

A58 INFLAMMATION AND AUTOIMMUNE RESPONSES ARE INDEPENDENT OF PERIPHERAL MHC CLASS II EXPRESSION DRIVEN BY CIITA PIV IN COLLAGEN INDUCED ARTHRITIS

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Background In rheumatoid arthritis (RA), non-professional antigen presenting cells (APCs) such as fibroblast-like synoviocytes (FLS) can express MHC class II (MHCII) molecules and function as non-professional APCs in vitro.

Objective To examine the regulation of MHCII expression in FLS and to investigate the role of FLS as non-professional APCs in collagen-induced arthritis (CIA).

Methods Expression of MHCII, CIITA and Ciita isoforms pI, pIII and pIV was examined by RT-qPCR, immunohistochemistry and flow cytometry in human synovial tissues, arthritic mouse joints and human as well as mouse FLS. CIA was induced in mice knockout for the isoform IV of Ciita (pIV^{-/-}), in pIV^{-/-} mice transgenic for CIITA in the thymus (pIV^{-/-} K14 CIITA) and in control littermates in the DBA/1 background by immunising with bovine collagen type II (CII) in complete Freund's adjuvant.

Results HLA-DRA, total CIITA and CIITA pIII mRNA levels were significantly increased in the synovial tissues from RA compared to osteoarthritis patients. Human FLS expressed surface MHCII via CIITA pIII and pIV, while MHCII expression in murine FLS was entirely mediated by pIV. pIV^{-/-} mice lacked both inducible MHCII expression on non-professional APCs including FLS, and in the thymic cortex. The thymic defect in pIV^{-/-} mice impaired CD4⁺ positive selection, thus protecting pIV^{-/-} mice from CIA by preventing CD4⁺ T cells immune responses against CII and blocking the release of IFN- γ and IL-17 in ex vivo stimulated lymph node cells. The production of T dependent, arthritogenic anti-CII antibodies was also impaired in pIV^{-/-} mice. A normal thymic expression of MHCII and CD4⁺ T cell repertoire was obtained in pIV^{-/-} K14 CIITA Tg mice. Immune responses against CII were restored in pIV^{-/-} K14 CIITA Tg mice, as well as the arthritis incidence and clinical severity despite the lack of MHCII expression by mouse FLS. At histology, inflammation and neutrophils infiltration scores were not reduced in pIV^{-/-} K14 CIITA Tg mice, while the bone erosion score was significantly lower than in controls.

Conclusion Over expression of MHCII is tightly correlated with CIITA pIII in the arthritic human synovium. MHCII is induced via CIITA pIII and pIV in human FLS. In the mouse, MHCII expression in the thymic cortex and in FLS is strictly dependent upon Ciita pIV. The lack of Ciita pIV in the periphery of pIV^{-/-} K14 CIITA Tg mice lowered the bone erosion score but did not significantly protect from inflammation and autoimmune responses in CIA.

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