**Complement Component C5a Permits the Co-existence of Pathogenic Th17 Cells and Type I Interferon in Lupus**

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**Disclosures**

There are no relevant disclosures related to this work.

**Systemic Lupus Erythematosus (SLE)**

Systemic autoimmune disorder with multi-organ involvement

- Dysregulated B cells
- Autoantibodies
- Immune complex deposition resulting in end organ damage

**CD4+ T helper cells in the pathogenesis of SLE**

Deplete CD4+ T cells → Resistant to Lupus Nephritis

- Auto Antibody production
- Chronic Inflammation
- Tissue damage

Deregulated production of **IL-17** and **IL-21** may be one of the critical mechanisms by which T helper cells contribute to SLE pathogenesis.

**TH17 cells: key players in autoimmunity**

- Th17 cells and their signature cytokine IL-17 drives lupus pathogenesis in multiple mouse models of lupus including MRL.Faspr, B6.1pr, 8XH2, FcgR2b−/− mice.
- Therapeutic interventions using IL-23R Ab, IL-21RFc or ROCK inhibitors that block Th17 differentiation ameliorated lupus nephritis in these mouse models.
- An increased frequency of Th17 cells was reported in SLE patients and Th17 cell numbers correlated with disease activity in the majority of studies.

**Type I IFN inhibits the differentiation of Th17 cells**

- Mice with defects in type I IFN receptor (IFNAR) developed more severe Experimental Autoimmune Encephalitis (EAE).
- Type I IFN-mediated IL-27 production by dendritic cells and macrophages blocked Th17 differentiation.
- IFN-β is widely used for the treatment of Multiple Sclerosis.

How are pathogenic Th17 cells generated in SLE in the presence of an environment characterized by high IFN-1 levels?
**Complement component C5a-C5aR activation on innate cells regulate Th17 differentiation**

- C5a is a protein fragment released from complement component C5.
- C5a binds to C5aR.
- Activation of C5aR is a primary event in the pathogenesis of SLE.

C5a-C5aR interactions inhibit Th17 differentiation through diminished production of TGF-β, IL-6 and IL-23 in a house dust mite extract challenge model.

C5a receptor (C5aR) deficiency in SKG mice inhibited the differentiation and expansion of Th17 cells after mannose or beta-glucan treatment, and consequently suppressed the development of arthritis.

**Proposed model of C5a-mediated regulation of Th17 cells via IL-27**

**C5a inhibition of IFN-I mediated suppression of Th17 differentiation in lupus-prone mice**

**C5a-C5aR interactions inhibited IFN-I mediated sIL-27 production in a PI3K/Akt dependent manner**

**C5aR activation on macrophages inhibited IRF-1 expression**

**Resistance to lupus nephritis development in C5aR−/− mice was associated with increased IL-27 production and diminished number of Th17 cells**
Inverse correlation between serum C5adesArg and IL-27 levels and between IL-27 and the percentage of Th17 cells in the peripheral blood of SLE patients

\[ r = -0.66; p < 0.001 \]

\[ r = -0.86; p < 0.0001 \]

\[ r = 0.74; p = 0.001 \]

C5a inhibits IFN-I-induced IL-27 production in macrophages from SLE patients.

\[ \Delta Ct (IL-27(p28)) \]

C5a in the serum of lupus patients inhibits IFN-I-induced IL-27 production in macrophages

\[ \Delta Ct (IFN-I) \]

Conclusion

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