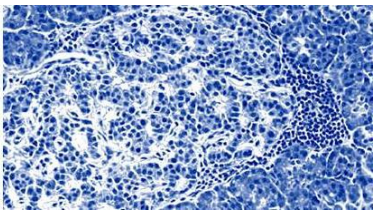
nPOD
Network for Pancreatic Organ Donors with Diabetes



Dextran Sulfate Ameliorates Type 1 Diabetes through Reducing IFNγ Effects and Increasing TGFß Signaling

AUTHORS

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PURPOSE

Type 1 Diabetes (T1D) results from immune tolerance failure and pancreatic beta cell destruction. Our lab has recently found that low molecular weight dextran sulfate (DS) markedly reduces the development and progression of early onset T1D in NOD mice. Furthermore, DS blunts cytokine-mediated beta cell death. In this study, we analyzed the molecular mechanisms involved in the beneficial effects of DS on beta cells and immune cells.

METHODS

Human islets were treated for 24h with cytokines (IFNγ, IL1β and TNFα) in presence or absence of DS. For each human islet preparation, RNA was collected for RNAseq analysis and protein was extracted for expression analysis of cytokine-induced pathways by western blot. IFN receptor expression was analyzed in INS1 cells treated with cytokines±DS. Non-diabetic NOD female mice were treated with DS or saline for four weeks and lymphocytes from spleen and pancreatic lymph nodes were analyzed by flow cytometry to profile T cells (IFNγ/PD-1/CD4/CD8 and Foxp3/CD4) and DCs/Macrophages (MHC II/CD86/CD80/PD-1L/ CD11b/CD11c). DS effects on TGFß signaling in T cells and macrophages was analyzed in vitro.

SUMMARY OF RESULTS

RNAseq analysis of human islets treated with cytokines±DS showed significant upregulation of 217 genes and downregulation of 353 genes in DS+cytokines compared with cytokine treatment alone. These genes were mostly involved in cellular processes such as reduced apoptosis, decreased inflammatory response, diminished chemokine production, increased oxidative phosphorylation and enhanced pyruvate metabolic activities. JAK2, pSTAT1, pP65 and iNOS protein expression was significantly reduced in human islets treated with cytokines+DS compared with cytokines alone. Furthermore, DS reduced cytokine-induced IFNγ receptor upregulation in beta cells. DS-treated NOD mice displayed decreased IFNγ and increased PD-1 expression in both CD8+ and CD4+ T cells. Interestingly, DS treatment significantly upregulated Foxp3+ CD4 T cells and enhanced PD-L1hi/CD80+/CD86+/MHC-IIhi/CD11b+/CD11c+ cells (tolerant dendritic cells) in pancreatic lymph nodes from these

mice. DS enhanced TGFß signaling and increased pSMAD2/3 in T cells what led to reduced number of IFNγ+Th1 cells and enhanced suppressive capacity of Foxp3+ Tregs. Moreover, DS decreased IL12P40, IL1ß and TNFα expression in inflammatory M1 macrophages and increased CD206, CD301 and Arg1 expression in M2 macrophages.

CONCLUSIONS

Collectively, these results indicate that DS reduces the onset of T1D in NOD mice by neutralizing IFNγ action in beta cells and increasing TGFß signaling in immune cells leading to enhanced immune suppressive functions in T cells and myeloid cells, and favoring M2 macrophage polarization. DS treatment can potentially be of great value for treating T1D.