Pathogenesis of IgA-Nephropathy: *What is new?*

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A few basic facts about IgA nephropathy …

510 Japanese zero-hour allograft biopsies:

1.6% of the kidneys exhibit IgA nephropathy

(i.e. glom. IgA + C3 deposits + mesangioproliferative changes)

Suzuki K et al. Kidney Int. 2003;63:2286

72 Chinese patients with isolated microhematuria due to IgAN. After 12 years of follow-up:

- **Proteinuria >1 g/d in 30%**
- **Renal failure in 10%**
- **Resolution of disease in 14%**

Szeto et al., Am J Med 2001; 110: 434

IgAN usually is a benign disease (at least in Asia)**. Most patients do not need us except for a few….**

Central patho-genetic steps in progressive IgAN

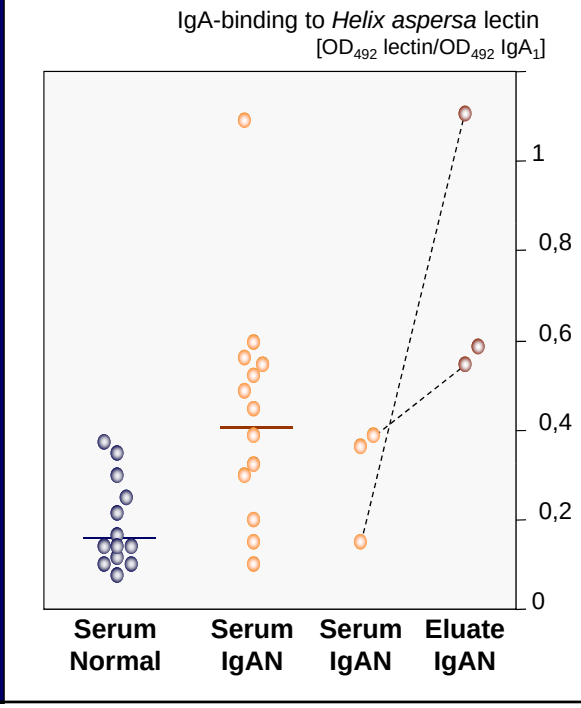
Modifiers (genetic background, generic progression factors)

Increased occurrence of IgA1 with poor galacto-sylation in the circulation

Mesangial IgA1 in IgA-nephropathy exhibits aberrant O-glycosylation: Observations in three patients

Alice C. Allen, Elaine M. Bailey, Paul E.C. Brenchley, Katherine S. Buck, Jonathan Barratt, John Feehally

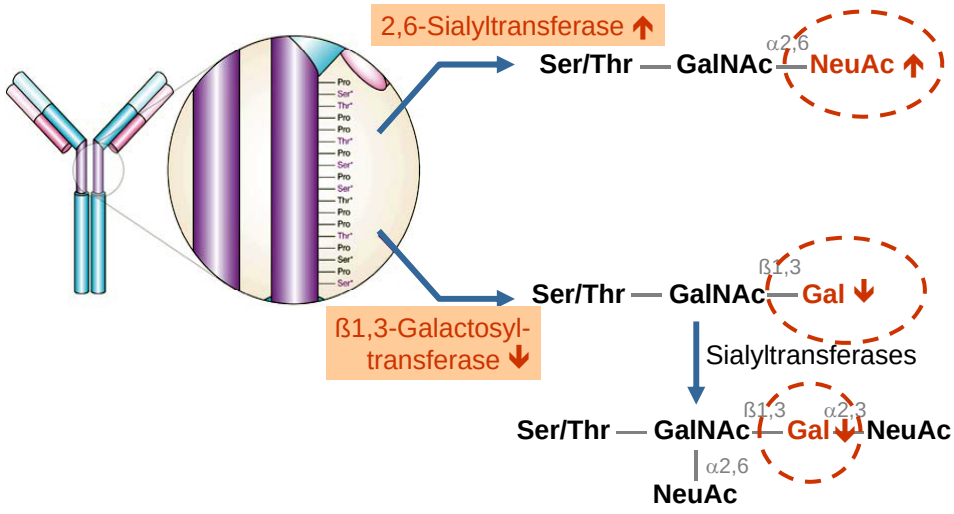
Kidney International 2001; 60: 969-973



Suzuki H et al, JCI 2008

Immortalized IgA-producing B-cells of IgAN patients release poorly galactosylated dimeric IgA

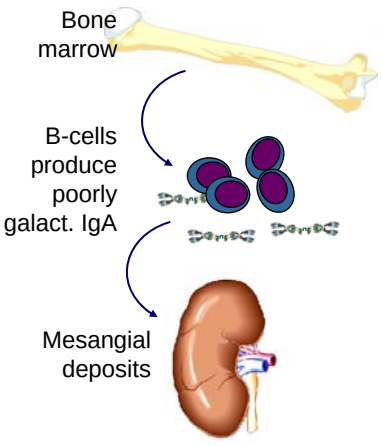
Enzyme activites in immortalized lymphocytes from IgAN patients



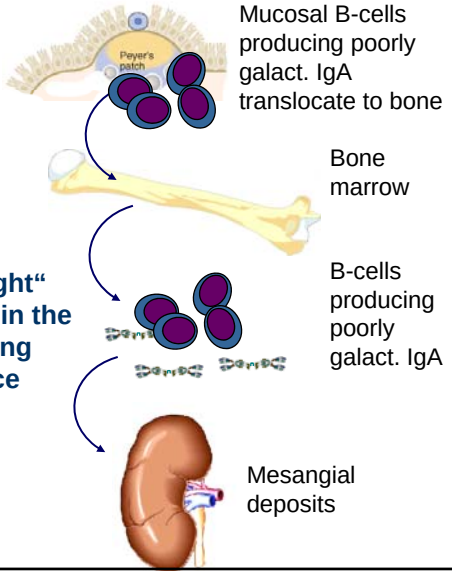
Barratt J, Eitner F, Feehally J, Floege J, NDT 2009

Poorly galactosylated IgA in IgAN: What is the cause?

„Wrong“ IgA in serum



„Right“ IgA in the wrong place



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Increased occurrence of IgA1 with poor galacto-sylation in the circulation

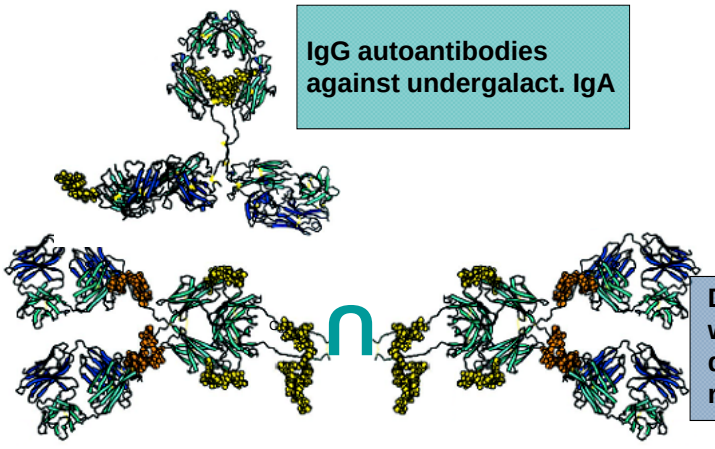
Generation of IgG-antibodies against poorly galactosylated IgA1

Elimination of causal infections or antigens

Tomana et al. J Clin Invest 1999; 104: 73

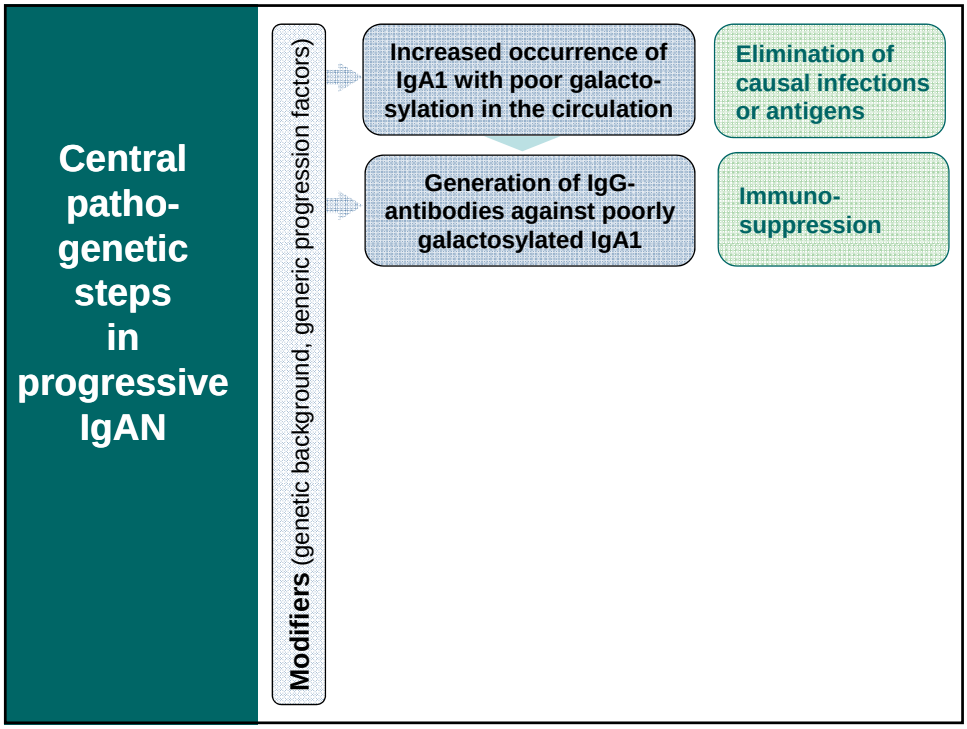
Suzuki H et al, J Clin Invest 2009, 119: 1668-1677

IgAN patients exhibit IgG autoantibodies against undergalactosylated IgA_1 in serum



IgG autoantibodies against undergalact. IgA

Dimeric IgA with galactose deficient hinge region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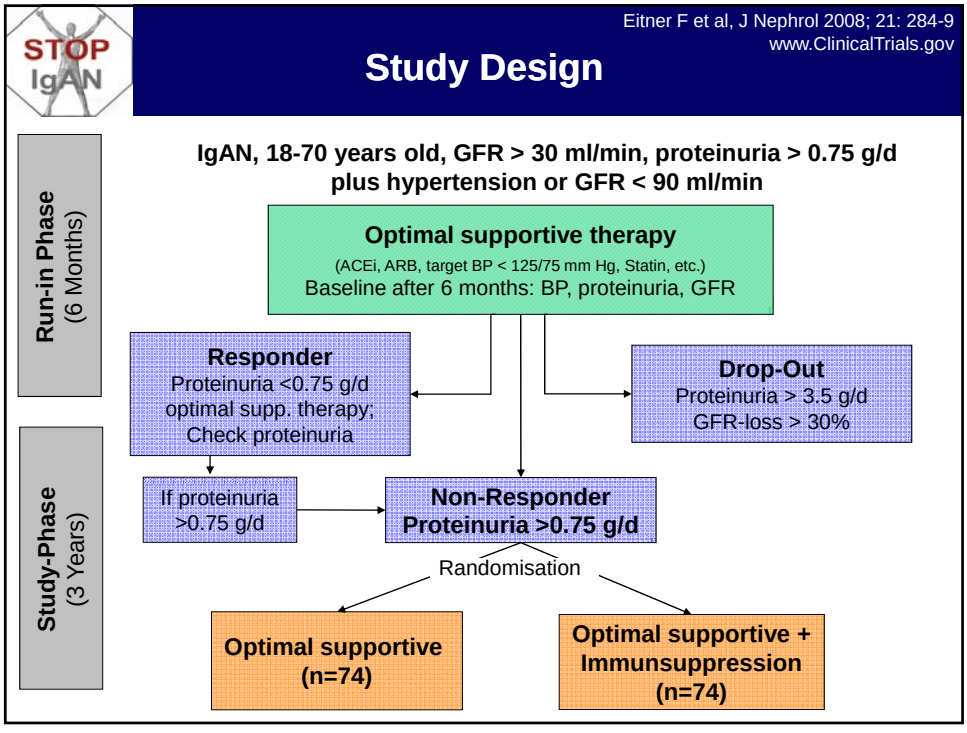
Generation of IgG-antibodies against poorly galactosylated IgA1
Elimination of causal infections or antigens
Immuno-suppression


STOP IgAN
Eitner F et al, J Nephrol 2008; 21: 284-9
www.ClinicalTrials.gov
Study Design
IgAN, 18-70 years old, GFR > 30 ml/min, proteinuria > 0.75 g/d
plus hypertension or GFR < 90 ml/min
Run-in Phase (6 Months)
Optimal supportive therapy
(ACEi, ARB, target BP < 125/75 mm Hg, Statin, etc.)
Baseline after 6 months: BP, proteinuria, GFR
Responder
Proteinuria <0.75 g/d
optimal supp. therapy;
Check proteinuria
Drop-Out
Proteinuria > 3.5 g/d
GFR-loss > 30%
Study-Phase (3 Years)
If proteinuria >0.75 g/d
Non-Responder
Proteinuria >0.75 g/d
Randomisation
Optimal supportive (n=74)
Optimal supportive + Immunsuppression (n=74)

Pozzi C et al. J Am Soc Nephrol 2010

Therapy of IgA-Nephropathy
- Combination Steroid + Azathioprine -

Steroid+Aza n=101

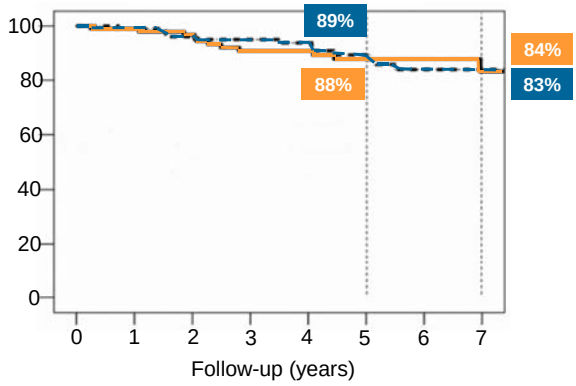
6 months „Pozzi“-scheme additionally azathioprine (1.5 mg/kg)

Steroid n=106

6 months „Pozzi“-scheme

Renal function

(% patients without 50% increase of s-creatinine)



- **No difference in proteinuria**
- **Markedly higher side effects of combination therapy**

Central patho-genetic steps in progressive IgAN

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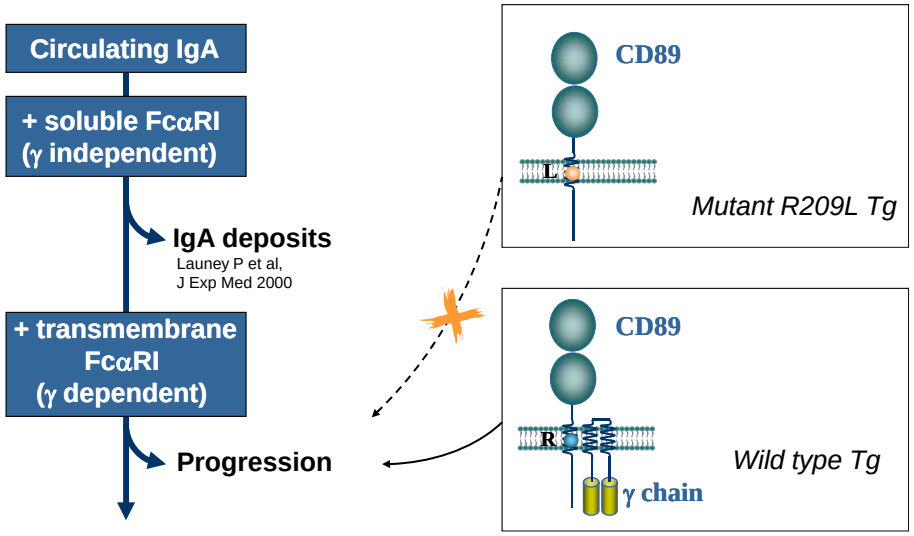
- Increased occurrence of IgA1 with poor galacto-sylation in the circulation
- Generation of IgG-antibodies against poorly galactosylated IgA1
- Mesangial deposition and/or formation of IgG-IgA1 immune complexes
- IgA receptors
- Complement activation

- Elimination of causal infections or antigens
- Immuno-suppression
- Removal of glomerular IgA

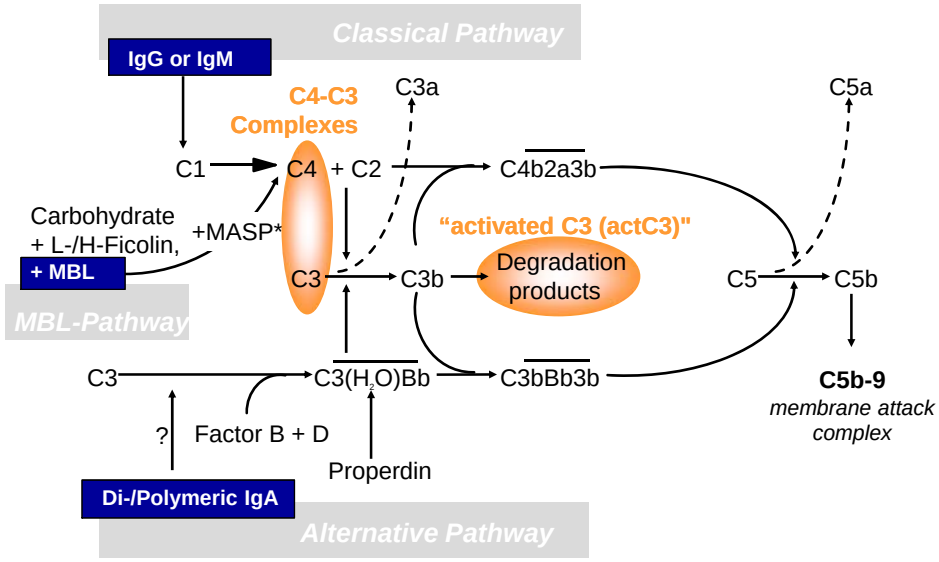
Kanamaru Y et al. J Immunol 2008; 180:2669-78

Role of Fcα Receptor I (CD89) Activating Pathway in the Progression of IgA Nephropathy

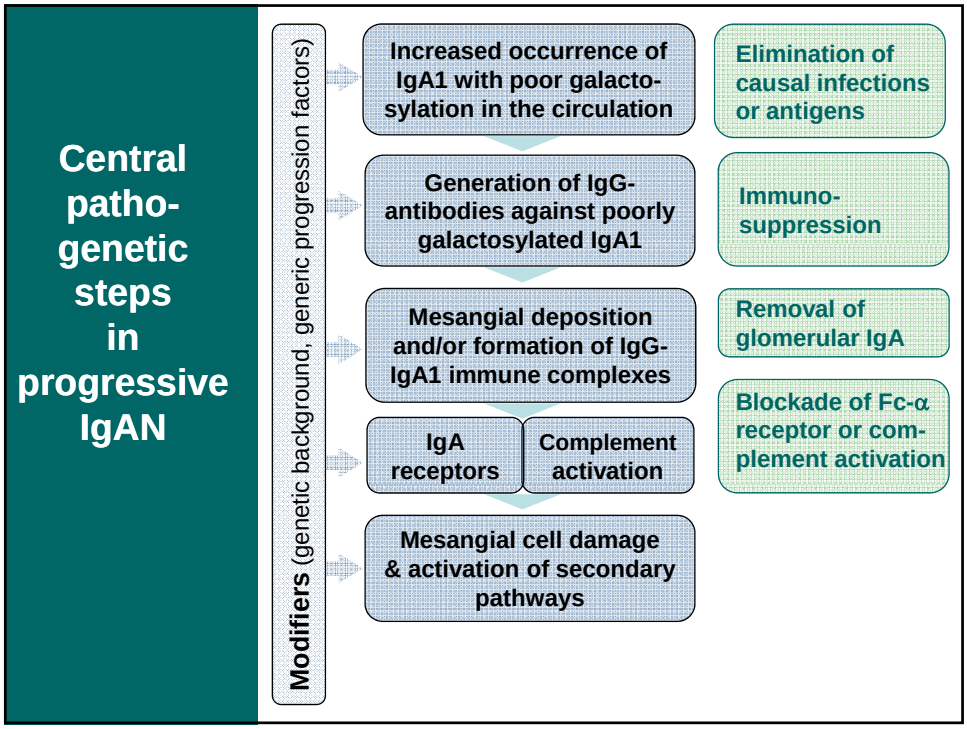


Zwirner et al., Kidney Int 1997; 51: 1257 — Roos A et al., JASN 2006; 17: 1724

Complement Activation in IgA Nephropathy



* - MBL associated serine protease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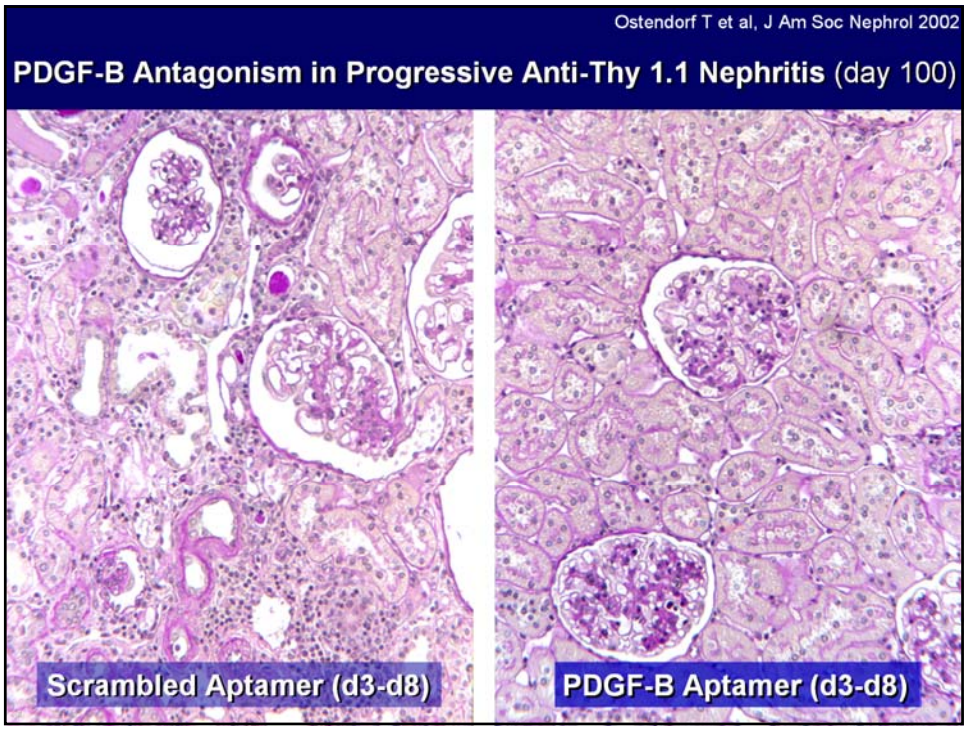
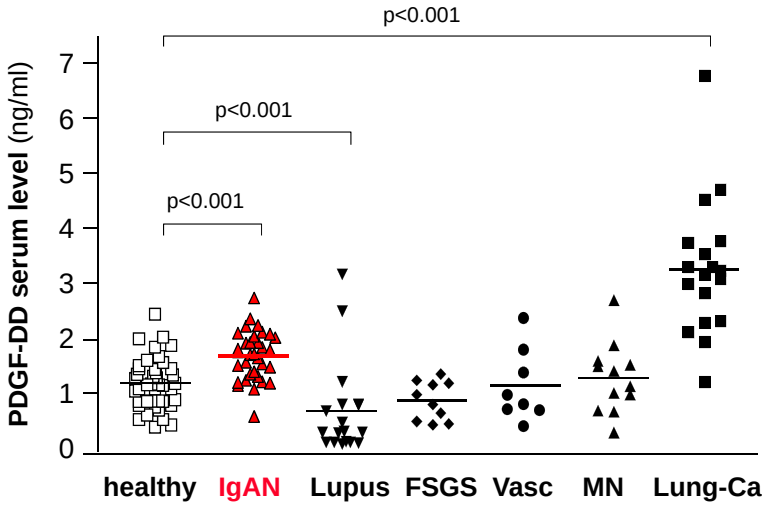
Generation of IgG-antibodies against poorly galactosylated IgA1
Mesangial deposition and/or formation of IgG-IgA1 immune complexes
IgA receptors
Complement activation
Mesangial cell damage & activation of secondary pathways
Elimination of causal infections or antigens
Immuno-suppression
Removal of glomerular IgA
Blockade of Fc-α receptor or com-plement activation


Ostendorf T et al, J Am Soc Nephrol 2002
PDGF-B Antagonism in Progressive Anti-Thy 1.1 Nephritis (day 100)
Scrambled Aptamer (d3-d8)
PDGF-B Aptamer (d3-d8)

Boor P et al, NDT 2009;24:2755-62

PDGF-DD serum levels are increased in IgAN patients



Vasc, vasculitis; MN, membranous nephropathy; Lung-Ca, lung carcinoma

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Modifiers (genetic background, generic progression factors)

- Increased occurrence of IgA1 with poor galacto-sylation in the circulation → Elimination of causal infections or antigens
- Generation of IgG-antibodies against poorly galactosylated IgA1 → Immuno-suppression
- Mesangial deposition and/or formation of IgG-IgA1 immune complexes → Removal of glomerular IgA
- IgA receptors; Complement activation → Blockade of Fc-α receptor or com-plement activation
- Mesangial cell damage & activation of secondary pathways → Growth factor antagonists etc.
- Glomerulosclerosis Tubulointerstitial fibrosis → Antifibrotic agents

Nat Rev Nephrol 2010 epub 14 Sept

Renal fibrosis: novel insights into mechanisms and therapeutic targets

Peter Boor, Tammo Ostendorf and Jürgen Floege

Abstract | Renal fibrosis is the common end point of virtually all progressive kidney diseases. Renal fibrosis should not be viewed as a simple and uniform 'scar', but rather as a dynamic system that involves extracellular matrix components and many, if not all, renal and infiltrating cell types. The involved cells exhibit enormous plasticity or phenotypic variability—a fact that we are only beginning to appreciate. Only a detailed understanding of the underlying mechanisms of renal fibrosis can facilitate the development of effective treatments. In this Review, we discuss the most recent advances in renal, or more specifically, tubulointerstitial fibrosis. Novel mechanisms as well as potential treatment targets based on different cell types are described. Problems that continue to plague the field are also discussed, including specific therapeutic targeting of the kidney, the development of improved diagnostic methods to assess renal fibrosis and the shortcomings of available animal models.