The gut-kidney axis in IgA nephropathy

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IgA nephropathy (IgAN):
a disease originated from mucosal immunity dysregulation

IgA: most prevalent Ig in mucosal secretions.
Deposited IgA are polymeric (of mucosal origins)
The tonsil-renal axis in IgAN

IgA

IgA immune complexes

oral immunity activation

Mesangial deposits

Mesangial deposits

Oral bacteria

Oral immunity activation

IgA immune complexes

Mesangial deposits
A potential treatment of IgAN: TONSILLECTOMY

Aimed at removing a source of pathogens reducing Mucosal Associated Lymphoid Tissue (MALT) decreasing polimeric mucosal IgA synthesis.

In Asia, benefits of tonsillectomy have been reported mostly in association with steroids.

In Western Countries no benefits of tonsillectomy in IgAN has been proven.
GALT (gut associated lymphoid tissue) intestinal immunity in IgAN: pathogenetical role and target for treatment
The gut–kidney axis in IgA nephropathy: role of microbiota and diet on genetic predisposition

Rosanna Coppo
Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens

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most loci associated with IgAN are also associated with risk of inflammatory bowel diseases or maintenance of the intestinal barrier in response to intestinal pathogens
INTESTINAL MICROBIOTA

$10^{14}$ micro-organisms, >500 different species

- **Stomach**: $10^2$ to $10^3$
- **Duodenum**: < $10^{4-5}$
- **Jejunum**: $10^3$ to $10^7$
- **Ileum**: $10^9$ to $10^{12}$
- **Colon with appendix**

**Lactobacilli**

**Enterobacteria**
- **Enterococcus**
- **Faecalis**

**Bacteroides**

**Bifidobacteria**

**Peptococcus**

**Peptostreptococcus**

**Ruminococcus**

**Clostridia**

**Lactobacilli**
the gut microbiota shapes intestinal MALT in health and disease

Modulated by diet, chemicals, host genes

The gut-kidney axis in IgA nephropathy: the role intestinal dysbiosis

Effect on maturation of lymphoid tissue with local and systemic modulation of innate and adaptive immunity
Pilot study in 34 IgAN patients:
different microbiota in progressive IgAN
Specific ligands for each TLR

Medzhitov, Nat Rev Immunol
The LPS binding receptor CD14 and TLR4 initiate the response to microbes and influence various chronic inflammatory conditions.

Association of the CD14 gene –159C polymorphism with progression of IgA nephropathy

H-J Yoon, J H Shin, S H Yang, D-W Chae, H Kim, D-S Lee, H L Kim, S Kim, J S Lee, Y S Kim

Table 4 Predictors for the progression of renal disease by the Cox proportional hazards analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>p value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria* †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3000 mg/day</td>
<td>4.0</td>
<td>0.0004</td>
<td>1.8 to 8.5</td>
</tr>
<tr>
<td>1000–3000 mg/day</td>
<td>1.6</td>
<td>0.28</td>
<td>0.7 to 3.9</td>
</tr>
<tr>
<td>Genotype of CD14†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>3.2</td>
<td>0.025</td>
<td>1.2 to 8.8</td>
</tr>
<tr>
<td>TC</td>
<td>1.7</td>
<td>0.21</td>
<td>0.7 to 4.1</td>
</tr>
<tr>
<td>Creatinine* §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.4 mg/dl</td>
<td>3.6</td>
<td>0.0015</td>
<td>1.9 to 5.8</td>
</tr>
</tbody>
</table>

*At the time of histological diagnosis. †Compared with proteinuria <1000 mg/day. ‡Compared with 11 genotype. §Compared with ≤1.4 mg/dl.

Figure 1 Probability of patients with IgAN not reaching doubling of baseline serum creatinine according to the genotypes of CD14 (Kaplan-Meier analysis, p=0.03 by log rank test).

a genetic modification of the membrane receptor for LPS may modulate the inflammatory response and the progression of IgAN
Toll-like receptor 4 expression is increased in circulating mononuclear cells of patients with immunoglobulin A nephropathy

Significant correlation in IgAN between TLR4 expression in PBMC and proteinuria

Pediatr Nephrol.
2014 Sep;29(9):1545-51.
External suppression causes the low expression of the Cosmc gene in IgA nephropathy

Wei Qin¹, Xiang Zhong¹, Jun Ming Fan, Ying Juan Zhang, Xian Rong Liu and Xing Yi Ma

Department of Medicine, Division of Nephrology, West China Hospital of Sichuan University, Chengdu, Sichuan, People’s Republic of China
The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease
Hans-Joachim Anders³, Kirstin Andersen¹ and Bärbel Stecher²

LPS Endotoxin from Gram− intestinal germ dysbiosis as a trigger for intestinal immunity response in IgAN
The gut-kidney axis in IgA nephropathy

High intestinal permeability in children and adults with IgAN (Davin & Nagy 1985)

High levels of IgA anti alimentary antigens in IgAN

Case reports of association between celiac disease and IgAN
Gluten-induced experimental IgA glomerulopathy

Figure 2. Semiquantitative analysis of IgA immune deposits in BALB/c mice after 14 wk of different diets.
Spontaneous IgAN mouse model expressing human IgA1 and CD89 (double transgenic alpha1KI-CD89Tg mice)
Gluten free diet for 3 generations

reduction in
• IgA1 mesangial deposition
• glomerular inflammatory-cell infiltration
• IgA1–sCD89 complexes in serum and kidney eluates
• hematuria

Gluten diet for 30 days

Intestinal injury
(inflammation and villous atrophy)

Increase in
• IgA1–sCD89 complexes
• IgA1 mesangial deposition
• IgA1 antigliadin Ab
• correlation with proteinuria
Correlation between anti-gliadin antibodies and proteinuria in experimental alpha1KI-CD89 mice on gluten diet
Early gluten-free diet abolishes IgAN development, hematuria and proteinuria in alpha1KI-CD89Tg mice
MAY GLUTEN-FREE DIET REDUCE THE LEVELS OF IgA IMMUNE COMPLEXES IN PRIMARY IgA NEPHROPATHY?

R Coppo, B Basolo, C Rollino, D Roccatello, G Martina, A Amore, *G Bongiorno, G Piccoli

University of Turin Nephrology and Dialysis Unit, *Dietetic Service, S Giovanni Hospital, Turin, Italy

![Bar graph showing effects of a gluten-free diet on IgAIC levels in IgAGN patients.](image)

Figure 4. Effects of a gluten-free diet on the levels of IgAIC in IgAGN patients.

Dietary Antigens and Primary Immunoglobulin A Nephropathy

Conclusion of early studies (30 years ago) to target gluten for treating patients with IgAN

- **Gluten-free diet** was of some benefit in our exploratory study (29 patients without evidence of celiac disease) with reduction of proteinuria, but without effect on renal function decline after 4 years.

- The gluten-free diet is difficult to be followed by patients without GI symptoms

A next RCT testing gluten-free diet in IgAN?
Celiac disease

1. Increased intestinal permeability
2. Deamidation of gliadin by TG2
3. CD4+ T cell response
4. Th1 response
5. Th2 response
6. Production of antibodies to gliadin and TG2
7. Celiac AGA Anti TG2
• In IgAN: increased risk of celiac disease (4% vs 0.5-1%)
• In celiac disease increased risk of IgAN (0.26% vs 0.08%)

• Anti-gliadin AGA in 3-70% IgAN
  Negative anti-endomisium /tissue transglutaminase antibodies in IgAN
• No association with HLA DQ2-DQ8

In inflammatory bowel diseases IgAN is more frequent than other glomerular diseases (24% vs 8%)

In IgAN
• Duodenal inflammation of varying degree
• Ongoing small bowel inflammation with signs of stress, despite normal morphology.
• Increase in intestinal permeability
Can we target the GALT to treat IgAN?
Factors controlling the switch to IgA:
TNF family members
B cell activator factor
BAFF (BlyS)
APRIL

Critical role for IgA production
IgAN in transgenic mice hyperexpressing BAFF

MICROBIICAL AGENTS

IFN γ and α

TLRs

Dendritic cell

BAFF Blys

BR3 TACI BMCA

B cell

B cell

B cell

B cell

IgA
Mice overexpressing BAFF develop a commensal flora–dependent, IgA-associated nephropathy

Douglas D. McCarthy, Julie Kujawa, Cheryl Wilson, Adrian Papandile, Uriana Poreci,

PATHOGENESIS of IgAN

Genes

B cell activity and IgA synthesis

Intestinal immunity (GALT)

Diet
Clinical data

Experimental evidence

BAFF promotes proliferation of mesangial cells

Serum BAFF is increased in IgAN patients
Clinica

Clinical Trials. Gov

NCT02062684  BRIGHT-SC: Blisibimod Response in IgA Nephropathy Following At-Home Treatment by Subcutaneous Administration

- Recruiting
- Interventions
  - drug: Blisibimod;
  - drug: Placebo

Target: BAFF

NCT02808429  Safety and Efficacy Study of Atacicept 25 mg to treat IgAN

- Recruiting
- Interventions
  - drug: Atacicept 25 mg
  - drug: Placebo

Target: TACI
Activation of intestinal immunity in IgAN: subclinical intestinal mucosa inflammation leading to IgA dysregulated synthesis

Sites of mucosal B cell induction: lower ileum and ascending colon with high density of Peyer’s patches.

target release formulation of the glucocorticoid budesonide: coated starch capsules for site-specific drug delivery at the ileo-cecal junction
Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Bengt C Fellstrom, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jurgen Hoege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren Sørensen, Vladimír Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators

www.thelancet.com Published online March 28, 2017 http://dx.doi.o
Genetic factors for the control of intestinal barrier & GALT response

Epigenetic factors: exposure to alimentary components (gluten) and/or intestinal microbiota dysbiosis and/or intestinal microbiota dysbiosis microbe products (LPS)

Increased intestinal permeability

GALT response subclinical inflammation

IgA mesangial deposits IgAN

Inflammatory mediators

IgALC

IgG anti deGal IgA1

Galactose deficient IgA1 (deGal IgA1)

The gut-kidney connection in IgA nephropathy

Coppo R
Ped Nephrol 2018
Muchas gracias

Thank you for your attention
50 years later

15th International Symposium on IgANephropathy

IiGANN 2018

September 27th-29th, 2018 - The Brick Hotel, Buenos Aires, Argentina

https://www.iigann2018.com