Literature seminar

Diabetes treatment and latest research

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2019/10/31

Contents

1. Introduction
    - Recent trend
    - Types of Diabetes
    - Main etiology
2. Treatment and latest research for Diabetes
    - Incretin-based anti-diabetic drugs
    - Adiponectin as the innovative drug development target
    - GPR119 as a drug target of new oral hypoglycemic agent
    - Diabetes research for the insight of epigenome
3. Summary

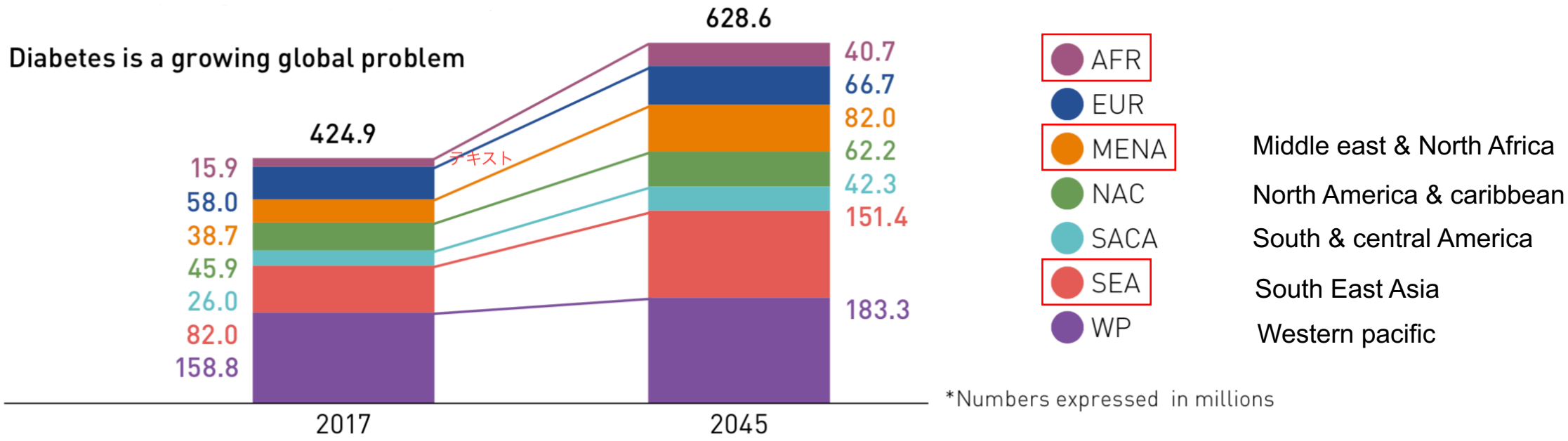
What is Diabetes ?

- ✓ Metabolic disorders characterized by high blood sugar levels over a prolonged period.
- ✓ Diabetes can cause many complications.
  (cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes etc.)
- ✓ Diabetes at least doubles a person's risk of early death.

https://time.com/5183350/diabetes-five-types/

Trend of diabetes in the world

- ✓ Estimated 425 million people had diabetes worldwide (2017).
- ✓ The number of patients in Asia and Africa is expected to increase.



IDF DIABETES ATLAS Eighth edition 2017

Diabetes Complications

- ✓ Complications such as myocardial infarction, stroke, lower limb amputation, kidney disease, and hyperglycemia are known to occur.
- ✓ Reductions in a diverse spectrum of diabetes-related complications were captured in a 2014 study.

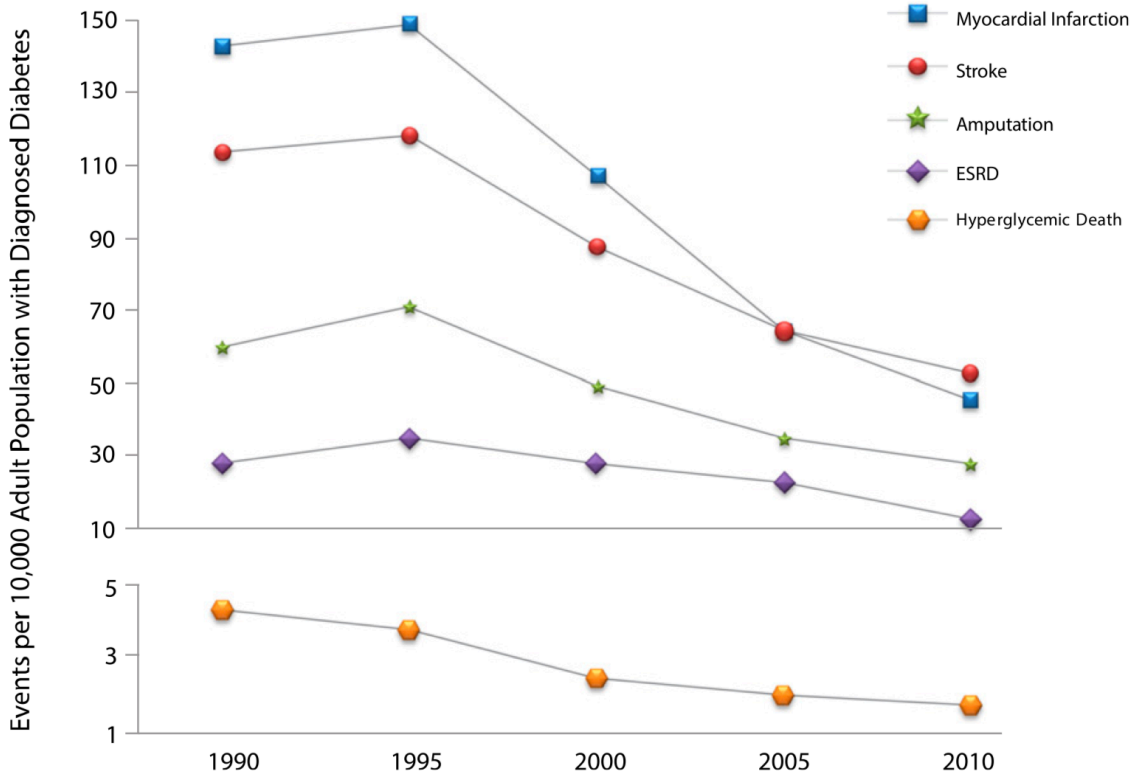


Figure 1—Trends in age-standardized rates of diabetes-related complications from 1990 to 2010 among U.S. adults with diagnosed diabetes. Previously published in *The New England Journal of Medicine* (26).

Diabetes Care **2017,** 40(10), 1289-129

Types of diabetes

■ Type I diabetes:

This type occurs when the body fails to produce insulin. People with type I diabetes are insulin-dependent, which means they must take artificial insulin daily to stay alive.

■ Type 2 diabetes:

Type 2 diabetes affects the way the body uses insulin. While the body still makes insulin, unlike in type I, the cells in the body do not respond to it as effectively as they once did. This is the most common type of diabetes,and it has strong links with obesity.

■ Gestational diabetes:

This type occurs in women during pregnancy when the body can become less sensitive to insulin. Gestational diabetes does not occur in all women and usually resolves after giving birth.

Main etiology

Diabetes

Type I diabetes

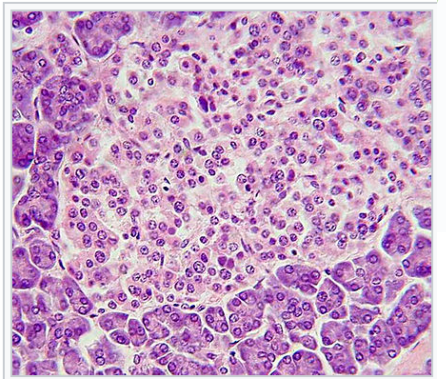
Pancreatic β-cell destruction by autoimmunity

Islet cell injury by virus

Type 2 diabetes

Insulin resistance

Islet dysfunction



https://en.wikipedia.org/wiki/Pancreatic_islets

Pancreatic islets: The β-cells of the pancreatic islets secrete insulin and regulate glucose level.

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3. Summary

Treatment (Incretin-based anti-diabetic drugs)

Incretin(Intestine secretion insulin)

a group of metabolic hormones that stimulate a decrease in blood glucose levels. Incretins are released after eating and augment the secretion of insulin released from pancreatic β-cells of the islets of Langerhans by a blood glucose dependent mechanism.

（GIP、GLP-1）

GLP-1：glucogan-likepeptide-1
GIP：glucose-dependent insulinotropic polypeptide

In particular, drugs targeting GLP-1 and GLP-1 receptor are used in the treatment of diabetes.

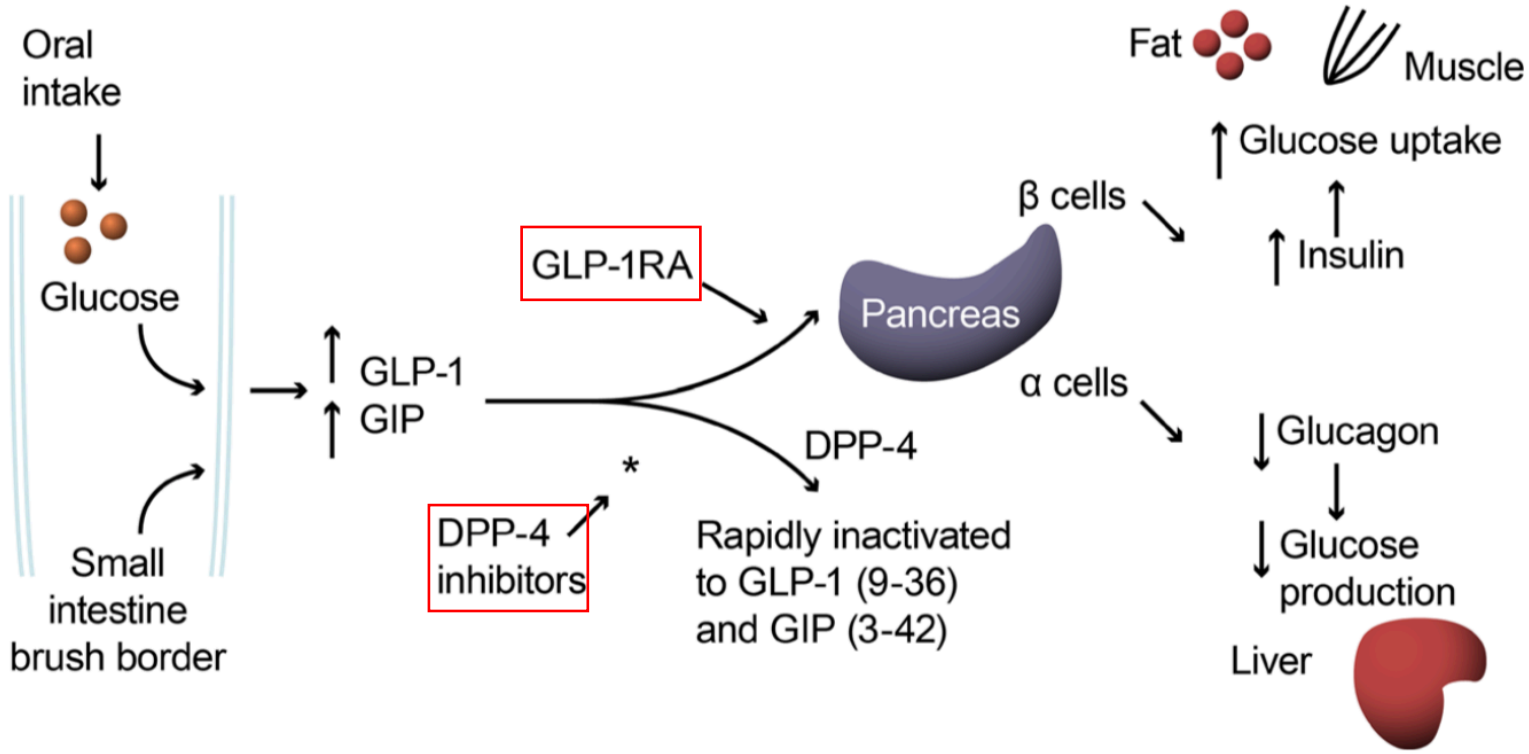
Treatment (Incretin-based anti-diabetic drugs)

GLP-1 receptor agonists (GLP-1RA)

- enhance glucose- dependent insulin secretion by mimicking the glucoregulatory effects of endogenous GLP-1 and by providing pharmacological (high) levels of GLP-1 activity, and also suppress glucagon release

DPP-4 inhibitors

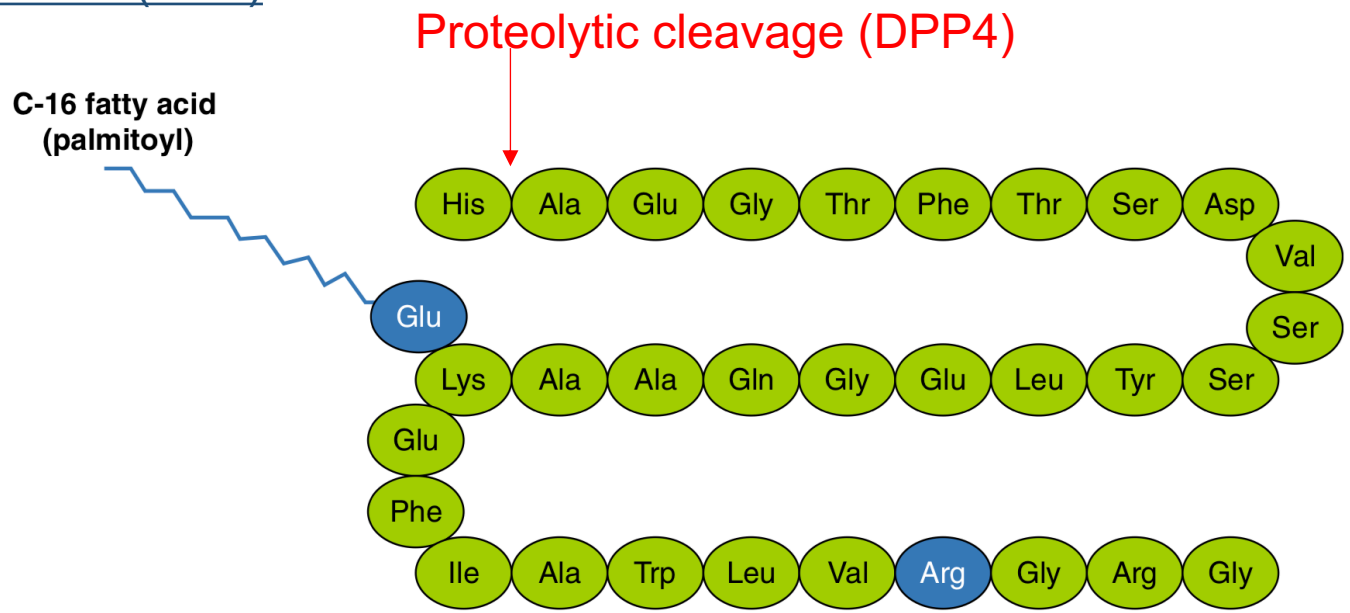
- prevent enzymatic inactivation of endogenous GLP-1, resulting in prolonged availability of physiological levels of native GLP-1 and GIP and modest receptor activation



Adv Ther, **2014**, *31*, 289–317

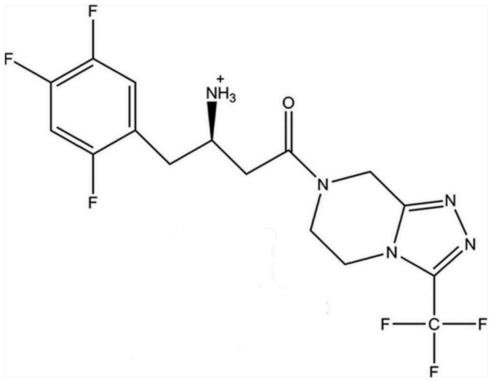
Treatment (Incretin-based anti-diabetic drugs)

GLP-1 receptor agonists (7-37)



- Stability against DPP4
- Long plasma half-life

DPP-4 inhibitors



sitagliptin

Clin Pharmacokinet, **2016**, *55*, 657–672

Spectrochim. Acta A Mol. Biomol. Spectrosc,**2019** , *223* , 117286

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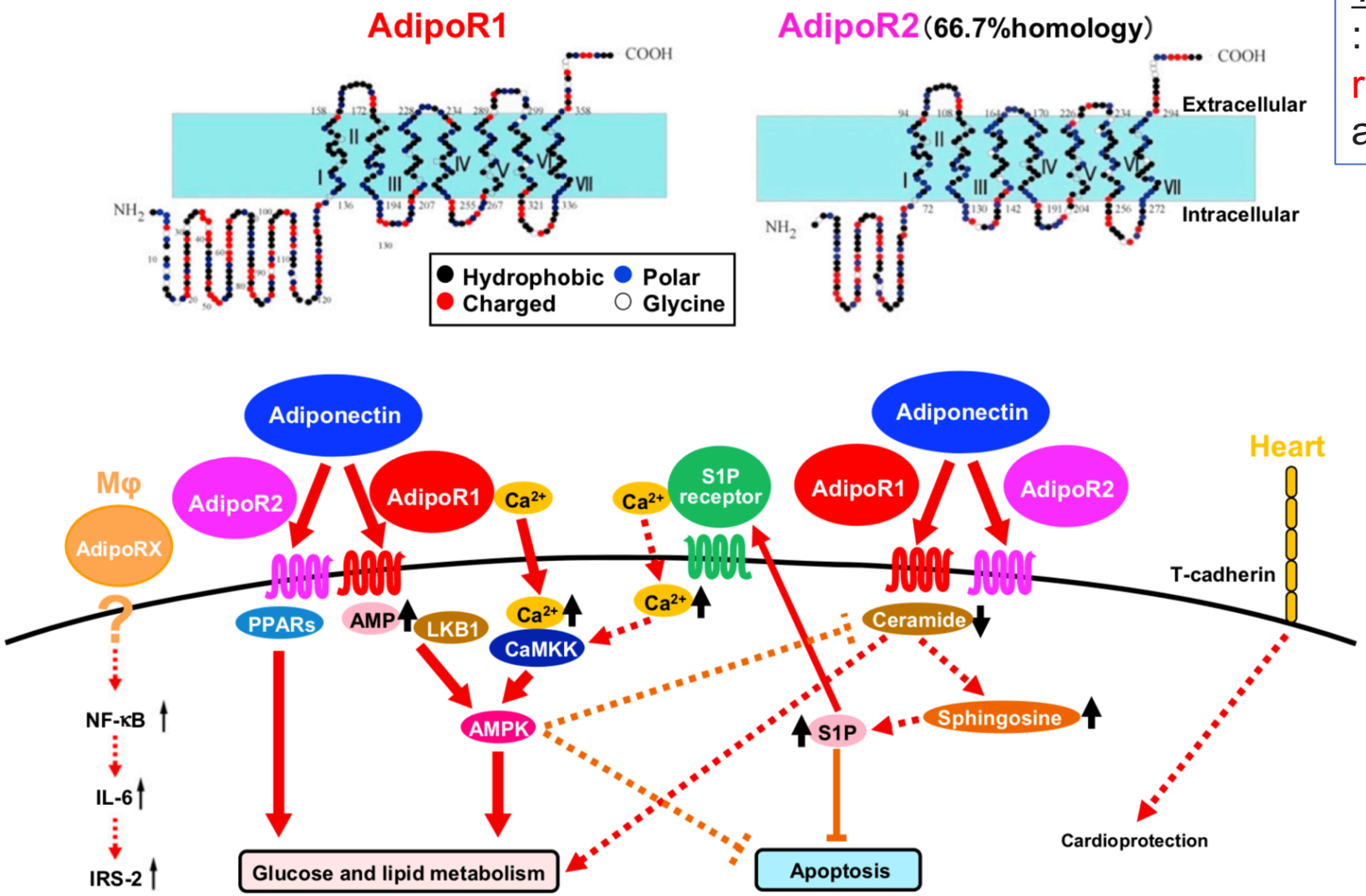
3. Summary

Treatment (Adiponectin as the innovative drug development target)

Impaired Adiponectin Action Is a Hallmark of Obesity- Related Diseases



Adiponectin

: protein hormone which is involved in regulating glucose levels as well as fatty acid breakdown.

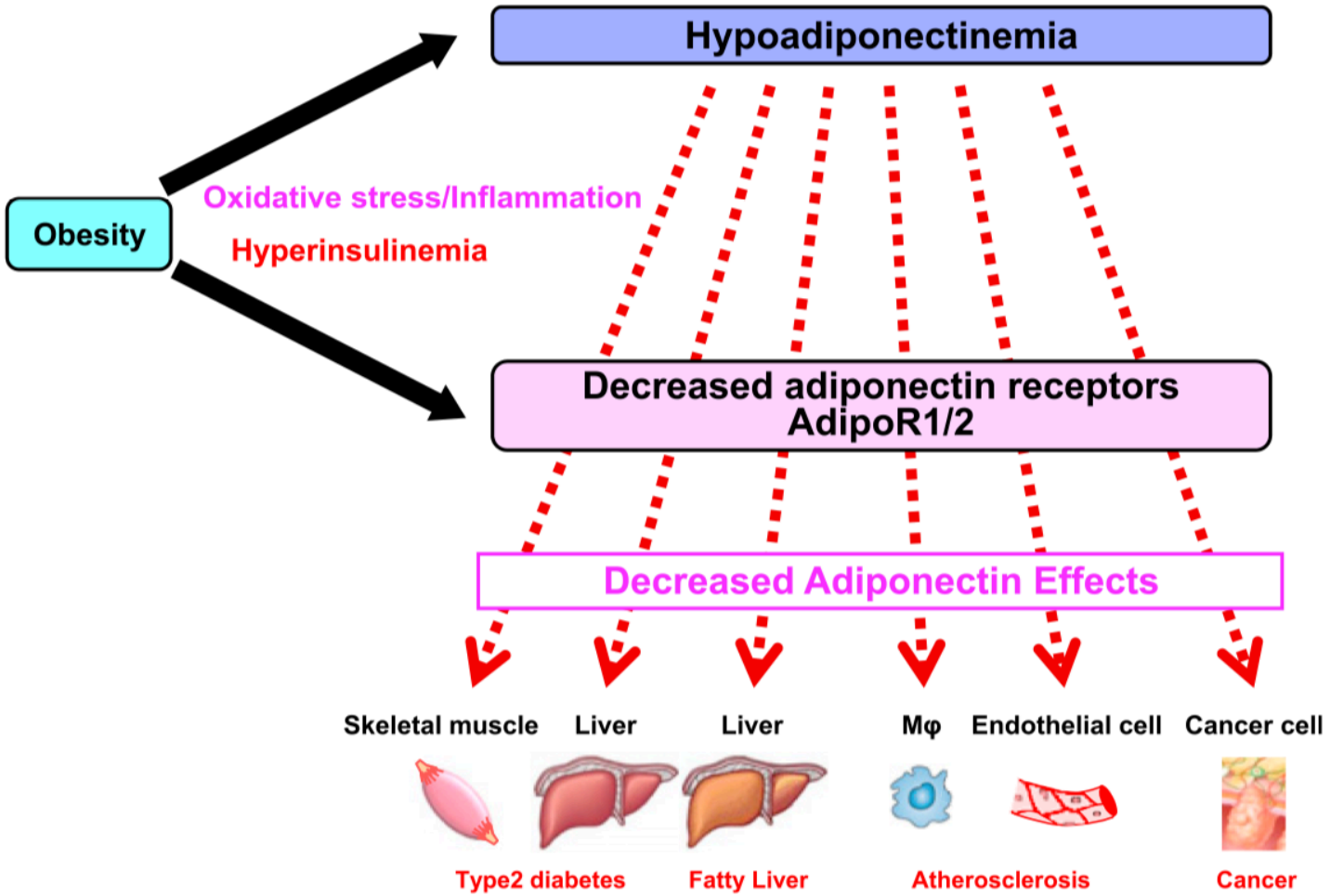
Function

- Glucose uptake promoting action without insulin receptor
- fatty acid burning
- increase insulin receptor sensitivity
- Increased insulin sensitivity
- suppression of arteriosclerosis
- anti-inflammatory
- suppression of myocardial hypertrophy

Cell Metab. **2013,** *17*, 185-96

Treatment (Adiponectin as the innovative drug development target)

Impaired Adiponectin Action Is a Hallmark of Obesity- Related Diseases



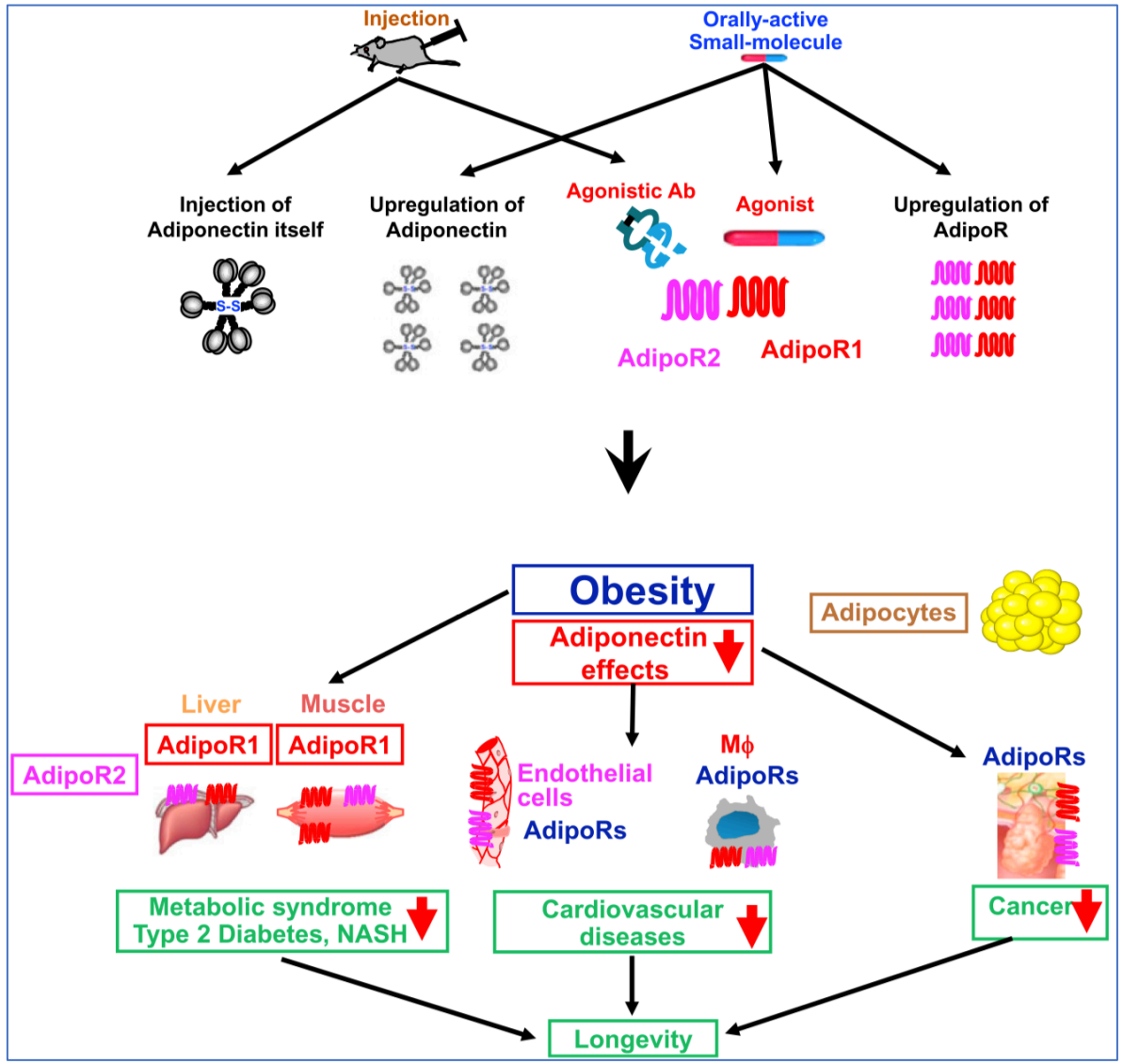
Adiponectin
: protein hormone which is involved in regulating glucose levels as well as fatty acid breakdown.

✓ Decreased adiponectin effects cause various types of obesity-related diseases.

Cell Metab. **2013,** *17*, 185-96

Treatment (Adiponectin as the innovative drug development target)

Strategies to Increase Adiponectin Effects and Pathophysiological Roles of Adiponectin/AdipoR in Obesity

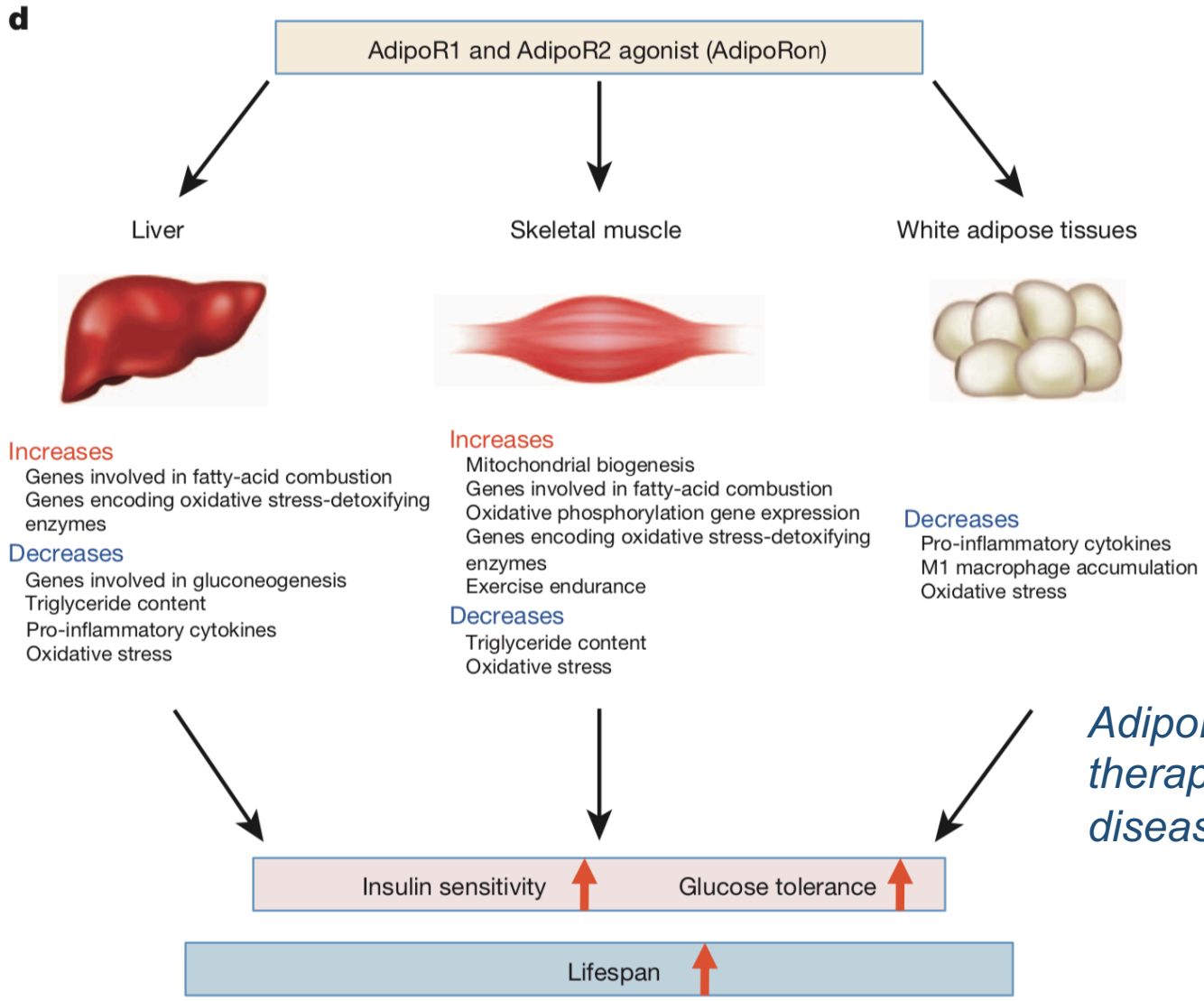


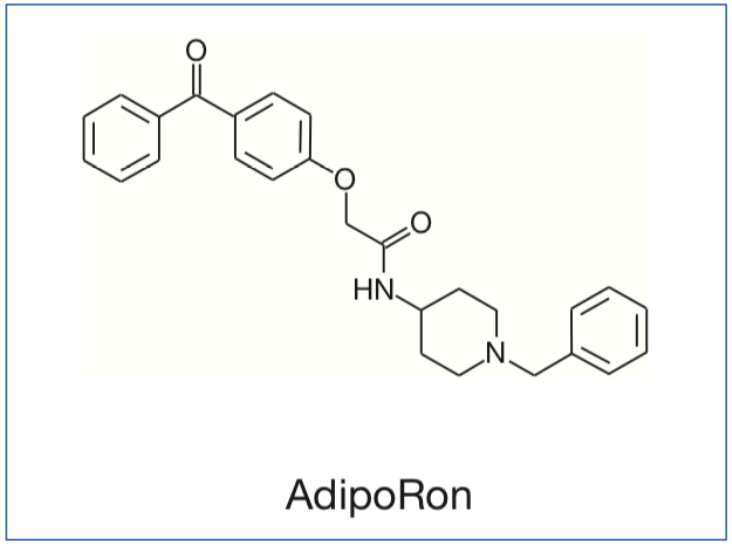
- Injection of adiponectin itself
- Upregulation of adiponectin
- Adiponectin receptor agonist
- Upregulation of AdipoR

Cell Metab. **2013,** *17*, 185-96

Treatment (Adiponectin as the innovative drug development target)

Translational Research Targeted to Adiponectin and AdipoRs





AdipoR agonists such as AdipoRon are a promising therapeutic approach for the treatment of obesity-related diseases such as type 2 diabetes.

Nature, 2013, 503, 493-499

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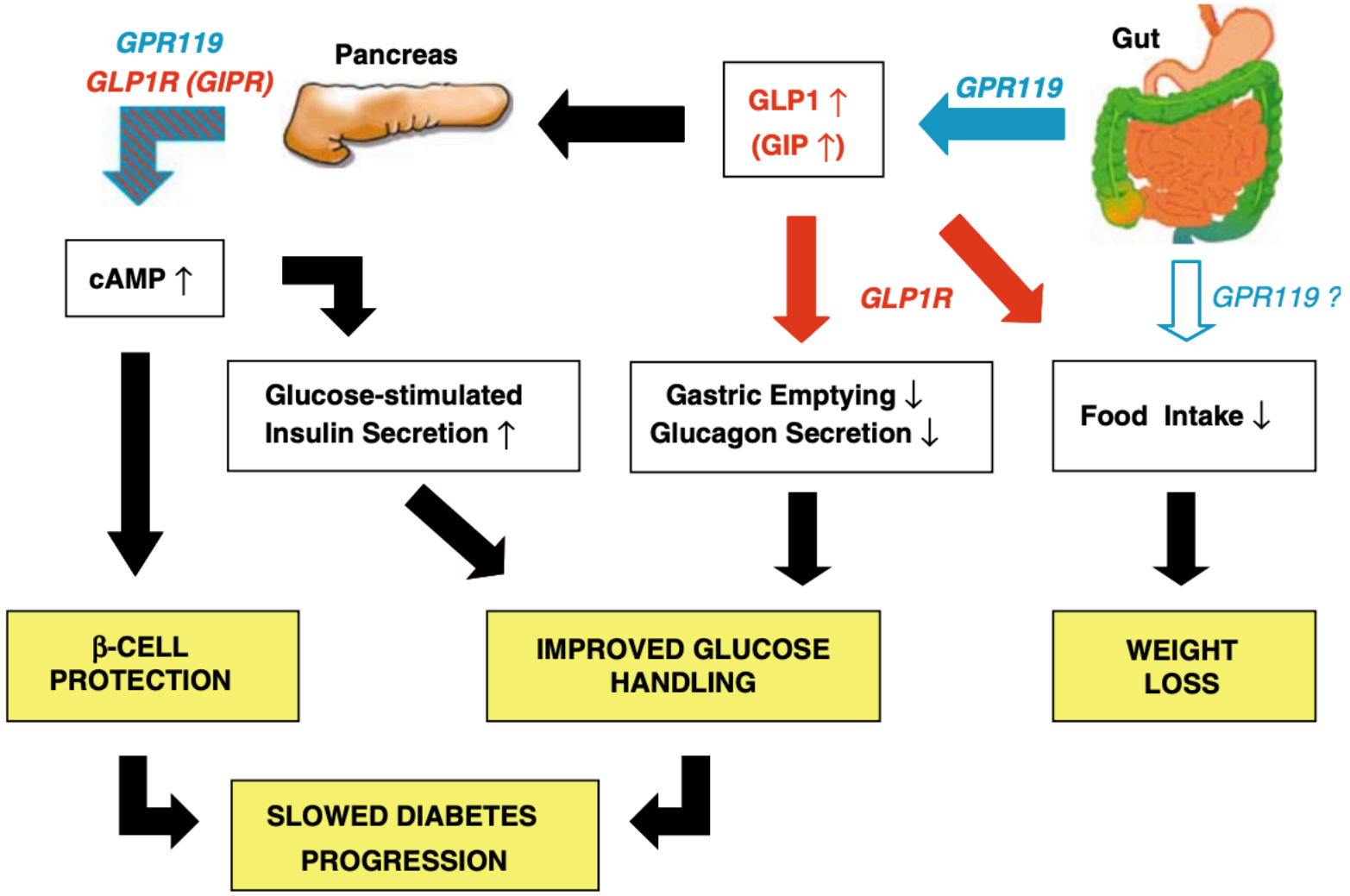
Treatment (GPR119 as a drug target of new oral hypoglycemic agent)

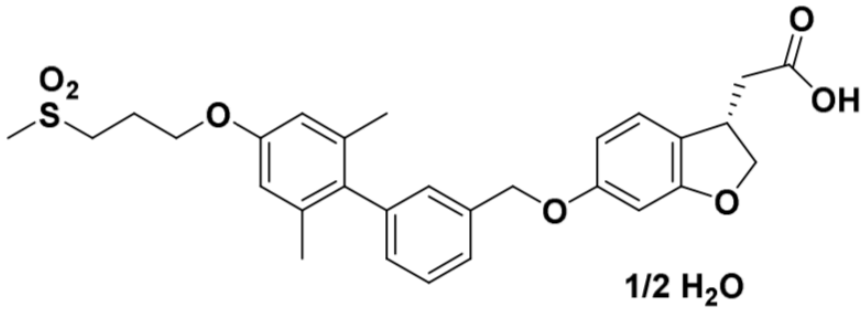
Proposed mechanisms of GPR119 agonist action



GPR119 :
regulate incretin and insulin hormone secretion.

British Journal of Pharmacology, **2008**, *153*, S76–S81

Treatment (GPR119 as a drug target of new oral hypoglycemic agent)



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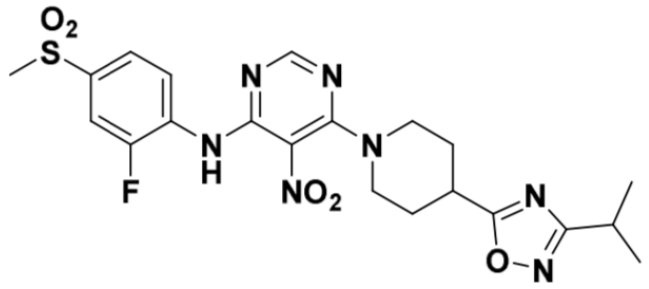

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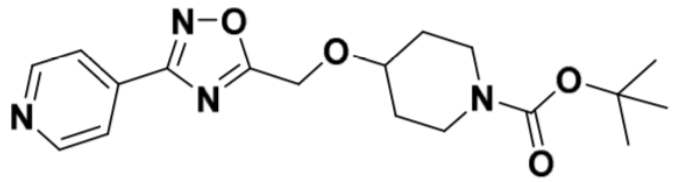

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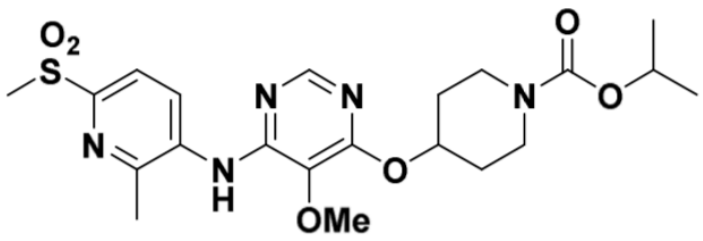
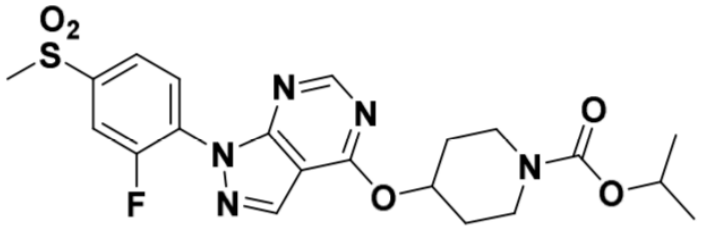
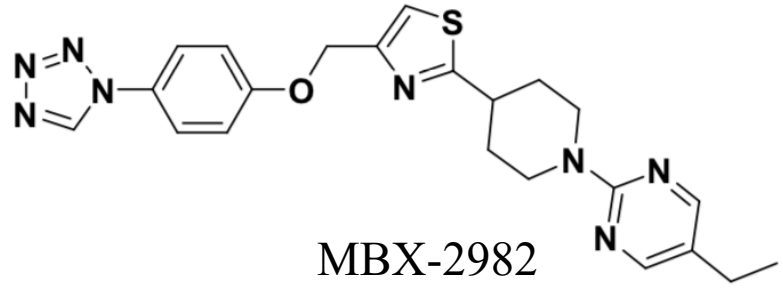


APD597



APD668



MBX-2982

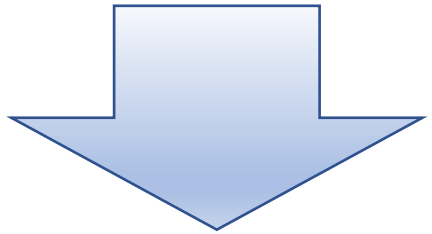
GPR119 agonist can stimulate secretion of endogenous GLP-1 ,and give improved glycaemic control and associated weight loss through an oral dosing regime.

Diabetes research from the insight of epigenome

- Type 2 diabetes is fundamentally a heterogeneous disease.
- To what extent do genetic and environmental factors contribute to its pathogenesis?
- To what extent do insulin resistance and islet insufficiency contribute to the condition?
- How likely are individuals to develop complications?

?

Large individual differences



Personalized medicine

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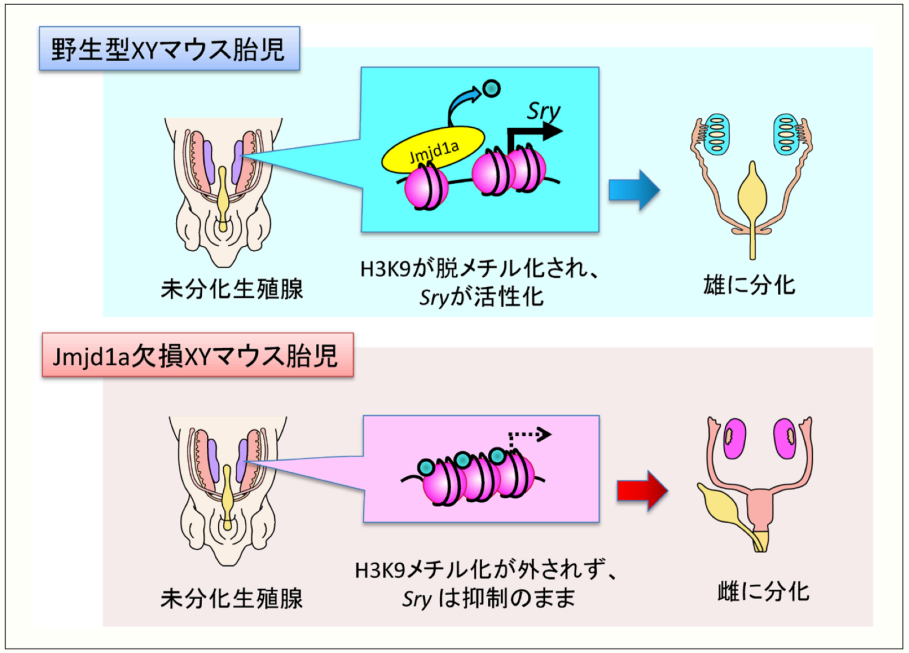
Diabetes research from the insight of epigenome

JMJD1A：(Jumonji domain-containing 1a)

- The H3K9-specific demethylase.
- It has an important role in nuclear hormone receptor-mediated gene activation and male germ cell development.

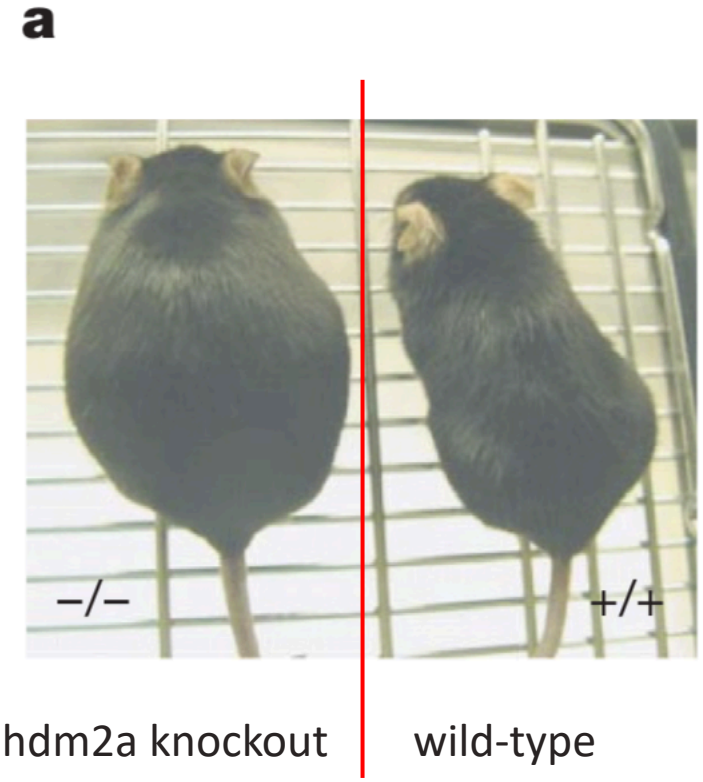


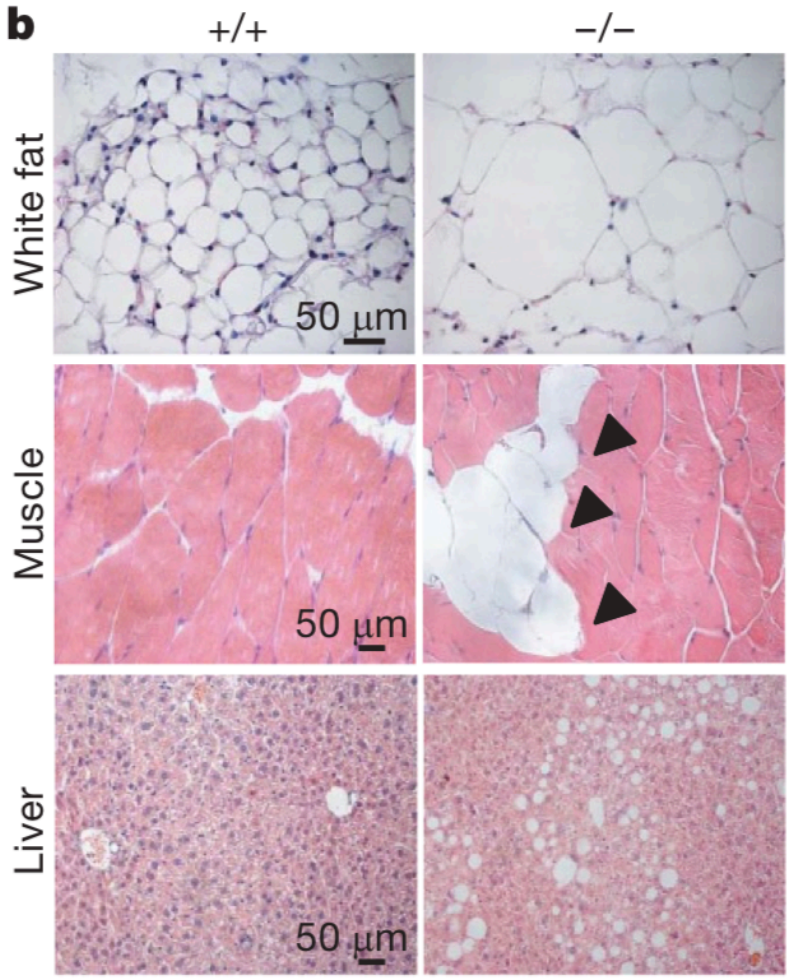
化学と生物, **2014,** Vol. 52, No. 4

Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A

The loss of Jhdm2a function results in abnormal fat metabolism and obesity.



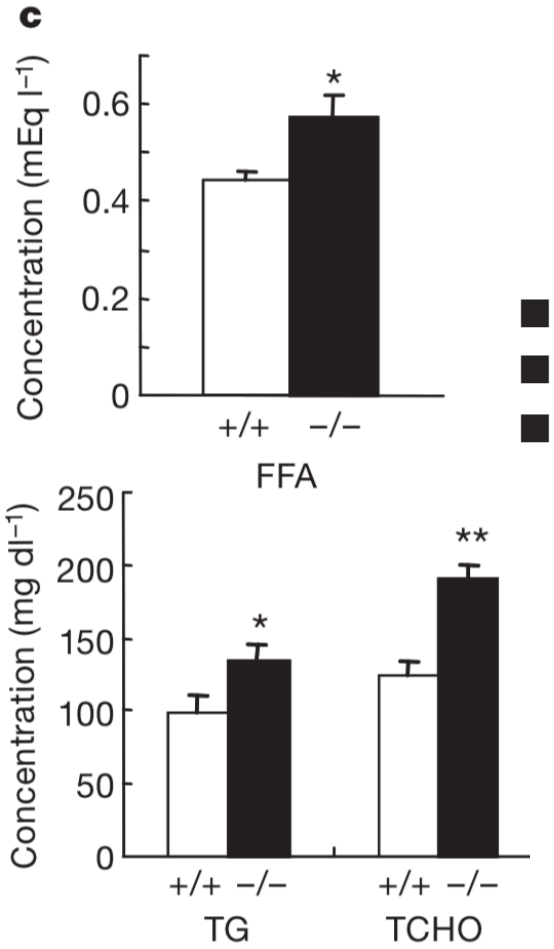


⇦Abnormal fat accumulation in organs of Jhdm2a$_{2/2}$ mice

Nature, **2009**, *458*, 757–761

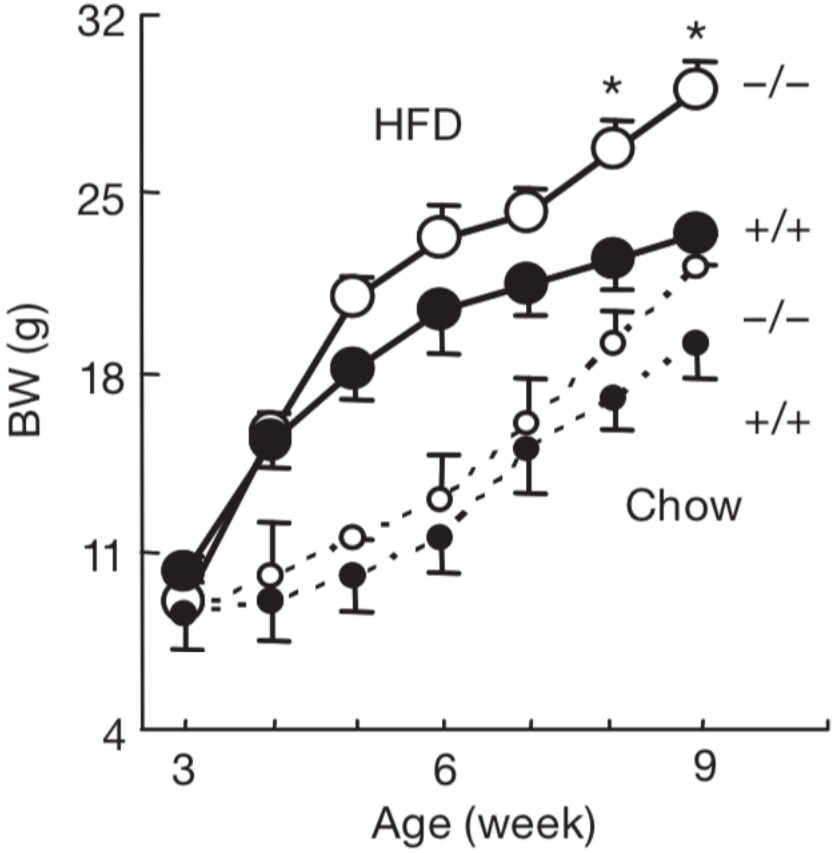
Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A



- Serum free fatty acid (FFA)
- Triglyceride (TG)
- Total cholesterol (TCHO)

✓ The increased levels of FFA,TG, and TCHO were observed.



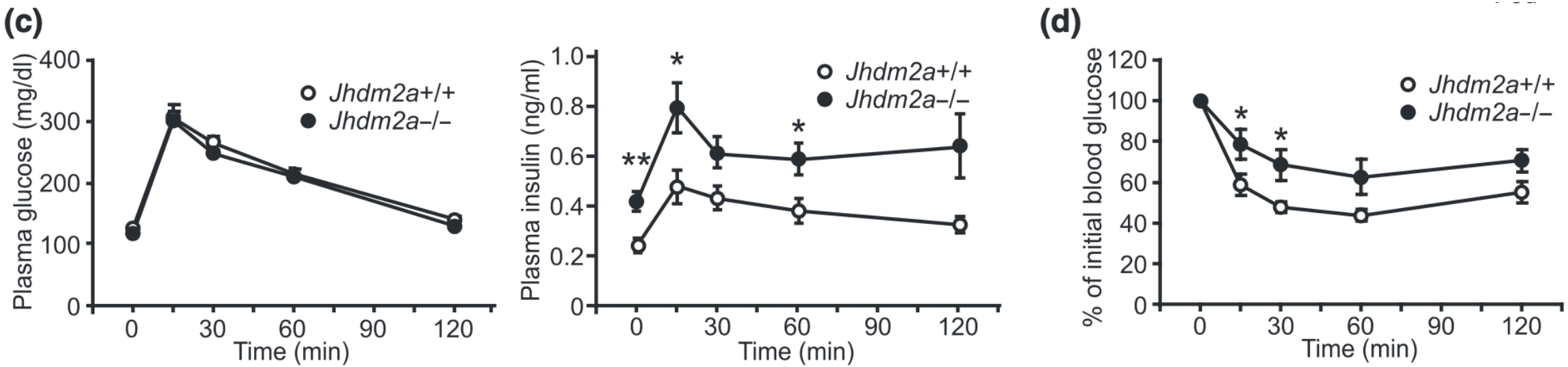
✓ Growth curve of littermates fed with a high-fat diet (HFD) or normal chow

Nature, **2009**, *458*, 757–761

Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A

Mice with abnormal methylation with histone H3K9 show obesity insulin resistance.



- ✓ Whole-body insulin insensitivity is associated with adult onset obesity JHDM2a-/- mice.
- ✓ These mice mimic a pre-diabetic state.

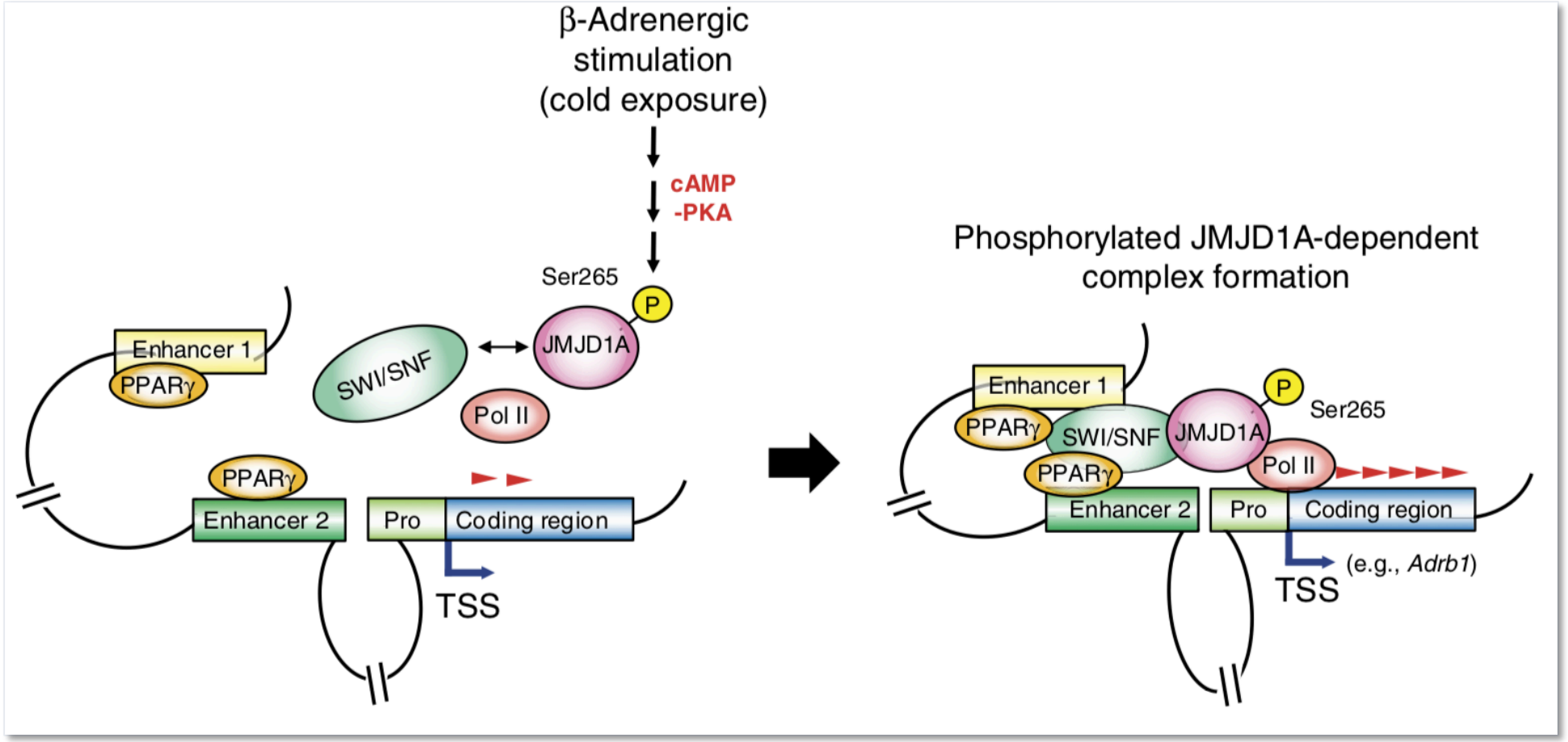
It became clear that the mouse exhibits a characteristic of the human metabolic syndrome.

Genes to Cells, **2009**, *14*, 991–1001

Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A

JMJD1A：

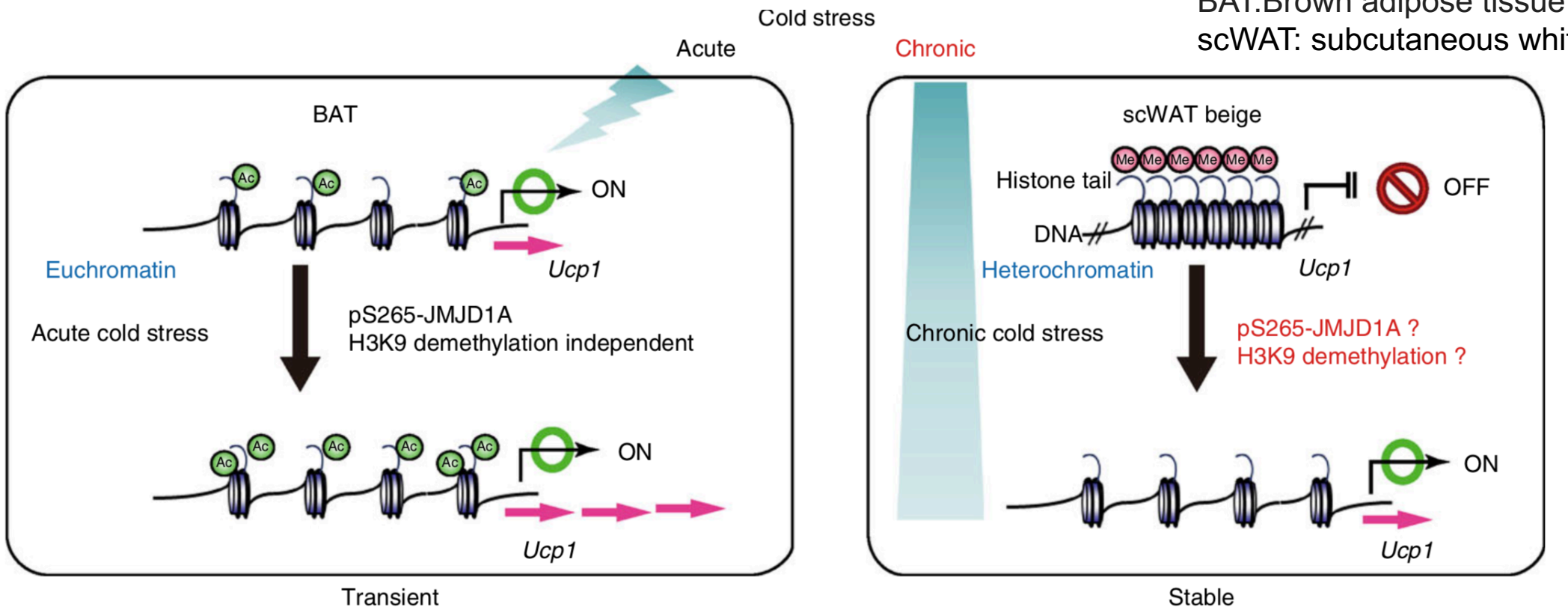


JMJD1A regulates β-adrenergic-induced systemic metabolism and body weight control. *Nat Com,* **2015** *,6* **,** 7052

Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A

BAT:Brown adipose tissue
scWAT: subcutaneous white adipose tissue



- In BAT, Ucp1 locus is in euchromatin
- Cold exposure leads to acute induction of Ucp1 mRNA through the mechanisms independent of H3K9me2 demethylation.

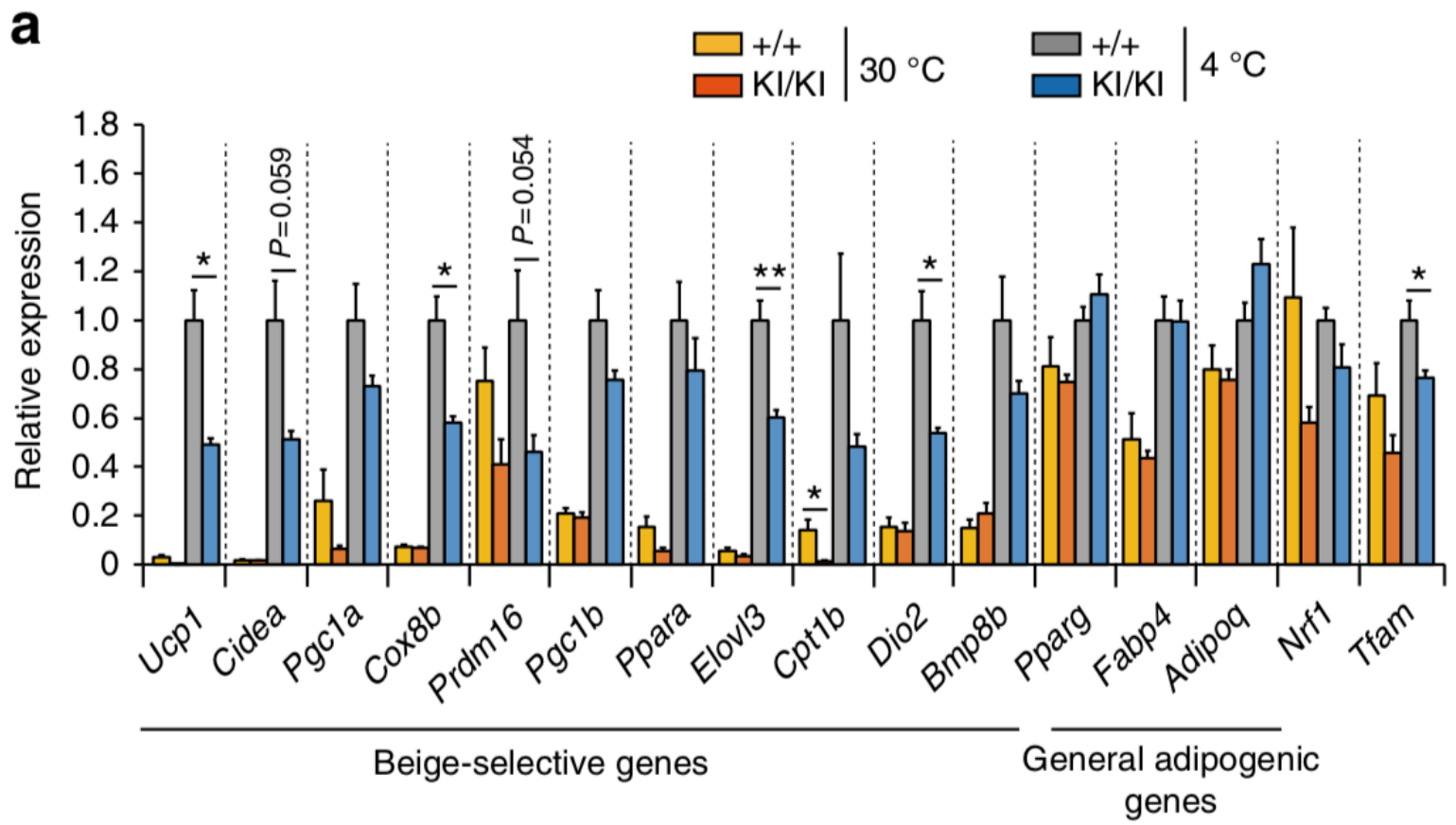
- In scWAT, Usp1 locus is in heterochromatin with H3K9me2
- H3K9me2 at Ucp1 gene locus needs to be removed for beige adipogenesis.

Nat. com., **2018**, *9*, 1566

Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A

Phospho-S265 JMJD1A induces beige biogenesis



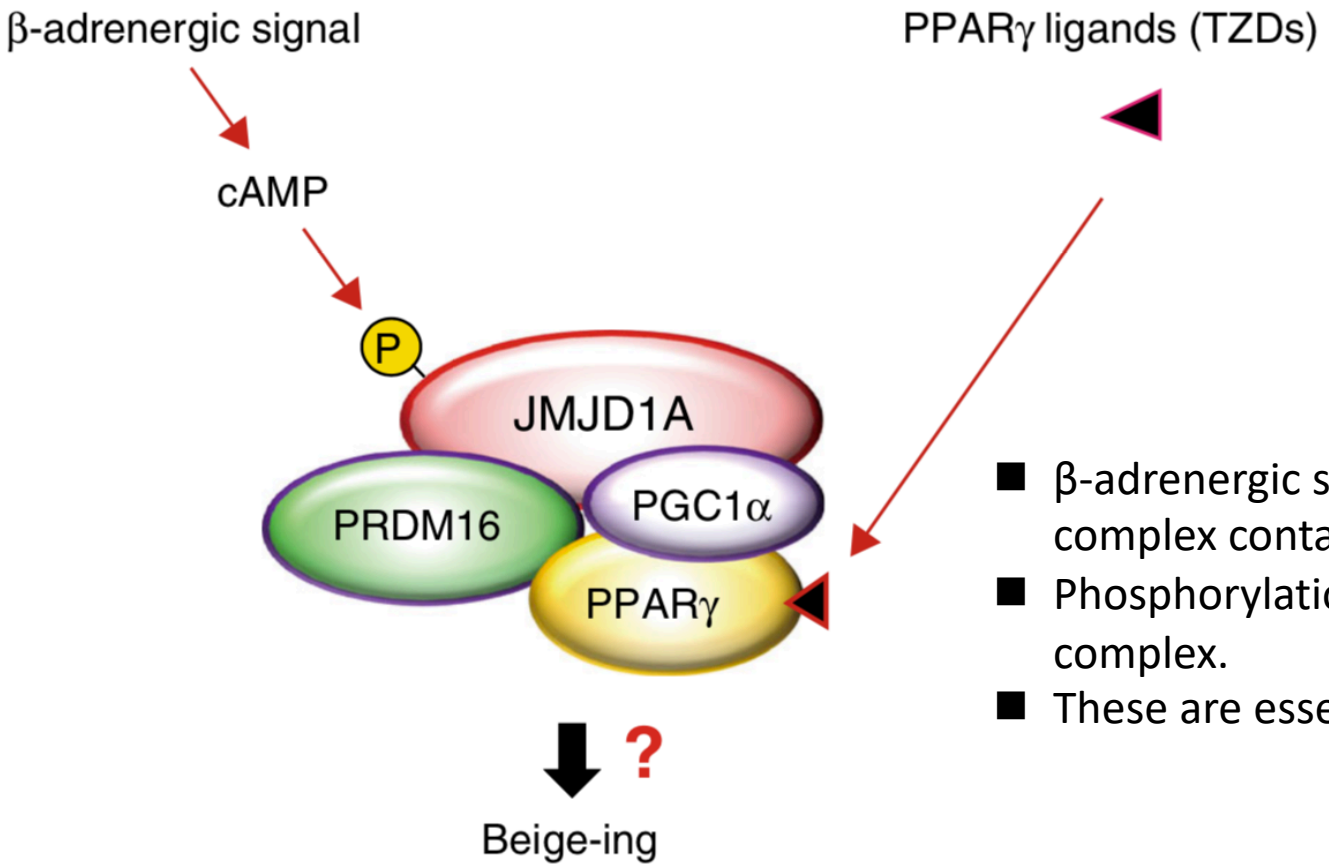
- A 4℃ treatment induced the expression of the core set of thermogenic genes in scWAT, including Ucp1, Cidea, Pgc1a, Cox8b, Elovl3, and Dio2 in WT mice.

Nat. com., **2018**, *9*, 1566

Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A

p265-JMJD1A-PPARγ-PGC1α-PRDM16 protein complex



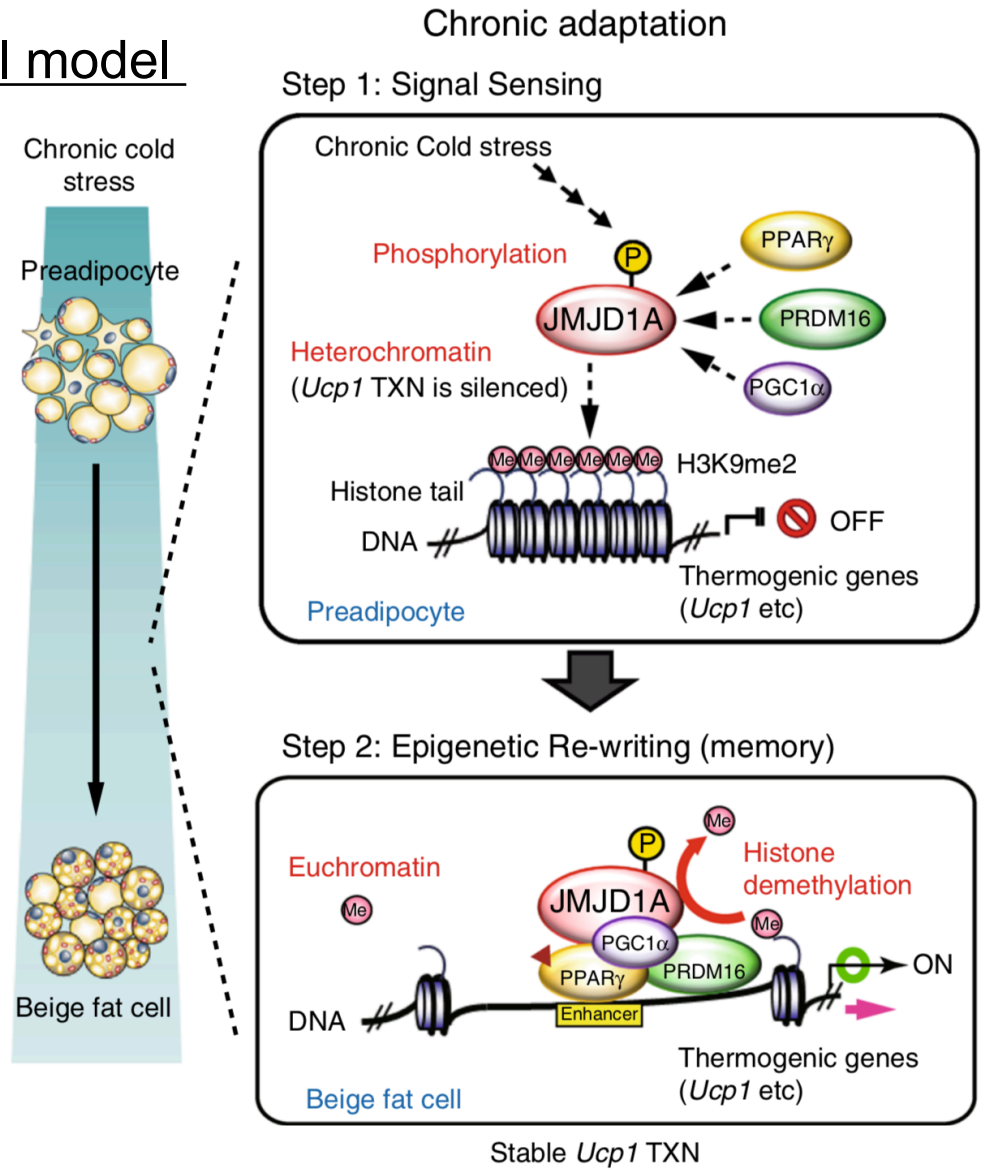
- β-adrenergic signaling mediates the formation of a multi-protein complex containing JMJD1A-PPARγ-PGC1α-PRDM16.
- Phosphorylation of S265 in JMJD1A nucleates formation of the entire complex.
- These are essential for beige-selective gene induction in scWAT.

Nat. com., **2018**, *9*, 1566

Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A

Hypothetical model



Step1

β-adrenergic signal leads to phosphorylation of JMJD1A

Step1,top

JMJD1A triggers the formation of a PRDM16-PGC1α-PPARγ transcription complex that targets beige-selective genes

Step2

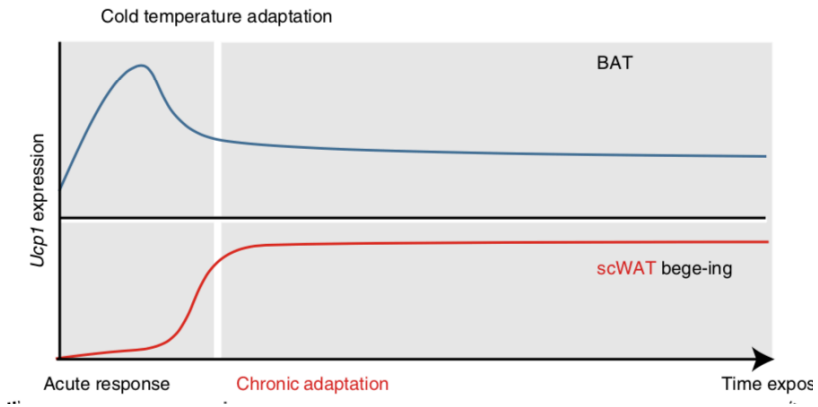
JMJD1A then demethylates H3K9me2 to turn on the transcription of these genes in scWAT.

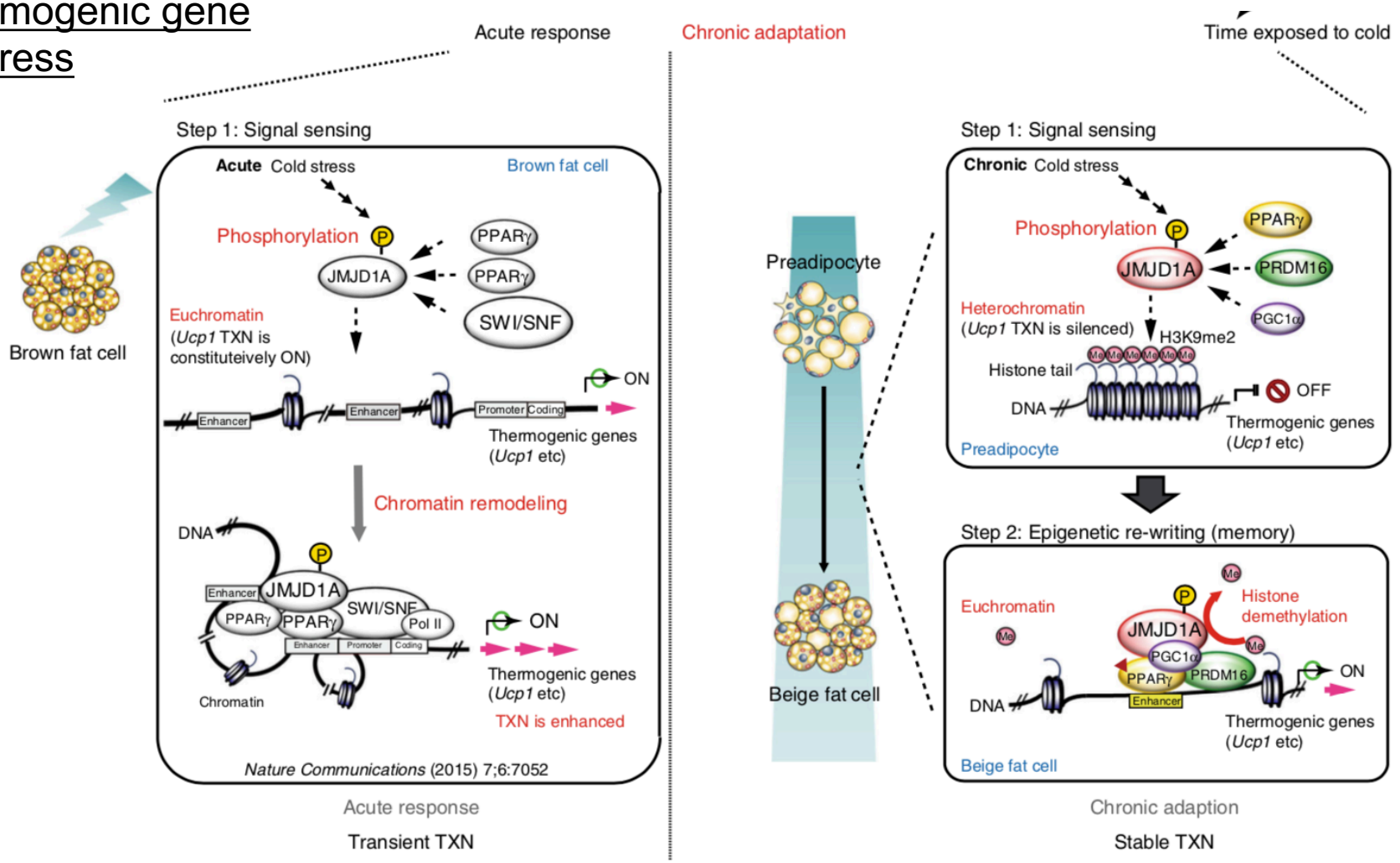
Nat. com., **2018**, *9*, 1566

Diabetes research from the insight of epigenome

Jhdm2a=JMJD1A

Complementary mechanisms for thermogenic gene induction in acute and chronic cold stress





Nat. com., **2018**, *9*, 1566

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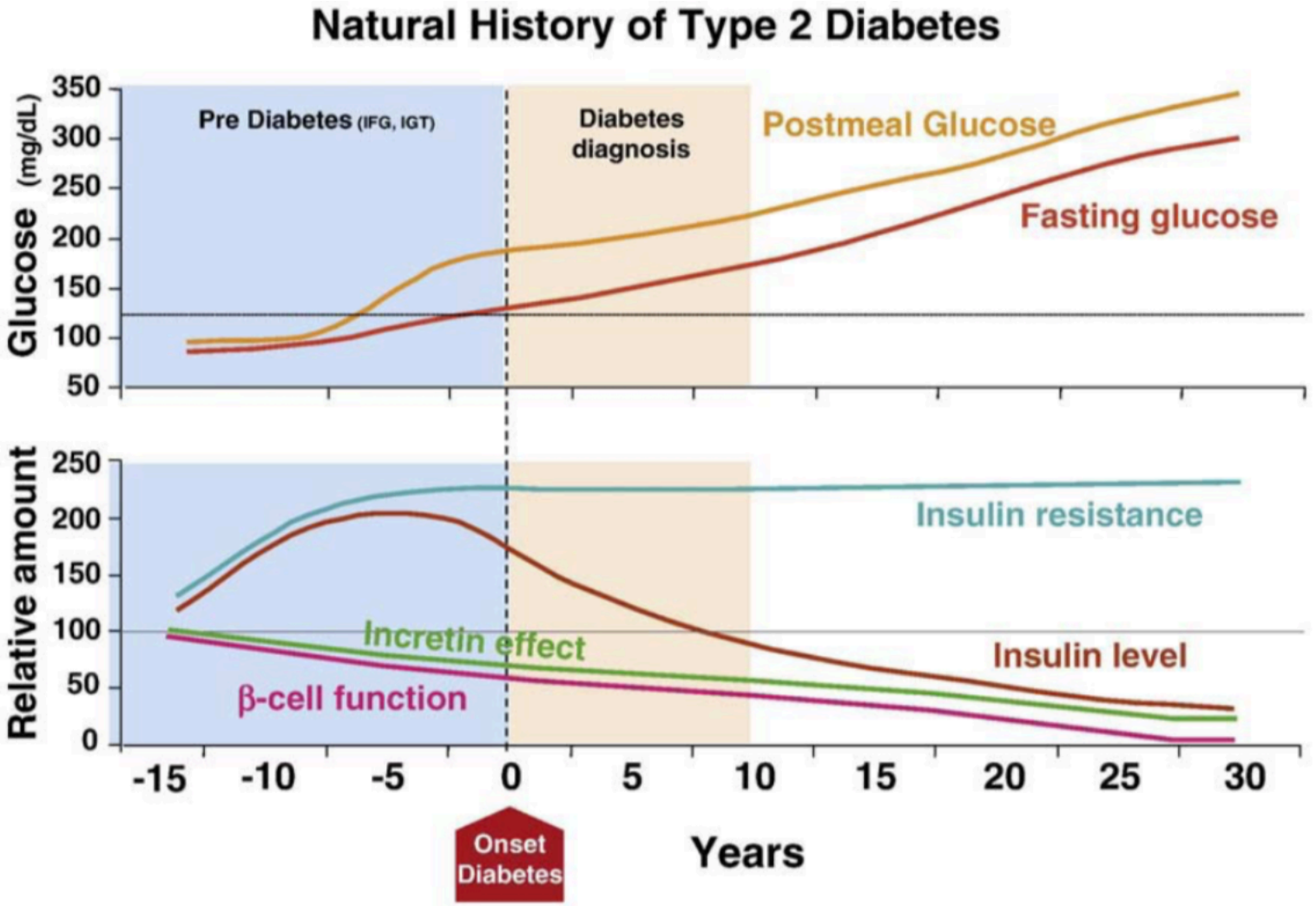
Summary

- Diabetes has various types of serious complications.
- Various strenuous studies have been conducted to overcome diabetes.
- There are individual differences such as ineffectiveness of existing therapies when various complications occur.
- Diabetes mellitus is a disease that still has many medical unmet medical needs, and research to eliminate unmet medical needs and the development of new therapies are indispensable fields.
- Clarifying the protein that regulates phosphorylation of JMJD1A is expected to provide important knowledge for the development of treatments for diabetes.

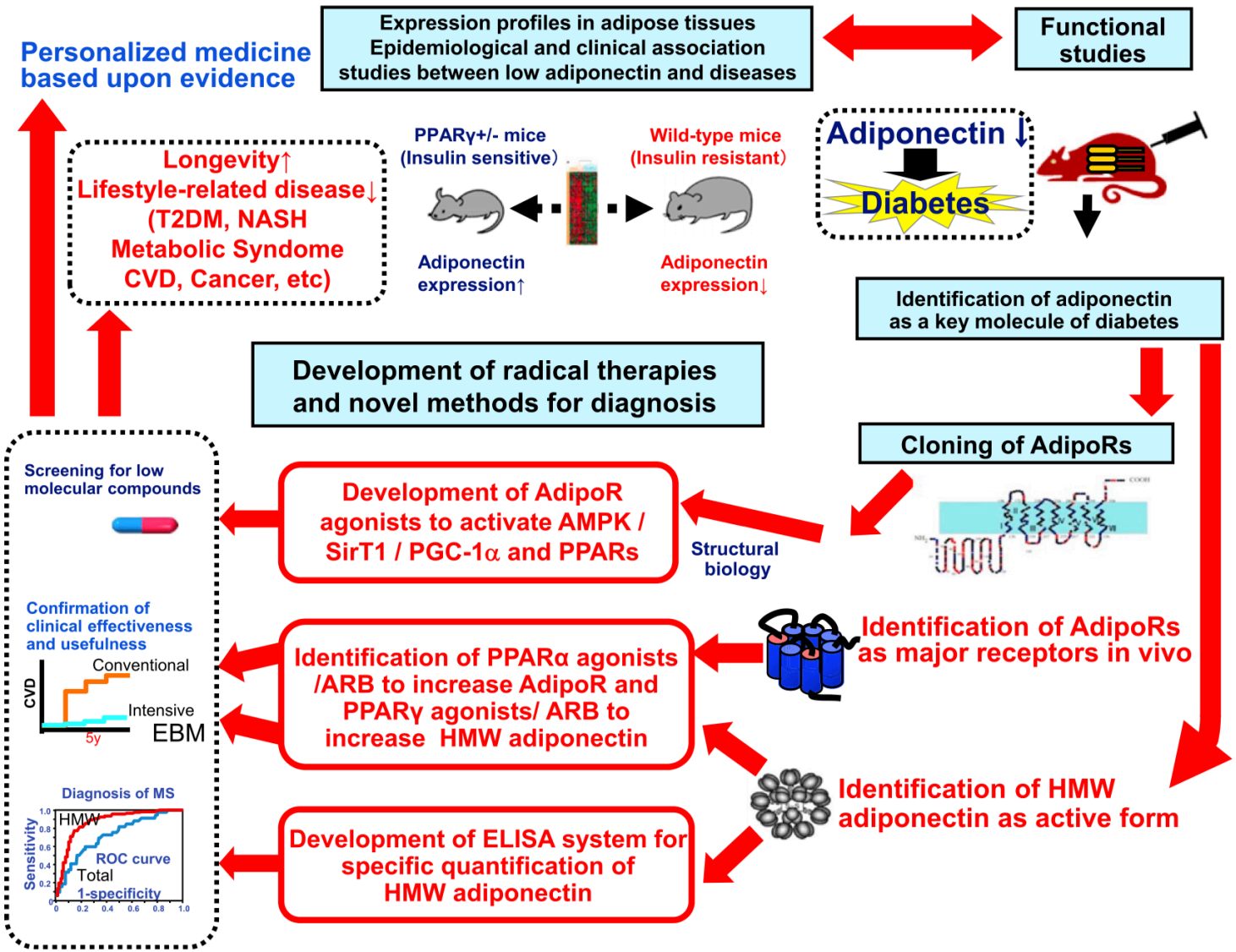
Appendix

Natural History of Type 2 Diabetes



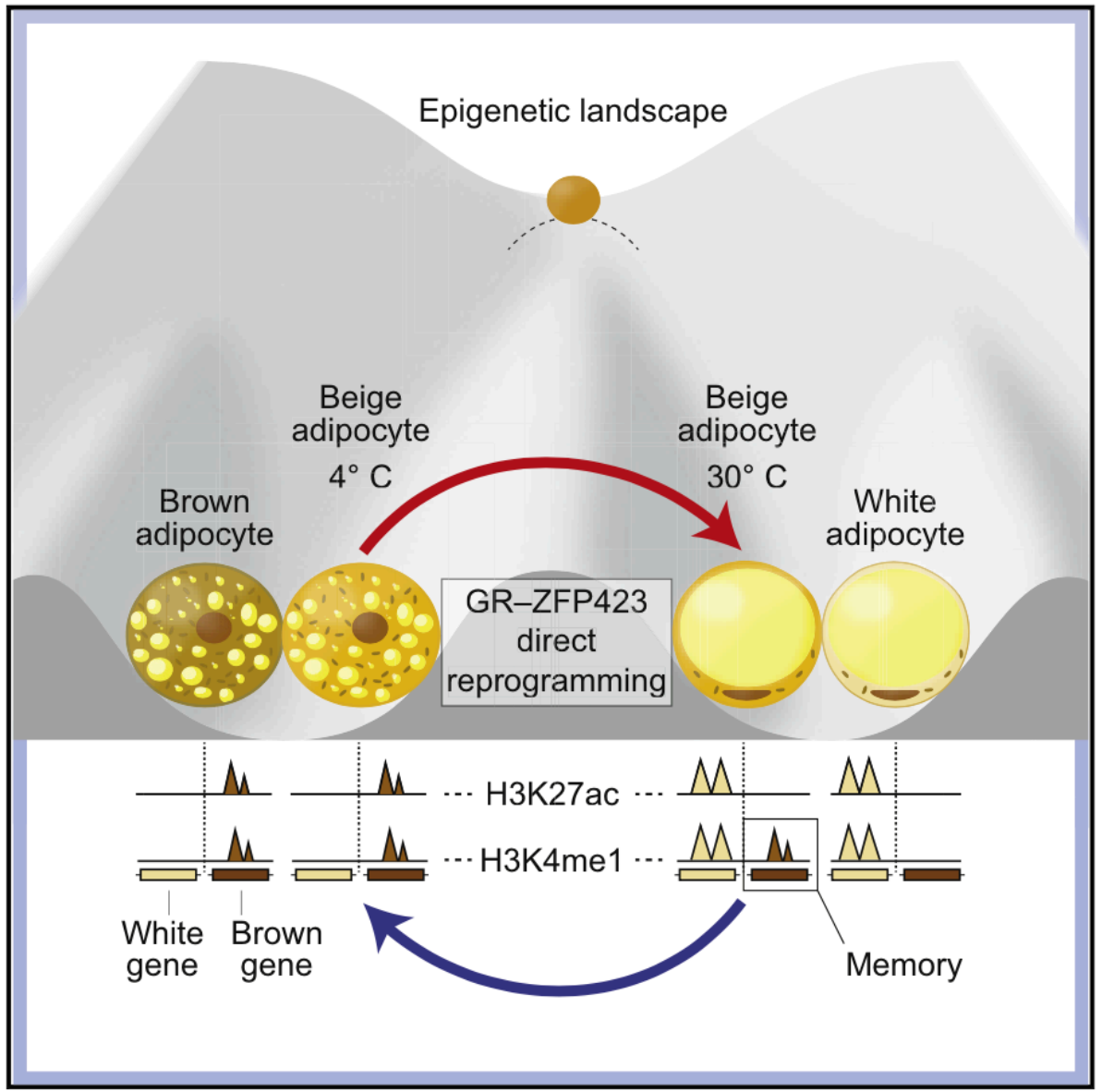
Treatment (Adiponectin as the innovative drug development target)

Translational Research Targeted to Adiponectin and AdipoRs



Cell Metab. **2013,** *17*, 185-96

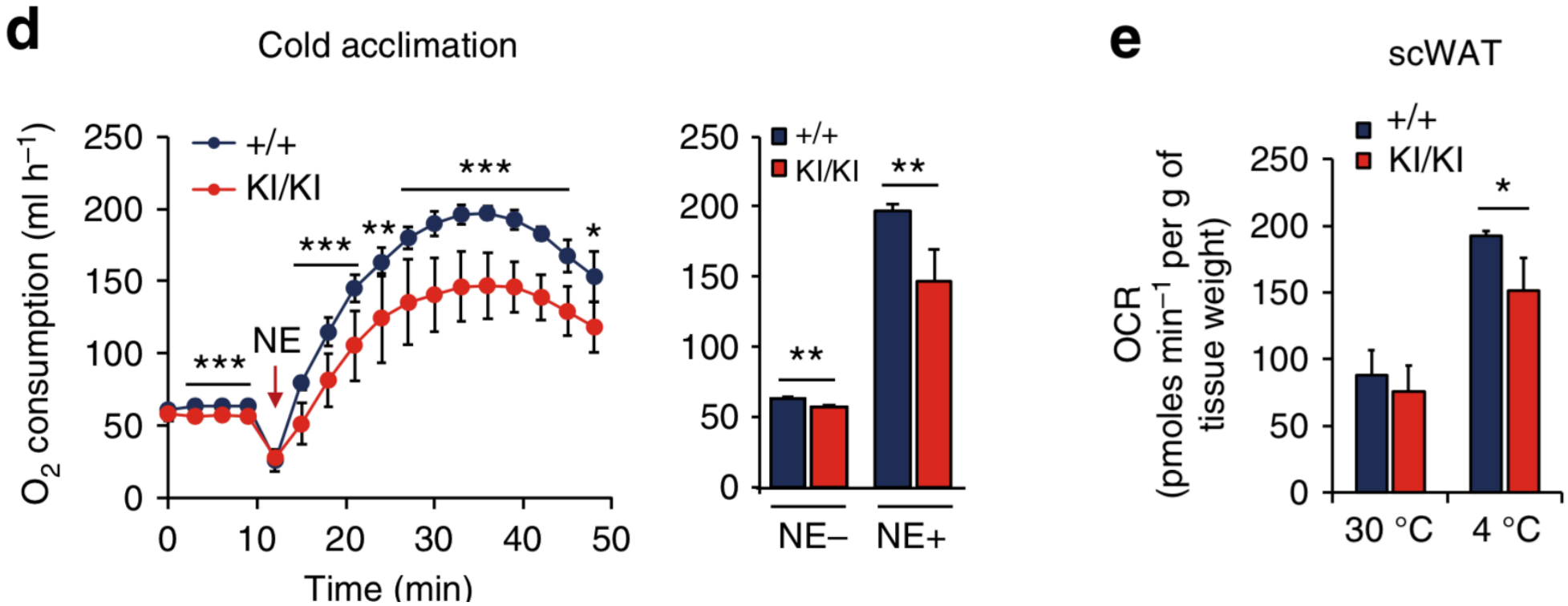
Diabetes research from the insight of epigenome



Cell Metab, **2018**, *27*, 1121–1137

Diabetes research from the insight of epigenome

Phospho-S265 JMJD1A induces beige biogenesis



- Basal whole-body oxygen consumption rate (OCR) before NE injection was significantly higher in the 4 ℃- acclimated WT mice.
- OCR response was 20–25% lower in Jmjd1a-S265AKI/KI mice, relative to WT mice.

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