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Synovial inflammation in children with Antibiotic-refractory Lyme Arthritis is characterized by clonal expansion of peripheral T helper cells with distinct TCR Vβ repertoire

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Introduction

Antibiotic-refractory Lyme arthritis (ARLA) is defined by persistent arthritis after sufficient antibiotic treatment of acute Lyme arthritis and is seen in approximately 10 % of patients with Lyme arthritis. Although some clinical and genetic risk markers for ARLA have been elucidated, the disease pathogenesis is still inadequately understood. In detail, whether chronic inflammation is sustained by persistent borrelial antigens or triggered by autoantigens is not elucidated yet.

Objectives

Identifying the cellular correlate of ongoing immune responses in the inflamed joints of children with ARLA to elucidate antigen targets and disease specific pathomechanisms.

Methods

Flow cytometric analysis of T and B cell populations in synovial fluid (SF) samples of children with ARLA and juvenile idiopathic arthritis (JIA). High-throughput sequencing of the T cell receptor β (TCR Vβ) repertoire of SF T cells and single cell immunoglobulin expression cloning of SF B cells in children with ARLA and JIA.

Results

Multidimensional flow-cytometric analysis revealed a striking expansion of an IL-21 and IFN-γ co-expressing PD-1hiCXCR5-HLA-DR+ CD4+ T cell population resembling peripheral T helper (TPH) cells in the joints of pediatric ARLA patients compared to JIA patients. Indeed, ARLA patients display the highest frequencies of TPH cells, which could separate this group of patients from JIA. Accumulating TPH cells exhibited signs of clonal expansion with restricted TCR clonotypes. Those clonotypes showed an overlap between different ARLA patients but not to JIA patients. Furthermore, distinct molecular patterns within the TCR Vβ repertoires diverged in ARLA and JIA patients. Paralleling the observations made in the T cell compartment, accumulating SF B cells showed oligoclonal expansion and almost exclusively displayed the phenotype of CD-21lo/-CD11c+ double-negative (DN) B cells.

Conclusion

The inflamed joints of children with ARLA are characterized by a striking expansion of oligoclonal TPH cells and DN B cells. The distinct features of the TCR Vβ repertoire of TPH from ARLA patients suggest that disease specific immune response may sustain chronic inflammation in ARLA. Having defined the cellular subsets of an ongoing immune response in the joints of children with ARLA, current experiments are ongoing to dissect whether this maladaptive immune response targets persisting Borrelial antigens or rather autoantigens.