

 AUTOIMMUNITY

New players in lupus nephritis

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody (IgM, IgG and IgA)-containing immune complexes that are deposited in, and cause damage to, numerous organs — including the kidneys (lupus nephritis). In addition to B cells, T helper 1 (T_H1) cells, T_H17 cells, macrophages and dendritic cells have all been shown to have a role in SLE. Now, Rivera and colleagues show that the induction of T_H2 -type responses through the activation of basophils by IgE autoantibodies contributes to the development of lupus nephritis in both mice and humans.

Immune responses in mice deficient for the signalling molecule **LYN** ($Lyn^{-/-}$ mice) are strongly skewed towards the T_H2 -type response, and the mice develop lupus-like nephritis late in life. To determine if these two observations are related, the authors assessed the development of lupus-like nephritis in $Lyn^{-/-}$ mice that were

also deficient for interleukin-4 (IL-4), IgE or mast cells. $Lyn^{-/-}$ mice that lacked IL-4 or IgE (but not mast cells) did not develop glomerulonephritis, had normal kidney function and had a twofold reduction in double-stranded DNA (dsDNA)-specific antibodies and antinuclear antibodies (ANAs), indicating that the disease in $Lyn^{-/-}$ mice is dependent on IL-4 and IgE expression.

Recent evidence has shown that basophils can induce T_H2 cell differentiation and enhance humoral immunity *in vivo*. Depletion of basophils in $Lyn^{-/-}$ mice resulted in decreased levels of ANAs, a smaller proportion of plasma cells in the spleen and reduced pro-inflammatory cytokine production (IL-1 β , IL-6, IL-13 and IFN γ) in the kidneys compared with control mice.

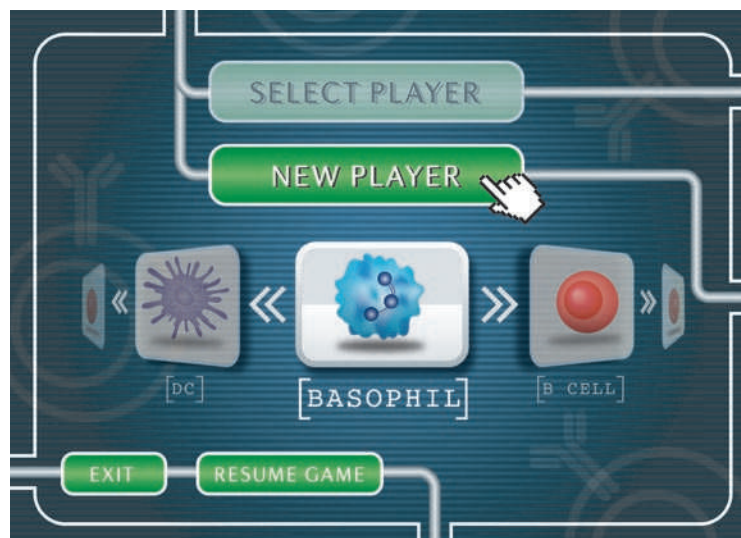
Immune complexes containing IgE (but not IgG) induced IL-4 production by basophils, and basophils from $Lyn^{-/-}$ mice were more sensitive

to IgE-containing immune-complex stimulation than basophils from wild-type mice. These cells also expressed higher levels of the lymphoid tissue-homing receptor CD62L (also known as L-selectin). In addition, $Lyn^{-/-}$ mice had more basophils in both the lymph nodes and spleen, and both CD62L expression levels and the proportion of basophils in these tissues were reduced in the absence of IL-4 or IgE. Furthermore, basophils from $Lyn^{-/-}$ mice expressed BAFF (B cell-activating factor) and high levels of MHC class II molecules. So, the data suggest that IgE-containing immune complexes can activate basophils, which is necessary for the homing of these cells to lymphoid tissues, and that basophils maintained plasma cell numbers in the spleen and increased the production of autoantibodies, leading to nephritis.

Finally, patients with SLE were shown to have elevated levels of circulating dsDNA-specific IgE, which were associated with increased disease activity and active nephritis. Furthermore, blood basophils from these patients were activated, expressed high levels of CD62L and showed elevated HLA-DR expression. Basophils were also found in the lymph nodes and spleen of two patients with SLE.

So, IgE, IL-4 and basophils contribute to the production of autoantibodies and promote the development of lupus-like nephritis.

Olive Leavy



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