Molecular Pathways to Type 2 Diabetes Risk in Humans

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Why is Diabetes So Important?
Global Projections for Top Countries in Number of People with Diabetes

- U.S.: 19.2 M, 25.4 M (↑ 32%)
- Germany: 7.4 M, 8.1 M (↑ 9%)
- Russia: 9.6 M, 10.3 M (↑ 7%)
- China: 39.8 M, 59.3 M (↑ 49%)
- Mexico: 6.1 M, 10.8 M (↑ 77%)
- Brazil: 6.9 M, 17.6 M (↑ 155%)
- Egypt: 4.4 M, 7.6 M (↑ 73%)
- Pakistan: 6.9 M, 11.5 M (↑ 67%)
- India: 40.9 M, 69.9 M (↑ 71%)

World:
- 2007 = 246 M
- 2025 = 380 M (↑ 54%)

M = millions

Diabetes & Obesity - Dual Epidemics: A Global Crisis of “Affluenza”
Obesity and Insulin Resistance: A Driving Force for Many Problems

- Genes
  - Dyslipidemia
  - Gallstones
  - Hepatic Steatosis
  - Alzheimer’s Disease and Some Cancers
- Environment
  - Hypertension
  - Accelerated Atherosclerosis
  - Reproductive Dysfunction
  - Increased Infection and Decreased Oral Health

Central Obesity Insulin Resistance

Type 2 Diabetes Glucose Intolerance
How Do We Define Diabetes? Prediabetes?

Fasting Blood Test

Glucose Tolerance Test

OR
Types of Diabetes

- **Type 1**: AKA insulin-dependent, juvenile onset
- **Type 2**: previously known as insulin-independent, adult onset
- **Gestational diabetes**: occurring during pregnancy
- **MODY** (maturity onset diabetes of youth) – autosomal dominant, mutations in transcription factors
- **Rare forms** associated with abnormal fat distribution, mitochondrial DNA mutations, etc.
Type 1 Diabetes

- Pancreas loses its ability to secrete insulin
- Almost always caused by specific immune attack on insulin-producing cells of pancreas
- Both genetic and environmental factors
- Can be diagnosed at any age, most commonly <30
- Must inject insulin to prevent ketoacidosis & death

- Research: Understanding immunology, harness to prevent, or allowing insulin-producing cells to survive despite immune attack
Exactly 2 months later, weight 29 lbs

3 year-old J.L., weight 15 lbs

The Discovery of Insulin - 1922
Type 2 Diabetes

• Previously known as insulin-independent, adult onset

• Insulin resistance:
  • Body makes plenty of insulin initially, but doesn’t respond well to it
  • Eventually, loss of insulin secretion by pancreas \ diamond increased glucose

• Can be diagnosed at any age, most commonly middle age (but more in children now)

• Often treated with medications other than insulin initially

• Some basal insulin secretion, so low risk for ketoacidosis
WHO GETS TYPE 2 DIABETES?

- Family history of diabetes
  - Impact greater for type 2
- Ethnic background
- Birth weight – either high or low!
- Obesity, particularly abdominal location
- History of diabetes during a previous pregnancy
- Age > 45
- High blood pressure
- High lipids
- Inactivity
Inactivity
Obesity
Poor Nutrition
Family History
Intrauterine Environment
Dad
Mom
2100 AD?
Type 2 Diabetes: Disordered Metabolism in Multiple Tissues

Skeletal Muscle
↓ Glucose Uptake (Insulin Resistance)

Liver
↑ Glucose & Lipid Production

Adipose Tissue
Insulin Resistance
Altered Secretion of Hormones & Adipocytokines

Brain, Intestinal Tract
Altered Satiety, Food Intake, Incretin Secretion, Gut Flora

Pancreas
↓ Insulin Secretion
↑ Glucagon Secretion
Altered Incretin Responses

Diabetes Metabolic Environment
THE TYPE 2 DIABETES “PUZZLE”
Many Unanswered Questions!

1. Which comes first?
   Insulin resistance?
   OR
   Decreased insulin secretion?

2. Which tissues are responsible for insulin resistance?

3. What are the molecular problems causing insulin resistance in high risk people BEFORE diabetes develops?

4. How can we use this information to improve treatment and to PREVENT diabetes?
Progression of Type 2 diabetes

- **Diagnosis**
  - Glucose (mg/dL)
    - Post-Meal Glucose
    - Fasting Glucose
  - Insulin Resistance

- **Relative β-cell Function (%)**
  - B-cell failure

- **Clinical Features**
  - Obesity
  - IGT
  - Diabetes
  - Uncontrolled Hyperglycemia

- **Macrovascular Changes**
- **Microvascular Changes**

Years:
- 30
- 25
- 20
- 15
- 10
- 5
- 0
- -5
- -10
THE TYPE 2 DIABETES “PUZZLE”
Many Unanswered Questions!

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   - Insulin resistance?
   - OR
   - Decreased insulin secretion?

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What Are the Earliest Abnormalities in Individuals at High Risk for DM2?
Insulin-Stimulated Glucose Metabolism is Reduced in First-Degree Relatives of DM Subjects

Eriksson J, NEJM, 1989

Hyperinsulinemic euglycemic clamp, 100 uU/ml
Overview

• What are the principal risk factors for type 2 diabetes?
• What are the patterns of gene expression in key target tissues in humans with established type 2 diabetes or at risk for diabetes?
• The mitochondrial hypothesis of diabetes pathogenesis
• Novel molecular pathways associated with insulin resistance and family history of diabetes
How Do DM Risk Factors Mediate Insulin Resistance at a Molecular Level in Humans?

- Adverse Intrauterine Environment
  - Epigenetics
  - Altered Development
- Family History
  - Genetics
  - Shared Environment
- Other Risk Factors
  - Aging

Altered Gene & Protein Expression and Function

- Mitochondrial Dysfunction
- Lipid Accumulation
- Oxidative Stress
- ER Stress
- Inflammation

Cellular Energy Excess
- Obesity
- Inactivity
- Dietary Excess

Insulin Resistance
- Beta Cell Dysfunction
  - “Glucolipotoxicity”

Type 2 Diabetes
Strategy: Analyze Metabolic and Molecular Phenotypes in Insulin Resistance or DM2

- Muscle and adipose tissue biopsies from metabolically characterized human volunteers
- Gene chip arrays to assess global gene expression patterns (integration of genetic and environmental factors)
- Biological validation in animal and cell culture models
  - Protein, metabolomics, cell biology
What Have We Learned from These Approaches?

Insulin Resistance

- Insulin Sensitive
- Insulin Resistant
- IGT & Established DM

Altered Mitochondrial Function in Muscle and Adipose
Potential Role of Mitochondrial Function in Development of Diabetes, Obesity, and the Metabolic Syndrome
Decreases in Mitochondrial Metabolism Genes in Type 2 Diabetes and Family Members

Patti et al. 2003; Mootha et al. 2003.

Red = Low decreased
Green = High decreased

Complex I 2 of 7 decreased
Complex II 3 of 6 decreased
Complex III 3 of 5 decreased
Complex IV 3 of 15 decreased
Complex V 4 of 5 decreased
Mitochondrial Function is Decreased in Muscle in Type 2 Diabetes


Electron Microscopy

Subsarcolemmal Mito
Potential Role of Mitochondrial Function in Development of Diabetes, Obesity, and the Metabolic Syndrome

- Mitochondria are involved in converting all nutritional fuels into energy.
- Mitochondrial activity is decreased in aging, obesity, and type 2 diabetes.
- Mitochondrial activity is increased with exercise and dietary and pharmacological treatments for DM2 that improve metabolism.
- Mice of different strains and resistance to obesity have different levels of muscle mitochondrial activity.
Lifestyle Factors Can Also Modulate Mitochondrial Function

- Sirtuins: NAD-dependent protein deacetylases
- Involved in control of metabolism and aging
- Act in part by stimulating mitochondria
- Sirt1 can be activated by Resveratrol – a natural product found in the skin of red grapes
The Mitochondrial Hypothesis” of Diabetes Pathogenesis

- Decreased Transcription of Metabolic and Nuclear-Encoded Mitochondrial Genes
- Insulin Resistance and Diabetes

Alterations in Mitochondrial Functional Capacity
↓ Oxidative Capacity
Impaired Metabolic Flexibility
↓ Lipid Oxidation
↑ Lipid Accumulation
↓ ATP Synthesis

Which upstream mechanisms are responsible?
Could the PGC-1 Family of Genes Be Responsible?

PGC-1

NRF-1/2
ERR_
PPAR_
Other NR

DNA

↓ Transcription Nuclear-Encoded Mitochondrial Genes

♣ PGC-1 = PPARγ Coactivator 1; PGC-1α, β, and PERC
♣ PGC-1 coactivates NRF, PPARγ, PPARα, HNF4, others
♣ Important role in many tissues related to whole-body metabolism

Adipose

Muscle

Thermogenesis
Oxidative Capacity

Lin & Spiegelman
Expression of PGC1α & β is Decreased in Muscle From Humans with Both Insulin Resistance and DM

Mexican-American subjects (Larry Mandarino)
Similar decreases in adipose tissue from humans with obesity
Decreased Expression or Function of PGC1α and β

Decreased Transcription of Metabolic and Mitochondrial Genes

DM2

DM Risk

PGC-1 Dependent Pathways to DM Risk

NRF
ERR
PPAR
others
Non-OXPHOS Mito Dysregulation: BCAA & Lipid Oxidative Pathways

Genetics

OXPHOS Expression

Non-OXPHOS Mito Dysregulation: BCAA & Lipid Oxidative Pathways

_SRF Transcriptional Activity

Inflammation

Environment

Obesity Saturated FFA Intramuscular Lipid

↓ Adiponectin

Inactivity Aging

Decreased Expression PGC1α and β

Other Transcriptional Regulators

Altered Transcription & Splicing

Metabolic Inflexibility

Insulin Resistance DM Risk

2009

Other Transcriptional Regulators

2009
Which Comes First?

Insulin Resistance?

Abnormal Mitochondrial Function?
Chronic Fuel Excess
- Obesity
- Inactivity

↑ Oxidative Stress
- Lipid accumulation
- Incomplete Oxidation

Decreased Oxidative Capacity

Mitochondrial damage
↓ OXPHOS

Insulin Resistance
- Impaired Insulin Secretion

- Genetics
- Ethnicity
- Intrauterine exposures
- Aging
If oxidative capacity is limited relative to nutrient intake…
Possible compensatory responses to establish equilibrium:

Reduce nutrient intake & body weight to reduce oxidative load

Enhance mitochondrial capacity with exercise, weight loss

Failure of compensation

Insulin Resistance _ Insulin Secretion
Can These Patterns Be Reversed?

Weight Management
Exercise! Exercise! Exercise!
Metformin, other insulin sensitizers (TZD)
Future Therapies: Anti-Inflammatory, Anti-SRF?
Future Directions

• Analysis of metabolic intermediates in tissues to determine functional correlates of alterations in gene expression in insulin resistance
  – Lipidomics, metabolomics

• Can we identify markers of insulin resistance and DM risk in *circulating blood samples* which can be used to identify high-risk individuals for targeted prevention?

• How can we better target pathogenic pathways for treatment of type 2 diabetes?
Take-home Messages about Type 2 Diabetes and Obesity

• Obesity, diabetes, and the metabolic syndrome are major challenges to human health worldwide
• These disorders are linked to each other by complex metabolic and inflammatory pathways
• Defining these links at a cellular and molecular level is a key to defining new approaches to identification of high-risk individuals for prevention and treatment of these diseases
• Targeting metabolic function by nutrition, exercise, and anti-inflammatory medication may also present a key opportunity to possible prevention and treatment of diabetes and other obesity-linked disorders.