


**MORL** The basis of C3G: the kidney and the complement system



Resolving the confusion...

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**MORL** The basis of C3G: the kidney and the complement system



Resolving *some of* the confusion...*hopefully*

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**Goals – to understand.....**

- To understand the anatomy of the kidney and glomerulus
- To understand how C3G is diagnosed from a kidney biopsy
- To understand normal complement activity

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**MORL** **Understanding the kidney**

1. A kidney weighs about 4-6 ounces and is as big as a cell phone. That means is accounts for about 0.5% of your body weight.
2. Each of us has about 5-6 quarts of blood in circulation and yet your kidneys filter about 120 and 150 quarts of blood daily. Stated another way, they receive 25% of the cardiac output.
3. This means they filter all the blood in your body about 20 to 25 times per day and in doing so keep the blood's components stable.
4. The actual filters are tiny structures called nephrons. Each kidney has about 1,000,000 nephrons (ranging from about 200,000 - 1,800,000. With two kidneys, a person has on average 2,000,000 nephrons working 24-7.

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**MORL** **Understanding the kidney**

5. Your kidneys control your blood pressure.
6. Your kidneys make a hormone called erythropoietin (EPO), which is produced by the peritubular cells of the kidney. EPO stimulates red blood cell production.
7. Your kidneys convert vitamin D from supplements or the sun to its active form. With chronic kidney disease, low vitamin D levels can be found, sometimes even severely low levels.
8. Your kidneys control the pH of your blood. They reabsorb bicarbonate  $\text{HCO}_3^-$  from the urine back to the blood and they secrete hydrogen ( $\text{H}^+$ ) ions into the urine.

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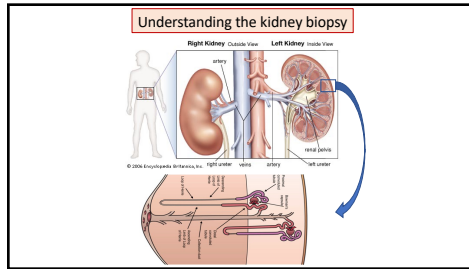
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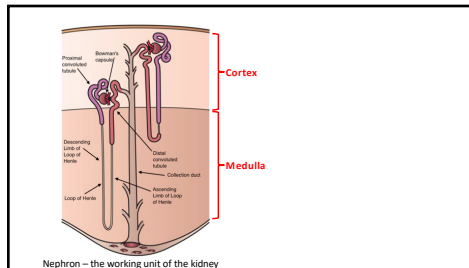
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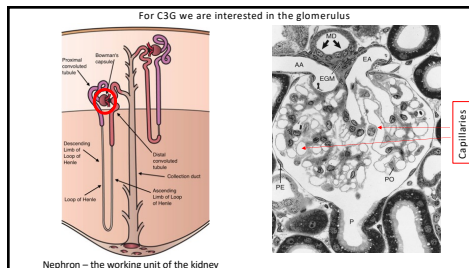
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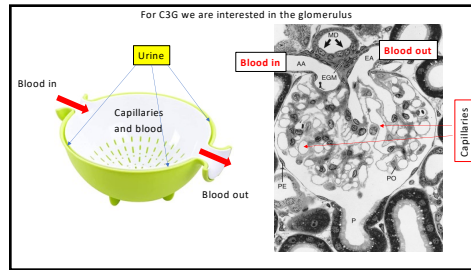
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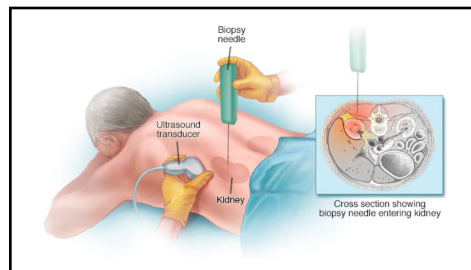
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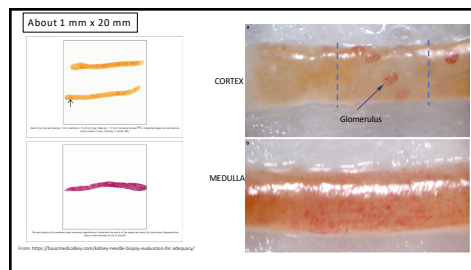
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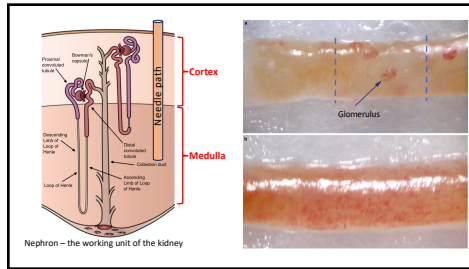
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### Kidney Pathology

- Light microscopy – different stains are used to evaluate different parts of the kidney. E.g. uses objectives to magnify eye vision up to 1000x.
- Electron microscopy – transmission beam, magnifies to 100,000x; used to tell whether you have C3GN or DDD
- Immunofluorescence microscopy – uses stains (antibodies) that fluoresce under the dark field microscope (same magnification as LM); used to diagnose C3G. There are strict criteria that must be met to make this diagnosis.

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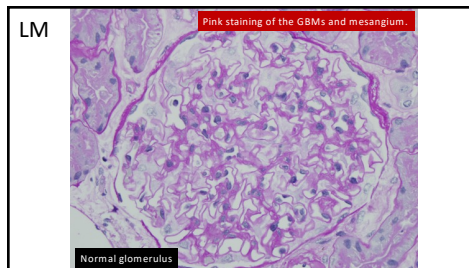
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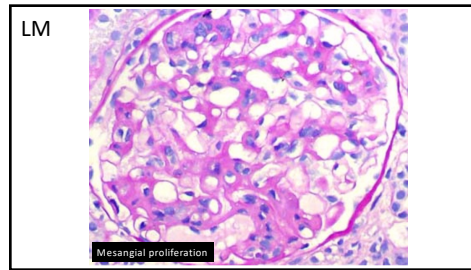
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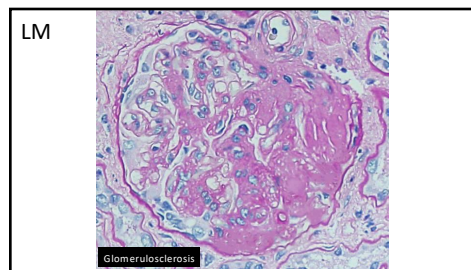
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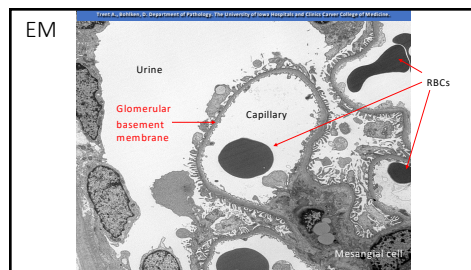
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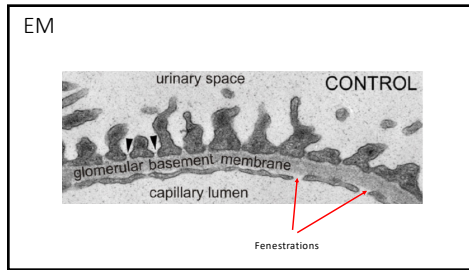
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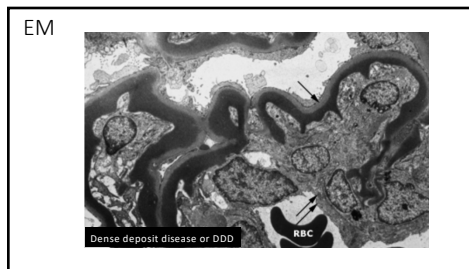
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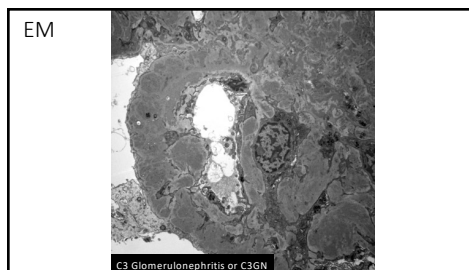
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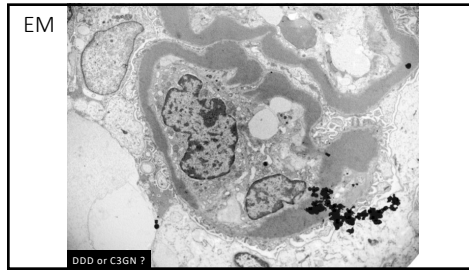
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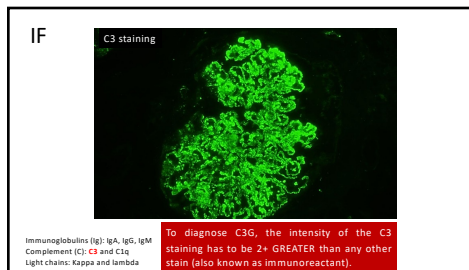
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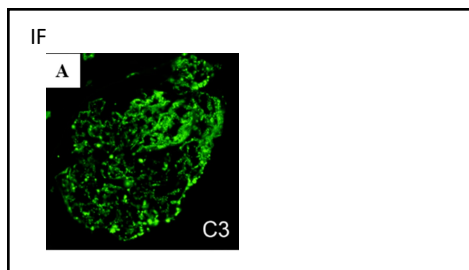
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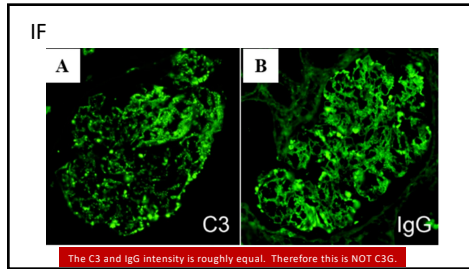
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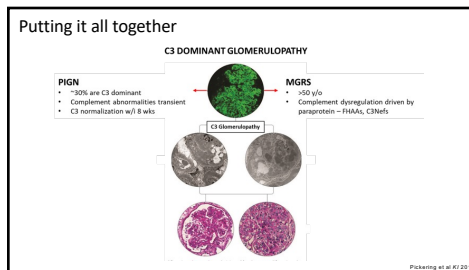
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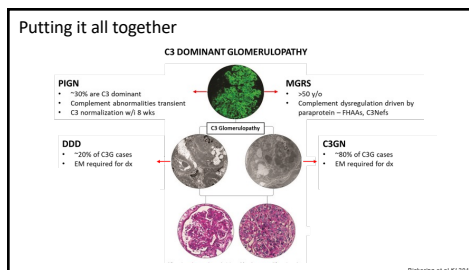
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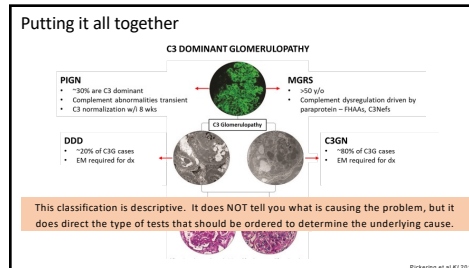
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- Goals – to understand.....**
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  - To understand normal complement activity

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- What does the complement system do?**
- It provides the first line of defense against infection
  - It tags dead and foreign cells for clearance (handles the garbage)
  - It talks to other systems in your body so your response is coordinated
  - It is "on" all the time. We call that "tick over"

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What the complement system cannot do

- Complement *cannot* distinguish "you" from "not you"
- Complement *cannot* distinguish good from evil
- Health relies on **control** of the complement system
  - Too little control or over-activation on self surfaces leads to disease
  - Too much control or under-activation on self surfaces leads to disease
- There is a delicate balance between activation and regulation



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**Activation**  
Too much activation  
inflammation

**Regulation**  
Too much control  
infection

The Setting

Dysregulation = Disease

Causes of dysregulation

1. Genetic factors
2. Acquired factors
3. Environmental factors and triggers (drugs, infections, etc.)

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**Activation**  
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How does complement work?

- There are three ways to start the complement system going. This is called the **initiation phase**.
- Once started, there is an amplification step. This is called the **amplification loop**.
- The final step is the terminal pathway. It is the **effector phase** and leads to generation of the terminal complement complex, inflammation, cell destruction, and marking of cells for removal (garbage pickup).

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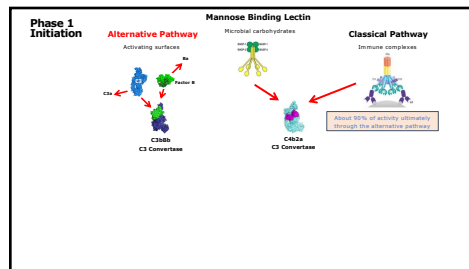
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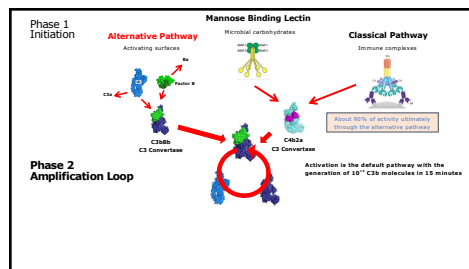
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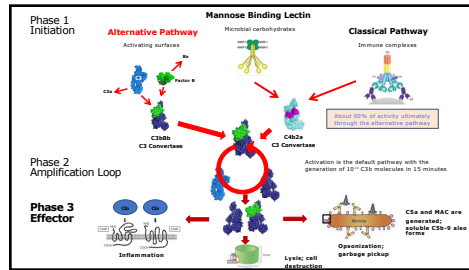
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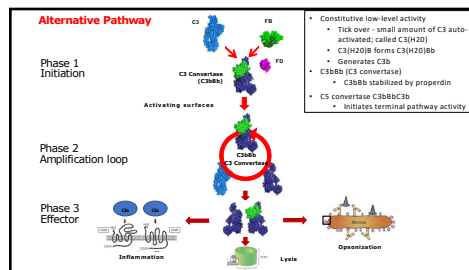
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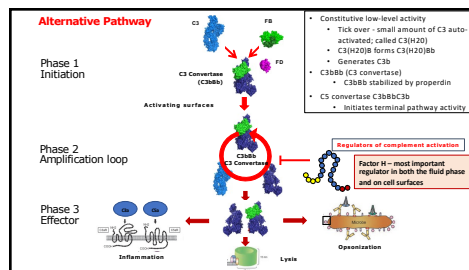
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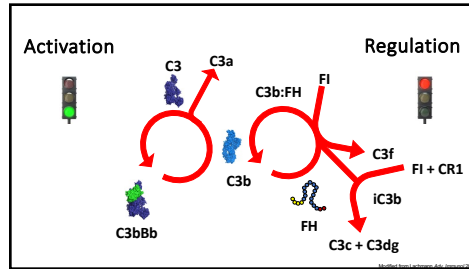
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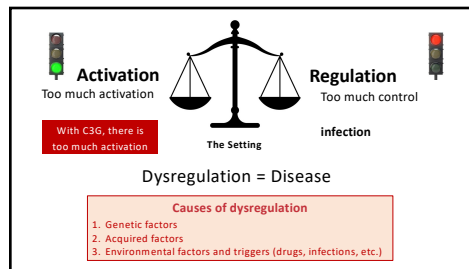
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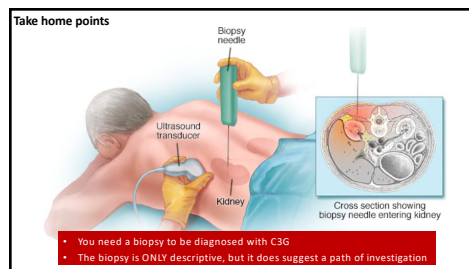
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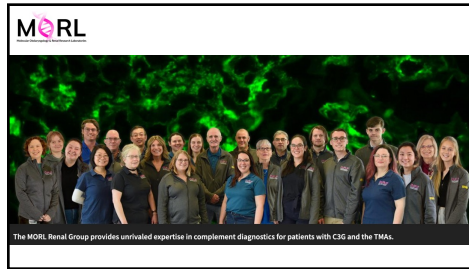
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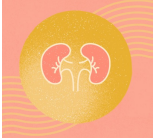
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**MERL** C3G – Disease Overview



Resolving the confusion...

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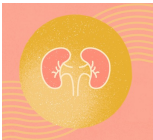
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**MERL** C3G – Disease Overview



Resolving *some of* the confusion...*hopefully*

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**Goals – to understand.....**

- To understand how complement activity drives C3G
- To understand the role of genetics in C3G
- To understand the role of nephritic factors in C3G

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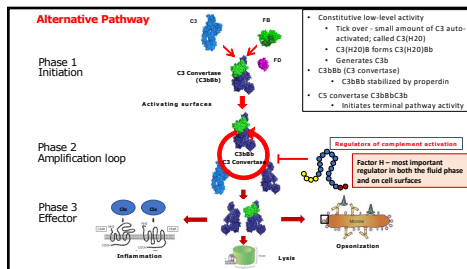
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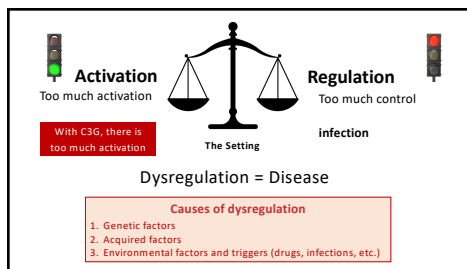
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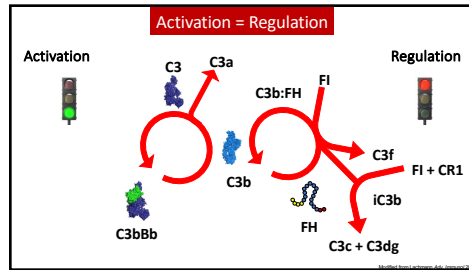
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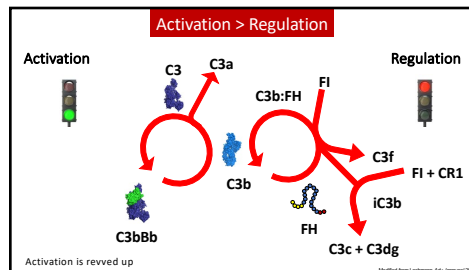
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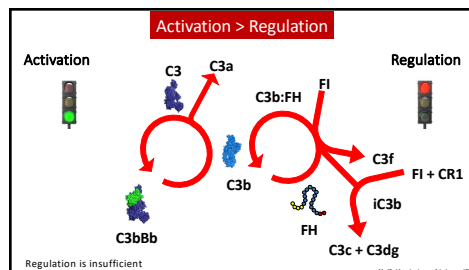
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**Activation**  
Too much activation

**Regulation**  
Too little control

The Setting

**C3 Glomerulopathy**

Causes of dysregulation

1. Genetic factors
2. Acquired factors
3. Environmental factors and triggers (drugs, infections, etc.)

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What's happening in the kidney in C3G?

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Diagram of kidney structure with a red arrow pointing to the site of C3 activation.

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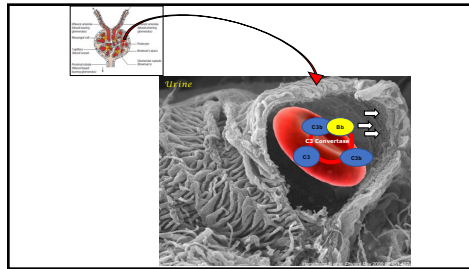
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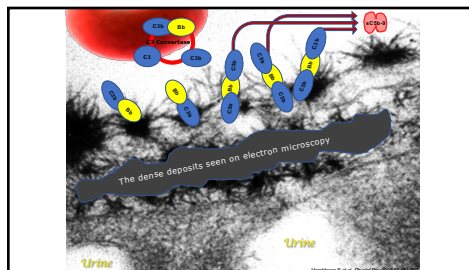
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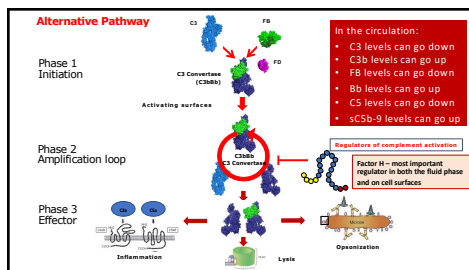
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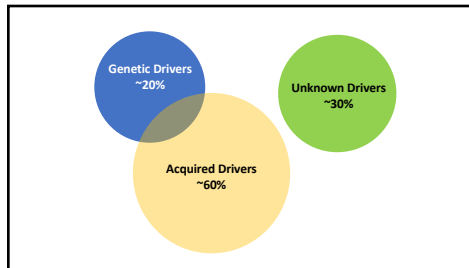
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**The Role of Genetics**

- A new fusion gene
- The endemic of C3G in Cyprus
- A mutational hotspot in C3 accounts for about 2% of cases

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**Novel FHR5/2 Fusion Protein**

Family Pedigree

- 26 y/o female with C3GN
- Nephrotic syndrome
- Cousin with similar diagnosis
- Complex genetic rearrangement leading to a novel fusion gene

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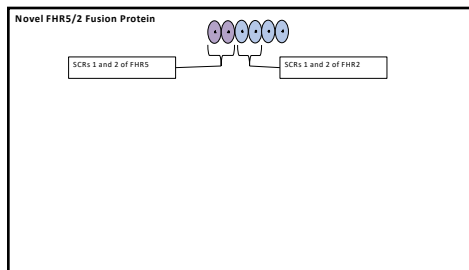
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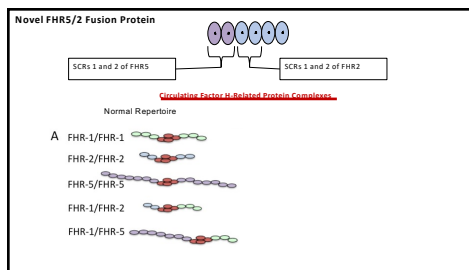
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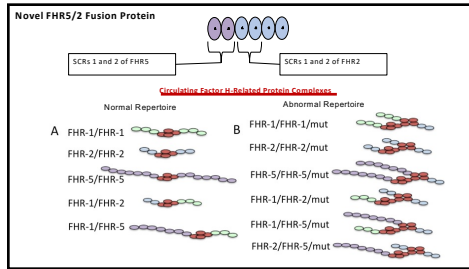
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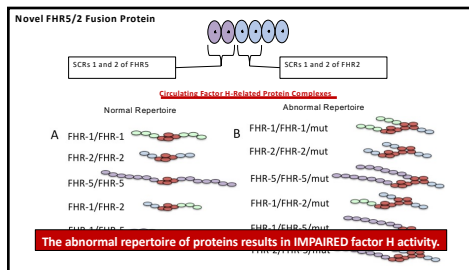
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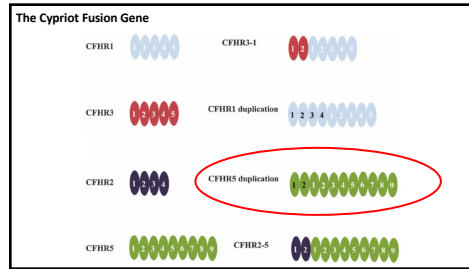
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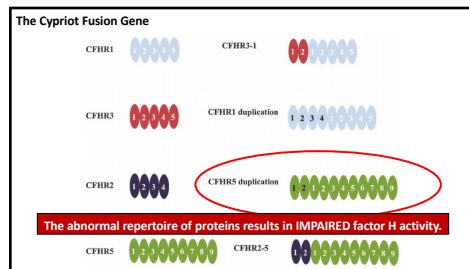
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**The Cypriot Fusion Gene**

**Prevalence**

- ~1 in 6000 persons (each affected person carries one copy of a novel *CFHR5* gene)

**Mechanism**

- Mutant protein interacts with C3 in glomeruli more efficiently than factor H
- Function of factor H is thereby impaired

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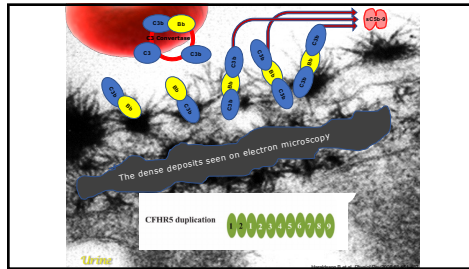
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**The Cypriot Fusion Gene**

**Clinical findings**

- Microscopic hematuria, usually worse with respiratory infections
- 25-50% of affected persons have visible hematuria
- **Generally no evidence of systemic complement dysregulation**
- Rather, AP dysregulation **confined to the glomerulus**

**Outcome**

- >80% of males but only a small proportion of females suffer a stepwise deterioration in renal function that leads to ESRD usually between 30-70 years of age
- Why there is a male bias is not clear

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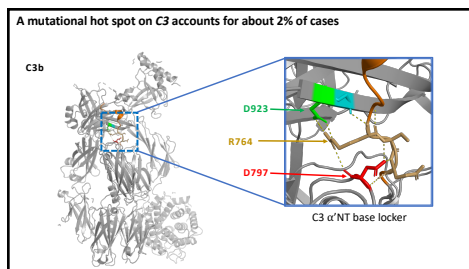
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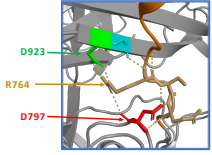
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A mutational hot spot on C3 accounts for about 2% of cases

Nine patients (all with C3GN)

- G924S – 5 patients
- D923A – 1 patient
- D797V – 2 patients
- D797G – 1 patient



D923  
R764  
D797  
C3  $\alpha$ /NT base locker

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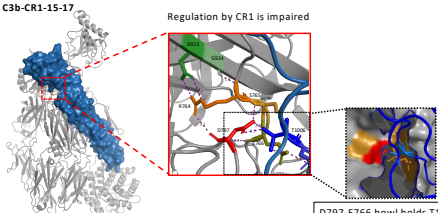
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A mutational hot spot on C3 accounts for about 2% of cases

C3b-CR1-15-17

Regulation by CR1 is impaired



D797-E766 bowl holds T1006

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Goals – to understand.....

- To understand how complement activity drives C3G
- To understand the role of genetics in C3G
- To understand the role of nephritic factors in C3G

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### The Role of Nephritic Factors

- They are autoantibodies; C3Nefs are autoantibodies to C3 convertase
- C3Nefs, C5Nefs and C4 Nefs are most common; often, a person will have multiple Nefs
- The degree of Nef positivity correlates with systemic complement dysregulation

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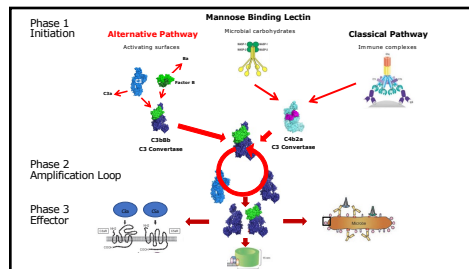
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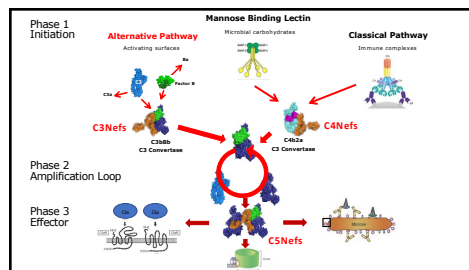
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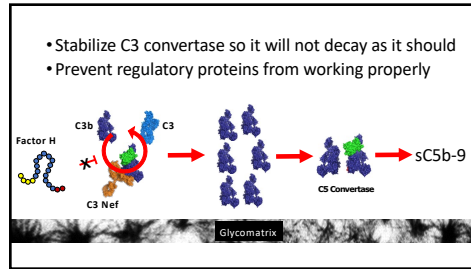
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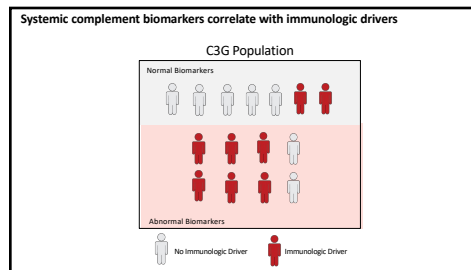
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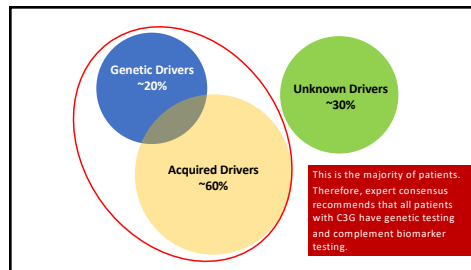
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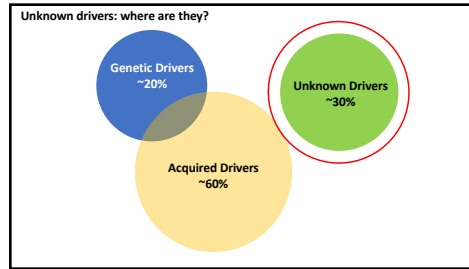
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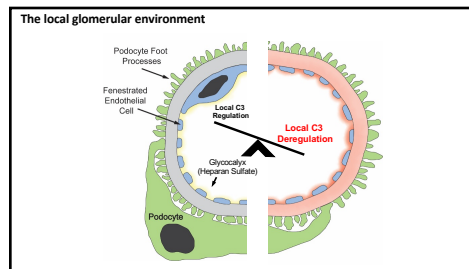
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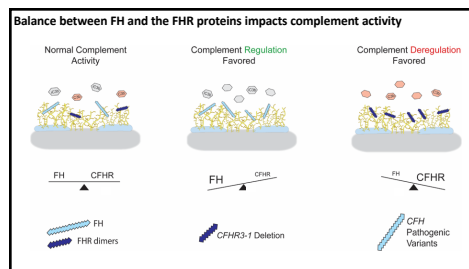
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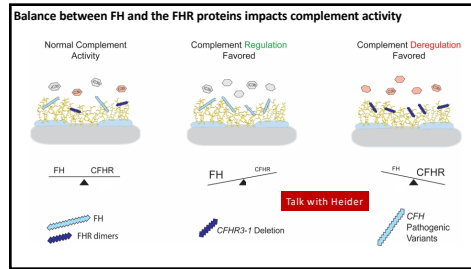
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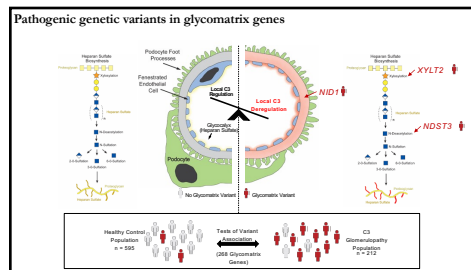
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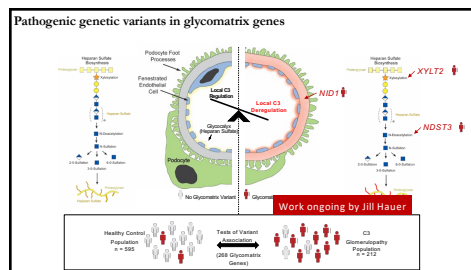
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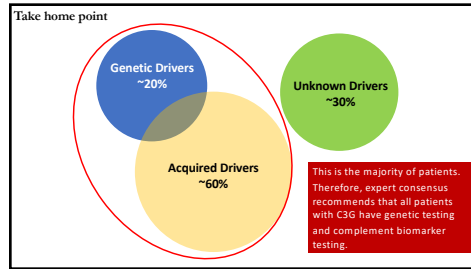
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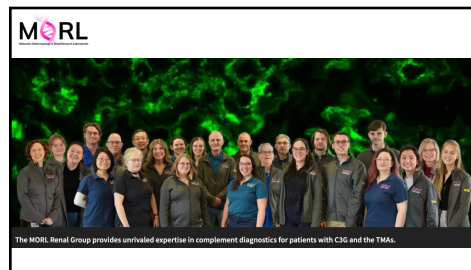
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