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Understanding the pathological Role of APRIL in IgA nephropathy

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The "multi-hit/four-hit" hypothesis of IgA nephropathy (IgAN) is widely accepted for pathogenesis of IgAN. IgAN is thus understood to be an inflammatory disease caused by the glomerular deposition of hit 1, galactose-deficient IgA1 (GdIgA1). In recent years, the molecular mechanism of GdIgA1 production has been gradually elucidated, and several novel therapeutic agents targeting the responsible B cells that produce GdIgA1 have been developed and are being investigated internationally. Many previous clinical and basic research findings indicate that nephritogenic GdIgA1 is a macromolecular IgA1 of mucosal origin. Furthermore, the B cells involved in the nephritogenic GdIgA1 production are primarily differentiated mature B cells, such as plasma cells, which may migrate to the bone marrow as well as the mucosa. The innate immune system of the mucosa, particularly Toll-like receptors (TLRs), is thought to be involved in its production; among TLRs, TLT9 and TLR7, which recognize unmethylated DNA and RNA of bacteria and viruses, have been reported to be involved. Mucosal activation of these TLRs is associated with the production of APRIL (A Proliferation Inducing Ligand) and BAFF (B cell activating factor), cytokines of the TNF superfamily that are involved in B cell maturation, survival, and IgA class switching, and are associated with renal nephritogenic GdIgA1 production; whether APRIL or BAFF is more closely involved in the production of nephritogenic GdIgA1 is still inconclusive. While the phenotype of transgenic animal models suggests BAFF involvement, genome-wide association study (GWAS) analysis of human IgAN has identified APRIL, but not BAFF, as a candidate gene. Moreover, clinical and experimental studies further suggest APRIL involvement. In this session, I would like to discuss the role of APRIL in this disease, outlining the responsible B cells and their mechanism of GdIgA1 production, as well as the results of ongoing clinical trials of drugs targeting APRIL.

Keywords: APRIL, GdIgA 1 , mucosa