Immunoglobulin A nephropathy was first described by Berger and Hinglais in 1968 in Paris.
Incidence

- Incidence rate: 2.5% in 100,000 population
- Higher incidence in Eastern Asian population (40% renal biopsy in primary GN in China)
- Lower incidence in Black population
- 15-20% progress to ESRD in 10 years and 20-40% in 20 years.
Introduction

- It has clinical manifestation from microscopic hematuria to RPGN.

- It is a systemic involvement and kidney is as innocent bystander:
  1. It recurs after renal Tx.
  2. The IgA deposition clears in glomeruli in donors with subclinical IgA nephropathy.

Floege J 2004, Semin Nephrol
First Hit
Poorly Glycosylated IgA1
Is abnormal IgA glycosylation sufficient for IgAN onset?

- In a cohort of 89 IgAN patients and 266 of their relatives. High Gd-IgA1 levels were observed in all 5 available patients with familial IgAN, in 21 of 45 (47%) of their at-risk relatives and in only 1 of 19 (5%) of unrelated individuals who married into the family.

Gharavi et al JASN 2008
Second Hit: Anti IgA1 Antibody formation

- Some viruses and bacteria express *N-acetylgalactosamine* on their cell surfaces; an infection with such microbes may facilitate synthesis of anti-glycan antibodies that cross-react with galactose-deficient IgA1.
- It should be polymeric IgA
- The circulating galactose deficient IgA1 in patients is almost entirely coupled with the IgA1 or IgG isotypes.
- One pathogenic consequence of forming such a complex is the impaired hepatic catabolism of IgA1.
IgA Receptors

CD 89 is the only receptor which exclusively binds IgA.
In IgAN pathogenesis two IgA-R expressing components have been implicated:
1- Mesangial cells which involved in kidney injury
2- Myeloid cells (modulate extent of inflammation)

Zhang et al, Transplant research 2015
Role of Complement in IgA nephropathy

**Hit 1:** Increased circulating galactose-deficient IgA1

**Hit 2:** Production of unique antiglycan antibodies

Activation in formation of C3 participates in the formation of pathogenic immune complexes

**Hit 3:** Formation of pathogenic IgA1-containing circulating immune complexes

**Hit 4:** Mesangial deposition and mesangial cells activation leading to glomerular injury

Mesangial cells have an active role in complement activation

Lectin and alternative pathways are activated and contribute to tissue injury

Maillard, Jasn 2015
Platelet derived growth Factor

- PDGF is one of the best-characterized growth factor systems in renal disease.
- They are four isoforms: A, B, C, D
- B and D isoform are more active cause of kidney inflammation.
- Central mediators of membranoprolifeartive disease and secondary tubulointerstitial damage.
- Anti-PDGF interventions can prevent important long-term sequelae in experimental models of renal disease

Floeg JASN 2008
Podocytopenia and disease severity in IgA nephropathy

KEVIN V. LEMLEY, RICHARD A. LAFAYETTE, MASSY SAFAI, GERALDINE DERBY,
KRISTINA BLOUCH, ADDY SQUARER, and BRYAN D. MYERS

- Loss of podocytes is central pathogenetic step in development of glomerular and ultimately renal scarring.
- Threshold podocyte number of about 250 cells is threshold for worsening of kidney injury.
- There was no correlation to mesangial and endothelial cell number to indices of injury.
1. Increased circulating levels of Gd-IgA1
   - Genetic predisposition
   - Mis-trafficking of B cells from mucosal to systemic sites

2. Production of Anti-IgA1 antibodies (IgA or IgG)
   - Genetic predisposition, HLA haplotype
   - Molecular mimicry
   - Viral infection
   - Food antigens

3a. Immune complexes form in the circulation
3b. Immune complexes form in situ

4. Immune complexes in the mesangium cause local immune activation & injury
   - Complement activation
   - Cytokine/chemokine release
   - Matrix production
   - Mesangial proliferation
   - Glomerular sclerosis
   - Interstitial fibrosis
Blood vessel

- Anti-glycan IgG or IgA1 autoantibodies → Galactose-deficient IgA1 → IgA1 immune complex

secretion

B cells

- Genetic polymorphism (e.g., C1GALT1)
- Susceptibility loci (e.g., HLA)
- Local pathogen diversity (e.g., helminth)

deposition

Mesangial cells

- Local inflammation
- Proliferation
- Extracellular matrix expansion

Kidney failure
Proposed pathways involved in the mesangial deposition of IgA1 in IgA nephropathy—a multihit mechanism

Genes in IgA nephropathy

• Abnormal serum levels of galactose-deficient in 47% and 25% of the first-degree relatives of patients with familial and sporadic IgA nephropathy.
• A white European ancestry study showed an association with MHC in the DQ locus*.
• Chinese and Europeans identified 7 susceptibility loci: Three on chromosome 6p21 in the MHC Chromosome 1q32 in CFH Chromosome 22q12.**

Berthoux JASN 2012, Gharavi Nat Gene 2011,
<table>
<thead>
<tr>
<th>Genetic locus</th>
<th>Genes</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>6q21</td>
<td>HLA-DRB1, HLA-DQA1 and HLA-DQB1, PSMB8/9 and TAP/2</td>
<td>Class II major histocompatibility complex, Regulators for antigen processing and presentation</td>
</tr>
<tr>
<td>1q32</td>
<td>CFHR1/3</td>
<td>Modulators for complement activation and inflammation</td>
</tr>
<tr>
<td>22q12</td>
<td>HORMAD2</td>
<td>Unknown</td>
</tr>
<tr>
<td>17q13</td>
<td>TNFSF13</td>
<td>Important for B cell development and IgA isotype switching</td>
</tr>
<tr>
<td>8p23</td>
<td>DEFA1</td>
<td>Encoding $\alpha$-defensins as a type of endogenous antimicrobial mediators</td>
</tr>
<tr>
<td>1p13</td>
<td>VAV3</td>
<td>Regulators for lymphocyte development and antigen presentation</td>
</tr>
<tr>
<td>9q34</td>
<td>CARD9</td>
<td>Participant in antigen-induced signalosome formation (CARD9-BCL10-MALT1) and NF-$\kappa$B activation</td>
</tr>
<tr>
<td>16p11</td>
<td>ITGAM and ITGAX</td>
<td>Mediators for immune cell adhesion and phagocytosis</td>
</tr>
</tbody>
</table>
World-wide genetic risk for IgA nephropathy
Red areas shows high risk and green areas low risk
The intestine - renal connection in IgA nephropathy

• A gross hematuria follows mucosal infection
• Association of celiac disease and dermatitis herpetiformis with IgA nephropathy.
• There are frequent case report of IBD and IgA nephropathy.
• High association of IgA against gliadin, bovine serum albumin and lactoglobulin in 20-30% of cases

Coppo, NDT 2015
Gluten exacerbates IgA nephropathy in humanized mice through gliadin–CD89 interaction

- Mice on a gluten-free diet lacked IgA1-sCD89 complexes in serum and kidney eluates.
- A gluten diet exacerbated intestinal IgA1 secretion, inflammation, and villous atrophy, and increased serum IgA1 anti-gliadin antibodies, which correlated with proteinuria in mice and patients.
- Early treatment of humanized mice with a gluten-free diet prevented mesangial IgA1 deposits and hematuria.
Genetic factors for control of intestinal barrier & MALT response

Epigenetic factors: exposure to alimentary components or microbes products (LPS) triggering the immune response

Inductive site: intestinal microbiota

Immunomodulation of MALT response, increased antigen absorption and activation of inflammation pathways

IgA mesangial deposits: IgAN

Complement activation
- IgG anti GalNac IgA1
- Galactose deficient IgA1 (GalNacIgA1)

Systemic distribution
Clinical course of IgA nephropathy
Ungalactosylated IgA1 | Core antigen of the pathogenic IgA1 immune complex; lead to activation of mesangial cells and glomerulonephritis

Gycan specific IgG | Form glycan-dependent complex with galactosedeficient IgA1; alanine to serine substitution in complementarity-determining region 3 of IgG heavy chain; able to differentiate IgA nephropathy patients from controls with 88% specificity and 95% sensitivity

Uric acid | Correlate with great prevalence of glomerular sclerosis, aggravated tubulointerstitial and vascular damage, and high frequency of end-stage renal disease

Soluble CD89 | Low levels in patients with disease progression compared with those without disease progression

Activated C3 | Upregulated level in 30% of patients; correlated with deteriorating renal function

Oxidative protein products | Higher levels in patients than healthy controls; correlate with proteinuria
### Potential clinical biomarkers for IgA nephropathy in Urine

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Associated with histologic progression of the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 6</td>
<td>Associated with histologic progression of the disease</td>
</tr>
<tr>
<td>Epidermal growth factor (EGF) and monocyte chemotactic peptide-1 (MCP-1)</td>
<td>An EGF/MCP-1 ratio greater than 366.66 extends renal survival to at least 84 months in a cohort of 44 patients</td>
</tr>
<tr>
<td>a1/b2-Microglobulin</td>
<td>Correlate with serum creatinine and total proteinuria</td>
</tr>
<tr>
<td>Mannose binding lecitin</td>
<td>Significantly higher in patients than healthy controls; associate with histopathologic aggravations, such as mesangial hypercellularity, tubular atrophy, interstitial fibrosis</td>
</tr>
<tr>
<td>Proteomic pattern</td>
<td>High-throughput characterization of 2000 polypeptide using capillary electrophoreses on-line coupled to a mass spectrometer</td>
</tr>
<tr>
<td>Micro RNA profile</td>
<td>Sequencing identified microRNA profiling that is specific to IgA nephropathy</td>
</tr>
</tbody>
</table>
The 10 most significant differentially expressed proteins (upregulated or downregulated) are demonstrated in table as the valuable diagnostic biomarkers involved in pathogenesis of IgAN.

<table>
<thead>
<tr>
<th>Protein ID</th>
<th>Protein Name</th>
<th>Biological Process</th>
<th>Change</th>
<th>Change Magnitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD44</td>
<td>CD44 antigen</td>
<td>Positive regulation of peptidyl-serine, tyrosin phosphorylation, negative regulation of apoptotic process</td>
<td>Downregulation</td>
<td>10.6</td>
</tr>
<tr>
<td>APOD</td>
<td>Apolipoprotein D</td>
<td>Lipid metabolic process, response to reactive oxygen species</td>
<td>Downregulation</td>
<td>6.8</td>
</tr>
<tr>
<td>P3IP1</td>
<td>Phosphoinositide-3-kinase-interacting protein 1</td>
<td>Negative regulation of phosphatidylinositol 3-kinase cascade</td>
<td>Downregulation</td>
<td>3.9</td>
</tr>
<tr>
<td>GP2</td>
<td>Pancreatic secretory granule membrane major glycoprotein 2</td>
<td>Antigen transcytosis by M cells in mucosal-associated lymphoid tissue</td>
<td>Downregulation</td>
<td>3.7</td>
</tr>
<tr>
<td>VASN</td>
<td>Vasohin</td>
<td>Inhibitor of transforming growth factor-β signaling</td>
<td>Downregulation</td>
<td>3.7</td>
</tr>
<tr>
<td>KLK1</td>
<td>Kallikrein-1</td>
<td>Proteolysis</td>
<td>Downregulation</td>
<td>3.6</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor</td>
<td>Innate immune response, positive regulation of cell proliferation</td>
<td>Downregulation</td>
<td>3.1</td>
</tr>
<tr>
<td>PVR</td>
<td>Poliovirus receptor</td>
<td>Cell-cell adhesion, susceptibility to T-cell mediated cytotoxicity, susceptibility to natural killer cell-mediated cytotoxicity</td>
<td>Downregulation</td>
<td>3.1</td>
</tr>
<tr>
<td>SHSA5</td>
<td>Protein shisa-5</td>
<td>Induction of apoptosis, positive regulation of I-kappaB kinase, NF-kappaB cascade</td>
<td>Downregulation</td>
<td>3.1</td>
</tr>
<tr>
<td>CLM9</td>
<td>CMRF35-like molecule 9</td>
<td>Immunity</td>
<td>Downregulation</td>
<td>2.9</td>
</tr>
<tr>
<td>PCDH1</td>
<td>Protocadherin-1</td>
<td>Cell-cell signaling</td>
<td>Upregulation</td>
<td>8.9</td>
</tr>
<tr>
<td>A1BG</td>
<td>Alpha-1B-glycoprotein</td>
<td>Immune system</td>
<td>Upregulation</td>
<td>5.5</td>
</tr>
<tr>
<td>UTER</td>
<td>Uteroglobin</td>
<td>Regulation of inflammatory response</td>
<td>Upregulation</td>
<td>3.5</td>
</tr>
<tr>
<td>DPP4</td>
<td>Dipeptidyl peptidase 4</td>
<td>Positive regulation of cell proliferation, T cell activation</td>
<td>Upregulation</td>
<td>3.5</td>
</tr>
<tr>
<td>IGH-G2</td>
<td>Ig gamma-2 chain C region</td>
<td>Complement activation, classical pathway</td>
<td>Upregulation</td>
<td>2.9</td>
</tr>
<tr>
<td>SLA5F</td>
<td>SLAM family member 5 (CD84)</td>
<td>Blood coagulation, leukocyte migration</td>
<td>Upregulation</td>
<td>2.7</td>
</tr>
<tr>
<td>A2AP</td>
<td>Alpha-2-antiplasmin</td>
<td>Positive regulation of cell differentiation, positive regulation of ERK1 and ERK2 cascade</td>
<td>Upregulation</td>
<td>2.0</td>
</tr>
<tr>
<td>ABP1</td>
<td>Aminoacyl-tRNA synthetase</td>
<td>Amino metabolic process, response to drug</td>
<td>Upregulation</td>
<td>2.0</td>
</tr>
<tr>
<td>6PGL</td>
<td>6-Phosphogluconolactone</td>
<td>Pentose-phosphate shunt, oxidative branch</td>
<td>Upregulation</td>
<td>1.9</td>
</tr>
<tr>
<td>NHLC3</td>
<td>NHL repeat-containing protein 3</td>
<td>Possibility of involvement in a variety of enzymatic processes, including protein modification through ubiquitination</td>
<td>Upregulation</td>
<td>1.9</td>
</tr>
</tbody>
</table>
What is the function of Micro RNA?

MicroRNA is cut from a pre-mRNA and binds with proteins to form RISC.

Complementary base pairing between RNAs allows RISC to bind to mRNA.

Translation is inhibited. or The mRNA is degraded.
Of the 401 miRNAs identified in samples from patients with IgA nephropathy. Additionally, 55 novel miRNAs were also identified, seven of which were detected in the IgA nephropathy group and 49 in the control group.

Szeto et al. Nature reviews 2014
Micro RNA in pathogenesis of IgA nephropathy
## Potential Application of mRNA in IgA Nephropathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients ($n$)</th>
<th>miRNA</th>
<th>miRNA Levels</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al. (2011)</td>
<td>43</td>
<td>miR-146a, miR-155</td>
<td>↑↑</td>
<td>Proteinuria, Proteinuria</td>
</tr>
<tr>
<td>Wang et al. (2012)</td>
<td>43</td>
<td>miR-21, miR-29b, miR-29c</td>
<td>No difference</td>
<td>Baseline GFR, Proteinuria, Baseline GFR and proteinuria, Glomerulosclerosis</td>
</tr>
<tr>
<td>Szeto et al. (2012)</td>
<td>17</td>
<td>miR-17</td>
<td>↑</td>
<td>Baseline GFR</td>
</tr>
<tr>
<td>Wang et al. (2010)</td>
<td>43</td>
<td>miR-200a, miR-200b, miR-429</td>
<td>↓↓</td>
<td>Proteinuria, Baseline GFR, proteinuria and declining renal function, Baseline GFR and proteinuria</td>
</tr>
</tbody>
</table>

*Healthy. ‡Consistent with findings in renal nephrectomy specimens. ‡‡17 patients with diabetic glomerulosclerosis and 22 with hypertensive nephrosclerosis. Abbreviations: ↓, decrease; ↑, increase; GFR, glomerular filtration rate; miRNA, microRNA.
Conclusion

- IgA nephropathy can be considered an autoimmune disease.
- Advances in understanding the molecular basis of the pathogenesis may lead to earlier diagnosis, better monitoring of the clinical course or response to treatment, and, ultimately, targeted therapy.