Top Reads

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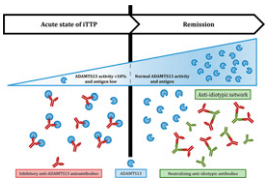
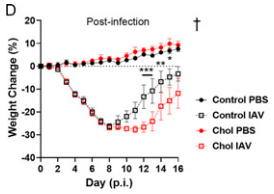
The Journal of Immunology

Anti-Idiotypic Abs Keep Autoantibodies in Check



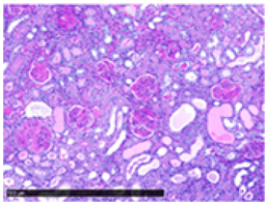
Patients with the blood clotting disorder known as immune-mediated thrombotic thrombocytopenic purpura (iTTP) have a severe autoantibody-mediated deficiency in the ADAMTS13 protease. Remission from iTTP may be mediated by naturally occurring anti-idiotypic Abs that neutralize anti-ADAMTS13 autoantibodies. In this Top Read, Heeb et al. (p. 2497) address this hypothesis by examining the repertoire of anti-ADAMTS13 autoantibodies, as well as a library of anti-idiotypic, anti-ADAMTS13 autoantibody-binding Fabs from splenic mononuclear cells of three relapsing iTTP patients. The anti-idiotypic Fabs were unique to individual patients, having undergone very little somatic hypermutation. Although anti-idiotypic Fabs had low binding affinity, they were able to restore ADAMTS13 proteolytic activity in vitro, within patient samples. Cross-patient anti-idiotypic Fabs were insufficient to restore ADAMTS13 activity. Together, these data suggest that the anti-idiotypic repertoire is patient specific and may have the potential to ameliorate iTTP symptoms within an individual.

High-Cholesterol Diet Exacerbates Flu



In this Top Read, Louie et al. (p. 2523) showed that a high-cholesterol diet leads to an exaggerated immune response and higher morbidity during infection with influenza A virus (IAV). Mice were fed a standard or high-cholesterol diet for 5 wk and then infected with mouse-adapted IAV. Prior to infection, the mice in the high-cholesterol group presented with dyslipidemia and fatty liver disease. Following infection, the high cholesterol mice showed increased morbidity compared with control animals. Lung transcriptomes of both diet groups postinfection showed a dietary cholesterol–dependent increase in expression of genes associated with chemokine signaling, cell division, and leukocyte trafficking and activation. Furthermore, there were increased numbers of IFN-γ–producing lymphocytes in lungs of the high-cholesterol–fed mice. The humoral response, viral titers, and RNA load were unaffected by diet. Together, these data suggest that a high-cholesterol diet exacerbates disease severity after infection with IAV by driving an aberrant immune response.

Immunotherapy for Lupus Nephritis



In this Top Read, Kumar et al. (p. 2467) investigated the role of T follicular regulatory (TFR) cells in lupus nephritis (LN). LN-prone mice with onset of proteinuria showed reduced TFR cells and increased Tfh cells, germinal center (GC) B cells, and pathogenic anti-dsDNA IgG compared with LN-prone mice without onset of proteinuria. Treatment of LN-prone mice with soluble OX40L and Jagged-1 (JAG1) proteins increased the number of T regulatory cells (Tregs) and TFR cells, decreased GC B cells and anti-dsDNA IgG Ab levels, and suppressed LN onset compared with control-treated animals. The authors further showed that OX40L and JAG1 treatment attenuated Tfh cell function, T cell activation, and GC B cell somatic hypermutation and isotype switching. T cells from OX40L- and JAG1-treated mice had reduced glycolysis and increased signs of exhaustion, which may impair their ability to differentiate into Tfh cells. Collectively, this study showed that OX40L and JAG1 treatment suppressed LN onset and may have therapeutic implications for patients suffering from LN.

ATM Kinase Diversifies the TCRβ Repertoire

In this Top Read, Wu et al. (p. 2583) used transgenic mice with either weak or strong Vβ recombination signal sequences (RSSs) on ATM kinase deficient or sufficient backgrounds. They demonstrated that inefficient Vβ recombination and ATM kinase–mediated DNA damage response establish diversity and allelic exclusion of the TCRβ genes. In ATM-deficient mice, usage of *V31* was decreased and *V2* was increased when under strong RSS control, suggesting that ATM differentially functions with poor-quality RSSs to shape the TCRβ repertoire. In addition, ATM suppressed nonfunctional rearrangements of Vβ genes. ATM interactions with a weak Vβ RSS resulted in allelic exclusion in the TCRβ repertoire. However, ATM-deficient mice with strong Vβ RSSs had increased frequencies of T cells expressing multiple TCRβ proteins. The authors suggest that weak RSSs in combination with ATM function to facilitate interallelic competition during Vβ recombination. Together, these data provide a mechanism by which ATM and RSS strength synergize to diversify the TCRβ repertoire.

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