FGF21 Resistance in Adipose Tissues as a Cause of Insulin Resistance

The ICDM 2013 & 5th AASD Scientific Meeting
Seoul, Korea, Nov 08, 2013

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

**A-FABP**
(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)
(Hoo R, J Hepatology, 2012)

**Adiponectin**
(Xu A et al, J. Clin. Invest, 2003,

**Lipocalin-2**
(Law I, Diabetes, 2010)
JBC, 2012; Liu Y, BJP, 2012

**FGF21**
(Zhang X, Diabetes, 2008; Diabetes,
2010; Chen C; Diabetes Care, 2011;

Adipose tissue
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

- Glucose Uptake
- Insulin Sensitivity
- Fat Utilization
- Energy Expenditure
- HDL-c

- Body Weight
- Blood Glucose
- Triglyceride
- Blood Insulin
- Glucagon
- LDL-c

Coskun et al, Endocrinology, 2008
Xu et al, Diabetes, 2009
Kharitonenkov et al, JCI, 2005
Adipose tissue as a major action site of FGF21
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

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

Cold or β3-Adrenergic Stimuli

FGF21

Promoter

FGF21

PGC-1α

(PTM Level)

UCP1 Production

Thermogenesis

Transdifferentiation

WAT

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

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

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

- Insulin sensitivity
- Hypertension
- Myocardial infarction
- Cardiomyopathy
- Atherosclerosis
- Fatty liver, NASH
  - fibrosis (Xu A, JCI, 2003)
  - (Ding X, Am J Path, 2005)
  - Zhou M, Hepatology, 2008 and 2011)
- Vascular protection
  - (Cheng K, Diabetes, 2007)
  - (Chang J, Diabetes, 2010)
  - (Wang Y, Diabetes, 2011)
  - (Wong J, Cell Metabolism, 2011)
- Inflammation (Fayad R, Gastroenterology, 2007)
  - Hoo R, ATVB, 2008)
- Dyslipidemia (Xu A, Endocrinology, 2005)
- Obesity-related asthma
  - (Shore S, J Allergy Clin Immunol, 2006)
FGF21 induces both expression and secretion of adiponectin in mouse adipocytes

FGF21 enhances adiponectin secretion in mouse adipocytes

**A**

Pulse-chase experiment with $^{35}$S methionine

<table>
<thead>
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<td><strong>CL</strong> Vehicle</td>
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**B**

Percentage of adiponectin released

- **CL**: Cell lysates; **CM**: Conditioned medium

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* denotes significant differences, ** denotes highly significant differences.
PPARγ agonists increase adiponectin expression and secretion

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

GW9662: PPARγ 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.
FGF21 induces adiponectin production in mice.
The acute metabolic benefits of FGF21 are abrogated in adiponectin-deficient mice with dietary obesity.

**A**

![Graph showing Glucose levels over time for WT+Vehicle, ADN(-/-)+Vehicle, WT+FGF21, and ADN(-/-)+FGF21 groups.]

**B**

![Graph showing Insulin levels over time for WT+Vehicle, ADN(-/-)+Vehicle, WT+FGF21, and ADN(-/-)+FGF21 groups.]

**C**

![Graph showing Triglycerides levels over time for WT+Vehicle, ADN(-/-)+Vehicle, WT+FGF21, and ADN(-/-)+FGF21 groups.]

**D**

![Graph showing p-Erk1/2 and Erk1/2 levels under different conditions.]

WT+Vehicle, ADN(-/-)+Vehicle, WT+FGF21, ADN(-/-)+FGF21.
The beneficial Effects of FGF21 on glucose metabolism and insulin sensitivity are impaired in adiponectin KO mice

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

[A] WT

[B] ADN(-/-)

*\(p<0.05\); **\(p<0.01\). \(n=5\) in each group
Adiponectin is required for FGF21-mediated alleviation of fatty liver disease in obese mice

A

WT

ADN(-/-)

B

C

*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

**Graphs showing TG levels in Soleus and Gastrocnemius muscles for WT and ADNKO mice with Vehicle and FGF21 treatment.**

- **Soleus:**
  - Vehicle: WT, ADNKO
  - FGF21: WT, ADNKO

- **Gastrocnemius:**
  - Vehicle: WT, ADNKO
  - FGF21: WT, ADNKO
The insulin-sensitizing effects of FGF21 in skeletal muscle are dependent on adiponectin

**A**

- **WT**
  - p-Akt
  - Akt
  - p-GSK3β
  - GSK3β

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**B**

- **ADNKO**
  - p-Akt
  - Akt
  - p-GSK3β
  - GSK3β

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

* *p<0.05; **p<0.01

A

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

Serum FGF21 levels are significantly elevated in overweight/obese subjects

![Graph showing serum FGF21 levels in lean and overweight/obese subjects.](image1)

**Serum FGF21 levels**

- Lean: N=105
- Overweight/obese: N=127

**BMI (kg/m²)**

- **r² = 0.229, p<0.001**

**Log Serum FGF21 levels**

- **r² = 0.240, P < .001**

**Human**

- Giannini C et al., J Clin Endocrinol Metab. 2013
Elevated circulating FGF21 is associated with a cluster of obesity-related complications

Coronary heart disease

Atherosclerosis
Chow WS, et al. ATVB. 2013

Diabetes

NAFLD
Li, H., et al. J Hepatol 2010
Dushay, J., et al. Gastroenterology 2010

Metabolic syndrome
Reinehr, T. et al. JCEM 2012

Obesity
Reinehr, T. et al. JCEM 2012

Diabetic Nephropathy
Elevated FGF21 production in obese animals

**Genetic-induced obesity**

- **Tissue**
  - Liver

**Diet-induced obesity**

- **Liver**
- **Epid**

**Serum**

- **FGF21 Resistance**

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Impaired actions of FGF21 in ob/ob obese mice

Fasting glucose and free fatty acid

Glucose clamping

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

Serum triglyceride levels (fold changes)

Time after FGF21 injection

FGF21: 1 mg/kg; n=5

HFHC diet induction
The ability of recombinant FGF21 (rmFGF21) to increase circulating adiponectin is progressively impaired in diet-induced obesity.
FGF21-induced signal transduction pathways in adipose tissues are impaired in obesity

Mechanisms of FGF21 resistance?

Adipocyte

FGFR?β-Klotho?

Glucose uptake

SRF SRF Elk-1

Lipolysis

PPARγ

AMPK

SIRT1

PGC1α

UCP1

Heat dissipation

Glut1 transcription

GLUT1

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

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<td><img src="fgfr1-hfhc.png" alt="Image" /></td>
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How does obesity cause reduced \(\beta\)-klotho and FGFR1 expression?
Involvement of TNFα-JNK pathway in modulating β-klotho expression???

Adipocyte

FGF21

Obesity

TNFα

FGFR1

β-Klotho

Glucose uptake

JNK activation

???
FGF21 resistance as a cause of systemic insulin resistance

Adipocytes

FGF21

FGFR1c

βklotho

Liver

Muscle

Blood vessel

APN

Secretion

Insulin Sensitivity

Systemic Insulin resistance

Autocrine

Endocrine

Obesity
Acknowledgement

• HKU team

Prof. Karen Lam

• Kyoto University
  Prof. Nobuyuki Itoh & Dr. Yuhei Hotta

Xiangya 2nd Hospital, Hunan
*Prof. Zhi-guang Zhou

• Shanghai Diabetes Center,
  Jiao Tong University
  Prof. Jia Weiping, Dr. Li Huating
Thank you!