Human Endogenous Retrovirus type W is strongly upregulated in T1D pancreas and dysregulates insulin production *in vitro* and *in vivo*

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Type 1 diabetes (T1D) is a severe autoimmune disease characterized by a destruction of insulin-producing beta-cells and, when infiltrating the pancreatic Langerhans islets, T lymphocytes and macrophages are usually incriminated. Consequently, subjects with T1D are usually dependent on insulin injections for their entire life. This disease accounts for 5 to 10% of total number of diabetes cases, Europe having the highest incidence, with peak rates in Finland and Sardinia. While precise etiology(ies) is (are) not yet entirely understood, it has long been suggested that both genetic factors and environmental triggers, and viruses in particular, can be involved.

Endogenous retroviruses are known to represent 8% of the human genome. Among them, HERV-W has recently been implicated in Multiple Sclerosis (MS), another autoimmune disease. More precisely, the viral HERV-W envelope protein (Env), activates a pro-inflammatory and autoimmune cascade leading to demyelination, and a neutralizing monoclonal antibody is now in phase IIa clinical trial for MS indication. Importantly, an MS preclinical study had highlighted the presence MSRV-Env antigen in approximatively 1/3 sera of patients with T1D, when tested among various control groups with autoimmune diseases. When no significant detection was found in, e.g., patients with Systemic Lupus (SLE) or Rhumatoid Arthritis, this unforeseen observation led to the hypothesis of an implication of HERV-W in the etiology of a proportion of T1D cases, at least.

To further evaluate this new hypothesis, the expression pattern of endogenous HERV-W proteins was studied in human pancreas biopsies, from patients with and without T1D, provided by the nPOD biobank (Univeristy of Florida, USA) by immunohistochemistry (IHC). HERV-W Env protein was detected in a subset of T1D patients and it appeared to be mainly produced by acinar cells surrounding Langerhans islets. The HERV-W Gag proteins were detected in acinar cells as well, but also in Langerhans islets.
In vitro effects of the HERV-W Env protein on insulin secretion were tested on cultured insulinoma cell line (INS-1E). Results showed a biphasic response: low HERV-W Env doses, up to 50ng/mL, lead to a rise of insulin secretion in response to glucose stimulation, while higher HERV-W Env doses induced a progressive decrease in insulin secretion. In presence of the neutralizing antibody specific for HERV-W Env protein, previously observed hyper- and hypo-secretion of insulin were both abolished and a normal response to glucose stimulation was restored at any of the HERV-W Env concentrations studied.

In vivo effects of HERV-W Env were assessed on a humanized NOD-SCID mouse model. Results showed that HERV-W Env leads to hyperglycemia and hypoinsulinemia which can be prevent by the monoclonal anti-HERV-W Env antibody.

Consistency between our present results from human pancreatic IHC, *in vitro* and *in vitro* models thus suggest that HERV-W could be involved in T1D etiopathogeny, all the more when insulin-secreting beta cells are known to express TLR4 receptor targeted by HERV-W Env. These preliminary results call for further investigation on larger cohorts but already provide perspectives for novel therapeutic avenues in T1D.