Pathogenesis of Type 2 Diabetes Mellitus - What it Can Teach Us About Early Intervention

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Disclosures

- Honoraria for advisory boards from Merck, Novo-Nordisk, Sanofi, Bristol Myers Squibb, Takeda.
- Speaker at international Diabetes meetings - travel and honorarium sponsored by Sanofi.
- Principal investigator with salary on research grants from National Institutes of Health, American Diabetes Association, and Takeda Pharmaceuticals.

Diabetes Prevalence

- USA 2011 CDC statistics:
  - 25.8 million (8.3% of population) with diabetes, 18.6 million diagnosed, 7.0 million undiagnosed.
  - 11.3% ≥ 20 y.o have diabetes, 35% have prediabetes.
- China 2008:
  - 9.7% ≥ 20 y.o. have diabetes (92 million), 15.5% have prediabetes (148 million).
- Publication from CDC October 2010:
  - Diabetes prevalence in US will be 1 in 3 in 2050 if continued rise in incidence and lowering of mortality.


Country Prevalence of Diabetes 20-79 y.o. 2010 and 2030

<table>
<thead>
<tr>
<th>COUNTRY/TERRITORY</th>
<th>2010 PREVALENCE (%)</th>
<th>2030 PREVALENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 United Arab Emirates</td>
<td>18.7</td>
<td>21.1</td>
</tr>
<tr>
<td>2 Russian Federation</td>
<td>17.6</td>
<td>19.9</td>
</tr>
<tr>
<td>3 Mexico</td>
<td>19.3</td>
<td>21.1</td>
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<tr>
<td>4 Britain</td>
<td>12.3</td>
<td>13.3</td>
</tr>
<tr>
<td>5 Canada</td>
<td>14.8</td>
<td>15.7</td>
</tr>
<tr>
<td>6 Ireland</td>
<td>13.0</td>
<td>13.9</td>
</tr>
<tr>
<td>7 India</td>
<td>12.6</td>
<td>13.5</td>
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<tr>
<td>8 China</td>
<td>12.7</td>
<td>13.6</td>
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<tr>
<td>9 Singapore</td>
<td>13.1</td>
<td>14.0</td>
</tr>
<tr>
<td>10 Malaysia</td>
<td>11.8</td>
<td>12.7</td>
</tr>
</tbody>
</table>

USA 10.3 12.0

IFDi Diabetes Atlas 2010

Relationship BMI and Risk Type 2 Diabetes

Body Mass index (kg/m²)

Pathogenesis of Type 2 Diabetes

Causes of Hyperglycemia in Type 2 Diabetes

- Insulin Resistance
- β-cell Dysfunction/Failure

β-cell Dysfunction versus Insulin Resistance in High Risk Subjects

- 48 Pima Indians all normal glucose tolerance studied for an average 5.1±1.4 years:
  - IVGTT and euglycemic pumps with calculation of disposition index.
  - 17 progressed from NGT to IGT to Type DM.
  - 38 remained NGT.


Conclusions

- Insulin resistance is common, and becoming more common worldwide related to environmental stresses:
  - Obesity, high fat/calorie diets, inactivity
  - Westernization
  - Emotional stress
- Even in the face of profound insulin resistance, healthy β-cells can compensate - perfectly - resulting in normal glucose tolerance.
- Speculation:
  - People with DM or pre-DM MUST have unhealthy β-cells.
  - Must occur very early and be a major mechanism of DM predisposition.


β-cell Dysfunction versus Insulin Resistance in High Risk Subjects

- Nonprogressors
  - NGT
  - NGT
  - NGT
- Progressors
  - DIA
  - IGT
  - NGT


All Diabetes Starts With β-cell “Problems”
Normal β-cell Function

Islet Hormones

β-cells - Insulin
α-cells - Glucagon
δ-cells - Somatostatin

The Normal β-Cell Insulin Response to Intravenous Glucose Is Biphasic


β-Cell Glucose Signaling

Post-Meal Insulin and Glucagon

Mealtime Incretin Effect on Glucose Homeostasis

Ingestion of food leads to Release of GLP-1 and GIP, which increases insulin output and reduces glucagon output by 

**β**-cells and 

**α**-cells.

Incretin effect on Glucose Homeostasis:

- **↑ Insulin**
- **↓ Glucagon**

**β**-cell responses include:

- Release of GLP-1 and GIP

GLP-1 Related ß-Cell Signaling:

- **GLUT2** glucose entry
- **Ca**\(^{2+}\) calcium channel
- **Potassium (K\(_{\text{ATP}}\)) channel closes**

Enhanced lipolysis, LC-CoA amplification, and increased proinsulin synthesis lead to increased insulin secretion.

Hyperbolic Relationship Between Insulin Secretion and Resistance:

Puberty, pregnancy, aging, “good life”

What is the Biological Basis for Susceptible ß-cells?

Factors such as insulin, fatty acids, glucose, incretins, and neural peptides interact with mass and function.


A genome-wide association study identifies novel risk loci for type 2 diabetes

Robert Stodieck,1,2*, Christian Rochette,1*, Jason Kong3*, Christine Diniz,4,5 Unguang Shi,6 David Seneviratne,7 Philippe Brulet,8 Daniel Vincenzi,9 Alexandre Bardou,6 Terry Hudson,6 Barry Babcock,7 Barbara Floud,4 Guillaume Cossins,5*, Thomas J. Hulbert3*, Alexandre Manoukian,5*, Alyson S. Paterson5, and Marc Perret7,8,10

Type 2 diabetes etiology results from the interaction of environmental factors with genetic variants. A systematic search for these variants was recently made possible by the development of high-density arrays that permit the genotyping of thousands of single nucleotide polymorphisms (SNPs). We tested 721,336 single nucleotide polymorphisms in 4,963 type 2 diabetic patients with the most significant differences in genotype frequencies to be attributed to genetic polymorphisms. Inferences about the functional significance of the best SNPs were made based on the literature, on haplotype formation, and on the known genetic architecture of other common complex traits that confer type 2 diabetes risk. We identified 10 previously unreported loci with evidence of association with type 2 diabetes.


Chronology of the Discovery of Type 2 Diabetes-Associated Genes

<table>
<thead>
<tr>
<th>Year of confirmation</th>
<th>Year of publication</th>
<th>Gene(s)</th>
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<td>2000</td>
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<tr>
<td>2001</td>
<td>2002</td>
<td>KCNJ11</td>
</tr>
<tr>
<td>2002</td>
<td>2003</td>
<td>TCF7L2</td>
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<td>2003</td>
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<td>SLC30A8</td>
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<tr>
<td>2004</td>
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<tr>
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<td>SCL30A8</td>
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<tr>
<td>2006</td>
<td>2007</td>
<td>HHEX-IDE</td>
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<tr>
<td>2007</td>
<td></td>
<td>CDKAL1</td>
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<td>2007</td>
<td></td>
<td>CDKN2A/B</td>
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<tr>
<td>2008</td>
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<td>FTO</td>
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<td>CAPN10</td>
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<tr>
<td>2010</td>
<td></td>
<td>ENPP1</td>
</tr>
</tbody>
</table>

Genetics - 2011

- Currently 50+ susceptibility genes identified - and counting.
  - Surprisingly few affect insulin sensitivity, obesity, or insulin action cascade.
  - All of very modest effect.
- Specifics:
  - TCF7L2 - impact GLP-1 and GIP receptor expression in β-cells, and regulator of β-cell Wnt signaling.
  - SLC30A8 - islet zinc transporter.
  - KCNJ11 - β-cell KATP channel.
- Evolving concept:
  - Many impact some aspect of the incretin system.

Genetic variants affecting incretin sensitivity and incretin secretion

- Impaired incretin effect first-degree relatives type 2 DM (Meier JJ et al. Diabetes 50:2497-2504, 2001)
- Impaired incretin effect IGT (Faerch K et al. Diabetologia 51:853-861, 2008)
Diabetes Predisposition Related to Intrauterine and Childhood Environment

- Epidemiologic and animal studies showing diabetes and obesity predisposition:
  - Intrauterine growth retardation
  - Childhood malnutrition
  - Poor maternal diabetes care
  - Imprinting of impaired insulin secretory capacity
- Impact ß-cell mass and development

β-cell Mass: Normoglycemia and Diabetes
An Autopsy Study

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β-cell Mass: Normoglycemia and Diabetes
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Fasting Plasma Glucose (FPG) and Acute Insulin Response

Increased Plasma Free Fatty Acids Impairs Insulin Secretion in Nondiabetic Subjects with Family History Type 2 DM
Progressive Mechanisms for Decline in β-cell Mass and Function

- **Glucose toxicity.**
  - Direct effect.
  - Indirect effect: β-cell overwork or exhaustion.
- Amyloid infiltration of islets.
- Islet inflammation.
- Impaired incretin regulation.
  - Markedly decreased GIP response; lowered GIP and GLP-1 receptor expression.
- Metabolic stresses: ER, oxidative, glucolipotoxicity.
  - Proven in animal models; modest evidence in isolated islets from persons with type 2 DM.

Islet Amyloid in Type 2 Diabetes

- Made up of a normal β-cell secreted protein - IAPP.
- Same temporal relationship between onset DM in monkeys and appearance islet amyloid.
- Transgenic mice overexpressing human IAPP develop diabetes and islet amyloid.
- IAPP linked to activation of NLRP3 inflammasome and β-cell ER stress.

Infiltrating Macrophages in Islet of Type 2 Diabetes

- Donath MY et al. Diabetes Care 2008;31 Suppl 2:S161-S164
- Donath MY, Shoelson S. Nat Rev Immunol 2011;11:98-107

Can We Intervene?

Environment stresses and obesity causing insulin resistance and/or β-cell dysfunction.

<table>
<thead>
<tr>
<th>Normal glucose tolerance</th>
<th>Prediabetes</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal or postnatal environment</td>
<td>Susceptible β-cells</td>
<td>7 β-cell mass ↓40%</td>
</tr>
<tr>
<td>Acquired - loss first phase</td>
<td>7 β-cell dysfunction</td>
<td>5-cell mass ↓10%</td>
</tr>
<tr>
<td>Multifactorial</td>
<td>↓β-secretory capacity</td>
<td></td>
</tr>
</tbody>
</table>

Postulated β-cell Pathogenesis:

- Islet amyloid
- ER stress
- Oxidative stress
- Glucose toxicity
- Defective incretin regulation
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Diabetes Remission after Intensive Insulin Therapy New Onset Type 2 Diabetes

- 382 patients with newly diagnosed type 2 DM
- CSII, MDI, or OHAs until reversal of hyperglycemia. Treat for 2 weeks
- Remission defined as FPG > 126 mg/dL or 2-hr PP > 180 mg/dL
- Initial HbA1c 9.5%-9.8%

β-cell Function after Intensive Insulin Therapy New Onset Type 2 Diabetes

ORIGIN Trial: Effect of Insulin Glargine in Early T2 DM

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Interleukin-1 Receptor Antagonist Therapy in Type 2 DM

Double-blind placebo controlled 13 week trial n = 70.
Improved C-peptide secretion; lowered IL-6 and C-reactive protein; unchanged parameters of insulin resistance.


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β-cell Function Following One Year Exenatide Therapy, And After 4 Week Washout

Enduring Effect of 3-Year Exenatide on β-Cell Disposition Index


Summary of β-cell Role in Pathogenesis and Prevention of Type 2 DM

- Insulin resistance occurs early - before glucose intolerance.
  - Genetic?
  - Obesity, ageing, lifestyle, and/or other environmental stresses.
- If healthy β-cells, compensate and remain euglycemic.
- If "susceptible" β-cells:
  - β-cell dysfunction results in imperfect compensation.
  - Hyperglycemia and dysmetabolism worsens - vicious cycle.
  - Progressive loss of β-cell mass and function - multifactorial.
- Intervention today - intensive glucose management and incretin therapy, better maternal and childhood care.
- Future - early identification of those at risk and targeted intervention.

Bunck MC, et al. ADA 70th Scientific Sessions. 2010;728-P.