

Toll like receptor 7- and 8-dependent double-stranded DNA antibodies in a Lupus mouse model

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Antibodies recognizing self RNA and dsDNA are implicated in the pathogenesis of systemic lupus erythematosus (SLE). Anti-RNA and anti-dsDNA IgG are thought to be TLR 7/8- and TLR 9-dependent, respectively. Paradoxically, recent results show TLR 9 is protective in murine models of SLE, calling into question the pathogenicity and/or the mechanism of anti-dsDNA antibody generation. We study SLE “564Igi” mice that express knocked-in immunoglobulin (Ig) heavy (H) and light (L) chain genes that encode an RNA-specific antibody. Our preliminary results indicate that aged 564Igi mice shift their antibody repertoire from anti-RNA IgG to anti-dsDNA IgG. Surprisingly, the production of this anti-dsDNA antibody is TLR 7/8-dependent and TLR 9-independent. Our hypothesis is that these anti-dsDNA antibodies arise via somatic hypermutation (SHM) of Ig genes in B cells that are activated via the RNA-sensing TLR 7/8 pathway yet are polyreactive to dsDNA in addition to RNA. This work defines a novel mechanism for the generation of self-reactive IgG antibodies and may explain why RNA reactivity precedes polyreactivity in SLE, as is suggested by human data.

Biography

Craig Weinkauf, received his degree from Tufts University School of Medicine and the Sackler School of Biomedical Research.

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