Unmet Biological Needs in ITP

JOHN W. SEMPLE
PROFESSOR OF TRANSFUSION MEDICINE, LUND UNIVERSITY, LUND SWEDEN
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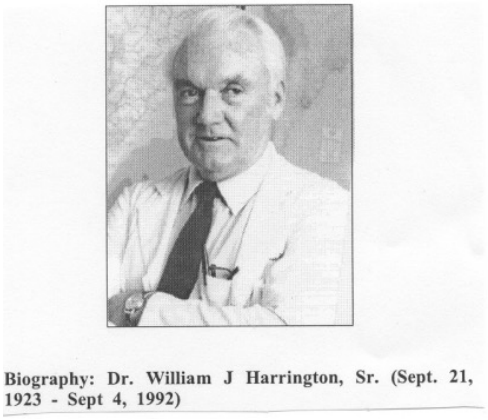
Harrington-Hollingsworth Experiment



Biography: Dr. William J Harrington, Sr. (Sept. 21, 1923 - Sept 4, 1992)

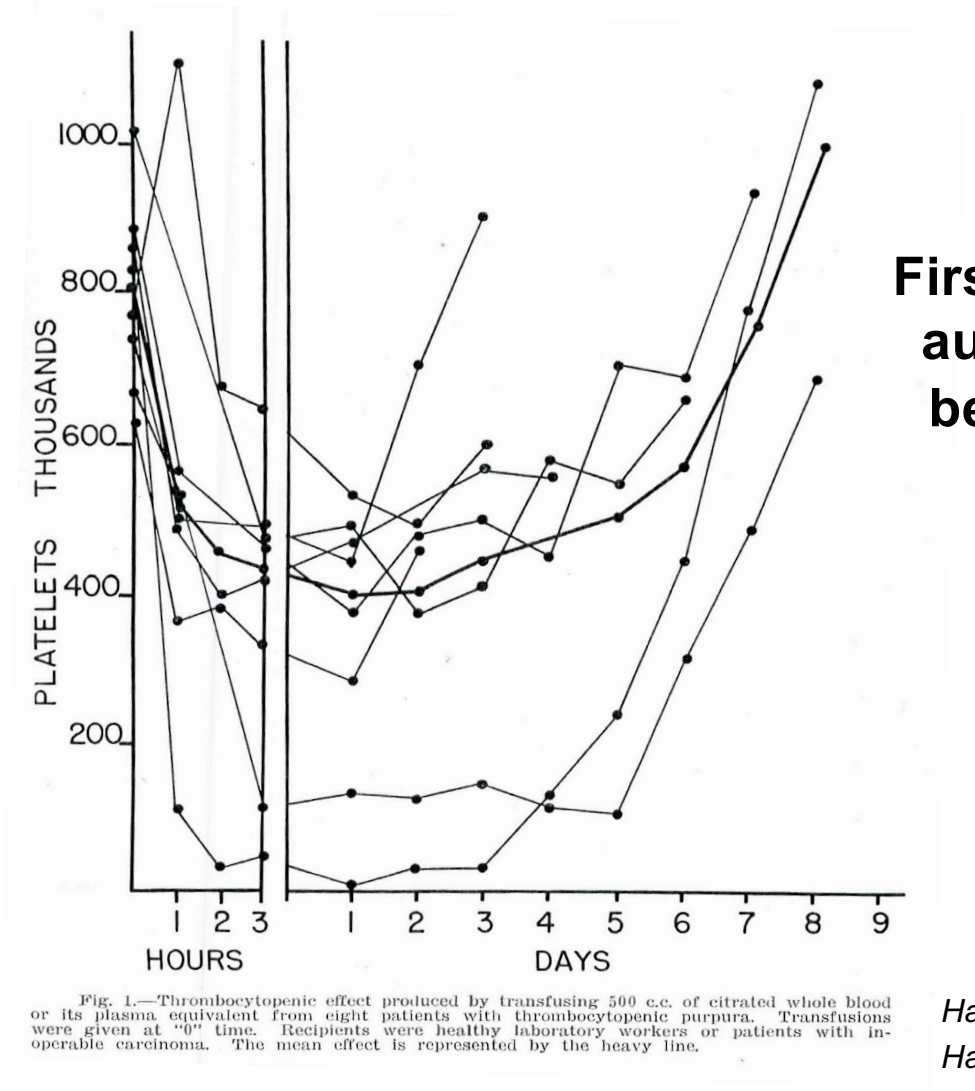
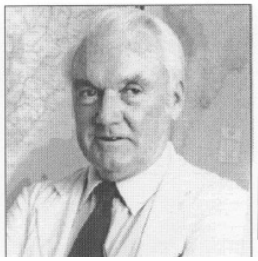


Fig. 1.—Thrombocytopenic effect produced by transfusing 500 c.c. of citrated whole blood or its plasma equivalent from eight patients with thrombocytopenic purpura. Transfusions were given at "0" time. Recipients were healthy laboratory workers or patients with inoperable carcinoma. The mean effect is represented by the heavy line.

First demonstration that an autoimmune disease can be transferred by plasma

Harrington et al, J Lab Clin Med 38:1, 1951
Harrington et al: Ann Int Medicine 38:433, 1953

Harrington-Hollingsworth Experiment



DEMONSTRATION OF A THROMBOCYTOPENIC FACTOR IN THE BLOOD OF PATIENTS WITH THROMBOCYTOPENIC PURPURA

WILLIAM J. HARRINGTON, M.D., VIRGINIA MINNICH, M.S., JAMES W. HOLLINGSWORTH, M.D., AND CARL V. MOORE, M.D.
ST. LOUIS, MO.

Biography:
1923 - Sep

sible that the frequent relief of thrombocytopenia by splenectomy is due in part to a decrease in the rate of platelet destruction sufficient to permit the marrow to compensate for the platelet-removing effect of the thrombocytopenic factor. Much more experience will be needed before all possibilities can be adequately evaluated. Idiopathic thrombocytopenic purpura may not be a single entity, but a syndrome in which more than one pathogenic mechanism may be involved. The role of the spleen, and of the spleen-bone marrow interrelationship still lacks precise definition.

Fig. 1.—Thrombocytopenic effect produced by transfusing 500 c.c. of citrated whole blood or its plasma equivalent from eight patients with thrombocytopenic purpura. Transfusions were given at "0" time. Recipients were healthy laboratory workers or patients with inoperable carcinoma. The mean effect is represented by the heavy line.

Harrington et al, J Lab Clin Med 38:1, 1951
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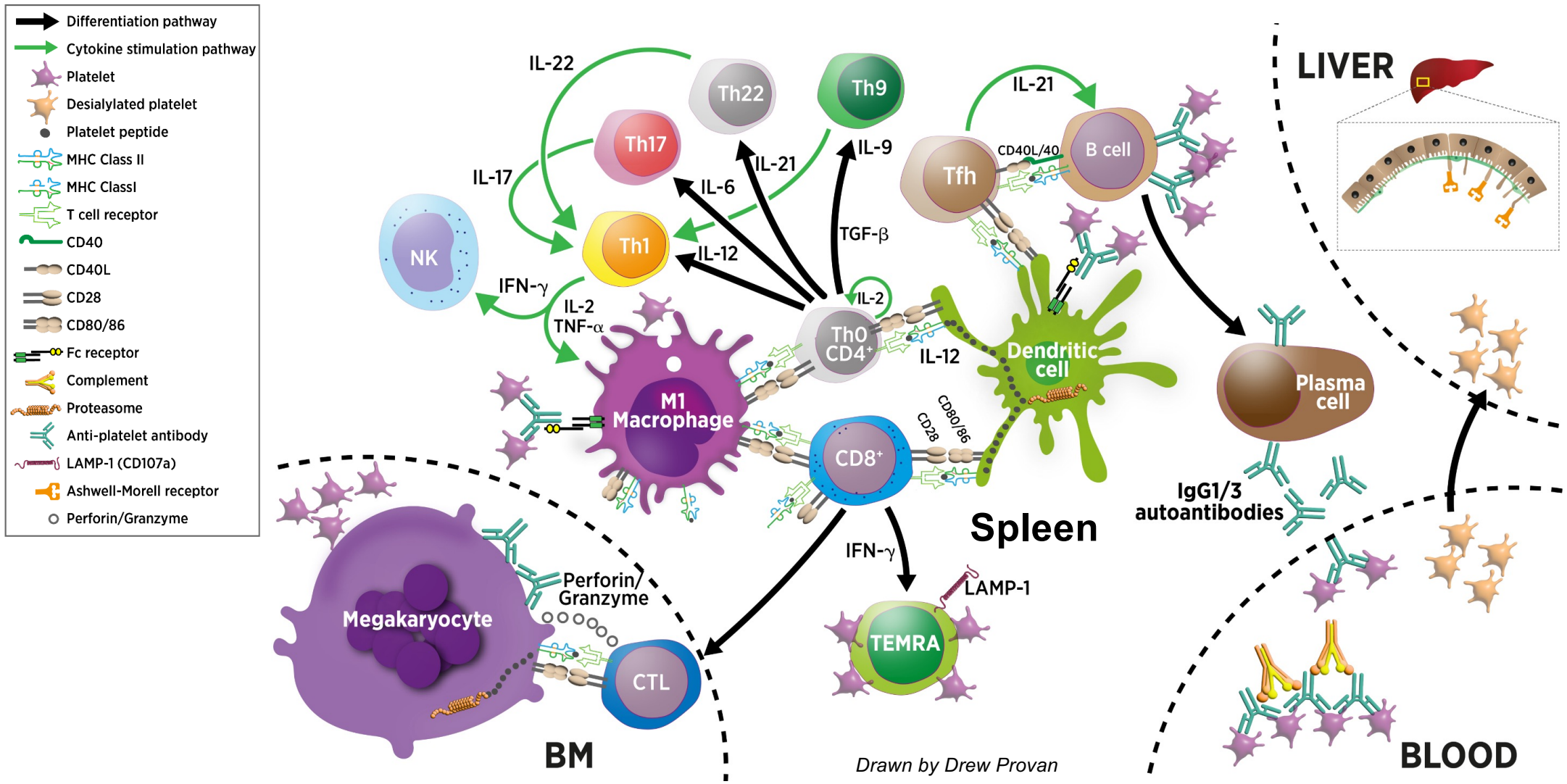
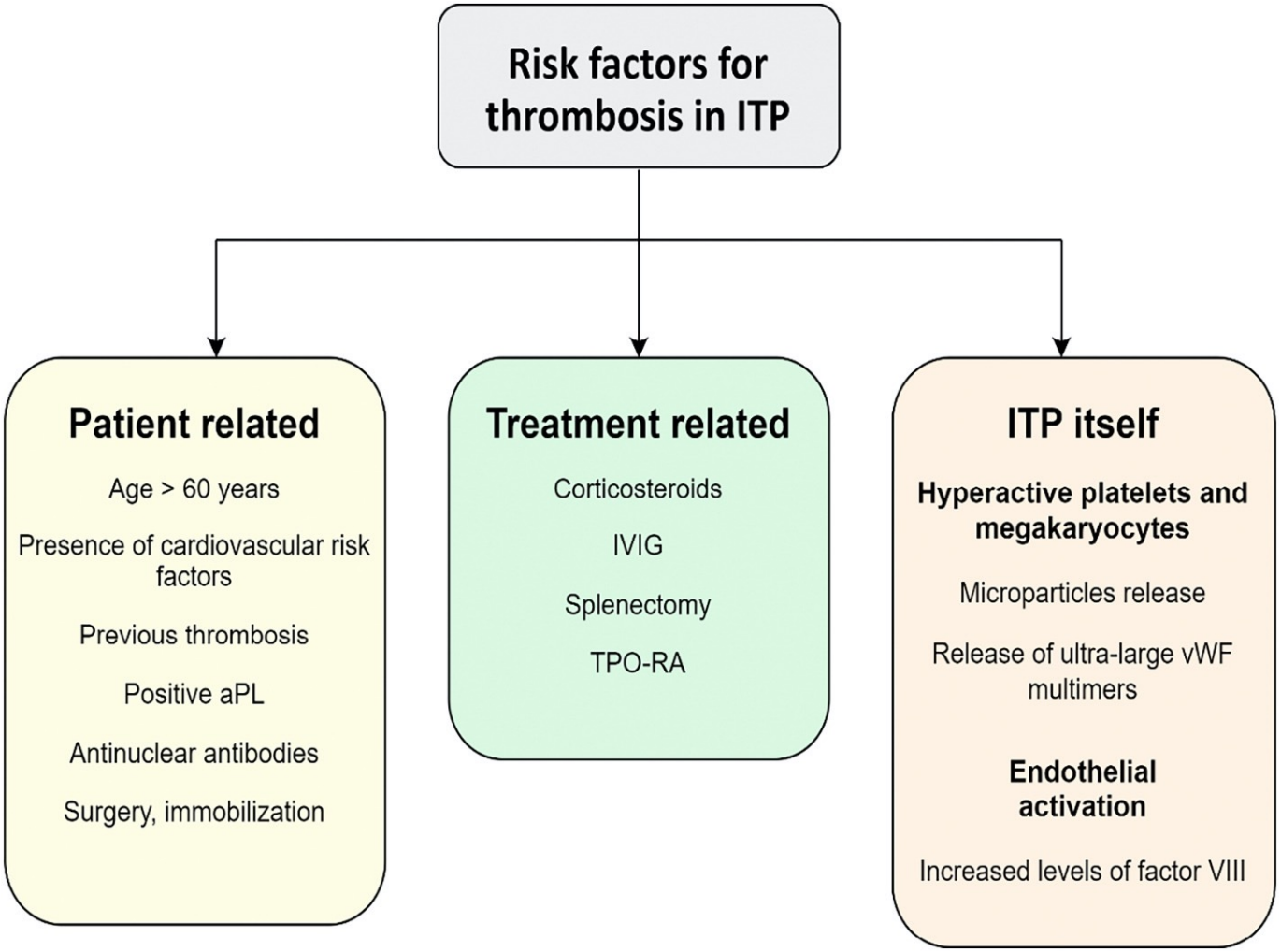
In ITP

Lack of tolerance leads to significant immune dysregulation

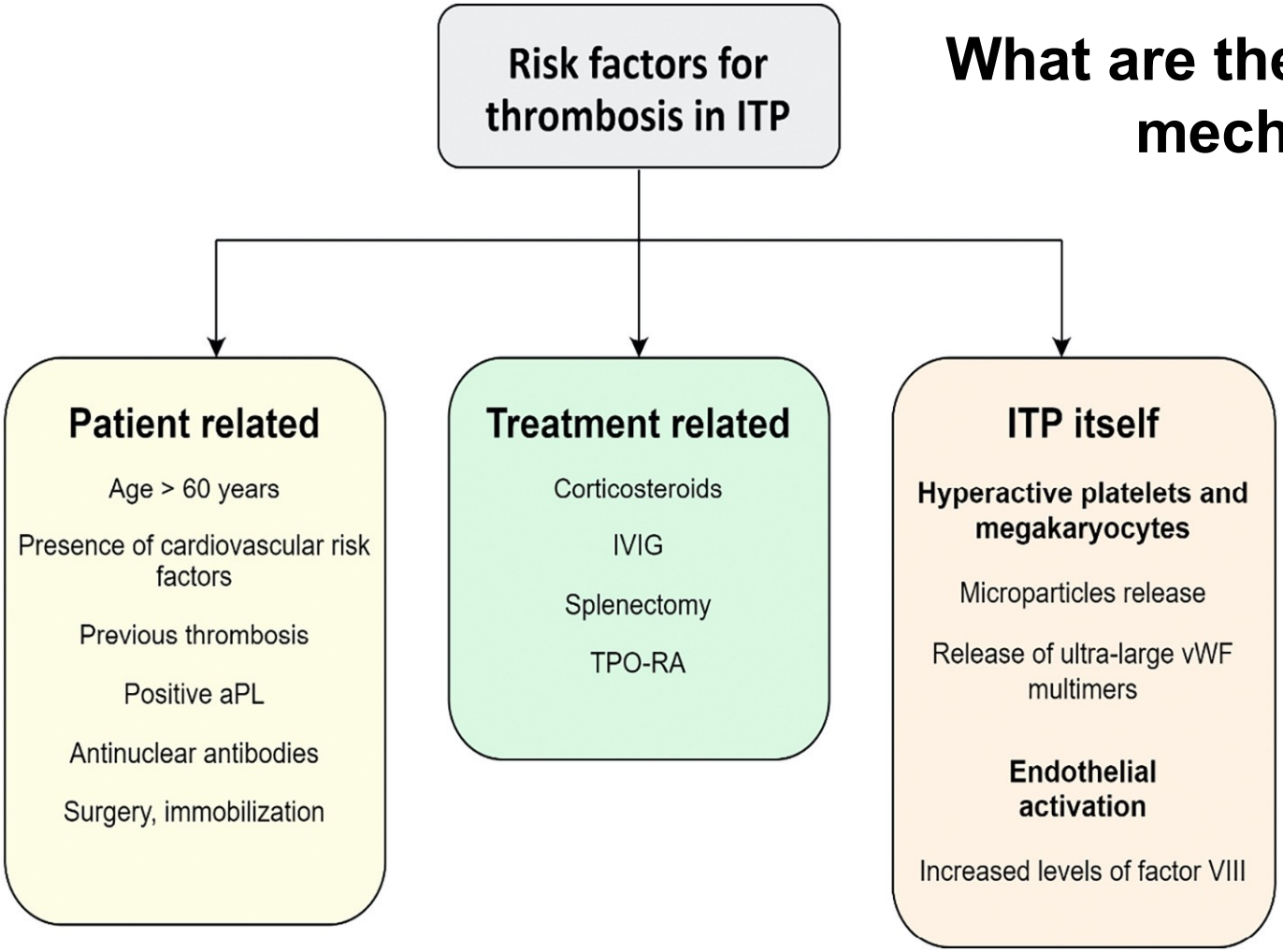


The ITP paradox



Saldanha A et al. Thromb Res 241: 109109, 2024

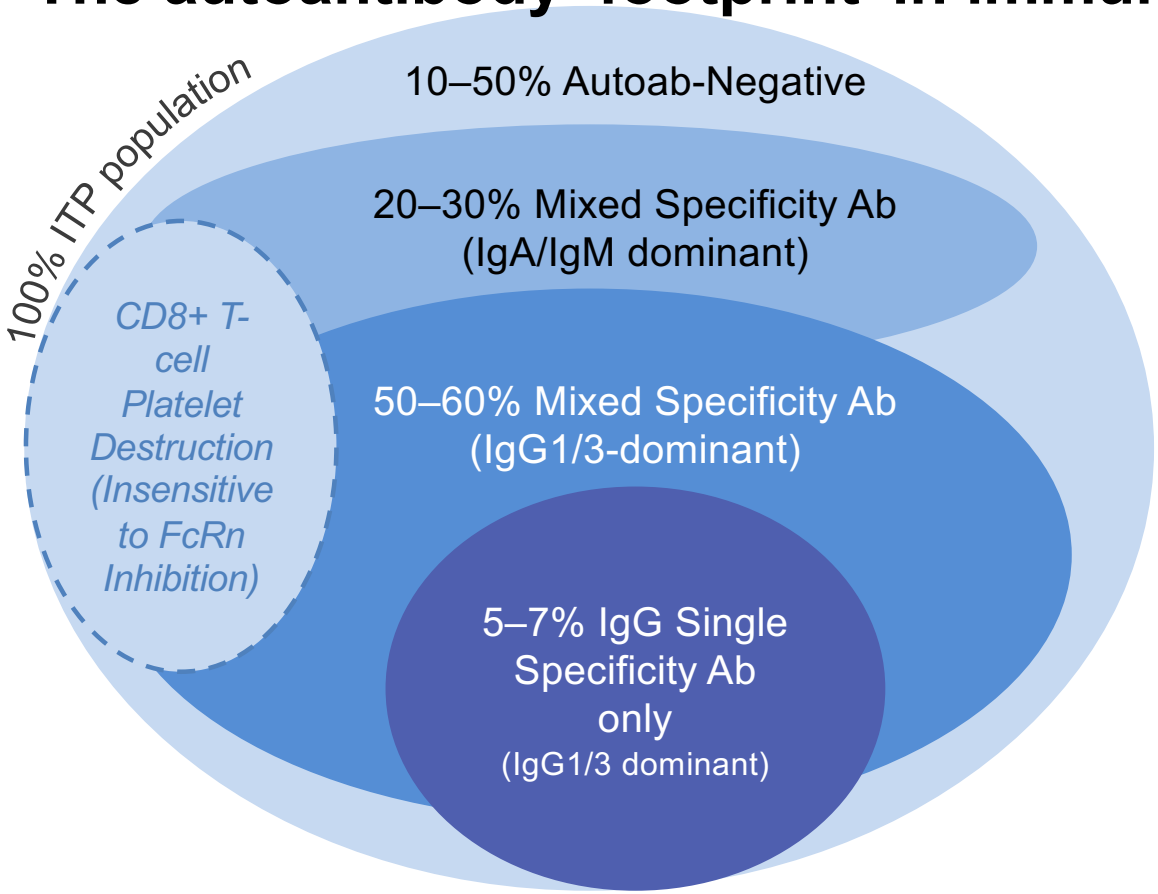
The ITP paradox

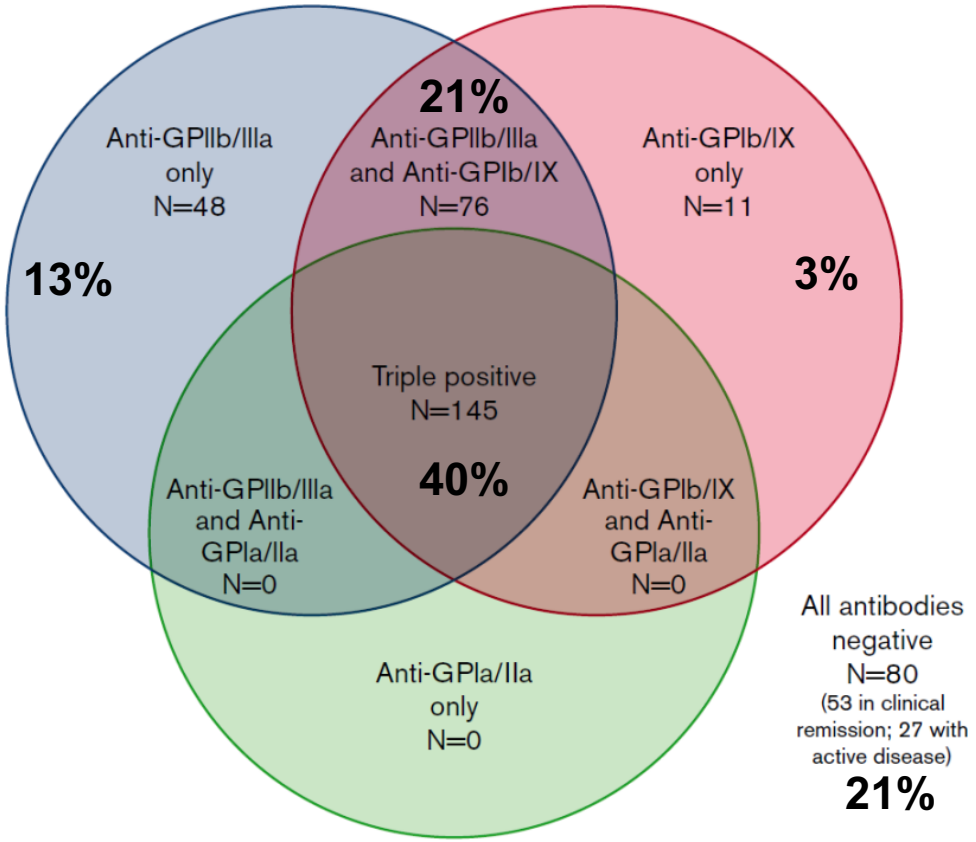


What are the immunoinflammatory mechanisms for this?

Saldanha A et al. Thromb Res 241: 109109, 2024

The autoantibody ‘footprint’ in immune thrombocytopenia:





Results of PA assays in patients with ITP (360 assays total in 260 patients).

1 .Chan H et al. Br J Haematol 2003;122:818–24; 2. He R et al. Blood 1994;83:1024-32; 3. McMillan R. Semin Hematol 2000;37:239-48; 4. Porcelijn L et al. Bailliere’s Clin Hematol 1998;11:331–41; 5. Stahl D et al. Eur J Haematol 2005;75:318–27; 6. Zhao C et al. Haematologica 2008;93:428; 7. Guo L et al. Blood 2006;127:735; 8. Nishioka T et al. Cytometry B Clin Cytom 2005;68:37–42; 9. Hymes K et al. Blood 1980;56:84; 10. Olsson B et al. Nat Med 2003;9:1123–4; 11. Al-Samkari H et al. Blood Adv 2020;4:9–18; 12. Porcelijn L et al. Br J Haematol 2018;182,423–6.

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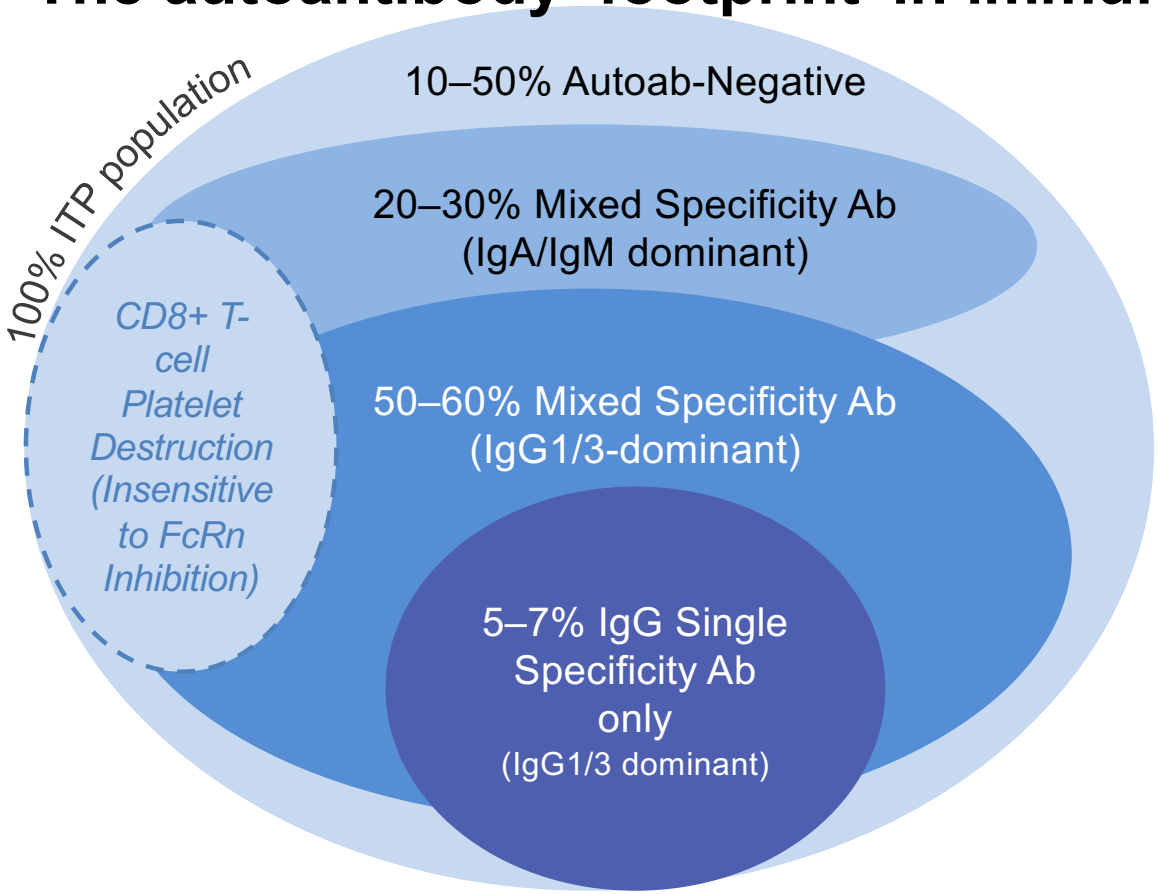

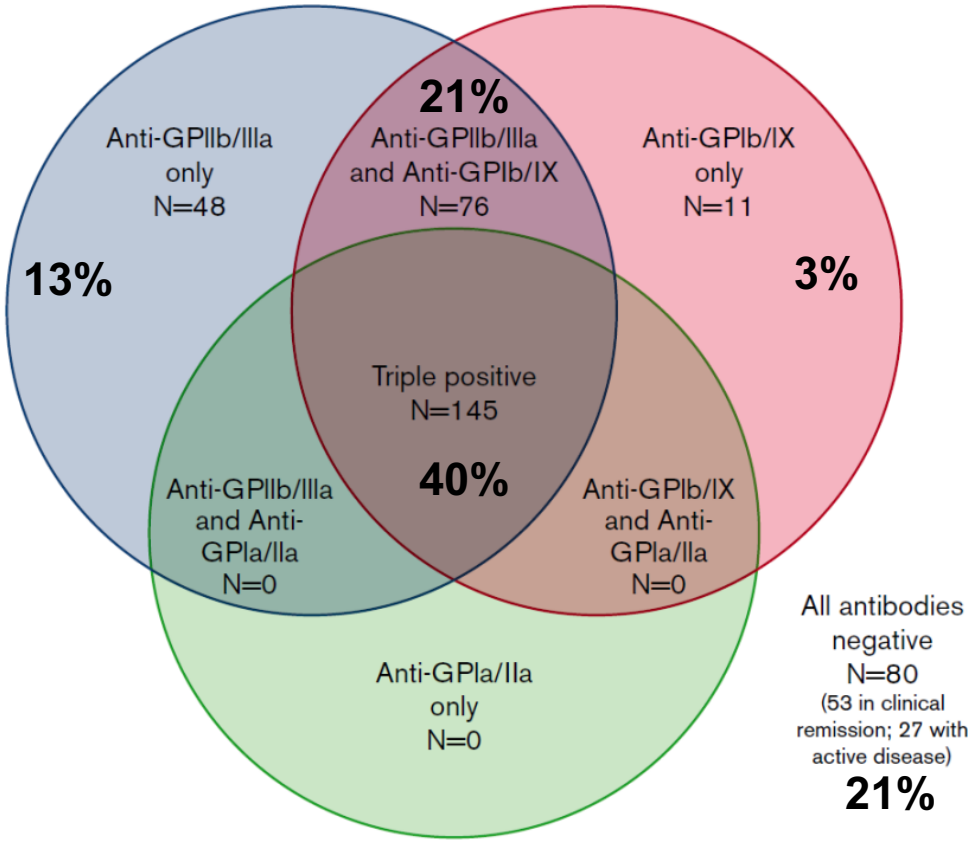

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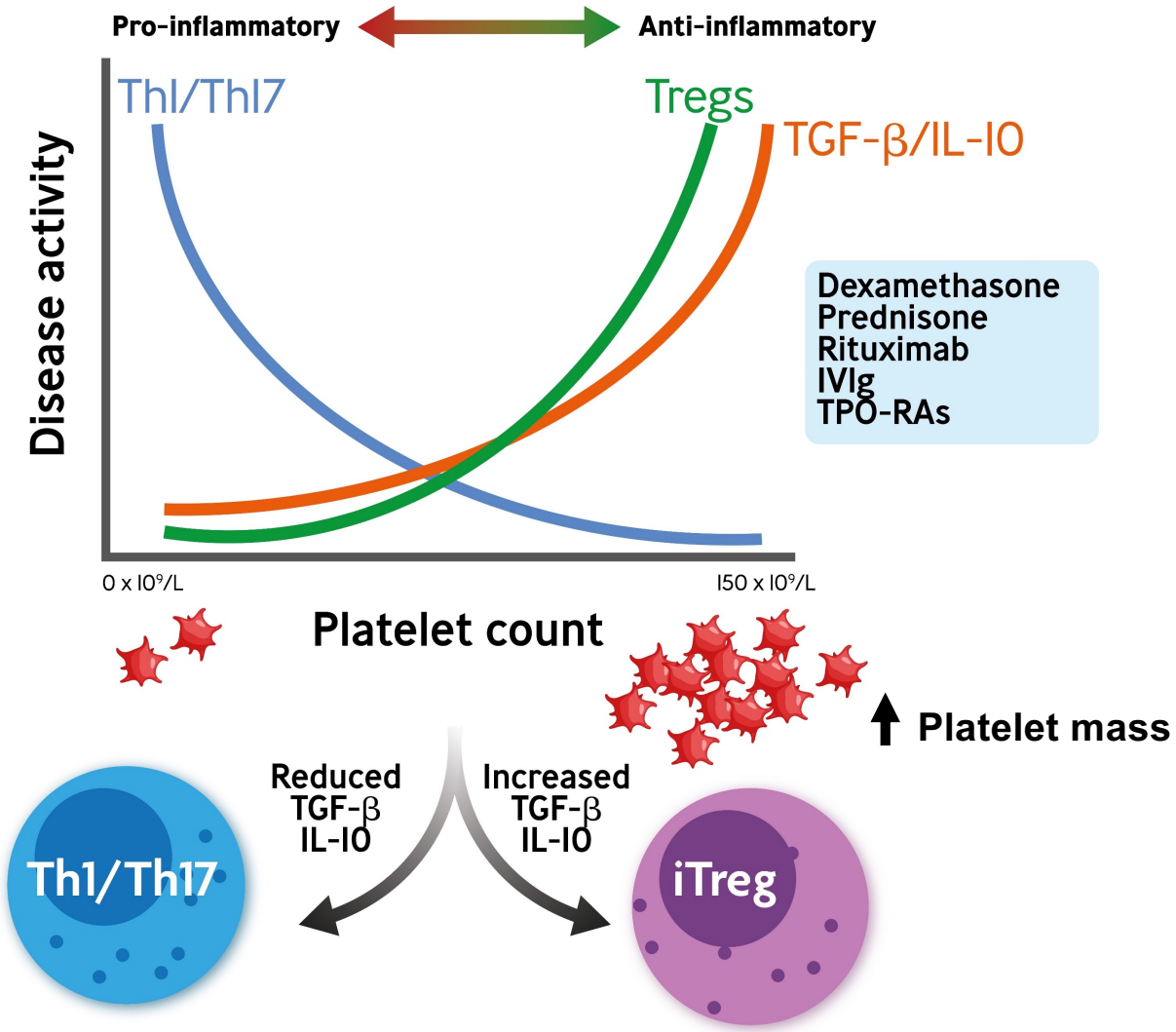
Does the antibody isotype or specificity play a role in how platelets are destroyed?

1 .Chan H et al. Br J Haematol 2003;122:818–24; 2. He R et al. Blood 1994;83:1024-32; 3. McMillan R. Semin Hematol 2000;37:239-48; 4. Porcelijn L et al. Bailliere’s Clin Hematol 1998;11:331–41; 5. Stahl D et al. Eur J Haematol 2005;75:318–27; 6. Zhao C et al. Haematologica 2008;93:428; 7. Guo L et al. Blood 2006;127:735; 8. Nishioka T et al. Cytometry B Clin Cytom 2005;68:37–42; 9. Hymes K et al. Blood 1980;56:84; 10. Olsson B et al. Nat Med 2003;9:1123–4; 11. Al-Samkari H et al. Blood Adv 2020;4:9–18; 12. Porcelijn L et al. Br J Haematol 2018;182,423–6.

Platelet – Treg Relationships in ITP:



Semple JW et al. ISBT Science Series (2020) 15, 315–319

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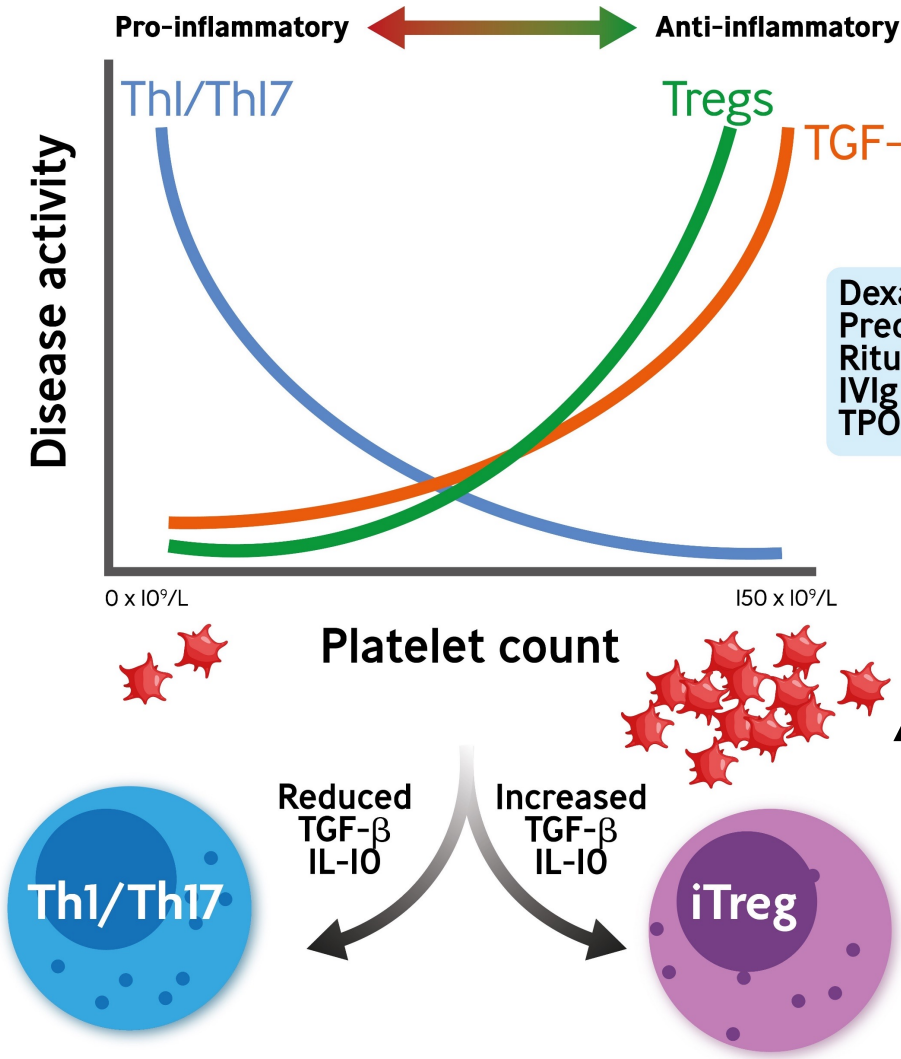
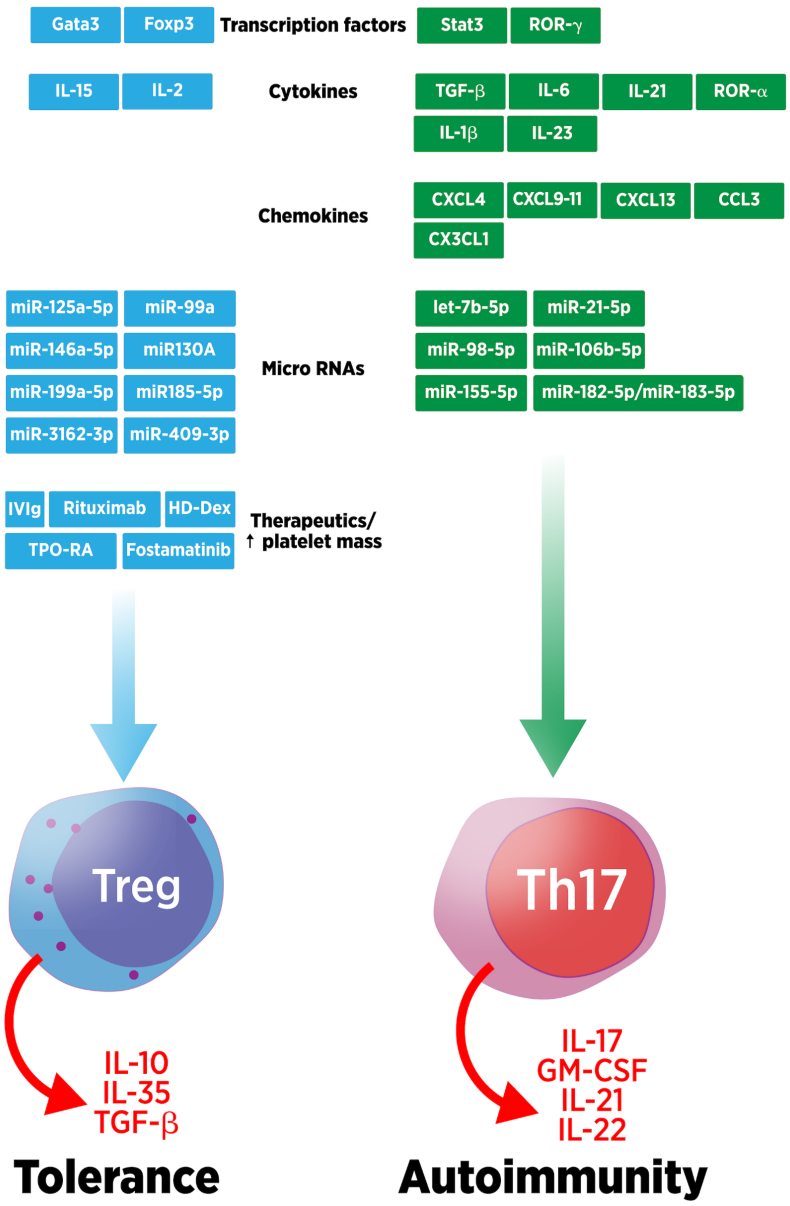


How does the increase in platelet mass affect immunomodulation?

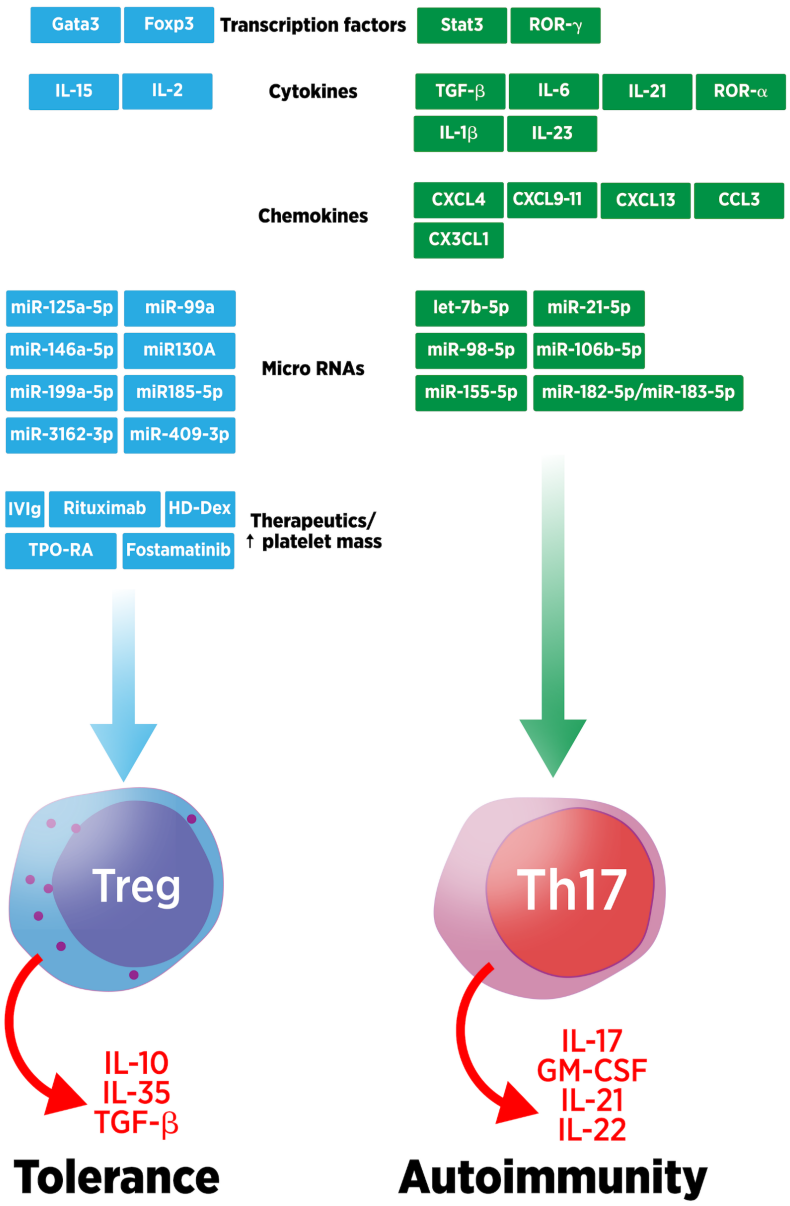
Semple JW et al. ISBT Science Series (2020) 15, 315–319

Factors affecting the Treg/Th17 balance in ITP

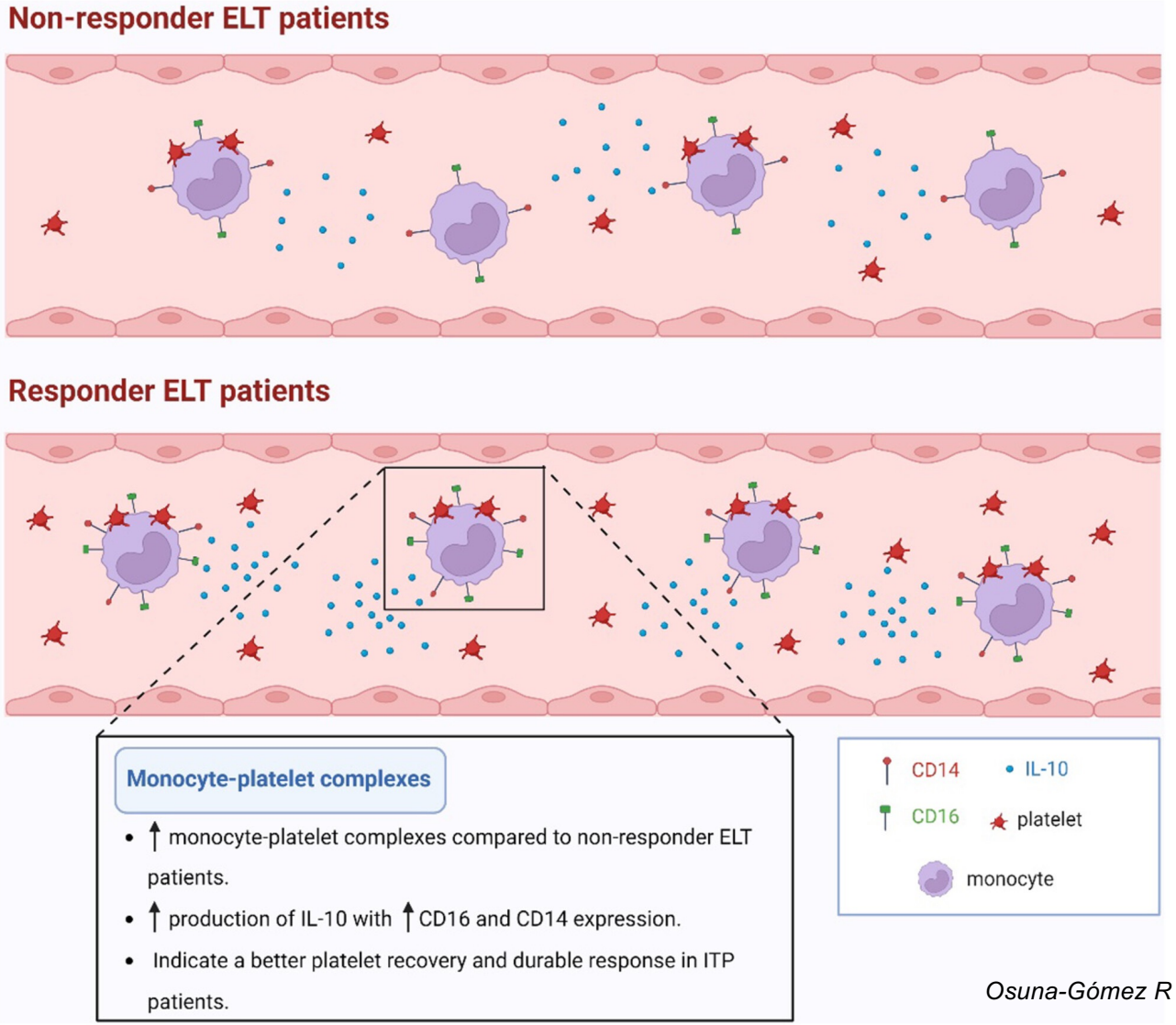


Factors affecting the Treg/Th17 balance in ITP

Are these biomarkers?
Or, associations?



Increased monocyte/platelet complexes and secretion of IL-10



Osuna-Gómez R et al. Br J Haematol.2024;00:1–13. https://doi.org/10.1111/bjh.19779

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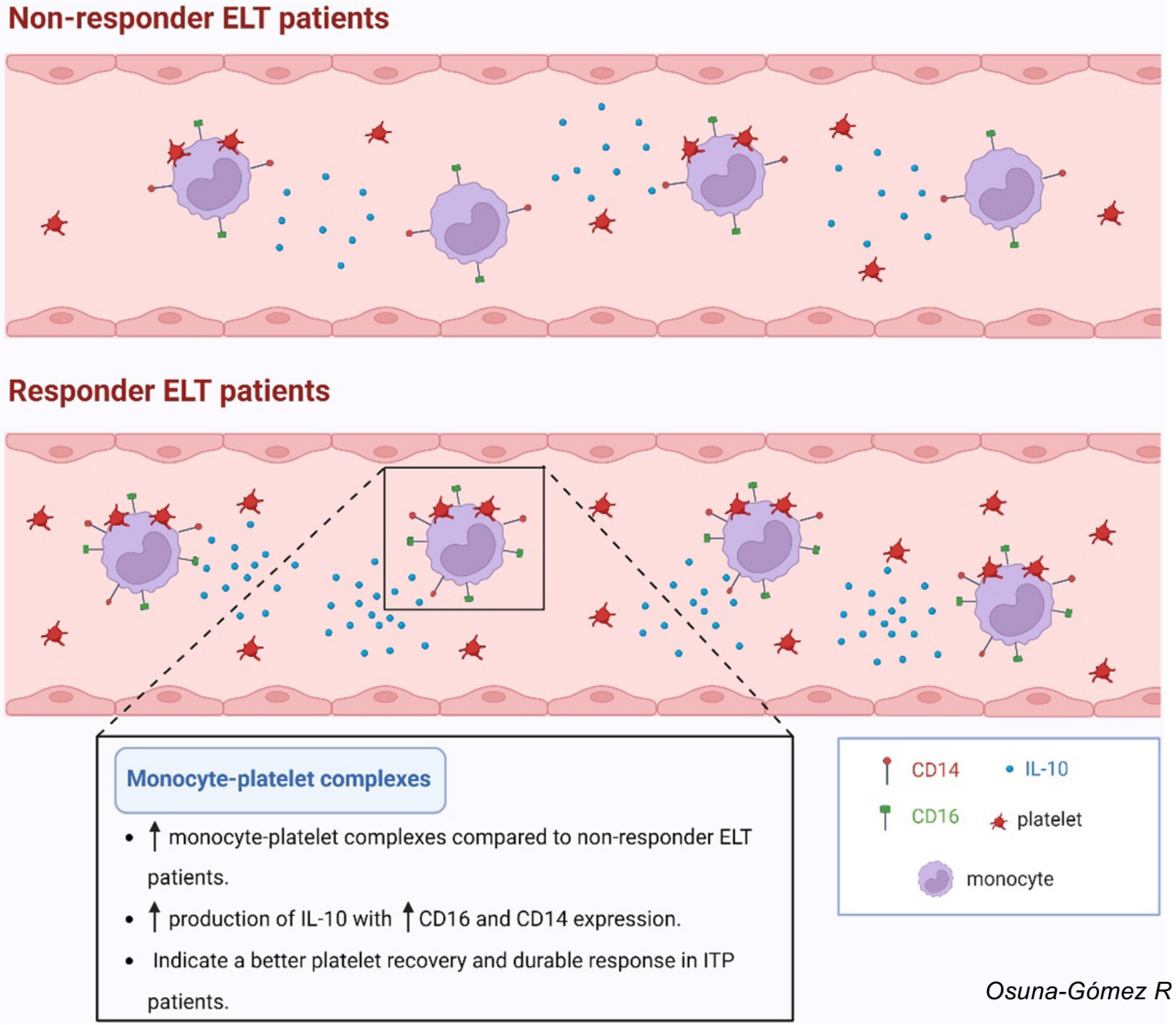
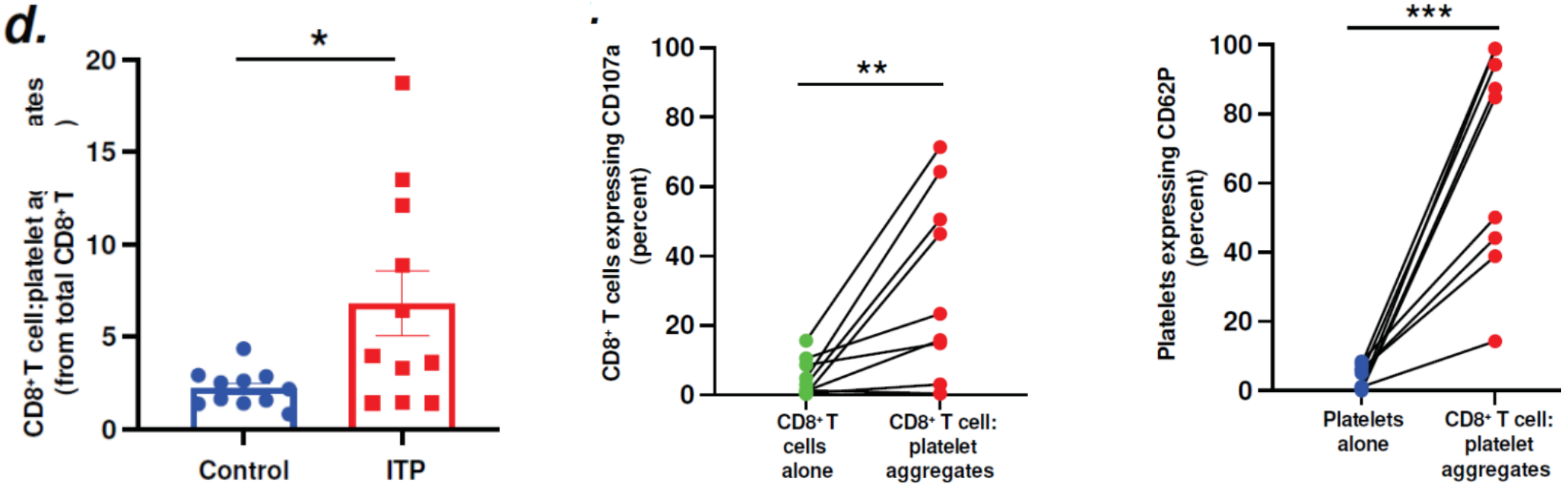


Is this part of the immunomodulation?

Osuna-Gómez R et al. Br J Haematol.2024;00:1–13. https://doi.org/10.1111/bjh.19779

CD8+ T cell: platelet aggregates with increased CD107a and CD62P



Malik et al. Blood. 2023;141(20):2417–2429.

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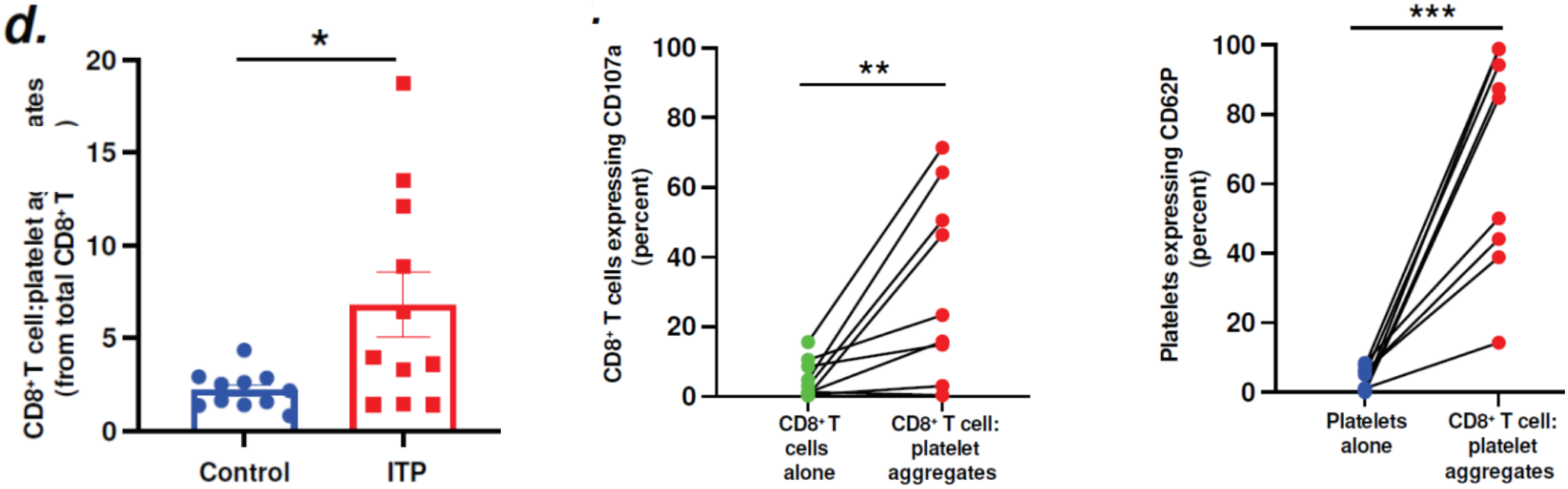
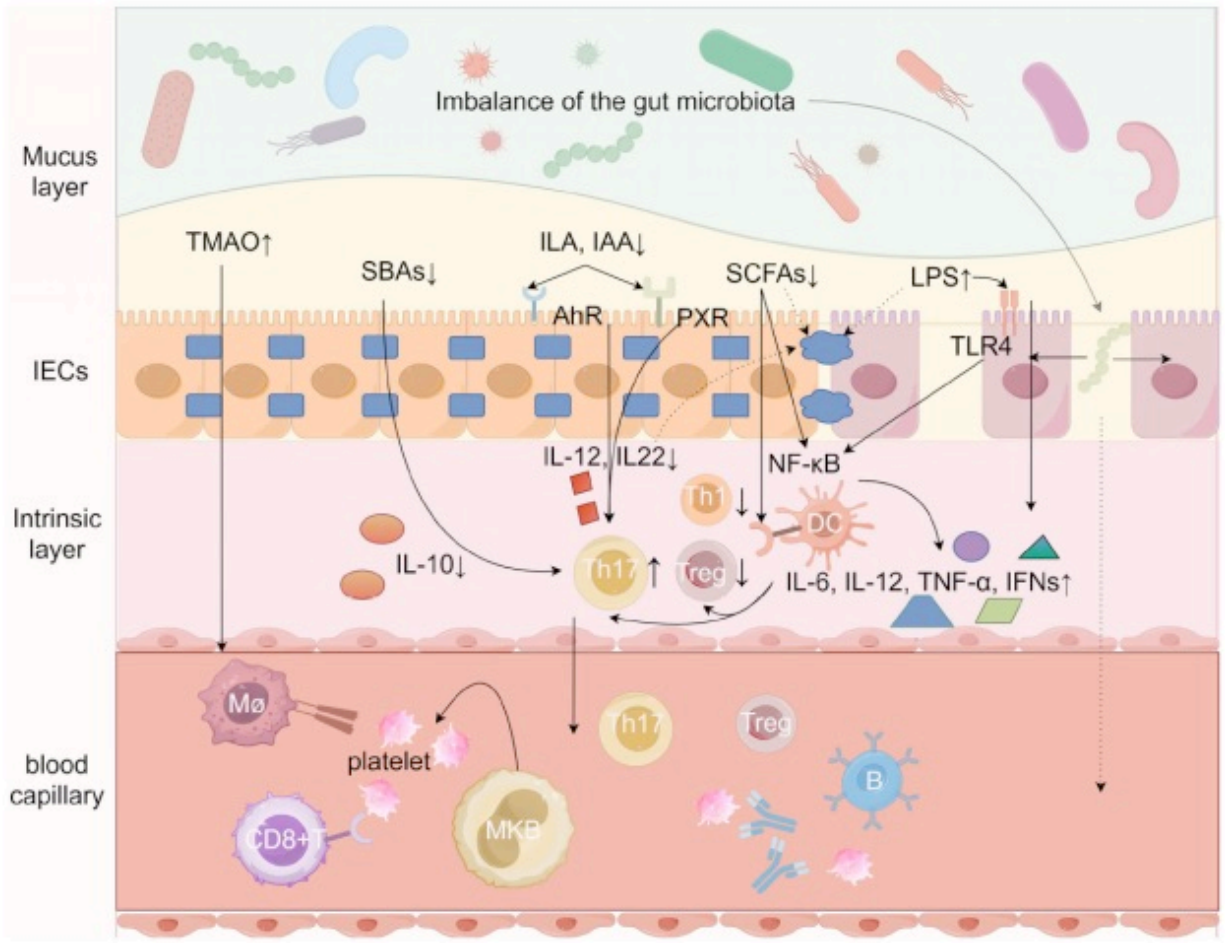


What do these CD8+ T cells do? (Bone marrow?)
Are they involved in refractoriness?

Malik et al. Blood. 2023;141(20):2417–2429.

Potential role of the gut flora in influencing immunity in ITP



LPS, lipopolysaccharides; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; SBAs, secondary bile acids; ILA, indole-3-lactic acid; IAA, indoleacetic acid; AhR, aromatic hydrocarbon receptor; Th1, helper T-cell 1; Th17, helper T-cell 17; Treg, regulatory T-cell, TLR4, toll-like receptor 4; NF-kB, nuclear factor-κB; mø, macrophage, IL, Interleukin; PXR, pregnane X receptor.

Zhu G et al. Front. Microbiol. 15:1426911. doi: 10.3389/fmicb.2024.1426911, 2024.

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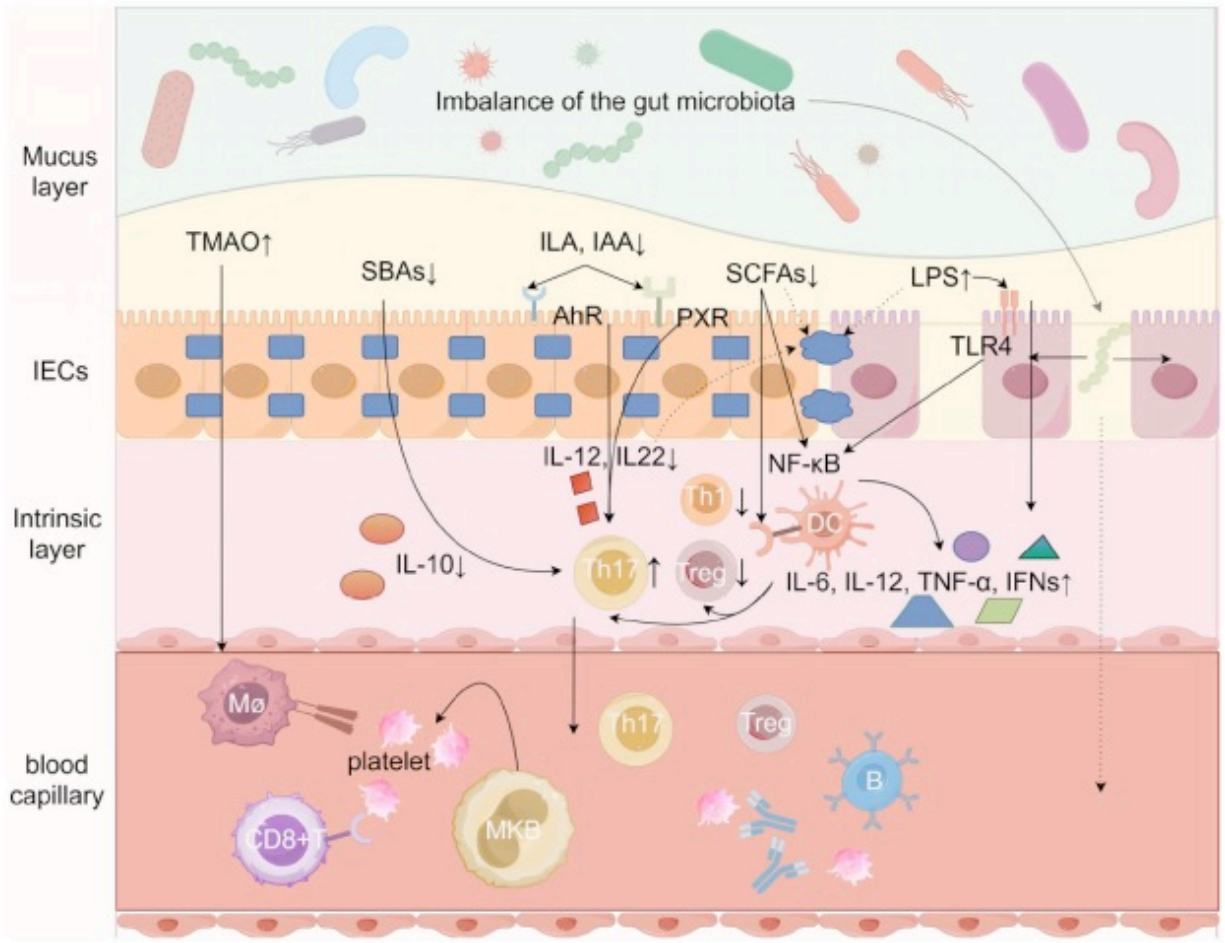

Is it as simple as this?
Antibiotics?

LPS, lipopolysaccharides; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; SBAs, secondary bile acids; ILA, indole-3-lactic acid; IAA, indoleacetic acid; AhR, aromatic hydrocarbon receptor; Th1, helper T-cell 1; Th17, helper T-cell 17; Treg, regulatory T-cell, TLR4, toll-like receptor 4; NF-kB, nuclear factor-κB; mø, macrophage, IL, Interleukin; PXR, pregnane X receptor.

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ITP Genetic Studies are beginning

Genetic variants in toll-like receptor 4 are associated with lack of steroid-responsiveness in pediatric ITP patients

Taylor Olmsted Kim[1,2] | Jonathan M. Flanagan[1,2] | Ali Habibi[1] | Abinaya Arulselvan[3] | Michele P. Lambert[3,4] | Rachael F. Grace[5,6] | Jenny M. Despotovic[1,2]

Kim TO et al. Am J Hematol. 2020;95:395–400. https://doi.org/10.1002/ajh.25716

RESEARCH ARTICLE | AUGUST 27, 2024

Genetic Variants in Canonical Wnt Signaling Pathway Associated with Pediatric Immune Thrombocytopenia

Taylor Olmsted Kim, Jennifer M Geris, Dr, Jonathan Michael Flanagan, Rachael F. Grace, Michele P Lambert, Candelaria O'Farrell, Melissa J Rose, Kristin A Shimano, Omar Niss, Cindy E. Neunert, Taizo A Nakano, Derek MacMath, Bogdan Dinu, Susan E Kirk, Ellis J Neufeld, Jenny McDade Despotovic, Michael E Scheurer, Amanda B Grimes

Blood Adv bloodadvances.2024012776.

Immune Checkpoint-Related Gene Polymorphisms Are Associated With Primary Immune Thrombocytopenia

Shuwen Wang[1], Xiaoyu Zhang[1], Shaoqiu Leng[1], Qirui Xu[1], Zi Sheng[1], Yanqi Zhang[2], Jie Yu[3], Qi Feng[1], Ming Hou[1], Jun Peng[1] and Xiang Hu[2]**

Front. Immunol. 11:615941. 2020.

High-throughput sequencing of IgG B-cell receptors reveals frequent usage of the rearranged IGHV4–28/IGHJ4 gene in primary immune thrombocytopenia

Makoto Hirokawa[1], Naohito Fujishima[2,3], Masaru Togashi[3], Akiko Saga[1], Ayumi Omokawa[1], Tomoo Saga[1], Yuki Moritoki[1], Shigeharu Ueki[1], Naoto Takahashi[3], Kazutaka Kitaura[4] & Ryuji Suzuki[4,5]

Sci Rep. (2019) 9:8645 https://doi.org/10.1038/s41598-019-45264-2

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Front. Immunol. 11:615941. 2020.

Need sufficiently large sample sizes within informative patient populations (need for collection of well-annotated biomaterials in clinical trials or registry projects).

Need to go beyond performing association studies alone and to establish genotype-phenotype associations, thus proving causality between a genetic alteration and ITP pathogenesis.

Julia-Annabell G et al Blood Adv (2023) 7 (14): 3710–3724.

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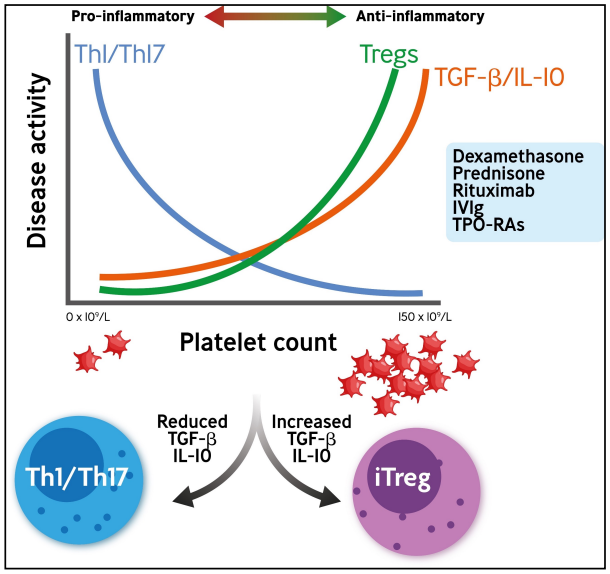
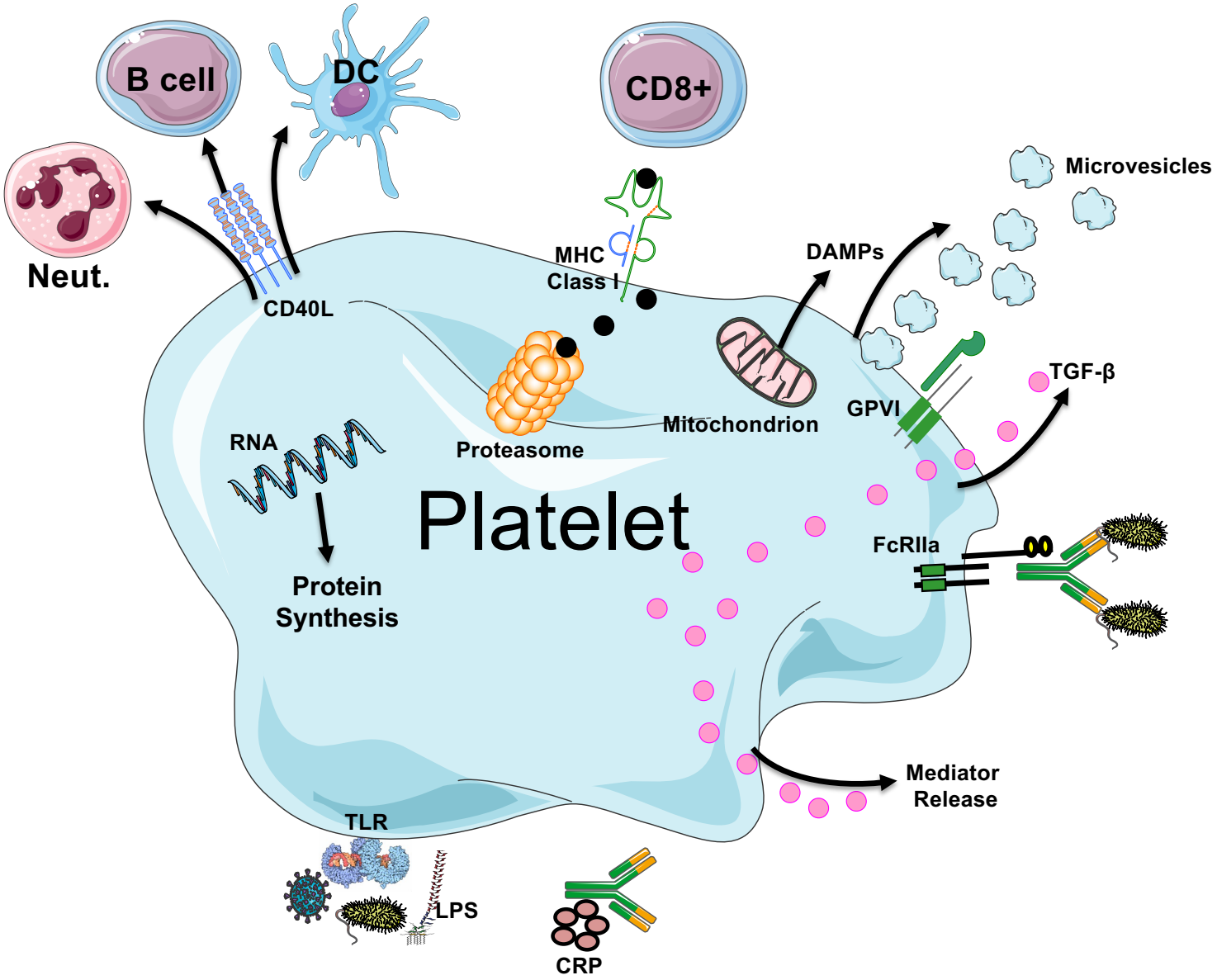
Platelets are Immune Cells

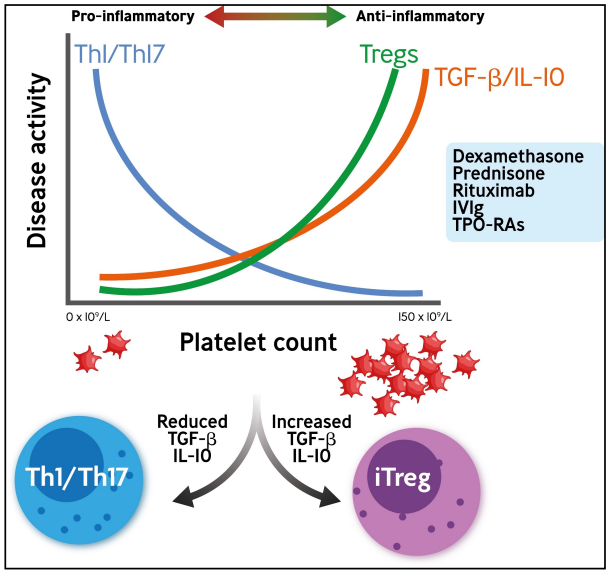


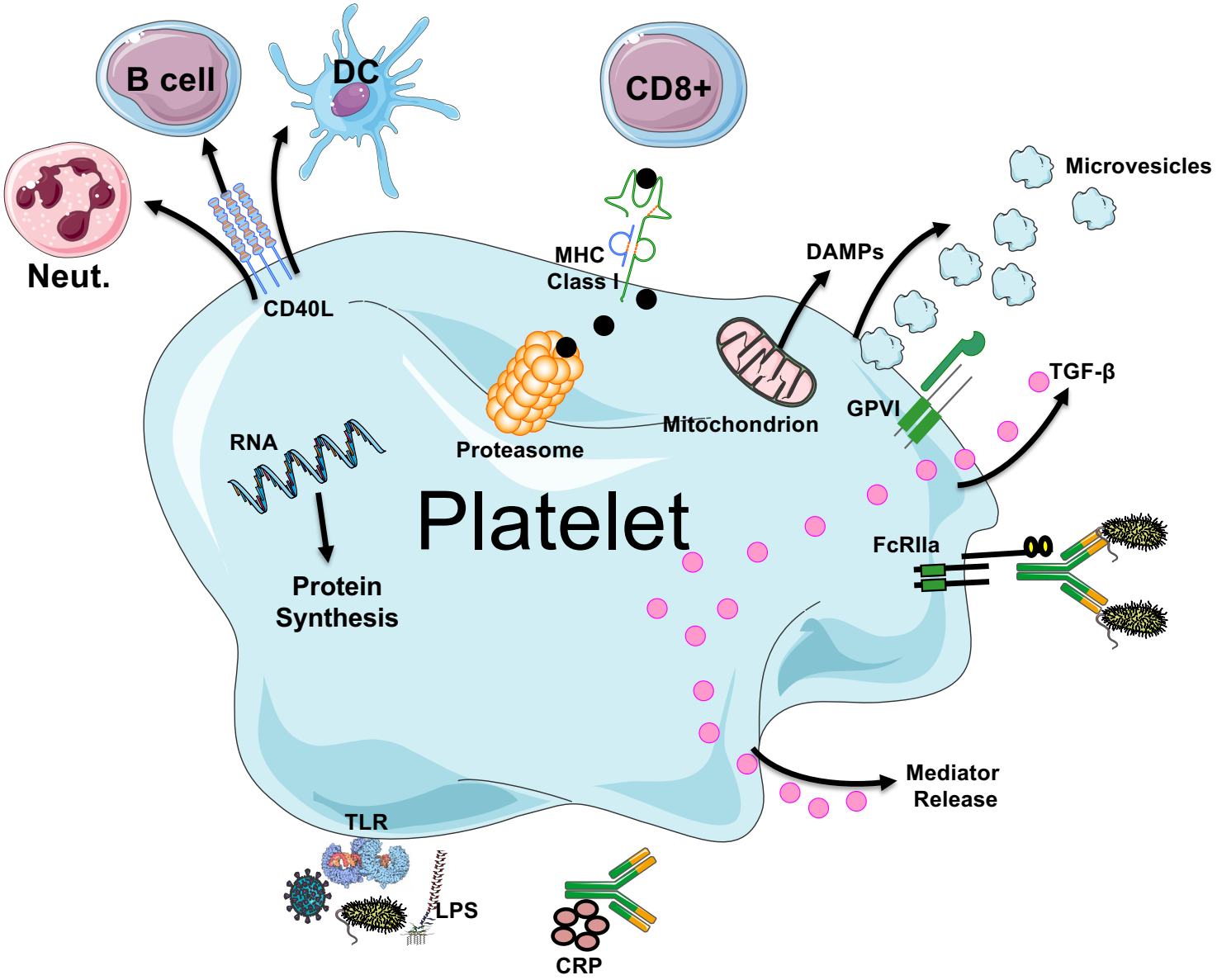


Adapted from Kapur R et al. J Immunol 2015, 194: 5579–5587

Platelets are Immune Cells

Need to understand how platelets affect their own fate in ITP





Adapted from Kapur R et al. J Immunol 2015, 194: 5579–5587

A (next to) final thought:

Patients with ITP are 3-5 times more susceptible to infections compared with healthy controls.

Is this due to the low platelet counts?

It’s not just bleeding (or clotting)

H. Frederiksen, Danish Registry Database, ASH oral, 2023.

Food for thought

Investigation on glucocorticoid receptors within platelets from adult patients with immune thrombocytopenia

Hematol. 2020; 25: 37–42

Kam Chau Yung[a*], Cheng Wei Xu[b*], Ze Wen Zhang[a], Wen Jun Yu[a], Qian Li[a], Xian Ru Xu[a], Ya Fei Han[c], Xin Jia Wang[c] and Jun Yin [a,d,e]

MK and platelets express:

- Mpl
- Syk
- Btk
- mTOR
- FcRIIA
- CD40L
- JAK/STAT
- Complement fragments
- BAFF, APRIL,TACI (a few papers)
- CTLA-4, PDL-1 (other checkpoint inhibitors, controversial)

  etc……

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etc……

Do platelets play any role in ITP refractoriness (a sink)?

Conclusions

There are still many unmet biological needs in ITP:

- Pathophysiology clarifications (e.g. Treg/MDSC roles with Th1/Th17 cells, monocyte effects, CD8+ T cell effects etc.). The role of T cells in refractoriness.
- Biological reason(s) for the bleeding and clotting.
- Gut flora issues.
- Genetic studies are still lacking…..NO BIOMARKERS YET.
- The platelets' role in controlling the disease (and potential infections) and refractoriness.

Acknowledgements

Semple lab (Lund):

- Johan Rebetz
- Geneviève Marcoux
- Karl Johansson
- Hilma Cederholm
- Johanna Lundin
- Amal Maouia

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- Rick Kapur (Amsterdam)
- Joe Italiano (Boston)
- Ming Hou/Jun Peng (Jinan)

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