The "Four Hit" IgA Nephropathy (IgAN) Pathogenesis Theory

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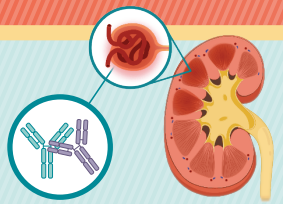
Improving Awareness & Patient Outcomes



Pathogenesis of IgA Nephropathy (IgAN)

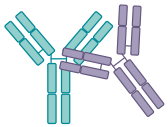
Normally, immunoglobulin A (IgA) is produced on the body's mucosal surfaces as part of the innate immune response. However, in patients with IgAN a **galactose-deficient IgA (Gd-IgA1)** is produced leading to an autoimmune response, deposition of Gd-IgA1 containing immune complexes in the kidney tissue, and ultimately kidney injury. The current model of pathogenicity in IgAN involves four hits that drive disease development and progression.[1]

Hit #1

Production of aberrant, galactose-deficient IgA1 (Gd-IgA1), by plasma cells.[1]

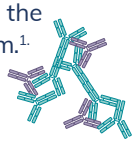
Hit #2

Synthesis of **autoantibodies** directed against the aberrant, Gd-IgA1.[1]



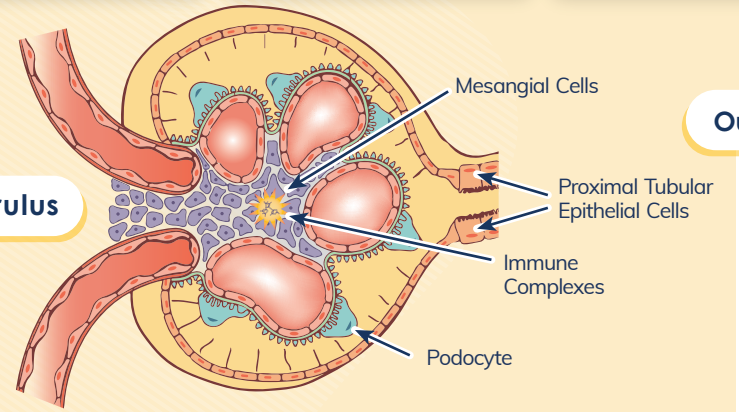
Hit #3

Binding of autoantibodies to the Gd-IgA1 generates **pathogenic immune complexes**, which circulate in the bloodstream.[1.]



Hit #4

Circulating immune complexes deposit at the points of filtration (mesangial cells, located between glomerular basement membrane and fenestrated endothelium of the kidney). **Deposition of immune complexes result in local immune activation, inflammation, and glomerular injury.**



Glomerulus

Outcome Of The Four Hit Pathogenic Process:

- Injury to the podocytes and proximal tubular epithelial cells
- Worsening kidney function progressing to chronic kidney disease.
- Which left unaddressed, can lead to kidney failure and the need for renal replacement therapy, such as transplant or dialysis.[1,4]

For More Information on IgAN:

- IgA Nephropathy Foundation: **IgAN.org**
- National Kidney Foundation: **Kidney.org**
- KDIGO 2021 Clinical Practice Guideline For the Management Of Glomerular Diseases: **KDIGO.org/guidelines/gd**

IgAN Clinical Trials

As we learn more about the pathophysiology of IgAN, there are more clinical trials targeting various "hits" within the overall disease process.

Patient participation in clinical trials is crucial for evaluating novel therapies for IgAN.[2] A full listing of the 100+ IgAN clinical trials can be found at[3] **clinicaltrials.gov.**

Potential New Diagnostic & Prognostic Markers

In Blood:

Serum levels of galactose-deficient IgA1 (Gd-IgA1) protein may serve as a diagnostic test, as they may be significantly elevated long before IgAN diagnosis.[1]

In Urine:

Noninvasive tests for IgAN through urinary proteomics may detect a subset of mesangial immune complexes, or Gd-IgA1 within immune complexes.[1]

Genetic:

A genome-wide association study (GWAS) of "sporadic IgAN identified five novel genetic variants with relatively strong protective effects against IgAN."[1]

References
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2. KDIGO 2021 Clinical Practice Guideline. https://www.kidney-international.org/article/S0085-2538(21)00562-7/fulltext/ Published October 01, 2021.
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4. Xu L et al. Mod Pathol. 2010;23:1241-1250.
5. Perše M, Večerić-Haler Ž. Int J Mol Sci. 2019;20:6199.
6. Lai et al. Nat Rev Dis Primers. 2016;2:16001.

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