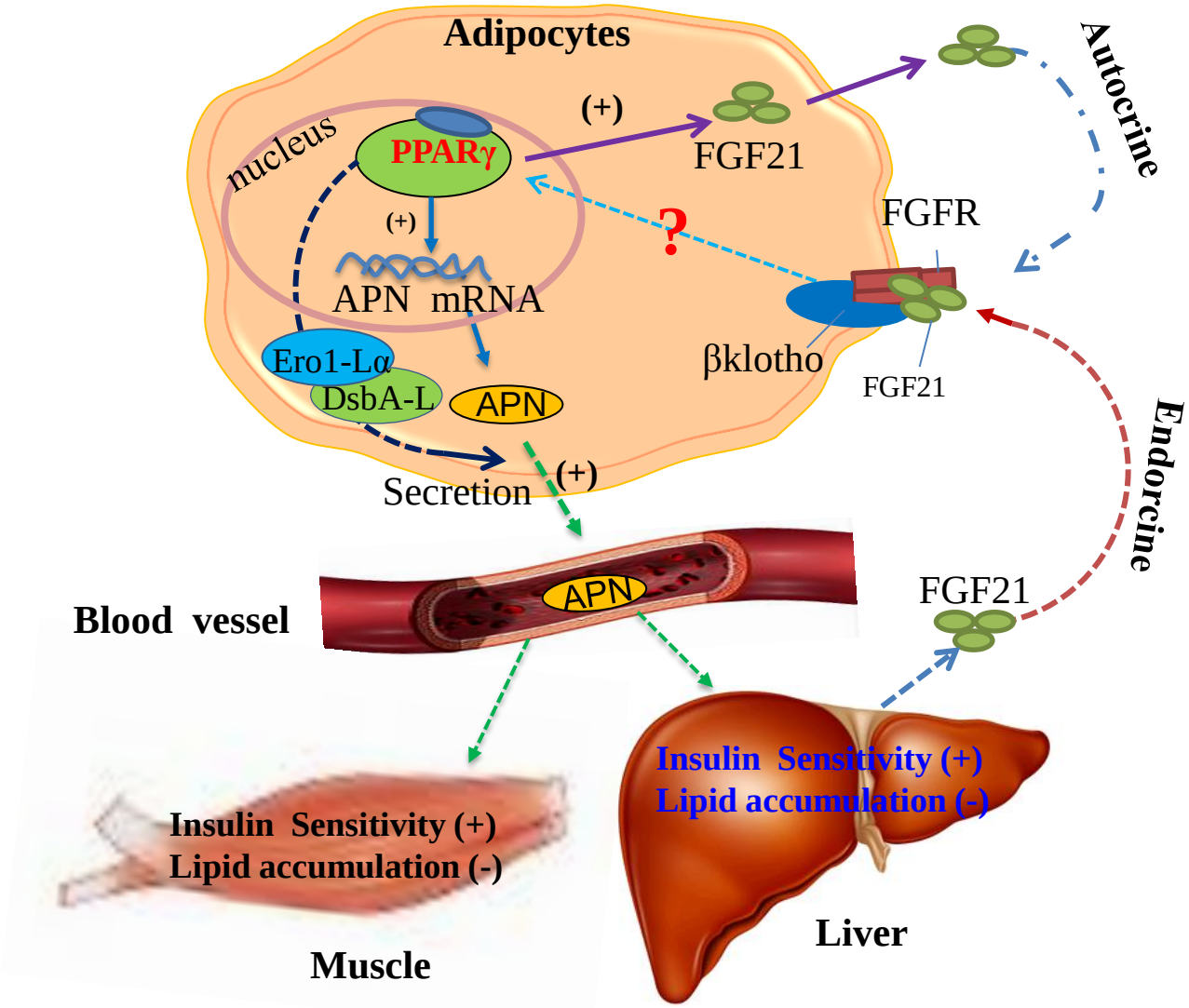


The insulin-sensitizing effects of FGF21 in skeletal muscle are dependent on adiponectin



*p<0.05; **p<0.01

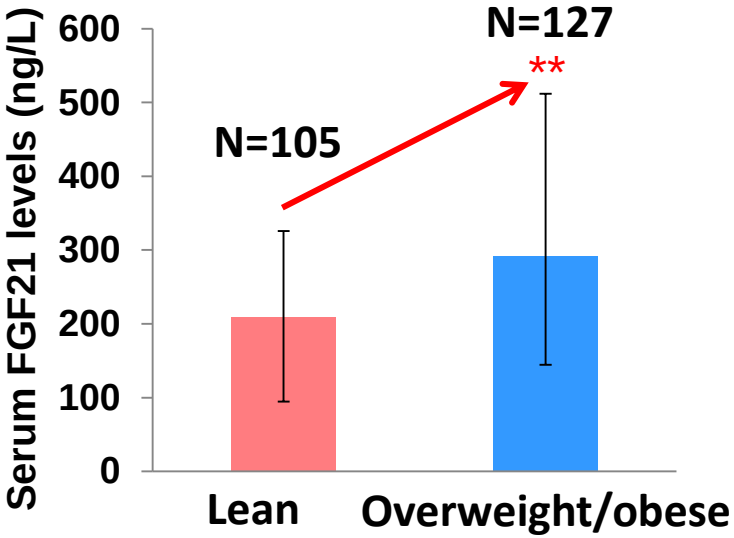
Adiponectin confers the metabolic actions of FGF21 in the liver and skeletal muscle

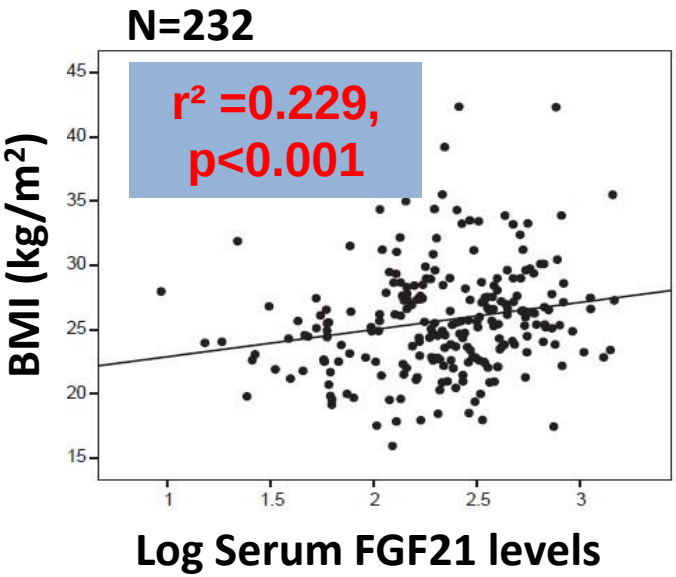


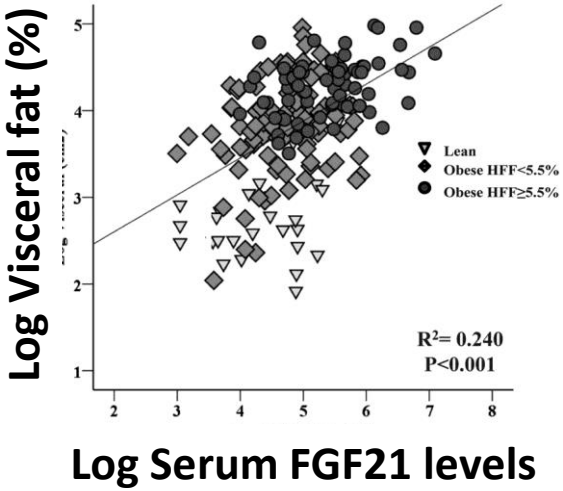
Lin ZF, Cell Metabolism, 2013: 7;17:779-8

Serum FGF21 levels are significantly elevated in overweight/obese subjects

Human





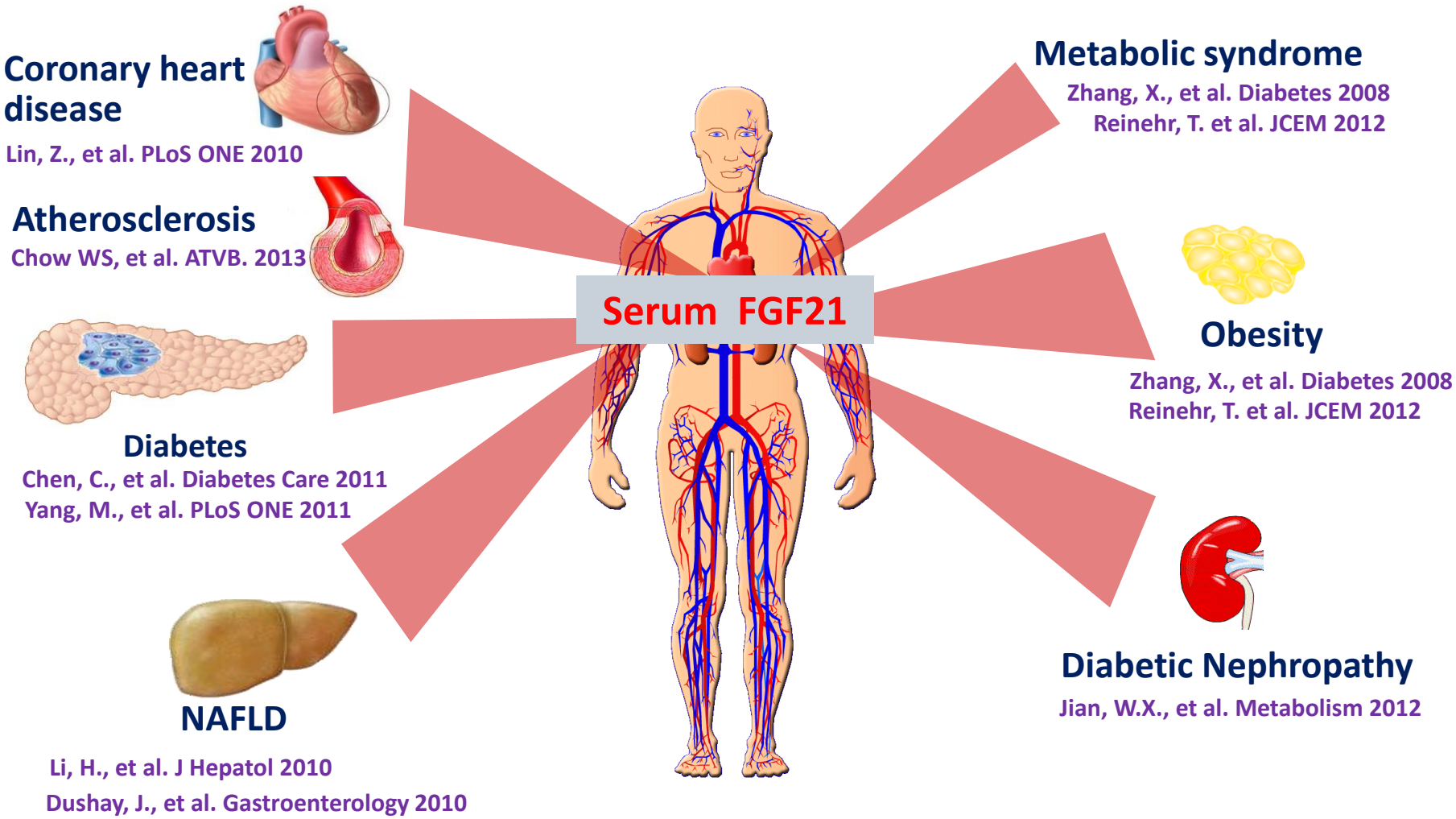


$r^2 = 0.240$,
$P < .001$

N=217

Zhang, X., et al. Diabetes 2008
Giannini C et al., J Clin Endocrinol Metab. 2013

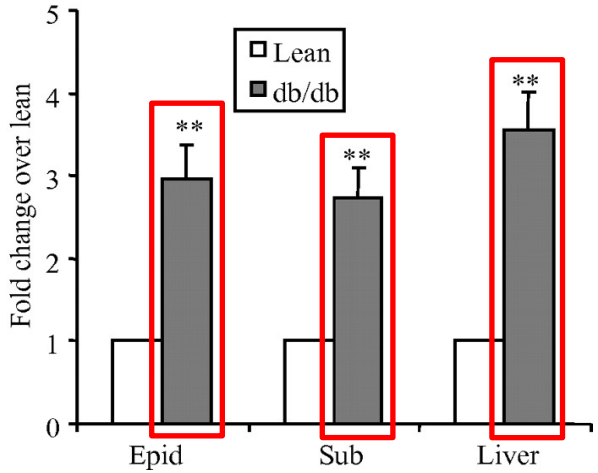
Elevated circulating FGF21 is associated with a cluster of obesity-related complications



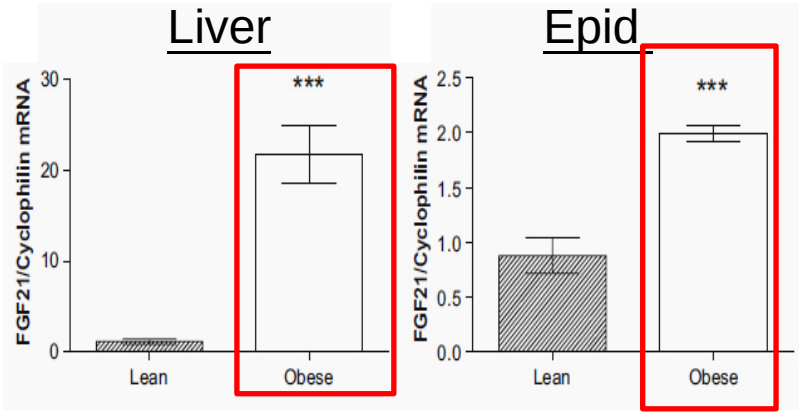
Elevated FGF21 production in obese animals

Tissue

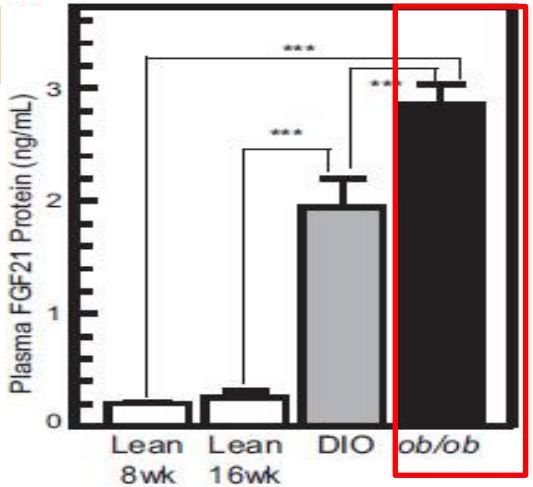
Genetic-induced obesity

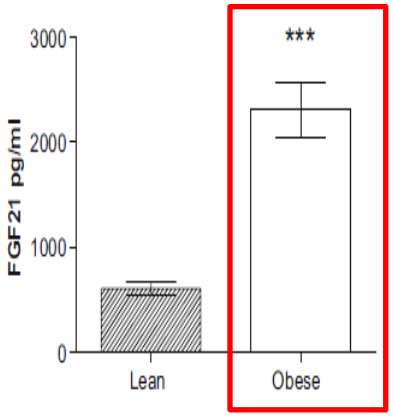


Diet-induced obesity



Serum



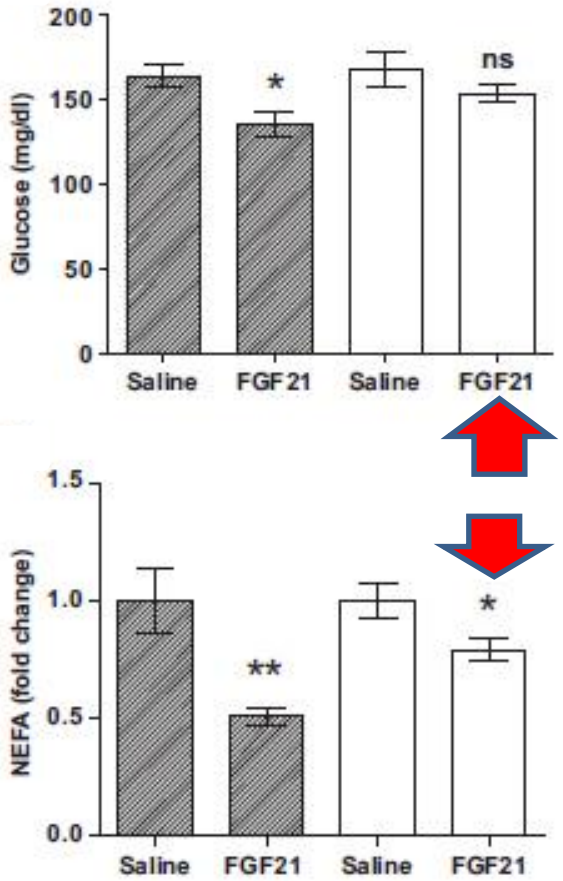


FGF21 Resistance ??

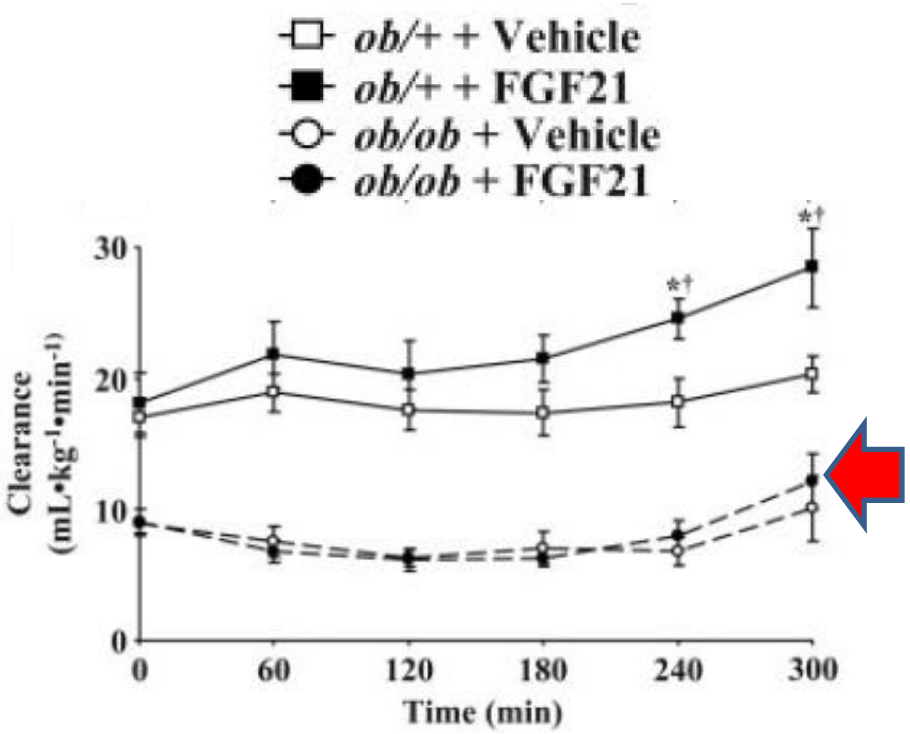
Zhang X, et al. Diabetes 2008; Fisher FM, et al. Diabetes 2010; Hale C, et al. Endocrinology 2012

Impaired actions of FGF21 in ob/ob obese mice

Fasting glucose and free fatty acid

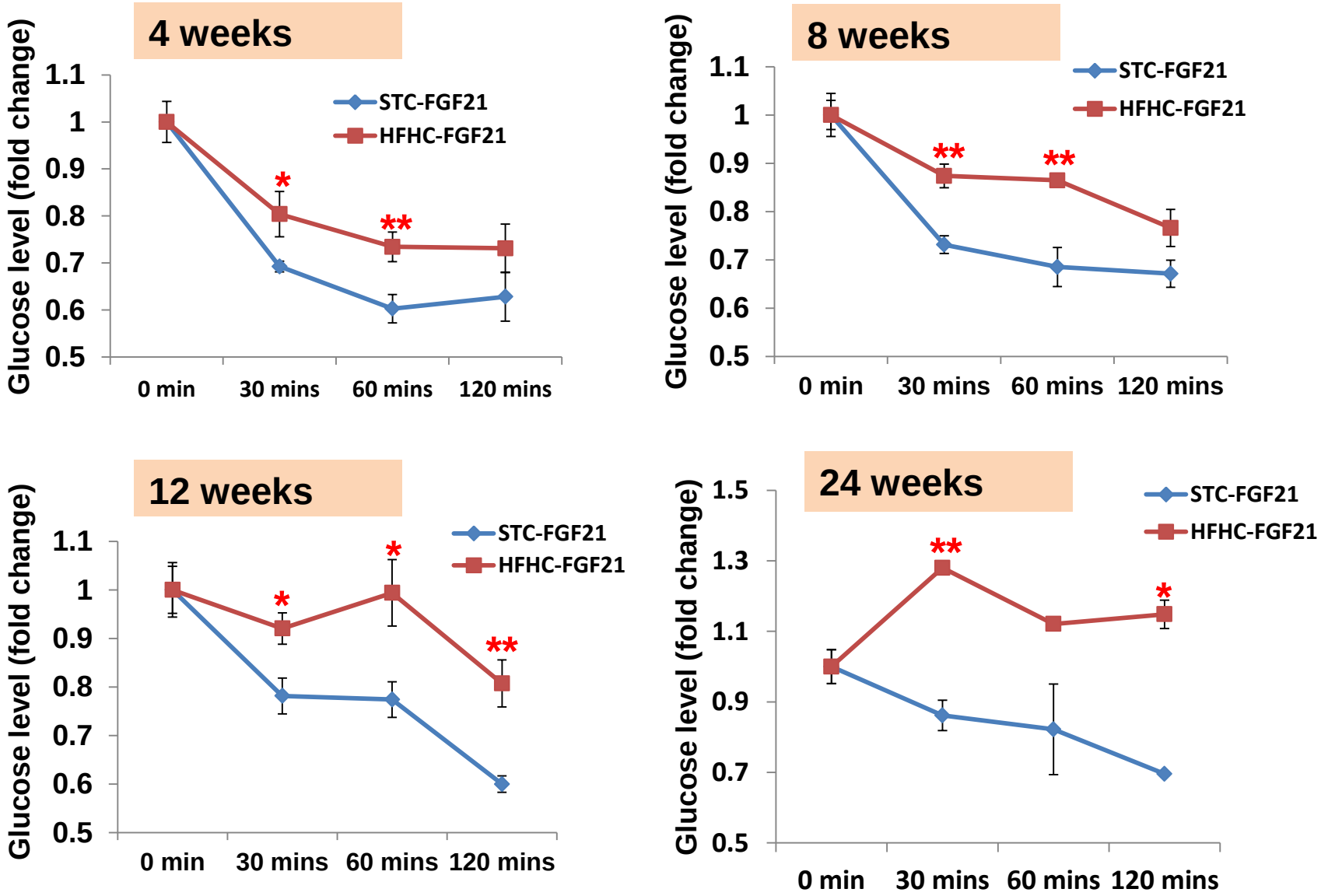


Glucose clamping

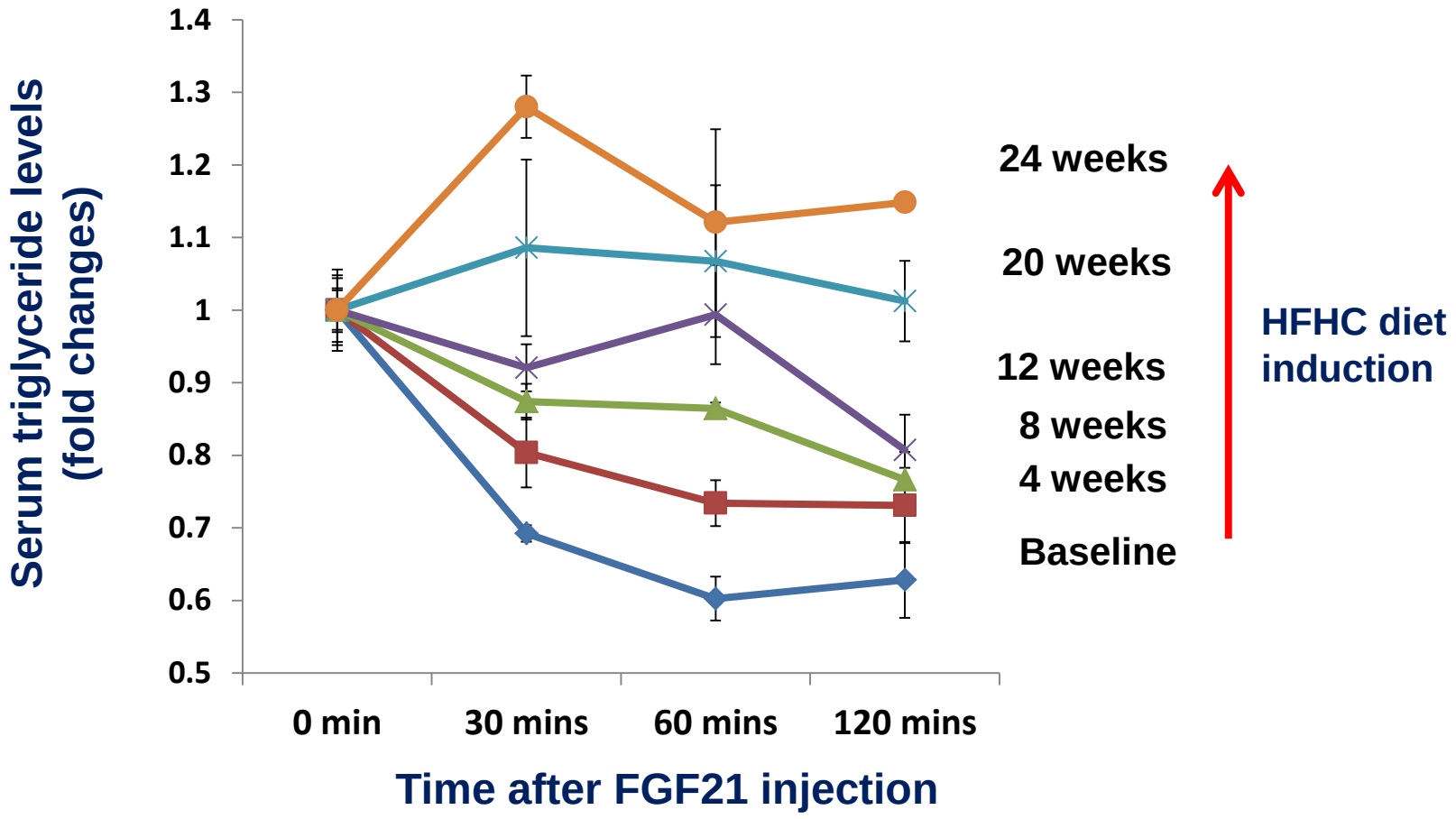


Berglund ED et al., Endocrinology. 2009 ;
Fisher FM, et al. Diabetes 2010

The glucose-lowering effects of FGF21 are progressively decreased in High Fat High Cholesterol (HFHC) diet-induced obese mice

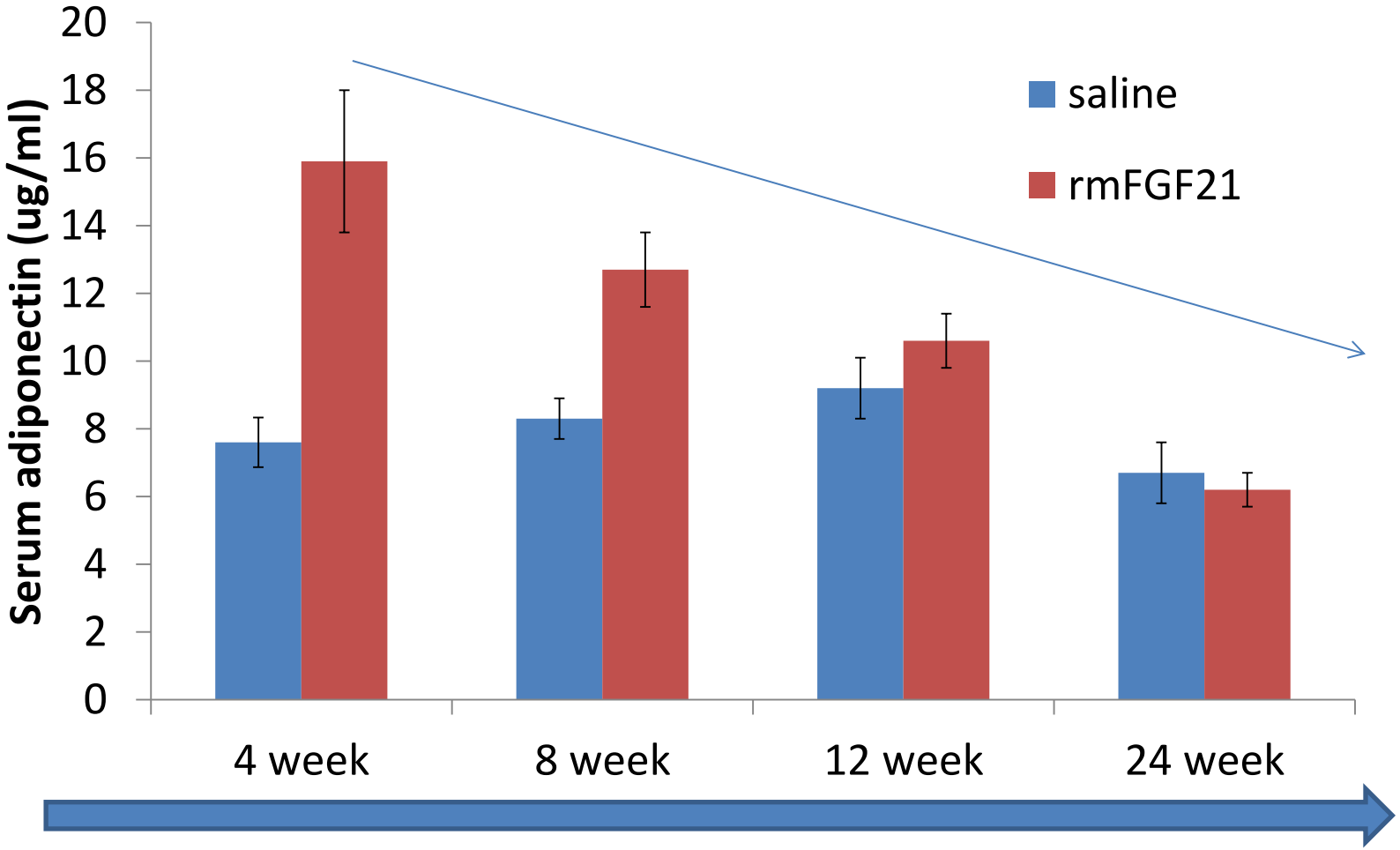


A progress development of FGF21 resistance during diet-induced obesity



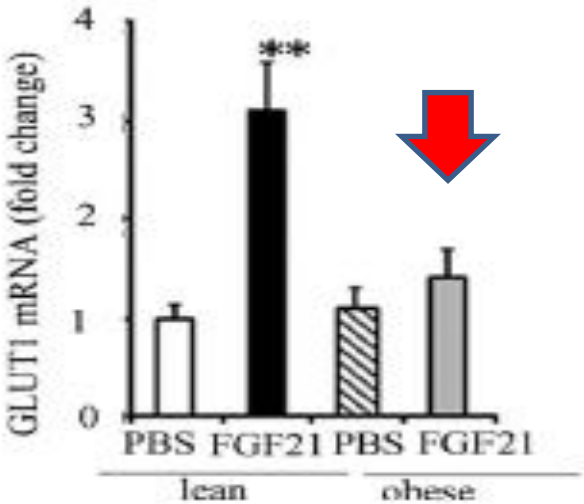
FGF21: 1 mg/kg; n=5

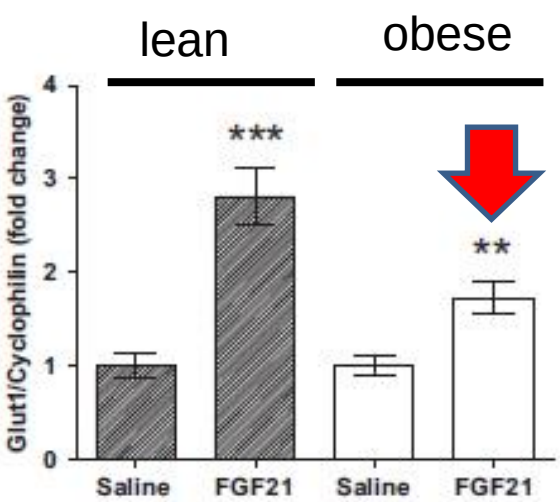
The ability of recombinant FGF21 (rmFGF21) to increase circulating adiponectin is progressively impaired in diet-induced obesity

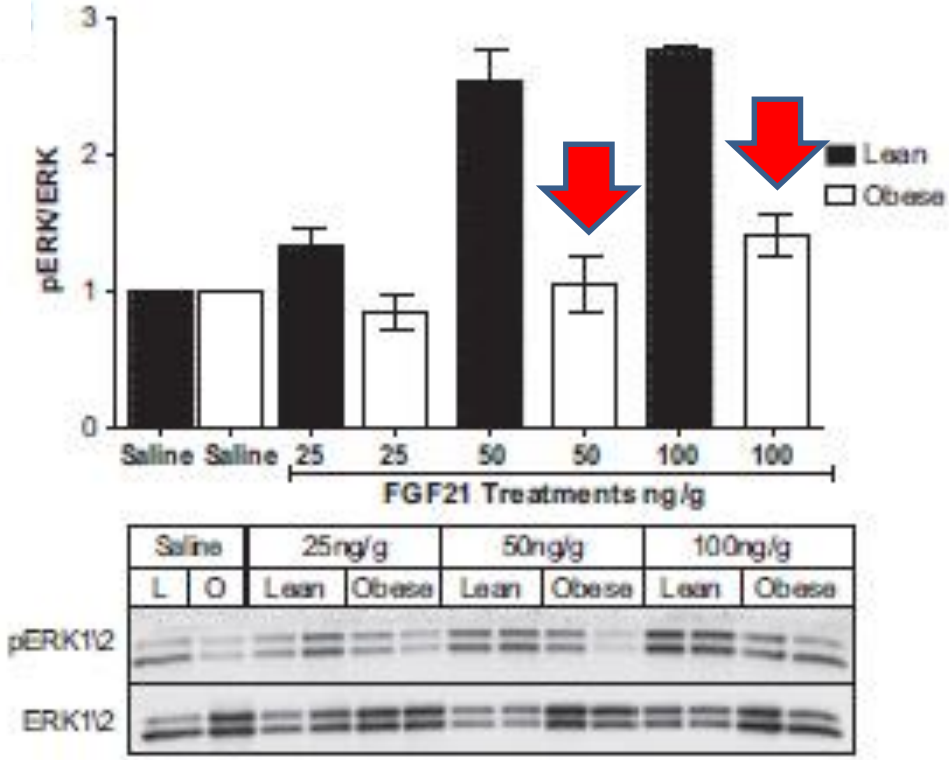


High fat high cholesterol diet

FGF21-induced signal transduction pathways in adipose tissues are impaired in obesity

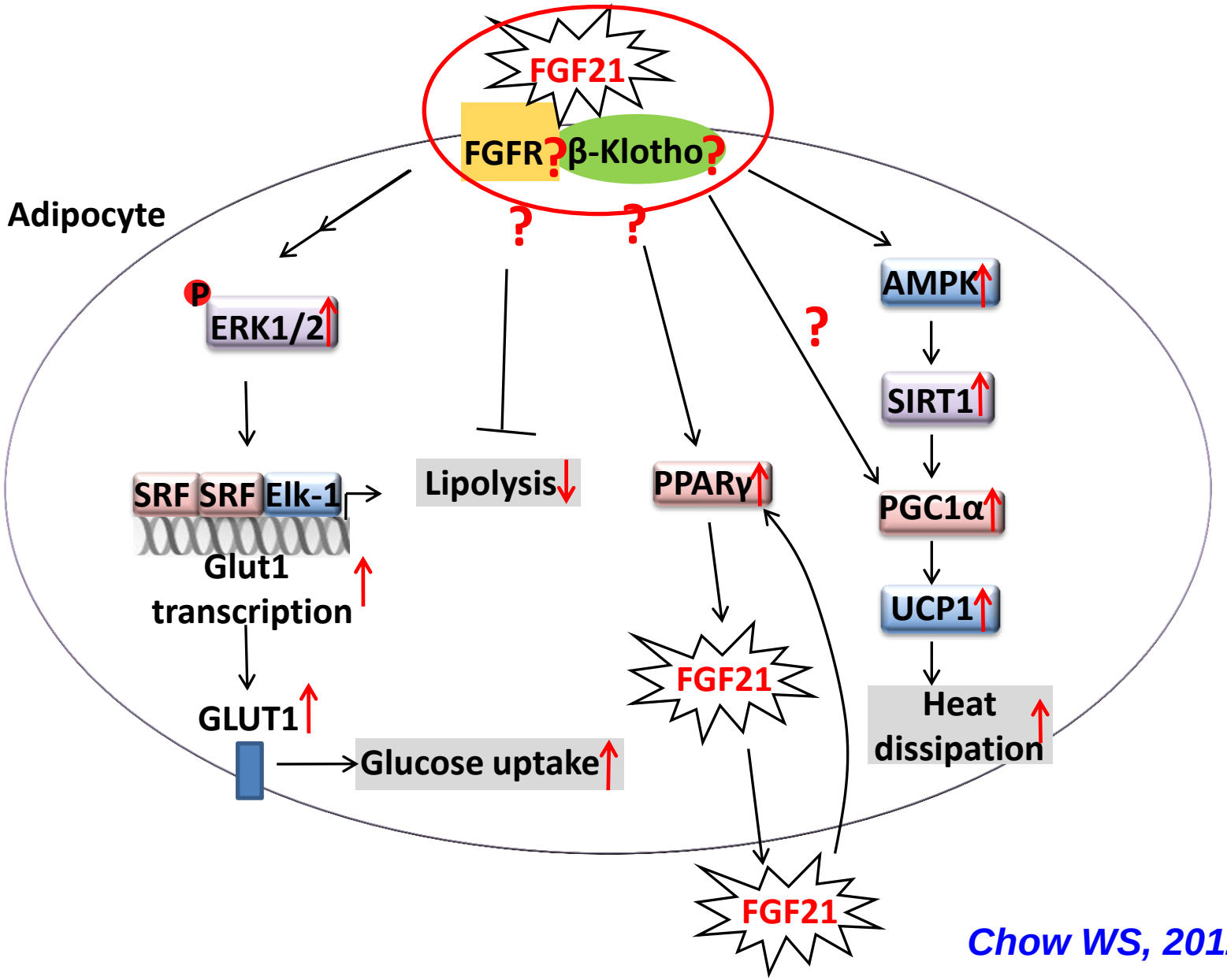






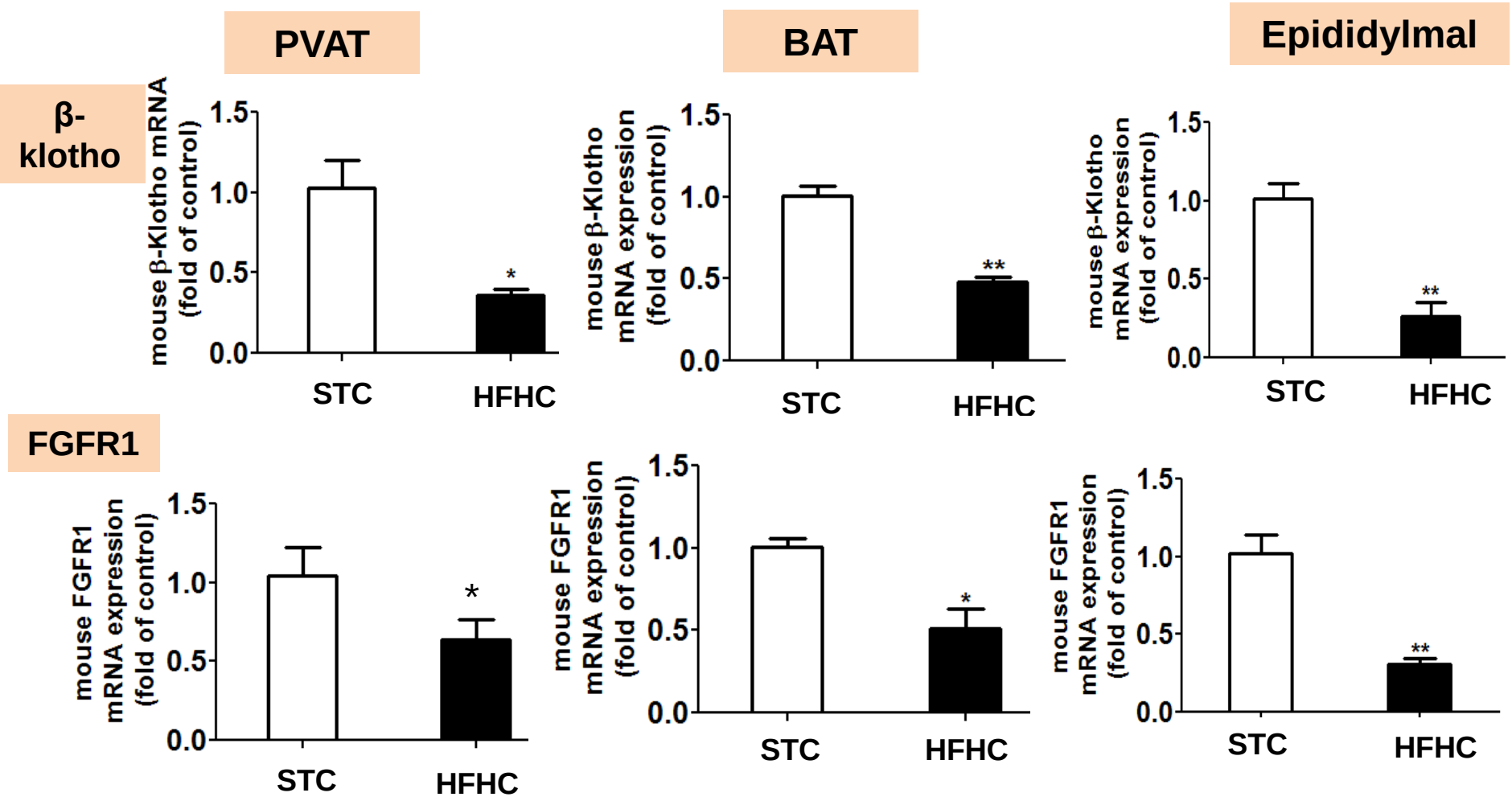
Ge X, et al. J Biol Chem 2011; Fisher FM, et al. Diabetes 2010

Mechanisms of FGF21 resistance?



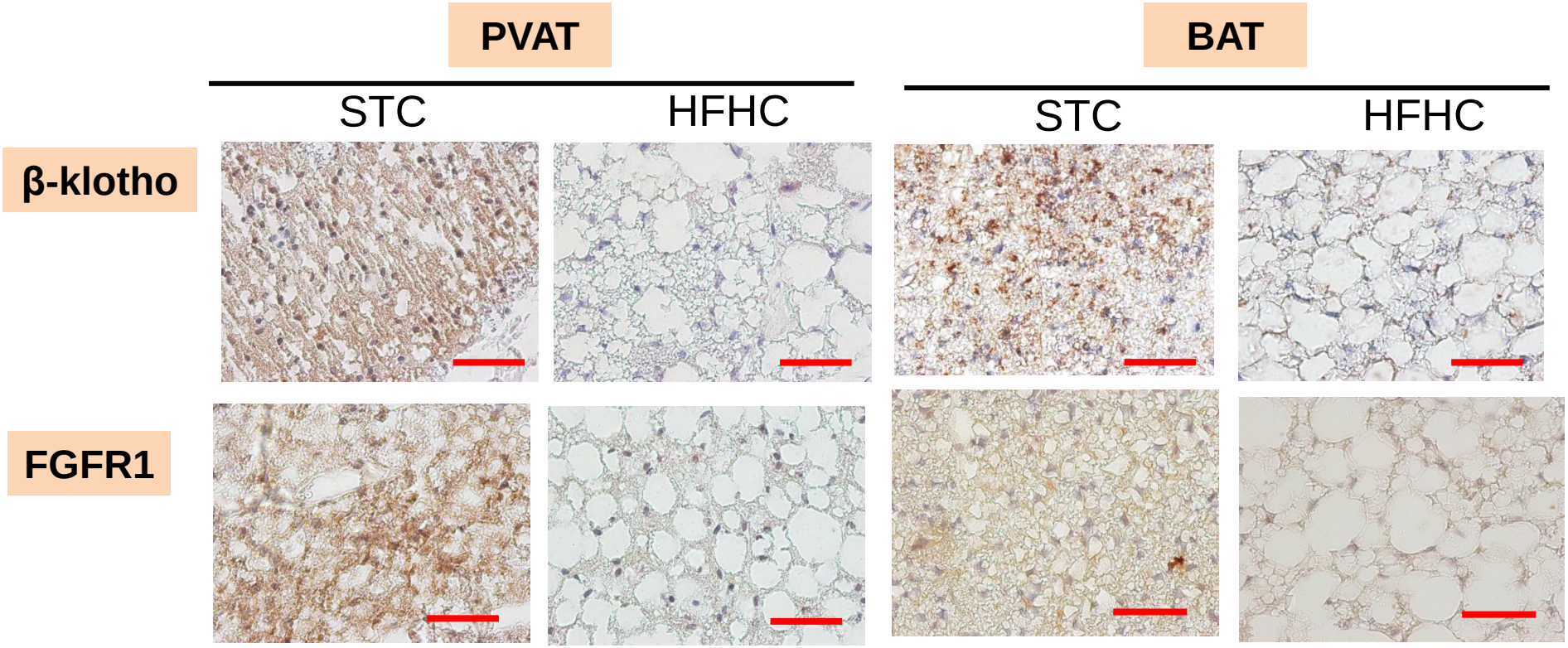
Chow WS, 2012

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



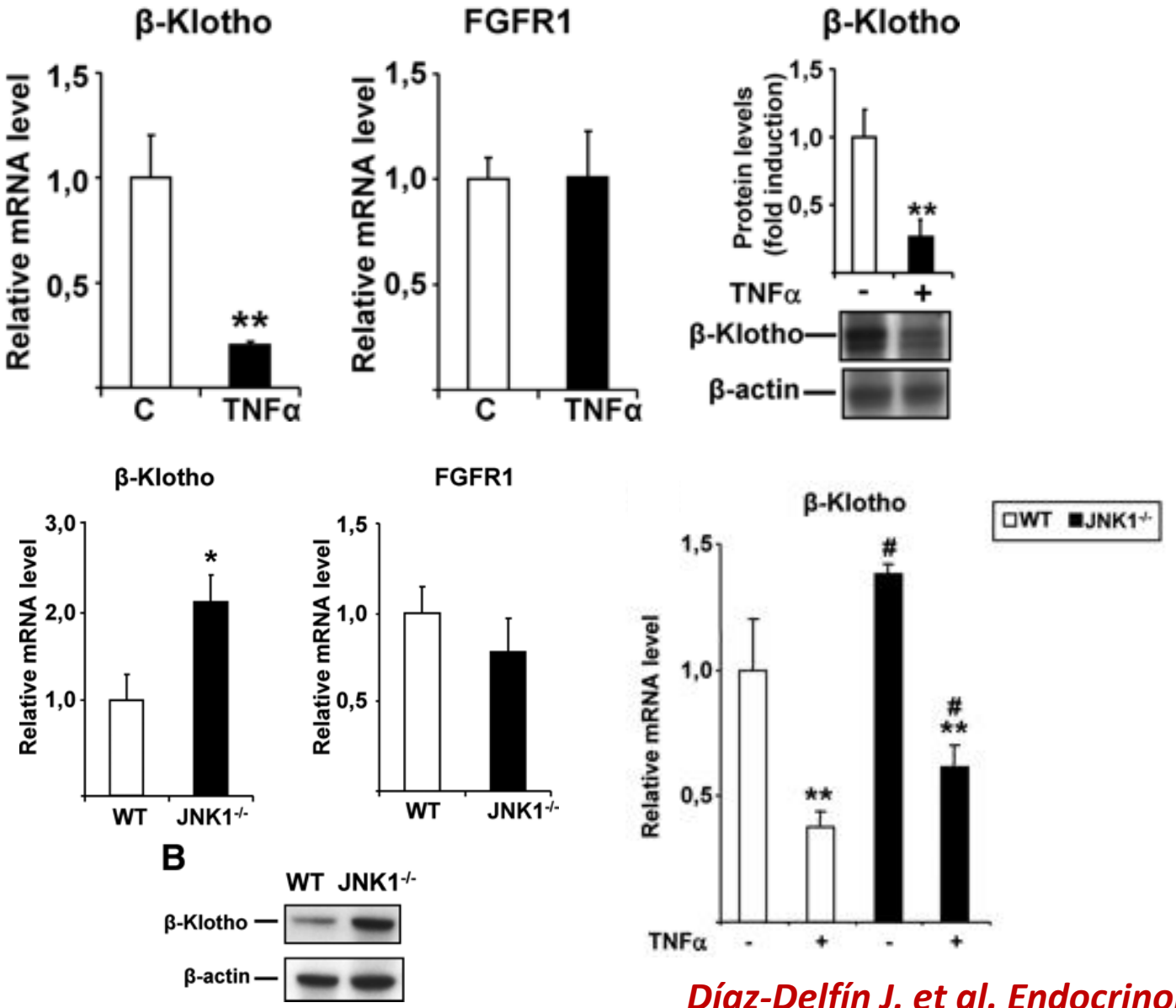
HFHC: High fat high cholesterol diet

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

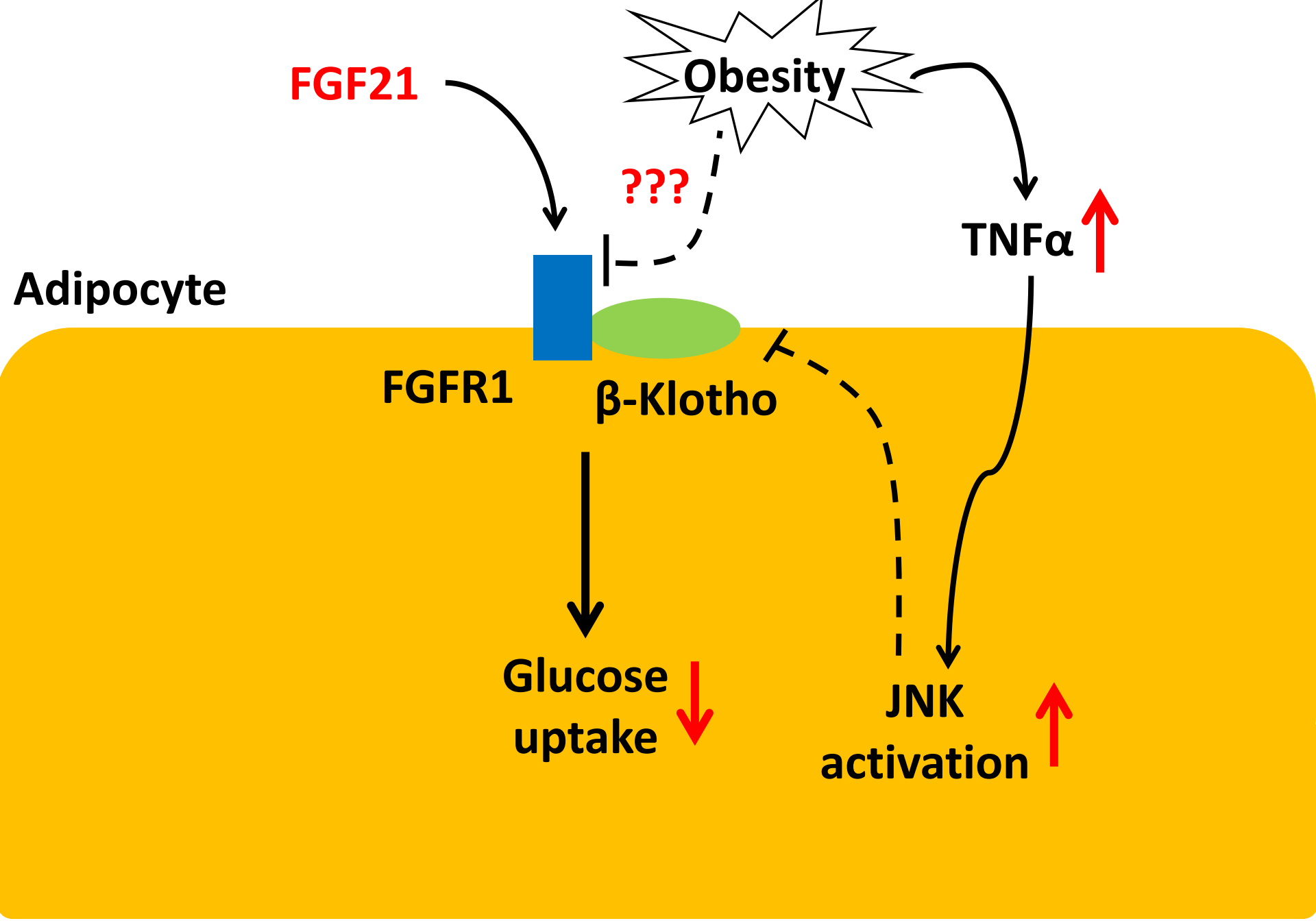


How does obesity cause reduced β-klotho and FGFR1 expression?

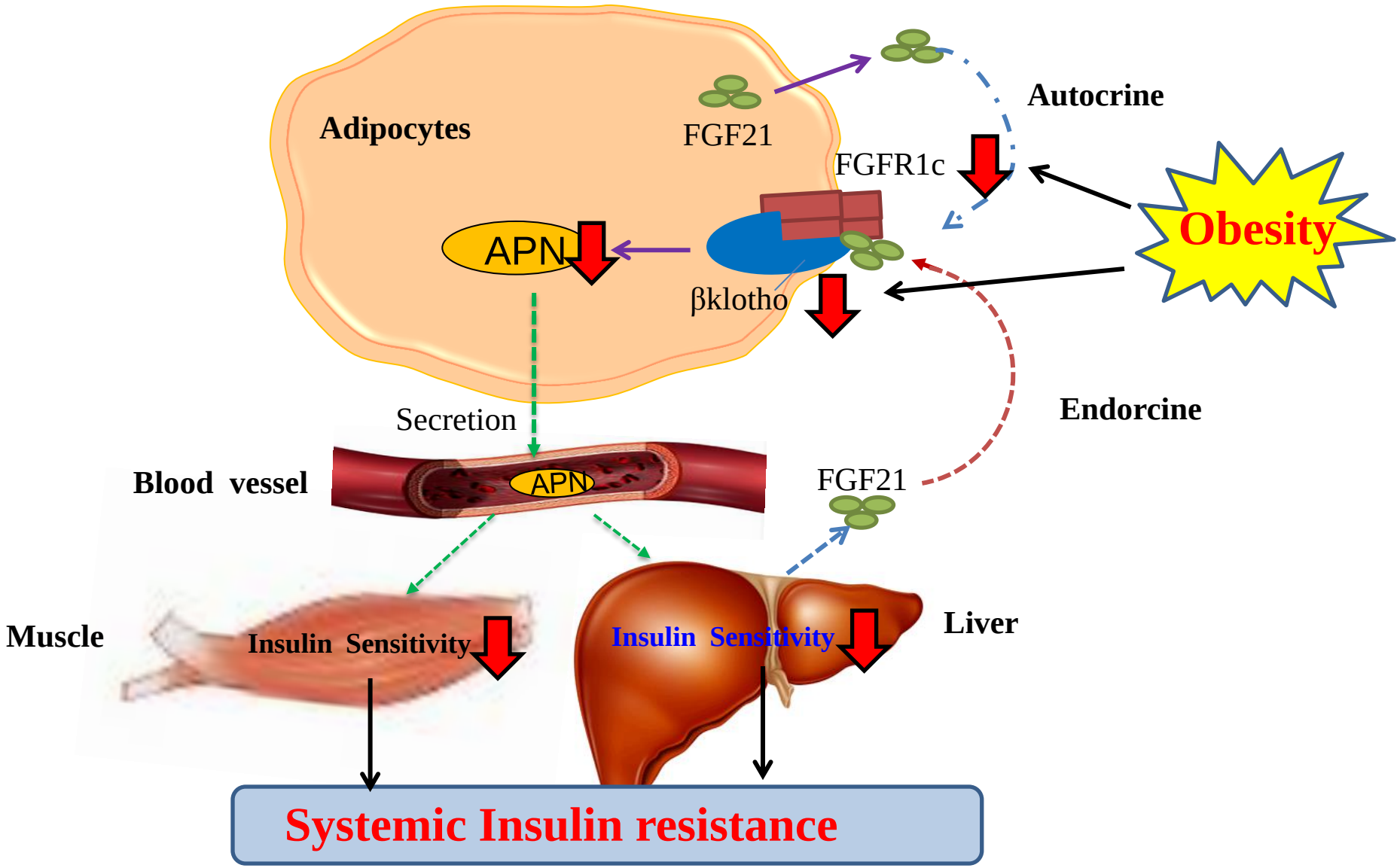
Involvement of TNFα-JNK pathway in modulating β-klotho expression???



Díaz-Delfín J, et al. Endocrinology. 2012


FGF21
Obesity
???
TNFα
Adipocyte
FGFR1
β-Klotho
Glucose uptake
JNK activation

FGF21 resistance as a cause of systemic insulin resistance



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Thank you!