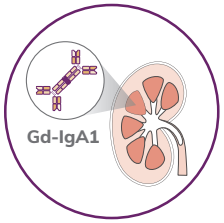
APRIL and the Four-Hit Pathogenic Cascade of IgA Nephropathy (IgAN)

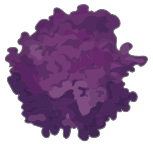


Pathogenesis of IgAN

Normally, immunoglobulin A (IgA) is produced by cells in the mucosa as part of the innate immune response.[1] However, patients with IgA nephropathy (IgAN) have elevated levels of pathogenic galactose-deficient IgA1 (Gd-IgA1) that is targeted by autoantibodies that bind to Gd-IgA1 and form immune complexes.[1,2] Deposition of these immune complexes in the mesangium results in kidney injury and leads to end-stage kidney disease (ESKD) within the lifetime of most patients.[2-4] The pathogenesis of IgAN is explained by the four-hit cascade that drives disease development and progression.[2,5]

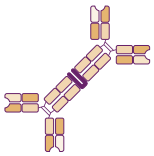
Pre-Hit 1

APRIL, a B-cell growth factor, plays a pivotal role in the four-hit cascade by promoting the production of IgA and pathogenic Gd-IgA1[6,7]



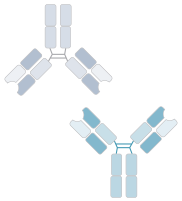
Hit 1

Production of aberrant Gd-IgA1 by plasma cells[2]



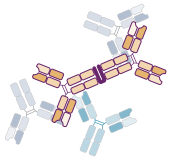
Hit 2

Synthesis of anti–Gd-IgA1 autoantibodies[2]



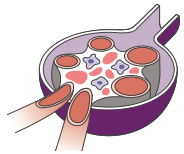
Hit 3

Binding of autoantibodies to Gd-IgA1 in circulation results in the formation of pathogenic immune complexes[2]



Hit 4

Deposition of immune complexes in the glomerular mesangium results in local immune activation, inflammation, and glomerular injury[2]



Role of APRIL

A primary role of APRIL is to induce antibody class switching in activated B cells and promote the survival of plasma cells (antibody-producing B cells).[6-9]

Clinical Correlates of APRIL

Serum APRIL levels are elevated in patients with IgAN.[9] APRIL levels are associated with Gd-IgA1 levels, more rapid progression to kidney failure, and post–kidney transplantation recurrence.[9-11]

The Four-Hit Cascade Drives IgAN Progression

- Outcomes include kidney injury that can progress to ESKD within the lifetime of the majority of patients with IgAN[2-4,12]
  - In observational studies, most patients develop ESKD within 10 to 15 years of diagnosis[3,4]
- APRIL is an important sustaining factor in IgAN progression[6-8]

Most current treatments aim to treat the clinical manifestations of chronic kidney disease, highlighting the need for a disease-modifying treatment that specifically targets the underlying cause of IgAN to delay progression to ESKD.[13,14]

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Learn More About the Pathogenesis of IgAN

References:

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