Non-thrombotic Neurological Manifestations of Anti-phospholipid Syndrome

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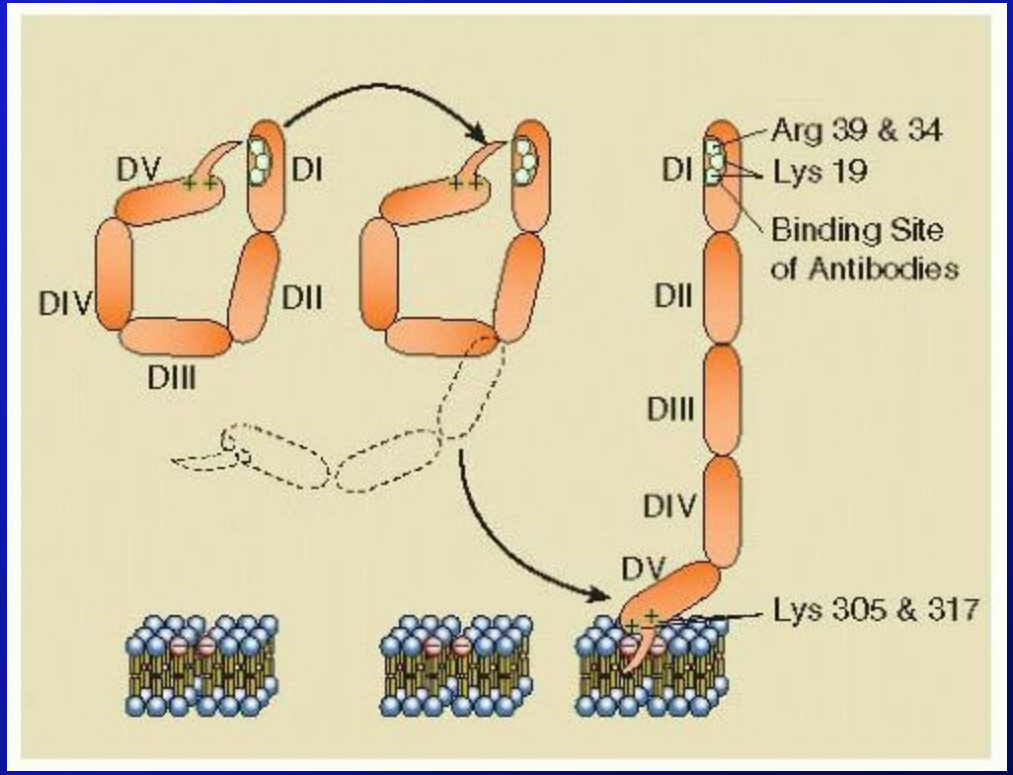
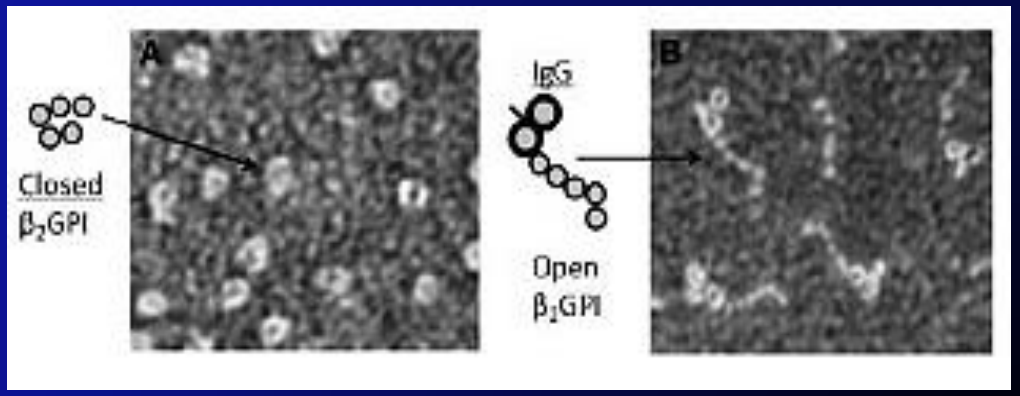
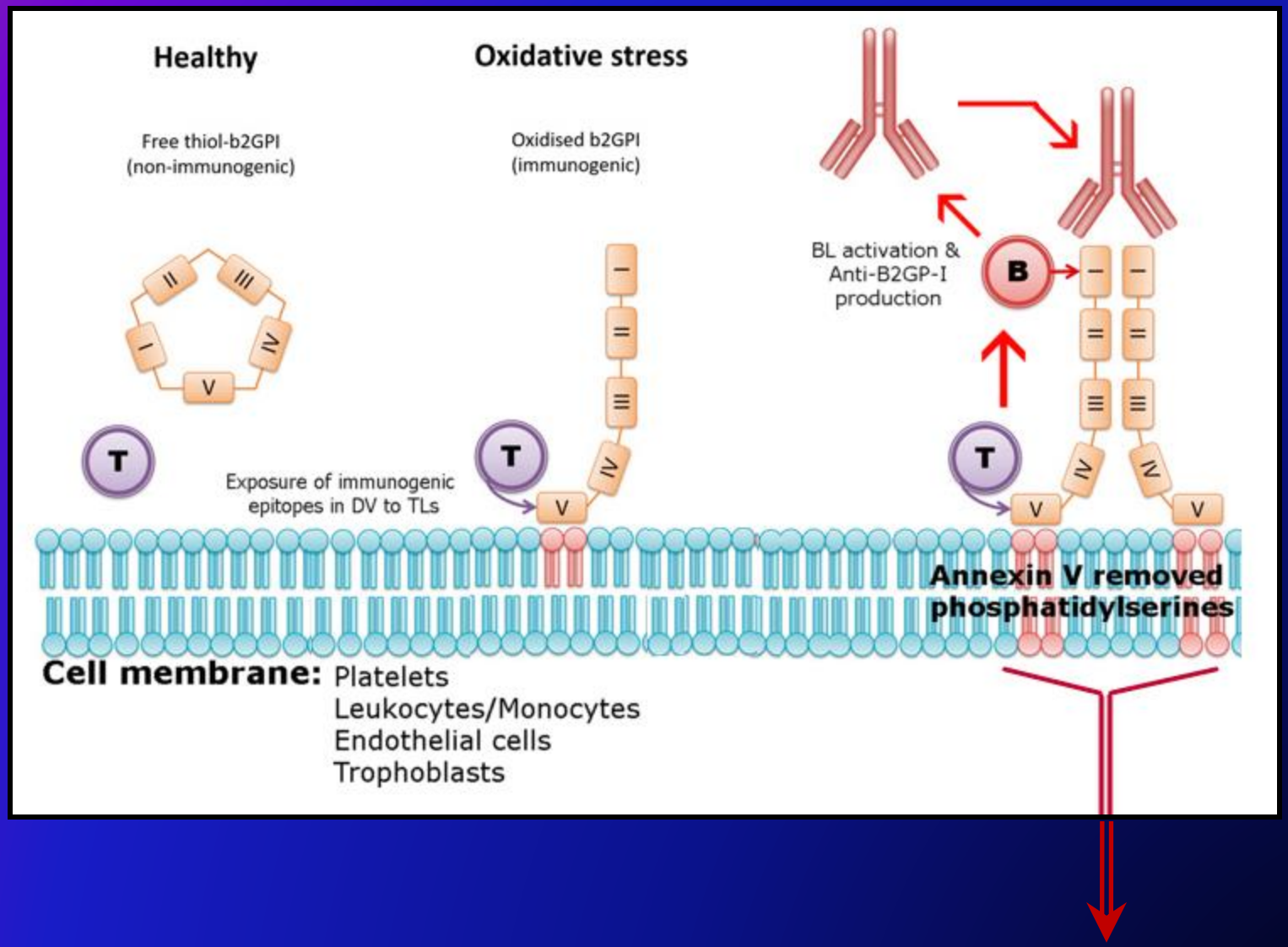
- B2GP-I has 5 domains, DV binds cell membrane phospholipid bilayer and DI which is immunogenic.
- In its regular circular form various epitopes of DI are shielded that become exposed in its hook form.
- The change from circular to linear form is determined by Cyc288 & Cys326 tiol (circular) or disulfide bond (linear).
- Presence of LPS, hydrophilic surfaces, binding to anionic PLs & oxidative stress turns circular to linear form.





Front Imm May 2018 vol 9
Blood July 2012 vol 120 No 2



Semin Throm Hemost 2018,44(5) 475-482
Vasa 2018,47(6) 451-464

Signaling of cell

Cell Signaling in APS

Annexin A2

ApoER2

TLR4

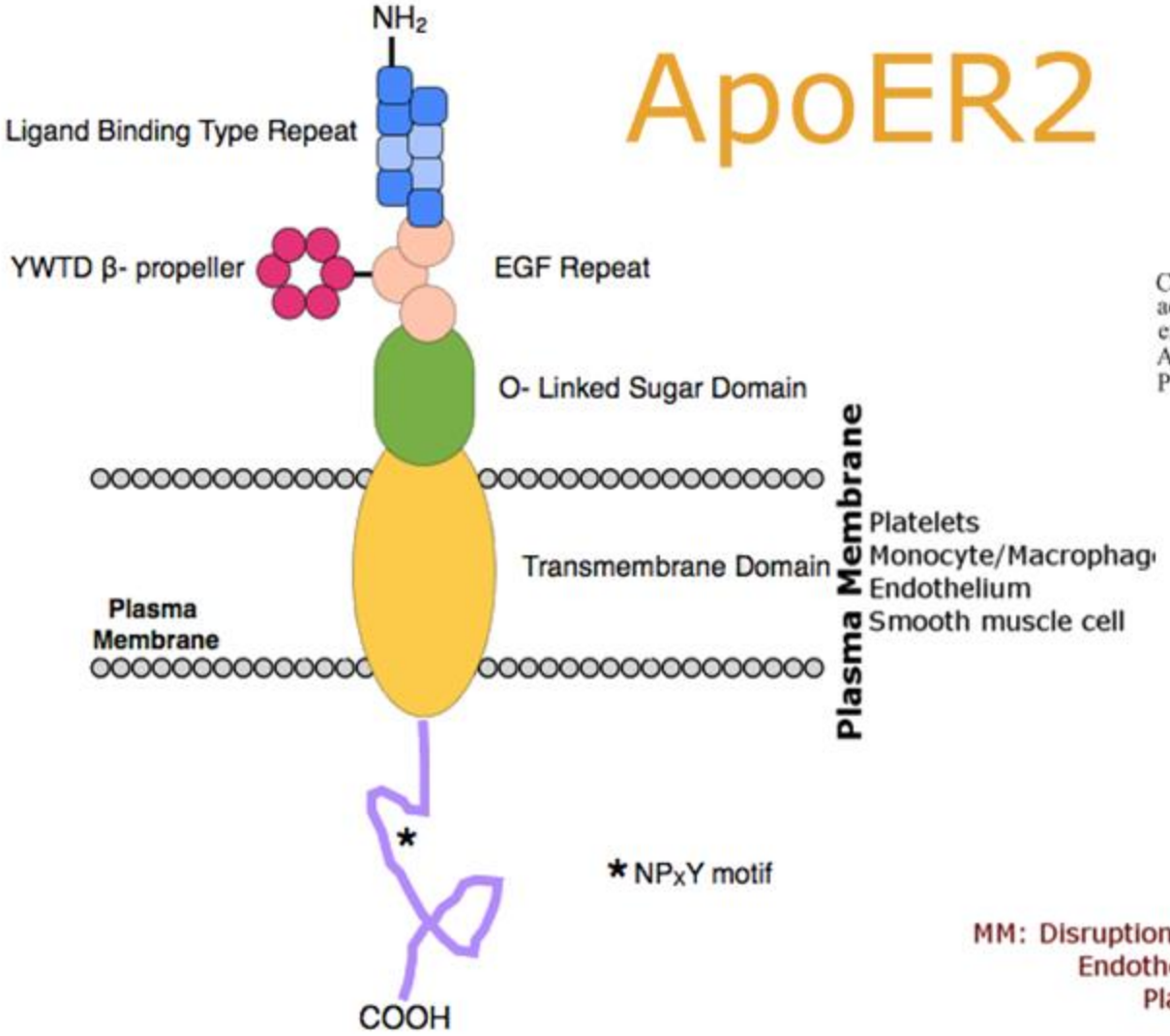
TLR2

Neutrophil NETosis

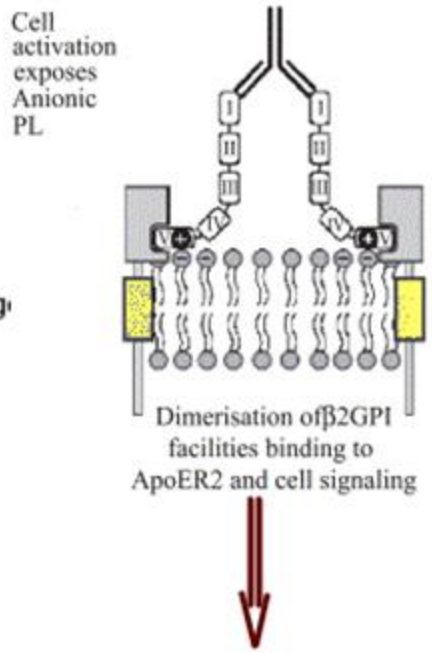
Mamalian target of Rapamycin complex (mTORC)

Complement

ApoER2



Mechanicsm of action of anti-β_2GPI auto antibodies from APS patients

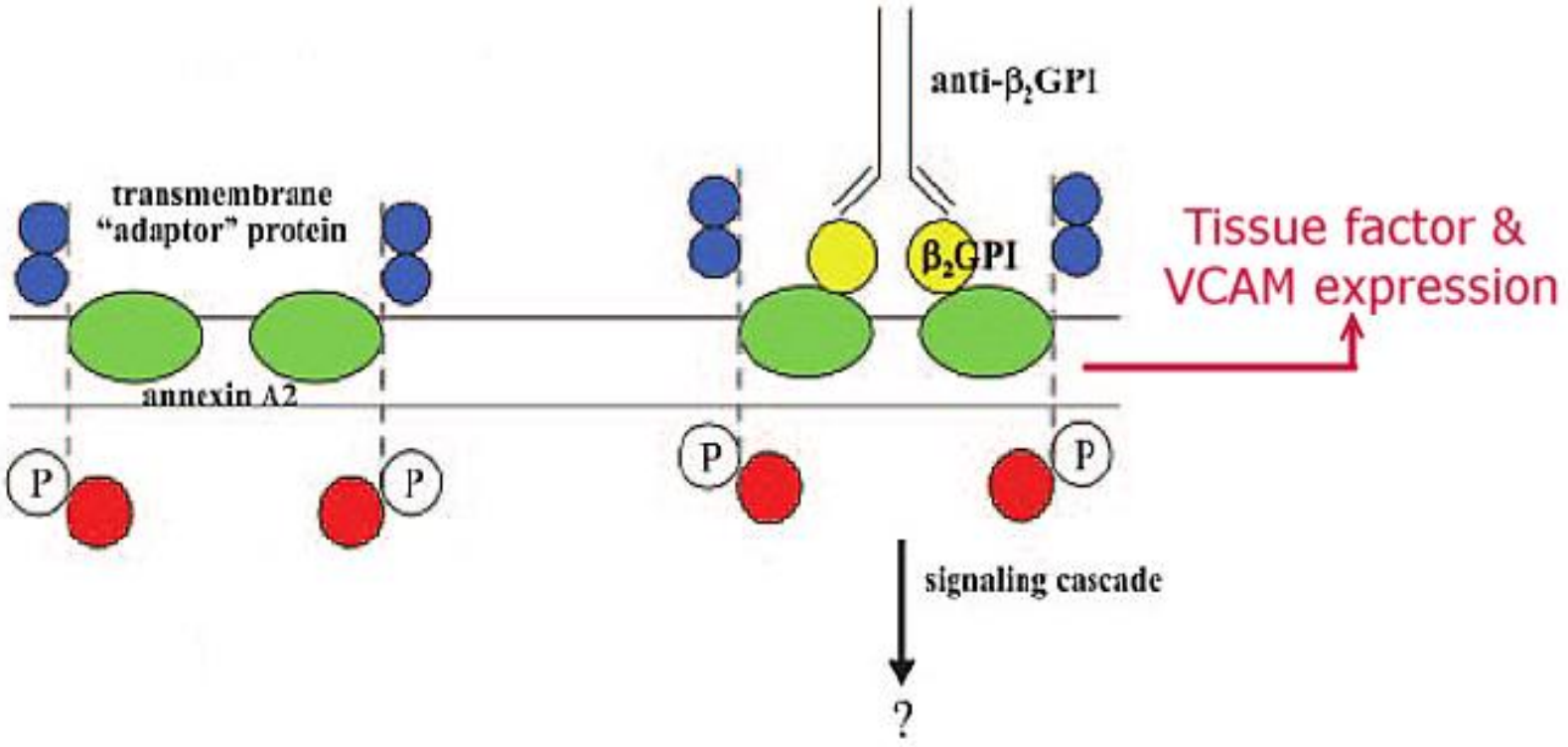


MM: Disruption of anti-inflammatory function of ApoER2
Endothelium: Disruption of NO production
Placenta: Decreased vascularity

Cur Op Rheum 2017 29 (5) 458-66
Sem Throm Hem 201844(5) 475-82
Throm Res 2004 114(5) 335-46

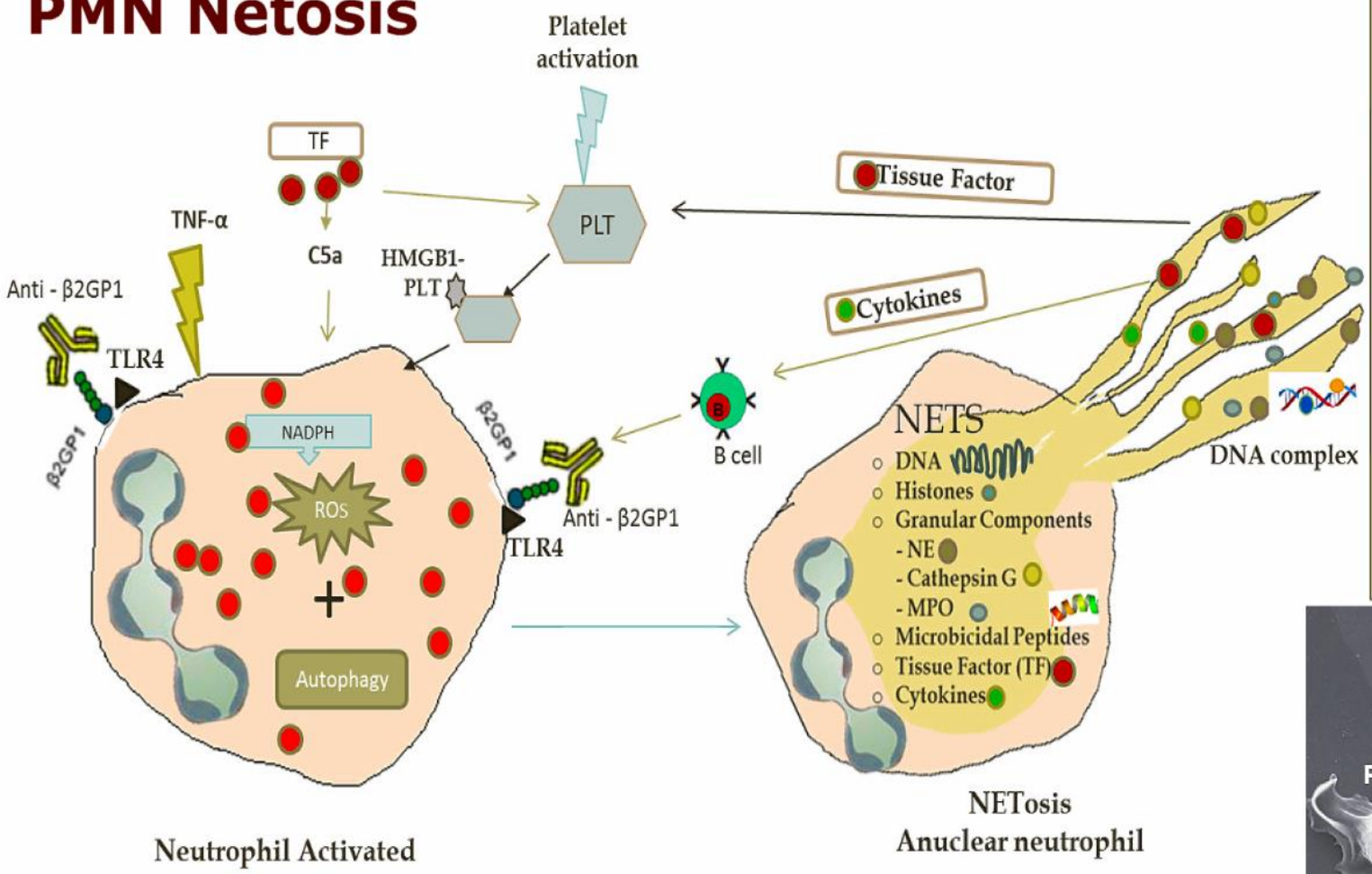
Annexin A2 is present on Endothelium & Monocyte/macrophages.

Cross-linking of Annexin A2/B2GP-I complexes on endothelial cells by anti-B2GP-I activates the cell.

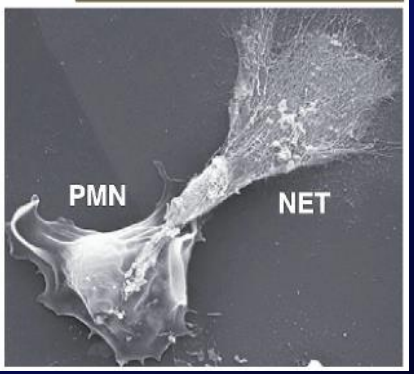


Sem Throm Hem 2018 44(%) 483-492
Blood 2005 105: 1964-1969

PMN Netosis



- *Hipoxia in fetus*
- *Reduction of blood flow*
- *Obstruction of Intervillous space*
- *Supression of Fibrinolisis*
- *Activation of coagulation cascade*
- *Activation of factor XIII that iniciate coagulation and fibrin formation*
- *Activation of sequester of thrombomodulin and protein*
- *Inactivation of anticoagulant molecules*

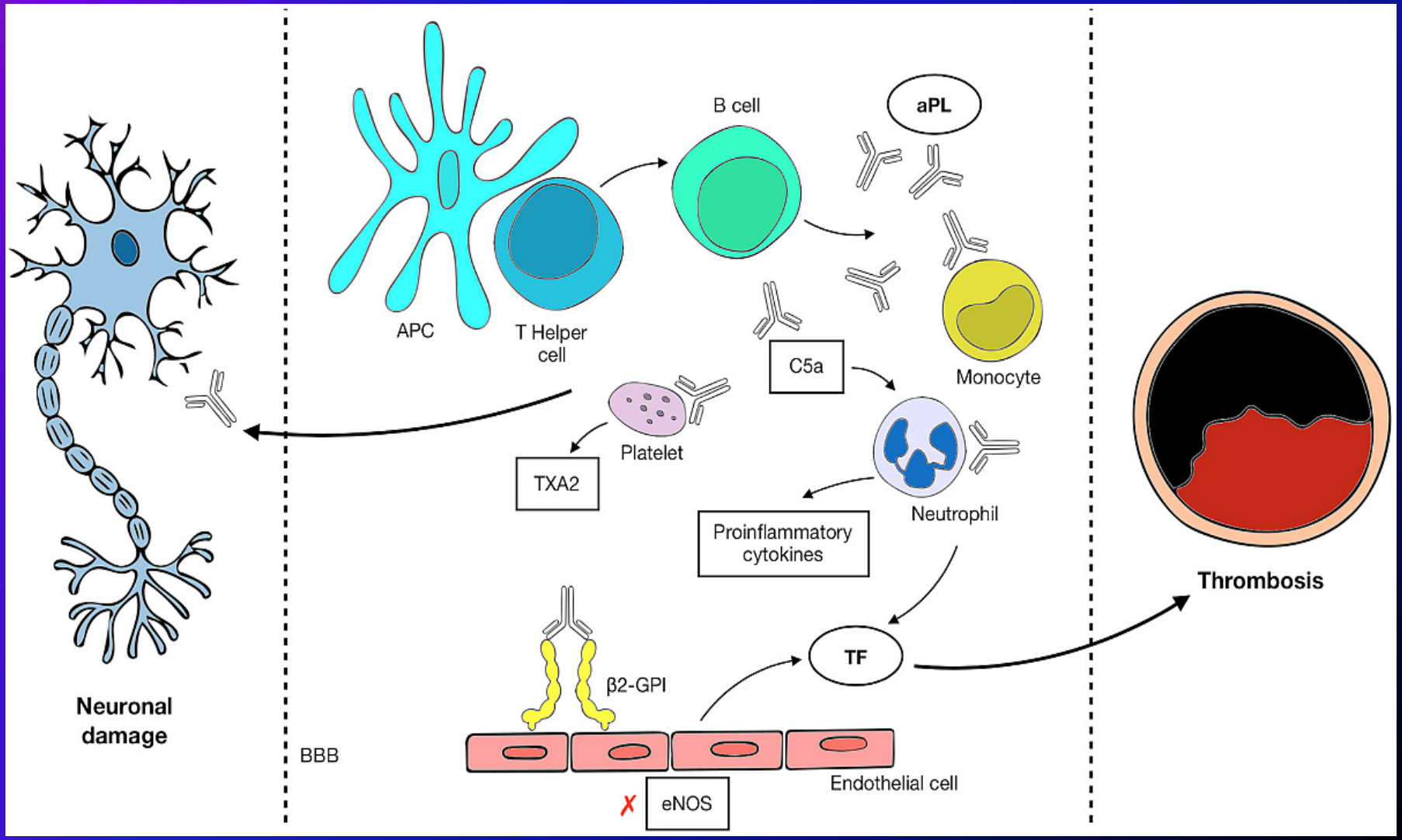


High Mobility Group Box-1
Complement activation & C5a production
Anti-B2GP-I complex with B2GP-I
TNF-α

→ **PMN Netosis**

Antibodies 2017, 6 4
Front Imm 2018 vol 9 art 969

Pathogenesis of Neuro-APS



Neuro-APS

Neurological manifestations associated with antiphospholipid syndrome	Features
Thrombotic manifestations	
Spinal cord stroke	Uncommon feature; less frequent than transverse myelitis
Acute ischemic encephalopathy	Uncommon feature in APS secondary to SLE; presents with tetraparesis, confusion, and hyperreflexia
Ischemic stroke Transient ischemic attack (TIA)	The most common manifestations of APS; important cause of juvenile stroke; any brain region can be interested
Cerebral venous thrombosis	Uncommon vascular manifestation
Nonthrombotic manifestations	
Headache	Frequent and often untreatable; no definite association between aPL positivity and type of headache [34]
Multiple sclerosis	APS can mimic multiple sclerosis; no definite tests to differentiate these entities are available
Transverse myelitis	Rare acute inflammatory manifestation; more common in APS secondary to SLE
Sensorineural hearing loss	Acute onset in the presence of aPL may be a manifestation of APS [37]
Guillain-Barrè syndrome	Antiphospholipid antibodies probably produced as a result of myelin damage
Peripheral neuropathy	*Mononeuritis multiplex* due to vasculitis is most commonly found in SLE; axonal neuropathy can be asymptomatic in PAPS
Cognitive dysfunction and dementia	Caused by multiple brain strokes; Alzheimer's disease-like dementia in 6% of cases
Idiopathic intracranial hypertension	Can be the presenting feature of APS
Epilepsy	In 10% of patients; primary or secondary to stroke
Chorea and other movement disorders	Rarely due to stroke in the basal ganglia; frequent in patients with APS secondary to SLE

Non-thrombotic Neuro-APS

Experimental Evidence of Direct Effect of aPL on Neurons

Resting lymphocytes cannot cross BBB but activated lymphocytes can; then in the presence of autoantigen they can expand there and produce aPLs. *J Imm Research 2014 ID 239398*

Anti-β2GP-I antibodies can bind various CNS cells in animal models. *J Neurological Sciences, 1998 vol. 156, no. 2, pp. 211–219,*

Long-term exposure of mice to anti-phospholipid antibodies leads to behavioral changes and cognitive decline. *Lupus (2001) 10:496–9*

Anti-phospholipid–immunized mice show BBB disruption and accumulation of aPLs in hippocampus neurons. *Neurobiol Dis. (2008) 30:56–64*

Serum IgG of pediatric APS patients who developed chorea, binds to cell-surface of cultured neuronal cells. *Dev Med Child Neurol. (2011) 53:522–8*

Nonthrombotic NeuroAPS

- Nonthrombotic neurological manifestations occur in up to 40% of patients with elevated anti-phospholipid antibodies .

Clinical Neurology & Neurosurgery, vol. 108, no. 2, pp. 135–142, 2006

- Transverse Myelitis in APS could be either thrombotic, vasculitis or the result of antineuronal antibodies, or even demyelinating!

J Clin Investigation, 2010, vol. 40, no. 4, pp. 350–359,

- Cognitive impairment is seen in 42-80% of primary APS patients. In a subset of these patients no vascular lesion can be found which indicates to the direct aPL effect.

Curr Rheum Rep (2016) 18:11, Clin Rheumatol. (2012) 31:403–6

- Peripheral neuropathy in primary APS is either secondary to vasculitis or thrombosis of vasa vasarum. However, targeting lipid components of myelin by aPL is a possible cause, especially in cases of Guillain-Barre that is reported in primary APS. *Clin Rheumatol. (2012) 31:403–6*

Prevalence of aPL in MS Patients

Study	Population	aPL antibodies positivity
Filippidou et al. (2016)	127 MS (Serum); 88 RR, 11 PP, 28 SP	RR: aCL: 10.2% IgM, 18.2% IgG PP: aCL: 36.4% IgM, 18.2% IgG SP: aCL: 35.7% IgM, 32.1% IgG
Mandoj et al. (2015)	100 MS (Serum); 58 REM, 26 REL, 16 SP	REM: aCL: 1.7% IgM, 1.7% IgG, aβ2GPI: 1.7% IgM, aPT: 3.4% IgM, 5.2% IgG, aAnV: 1.7% IgM, 6.9% IgG REL: aCL: 7.7% IgM, 11.5% IgG, aβ2GPI: 26.9% IgM, aPT: 15.4% IgM, 19.2%IgG, aAnV: 3.8% IgM,15.4% IgG SP: aCL: 6.3% IgM, 6.3% IgG, aβ2GPI: 6.3% IgM, aPT: 6.3% IgM, aAnV: 6.3% IgM, 18.8% IgG
Shor et al. (2015)	98 MS (Serum)	aPS-β2: 14.6% IgM, 22.4% IgG, aPT: 46.9% IgM, aPT-PT: 71.4% IgG
Koudriavtseva et al. (2014)	100 MS (Serum)	aCL: 4% IgM, 5% IgG, aβ2GPI: 9% IgM, aPT: 7% IgM, 8% IgG, aAnV: 3% IgM, 11% IgG
Szmyrka-Kaczmarek et al. (2012)	85 MS (Serum)	aβ2GPI: 20% IgM, aCL: 4.7% IgM, 1% IgG
Stosic et al. (2010)	49 MS (Serum)	aCL: 18.4%, aβ2GPI: 10.2%, aPS: 18.4%, aPE: 32.6%
Garg et al. (2007)	111 MS, 27 CIS (Serum)	MS: aCL: 6%, aβ2GPI: 2%, CIS: aβ2GPI: 4%
Bidot et al. (2007)	24 RRMS (Serum); 7 REM, 17 REL	REM: aβ2GPI: 28% IgM, aCL: 28% IgM, aPS: 14% IgM, aPE: 28% IgM, aPC: 14% IgM REL: aβ2GPI: 82% IgM, aCL: 82% IgM, aFVIIa: 59% IgM, aPS: 71% IgM, aPE: 82% IgM, aPC: 76% IgM
Roussel et al. (2000)	89 MS (Serum)	aCL: 4.5% IgM, 16.9% IgG aβ2GPI: 13.5% IgM, 2.2% IgG
Karussis et al. (1998)	170 MS (Serum); 100 atypical, 70 classical	aCL: 27% atypical MS aCL: 5.7% classical MS
Sugiyama and Yamamoto (1996)	32 MS (Serum)	aCL: 44% IgM, 9% IgG
Marchiori et al. (1990)	33 MS (Serum, CSF)	aCL: 46.2% IgG (CSF)

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Anti-Cardiolipin Targets Astrocytes in MS

The results of this in vitro study show that IgG fractions from MS patients who are positive for anti-cardiolipin antibodies activates cultured astrocytes, while IgG from MS patients who are no positive for anti-cardiolipin antibodies do not activate astrocytes.

Clinical features and immunological characterization of the subjects used as a source of IgG

	MS (n = 127)	HC (n = 92)
Gender (Female:Male)[a]	89:38	55:37
Mean age (SD)	51.69 (12.19)	52.1 (17.75)
RRMS	88	N/A
SPMS	23	N/A
SPMS with relapse	5	N/A
PPMS	11	N/A
Anti-Cardiolipin IgM	27/127 (21.3%)	1/92 (1.1%)
Anti-Cardiolipin IgG	23/127 (18.1%)	1/92 (1.1%)
Anti-β2-Glycoprotein I IgM	6/127 (4.7%)	0/92 (0%)
Anti-β2-Glycoprotein I IgG	3/127 (2.4%)	0/92 (0%)
Anti-Domain I IgM	8/127 (6.3%)	1/92 (1.1%)
Anti-Domain I IgG	9/127 (7.1%)	1/92 (1.1%)

It seems that TLR2 &/or TLR4 can be involved in antiphospholipid signaling and astrocyte response in MS patients.

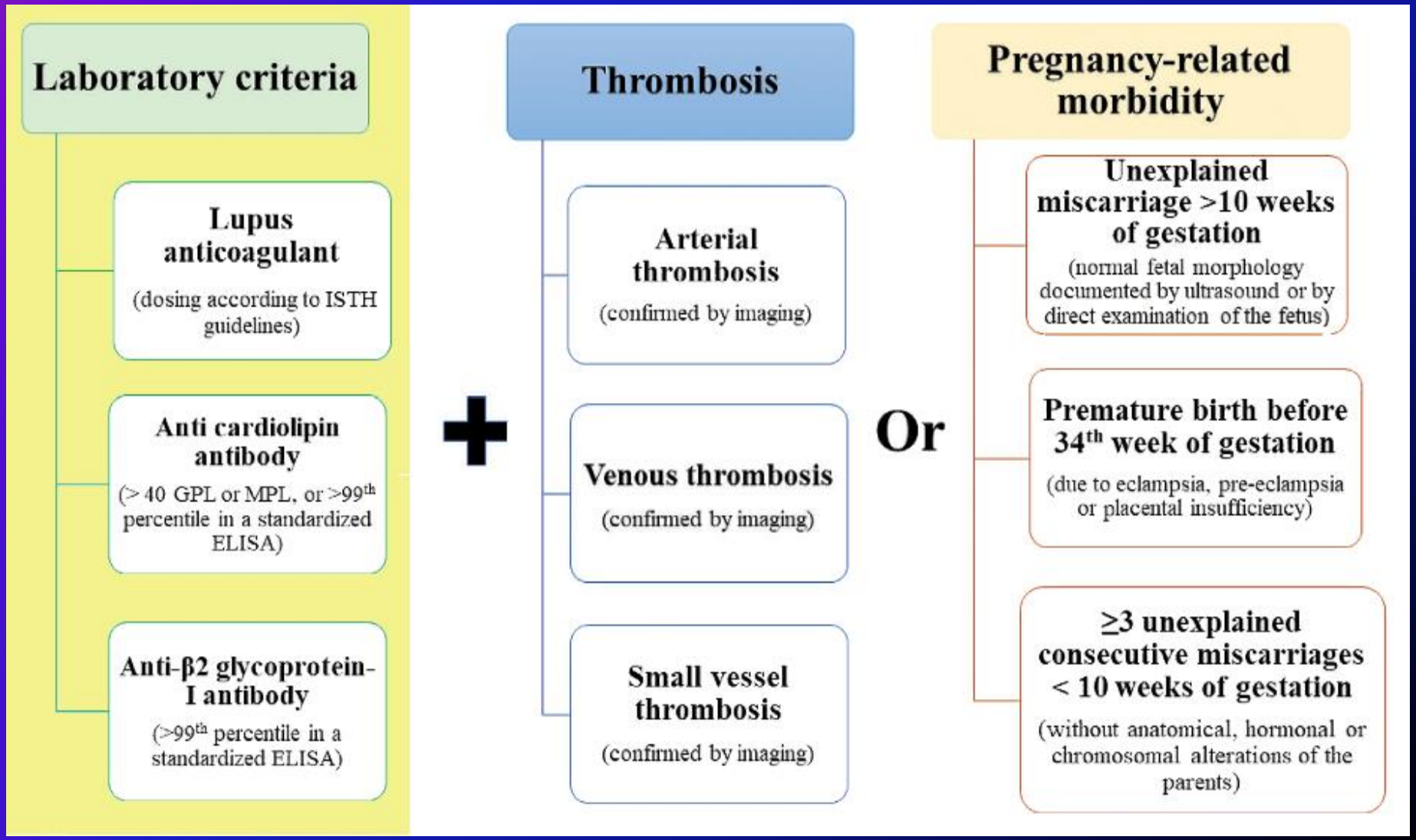
Journal of Immunological Methods 474 (2019)

MS-like CNS Lesions in NeuroAPS

The following are in favor of MS-like Primary NeuroAPS (and against the diagnosis of MS):

1) Negative VEP
2) Negative Oligoclonal bands in CSF
3) Atypical (for MS) CNS MRI intensity changes:
   - Small and non-expanding lesions
   - Subcortical lesions
   - Spinal lesions extending 3 or more segments

APS Diagnostic Criteria



The Prospect of Future Changes in APS Diagnostic Criteria

1) Addition of some non-criteria Clinical Manifestations, (especially non-thrombotic manifestations)

2) Cut-off lowering in serologic criteria

3) Addition of IgA isotype to the serologic criteria

4) Addition of anti-phosphatidylserin-prothrombin complex

*) Emergence of a whole new concept (?):

"**Anti-lipid Autoimmune Disease**"!

Seizures in NT-APS

Epilepsy and seizures are reported among the neurological manifestations of antiphospholipid syndrome (APS) at a prevalence rate of approximately 8%, which is nearly 10 times the prevalence of epilepsy in the general population.

Seizures in APS may develop in structurally normal brains, suggesting antibody-mediated mechanism.

Clin Dev Immunol. (2012) 2012:981519