HERV-W-Env involvement in human T1D pathogenesis
New insights from HERV-W-Env transgenic mouse models

S. Levet1, J. Joanoï3, N. Queruel1, J. Pierquin1 & H. Perron1,2
1. Génome@medecine, Lyon, France; 2. University of Lyon, France.

Introduction

Endogenous retroviruses (ERVs) have entered the genome of primates during repeated infections of the germ cell lineage by environmental retroviruses over millions years of evolution. They represent 8% of the human genome, and have been involved in several autoimmune diseases, when aberrantly expressed. In particular, HERV-W Env, the envelope protein of HERV-W endogenous retrovirus, has been associated with Multiple Sclerosis (MS) pathogenesis.1

2 - HERV-W-Env transgenic mouse model

- Low level chronic expression of HERV-W-Env in mice causes hyperglycemia and impairs insulin secretion.
- However, this is not a completely persistent and full-blown T1D phenotype. An additional environmental stress could be required for HERV-W-Env transgenic mice to develop a severe T1D phenotype.
- We tested this hypothesis by challenging CAG-Env transgenic mice with streptozocin (STZ).

3 - HERV-W transgenic mice challenged with STZ

- STZ injections induce a statistically stronger glycemia in CAG-Env mice than in CYNB6/Env mice.
- Decrease in beta cell mass (HOMA-B) is statistically stronger in CAG-Env mice than in CYNB6/Env.
- Mice expressing HERV-W-Env transgene are prone to develop diabetes following environmental insult (STZ).

Conclusions, Working model and Clinical perspectives

- We have previously demonstrated the involvement of HERV-W-Env protein in the pathogenesis of T1D:
  - The overall prevalence of HERV-W-Env expression in T1D patients is beyond 50% with present methods of antigen or RNA detection.
  - HERV-W-Env inhibits insulin secretion.
  - HERV-W-Env expression is associated with pancreatic immune cell infiltration.
- In this new study we demonstrate that mice expressing HERV-W-Env are prone to develop symptoms relevant for T1D following environmental insult (targeting beta cells).
- Immune cells recruitment and pancreatic exocrine abnormalities observed in HERV-W-Env transgenic mice could explain their susceptibility to STZ injections leading to immune-mediated endocrine pancreatic damage.

4 - Pancreas histology of HERV-W-Env transgenic mice

- STZ injections cause Insulins in CAG-Env mice only and not in CYNB6/Env mice in our conditions.
- Susceptibility to environmental insults (STZ) targeting beta cells may be promoted by surrounding HERV-W-Env expression and related to immune cells recruitment in HERV-W-Env transgenic mice.
- Mice expressing HERV-W-Env transgene are prone to endocrine pancreatic damages.

1 Levet et al. JCI insights 2017

2 RAINBOW: Phase IIa clinical trial in T1D Neutralization of HERV-W-Env with GNbAC1 monoclonal antibody.
   - Placebo-controlled, randomized phase IIa in 60 recently diagnosed T1D adults. One year study.
   - Primary endpoints: Safety
   - Secondary endpoints: HbA1c, C-peptide, daily use of insulin, sub-antibody.

3 6 months interim results expected 3rd quarter 2018.
- GNbAC1 is in late clinical development for Multiple Sclerosis indication: positive results in a phase IIb study.