Pathogenesis of IgA Nephropathy

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IgA NEPHROPATHY

- How do the IgA mesangial deposits evolve and initiate immunopathogenetic events leading to renal injury ?

PATHOGENESIS OF IgAN

1. Familial or genetic influence
2. Dysregulation of immune response
3. Mucosal immunity
4. Abnormal IgA structure
5. Delayed clearance
6. Polymeric IgA deposition
7. Mesangial injury

Experimental models for IgAN

- IgA circulating immune complex
- Systemic immunization
- Oral mucosal immunization
- Viral infection
- Hepatobiliary dysfunction (Clearance defect)
- Spontaneous

GENETIC PREDISPOSITION

- Familial clustering of IgAN
- No positive or negative association of HLA antigens for diagnosis

Genetic influence

- HLA DQw7, DQA1b, DRw12 in sporadic or familial cases
- HLA B12, B27, Bw35, DR1, DR4, DQw7, DR12
- HLA-DQ gene polymorphism in European populations
- Polymorphism of Ig heavy chain switch region
- ACE gene polymorphism (D allele)
- Vmax/Km ratio of sodium-lithium countertransport

DYSREGULATION OF IgA PRODUCTION (Hyperresponders)

- Circulating IgA1-containing immune complex ↑
- Peripheral IgA-bearing lymphocytes ↑
- Production of IgA, IgG and/or IgM by B lymphocytes ↑
- Helper T cell (CD4) ↑ / Suppressor T cell (CD8) ↓
- Serum IgA levels ∞ % of CD4+, CD45RO+ cells
- CD4 (+) T cells bearing Fc receptor of IgA (Tα4) ↑
- Cytokines : IL-2, IL-4, IL-5, IL-6, IFNγ, TGFβIL-4, IL-5, and TGFβ induces the IgA isotype switch.

T cells and Cytokines

- Th1 cell secrete IL-2 and IFNγ.
  - Cell-mediated inflammatory reaction
  - Phagocytic cell function
  - --> Proliferative and progressive GN
- Th2 cell secrete IL-4, IL-5, IL-10 and IL-13.
  - Synthesis of antibodies
  - Inhibit several macrophage functions
  - --> Systemic autoimmunity

Heterogeneity of Th1/Th2 Cytokine expression in IgAN

- IgG1 & IgG3 codeposit (Th1)
- Crescentic IgAN: Th1 predominance
- Renal cytokines: both Th1/Th2
  - IL-4 expression
  - IFN γ expression
- IL-4 & IL-5 --> B cells
  - Abnormal glycosylation of IgA

MUCOSAL IMMUNITY

- Pharyngeal washings, tonsillar cells : More IgA
- Salivary IgA production after immunization with tetanus toxoid
- Antigens
  - Dietary antigens: Gluten, bovine albumin
  - Infectious antigen: CMV, herpesvirus, H. parainfluenzae, adenovirus
- Oral tolerance failure:
  - Persistent increased serum IgG & IgM

- Experimental IgAN induced by oral mucosal immunization --> mesangial deposition of immune complexes containing IgA

  Emancipator SN, et al
- Dietary antigens and primary IgAN

  A gluten free diet ⟶ antigliadin IgA Ab ↓
  IgA immune complexes ↓
  proteinuria ↓

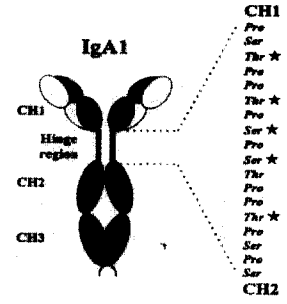
  Coppo R et al
- Exaggerated IgA response to mucosal H. pylori infection in IgAN *Barratt et al 1999*

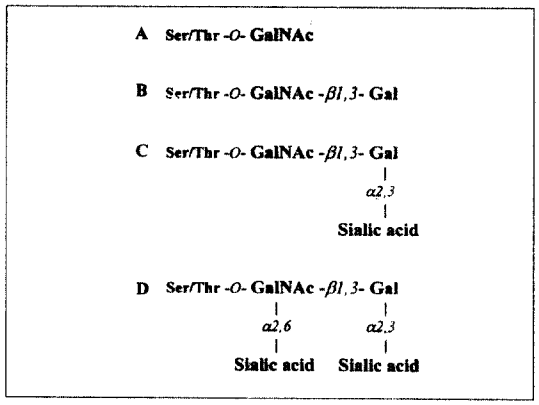
ABNORMAL IgA1 STRUCTURE

- Reduced terminal galactosylation of hinge region O-linked moieties
  - Not recognized in the feed-back mechanism
    - --> Augmented production
  - Affect interactions with receptors and ECM proteins
    - --> Failure of clearance of IgA1
    - Mesangial deposition

Allen AC et al *Tomana et al*

IgA1 has a unique glycosylated hinge possessing O-glycan side chains





- Decrease of Gal / GalNAc residues
  Increase in asialo-Galβ1,3GalNAc residue

  Hiki et al
- Increased terminal single GalNAc
  Fluorophore-assisted carbonic electrophoresis

  Allen et al, J Am Soc Nephrol 1999
- Circulating immune complexes in IgAN
  IgA1 with galactose-deficient hinge region (antigenic)
  and IgG for GalNAc residue in O-glycan

  Tomana et al, J Clin Invest 1999

- IgA1 self-aggregation &
  adhesion activities to ECM protein:
  Agalacto, asialo or naked > native IgA1
  –> Nonimmunologic formation of macro. IgA1
  Mesangial IgA1 deposition

  Kokubo et al, J Am Soc Nephrol 1998

Underglycosylation of IgA1
Neutral & Jakalin high affinity fractions
Macromolecular IgA1: Jakalin high affinity
Asialo-Galb1,3GalNAc chain: glomerulophilic

Hiki et al, J Am Soc Nephrol 1999

- Increased sialylation in polymeric IgA_1
  hinder clearance of p-IgA_1
  render p-IgA_1 more anionic
  –> selective glomerular deposition of p-IgA_1
- Reduced galactosylation in serum IgA and monomeric IgA_1 but not in p-IgA_1

Leung et al, J Lab Clin Med 1999

CLEARANCE

- Clearance of IgG-coated autologous RBC: prolonged
- Hepatic removal of macromolecular IgA: normal
- Increased FcαR1 occupation by IgA1 and
  decreased FcαR1 expression in blood phagocytic cells

MESANGIAL DEPOSITS OF IgA

- Predominantly IgA1 subclass (from circulation)
- Polymeric IgA
- J chain in some
- Secretory component of IgA : Uniformly negative
- Alternative pathway of complement and MAC
- IgG or IgM 3/4
- Immunoglobulin lambda light chain

PROPERTIES OF DEPOSITED IgA

- Antigenetic similarities between the circulating and the mesangial macromolecular IgA
- Eluting IgA from the kidney with IgAN : Significant increase of polymeric IgA peaks
- Polymeric IgA1 has a higher affinity to mesangial cell than monomeric IgA1
- Monomeric IgA protects glomerulus against polymeric IgA-IC in experimental IgAN
  : Deposited IgA is polymeric IgA1

Origin of Deposited IgA

Suggest mucosal origin:

- Higher proportion of polymeric IgA in secretions than in serum
- Higher proportion of plasma cells staining for polymeric IgA in mucosae than in bone marrow
- Microscopic hematuria shortly after an infection along a mucosal surface

Suggest systemic origin:

- Increased level of both IgA1 and IgA-containing immune complexes in IgAN
- Absence of IgA2 and secretory component in mesangial deposit
- IgA-positive bone marrow cells contain IgA in dimeric form

Relationship between the mucosal immune system and BM response:

- Ongoing stimulation at mucosal surface
  -> Activation & proliferation of B lymphocyte
  -> Circulation
  -> Return to mucosal sites or localize in BM
  -> BM plasma cells produce IgA1 for long term

  (van der Wall Bake AW, et al. Clin Exp Immunol. 1988)
- Systemic immunization with tetanus toxoid in IgAN
  Increased IgA production in
  both the systemic and mucosal IgA system

  (Layward L. et al. Clin Immunol Immunopathol. 1993)

BM Stem cell disorder

- BM transplantation: NL->ddY mice
  Serum IgA levels & Macromolecular IgA ↓
  Mesangial deposits of IgA & C3 ↓
- Qualitative & quantitative changes of serum IgA are determined at the level of stem cells
- Which types of cells and what factors are defective ?
  Induction of tolerance ?

Imaizumi et al, KI 1989

Mechanism responsible for mesangial deposition of IgA

Still unclear

1. Deposited exogenous antigens
2. Intrinsic mesangial antigen
3. Physiochemical or immunological properties

Factors Influencing IgA Deposit

1) Antigen specificity
- Exogenous antigen
- 48 & 58 kd mesangial components and IgG autoAb
- Idiotype 133.5 with monoclonal anti-idiotypic Ab

2) Unrelated to the specificity of IgA
- Abnormal glycosylation of circulating IgA
- More negative charge of IgA
- IgA impairs complement-mediated clearance of immune complex
- Polymeric IgA1 : Higher affinity to mesangial cells
- IgA-fibronectin aggregates attach to collagen

IgA Receptors

- IgA Fc receptor (FcαR1)
- Asialoglycoprotein receptor (ASGPR)
- Polymeric Ig receptors (pIgR)

--> An absence on human mesangial cells

Leung et al JASN 2000

MESANGIAL INJURY

- Mesangial IgA deposition ≠ Development of GN
  Ex) Celiac disease, Hepatobiliary disease,
  Experimental models with IgA deposition
- Co-deposition of IgG or IgM antibody response
  (Oral tolerance failure)
- Complement-mediated injury
  Co-deposition of C3, properdin without C1q & C4
  - Activation of the alternative pathway
  C5b-9 deposition

Codeposition of IgA together with IgG or IgM

- More progressive course in patients
  - Inadequate suppression of systemic IgG or IgM response to persistent mucosal exposure to Ags
- Anti-Thy-1 antibody mediated MsPGN:
  Combination of IgA and IgG anti-Thy-1 antibodies
  --> A synergistic increase in albuminuria
  --> Pronounced increased matrix expansion

Maneke et al KI 1999

Mediators of mesangial injury

- Glomerular thromboxane B2 production
- Inflammatory cytokines in PBMC, monocytes, glomeruli & urine : IL-1, IL-6, TNFα, TGFβ, PDGF, endothelin
- Neutrophil and monocytes / macrophages ;
  Monocyte chemoattractant protein-1 and its receptors
  Glomerular and interstitial LFA-1 expression
  IgA aggregates produce IL-1, PAF, superoxide & C3.
- Mesangial cells :
  IgA-IC --> IL-1, IL-6, PAF, TNF, MCP-1 & superoxide

IgA or IgG Aggregates

- Fc receptors for IgG or IgA are demonstrated in neutrophil, monocyte/macrophage & mesangial cell (?).
- Stimulate neutrophil & monocytes to produce IL-1, PAF, C3 & superoxide.
- Stimulate mesangial Cells to produce IL-1, IL-6, PAF, TNF, MCP-1, superoxide & PGE_2

DETERMINANTS OF CLINICAL COURSE

- Quantity of polymeric IgA deposited
- Degree of complement activation
- Chemoattraction of monocytes
- Local inflammatory reaction
- Local generation of angiotensin II
- Intraglomerular pressure

Angiotensin II local hyperactivity in the progression of IgAN

- After administration of ACEI : ERPF↑ FF↓
- ΔFF & %ΔFF :
  IgAN pts with initial renal failure or proteinuria
  >> IgAN pts with NL renal function
  Other GN
  Healthy control

Coppo et al, Am J Kidney Dis 1993

Relationship between IgAN and HSP

- Variants of the same process
  IgAN is HSP nephritis without rash ?
  The two diseases
  - coexist in different members of the same family including a pair of monozygotic twins.
  - affect the same patient at different times.
- Different clinicopathologic entities
  - IgAN ; chronic slowly progressive glomerular lesion
  - HSP ; an acute disease and nonprogressive