SLE, Sjöns and APS - aetiology, pathogenesis and animal models

**DEFICIENCY OF PPM1A IN MACROPHAGE AGGRAVATES PRISTANE-INDUCED LUPUS-LIKE DISEASE**

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**Background:** Protein phosphatase Mg2+/Mn2+-dependent 1A (PPM1A) is a phosphatase which regulates various intracellular cell signaling pathways including inflammation. We previously suggested that the inflammatory signal decreased the PPM1A protein level in macrophage and this reduction had correlation with the chronic inflammatory bone disease, implying the possible role of PPM1A in inflammatory responses of macrophage.

**Objectives:** In this study, we aim to elucidate the potential role of PPM1A in macrophage to regulate inflammatory response during the disease progression of systemic lupus erythematosus.

**Methods:** We generated macrophage-specific conditional gene-knockout (PPM1Afl/fl;LysoM-Cre) and a developed a lupus-like disease with immune complex glomerulonephritis in these PPM1Afl/fl;LysoM-Cre mice by intraperitoneal pristane injection. We generated macrophage-specific conditional gene-knockout (PPM1Afl/fl;LysoM-Cre) and a developed a lupus-like disease with immune complex glomerulonephritis in these PPM1Afl/fl;LysoM-Cre mice by intraperitoneal pristane injection. Mouse serum was collected every 4 weeks after pristane injection. Serum anti-dsDNA IgG, anti-ssDNA IgG, interleukin-17 (IL-17) and tumor necrosis factor-α (TNF-α) was quantified by ELISA. After 41 weeks from pristane injection, histological changes in the kidney, spleen, and lung tissues were observed. To analyze M1/M2 polarization in vitro, LysoM-Cre and PPM1Afl/fl;LysoM-Cre mouse bone marrow-derived macrophages were cultured with lipopolysaccharide (LPS)/Interferon-gamma (IFN-γ) or interleukin-4 (IL-4) to check M1 or M2 related genes.

**Results:** We found that macrophages of PPM1Afl/fl;LysoM-Cre mice displayed different gene expression with LPS stimulation especially in M1/M2 related genes through the RNA-seq analysis and showed a decrease in both M1 and M2 polarization induced by LPS/IFN-γ or IL-4 stimulation. Notably, we found that PPM1Afl/fl;LysoM-Cre mice with pristane injection showed a significant increase of anti-ssDNA IgG compared to LysoM-Cre mice. PPM1Afl/fl;LysoM-Cre mice showed severe lupus-like phenotypes such as global glomerular enlargement indicated by endocapillary proliferation and glomerular cellularity in kidney and lung inflammation accompanied by fibrosis, compared to LysoM-Cre mice by pristane injection. Together, IL-17 and TNF-α, which are proinflammatory cytokines, were increased in PPM1Afl/fl;LysoM-Cre after pristane injection. These results indicate that PPM1A depletion in macrophage deteriorates inflammation and contributes to the tissue damage in lupus-like disease.

**Conclusion:** Our findings suggest that the deficiency of PPM1A in macrophages may impair M1/M2 macrophage polarization leading to an immune imbalance in lupus-like disease model, providing a potential link between the loss of function of PPM1A in macrophages and its molecular target for treatment of systemic lupus erythematosus.

**REFERENCES:**


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**EXPLORATORY IMMUNOPHENOTYPE OF THE RARE DISEASE JUVENILE SJÖGREN’S SYNDROME REVEALS A DYSREGULATION OF B AND T MEMORY CELL FREQUENCIES**

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**Background:** Sjögren’s syndrome (SS) is an autoimmune rheumatic disease characterised by dryness resulting from chronic lymphocytic infiltration of the exocrine glands. Patients also present with other extraglandular manifestations such as arthritis, anemia and fatigue or various organ and systems involvement. The disease is more frequent in women aged 30-50. However, in rare cases, the disease onset is in childhood and is known as juvenile SS (JSS) or childhood SS. Children have different clinical manifestations compared to adults, with dryness being less common, making the diagnosis very challenging.

**Objectives:** To investigate in depth the immune cell profile of patients with JSS for better understanding of disease pathogenesis.

**Methods:** Peripheral blood was collected from a cohort of patients with JSS who had attending appointments at UCLH clinics. None had received B-cell depletion therapy. Immune-phenotyping of 29 immune-cell subsets, including B and T cells, in peripheral blood from patients with JSS (n=10) and age and sex-matched healthy controls (n=10) was performed using flow cytometry as we have performed previously for patients with adult onset SS. Data were analysed using multiple t-tests and compared with the adult SS immune phenotype.

**Results:** Patients with JSS had an average age of 18 years (range 16-21) with an average age of disease onset at 14 years (range 12-18). Up to 60% of patients presented Anti-Ro autoantibodies while 50% presented Anti-La autoantibodies. Patients with JSS had an altered immune profile compared to age matched healthy controls (average of 18 years, range 15-25). In the B cell compartment,