Long-RNA sequencing and ribosome profiling reveal novel candidate autoantigens in type 1 diabetes

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BACKGROUND: Type 1 diabetes is an autoimmune disease characterized by autoreactive T-cell mediated destruction of the pancreatic beta-cells. Increasing evidence suggest that beta-cells contribute to their own destruction by generating neo-antigens through the production of aberrant or modified proteins that escape central tolerance. We have recently demonstrated that ribosomal infidelity amplified by stress could lead to the generation of neoantigens in human beta-cells, emphasizing the participation of nonconventional translation events to autoimmunity, as occurring in cancer or virus-infected tissues.

METHODS: Human beta cells were cultured in the presence or absence of proinflammatory cytokines for 24h. Following stimulation, protein synthesis initiation was blocked by harringtonine/cycloheximide combined treatment and a ribosome profiling library was generated and processed on next generation sequencing. In parallel beta cell transcriptome was deciphered by long-RNA sequencing. Resulting databases were integrated for identification of inflammatory specific RNA isoforms and translation start sites (TIS).

RESULTS: We show that nearly 40% of the overall TIS derived from events of non-canonical translation and could potentially generate neo-polypeptides. A fraction (~3%) of TIS occurs within lncRNA, even in resting conditions. Moreover, inflammation leads to a significant increase in the number of ORFs per transcript and in particular an increased ribosome density within 5'-UTR regions. Finally, we describe the presence of potential neoantigens in T1D associated genes, showing alternative splicing in combination with non-canonical translation initiation.

CONCLUSIONS: Our data underline the extreme diversity of the beta-cell translatome and the profound changes induced by T1D pathophysiological environment. Our database, may reveal new functional biomarkers for beta-cell distress, disease prediction and progression and therapeutic intervention in type 1 diabetes.