Mechanism of Membranous Glomerulonephritis

IgG subclass 4
- is the culprit
  - the rarest of the circulating IgG subclasses
  - accounts for only 3-6% of total IgG
  - unique in its inability to activate classical complement pathway.

**THIS IS IMPORTANT!!**
Classical pathway is responsible for preventing immune complex deposition
- C3 binds to the antigen/antibody complexes, then links the complex to the CR1 Receptor on erythrocytes, which then circulate to the liver where the immune complexes are destroyed

**IgG is also a LOW AFFINITY antibody**
Hence it is able to dissociate pre-GBM, then penetrate the GBM and allegedly re-aggregate afterwards (inside the membrane)

**Genetic component:**
HLA DR3 = risk factor
Also Cancer, SLE, lead, mercury, gold, penicillamine, hep B/C, and syphilis

**Exposure to endogenous or exogenous antigen(s)**
In the Heymann mouse model this is a glomerular epithelial glycoprotein called megalin, but it has no equivalent in humans

**Induction of low affinity IgG immune response**

**Antibody + antigen complexes CIRCULATE FREELY**

**DEPOSITION OF IMMUNE COMPLEXES IN THE GLOMERULAR BASEMENT MEMBRANE**

**GEN KIDNEY:**
low affinity of the IgG4 allows dissociation of the complexes
- thus their FILTRATION through the GBM and fixation in it
- then, re-aggregation? ...PLUS hemodynamic stress eg. tortuous capillaries also increase the likelihood of immune complex deposition) either way...

4 stages:

**Stage 1:**
Scattered subendothelial deposits (subendothelial meaning behind the GBM, on the urine side of things)

**Stage 2:**
Large uniform deposits; Spikes of epithelium between them
Foot processes are being destroyed by the membrane attack complex (invoked by complement cascade, the alternative pathway)

**Stage 3:**
DEPOSITS ENCIRCLED and incorporated into the glomerular basement membrane; this is the famed "membranous transformation"

**Stage 4:**
Complete absorption of antibody complexes into the now-homogenous, irregular basement membrane.

**TUBULAR DAMAGE:**

NORMALLY:
Some proteins slip through the GBM
Eg. low mol. weight proteins with neutral charge
The low molecular weight proteins are usually reabsorbed by the proximal tubule

In Membranous Glomerulonephritis:
The poor tubule tries to reabsorb (pinocytose) the extra protein out of the urine and is thus overloaded with it
(vis. histological finding: vacuolisation” of the tubule)

**THIS MUCH PROTEIN IS TOXIC:**
- Toxic on its own eg. heme
- The act of pumping it depletes ATP
- THUS the tubules atrophy and die
  - then release cytokines thus attract FIBROBLASTS
  - FIBROSIS

**Antibody-associated Glomerular Injury**

Trapping of soluble circulating Ag-Ab complexes in the glomerulus
Strep Post-infectious, Serum-sickness, Hep C

Injury by Ab reacting in situ within the glomerulus
Anti-GBM or mesangial Ag
Ag planted within the glomerulus (drugs, bugs, DNA)

Site of immune complexes largely determine glomerular response:
- Subendothelial activate complement, acute inflammatory response
- Mesangial mesangiolproliferative response
- Subepithelial induce production of basement membrane material

**NORMAL:**
The filtering in the GBM is done by
- a size-barrier (i.e. the type IV collagen mesh)
- a charge barrier (i.e. the polyanionic inclusions in the mesh and the nephrin on the podocyte foot processes)

**In Membranous Glomerulonephritis:**
the defect in membranous glomerulonephritis results mainly from a loss of size selectivity - NEJM 1998