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Mucosal immune dysregulation and galactose-deficient IgA1 production in IgA nephropathy

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Impaired immune regulation along the “mucosa-bone marrow axis” has been postulated to play an important role in the pathogenesis of IgA nephropathy (IgAN). Accumulating evidence from experimental approaches with animal models suggests that there is dysregulation of innate immunity in IgAN resulting in changes in the mucosal immune system. Our recent experimental studies with IgAN prone mice revealed that mucosal activation of Toll like receptors (TLR) are involved in the production of nephritogenic IgA and IgA immune complex (IC).

On the other hand, the nephritogenic roles of galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1 bound with anti-glycan IgG in IC (IgA/IgG-IC) have been discussed in human IgAN. Although many clinical studies indeed show serum elevation of GdIgA1 and IgA/IgG IC in IgAN patients and association between these serum levels and the disease activity, their production sites and relevant cell types remain unclear. Our recent clinical studies indicate that the palatine tonsils may be one of major sites for the production of GdIgA1 and tonsillar TLR9 activation may contribute to the extent of glomerular injury via the GdIgA1 production. We also found that pathological contribution of B cell related cytokines such as a proliferation-inducing ligand (APRIL) in tonsillar B cells enhanced by TLR9 are likely involved in nephritogenic IgA/GdIgA1 production in IgAN, being consistent with recent GWAS data. In this session, I would like to discuss mucosal immune dysregulation leading to nephritogenic GdIgA1 production in IgAN.