The Quest for Precision Medicine: A Metabolic Approach

Demystifying Medicine
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Concept of a Disease “Cure”

- Penicillin – Pneumococcal pneumonia
- Vaccines – Eradication of polio in the US, and smallpox in the world
- Duodenal Ulcer – H2 blockers and proton pump inhibitors (excellent treatment, but do they treat the etiologic basis of the disease?)

No – specific treatment of H. Pylori actually eradicates the cause of the disease
Discovery of Etiologic or Pathophysiologic Basis of Metabolic Diseases
Etiologic Basis of Conditions

- Hypertension
- Dyslipidemia
- Diabetes

Known roughly 10-15%. Thus therapy is largely nonspecific.
Diabetes – A Metabolic Disease

Classifications:

- **Type 1** (β-cell destruction, usually leading to absolute insulin deficiency), 5-10%
- **Type 2**, (Insulin resistance with relative insulin deficiency), 90-95%
- **Other Specific Types**
- **Gestational**
Insulin Resistance Spectrum

Least Severe

Common forms
• Metabolic Syndrome
• Polycystic Ovarian Syndrome
• Type 2 Diabetes

Most Severe

Syndromic Forms
• Lipodystrophy
• Insulin Receptor Mutations
• Type B insulin resistance
Lipodystrophy Syndromes

- Heterogeneous group of disorders characterized by selective loss of adipose tissue
The Insulin Receptoropathy

- Acquired
  - Autoantibodies to the insulin receptor

- Genetic
  - Mutations of the insulin receptor
Insulin Receptor Structure

Ligand Binding Domain
Cystein-rich Domain
Alternatively Spliced Exon 11
Transmembrane Domain
Juxtamembrane Domain
ATP Binding Site
Catalytic Domain
C-Terminal Domain

Disulfide Bridges

α

β

J Clin Endocrinol Metab. 2001 Mar;86(3):972-9
The Clinical Challenge

Three Stories:

- Development of new technology.
- New use of existing technology.
- Combinations of the old and the new.
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Lipodystrophy Syndromes

- Paucity of fat
- Deficiency of adipocyte hormones (e.g. leptin)
- Insulin resistance
- Hypertriglyceridemia
- Fatty infiltration of liver and other tissues
This story begins with an obese mouse...
Leptin is the major hormone regulating energy balance.

Plasma leptin concentration is a function of adiposity.

In obesity plasma leptin is elevated and leptin administration has little effect in regulating energy intake.
Adipose Tissue as an Endocrine Organ and Regulators of Glucose Homeostasis

Leptin: From Hormone to Major Pharmaceutical
Leptin: Of Mice and Man

Before Replacement  
After Replacement 

Before Replacement  
After Replacement 

3-year-old weighing 42 kg  
7-year-old weighing 32 kg 

Farooqi S. NEJM, September 1999
Dramatic Effects of Leptin

- 21 year old woman with generalized lipodystrophy
- Poorly controlled diabetes with h/o DKA
- Severe hypertriglyceridemia
- Nephrotic range proteinuria
Based on the NIH data, metreleptin was approved for patients with generalized lipodystrophy, with or without metabolic complications.

- Not approved for partial lipodystrophy, regardless of metabolic disease.
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The patient

- 21 year old African American female
- Average Fasting blood glucose: 371 mg/dL
- Extreme weight loss
- Massive polyuria (Up to 15 liters urine/day)
- Acanthosis nigricans
- Extreme insulin resistance
Strategy of Therapeutic Approach

- Goal: elimination of the autoantibody

- Rituximab: antibody against CD-20, a cell surface molecule expressed by B-cells

- High dose pulsed steroids: to reduce pre-existing antibody-producing plasma cells

- Non-specific T-cell directed immunosuppression
  - Cyclophosphamide
  - Cyclosporine
Our Type B Insulin resistance patient after treatment
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Patient

- 12 year old Korean male
- At age 8 months of age presented with:
  - Extreme Hyperinsulinemia
  - Acanthosis nigricans
  - Increased body hair
  - Abnormal dentition

- At age 9 years old → Diabetes → A1c 11.8%
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