Mechanisms of *Igf2* inhibition in thymic epithelial cells infected with CVB4 E2

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**BACKGROUND**

In type 1 diabetes (T1D), β cells are destroyed by self-reactive T-cells resulting in progressive insulin deficiency. More and more studies show that T1D could be initiated/favored by viral infections and especially Coxsackievirus B4 (enterovirus family, CVB4) but the mechanism is still not clear (1). T-cells are produced in the thymus and selected by thymic epithelial cells (TEC) in order to tolerate self-antigens like insulin (2a). TEC express numerous self-antigens, including insulin, and and Insulin-like growth factor 2 (*Igf2*) is the dominant thymic peptide of the insulin family (2a). As *Igf2* is structurally highly similar to insulin, *Igf2* expression in the thymus could increase the negative selection of insulin specific T-cell and thus play a protective role against T1D (2b). We have shown that CVB4 is able to infect the thymus (in vivo and 3D culture) including TEC (primary cells and cell line), and is able to decrease *Igf2* (TEC cell line) (3). We hypothesize that CVB4 could also affect thymic selection and induce a tolerance break against insulin family, thus feeding the autoimmune mechanism in T1D (4). The goal of this project is to decipher the mechanisms which are implicated.

**METHODS**

Cell seeding (MTE4-14 cells) with/without transfection (pGL3+ *Igf2P3* Naranic vector) CVB4 E2

RNA and/or protein

DNA and/or protein

Luciferase assay

**RESULTS**

1. CVB4 decreases *Igf2* including variant 3 mRNA

2. CVB4 replication in MTE4-14 cells

3. CVB4 decreases *Igf2* P3 promoter activity and does not affect *Igf2* mRNA degradation

4. CVB4 affects promoter activity only in the -167 to -113 region

5. In silico analysis of the -167/-113 region reveals STAT3 binding site

6. CVB4 decreases STAT3 phosphorylation

**CONCLUSIONS**

These results show that the CVB4-induced decrease in *Igf2* expression, and more precisely *Igf2* V3 mRNA, could result from a decrease in *Igf2* P3 transcriptional activity (without *Igf2* mRNA degradation). This loss of transcriptional activity could probably result from a modulation of the transcription factor STAT3 activity, since STAT3 phosphorylation decreases during CVB4 infection.

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