The Autoimmune Pathogenesis of Type 1 Diabetes

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Why trying to understand narcolepsy genetics and pathogenesis by contrasting it to type 1 diabetes?
The major players in autoimmune disease development

Genetic susceptibility

Environmental triggers

Immune system and β-cell
Genetic and immunology studies have demonstrated considerable overlap between autoimmune diseases.
Narcolepsy

T1D

Autoimmune Diseases Disproportionately Affecting Women

Hashimoto's thyroiditis
Systemic lupus erythematosus
Sjogren's syndrome
Primary biliary cirrhosis
Scleroderma
Rheumatoid arthritis
Multiple sclerosis

https://www.23andme.com
Target cells are dispersed and limited in number

Hypocretin staining


Insulin staining
Cell-specific destruction

Figure 4. Melanin-Concentrating Hormone Neurons in Normal and Narcoleptic Subjects
Normal is subject CK, and narcoleptic is subject NA. Narcoleptics have normal numbers of MCH neurons despite the loss of 93% of Hcrt cells in the same region. Cal. = 250 μm.

Mundinger et al (2016) Diabetes
# T1D vs Narcolepsy (genetics)

<table>
<thead>
<tr>
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<th>T1D</th>
<th>NAR</th>
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</thead>
<tbody>
<tr>
<td>Autoimmune</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.4%</td>
<td>0.02-0.2%</td>
</tr>
<tr>
<td>HLA major genetic risk component</td>
<td>&gt;50%</td>
<td>&gt;85%</td>
</tr>
<tr>
<td>HLA major risk genotype:</td>
<td>DQ2/DQ8</td>
<td>DQ6</td>
</tr>
<tr>
<td>Non-HLA risk</td>
<td>~ 50 loci</td>
<td>~ 3 -10* loci</td>
</tr>
<tr>
<td>OR non-HLA loci</td>
<td>1.05-1.8</td>
<td>1.05-1.5</td>
</tr>
<tr>
<td>Explained heritability</td>
<td>~ 80-85%</td>
<td>~ 50% **</td>
</tr>
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</table>

*: GWAS p-value <10E-6  **: Model-dependent
Natural history of type 1 diabetes

Proposed Nomenclature:
- Stage 1: Beta Cell Autoimmunity, Normoglycemia, Presymptomatic
- Stage 2: Beta Cell Autoimmunity, Dysglycemia, Presymptomatic
- Stage 3: Beta Cell Autoimmunity, Dysglycemia, Symptomatic

Phenotypic Characteristics:
- Variable Genetic & Environmental Risk for Type 1 Diabetes
- Presymptomatic Type 1 Diabetes
- Symptomatic Type 1 Diabetes

Interception

Studies of pathogenesis

Pociot and Lernmark (2016) Lancet
Autoantibodies are strong predictors of T1D risk but not causal factors
Figure 3: The incidence of β-cell autoantibodies in children followed up from birth.
Pathogenetic model – A dialogue between the target cell and the immune system

Type 1 diabetes

Narcolepsy
Cytokine-induced β-cell apoptosis

Eizirik et al. Nat Rev Endocrinol 2009
GWAS data NAR and T1D

Immunochip data - Narcolepsy

WTCCC T1D SNP Associations
Narcolepsy: > 90% DQB1*0602 positive (20-25% of the background population)

T1D: > 90% positive for DR3 and/or DR4 (45% of the background population)
Further insight into the pathogenesis from genetics

Immune genes

Insulin production and metabolism

Beta-cell apoptosis

Unknown function

KEGG/GO

Locus

: expressed in human islets/β-cells

GWAS data NAR and T1D (Manhattan plots)
CTSH region on 15q25.1

Supplementary Figure 5. Chromosome 15q25.1 expression of CTSH (probe ILMN_2390853)

Cysteine cathepsins

Lysosomal cysteine cathepsins:

- Proteases known for their presence in the lysosomes - protein degradation.
- Involved in cellular processes such as apoptosis, antigen presentation, and prohormone processing.
- Associated with diseases e.g. cancer, osteoporosis, rheumatoid arthritis, osteoarthritis, and type 1 diabetes

<table>
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<tr>
<th>Cathepsins</th>
<th>Involvement in diabetes</th>
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<tr>
<td>Cathepsin G, D, S, and V</td>
<td>Involved in proinsulin processing [Zou et al. PLoS ONE 2011]</td>
</tr>
<tr>
<td>Cathepsin G</td>
<td>Important for generation of proinsulin-reactive T cells [Zou et al. PLoS ONE 2011]</td>
</tr>
</tbody>
</table>
CTSH affects β-cell function

- T1D-associated single nucleotide polymorphisms (SNPs) affect the mRNA and protein expression of CTSH
- CTSH is expressed in human β-cells
- *CTSH* is downregulated by pro-inflammatory cytokines in human islets and rat β-cells
- Children with T1D who carries the SNP genotype causing low CTSH expression have less residual β-cell function
- Overexpression of *CTSH* decreases cytokine-induced apoptosis and increases insulin expression in INS-1 cells
- Islets from *Ctsh* knockout mice contain less insulin compared to wild-type mice

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Floyel et al. *PNAS* 2014
CTSH decreases cytokine signalling

**Diagram Description:**
- **Plasma membrane**
  - IFNγR1, IFNγR2
  - JAK1, JAK2
  - STAT1
  - JAK1, JAK2
- **Nucleus**
  - IkB
  - NFkB
  - Ub
  - Ub
  - Ub
  - NFkB
- **Transcription factors**
  - c-Jun, JunD
- **Non-transcription factors**
  - Bcl-2 family members
- **Gene transcription**
  - iNOS, DP5, c-Myc, Bim

**Key Components:**
- **IFNγ**
- **IL-1**
- **TRAF6**
- **MAPKK**
- **ERK, p38, JNK**
- **IKK**
- **JAK1, JAK2, IRAK1, IRAK4, MyD88, Tollip**
- **CTSH** decreases cytokine signalling
CTSH overexpression changes a limited number of β-cell genes
Genes affecting beta-cell function in type 1 diabetes

‘Classical’ immune genes are important in β-cell function

BACH2, a Candidate Risk Gene for Type 1 Diabetes, Regulates Apoptosis in Pancreatic β-Cells via JNK1 Modulation and Crosstalk With the Candidate Gene PTPN2

CTSH regulates β-cell function and disease progression in newly diagnosed type 1 diabetes patients

TYK2, a Candidate Gene for Type 1 Diabetes, Modulates Apoptosis and the Innate Immune Response in Human Pancreatic β-Cells
Challenges
Define ‘true’ risk (study the pre-diabetic phase)
Disease classification (e.g. based on biomarkers)
Uncover novel mechanisms (in vitro and in vivo studies)
Guiding therapeutic options
How will we address these issues?

1. The identification and understanding of type 1 diabetes biomarkers
2. Prediabetes biomarker discovery
3. Gene regulation, non-coding RNAs and epigenetics
4. New cohorts – e.g. TrialNet, TEDDY;
5. Collaboration (Local, national, and international)
An IMI2 EU Project

26 ACADEMIC INSTITUTIONS AND CLINICS
4 EFPIA PARTNERS
2 PATIENT ORGANIZATION
1 SME SMALL AND MEDIUM Sized ENTERPRISE

ECONOMY: TOTAL FUNDING 35 MIO EUR/7 YEARS

START 2016
Some INNODIA objectives

1. Develop a **European infrastructure** for the recruitment, detailed clinical phenotyping and bio-sampling of a large cohort of newly diagnosed subjects with T1D and at risk family members

2. Establish a tight collaborative **network of basic and clinical researchers** working in a coordinated and focused way to address key knowledge gaps in relation to β-cell autoimmunity, leading to a **better understanding of the pathogenesis** of T1D and a cure for this disease

3. Conceive **innovative clinical trial designs** that exploit novel validated biomarkers allowing better subject stratification and functioning as surrogate endpoints, thus yielding shorter and more focused intervention studies of single or combined therapies
"You've got to be very careful if you don't know where you're going, because you might not get there."

Yogi Berra

Thank you!