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Transcriptional profiling of CD4 T-lymphocytes reveals abnormal gene expression in young prediabetic NOD mice

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Background

CD4 T-lymphocytes play a prominent role in Type 1 DM. The NOD mouse is a model for this autoimmune disease. The earliest histological signs of autoimmunity in female NOD mice occur at approximately 5 weeks of age. We hypothesized that this process may be preceded by molecular events in the CD4 T-lymphocytes. To test this hypothesis, we analyzed the transcriptomes of CD4 T-lymphocytes of young "prepathologic" NOD mice.

Methods

Using a magnetic separation system (Miltenyi Biotec), we isolated CD4 T-lymphocytes from spleen leukocytes of female NOD mice, and two control strains, NOR and C57Bl/6, at 2, 3, and 4 weeks of age (n = 5 for each strain, except for NOD 2 wk where n = 4). CD4 T-lymphocyte transcriptomes were characterized on Affymetrix Mouse 430_2 expression arrays probing ~39,000 mouse genes/ESTs. Gene lists produced from statistical analyses were mined using Ingenuity Pathway Analysis http://www.ingenuity.com.

Results

Analysis by 1-way ANOVA ($p < 0.005$, Benjamin-Hochberg Multiple Test Correction (MTC) defined 311, 624, and 581 probesets (genes) with highly significant expression differences between strains at 2, 3 and 4 weeks, respectively. Hierarchical clustering of these probeset lists identified 58, 115, and 65 probesets, respectively for 2, 3, and 4 week old mice, as being differentially expressed in NOD mice relative to both control strains (17, 32, and 9 were upregulated in NOD mice while 41, 83, and 56 were downregulated). Pathway analysis of the 3 gene lists (58, 115 and 64 probesets) revealed that 7 (HNF4A, IFNG, IL4, TP53, BCL2L1, IL15, and prostaglandin E2) of the top 15 central genes in each network were common to all age groups. IL6 was central in networks of 2 and 4 week old mice but not of 3 week old mice. Uniquely central to individual networks were: MYC, JUN and HRAS at 2 weeks; TNF, NFKB, p38MAPK, and TGFB1 at 3 weeks; and Interferon alpha, IL12 and STAT4 at 4 weeks.

Conclusion

We conclude that young, prediabetic NOD mice have basic (i.e. common, most likely genetic) molecular defects in CD4 T-cells associated with apoptosis/cellular proliferation, Th1-Th2 differentiation and cytokine signaling. Furthermore, abnormalities in apoptosis/cellular proliferation predominate at 2 weeks of age while those in cellular activation/acute phase response signaling and inflammation predominate in 3 week old mice. Finally, abnormalities in the innate immune response and its link to the adaptive immune response are evident at 4 weeks of age.

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