Overview of Natural History and Pathogenesis of Type 1 Diabetes

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Type 1 Diabetes Is Accelerating at a Rate that Appears Tied to the Environment (Versus Genetics)

Atkinson et al, Lancet, 2014
Classic Model of T1D Pathogenesis

Genetic Predisposition

(?Precipitating Event)

Overt Immunologic abnormalities

Normal insulin release

Progressive loss insulin release

Glucose normal

Overt diabetes

C-peptide present

No C-peptide

Beta cell mass

Age (years+)

Eisenbarth, NEJM 1986
Beyond Triggering, Environment Likely Contributes throughout Natural History of T1D

Omega-3 Fatty Acids

Microbiome
Precipitating Events Might Begin In-Utero

- Born to diabetic fathers vs. mothers
- Diabetic mother diagnosed less than 8 years of age vs later age
- First born
- Increased maternal enterovirus infections
- ABO incompatibility
- Increasing maternal age at delivery
- Season of delivery
- Early cessation of breast feeding
The Evolution of Type 1 Diabetes Genetics

1980’s to Present – Biomarkers that Define Risk for Type 1 Diabetes

Note: Too many; Too little OR; Notions of GWAS “Bust”

Future – Genotype/Phenotype Studies in Type 1 Diabetes

Concannon P, Rich S, Nepom GT
Genetic Linkage to T1D Abnormalities

Compartment #1
Bone Marrow / Thymus Contributions
- Defective thymic selection (positive/negative)
- Potential for self-antigens presented in incorrect register of MHC binding
- Influence of Aire and VNTR expression in thymus
- Mobulpathy
- Intrinsic defects in lymphocyte precursors
- Inherited genetic susceptibility
- “Niche” for persistent autoreactive lymphocytes

Compartment #2
Immune Contributions
- Defective immune regulation (e.g., Teff resistance to Treg, Treg abnormalities, etc.)
- Chronic APC activation
- Autoantibody production
- Self-antigens with low affinity epitopes recognized by low avidity autoreactive TCRs
- Failure to resolve autoreactive immune memory
- Abnormal cytokine production/ regulation
- Cellular trafficking/adhesion defects

Compartment #3
Beta Cell Contributions
- Expression of Class I MHC
- Production of cytokines and chemokines
- Free radical sensitivity
- Sensitivity to stress protein response
- Potential to present high quantities of self-antigen via Class II MHC
- Susceptibility to viral tropism/inability to resolve inflammation
- Limited replication potential
- Rate of immune destruction influenced by metabolic activity

Atkinson, Eisenbarth, Michaels 2014 Lancet
Type 1 Diabetes Is Increasing in Populations That Do Not Carry Classic High Risk Genes

Steck, Diabetes, 2011
While Type 1 Diabetes is Increasing, Most of the Increase is in the Very Young...Maybe

Finland T1D Incidence 1965-1996 (32 years)
Relative Percent Increase
While Type 1 Diabetes is Increasing, Most of the Increase is in the Very Young...Maybe

Table 1. Prevalence of Type 1 Diabetes by Demographic Characteristics

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<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>No. of Youth</td>
<td>Prevalence per 1000 (95% CI)</td>
<td>No. of Youth</td>
<td>Prevalence per 1000 (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>4958</td>
<td>1.48 (1.44 to 1.52)</td>
<td>6666</td>
<td>1.93 (1.88 to 1.97)</td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Females</td>
<td>2420</td>
<td>1.48 (1.42 to 1.54)</td>
<td>3263</td>
<td>1.93 (1.86 to 2.00)</td>
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<tr>
<td>Males</td>
<td>2538</td>
<td>1.48 (1.43 to 1.54)</td>
<td>3403</td>
<td>1.93 (1.86 to 1.99)</td>
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<tr>
<td>0–4</td>
<td>217</td>
<td>0.28 (0.24 to 0.31)</td>
<td>241</td>
<td>0.29 (0.26 to 0.33)</td>
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<tr>
<td>5–9</td>
<td>977</td>
<td>1.17 (1.10 to 1.25)</td>
<td>1143</td>
<td>1.35 (1.28 to 1.43)</td>
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<tr>
<td>10–14</td>
<td>1727</td>
<td>1.95 (1.86 to 2.04)</td>
<td>2335</td>
<td>2.69 (2.59 to 2.80)</td>
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<tr>
<td>15–19</td>
<td>2037</td>
<td>2.42 (2.32 to 2.33)</td>
<td>2947</td>
<td>3.22 (3.11 to 3.34)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
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<tr>
<td>White</td>
<td>3718</td>
<td>1.85 (1.80 to 1.92)</td>
<td>4804</td>
<td>2.55 (2.48 to 2.62)</td>
</tr>
<tr>
<td>Black</td>
<td>471</td>
<td>1.29 (1.18 to 1.41)</td>
<td>621</td>
<td>1.62 (1.50 to 1.75)</td>
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<tr>
<td>Hispanic</td>
<td>625</td>
<td>0.96 (0.89 to 1.04)</td>
<td>1042</td>
<td>1.29 (1.21 to 1.37)</td>
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<tr>
<td>Asian Pacific Islander</td>
<td>107</td>
<td>0.50 (0.42 to 0.61)</td>
<td>156</td>
<td>0.60 (0.51 to 0.70)</td>
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<tr>
<td>American Indian</td>
<td>37</td>
<td>0.30 (0.22 to 0.42)</td>
<td>42</td>
<td>0.35 (0.26 to 0.47)</td>
</tr>
</tbody>
</table>

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\(^{a}\) Differences in the number of youth reported with type 1 diabetes in 2001\(^{b}\) and in this report are due to exclusion of 1 prior study site in both years (Hawaii) and continued data cleaning.

\(^{b}\) Age on December 23, 2001, and December 31, 2009.
An nPOD Organized Event

“Insulitis Through the Last Century”

Exeter “Insulitis” Workshop
November 6-7, 2013

Martha Campbell-Thompson
University of Florida, Gainesville
New and/or affirmed

- Consistency of insulitis through last 100 years
- Variations of T1D (versus normals) in islet size
- Insulitis intensity as function of age (breakpoint age ~15-20 years)
- Lobular distribution of insulin pos. versus psuedoatrohic islets
- Adaptation of insulitis definition (preclinical – potentially 3 WBC in 3 islets)
Organized Chaos in Therapeutics – Immune Centric
Beta Cell Destruction may be Homicide, Suicide, or Failed Mechanisms of Self-Protection

Disease Progression

- Glut 2 Receptor
- Empty Beta cells
- mRNA aberrancies
- ER Stress
- UPR

Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

1. Precipitating events might occur in utero
2. Genetic predisposition probably the key driver or linkage to immune abnormalities
3. Beyond precipitating, environment might influence entire natural history
4. Although overall loss of β cells is potentially linear, it could show a relapsing or remitting pattern
5. Presence of two or more islet autoantibodies might represent asymptomatic type 1 diabetes
6. Increasing glucose excursions as individual approaches symptomatic onset
7. Some patients produce low concentrations of C-peptide long after onset
8. β-cell mass not always zero in longstanding patients

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014
Thank You!