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Regulation of anergy-related genes in RA T cells

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Keywords

Anergy, calmodulin, rheumatoid arthritis, transcription

Context

Rheumatoid arthritis (RA) T cells share many features with anergic T cells. This study analysed changes in gene transcription in a T-cell during antigen-induced anergy and examined levels of anergy-associated transcripts in RA.

Significant findings

A total of 55 different cDNA sequences were identified, which formed the basis of an array used to confirm differential gene expression and compare transcription in RA and reactive arthritis (ReA) synovium. Of these sequences, 22 corresponded to known genes, the remainder being expressed sequence tags (ESTs), 20 of which gave no database match. Of the 55 cDNA sequences, 25 were anergy related transcripts, 11 being expressed in synovial tissues. Eight of these synovial transcripts were equally transcribed or upregulated in RA compared to ReA: PMA-ionophore-linked activation factor of T cells, T plastin, calumenin, eukaryotic elongation factor 1-d, ADP ribosylation-like factor-1, aortic carboxypeptidase-like protein and the ESTs BF626660 and BF626663. The three remaining transcripts were downregulated in RA: calmodulin, a calcium-binding protein that regulates other calcium-dependent proteins (100-fold lower); cellular apoptosis susceptibility protein (CAS) was fourfold lower; and the EST BF626661 was 10-fold lower. Calmodulin and BF626661 were downregulated in anergic T cells while CAS was not. Lower expression of calmodulin and CAS was confirmed in individual biopsies by real-time PCR. Calmodulin and BF626661 were downregulated in synovial fluid mononuclear cells compared with peripheral blood mononuclear cells. Anti-TNF-a therapy upregulated calmodulin transcription but not CAS transcription, while inhibiting calmodulin blocked antigen-induced proliferation.

Comments

The upregulation of calmodulin following infliximab treatment and the induction of anergy following calmodulin inhibition links the hyporesponsiveness of RA T cells to calmodulin expression. Calmodulin is a ubiquitous calcium-sensing protein, which is central to the regulation of signal transduction. T-cell hyporesponsiveness in arthritis has been linked to alterations in intracellular calcium (iCa) responses, which fail to transfer activating signals (see Additional information [1]). More recently Carruthers et al (see Additional information [2]) have demonstrated abnormalities in the magnitude, pattern and spatial distribution of iCa signaling in synovial fluid T cells. Hence, reduced calmodulin expression may magnify the inability of T cells to transfer activating signals. The observed hyporesponsiveness, however, is also affected by decreased intracellular glutathione, a decreased tyrosine phosphorylation pattern and diminished phosphorylation of the TCR ?-chain (see Additional information [3,4]). These results suggest that defective TCR signaling may contribute to the hyporesponsive nature of synovial T cells. While this is a preliminary study with a low sample number the data presented shed new light on the cellular defects observed in RA.

Methods

RNA extraction and cDNA generation, differential display RT-PCR, T-cell culture, differential hybridisation, northern blot

Additional information

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