Immunization Safety Review Committee 11/12/01

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Finland Incidence Type 1 DM/100K 1965-1996

Tuomilehto et al, Diabetes Care: 22:1066-1070, 1999
Finland Type 1 Diabetes Incidence 1965-1996 (32 years) Relative Percent Increase

Tuomilehto et al, Diabetes Care: 22:1066-1070, 1999
Changing Incidence

- **Something “Added”**
  - Maternal Age
  - Unknown virus
    - Congenital Rubella
  - Unknown Toxin
    - Nitosamines?

- **Something “Subtracted”**
  - Hygiene Hypothesis
  - Pinworms, etc.

- Change Food
  - Breast Feeding/Milk
Illustrated “Genetic” Risk Type 1 Diabetes Compared to Finland
Celiac Disease

- Gluten sensitive enteropathy
- Strongly Type 1 Diabetes Associated
- Anti-Transglutaminase autoantibodies with lymphocyte invasion intestine and extra-GI manifestations (e.g. dermatitis herpetiformis)
- Major environmental factor identified Gliadin
  Gliadin responsive T cells
Prevalence of Transglutaminase Autoantibodies by HLA-DR

Prevalence

- IDDM
- Relatives
- Population

1. Mix (125)I-insulin and sera

2. Incubate 72 hours at 4°C

3. Add Protein A/G-Sepharose to reaction mix in a 96-well filtration plate

4. Incubate for 45 min at 4°C

5. Wash each well using the vacuum-operated 96-well plate washer

6. Count radioactivity with 96-well plate beta counter
“Pathogenic” Peptide: Insulin B:9-23
Rapid induction of IAA by Insulin B:9-23 peptide immunization in Normal BALB/c mice
Poly-Inosinic/Cytidylic Acid

- Activates Toll Receptors
- Induces Interferon Alpha
- Induces Diabetes/Insulitis in BB/BB-DR Rats
- Induces Diabetes H-2d/poly-IC/B7-1 Mice
Innate Immune System: Toll-like receptor activation of APC

Signal 1
TCR-MHC

Signal 2
CD28
B7

Signal 3
IL-1,6,12
LPS

Toll Like Receptor (pattern Recognition R)

Anitgen Presenting Cell (APC)

T Cell

BDC
RIP (Rat Insulin Promoter)  
**B7-1 Transgene**

- B7-1 costimulatory molecule
- Islet Expression induces diabetes if combined with DQ8
- Induces diabetes and CD8 Infiltrates when combined with poly-IC and H-2(d)
Induction of insulitis in BC1-2 (B7-1 x BALB/c) Protocol #2

B9-23 peptide immunization at 4 wk of age (100µg/mouse)
Peptide B:9-23

B:9-23 in IFA + Poly IC (n=8, 6/8)

TT in IFA or IFA + Poly IC (n=16, 7/16)

Peptide B:9-23 in IFA
Poly-IC

B7-1 Mice with H-2(d)

TT in IFA or IFA + Poly IC

Poly-IC

B:9-23 in IFA alone

(Weeks of age)
No treatment: 11 11 11 11 10 7 7
TT in IFA or IFA: 16 16 16 11 6 2 0
B:9-23 in IFA: 8 8 5 3 1 0 0
Thoughts

• Type 1 Diabetes Increasing Worldwide
• Environmental Factors Can Change Diabetes Risk
• Genetic Risk Orders Magnitude Greater than Changes in risk over Time
• As we can now predict type 1 diabetes (immunogenetics and autoantibodies) and identify autoimmunity as early as 9 months of age, prospective studies can search for environmental precipitants of type 1 diabetes and a series of common autoimmune disorders (e.g. celiac disease).