AUTOIMMUNITY

Monitoring the health of pancreatic islets

The selective destruction of pancreatic β-cells causes type 1 diabetes mellitus (T1DM), and $CD8^+$ T cells, which include cytotoxic T cells, are key in this process. Now a study by Mark Peakman and colleagues shows that changes in the number of β-cell-specific effector memory T cells expressing CD57 reflect changes in levels of C-peptide (a surrogate marker for insulin levels) in patients with T1DM.

Previous studies have established that large numbers of $CD8^+$ T cells are present in the pancreatic islets of patients with T1DM. The $CD8^+$ T cells found in these islets recognize β-cell antigens; however, the relationship between $CD8^+$ T cells and β-cell function is unknown, leading Peakman and his team to investigate this link.

In the current study, the researchers used samples of peripheral blood mononuclear cells from 38 patients with T1DM (aged 6–34 years), who were followed up for 2 years. An initial characterization of the different T cell populations in the patient samples showed that the subset of β-cell-specific T cells were largely composed of effector memory T cells expressing the terminal differentiation marker CD57.

Next, Peakman and colleagues analysed the levels of C-peptide in relation to the number of $CD57^+$ effector memory $CD8^+$ T cells and found a positive correlation. The results suggest that the numbers of these T cells correspond to changes in β-cell function. Additionally, the researchers found that this positive correlation is more marked in children who are <12 years of age.

Finally, the researchers compared the transcription profiles of effector memory $CD8^+$ T cells with and without CD57 expression and found that $CD57^+$ cells show increased expression of genes related to cytotoxicity. The data suggest that the β-cell-specific $CD57^+$ effector memory $CD8^+$ T cells have increased cytotoxicity and are capable of causing β-cell destruction. Therefore, changes in circulating $CD57^+$ effector memory $CD8^+$ T cells can be used to monitor the health of pancreatic islets.

Ivone Leong

ORIGINAL ARTICLE Yeo, L. et al. Autoreactive T effector memory differentiation mirrors β cell function in type 1 diabetes. *J. Clin. Invest.* https://doi.org/10.1172/JCI120555 (2018)

THYROID CANCER

A microRNA panel for thyroid nodules

A new study by Haggi Mazeh, Iddo Ben-Dov and colleagues has identified 19 microRNAs (miRNAs) that could be used in a diagnostic panel to differentiate benign from malignant thyroid nodules with indeterminate cytology.

Fine needle aspiration biopsy is the current gold standard for the diagnosis of malignant thyroid nodules. However, 10–40% of patients who undergo this procedure have indeterminate results, meaning that molecular testing is then needed to determine the diagnosis. The currently available commercial tests are used to either rule out malignancy or to rule in malignancy, but no test can do both with high accuracy. Previous studies showed that miRNAs could be used as biomarkers to characterize thyroid nodules, leading the authors to try to identify an appropriate set of miRNAs for a diagnostic panel.

The researchers used next-generation sequencing to characterize the miRNA expression profiles of malignant (79) and benign (195) thyroid nodules. Of the 279 identified miRNAs, 19 were selected for the diagnostic panel as they showed the highest differential expression levels in malignant nodules compared with benign nodules. "Some of these miRNAs promote thyroid cancer proliferation, migration and invasion, while others inhibit proliferation of thyroid cancer cells and induce apoptosis," explains Mazeh.

Finally, the authors tested the performance of the diagnostic panel on a set of validation samples (22 malignant and 13 benign nodules). The panel had a sensitivity, specificity, negative predictive value, positive predictive value and overall accuracy score of 91%, 100%, 87%, 100% and 94%, respectively. The overall accuracy of the panel is potentially higher than commercially available tests.

The authors are now considering performing a follow-up clinical trial to prospectively test the panel on patients.

Ivone Leong

ORIGINAL ARTICLE Mazeh, H. et al. Next-generation sequencing identifies a highly accurate miRNA panel that distinguishes well-differentiated thyroid cancer from benign thyroid nodules. *Cancer Epidemiol. Biomarkers Prev.* https://doi.org/10.1158/1055-9965.EPI-18-0055 (2018)

PCOS

Mechanisms of insulin resistance

Despite polycystic ovary syndrome (PCOS) being highly prevalent, the aetiology of the disease is unclear. Now, new research demonstrates that transcriptional and epigenetic changes in skeletal muscle could contribute to the metabolic abnormalities (such as an increased risk of insulin resistance and type 2 diabetes mellitus) seen in women with PCOS.

Previous work has shown that transcriptional and epigenetic changes are present in the adipose tissue of women with PCOS. "As skeletal muscle accounts for the vast majority of glucose uptake, we decided to investigate differential DNA methylation and gene expression in skeletal muscle in women with PCOS and control individuals matched for weight, BMI and age," explains corresponding author Elisabet Stener-Victorin.

The researchers took muscle biopsy samples from 17 women with PCOS and 14 control individuals, which were then analysed using array-based DNA methylation and mRNA expression profiling. These analyses revealed that 85 transcripts were differentially expressed between the cases and controls; 66% were upregulated and 34% were downregulated in the women with PCOS. Several of the identified differentially expressed genes are known to be involved in muscle function and metabolism, including *COL1A1* and *MAP2K6*.

In addition, a gene-set enrichment analysis showed that women with PCOS had notable genetic alterations in 16 different pathways, many of which are known to be involved in the immune response or have been implicated in immune-related diseases. "Furthermore, we were able to identify, for the first time, specific changes in skeletal muscle DNA methylation that might affect gene expression," explains Stener-Victorin. "Thus, we demonstrate that women with PCOS have epigenetic and transcriptional changes in skeletal muscle that, in part, explain the metabolic abnormalities seen in these women."

Stener-Victorin and her colleagues are now hoping to investigate whether specific therapies can be used to remodel the genetic alterations in PCOS, with the aim of improving whole body glucose homeostasis.

Claire Greenhill

ORIGINAL ARTICLE Nilsson, E. et al. Transcriptional and epigenetic changes influencing skeletal muscle metabolism in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* https://doi.org/10.1210/jc.2018-00935 (2018)