Regulation of Systemic Energy Balance and Glucose Homeostasis by Protein-Tyrosine Phosphatase 1B

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Diagnosed Obesity and Diabetes for Adults aged ≥ 20 years in United States

**Obesity (BMI ≥30 kg/m²)**

- **1994**
- **2000**
- **2007**

**Diabetes**

- **1994**
- **2000**
- **2007**
The Obesity Epidemic Has Reached America’s Pets

A 28 pound cat!!
System Regulation of Glucose

- **Increased hepatic glucose production**
- **Impaired glucose utilization**
- **Insulin secretory defect**

Pancreas

Insulin

Glucose

Liver

Muscle

Adipocytes
Understand the Role of Cell Signaling, in Particular, Tyrosine Phosphorylation in the Pathogenesis of Metabolic Diseases
Phosphorylation is reversible

PTPs

Protein

PTKs

Protein
The Classical Protein-Tyrosine Phosphatase (PTP) Family

Nontransmembrane PTP subtypes (NT)  Receptor-like PTP Subtypes (R)

Andersen et al. 2001
http://ptp.cshl.edu
Protein-Tyrosine Phosphatase 1B (PTP1B)

Is ubiquitously expressed, including all insulin-responsive tissues

Generate PTP1B knockout (KO) mice (protein no longer expressed)

- PTP1B KO mice are insulin-sensitive, and have increased insulin receptor (IR) phosphorylation (Elchebly et al, 1999 and Klaman et al, 2000)

- PTP1B KO mice are lean and resistant to diet-induced obesity (Elchebly et al, 1999 and Klaman et al, 2000)
PTP1B Inhibition for Treatment of Metabolic Diseases

No obvious apparent side effects observed thus far, making PTP1B a good target for treating obesity and diabetes in humans.

Companies are competing to generate a readily bio-available, PTP1B-specific inhibitor.

Need to know the SITES and MECHANISMS of PTP1B action.
Approach

Genetically-engineered mice to achieve tissue-specific deletion of PTP1B

Quantitative cellular imaging to dissect the mechanism of PTP1B action
Genetically-engineered mice to achieve tissue-specific deletion of PTP1B

Quantitative cellular imaging to dissect the mechanism of PTP1B action
Tissue-Specific Deletion of PTP1B

- PTP1B fl/fl
- Alb-Cre
  - Liver
- Adp-Cre
  - Adipose
- PDX1-Cre
  - Pancreas
- MCK-Cre
  - Muscle
Generation of Adipose-Specific PTP1B Knockout Mice using $Adipoq$-Cre

$\text{PTP1B}^{fl/fl}$ × $\text{Adipoq-Cre}$ → $\text{FPTP1B}^{\text{KO}}$

PTP1B adipose-specific deletion
Efficient and Specific Deletion of PTP1B in Adipose Tissue
Resistance to HFD-Induced Obesity in adipose PTP1B KO Mice

**Males/HFD**
- flx/flx
- +/-, Cre
- flx/flx, Cre (KO)

**Females/HFD**
- flx/flx
- +/-, Cre
- flx/flx, Cre (KO)

**Males/Chow**

**Females/Chow**
Increased Energy Expenditure in Adipose PTP1B KO Mice

Energy Expenditure (KJ/Min/Kg^{0.75})

- **flx/flx, Cre (KO)**
- **+/+, Cre (Adipoq)**

Graph data points for:
- Dark Fed
- Light Fed
- Dark Fast
- Total
Approach

Genetically-engineered mice to achieve tissue-specific deletion of PTP1B

Quantitative cellular imaging to dissect the mechanism of PTP1B action
Fluorescence Recovery After Photobleaching (FRAP)
Dynamics of Cellular PTP1B Mobility

PTP1B WT (ER)  PTP1B D/A (ER)  PTP1B D/A (Cell-Cell)
Quantitative Determination of PTP1B Mobility Using FRAP

Recovery consistent with:
1) Rapid turnover (<10 sec)
2) Replenishment from ER pool
3) No significant “tight binding” fraction

WT ER, $D_{\text{eff}} = 0.20 \ \mu\text{m}^2\text{s}^{-1}$
D/A ER, $D_{\text{eff}} = 0.07 \ \mu\text{m}^2\text{s}^{-1}$
D/A cell-cell

($D_{\text{eff}}$: Effective diffusion)
Summary

Adipose-specific PTP1B deletion leads to decreased adiposity and resistance to high fat diet-induced obesity

This is due to increased energy expenditure in adipose PTP1B deficient mice

Cellular imaging identifies the endoplasmic reticulum and cell-cell contact as major cites of PTP1B action in the cell
Conclusion

Tissue-specific deletion and cell biology approaches are necessary to decipher the sites and mechanisms of PTP1B action.

This is important for developing drugs that targets PTP1B at the correct site(s).
Future Studies

Investigate the role of PTP1B in other tissues and its mechanism of action at these cites.

Investigate the role of other members of PTP superfamily as potential targets to treat obesity and diabetes.

Examine regulation of PTP activity by nutrients and diets.
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