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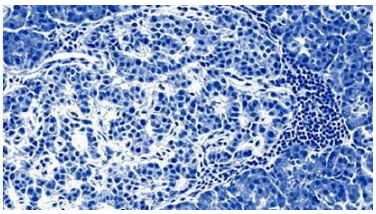

Upregulation of HLA class I and antiviral tissue responses in autoimmune thyroid disease

AUTHORS

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PURPOSE

Autoimmune thyroid diseases (AITD) and type 1 diabetes (T1D) share many similarities. Both diseases are autoimmune, endocrine, and organ specific diseases. Moreover, individuals with T1D have an increased risk of developing AITD. AITDs are multifactorial in origin; genetic as well as environmental factors are believed to contribute to the pathogenesis. However, the initiating factor leading to a break of tolerance remains unknown in both T1D and AITD. Enterovirus, viral receptors and viral immune response proteins have been detected in pancreata from patients with newly diagnosed T1D in the DiViD study. In the present study, we analyzed the same immune markers and viral protein products in thyroid tissue from patients with Hashimoto's thyroiditis (HT) and Graves' disease (GD).

METHODS

Thyroid tissue from 46 mainly newly diagnosed HT patients, and 48 GD patients with both newly diagnosed and chronic disease, were obtained using core needle biopsy or collected during thyroidectomy. To the best of our knowledge, this is the largest collection of thyroid tissue from newly diagnosed AITD patients. In addition, 24 thyroid tissue samples collected during neck surgery for other reasons than thyroid autoimmunity served as controls. Standard immunohistochemistry as well as combined immunofluorescence staining were used on formalin-fixed, paraffin embedded tissue samples.

SUMMARY OF RESULTS

HLA class I presents both endogenously and exogenously derived antigens to CD8+T cells and plays a vital role in the defense against virus. In the HT group, 31 out of 46 (67.4%) thyroid tissue samples had HLA class I positive thyroid cells (thyrocytes). In the GD group, 25 out of 48 (52.1%) tissue samples had HLA class I positive thyrocytes. Both patient groups had a significantly higher number of HLA class I positive samples compared to controls, where only five out of 24 (20.8%) samples were positive ($p<0.001$ for HT and $p=0.011$ for GD). Moreover, assessed with a semi-quantitative immunoreactivity score taking intensity and proportion into account, both patient groups had a significantly higher score than controls.

Signal transducer and activator of transcription 1 (STAT1) and protein kinase R (PKR) are antiviral proteins activated by interferons and the viral product dsRNA respectively. STAT1 was found in five out of six HT samples, seven out of 13 GD samples and in two out of four controls. Both cytosolic and nuclear STAT1 was found, and it was co-expressed with HLA class I. PKR was found in 11 out of 13 GD samples, three out of six HT samples and in one out of four control samples. PKR expression was co-localized with enterovirus capsid protein 1 (VP1).

The mean number of VP1 positive thyrocytes was significantly higher in GD (30.3%) than in controls (14.9%) ($p=0.005$). In the HT group, there were more, albeit not significantly, VP1 positive thyrocytes in the HT samples (20.1%) than in controls (14.9%). The coxsackie and adenovirus receptor (CAR) isoform (CAR-SIV) was found in a distinct granular expression in thyroid cells in all ten samples studied.

CONCLUSIONS

Our results show that thyrocytes express CAR, thus making them susceptible to enterovirus infection. HLA class I is upregulated in thyrocytes from both HT and GD. Furthermore, we demonstrate that STAT1 is co-localized with HLA class I in thyrocytes, and that PKR is co-localized with VP1, which is potentially indicative of an intracellular antiviral host response. Taken together with previously reported increase in the downstream interferon type 1 response protein, myxovirus resistance protein 1, plasmacytoid dendritic cells and CD8+ T cells in the same cohort, our results support the hypothesis of an association between enteroviral infections and AITD. In conclusion, similar findings in AITD and T1D point to new common features other than shared genetic risk factors.