Membranous Nephropathy
New Insights Regarding Pathogenesis

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Membranous Nephropathy

- A common cause of adult nephrotic syndrome
- Organ-specific, autoimmune disease
- Variable clinical course
  - Spontaneous remission
  - Persistent proteinuria
  - Progression to ESRD
- Pathological hallmark = subepithelial deposit

PODOCYTE
Injured podocytes cannot maintain an effective filtration barrier.

EXTRINSIC STRESS

INTRINSIC STRESS

FOOT PROCESS EFFACEMENT

PROTEIN
MN: Common pathology but different etiologies

Primary (Idiopathic)
- 75%

Secondary
- Lupus
- Hepatitis B
- NSAIDs
- Malignancy
- Toxins (Mercury)
- Others
- 25%
Images courtesy of Dr. Joel Henderson, Boston University Medical Center
An identical pattern would be present for complement factor C3.
HEYMANN NEPHRITIS: Experimental MN in a rat model

**Anti-Fx1A**
- α-megalin
- α-RAP
- α-Crry, α-CD59

**Downstream signaling**
- Calcium influx
- PLC, PLA₂ activation
- Lipid peroxidation
- ↑ ROS
- ↑ AA metabolites
- Cytoskeletal changes

**Anti-podocyte antibodies** ➔ **Subepithelial deposits** ➔ **Complement activation** ➔ **C5b-9 insertion** ➔ **Sublethal podocyte injury**

**MEGALIN is the target antigen in this rat model**

*What is the target antigen in human disease??*
Antenatal Membranous Glomerulonephritis Due to Anti–Neutral Endopeptidase Antibodies


- First evidence that pathogenesis of human MN involves reactivity of circulating antibodies with a podocyte-expressed antigen
- Mechanism (in this case) involves feto-maternal alloimmunization to *neutral endopeptidase* (NEP)
- Neonatal disease remitted after clearance of maternal antibodies
Identification of human antibodies reactive with glomerular proteins

S-S bonds must remain intact for human autoantibodies to detect MN antigen

Separate proteins by SDS-PAGE

Western blot to look for reactive bands

Identify by mass spec analysis
M-Type Phospholipase A₂ Receptor as Target Antigen in Idiopathic Membranous Nephropathy

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Evidence to support the pathogenicity of anti-PLA$_2$R:

- 70-80% prevalence of circulating anti-PLA$_2$R in **clinically-active** primary MN
- Co-localization of PLA$_2$R and IgG4 within immune deposits on biopsy
- Elution of anti-PLA$_2$R from biopsy tissue
- Strong association with clinical disease activity
- Exceptional case of MN with monoclonal IgG3$\kappa$ anti-PLA$_2$R; IF staining of deposits revealed only IgG3$\kappa$
- Genetic association of MN with $PLA2R1$ by GWAS
Primary MN can now be divided into subgroups

**Primary (Idiopathic)**
- 75%

**Secondary**
- Lupus
- Hepatitis B
- NSAIDs
- Malignancy
- Toxins (Mercury)
- Others

**PLA₂R-associated**
- 25%

**Truly idiopathic**
Disease initiation in MN

1. Onset of (auto)immune disease activity
2. Subepithelial deposits
3. Podocyte damage and foot process effacement
4. Proteinurria
Recurrent MN: A typical timeline

Proteinuria (g/day): 0.2 1.7

* POSITIVE anti-PLA$_2$R

2004
MN on native kidney biopsy

2007
ESRD

2010
LRD kidney transplant
Recurrent MN: A typical timeline

Proteinuria (g/day): 0.2 1.7 4 4.6

* POSITIVE anti-PLA$_2$R

2004
MN on native kidney biopsy

2007
ESRD

2010
LRD kidney transplant

2011
Progressive rMN

Recurrent MN
Immunological remission precedes clinical remission

Disease resolution in MN

Subepithelial deposits

Anti-PLA$_2$R

Proteinuria

Podocytes slowly regain normal morphology and function
Unresolved issues in MN pathogenesis

**Immunologic initiation**

- **Genetics**
  - PLA2R1
  - HLA region

**Complement-mediated cytotoxicity?**

- Interference with normal function of PLA$_2$R?

**Progression factors**

- ?

**Persistent proteinuria**

- ?

**Remission**

- ?

**Relapse**

- ?

**ESRD**
References


