Designing Antigen-specific Immunotherapy for Treatment of Type 1 Diabetes.

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Outline

• Background on type 1 diabetes

• The role of dendritic cells in type 1 diabetes pathogenesis

• Current Immunotherapies: global immunosuppression (not antigen-specific)

• Our work in mouse models to develop antigen-specific immunotherapies using dendritic cells
Islets of Langerhans within the Pancreas

In Type 1 diabetes the beta cells are the autoimmune target.
Clinical complications in Type 1 Diabetes Patients

Hyperglycemia (high blood sugar)

Acute effects: Diabetic Ketoacidosis: Low Insulin leads to a shift from carbohydrate to fat metabolism.

Chronic effects: increased risk for heart disease, neuropathy. Can be minimized by tight blood glucose control.

HbA$_1c$: a measure of average blood glucose.

Normal is 5. For T1D, goal is usually <7.

Hypoglycemia

The brain is the most sensitive to low blood glucose.

Some T1D patients are hypoglycemic unaware, and blood glucose is lowest at night. (increases mortality)
Type 1 Diabetes incidence is rising 3-5% /year

Incidence /100,000/ yr children age 0-14

Finland
Colorado
Germany

Rewers
Dendritic cells (DCs) are professional antigen presenting cells

- **Innate immunity** – DCs respond to environmental signals such as pathogens.
- **Adaptive immunity** – DCs take up, process, and present antigen via peptide-MHC complexes to T cells.

**Goal:** To use DCs to induce antigen-specific T cell tolerance for treatment of autoimmune diabetes.

**TOLERANCE**
- Regulatory T cell expansion/induction
- Anergy or deletion

**IMMUNITY**
- Effector T cell expansion and differentiation

Imbalance of tolerance vs immunity = autoimmunity
Type 1 Diabetes Pathogenesis

Aberrant activation of self-specific T cells
Failure of peripheral tolerance mechanisms

Beta-cell-specific CD4+ and CD8+ Effector T cells (T_{eff})

Non-Obese Diabetic (NOD) mice: 80% of females develop spontaneous autoimmune diabetes
Dendritic Cells are Important for Induction of Peripheral T cell Tolerance

**Anergy or Deletion**

Pathogenic cells become unable to respond, or die after antigen exposure from DCs

**Regulatory T cells**

Regulatory T cells turn off pathogenic cells via effects on both dendritic cells and T cells.

DCs are important stimulators of Treg proliferation and activation.
One approach to treating T1D is to alter T cell responses with antibodies specific for CD3 (anti-CD3).

Anti-CD3 may work by inducing cell death in pathogenic T cells or increasing regulatory T cells.

This treatment affects all T cells: not antigen-specific.
Anti-CD3 slightly preserves insulin (C-peptide) release in new onset type 1 Diabetics

But average blood glucose levels are the same

A recent Phase 3 trial failed to show efficacy, but a much lower dose was used because of toxicity concerns.

Blue= placebo   Red=anti-CD3

Keymeulen et al. 352 (25): 2598, NEJM 2005
Advantages of Antigen-Specific Therapy

A vast lymphocyte repertoire = many clones, each specific e.g., for a microbial, tumor, self or environmental antigen

Valuable antibody - based therapies for autoimmunity e.g., anti-TNF, anti-CD3

But these therapies are antigen non-specific and can potentially dampen responses against microbial or tumor antigens as well.
### Dendritic Cells Subsets: CD8+ and CD11b+ DCs

<table>
<thead>
<tr>
<th>CD8+ cDCs</th>
<th>CD11b+ cDCs</th>
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</thead>
<tbody>
<tr>
<td><strong>Other markers:</strong></td>
<td><strong>Other markers:</strong></td>
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<tr>
<td>DEC-205+</td>
<td>DCIR2+</td>
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<td><strong>Immunogenic functions:</strong></td>
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<tr>
<td>Can cross-present extracellular antigens to CD8+ (cytotoxic) T cells</td>
<td>Strong stimulation of CD4+ (helper) T cells</td>
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<td><strong>Tolerogenic functions:</strong></td>
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<tr>
<td>induces Tregs via TGFβ</td>
<td>and Tregs</td>
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<td>Uptake of apoptotic cells</td>
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Both subsets can induce deletion or anergy to antigen presented absent inflammation.

What pathogenic/ tolerogenic roles do these DC subsets have for autoimmune diabetes?
Targeting beta cell Autoantigens to Dendritic Cells in vivo

Does steady-state targeting of beta cell antigens to DCs induce tolerance during chronic autoimmunity?

Can we create a tolerogenic vaccine to turn off the autoreactive T cell responses that induce pathology in T1D patients?
How do CD4 T cells respond to DC-targeted antigen in the context of autoimmune diabetes?

Use autoreactive CD4+ TCR transgenic T cells specific for a beta cell antigen.

Thy1.1+ beta cell-specific CD4+ T cells

Anti-DEC205 or anti-DCIR2 conjugated to beta cell antigen

1 day

3-10 days

Harvest lymphoid tissue, measure T cell responses
T Cell Responses After Targeting Antigen to cDCs

Self Antigen in autoimmune NOD mice

CD8+ DEC-205+

No Tolerance: continued expansion and cytokine production

CD11b+ DCIR2+

Tolerance: deletion, anergy, and/or Treg induction

Model Antigen in wildtype mice

CD4+

Tolerance: deletion, anergy, and/or Treg proliferation

Tolerance: Some initial proliferation/expansion followed by partial deletion, but almost no cytokine production.
Interactions between CD40L on activated T cells and CD40 on DCs enhances immunity

Would blocking this interaction help restore tolerance when given with DC-targeted antigen?
T Cell Responses After Targeting Antigen to cDCs

**Self Antigen in autoimmune NOD mice**

**CD8+DEC-205+**

Tolerance:
- Initial proliferation followed by partial deletion, but without cytokine production.

**CD11b+DCIR2+**

Tolerance:
- Some initial proliferation/expansion followed by partial deletion, but almost no cytokine production.

No Tolerance: continued expansion and cytokine production.

+ αCD40L blocking antibody
Next steps:

• Test whether targeting beta cell antigens to either DC subset (with or without αCD40L) can alter diabetes development.

• Try inhibiting other proinflammatory signals.

• Find better ways to deliver inhibitory signal

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