

Presentation:

Accelerated Development of Glomerulonephritis in TNF Receptor 1 and 2 Double-Knockout Lupus-mice

Speaker:

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Abstract:

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We have developed lupus-prone (NZB x NZW)F1-derived congenic New Zealand Mixed (NZM) 2328 lines that are deficient in TNF receptor 1 (TNFR1), TNF receptor 2 (TNFR2) or in both TNFR1 and TNFR2. While the development of lupus-nephritis in TNFR2 deficient mice was very similar to wild type, TNFR1 deficient mice had only a slightly delayed disease development compared to TNF receptors intact NZM 2328 controls. On the other hand, mice that lacked both TNFR1 and TNFR2 developed a significantly accelerated lupus-nephritis and increased mortality associated with increased levels of IgG anti-double-stranded DNA autoantibodies both in the periphery and in the glomerular deposits. Double knockout mice have significantly enlarged spleens compared to all other lines, which is associated with increased number of B and T lymphocytes mostly of CD4⁺ subsets. Most notably, double KO mice have a 3-5 fold increase in the number of activated memory T cells (CD4⁺ CD25⁻ CD44^{high} CD62L^{low}) while TNFR1 deficient and TNFR2 deficient are not different from each other. Immunostaining of spleens shows spontaneous germinal center formation in wild type NZM 2328 and TNFR2 deficient mice. TNFR1 deficient mice have reduced germinal center formation at 2 months and still at 6 months of age while double KO mice have reduced GC formation at 2 months but by 6 months have as much or more than the control mice. These results suggest a fine and complex balance between the two TNF receptors and underscore the need for both receptors in the immune development of autoimmune kidney disease.