

## Biomarkers of autoimmune diabetes in a preclinical model

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Type 1 diabetes is a multigenic, complex autoimmune disorder in which the T lymphocytes mediate the destruction of insulin-producing beta cells. Classic genetic approaches have revealed the association of certain immune response genes with the risk of developing autoimmune diabetes. However, individuals harboring these risk genes and monozygotic twins do not consistently develop type 1 diabetes, indicating a role for epigenetic mechanisms in fine-tuning the manifestation of type 1 diabetes. Consistently, we have recently shown that treatment of prediabetic NOD mice with a histone deacetylase inhibitor provided long-term protection against autoimmune diabetes. This was accompanied by histone hyperacetylation in spleen and pancreas, preservation of insulin-producing beta cell mass and function, as well as increase in a subset of T regulatory cells. Importantly, chromatin remodeling resulted in selective up-regulation of stimulus-dependent interferon-gamma gene, implicated in diabetes prevention, and its transcription factor, Tbx21/Tbet. We extended the analysis of gene expression at the genome wide level using high-density oligonucleotide microarrays. Unbiased high-throughput microarray analysis unraveled the exaggerated expression of pro-inflammatory genes in un-induced splenocytes derived from acutely diabetic mice and their repression in protected mice. Microarray analysis of splenocytes of cured mice also indicated concurrent up-regulation of several genes with diversified functions. These observations were validated by qRT-PCR, using RNA derived from splenocytes and pancreata. Genes implicated in insulin sensitivity, antigen presentation, cell cycling, autophagy, and propagation of progenitor cells were also up-regulated in cured mice. Thus, chromatin remodeling can repeal the epistatic regulation of type 1 diabetes, resulting in the alleviation of type 1 diabetes. Importantly, the data provide a set of novel biomarkers for the diagnosis and prognosis of type 1 diabetes, as well as molecular targets for the intervention of this common autoimmune disease.

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