Thrombotic Microangiopathy
Classification & pathogenesis

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Classification of Thrombotic Microangiopathies

Historical classifications were on the basis of clinical findings:

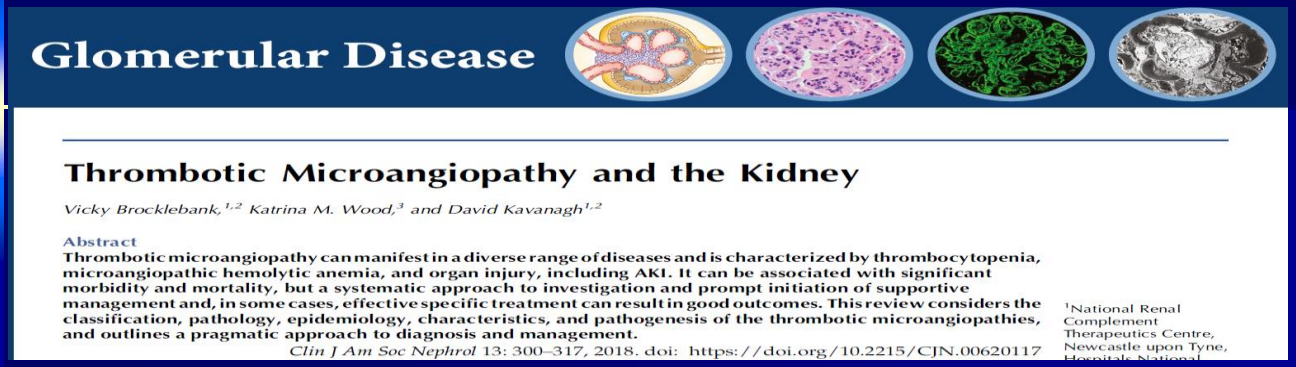
- TTP **for predominant neurologic involvement** and hemolytic uremic syndrome (HUS) for kidney dominant disease.

Classifications evolved with greater understanding of the molecular basis of disease:

- TTP was defined by severeADAMTS13 deficiency,
- (STEC-HUS) was defined by the presence of shiga toxin–producing bacteria
- aHUS was broadly used for all other causes of TMA.

- Subsequently discovery of the role ***of complement dysregulation*** in a proportion of patients with a HUS led to acceptance of complement mediated TMA

Current classifications describe



Glomerular Disease

Thrombotic Microangiopathy and the Kidney

Vicky Brocklebank,[1,2] Katrina M. Wood,[3] and David Kavanagh[1,2]

Abstract

Thrombotic microangiopathy can manifest in a diverse range of diseases and is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and organ injury, including AKI. It can be associated with significant morbidity and mortality, but a systematic approach to investigation and prompt initiation of supportive management and, in some cases, effective specific treatment can result in good outcomes. This review considers the classification, pathology, epidemiology, characteristics, and pathogenesis of the thrombotic microangiopathies, and outlines a pragmatic approach to diagnosis and management.

Clin J Am Soc Nephrol 13: 300–317, 2018. doi: https://doi.org/10.2215/CJN.00620117

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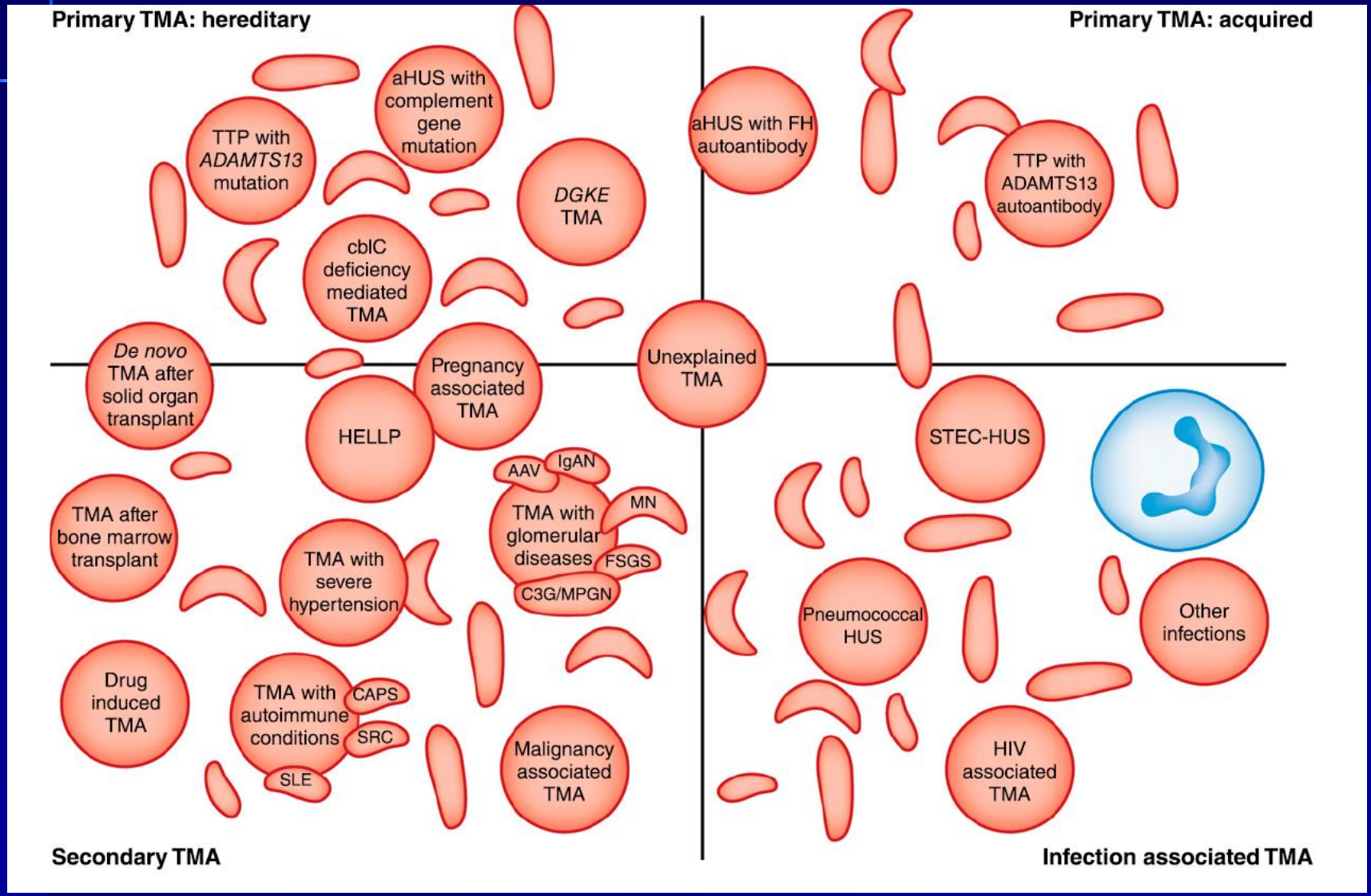
Primary TMAs

- **Inherited** Primary TMAs
- **Acquired** Primary TMAs

Infection-associated TMAs

secondary TMAs

Current classifications describe



Primary TMAs
Acquired & Inherited

- Thrombotic Thrombocytopenic Purpura

Hereditary TTP

Acquired TTP

- Complement-Mediated a HUS

Hereditary Complement-Mediated aHUS

Acquired Complement-Mediated aHUS

- Cobalamin C Deficiency
- DGKE TMA

Thrombotic Thrombocytopenic Purpura

Hereditary TTP

- hereditary TTP (<5 % of all TTP cases) results from recessive mutations in the ADAMTS13 gene . typically, undetectable ADAMTS13 activity without an autoantibody inhibitor.

Acquired TTP

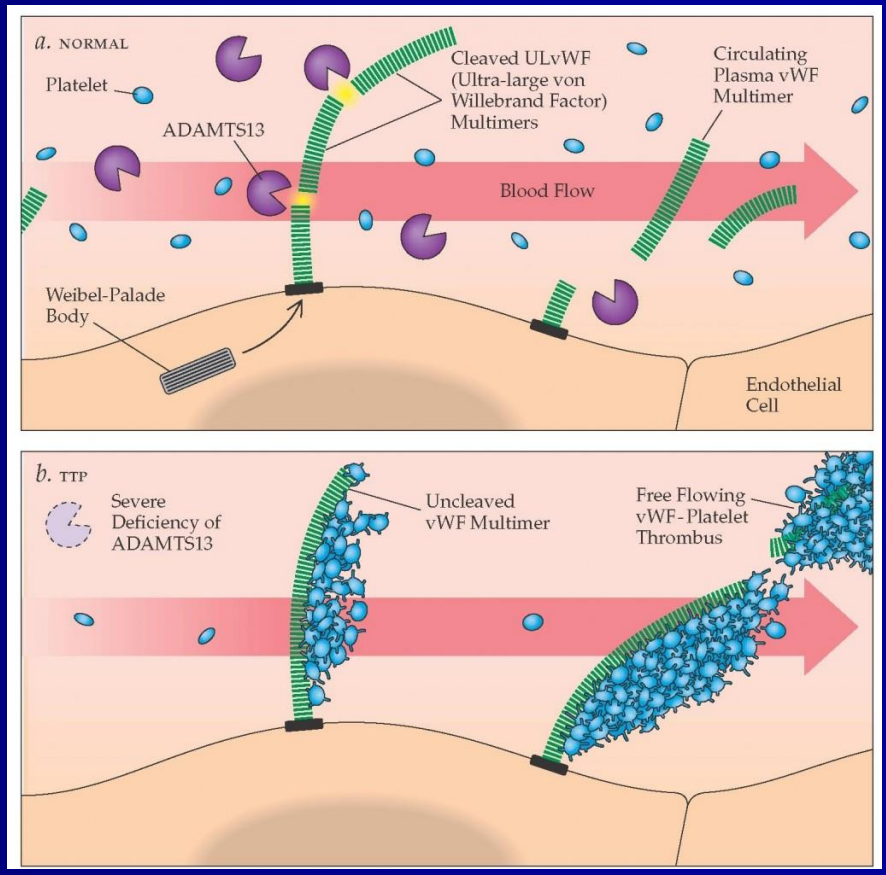
- In acquired TTP, ADAMTS13 activity is inhibited by autoantibodies. over 95 percent are acquired autoimmune TTP. Acquired TTP is characterized by severe ADAMTS13 deficiency (ie, activity <10 percent) and the presence of an inhibitor . It occurs in approximately three in one million adults and 1 in 10 million children annually.

Thrombotic Thrombocytopenic Purpura predisposing factors

- ADAMTS13 deficiency predisposes to microvascular thrombosis **after a triggering event**, including pregnancy, infections, neoplasia, autoimmune disorders and exposure to certain drugs, activates microvascular endothelial cells and causes the secretion of UL-VWF multimers.
- A significant proportion of women with TTP present during pregnancy particularly in the second and third trimesters. This might be explained by the physiologic increase in vWf during pregnancy, which consumes ADAMTS13, so in women with a genetic predisposition, its activity can fall low enough for TMA to manifest

Thrombotic Thrombocytopenic Purpura

- VWF is a Multimeric high-molecular-weight plasma glycoprotein, produced by endothelial cells and megakaryocytes and stored in the form of ultralarge multimers (UL-VWF)
- Under normal conditions, the ***thrombogenic potential*** of **UL-VWF** is rapidly held in check through **cleavage into smaller multimers** by ADAMTS13
- ADAMTS13 deficiency results in **large vWf multimers** and consequent **occlusive microvascular platelet aggregation**.

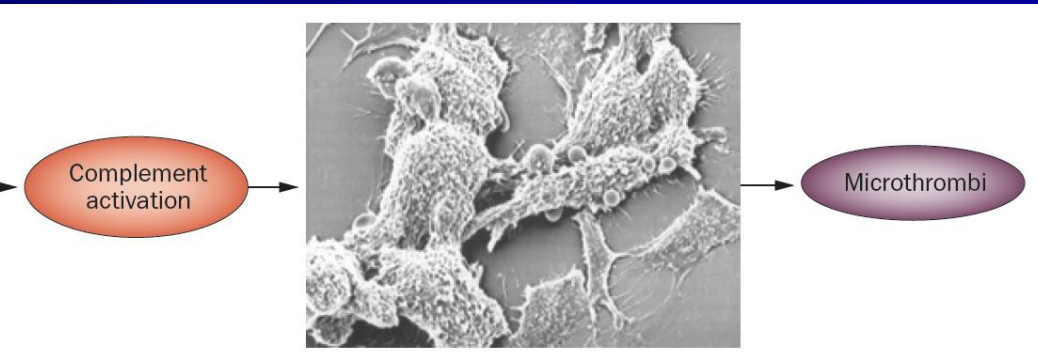


(**A** **D**isintegrin **A**nd **M**etalloprotease with a **T**hrombo**S**pondin type 1 motif, member **13**)

TTP and complement activation

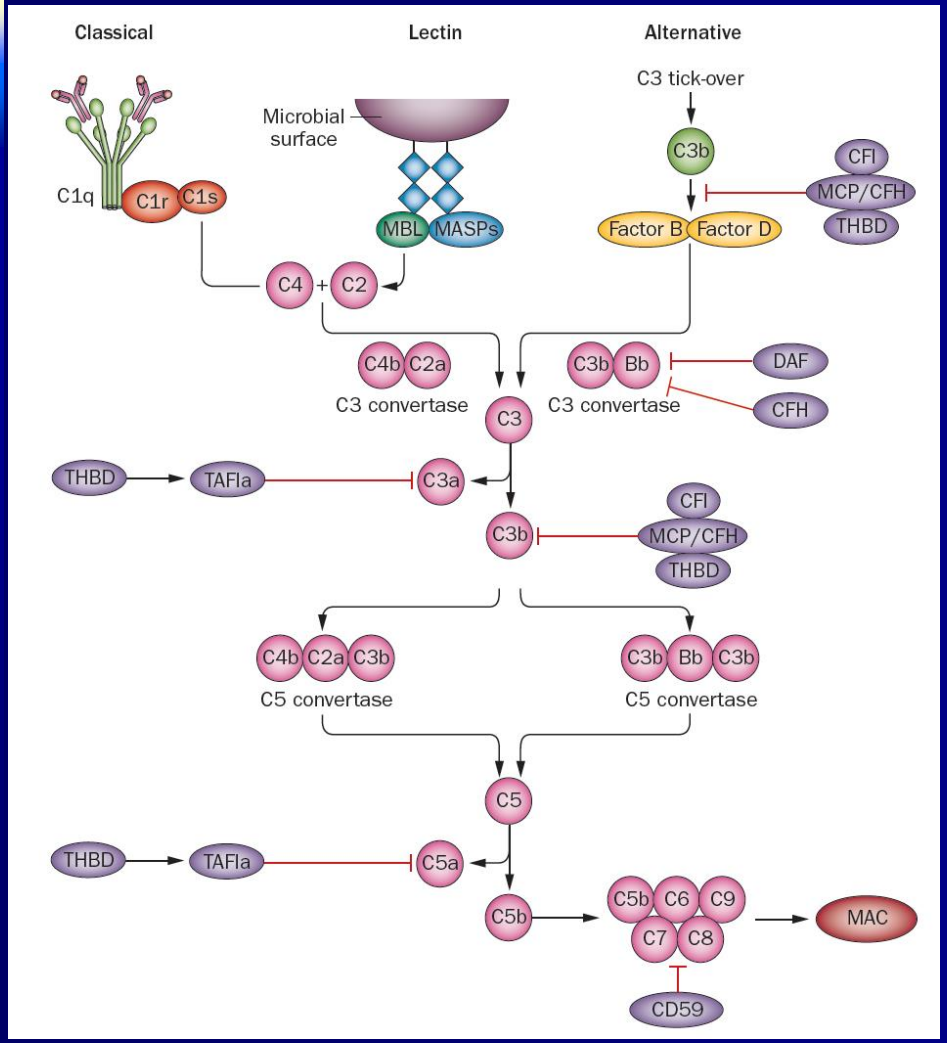
- Median plasma levels of C3a and C5b–9 were higher in patients with acute TTP, Interestingly, C3a and C5b–9 levels correlated with disease activity.
- The investigators identified **P-selectin**, an adhesion molecule expressed on activated platelets following α-granule secretion, **as a receptor for C3b**.

Disease	Cause	Effect
STEC-HUS	Stx	P-selectin expression
aHUS	Gene mutation Anti-CFH antibodies	Defective complement regulation
TTP	ADAMTS13 deficits	UL-VWF multimers



Complement system

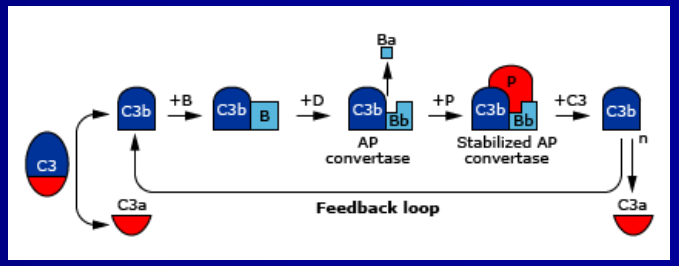
MBL, mannose-binding lectin, MASP, mannan-binding lectin serine protease



The classical pathway is activated by the **binding of C1q** in the C1 complex **to the Fc portion of IgG or IgM in immune complexes**.

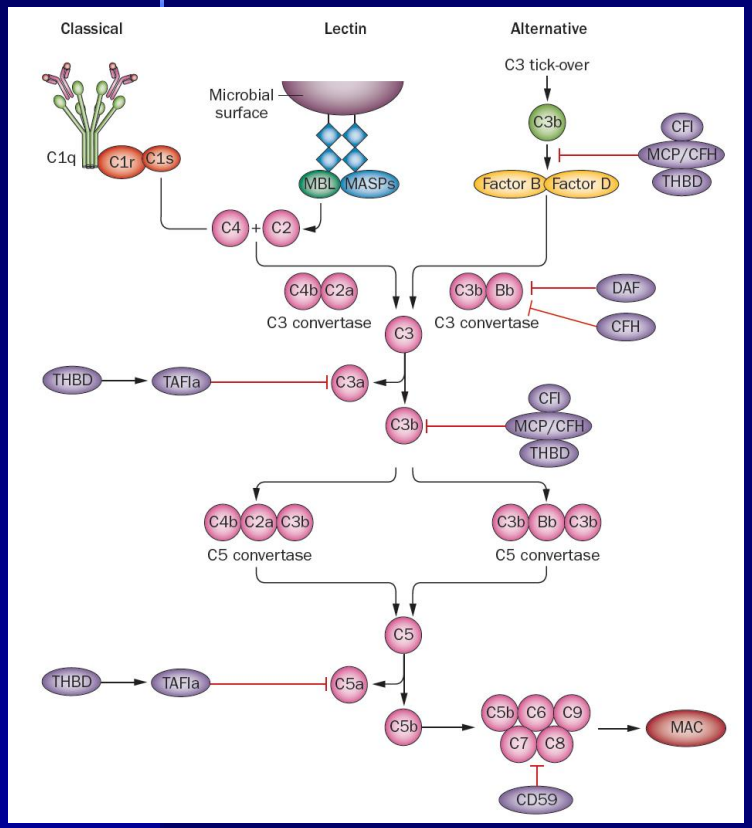
The lectin pathway is activated by mannose-binding lectin **(MBL)** binding to sugar moieties on the **surface of pathogens** leading to the engagement of proteases, analogous to C1r and C1s of the classical pathway.

The alternative pathway does not require antibody or contact with a microbe to become activated. Instead, C3 is constantly autoactivated **(C3 tickover)** at a low level, a process that is **rapidly amplified** in the **presence of a microbe, a damaged host cell, or lack of a complement regulatory protein.**



Complement-Mediated a HUS

Mutations in the following identified genes



- ✓ **Hereditary Complement-Mediated a HUS**

Activating mutation: C3, factor B (feedback loop amplification)

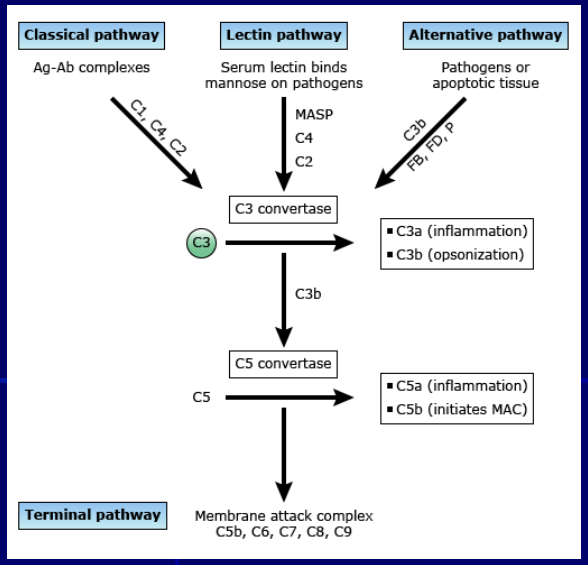
Loss of function mutation: CFH/CFHR, FI, CD46(MCP) (feedback loop amplification)

- ✓ **Acquired Complement-Mediated a HUS**

Autoantibody against CFH,CFI (feedback loop amplification)

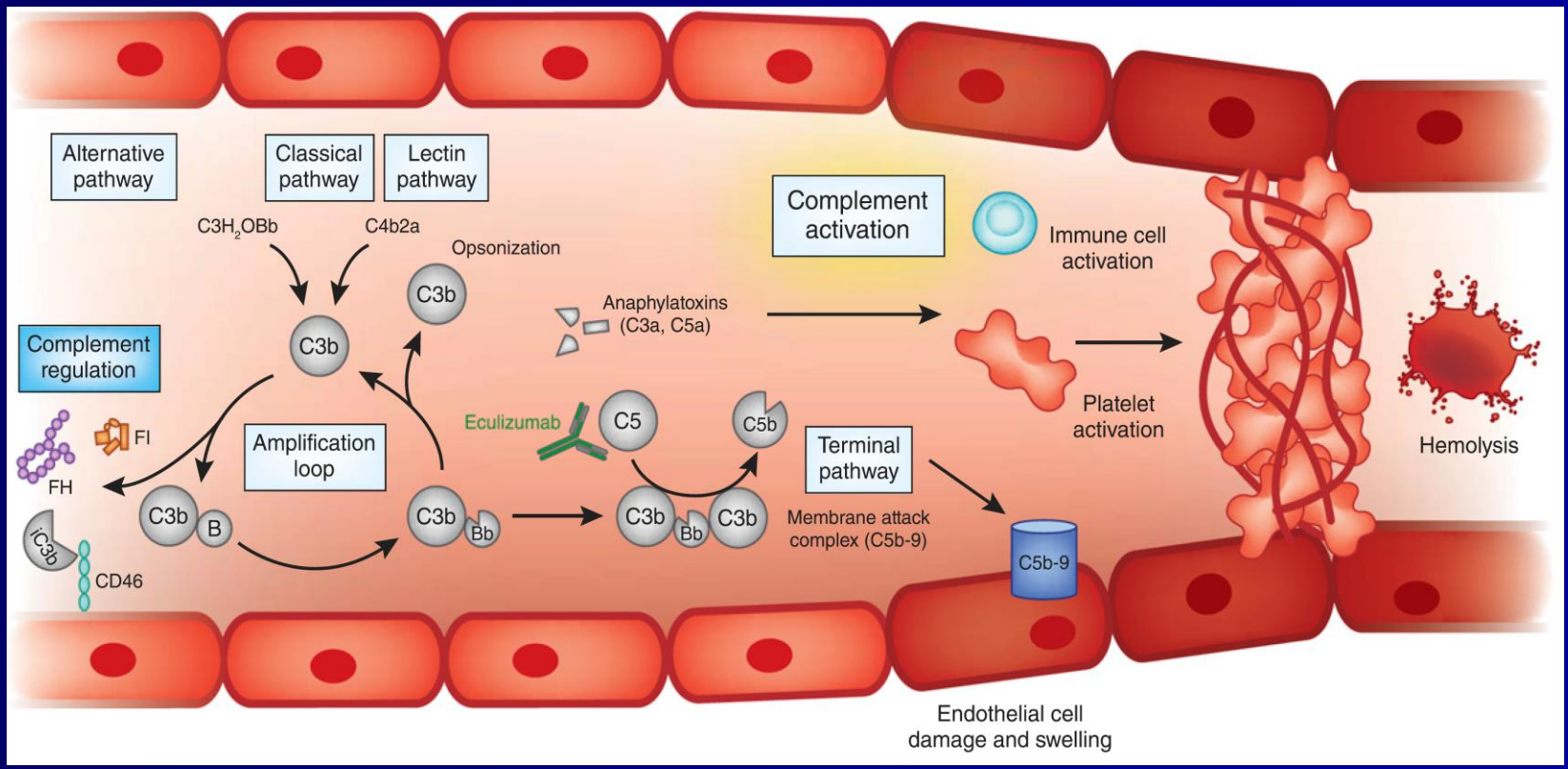
Hereditary Complement-Mediated a HUS

- Complement factor H (*CFH*, 20 to 30 percent) poor prognosis
- *CD46*, previously known as membrane cofactor protein (5 to 15 percent) good prognosis
- Complement factor I (*CFI*, 4 to 10 percent)
- Complement factor C3 (*C3*, 2 to 10 percent)
- Complement factor B (*CFB*, 1 to 4 percent)
- Thrombomodulin gene (*THBD*, 3 to 5 percent)



Complement-Mediated a HUS

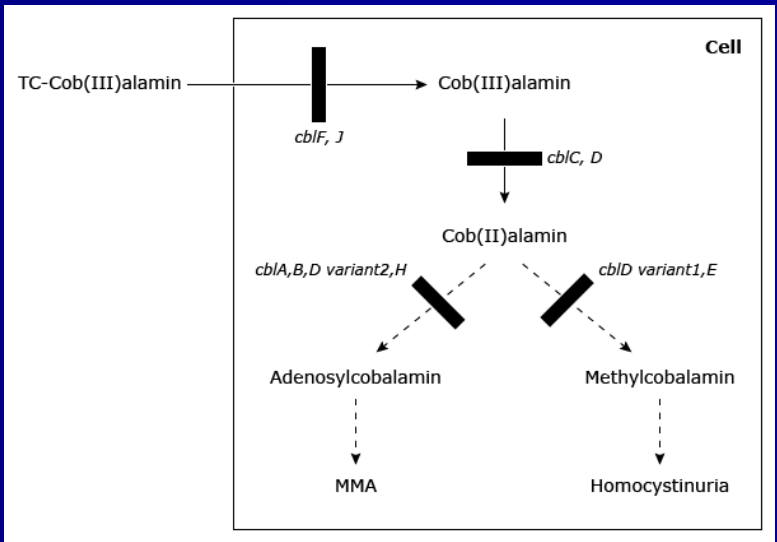
Unfettered complement activation ultimately results in thrombus formation, platelet consumption, vascular occlusion and mechanical hemolysis



Cobalamin C Deficiency

- ***Methylmalonic acidemia*** encompasses a heterogeneous group of disorders that is characterized by **impaired metabolism of methylmalonic acid** that is generated during the metabolism of certain amino acids (isoleucine, methionine, threonine, or valine)
- These disorders are **caused by** a deficiency of the **methylmalonyl-CoA mutase (mut), or its cofactor, cobalamin (cbl, vitamin B12).**
- **Mutations in at least nine different genes** can cause the MMA phenotype and are classified into the following complementation groups: mut(0), mut(-), cblA, cblB, cblC, cblD, cblF, cblH, and cblJ.

- The **mut(0), mut(-), cblA, and cblB** defects lead to MMA
- **CblC, cblF, and cblJ** defects lead to combined MMA and homocystinuria in all cases
- **cblD** defects may result in MMA, homocystinuria, or combined MMA and homocystinuria



Cobalamin C Deficiency

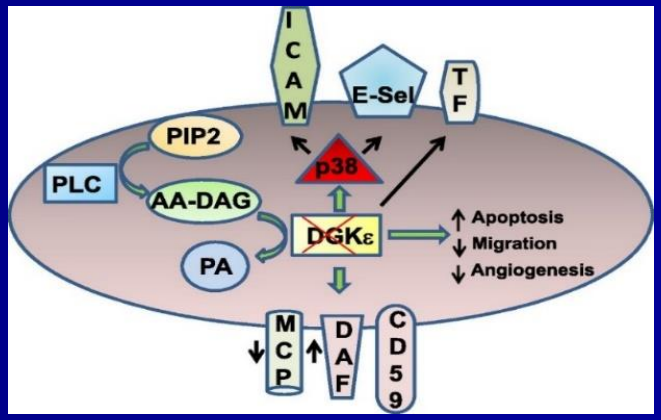
- Cobalamin C (cblC) type, is the most common genetic type of functional cobalamin deficiency
- **It can present in adulthood as well as childhood**, and the phenotype may comprise developmental, ophthalmologic, neurologic, cardiac, and kidney manifestations, although severity varies.
- The pathophysiologic mechanisms that cause **endothelial damage and subsequent TMA have not yet been determined**
- Consistent clinical features of renal disease were intravascular hemolysis, hematuria, and proteinuria in all patients
- Two thirds were diagnosed with atypical hemolytic uremic syndrome (a HUS)

All patients with MAHA and thrombocytopenia who have negative testing for TTP and ST-HUS should be tested for cobalamin C deficiency-mediated TMA using measurement of serum homocysteine and methylmalonic acid (MMA).

Beck BB, van Spronsen F, Diepstra A, Berger RM, Komhoff M: Renal thrombotic microangiopathy in patients with cblC defect: Review of an under-recognized entity. Pediatr Nephrol 32: 733– 741, 2017

Recessive DGKε mutations causing TMA

- Loss of DGKε can trigger endothelial activation and display a prothrombotic phenotype.
- Affected individuals present with TMA **before age 1 year,** have persistent hypertension, hematuria and proteinuria (sometimes in the nephrotic range), and develop chronic kidney disease



- DGKε is produced by endothelial cells, renal podocytes, and platelets
- DGK normaly inactivates Diacylglycerol (DAG) signaling
- DAG activate protein kinase C (PKC)
- PKC increases endothelial cell production of VWF,PAF,TPA,PAI-1,TF,over expression ICAM-1,E-selectin

intercellular adhesion molecule-1 (ICAM-1), E-selectin (E-Sel), and tissue factor (TF)

Other Genetic Associations

- Reported rare genetic variants in plasminogen (which plays an important role in fibrinolysis following conversion to plasmin) in TMA
- Functionally significant mutations in INF2 (encodes a member of the formin family of **actin-regulating proteins**) have been seen to segregate in families with TMAs

Infection-Associated TMAs

- STEC-HUS
- Pneumococcal HUS
- HIV-Associated TMA
- Other Infections

STEC-HUS

- The majority of cases of HUS (around 90%) are associated with infection by bacteria producing Stx, most often O157:H7 serotype enterohaemorrhagic *E. coli.*
- Stx **upregulate mRNA expression and protein levels of :**
  - **chemokines** (such as IL-8, MCP 1 and stromal cell-derived factor 1 (SDF1)
  - **chemokine receptors Type 4 and 7** (CXCR4 and CXCR7)
  - **cell adhesion molecules** (including VCAM, ICAM, P-selectin and PECAM 1)

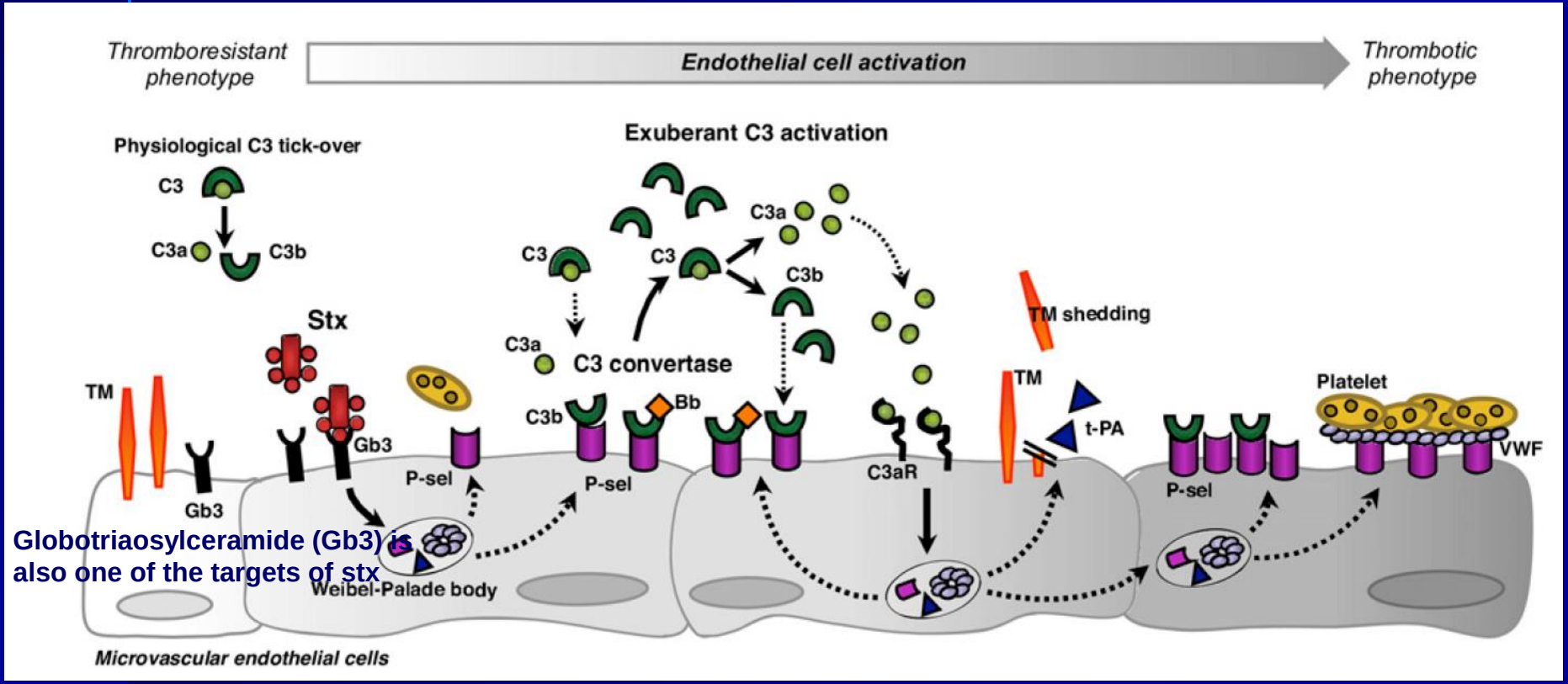
which favour leukocyte recruitment

- Stxs **increase endothelial tissue factor activity**
- Stxs directly **activate platelets and inflammatory cells**
- Stxs favour inflammation and **induce loss of endothelial thromboresistance**

leading to microvascular thrombosis

STEC-HUS

Low levels of C4 have also C3 reductions occasionally been observed in patients with STEC-HUS (indicating activation of the classical and/or lectin pathways leading to C4 consumption)



Globotriaosylceramide (Gb3) is also one of the targets of stx

Stx alters endothelial thromboresistance by triggering exuberant C activation via C3a, leading to microvascular thrombosis. The proposed scheme summarizes the sequence of events through which Stx binds to its specific endothelial receptor Gb3 and favors surface mobilization of P-selectin and thrombus formation under flow by either interacting with platelets or by binding and/or activating C proteins. Excessive C3 activation (dependent on increased C3 convertase assembly and activity) in response to Stx generates an increased amount of the anaphylatoxin C3a, which interacts with the specific endothelial C3aR, thereby potentiating P-selectin expression and t-PA-dependent TM shedding with final thrombus formation

Pneumococcal HUS

- TMA may occur in adults and children in the context of *invasive Streptococcus pneumoniae infection*

The hypothesized mechanism :

- Pneumococci produce neuraminidase, which cleaves sialic residues on erythrocyte, platelet, and endothelial cell membranes, exposing the T antigen , to which IgM in the plasma can then bind, resulting in cell damage and TMA
- Additionally, it has been suggested that cleavage of sialic acid may reduce CFH (C3 convertase inhibitor) binding, resulting in impaired endothelial complement regulation, thus contributing to disease pathogenesis

HIV-Associated TMA

- TMA has been reported in association with HIV, more commonly in the *pre-highly active antiretroviral therapy* era ,and in *association with lower CD4 cell counts* and *higher viral RNA levels* .
- The pathogenic mechanisms are poorly understood, although *endothelial damage* is thought to be the primary event.

Other Infections

- TMA has been reported in association with a wide range of viral, bacterial, fungal, and parasitic infections,
- A direct effect of the pathogen
- A side effect of treatment
- A trigger that unmasks a latent complement defect
- Reported undefined infectious triggers in 70% of patients with complement-mediated aHUS and CFH, CFI, or CD46 mutations