Proof-of-concept proposal

Development of a negative self-vaccine against Type 1 diabetes based on central tolerogenic properties of the thymus

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A thymus defect in type 1 diabetes (T1D)

Thymus physiology

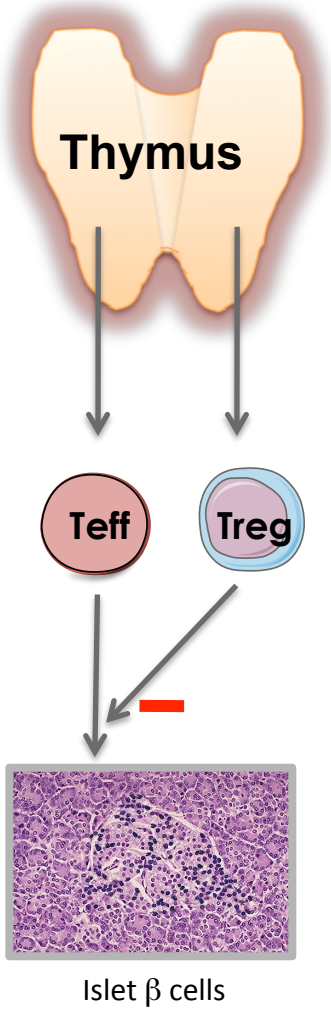
- *AIRE*-regulated transcription of T1D related self-antigens in thymus epithelium
  IGF2 > IGF1 >> INS
  GAD67 >> GAD65
- Deletion of T cells with high affinity for T1D related self-peptide complexes.
- Selection of CD4+ CD25+ Foxp3+ tTreg, specific of T1D related self-peptides.

Thymus physiopathology

- Absence or decrease in expression/presentation of T1D related self-peptides in the thymus (BB rat, APECED/APS-1, …)
- Enrichment of T-cell repertoire with 'forbidden' self-reactive effector T cells (Teff).
- Decrease in selection of tTreg with specificity to T1D related self-antigens.

Bridge between self-reactive Teff and target T1D antigens

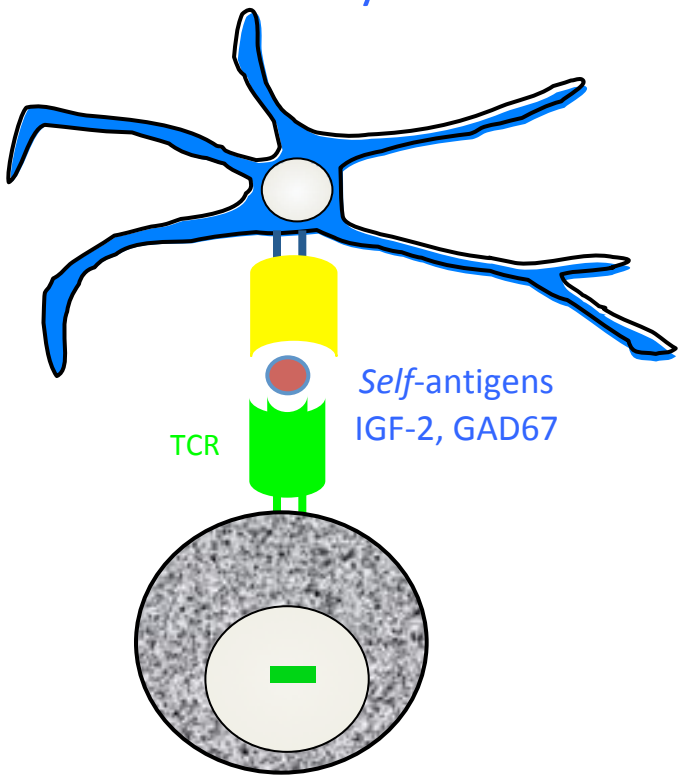
- Role of environmental factors (**viruses**, diet, vitamin D deficiency, stress…)



The concept of « *negative self-vaccination* »:

Thymus T1D self -antigens for reprogramming tolerance to β cells

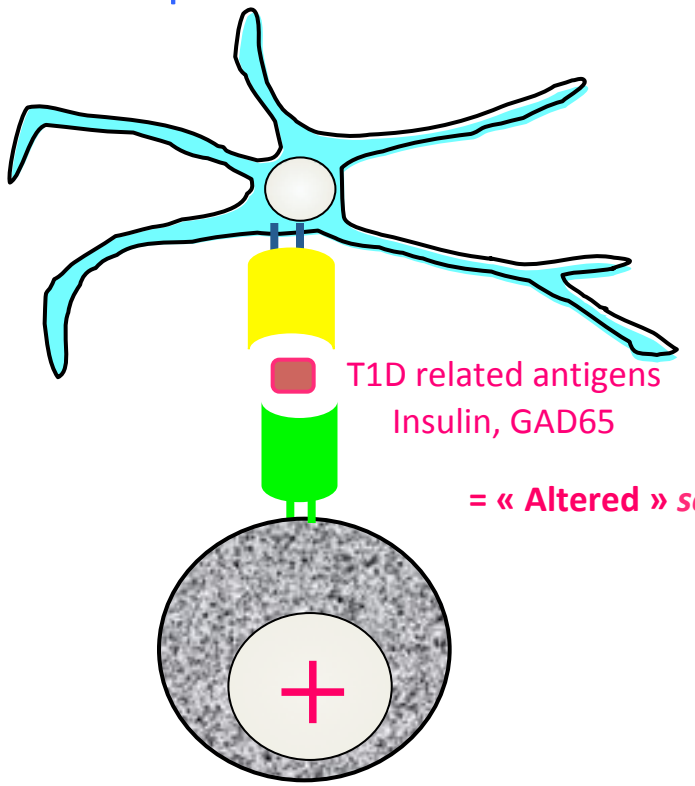
In the thymus



SELF-TOLERANCE TO β CELLS

Clonal deletion and anergy of self-reactive T cells
Generation of specific tTreg

In pancreatic islets



AUTOIMMUNITY TO β CELLS

Activation of self-reactive T cells
Induction of memory T cells

Acknowledgments

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