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Transcriptome analysis of epigenetically modulated genome of NOD mice reveals signature genes involved in autoimmune diabetes

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Type 1 diabetes is an autoimmune disease mediated by the destruction of insulin-producing beta cells by T lymphocytes. Genome wide association studies implicated several genes in the risk of developing this complex disorder. However, low concordance of diabetes incidence among monozygotic twins and other circumstantial evidence suggest a role for epigenetics in diabetes manifestation. To elucidate the epigenetic mechanisms involved in diabetes, we have recently developed a preclinical model in which NOD mice were treated with the histone deacetylase inhibitor, Trichostatin A. Pharmacological inhibition of histone deacetylases resulted in histone hyperacetylation, selective up-regulation of interferon-γ and its transactivator Tbx21/Tbet, and protection against autoimmune diabetes. Chromatin remodeling also resulted in the deletion of diabetes causing T lymphocytes as indicated by the inability of splenocytes from drug treated mice to transfer diabetes into immunodeficient NOD.Scid mice. Global gene expression profiling of splenocytes using high throughput microarray technology revealed the exaggerated expression of a novel set of closely related inflammatory genes in acutely diabetic mice and their repression in mice cured of diabetes by chromatin remodeling. In addition, higher-level expression of genes involved in insulin sensitivity, erythropoiesis, hemangioblast generation, and cellular redox control was evident in spleens of cured mice. These results are consistent with the involvement of epistatic mechanisms in the manifestation of autoimmune diabetes and indicate the utility of chromatin remodeling in treating this complex autoimmune disorder.

Biography

Sundararajan Jayaraman obtained his Ph.D from Madurai Kamaraj University, India and completed postdoctoral studies from St. Louis University and Harvard Medical School. He is currently at the University of Illinois at Chicago and has more than 60 publications and is serving as an editorial board member of four journals and reviewer for many reputed journals.

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