Torn between two diseases: Alteration in TGFβ Signaling Prevents Diabetes but Promotes Neuropathy

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What is Type 1 (Juvenile-Onset) Diabetes?

- Autoimmune disease where the pancreatic beta cells are destroyed by autoreactive T and B cells
  - Results in lack of insulin production and high glucose in blood
- Patients must take exogenous insulin for the remainder of their lives
- Associated with severe complications: cardiovascular, kidney, nerve damage
- Generally considered a disease of childhood
  - Approximately 3 million Americans have type 1 diabetes
  - Prevalence is increasing every year
Lymphocytes destroy pancreatic islets in T1D

Leukocytes (White blood cells)
Dysregulation between regulatory and effector mechanisms precipitates autoimmunity.
The non-obese diabetic (NOD) mouse models human type 1 diabetes

NOD mouse
“Wild type (WT)”

Foxp3-Cre x TGFbRII Δ/Δ
“Flox”

Cell type specific deletion of TGFβ receptor MEANS – there is no TGFβ signaling in regulatory T cells
WT and Flox mice seem to develop opposing either diabetes OR neuropathy
What is neuropathy?
Does the loss of TGFβ signaling in Tregs affect or lead to inflammation in different tissues?

- Pancreas
- Sciatic Nerve
- Salivary gland
- Thyroid
- Heart
- Ovary
- Kidney
- Small intestine
- Liver
- Lung
Inflammation observed in Flox islets similarly to WT NOD islets.

Uninflamed Score 0

Pancreatic islet

Highly inflamed Score 3

Dark purple spots - leukocytes

% Insulitis score

WT

Flox

3

2

1

0
Is neuropathy associated with inflammation in the sciatic nerve?

WT - uninflamed

Flox – heavily inflamed (score 2)
Less inflammation in Flox submandibular gland than WT NOD mice
Novel thyroid inflammation in Flox mice compared to WT NOD mice
Conclusions: Loss of TGFβ signaling in Tregs leads to inflammation in different tissues

<table>
<thead>
<tr>
<th>Organ</th>
<th>WT</th>
<th>Flox</th>
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</thead>
<tbody>
<tr>
<td>Pancreatic Islets</td>
<td>+ (↑ Db)</td>
<td>+ (↓ Db)</td>
</tr>
<tr>
<td>Sciatic Nerve</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Submandibular Gland</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Thyroid</td>
<td>-</td>
<td>+</td>
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Future Directions

- **Short term:**
  - Finish analyzing the rest of the organs – any other autoimmune diseases present in these mice
  - Analyze more WT NOD mice for confirmation of the phenotypes

- **Long term:**
  - Describe the mechanism of disease development in these different NOD mouse models
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Thank you all for listening!
Questions?