Glucose and Mitochondrial Function

Wednesday, March 11, 2015

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Assistant Professor
Inaugural Pittman Scholar
Division of Molecular and Cellular Pathology
Outline

• Define the question and model to determine the connection between metabolism and diabetic heart disease.

• Identify the molecular mechanisms by which glucose directly alters molecular function using systems biology.
  • Transcriptomics
  • Proteomics
  • Metabolomics
  • Methylomics and epigenetics
Obesity, Metabolic Syndrome, Diabetes, and Heart Failure

From: Roger Unger - UTSW
2010 – Obesity

2010 – Physical Inactivity

2010 – Diabetes

2010 – Heart Disease

www.cdc.gov/diabetes/statistics and www.cdc.gov/mmwr
Maintaining Cardiac Function Through Metabolic Substrate Balance

Glucose ↔ Fatty Acids
Studies on Myocardial Metabolism*

IV. Myocardial Metabolism in Diabetes

I. Ungar, M.D., M. Gilbert, M.D., A. Siegel, M.S., J. M. Blain, M.D. and R. J. Bing, M.D.

Lactate usage and a slight decline in that of pyruvate. There is no change in utilization of amino acids by the heart in both species. Myocardial glucose consumption is reduced in dog and man relative to the elevation in blood glucose concentration. The myocardial usage of ketones is slightly increased in diabetic hearts of patients and significantly elevated in the dog. The main difference concerns the utilization of fatty acids; this is significantly increased in the human heart but is unchanged in the dog. Whether this is due to a species difference or to differences in type and severity of diabetes is not clear. Anesthesia, which was used in the dogs, may have played some part. Different species variations in ketone body utilization.
# Metabolic Substrate Utilization in the Heart

## Table 2. Brief Overview of Myocardial Metabolism in Physiological and Pathophysiological Conditions

<table>
<thead>
<tr>
<th></th>
<th>$\text{MVO}_2$</th>
<th>Glucose Metabolism</th>
<th>Fatty Acid Metabolism</th>
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<tbody>
<tr>
<td>Aging</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>Female sex</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
<td>$\uparrow$</td>
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<tr>
<td>Obesity</td>
<td>$\uparrow$</td>
<td>—</td>
<td>$\uparrow$</td>
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<tr>
<td>Diabetes, types 1 and 2</td>
<td>— $\uparrow$</td>
<td>$\downarrow$</td>
<td>$\uparrow$</td>
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<tr>
<td>Hypertension: LV hypertrophy</td>
<td>—</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>—</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>Ischemia</td>
<td>$\downarrow$</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
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</table>
Point/Counterpoint - The Right Balance?

Cardiac Pathology via Diet-Induced Glucolipotoxicity

High Glycemic Carbs
↓ ω-3 PUFA
↑ Saturated Fat
Positive Energy Balance

Obesity & Metabolic Syndrome
↑ Triglycerides, FFA
↑ LDL, ↓ HDL
↓ Adiponectin
↑ Inflammation
↑ Leptin & ↑ Insulin
↑ Blood pressure

Atherosclerosis
↑ Myocyte size
↑ Apoptosis
↑ Fibrosis
Mitochondria Dysfunction

CAD, LVH, Heart Failure

Cardiac Health via Dietary Protection

Low Glycemic Carbs
↑ ω-3 PUFA
↓ Saturated Fat
Neutral Energy Balance

No Obesity & No Metabolic Syndrome
Normal Triglycerides, FFA
↓ LDL, ↑ HDL
↑ Adiponectin
↓ Inflammation
↓ Leptin & ↓ Insulin
Normal Blood pressure

Healthy Heart
↓ Atherosclerosis
Normal Myocyte Size
↓ Apoptosis
Optimal Mitochondria Function

Heinrich Taegtmeyer, MD, DPhil

William C. Stanley, PhD
1957 - 2013

Taegtmeyer and Stanley 2011 J Mol Cell Cardiol 50(1):2
Metabolomics is an integral part for understanding disease processes ... information garnered in the biomarker investigations, future research should shed more light on disease pathogenesis and explore new treatment options.
The hypertrophy, oxidative stress, and metabolic changes that occur within the heart when glucose supplants FA as a major energy source suggest that substrate switching to glucose is not entirely benign.
Mitochondria – a Dynamic Network
Facilitative Glucose Transporters: GLUTs
“Solute Carrier Family, SLC2A”

Scheepers … Schurmann 2004 J Parenter Enteral Nutr 28:364
Changes in Human Heart GLUT Levels

**RNA**
- Human heart failure

**Protein**
- Human heart diabetes

Biopsies obtained during coronary bypass surgery

HL = hyperlipidemia

DM2 = diabetes mellitus type 2

Razeghi ... Taegtmeyer 2002 *Cardiology* 280(41):34786

Armoni ... Karnieli 2005 *J Biol Chem* 280(41):34786
Glucose Utilization and Rodent Models of Type 1 Diabetes

Protein Diabetic Mouse Heart

Glucose Uptake Diabetic Mouse Heart

Panagia ... Clarke 2005 Am J Physiol 288:H2677
Constitutive GLUT4 Expression Prevents Development of Glucose Utilization Defects

Glycolysis

GLOX

Belke … Severson 2000 Am J Physiol 279:E1104
Question: Is the change in cardiac metabolic substrate flexibility adaptive or maladaptive?
Inducible Cardiomyocyte-Specific GLUT4 Expression (mG4H)

DOX absent = OFF

α-MHC
rtTA
MHC-rtTA

TRE
mycGLUT4
TRE-GLUT4

DOX present = ON

α-MHC
rtTA
MHC-rtTA

TRE
mycGLUT4
TRE-GLUT4
mG4H Mice Exhibit Inducible Cardiac-Specific Expression of GLUT4

<table>
<thead>
<tr>
<th>DOX (d)</th>
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<th>mG4H</th>
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<td>2</td>
<td>4</td>
<td>8</td>
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<tr>
<td>2</td>
<td>4</td>
<td>8</td>
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<tr>
<td>myc</td>
<td></td>
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<tr>
<td>Glut4</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>DOX (d)</th>
<th>Con</th>
<th>mG4H</th>
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<tr>
<td>0</td>
<td>14</td>
<td></td>
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<tr>
<td>0</td>
<td>14</td>
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Hrt = Heart  TA = Tibialis anterior
GC = Gastrocnemius  Sol = Soleus
Vas = Vastus lateralis
Insulin-induced GLUT4 Vesicle Fusion and Exofacial Myc-Epitope Exposure

Ariel Contreras-Ferrat
GLUT4 Induction Increases Basal and Insulin-Stimulated Glucose Uptake

$\text{Con}$  $\text{mG4H}$

$\text{Basal}$  $\text{0.1 nM Ins}$

$n = 3 – 4$

$^{a} P < 0.01 \text{ vs. Con-Basal}$

$^{b} P < 0.001 \text{ vs. All}$

Renata O. Pereira
Streptozotocin (STZ)-Induced Hyperglycemia is Not Altered by Transgene Induction
GLUT4 Induction Increases Glycolysis and Rescues Diabetic Cardiac Glycolytic Defects

$n = 6 - 10$

§ $P < 0.01$ vs. Con

Joseph Tuinei
Wende … Abel in prep
GLUT4 Induction Increases GLOX but Accelerates Diabetic Cardiac GLOX Defects

$n = 6 – 10$
‡ $P < 0.001$ vs. All
* $P < 0.01$ vs. Veh

Joseph Tuinei
Wende … Abel in prep
GLUT4 Induction Prevents Increased Cardiac POX in Diabetes

Isolated Working Hearts Palmitate Oxidation (POX)

\[ \mu \text{mol} \cdot \text{min}^{-1} \cdot \text{gdhw}^{-1} \]

\( n = 5 - 13 \)
\( \ddagger P < 0.001 \text{ vs. All} \)
Oxidative Phosphorylation

www.genome.jp/kegg/pathway.html
GLUT4 Induction Accelerates Development of Mitochondrial Dysfunction

$n = 3 – 4$

* $P < 0.05$

Oleh Khalimonchuk
Wende … Abel in prep
In the context of diabetes, enhancing glucose delivery by expression of GLUT4 accelerates the progression of mitochondrial dysfunction.
Diabetic Cardiomyopathy

“Death by a Thousand Cuts…”

- Insulin resistance
- Lipotoxicity
- Glucotoxicity
- Mitochondrial dysfunction
- Inflammation
- ER stress
- REDOX Imbalance

Adapted from Wende, Symons, and Abel 2012 *Curr Hypertens Rep* 14(6):517
Systems Biology

**Phenome**
Obesity, diabetes, heart failure, BHI, etc.

**Transcriptome**
Northerns, qPCR, microarray RNA-seq, miR, IncRNA, etc.

**Proteome**
Mass spec, western blot, Co-IP, IHC, PTMs, etc.

**Metabolome**
Glucometer, ELISA, GC-MS, HPLC, NMR, fluxomics, etc.

**Genome / Epigenome**
Southerns, sequencing, GenBank, ENCODE, ChIP-seq, bsDNA-seq, etc.

Adapted from Lewis and Abdel-Haleem 2013 Front Physiol 4:237
Transcriptomic Analysis Using the Agilent SurePrint G3 60K Microarray

mG4H-Veh

Microarray and Bioinformatic cores – Brian Dalley and Brett Milash
Wende … Abel in prep
Pathway Analysis of Microarray

Wende … Abel *in prep*

- Metabolic disease
- Amino acid metabolism
- Lipid metabolism
- Nucleic acid metabolism
- Carbohydrate metabolism
- Skeletal and muscular disorders
- Energy production
- Cardiovascular system development & function
- Post-translational modification
- Endocrine system development & function
- Inflammatory response
- Endocrine system disorders
- Cell death
- Cardiovascular disease
- Gene expression
- Nutritional disease
- Protein degradation
Glucose Regulated Gene Expression

Mouse STZ

Mouse mG4H

1611
2035

234
195
410

397
459

0 = up-regulated
0 = contra-regulated
0 = down-regulated

Wende, unpublished
Species Conservation of Gene Expression Changes in Diabetes

Human T1D

Mouse T1D

353

190

893

Drakos … Wende, unpublished
Species Conservation of Gene Expression Changes in Diabetes

- Mitochondrial dysfunction
- Calcium signaling
- 3-phosphoinositide degradation
- Oxidative phosphorylation

Drakos ... Wende, unpublished
Oxidative Phosphorylation
**Ndufa9 Gene Promoter Structure**

**KEY**
- TSS = Transcription start site
- CpG island
- Sp1 RE

http://ecrbrowser.dcode.org
**Ndufa9 Gene Promoter Mapping**

**Transient Transfection Promoter Activity**

-2 kb  
-0.5 kb TSS  
-0.3 kb  
+1 kb

**Glucose**
- 5.5 mM
- 25 mM

- **C2C12 Myotubes**
  - * P < 0.05

- **Wende … Abel in prep**
**Ndufa9 Gene Promoter Mapping**

Transient Transfection
Promoter Activity

C₂C₁₂ Myotubes
n = 9
* P < 0.05

Glucose
- 5.5 mM
- 25 mM

Wende ... Abel in prep
**Ndufa9 Gene Promoter Mapping**

**C2C12 Myotubes**

\( n = 9 \)

* \( P < 0.05 \)

Wende … Abel *in prep*
O-GlcNAcylation

30 years old: O-GlcNAc reaches age of reason - Regulation of cell signaling and metabolism by O-GlcNAcylation.
Metabolic Integration: Protein O-GlcNAcylation

O-GlcNAc Cycling

Hanover ... Love 2012 Nat Rev Mol Cell Biol 13(5):312
GlcNAc Regulation of Sp1

Vosseller ... Hart 2002 Curr Opin Chem Biol 6(6):851
GlcNAcylation Regulates *Ndufa9* Gene Expression

**Transient Transfection**

**Promoter Activity**

![Bar graph showing normalized RLU for C2C12 Myotubes with different glucose concentrations and treatments.](image)

- **None**
- **GFP**
- **OGA**

**Glucose**

- 5.5 mM
- 25 mM

**C2C12 Myotubes**

- *n = 3*
- *P < 0.05*

Li Wang

Wende ... Abel *in prep*
Conclusion – Part 2

Enhanced glucose delivery regulates oxidative capacity via transcriptional mechanisms including GlcNAcylation of transcription factors.
Mitochondrial Protein O-GlcNAcylation and Neonatal Cardiomyocyte Metabolic Function

Mitochondrial Protein O-GlcNAcylation

Complex I Activity

O-GlcNAcylation of NDUFA9

NDUFA9 – Complex I

OXPHOS Activity

Western Blot

Complex II activity (% of Con-Veh)

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<tr>
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<th>Con</th>
<th>mG4H</th>
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<tbody>
<tr>
<td>Veh</td>
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<tr>
<td>STZ</td>
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Complex I activity (% of Con-Veh)

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</tr>
<tr>
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CI - NDUFA9/VDAC (Normalized a.u.)

<table>
<thead>
<tr>
<th></th>
<th>Con</th>
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<tbody>
<tr>
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<td></td>
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<tr>
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* indicates significant difference.
GLUT4 Induction Alters Mitochondrial Protein O-GlcNAcylation

Mitochondrial Protein O-GlcNAcylation

<table>
<thead>
<tr>
<th></th>
<th>Veh</th>
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NDUFA9 Immunoprecipitation

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<tr>
<td>IB:</td>
<td></td>
<td></td>
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<tr>
<td>O-GlcNAc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDUFA9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Veh  STZ  Veh  STZ

Wende … Abel in prep
GLUT4 Induction Alters the Cardiac Mitochondrial Glycoproteome

Isolated Mitochondria
2D-PAGE
Pro-Q Emerald

Hansjörg Schwertz
Wende, unpublished
GLUT4 Induction Alters the Cardiac Mitochondrial Glycoproteome

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Gene ID</th>
<th>O-GlcNAc Target</th>
<th>LC-MS/MS PTM</th>
<th>Pathway</th>
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<tbody>
<tr>
<td>ATP5A1</td>
<td>ATP synthase F1 complex, α subunit 1</td>
<td>11946</td>
<td>known¹²</td>
<td>Ac-</td>
<td>OXPHOS</td>
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<tr>
<td>ATP5H</td>
<td>ATP synthase F0 complex, subunit d</td>
<td>71679</td>
<td>novel</td>
<td>Ac-</td>
<td>OXPHOS</td>
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<td>ATP5O</td>
<td>ATP synthase F1 complex, O subunit</td>
<td>28080</td>
<td>novel</td>
<td>Ac-</td>
<td>OXPHOS</td>
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<tr>
<td>ETFB</td>
<td>Electron transferring flavoprotein, β polypeptide</td>
<td>110326</td>
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<td>Ac-</td>
<td>OXPHOS</td>
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<tr>
<td>UQCRC1</td>
<td>Ubiquinol-cytochrome c reductase core protein 1</td>
<td>22273</td>
<td>known¹</td>
<td>Ac-</td>
<td>OXPHOS</td>
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<tr>
<td>UQCRFS1</td>
<td>Ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1</td>
<td>66694</td>
<td>novel</td>
<td>Ac-</td>
<td>OXPHOS</td>
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<tr>
<td>MDH2</td>
<td>Malate dehydrogenase 2, NAD (mitochondrial)</td>
<td>17448</td>
<td>novel</td>
<td>Ac-</td>
<td>TCA</td>
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<tr>
<td>OGDH</td>
<td>Oxoglutarate dehydrogenase (tropomodulin)</td>
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<td>known³</td>
<td>P-</td>
<td>TCA</td>
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<td>SUCLA2</td>
<td>Succinate-Coenzyme A ligase, ADP-forming, β subunit</td>
<td>20916</td>
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<td>Ac-, P-</td>
<td>TCA</td>
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<tr>
<td>DLAT</td>
<td>Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex)</td>
<td>235339</td>
<td>known¹</td>
<td>Glycolysis/ TCA</td>
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<td>ACADL</td>
<td>Acyl-Coenzyme A dehydrogenase, long-chain</td>
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<td>P-</td>
<td>FAO</td>
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<td>HADHB</td>
<td>Hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase ( trifunctional protein), β subunit</td>
<td>231086</td>
<td>novel</td>
<td>P-</td>
<td>FAO</td>
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</table>

PTM = post-translational modification; Ac- = acetylation; P- = phosphorylation; OXPHOS = Oxidative phosphorylation; TCA = Tricarboxylic acid cycle; FAO = Fatty acid β-oxidation

¹Clark et al 2008 J Am Chem Soc 130(35): 11576; Previously identified modification by O-GlcNAc in rat brain and HeLa cells.
²Teo et al 2010 Nat Chem Biol 6(5):338; Previously identified modification by O-GlcNAc in rat liver.
³Nandi et al 2006 Anal Chem 78(2):452; Previously identified modification by O-GlcNAc in HeLa cells.

Wende, unpublished

dbOGAP http://cbsb.lombardi.georgetown.edu and YinOYang www.cbs.dtu.dk
GLUT4 Induction Alters the Cardiac Mitochondrial Glycoproteome

<table>
<thead>
<tr>
<th>Glycoprotein</th>
<th>Con (Veh)</th>
<th>Con (STZ)</th>
<th>mG4H (Veh)</th>
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<tr>
<td>UQCRFS1</td>
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<tr>
<td>Control-VDAC</td>
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</tbody>
</table>

Chase Andrizzi
GLUT4 Induction Alters the Cardiac Mitochondrial Glycoproteome

IB: UQCRFS1

25 kDa

UQCRFS1 25 kDa

50 kDa

IB: Actin

37 kDa

Actin 42 kDa

Lamario Williams, Manoja Brahma, and Chase Andrizzi
Metabolomics
GLUT4 Induction Alters the Cardiac Mitochondrial Glycoproteome

Ketone Synthesis

Fatty acids → Acetyl-CoA → AcAc-CoA → HMG-CoA → Acetoacetate → BHB

Ketone Oxidation

BHB → BDH1/Bdh1 → Acetoacetate → SCOT/Oxct1 → AcAc-CoA → m-Thiolase/Acaa2 → Acetyl-CoA → TCA cycle

RNA - Microarray

Manoja Brahma
GLUT4 Induction Alters the Cardiac Mitochondrial Glycoproteome

<table>
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<td>Control-GAPDH</td>
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</table>

Lamario Williams, Manoja Brahma, and Chase Andrizzi
GLUT4 Induction Alters Mitochondrial Protein O-GlcNAcylation

SCOT immunoprecipitation from LV of 24h fasted mice

IP: SCOT

IB: SCOT

IB: O-GlcNAc

IB: GlcNAc-SCOT

Manoja Brahma
Enhanced cardiac glucose delivery alters metabolic flux through other pathways and regulates the mitochondrial proteome via O-GlcNAcylation.
From Human to Mouse and Back Again
Epigenetics - Programming
DCCT: Diabetes Control and Complications Trial

The New England Journal of Medicine

Volume 329 September 30, 1993 Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP

![Graph showing the effect of intensive treatment on glycosylated hemoglobin and percentage of patients over years of study.](image-url)
Epigenetics - Memory

EDIC: Epidemiology of Diabetes Interventions Trial

- DCCT
- EDIC follow-up

HbA1c (%)

Intensive therapy group

Conventional therapy group

Time (years)

0 1 9 10 18

Percentage of patients (%)

At completion of the DCCT

RET  ALB  NEU

At completion of the EDIC

mALB  ALB  HYP

2009 follow-up

RET  ALB  CVD

Pirola … El-Osta 2010 Nat Rev Endocrinol 6(12):665
Epigenetics: Transgenerational and Drift

Gut and Verdin 2013 Nature 502:489
Epigenetic Code

Fischer 2014 EMBO J 33(9):945-489
Metabolite Signaling to Chromatin

Gut and Verdin 2013 Nature 502:489
How does GlcNAc fit in?

Chromatin Regulation

Gräff and Tsai 2013 Nat Rev Neurosci 14(2):97
How does GlcNAc fit in?

Figure 1 Recently identified modifications on the core histones. Black, modifications found in vivo in human; red, modifications found in mouse brain; blue, modifications found in vitro. ac, acetylation; Ar, ADP-ribosylation; bu, butyrylation; cr, crotonylation; fo, formylation; gt, glutathionylation; ma, malonylation; me, methylation; Og, O-glcNAcylation; oh, hydroxylation; pr, propionylation; su, succinylation; ph, phosphorylation; ub, ubiquitination.
DNA Methylation 101

- **Unmethylated**
- **Methylated**

CpG Island → Gene

Gene Expression

Gene Expression Repressed
Exercise Alters DNA Methylation of Key Metabolic Genes

Low = 40% VO$_{2\text{peak}}$ High = 80% VO$_{2\text{peak}}$

Subjects fasted overnight and then consumed a high carbohydrate diet 4 hr prior to exercise.

Barres and Zierath 2012 Cell Metab 15:405
Diabetes Regulated Cardiac DNA Methylation

Targeted bsDNA-seq
5-mCpG

CpG : ○ = C, ● = 5mC

<table>
<thead>
<tr>
<th>Target</th>
<th>Con</th>
<th>STZ</th>
</tr>
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Heart, LV

*n = 10

* P < 0.05

Wende, unpublished
Methylation and Expression

RNA – microarray

Methylation – genome sequencing

Protein – western blot

GeneSifter and Zymo/UCSC Genome Browser
Other Human/Mouse Comparisons

Figure 2. Epigenome-wide association Manhattan plot for VLDL-C in the discovery dataset (n=991). VLDL-C indicates very-low-density lipoprotein cholesterol.

Figure 3. ENCODE annotation of the promoter region and intron 1 of CPT1A. Top CpGs for TG are positioned within the gene along with CpG islands, cell line chromatin state (Chrom-HMM), cell line methylation at CpG sites on the Methyl450 Beadchip according to Hudson Alpha Institute for Biotechnology (HAIB; note blue, purple, and orange highlights correspond to low, medium and high methylation state, respectively), and HMR conserved transcription factor binding sites. CpG indicates cytosine (phosphate)-guanine; and TG, triglyceride.
Other Human/Mouse Comparisons

Mouse Gene Expression

Mouse DNA Methylation

Wende, unpublished
Where Does Glycemic Memory Fit In?

DOX absent = OFF

MHC-rtTA

α-MHC

rtTA

MHC-rtTA

TRE-GLUT4

mycGLUT4

TRE

DOX present = ON OFF

MHC-rtTA

α-MHC

rtTA

MHC-rtTA

TRE-GLUT4

mycGLUT4

TRE
Glucose Cycling Alters Epigenetic Programming

Genomewide bsDNA-seq 5-mCpG

Legend:

- 0%
- 100%

Heart, LV

Zymo Research
Wende, unpublished
Background

5-hmC
Wyatt and Cohen 1952 Nature 170(4338):1072
Kriaucioni and Heintz 2009 Science 324(5929):929
Tahiliani ... Rao 2009 Science 324(5929):930

http://chemistry.uchicago.edu/faculty/faculty/person/member/chuan-he.html
Glucose Cycling Alters Epigenetic Programming

5-hmCpG ELISA

Heart, LV

Zymo Research
Wende, unpublished
How does GlcNAc fit in?

Mariappa ... Aalten 2013 EMBO J 32:612
Tissue Specific Promoter Utilization

RNA-seq Transcripts

Legend:

-1 | 1

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<th>RNA</th>
<th>Con Veh</th>
<th>mG4H Veh</th>
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<td>STZ</td>
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Bdh1

Con-Veh

Con-STZ

mG4H-Veh

mG4H-STZ

Heart, LV
n = 3

Heflin Center for Genomic Sciences, UAB
Nye ... Wende, unpublished
Combined Transcriptome/Methylome

Genomewide bsDNA-seq 5-mCpG

Legend:
-1 1
Legend:
0% 100%

Legend:

RNA

Con
Veh STZ
mG4H
Veh STZ

5-mCpG

Bdh1

Scale
chr16:

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CpG Islands (Islands < 300 Bases are Light Green)

RefSeq Genes

Bdh1

GC Percent in 5-Base Windows

Vertebrate Multiz Alignment & Conservation (60 Species)

Placental Cons Multiz Align

Heart, LV

Zymo Research and UCSC Genome Browser
Wende, unpublished
Combined Transcriptome/Methylome

Genomewide RRHP 5-hmCpG

RNA

Legend:

Con

mG4H

Veh STZ Veh STZ

Legend:

-1

1

Legend:

0%

100%

Bdh1

Scale

chr16:


100 bases

mm10

5-hmC

mG4H-Veh mCpG

mG4H-STZ mCpG

mG4H-Off mCpG

Heart, LV

Zymo Research and UCSC Genome Browser

Nye ... Wende, unpublished
Cellular glucose fluctuations regulate the epigenome via histone modifications and controlling the machinery for DNA methylation.
Sugar Gumming Up the Works
Using combined methylomics, transcriptomics, proteomics, and metabolomics we have begun to define the mechanism of glucotoxicity.
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UAB
Knowledge that will change your world

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R00 HL111322-S1

NIH
National Institute of Diabetes and Digestive and Kidney Diseases
U24 DK076169

American Heart Association
AHA 0725064Y

JDRF
Improving Lives. Curing Type 1 Diabetes.
JDRF 51002608