Platelet Immune Function

Keywords: Platelet, Innate Immunity, CD40L, Inflammation, TLRs, danger signals, Transfusion

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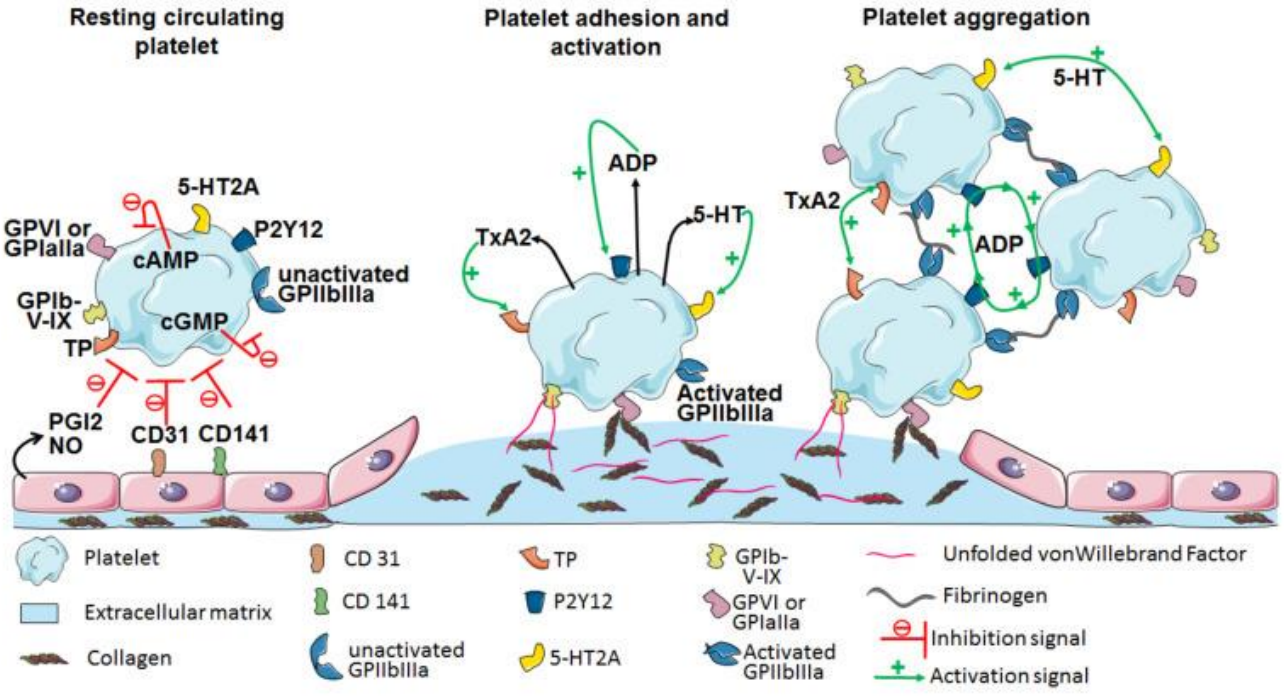
Review

Platelet Innate Immune Receptors and TLRs: A Double-Edged Sword

Théo Ebermeyer [1], Fabrice Cognasse [1,2], Philippe Berthelot [3,4], Patrick Mismetti [1,5], Olivier Garraud [1] and Hind Hamzeh-Cognasse [1,*]



- **Platelets are hematopoietic cells** whose main function has for a long time been considered to be the maintenance of vascular integrity.

- They also have functional capabilities that go far beyond it.
  - **Are platelets cells?**
  - **And if yes, are they immune cells?**

The Journal of Immunology

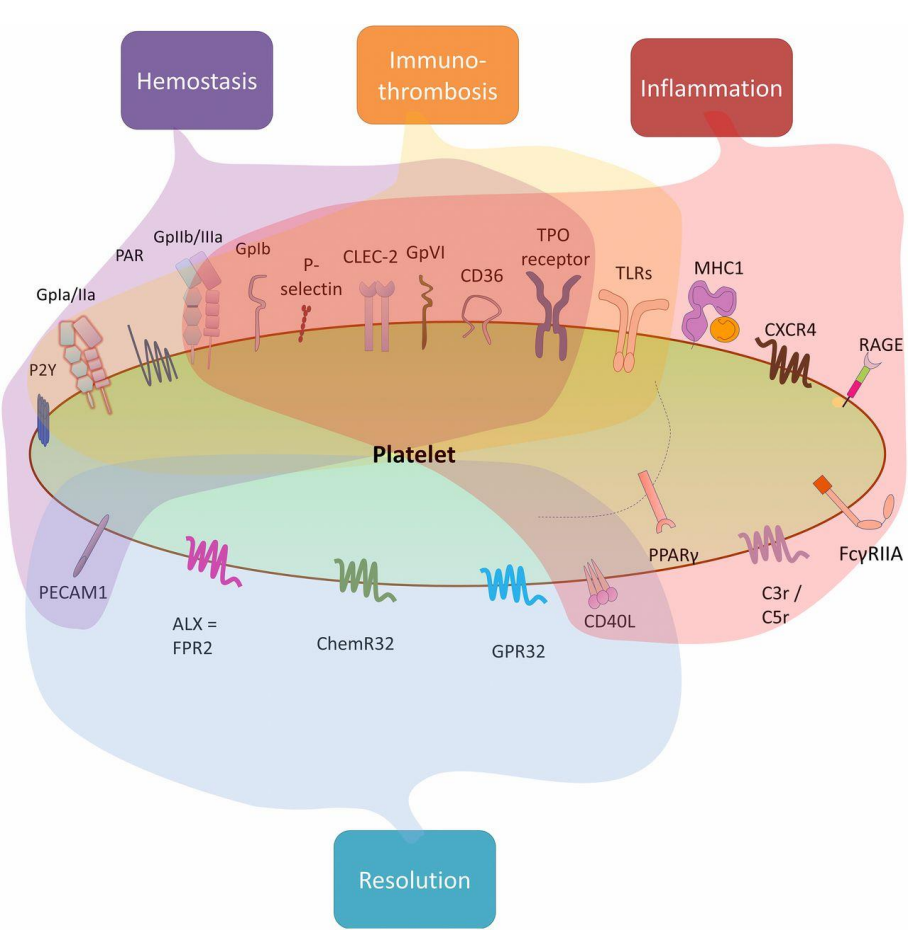
Platelets in Inflammation and Resolution

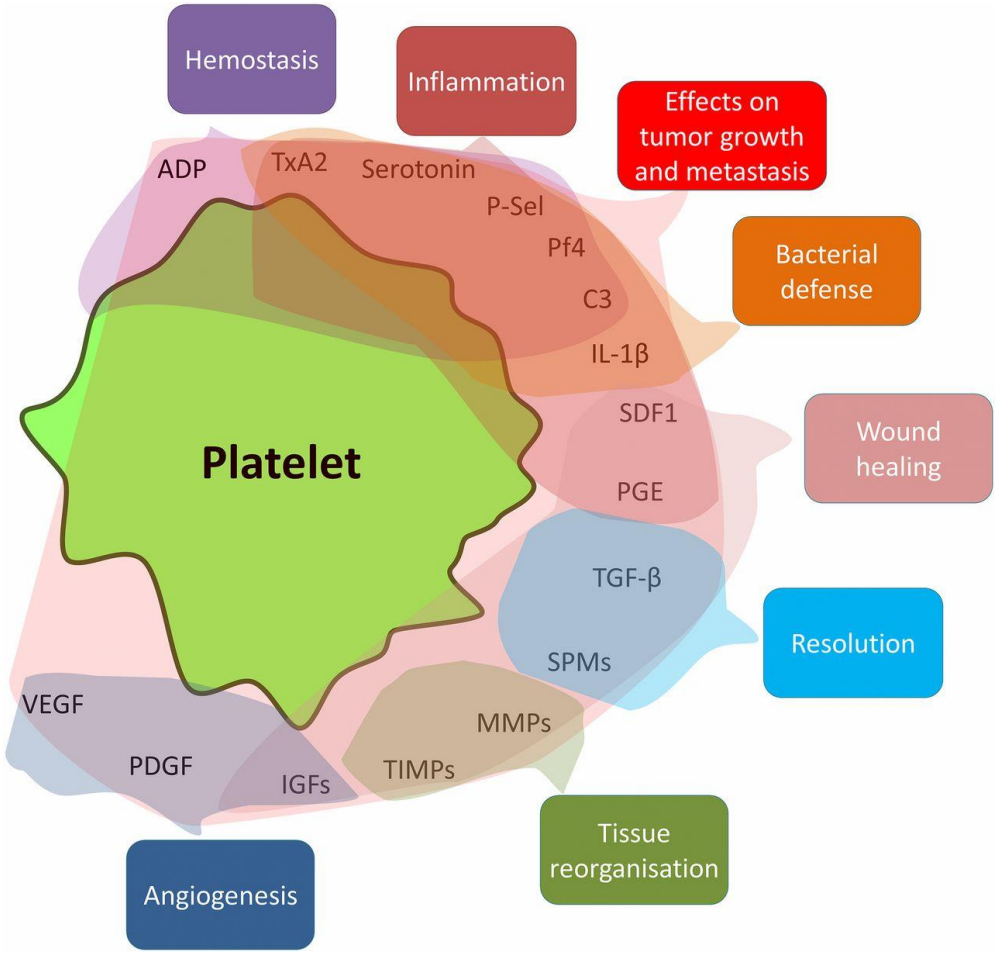
Andreas Margraf and Alexander Zarbock

J Immunol 2019; 203:2357-2367; ;
doi: 10.4049/jimmunol.1900899
http://www.jimmunol.org/content/203/9/2357

Receive signals

Send signals





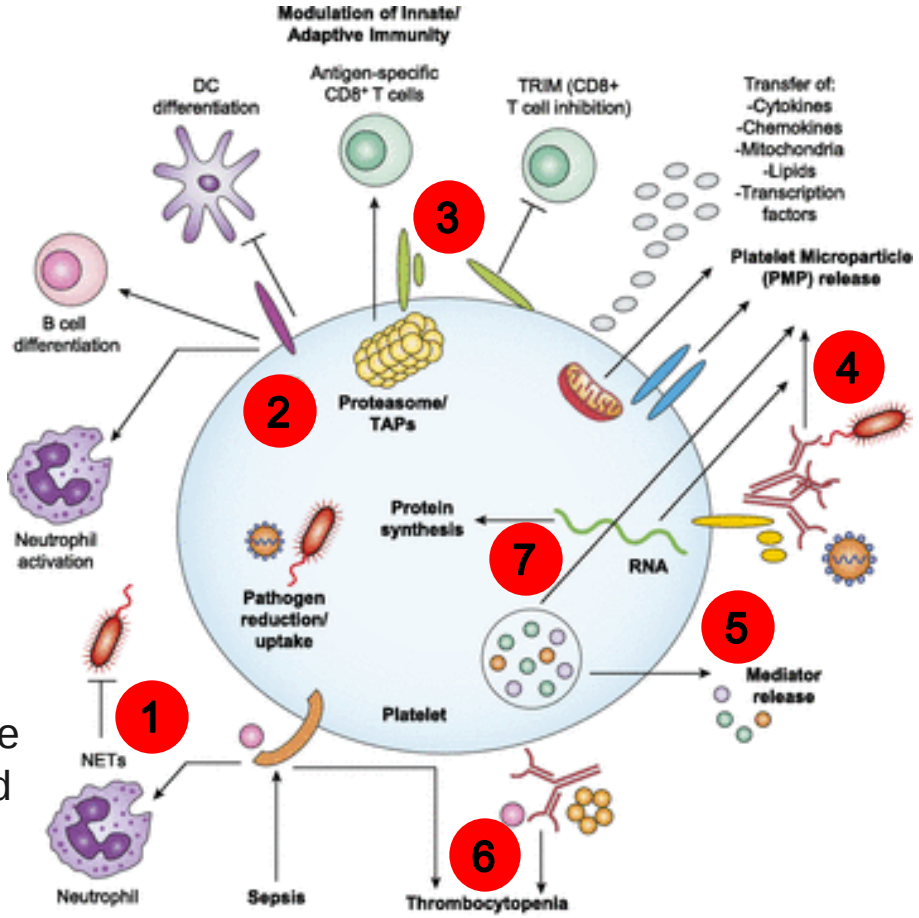
Platelets contribute to the resolution of inflammation by a multitude of factors

Brief Reviews
J Immunol (2015) 194 (12): 5579–5587.
https://doi.org/10.4049/jimmunol.1500259
The Journal of Immunology

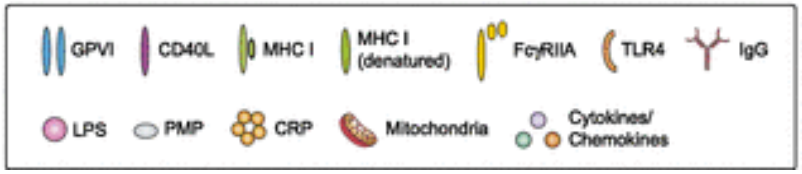
Nouvelle Cuisine: Platelets Served with Inflammation

Rick Kapur,*,† Anne Zufferey,* Eric Boilard,‡ and John W. Semple*,†,§,¶,‖

The key roles of platelets in modulating inflammatory processes



(**1**) Platelets can uptake infectious agents (via the expression of TLRs) and can activate neutrophils to, for example, secrete NETs.



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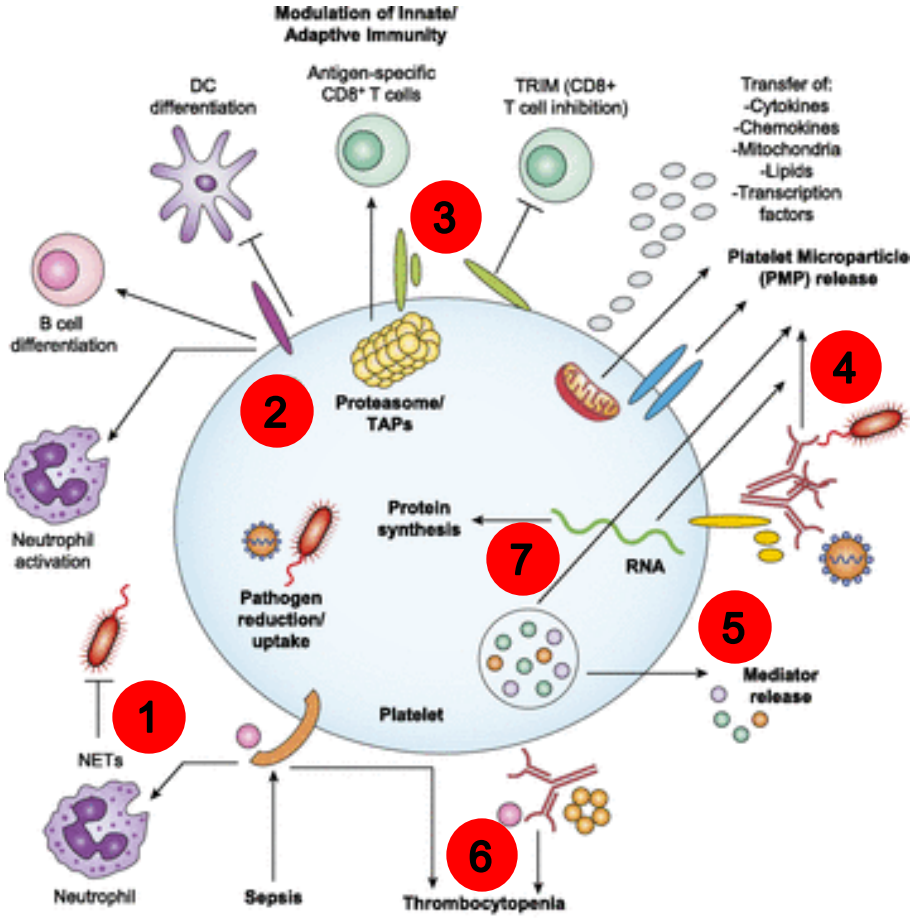
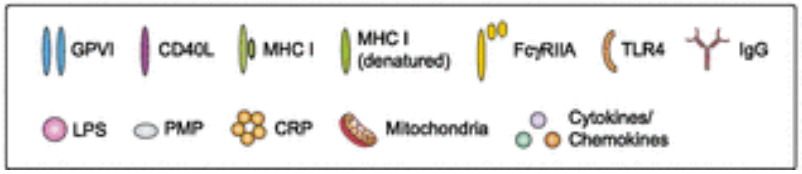
(**2**) Platelet CD40L expression allows them to interact with different cells of the immune system and either activate and/or suppress them.





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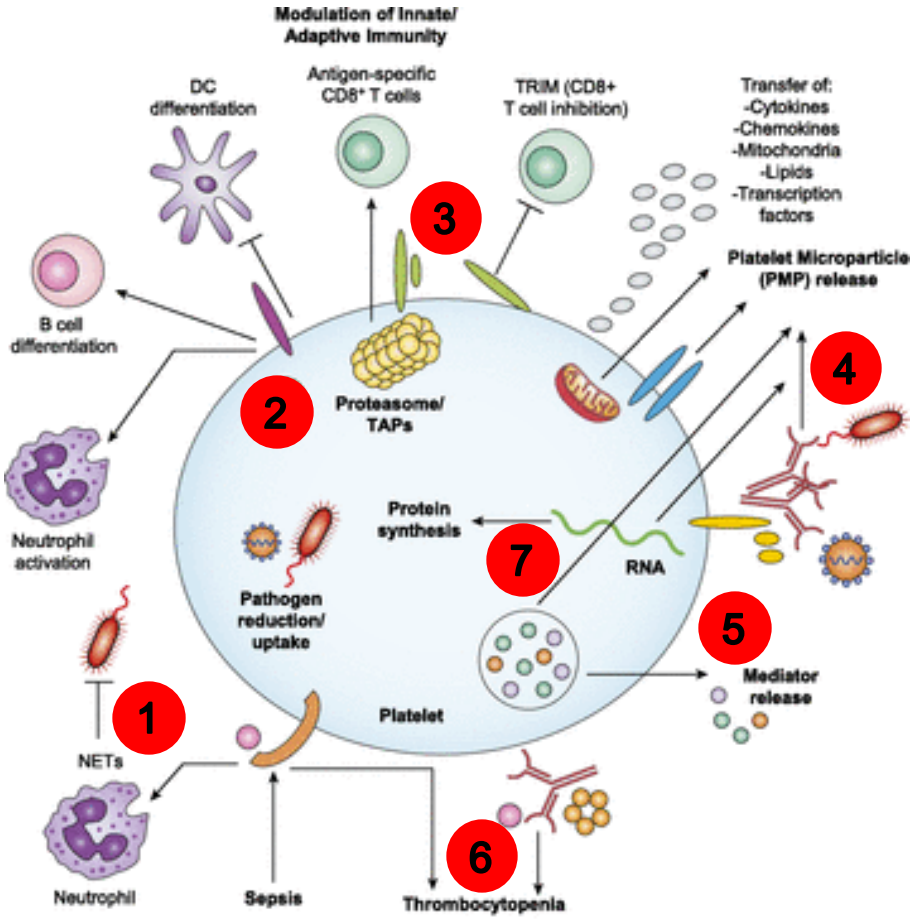
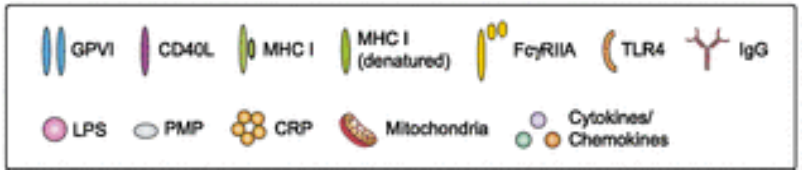
(**3**) Intact platelet MHC class I molecules are located intracellularly but upon activation are expressed and can activate Ag (e.g., malaria) - specific $CD8^+$ T cells.





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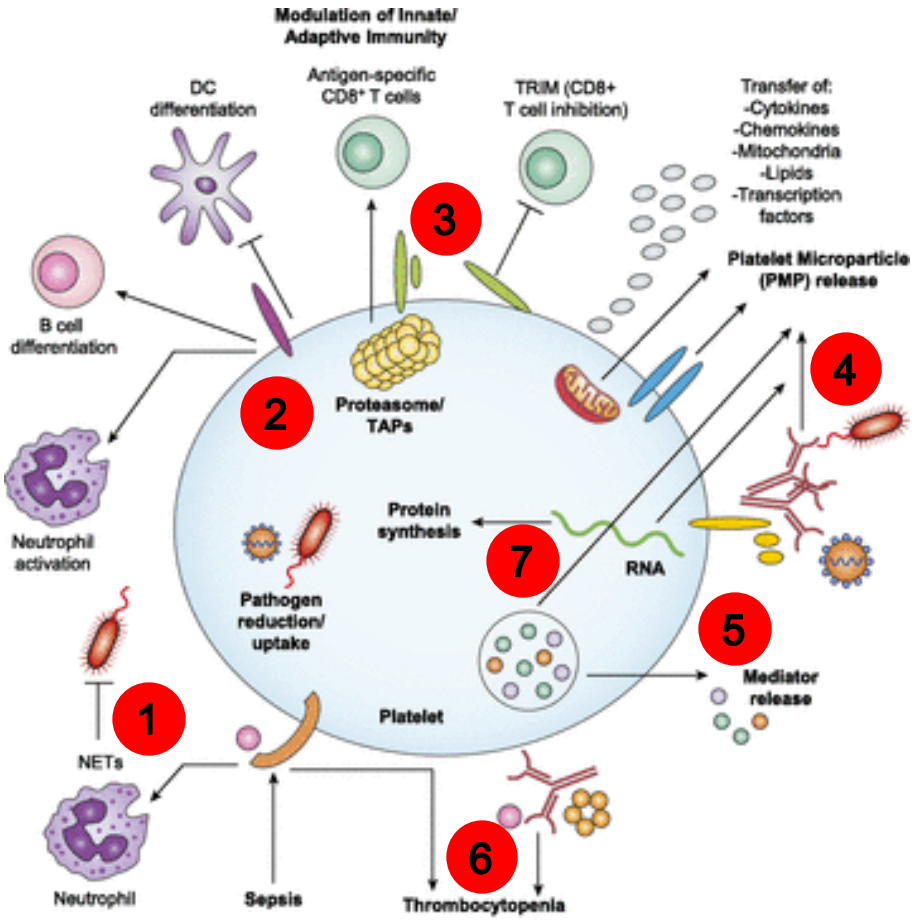
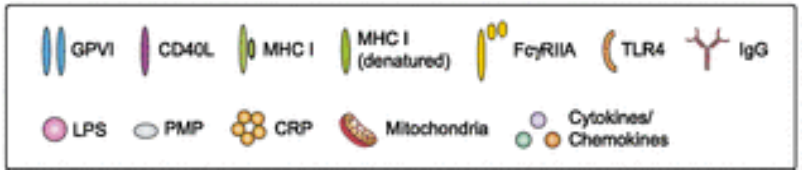


(**4**) Platelets release PMPs under a variety of stress conditions, and these PMPs can carry multiple cargos to other cells and sites of inflammation.



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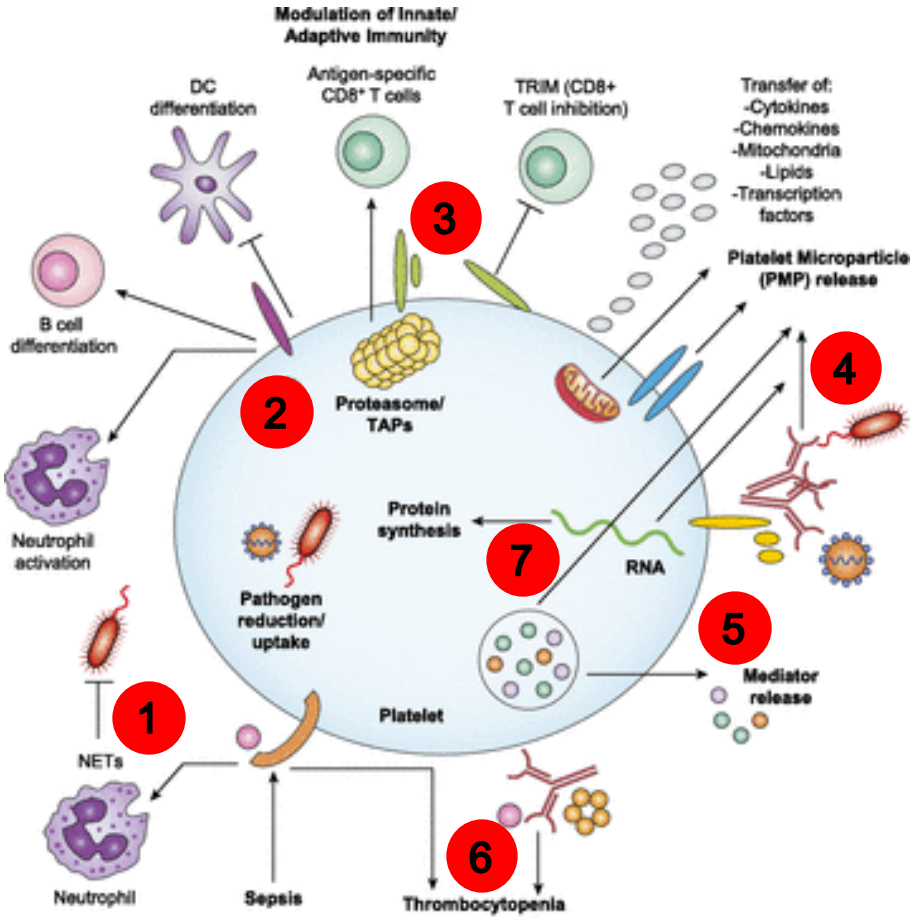

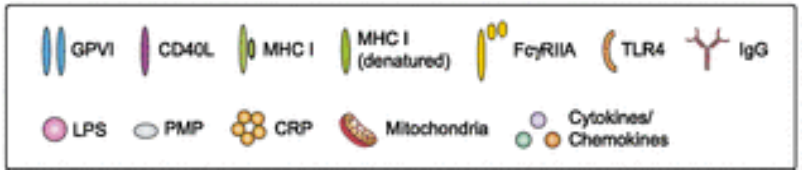

(**5**) Platelets contain many proinflammatory and anti-inflammatory cytokines and chemokines and, upon activation, can release them to the extracellular space.

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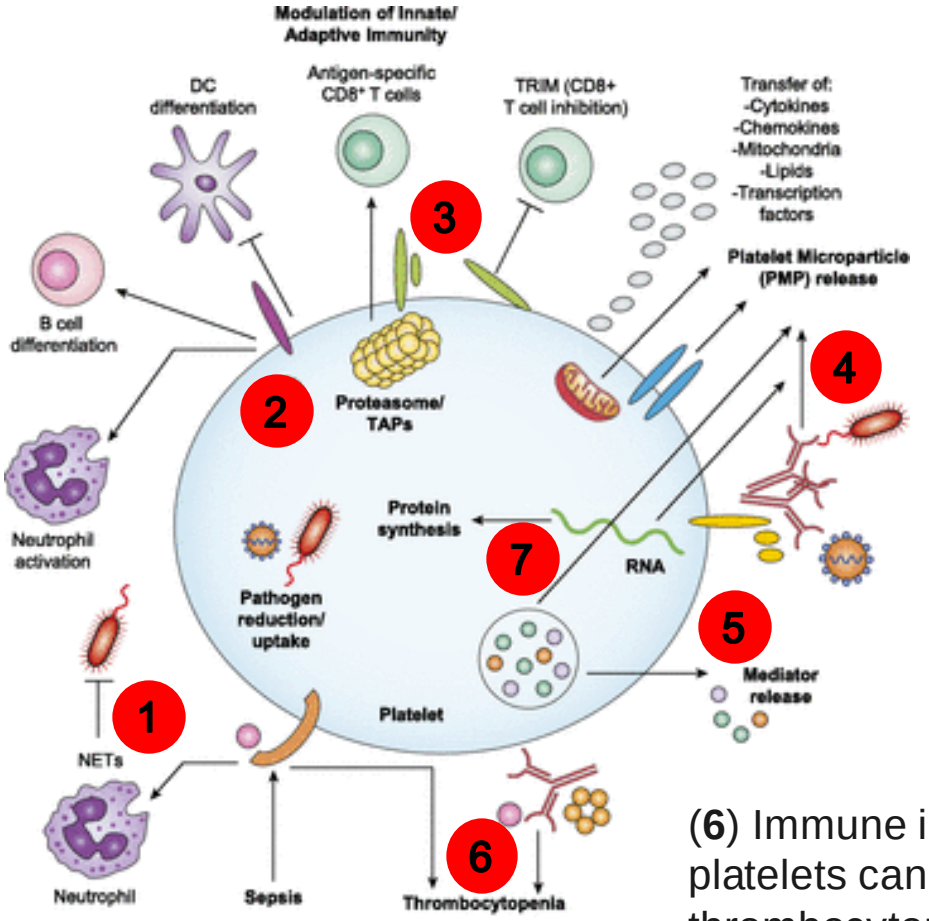

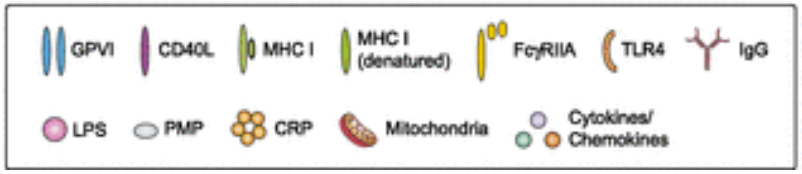

(**6**) Immune interactions with platelets can lead to severe thrombocytopenic states, such as in the case of sepsis.

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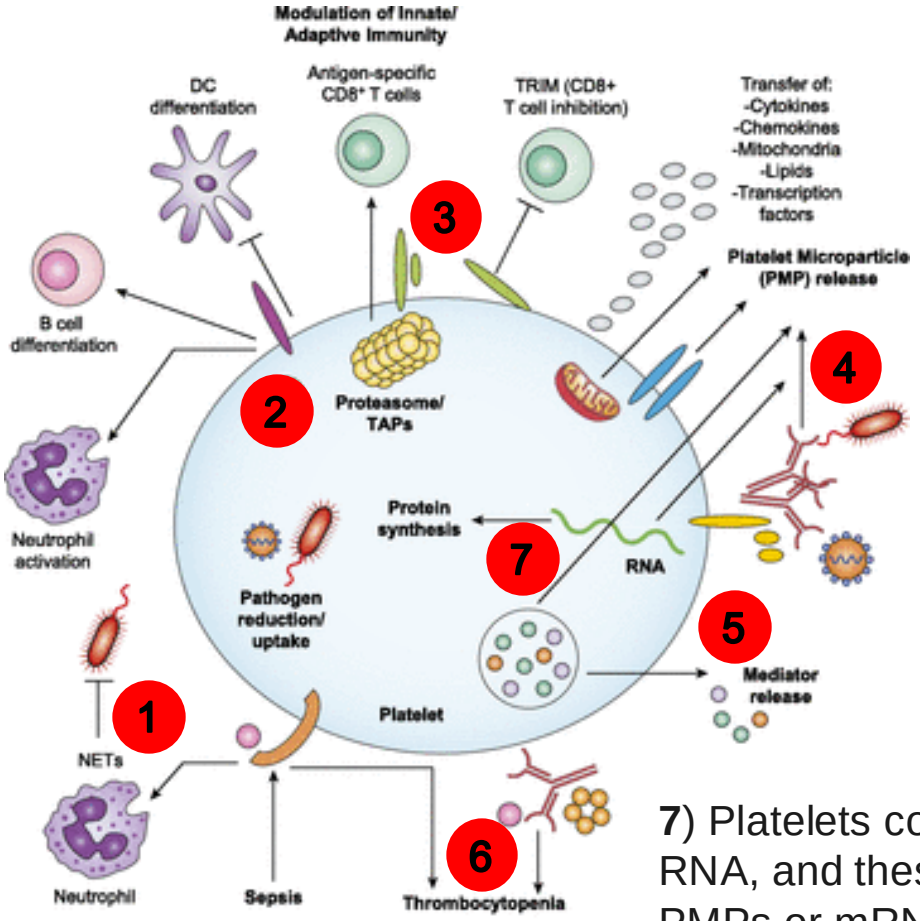

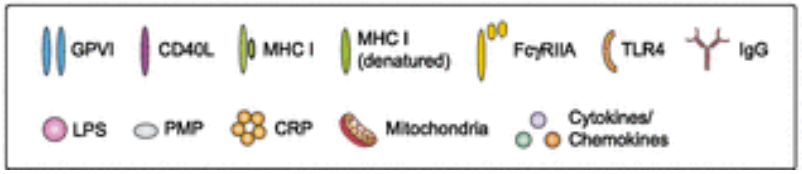

7) Platelets contain several species of RNA, and these can be exported via PMPs or mRNAs can be translated into nascent protein synthesis.

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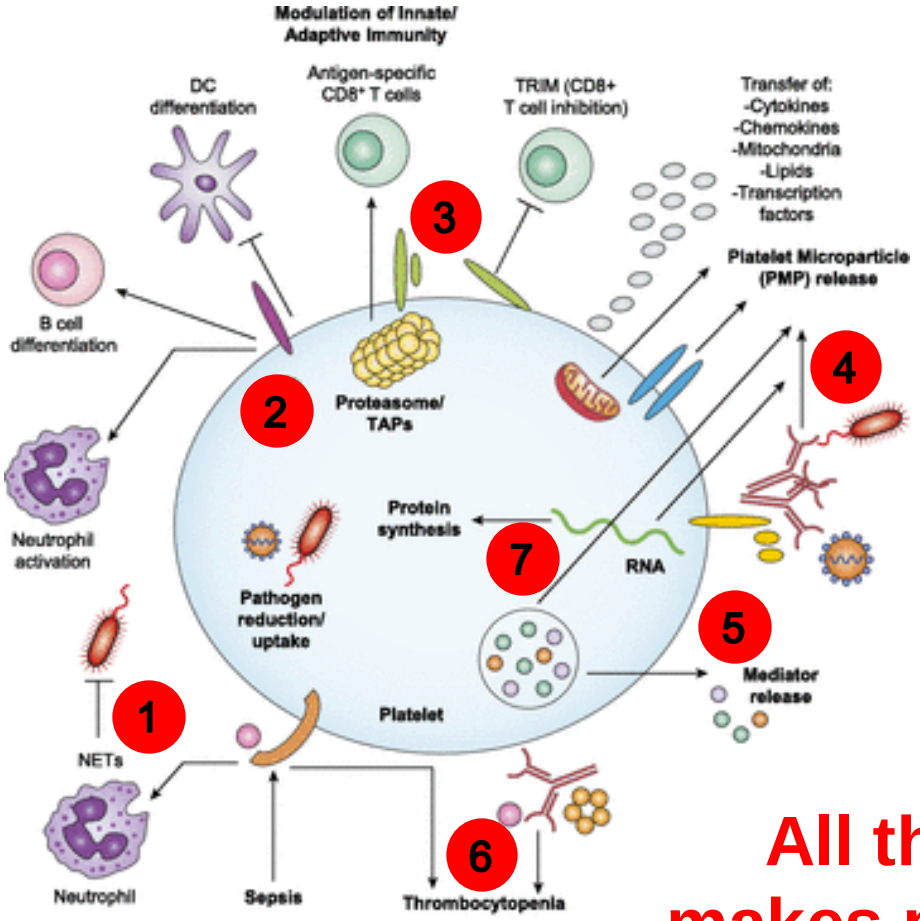
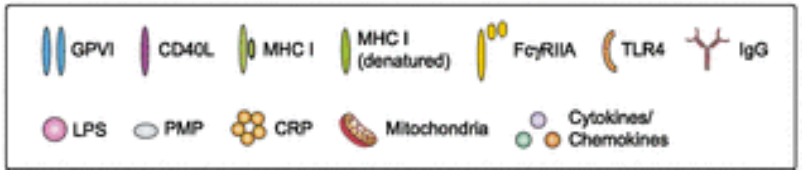


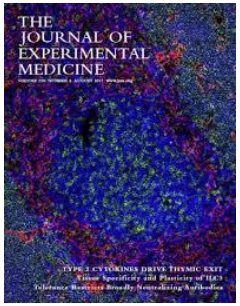


All these events makes platelet a great immunomodulatory cell

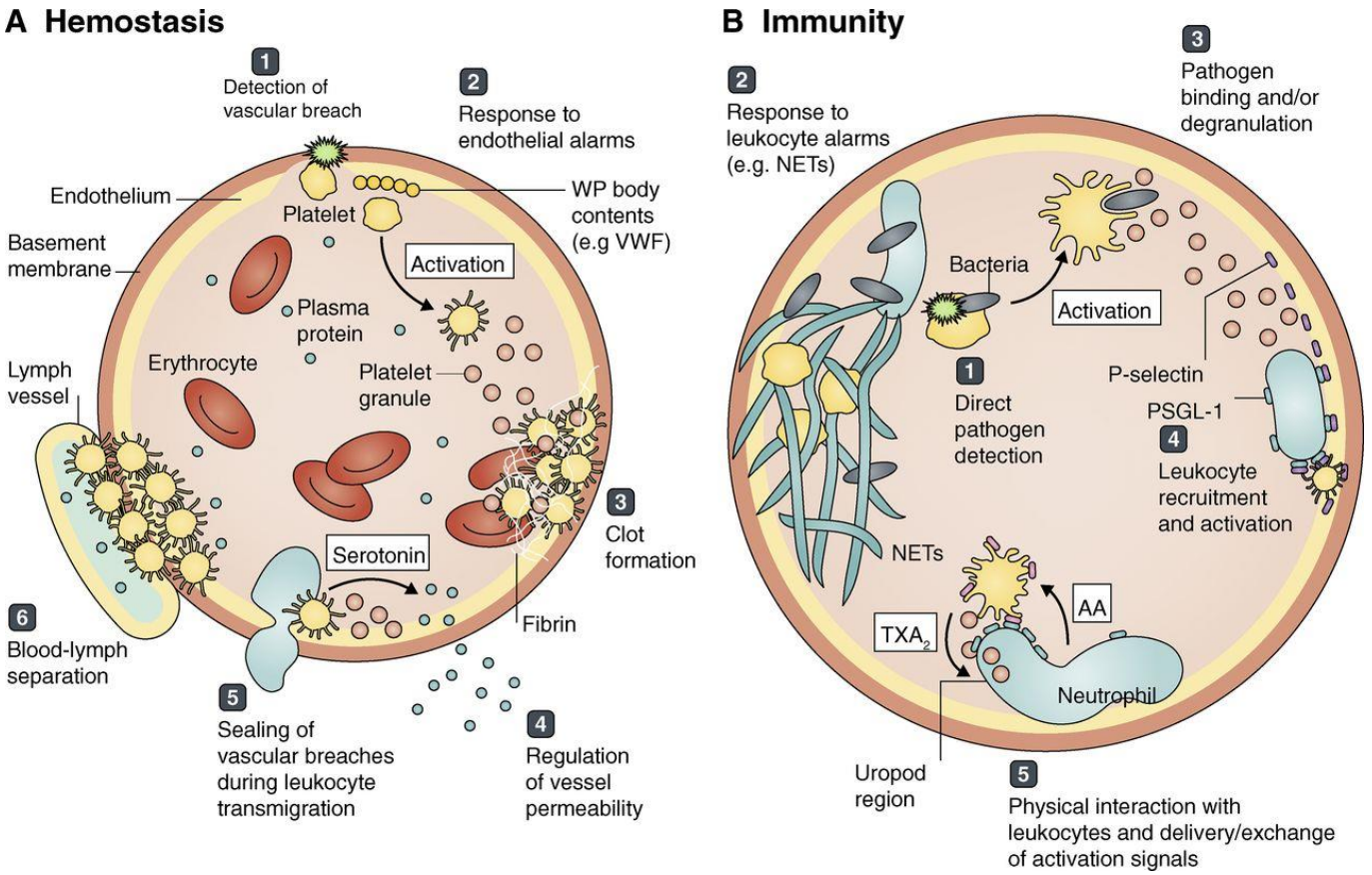
Platelets as autonomous drones for hemostatic and immune surveillance

Jackson LiangYao Li,[1,2] Alexander Zarbock,[3] and Andrés Hidalgo[1,4]

[1]Area of Developmental and Cell Biology, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain
[2]Singapore Immunology Network, Agency for Science, Technology and Research, Singapore, Singapore
[3]Department of Anesthesiology, Intensive Care, and Pain Medicine, University of Münster, Münster, Germany
[4]Institute for Cardiovascular Prevention, Ludwig-Maximillians-University, Munich, Germany



J. Exp. Med. 2017



Major platelet tasks in hemostasis and immunity.

Platelets circulate in blood, surveying the vasculature for

(A) hemostatic and
(B) immune stress

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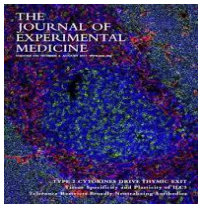
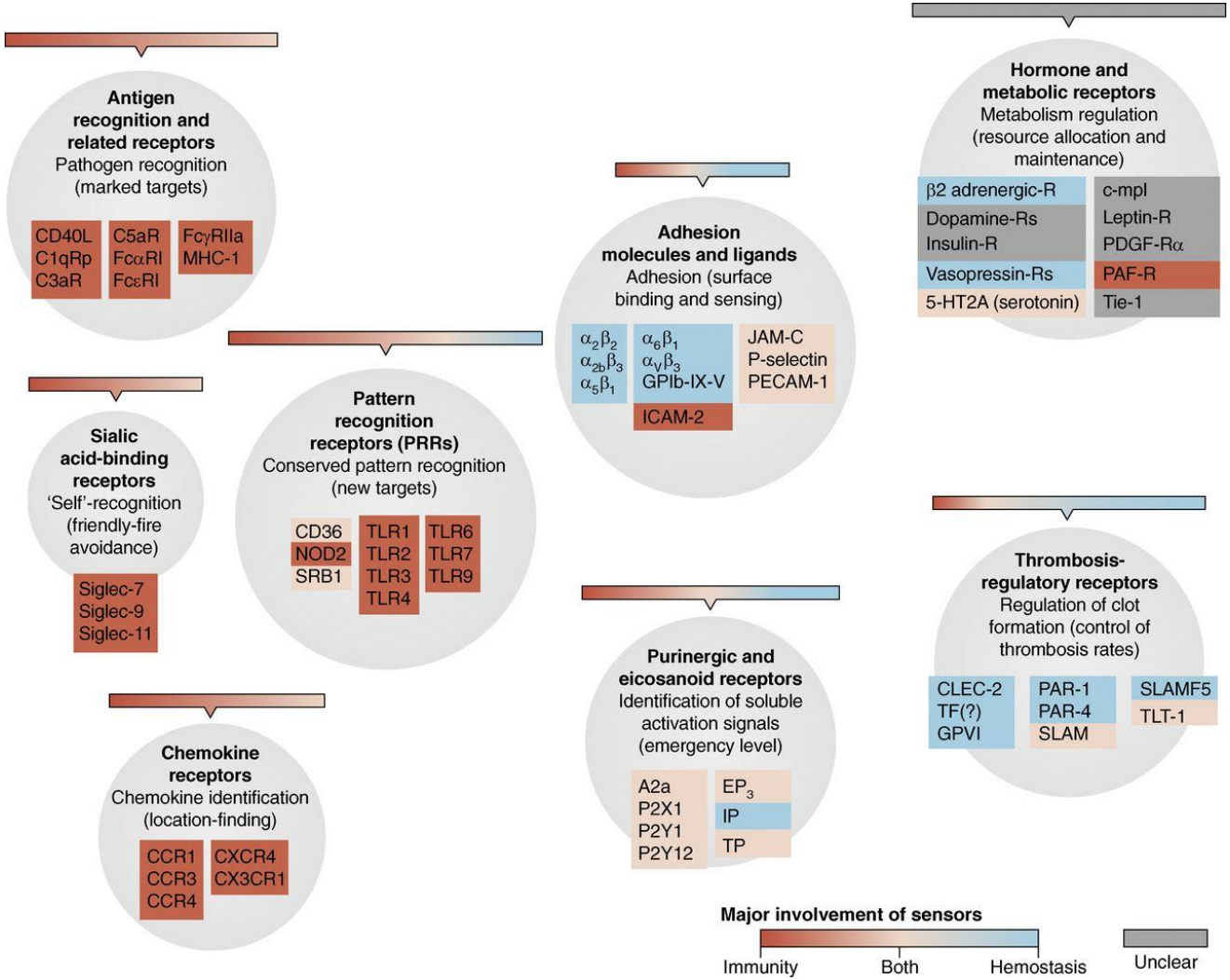


J. Exp. Med. 2017



Platelet receptors. List of receptors in human platelets categorized by their major functional types.

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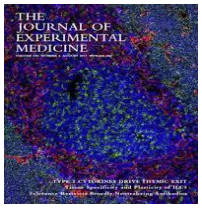


J. Exp. Med. 2017

Microbicidal effectors (Immune payload)

- C3 precursor
- C4 precursor
- Complement factor D
- CXCL7-derived peptides (PBP, TAP-III, thrombocidin-1 and 2, β-thromboglobulin)
- IgG
- MMP-1, 2 and 9
- Thymosin-β4
- Cathepsin D and E

Coagulation factors (Thrombotic payload)

- α2-antiplasmin
- Factor II/prothrombin
- Factor V
- Factor XI
- Factor XIII
- Fibrinogen
- Fibronectin
- HMW kininogens
- PAI-1
- Vitronectin
- VWF
- Glutamate

Signaling factors (communication)

- P-selectin (CD62P)
- TGF-β
- ADP
- ATP
- Calcium
- Epinephrine
- Histamine
- Polyphosphate
- Pyrophosphate
- Serotonin
- Acid phosphatase
- IL-1β
- Thromboxane A2

Chemokines (calling reinforcements)

- CCL2
- CCL3
- CCL5
- CXCL1
- CXCL12
- CXCL4/PF4
- CXCL5
- CXCL8
- NAP2 (CXCL7)

Anti-microbicidal factors (Immune regulation)

- C1 inhibitor
- Complement factor H
- TIMP-1 and 4

Anti-coagulative factors (Thrombotic regulation)

- α2-macroglobulin
- Antithrombin
- Plasmin
- Plasminogen
- Protein S
- TFPI

Growth/angiogenic regulators (support and delivery)

- Angiopoietin-1
- BDNF
- bFGF
- BMP-2,4 and 6
- CTGF
- Thrombospondin
- EGF
- Endostatin
- HGF
- IGF-1
- PDGF
- VEGF
- n-acetylglucosaminidase
- α-arabinosidase
- β-galactosidase
- β-glucuronidase
- RNA (mRNA, miRNA etc.)

Secretory package

α granules | Dense granules | Lysosomes | Microparticles or other

Platelet payloads. List of bioactive mediators released by human platelets categorized by their major functional roles.

Effects and Side Effects of Platelet Transfusion

Fabrice Cognasse[1,2] Kathryn Hally[3,4,5] Sebastien Fauteux-Daniel[1,2] Marie-Ange Eyraud[1,2] Charles-Antoine Arthaud[1,2] Jocelyne Fagan[1,2] Patrick Mismetti[2] Hind Hamzeh-Cognasse[2] Sandrine Laradi[1,2] Olivier Garraud[2] Peter Larsen[3,4,5]

Hämostaseologie 2021;41:128–135.

Table 1. Characteristics and physiological roles of platelet-released major Biological Response Modifiers (This list is non-exhaustive).

	Source	Ligand	Function
CD62P (P-selectin)	• Endothelial cells • **Platelets**	• P-selectin glycoprotein ligand-1 • Heparan sulfate • Fucoidans	• Initial recruitment of leukocytes • Recruitment and aggregation • Helps cancer cells invade into the bloodstream for metastasis • Contribute to the seeding of tumour microemboli in distant organs • Inflammatory reaction
PF4 (CXCL4)	• **Platelets**	• CXCR3B	• Promotes inflammatory fibrosis • Promotes blood coagulation by moderating the effects of heparin-like molecules. • Play a role in wound repair and inflammation • strong chemoattractant for neutrophils, monocyte and fibroblasts
RANTES (CCL5)	• **Platelets** • T cells	• CCR1 • CCR3 • CCR5	• Chemotactic for T cells, eosinophils, and basophils, and plays an active role in recruiting leukocytes into inflammatory sites • Induces the proliferation and activation of certain natural-killer (NK) cells to form CHAK (CC-Chemokine-activated killer) cells • Natural HIV-suppressive factor
Platelet microparticles (PMPs)	• **Platelets**		• Transport and delivery system for bioactive molecules • Participating in : i. hemostasis and thrombosis ii. inflammation iii. malignancy infection transfer iv. angiogenesis v. immunity
CD154 (sCD40L)	• T cells • **Platelets** • Mast cells • Macrophages • Basophils • NK cells • B lymphocytes • Smooth muscle cells • Endothelial cells • Epithelial cells	• CD40 • α5β1 integrin • αIIbβ3	• Promotes B cell maturation • Costimulation and regulation of the immune response • Activation of endothelial cells by CD40L leads to reactive oxygen species production, as well as chemokine and cytokine production, and expression of adhesion molecules such as E-selectin, ICAM-1, and VCAM-1. • Promotes recruitment of leukocytes to lesions and may potentially promote atherogenesis

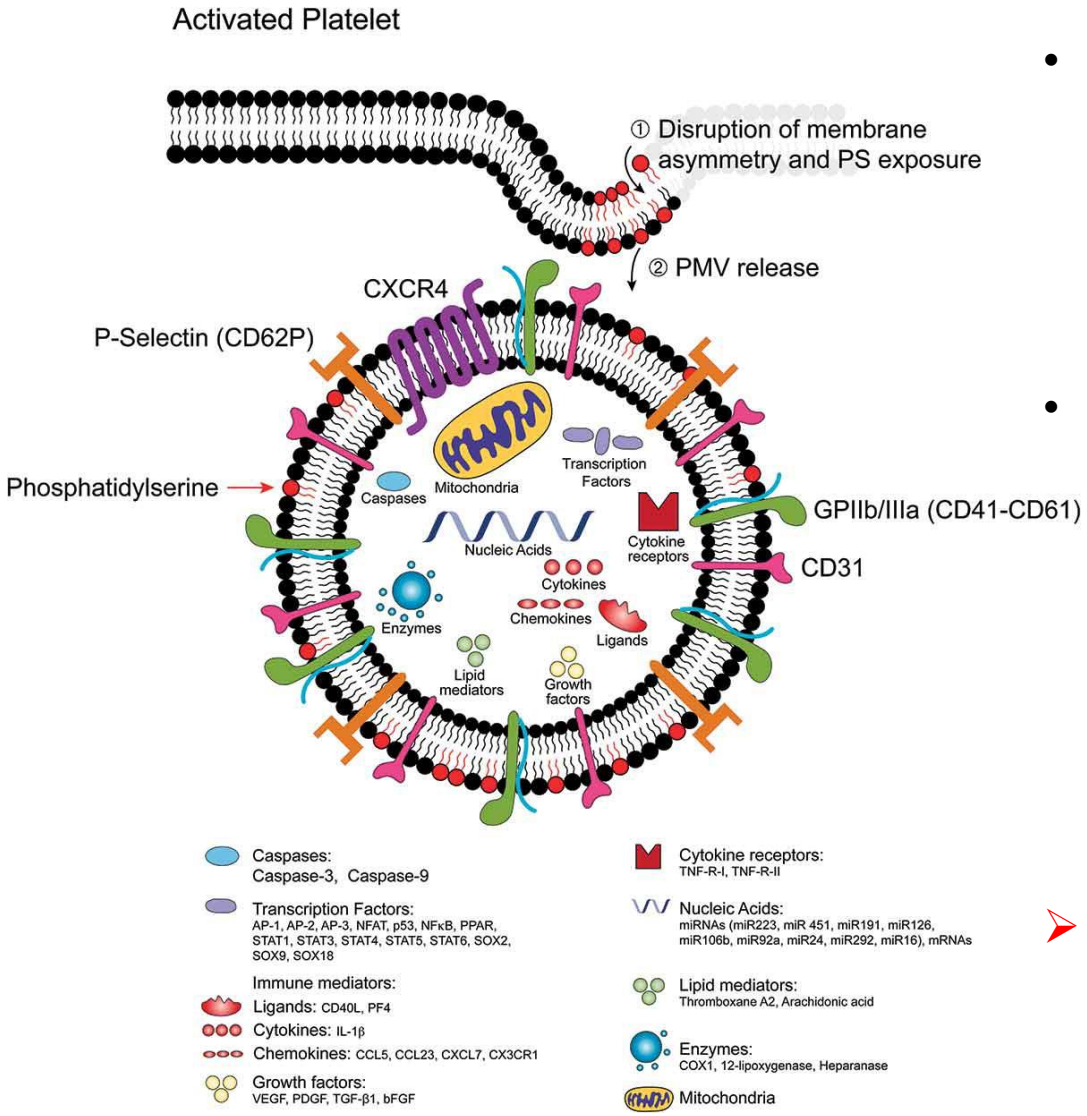
http://www.tandfonline.com/iplt
ISSN: 0953-7104 (print), 1369-1635 (electronic)
platelets
Taylor & Francis
Taylor & Francis Group
Platelets, 2017; 28(3): 214-221
© 2017 Taylor & Francis. DOI: 10.1080/09537104.2016.1265924

SPECIAL REVIEW: PLATELET MICROVESICLES

Platelet microvesicles in health and disease

Imene Melki, Nicolas Tessandier, Anne Zufferey, & Eric Boilard

The role of microparticles in inflammation



- **Despite the fact that PMVs derive, which are anucleated, from platelets various molecules and organelles are present either on or inside PMVs.**

- **The PMV cargo includes**
  - ✓ **functional enzymes,**
  - ✓ **transcription factors,**
  - ✓ **receptors,**
  - ✓ **cytokines,**
  - ✓ **nucleic acid,**
  - ✓ **lipid mediators**
  - ✓ **and mitochondria.**

➢ **Note that different platelet activating pathways or experimental parameters might have an impact on PMV content.**

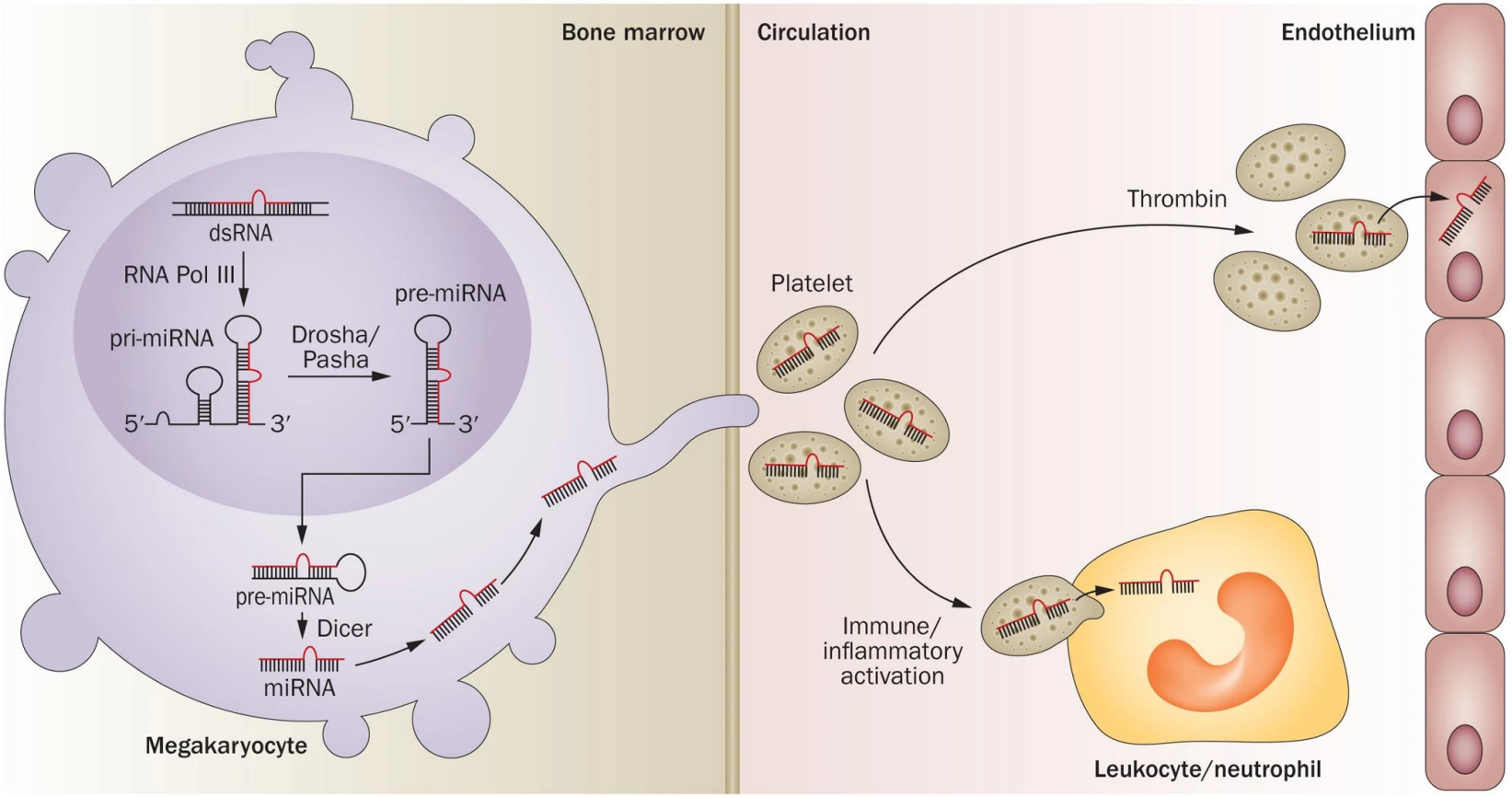
MicroRNA as Potential Biomarkers of Platelet Function on Antiplatelet Therapy: A Review

Pamela Czajka[1], Alex Fitas[1], Daniel Jakubik[1], Ceren Eyileten[1], Aleksandra Gasecka[2], Zofia Wicik[1,3], Jolanta M. Siller-Matula[1,4], Krzysztof J. Filipiak[2] and Marek Postula[1]

frontiers in Physiology

REVIEW
published: 15 April 2021
doi: 10.3389/fphys.2021.652579

- **Platelets contain RNAs, including small noncoding RNAs such as microRNAs, and the necessary machinery to perform translation**
- **Data suggest that microRNAs can influence platelet functions, including thrombosis, atherosclerosis, and angiogenesis**



Nature Reviews | Cardiology

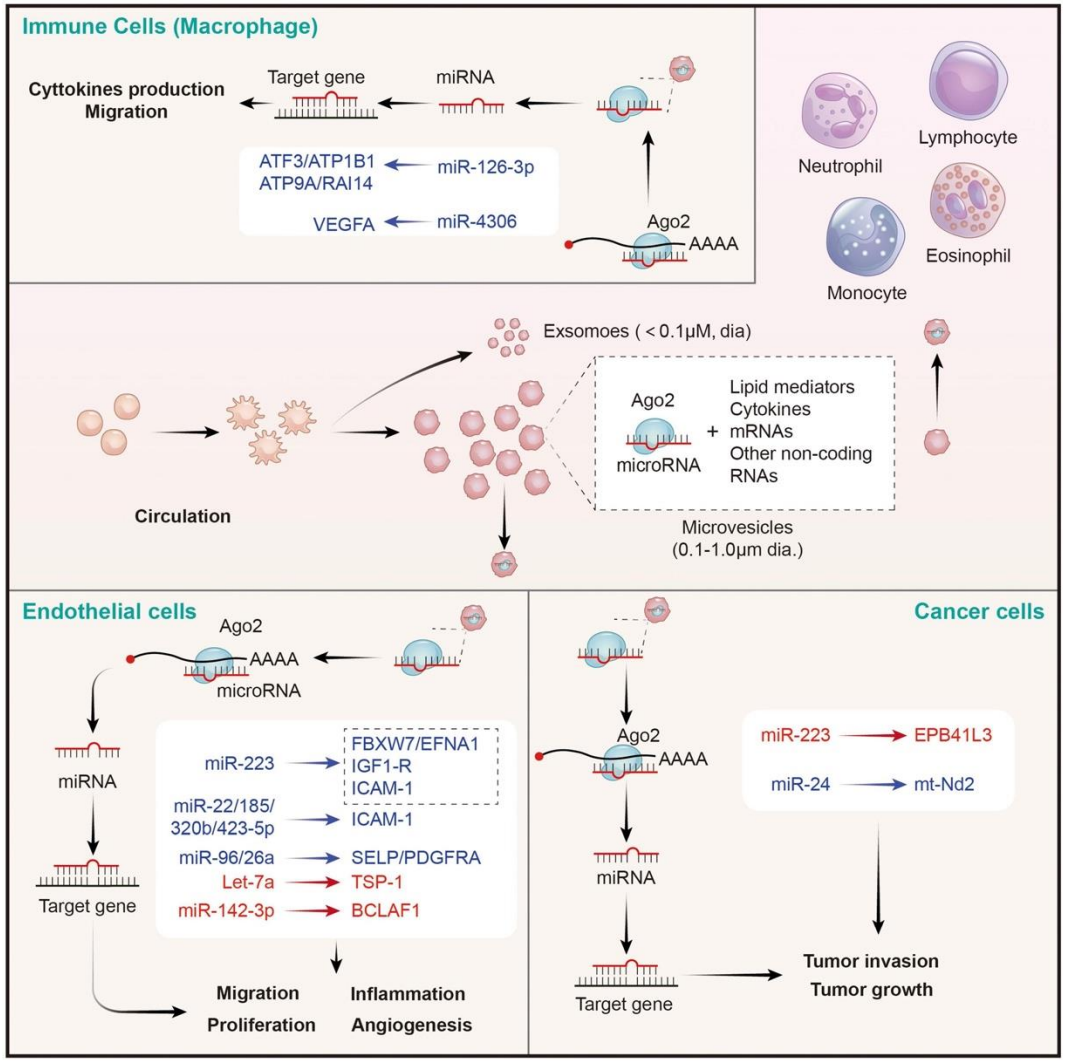
➢ **Platelet RNA can also be transferred to other vascular cells**

Insights Into Platelet-Derived MicroRNAs in Cardiovascular and Oncologic Diseases: Potential Predictor and Therapeutic Target

frontiers | Frontiers in Cardiovascular Medicine

REVIEW
published: 09 June 2022
doi: 10.3389/fcvm.2022.879351

Qianru Leng, Jie Ding, Meiyan Dai, Lei Liu, Qing Fang, Dao Wen Wang, Lujin Wu and Yan Wang**



Platelets contain fully functional miRNA processors in their microvesicles

Microvesicles are able to transport their miRNAs to neighboring cells and regulate their gene expression.

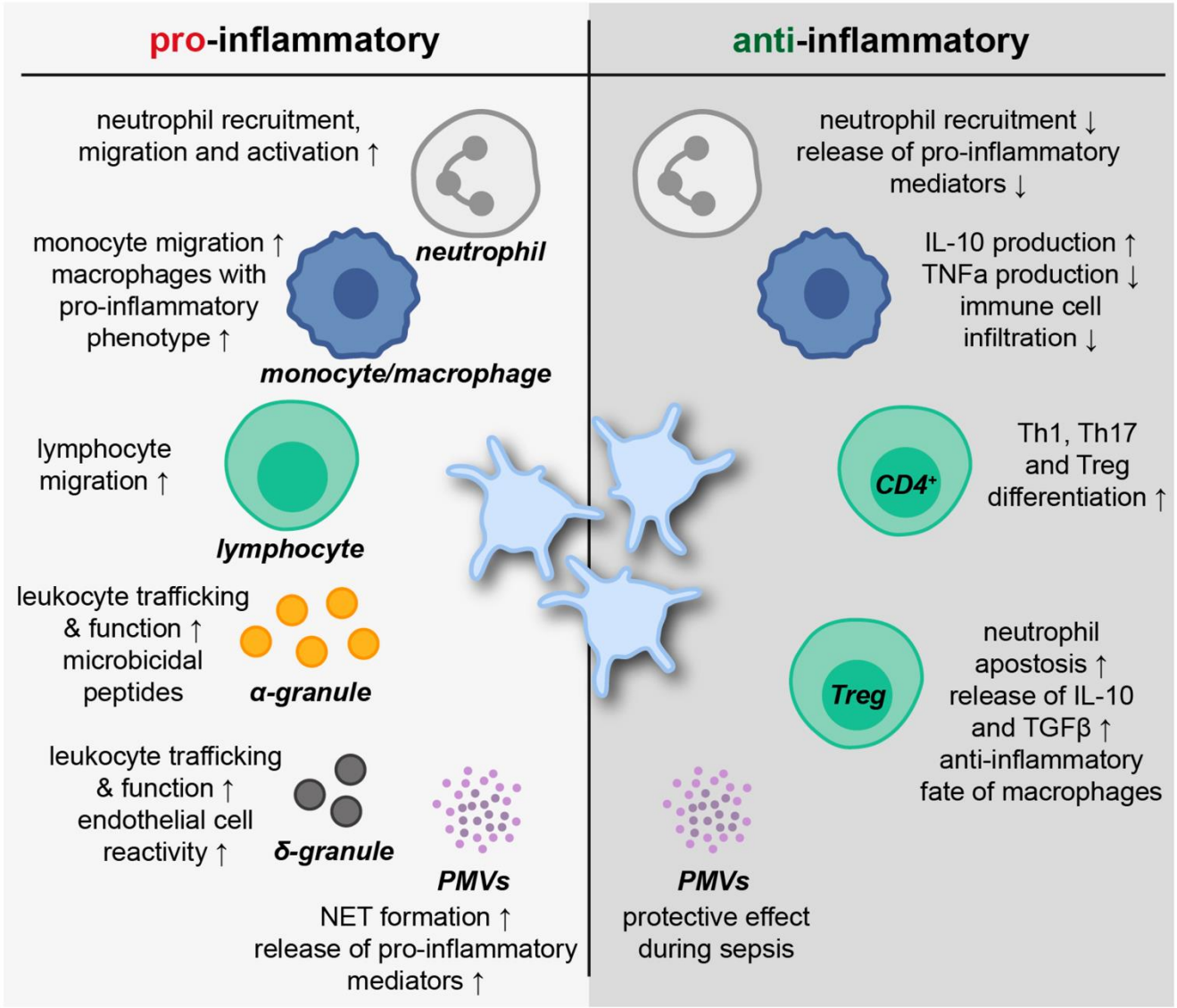
- **Platelet Microvesicles Transfer MicroRNAs to Immune Cells**
- **Platelet Microvesicles Transfer MicroRNAs to Endothelial Cells**
- **Platelet Microvesicles Transfer MicroRNAs to Cancer Cells**

cells
Published: 17 June 2022
MDPI
Review

Platelets at the Crossroads of Pro-Inflammatory and Resolution Pathways during Inflammation

Nadine Ludwig, Annika Hilger, Alexander Zarbock and Jan Rossaint *

Platelet-leukocyte interactions in pro- and anti-inflammatory processes.



- **The interaction of platelets with leukocytes via direct cell–cell contact and soluble mediators affects the immune response in multiple ways.**
- **In the context of inflammation, platelets were found to promote not only pro-inflammatory but also inflammatory resolution processes.**

Immunology and Cell Biology (2005) **83**, 196–198 doi:10.1111/j.1440-1711.2005.01314.x

Brief Communication

Evidence of Toll-like receptor molecules on human platelets

FABRICE COGNASSE,[1,2] HIND HAMZEH,[2] PATRICIA CHAVARIN,[1] SOPHIE ACQUART,[1] CHRISTIAN GENIN[2] and OLIVIER GARRAUD[1,2]

Review

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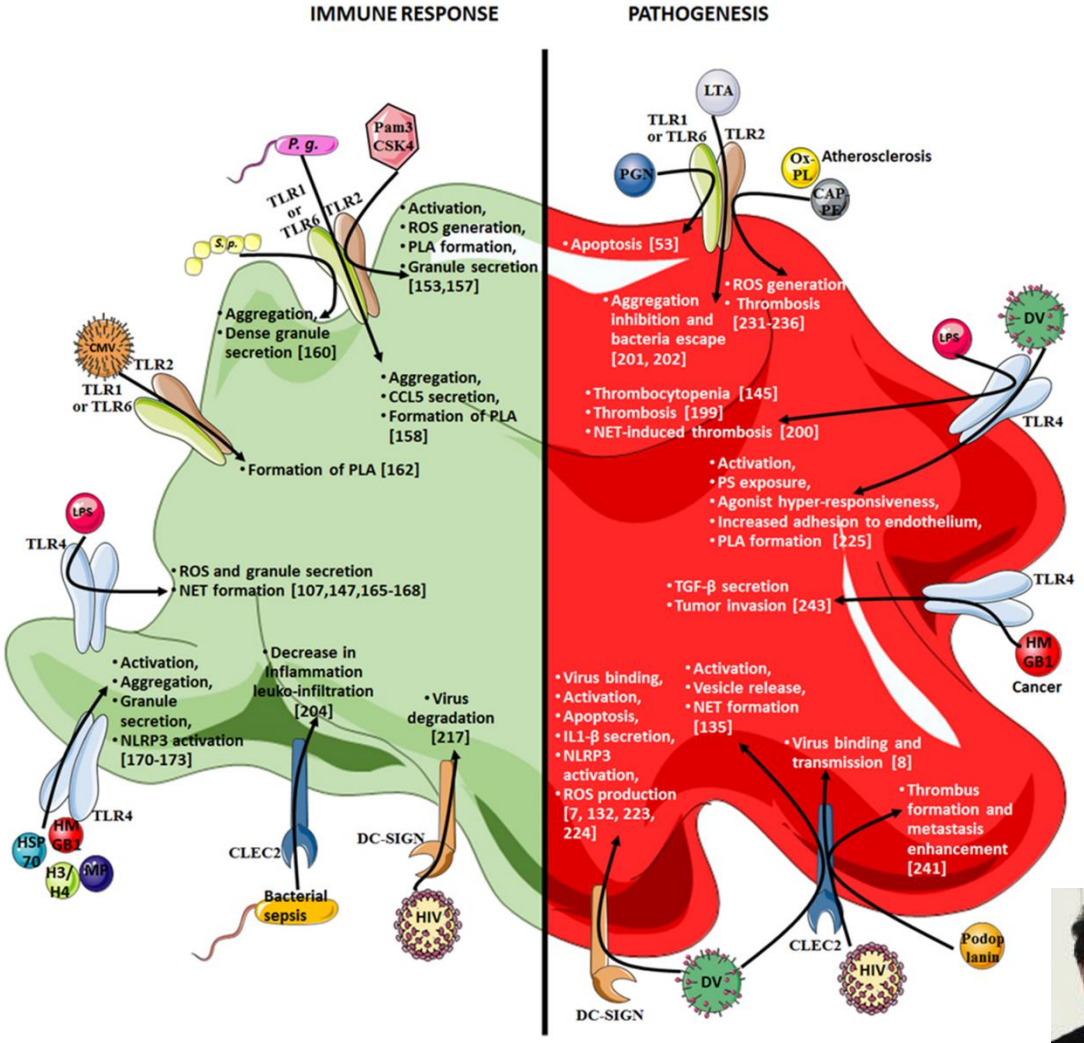


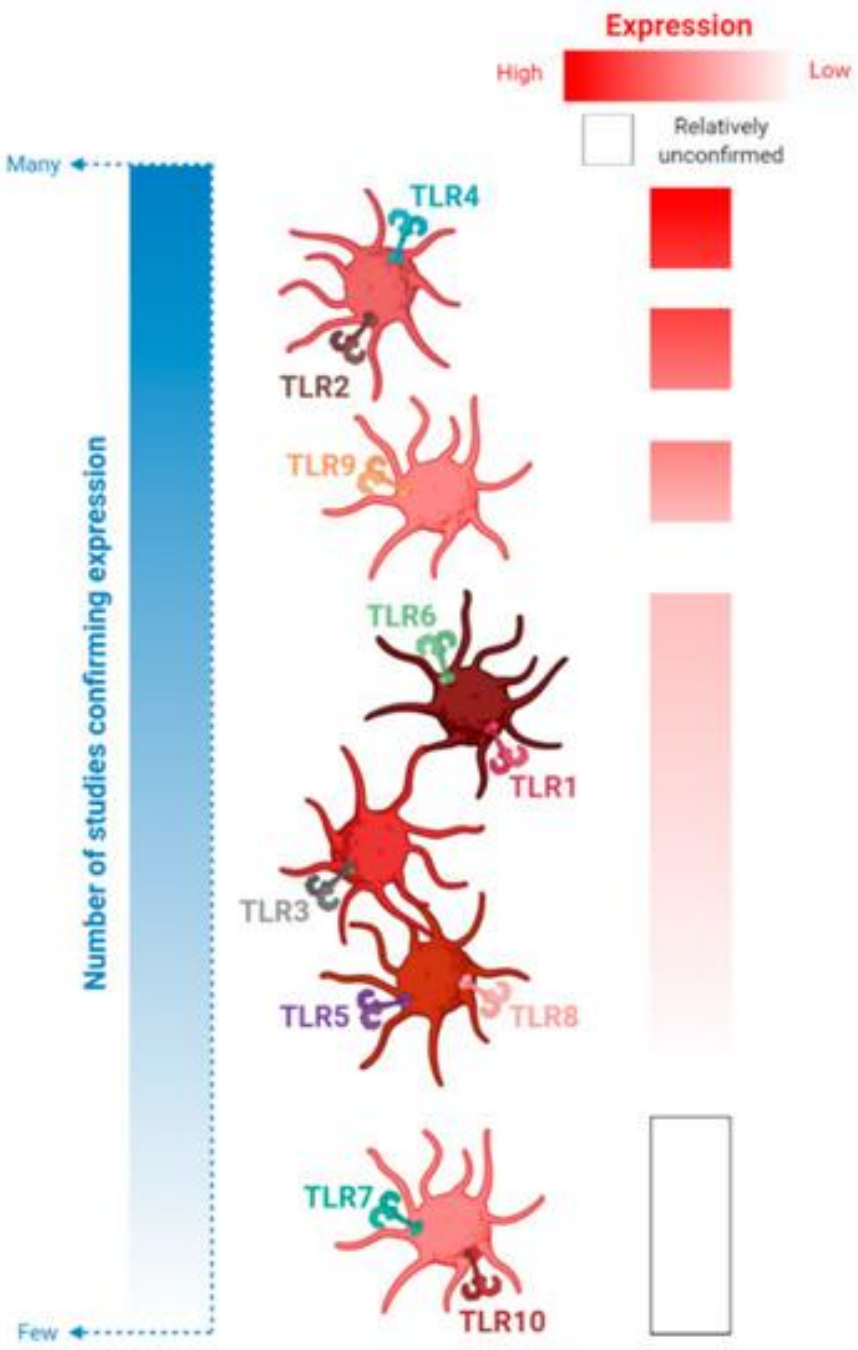
Platelet membrane innate immunity and toll-like receptors involved in the immune response and pathogenesis

TLRs can recognize :

- **Microbe-specific pathogen-associated molecular patterns (PAMPs)**
- **Host-derived damage-associated molecular patterns (DAMPs)**

These receptors are crucial for orchestrating the inflammatory response to both types of danger signals.

@ Hind Hamzeh-Cognasse



International Journal of *Molecular Sciences*

Int. J. Mol. Sci. **2020**, *21*, 6150; doi:10.3390/ijms21176150

MDPI

Review

Revisiting Platelets and Toll-Like Receptors (TLRs): At the Interface of Vascular Immunity and Thrombosis

Kathryn Hally [1,2,3,*], Sebastien Fauteux-Daniel [4,5], Hind Hamzeh-Cognasse [5], Peter Larsen [1,2,†] and Fabrice Cognasse [4,5,†]

- **All 10 TLRs have been identified on and within human platelets.**
- **In this figure, platelet-TLRs are stratified by the number of studies that have measured expression levels.**
- **Platelet-TLRs 2 and 4 are the most well-studied while only a few papers investigate expression of platelet-TLRs 7 and 10.**
- **Most platelet-TLRs (TLRs 1, 3, 5, 6 and 8) are expressed at low levels while others (TLRs 2, 4 and 9) are expressed more abundantly.**

Review Article

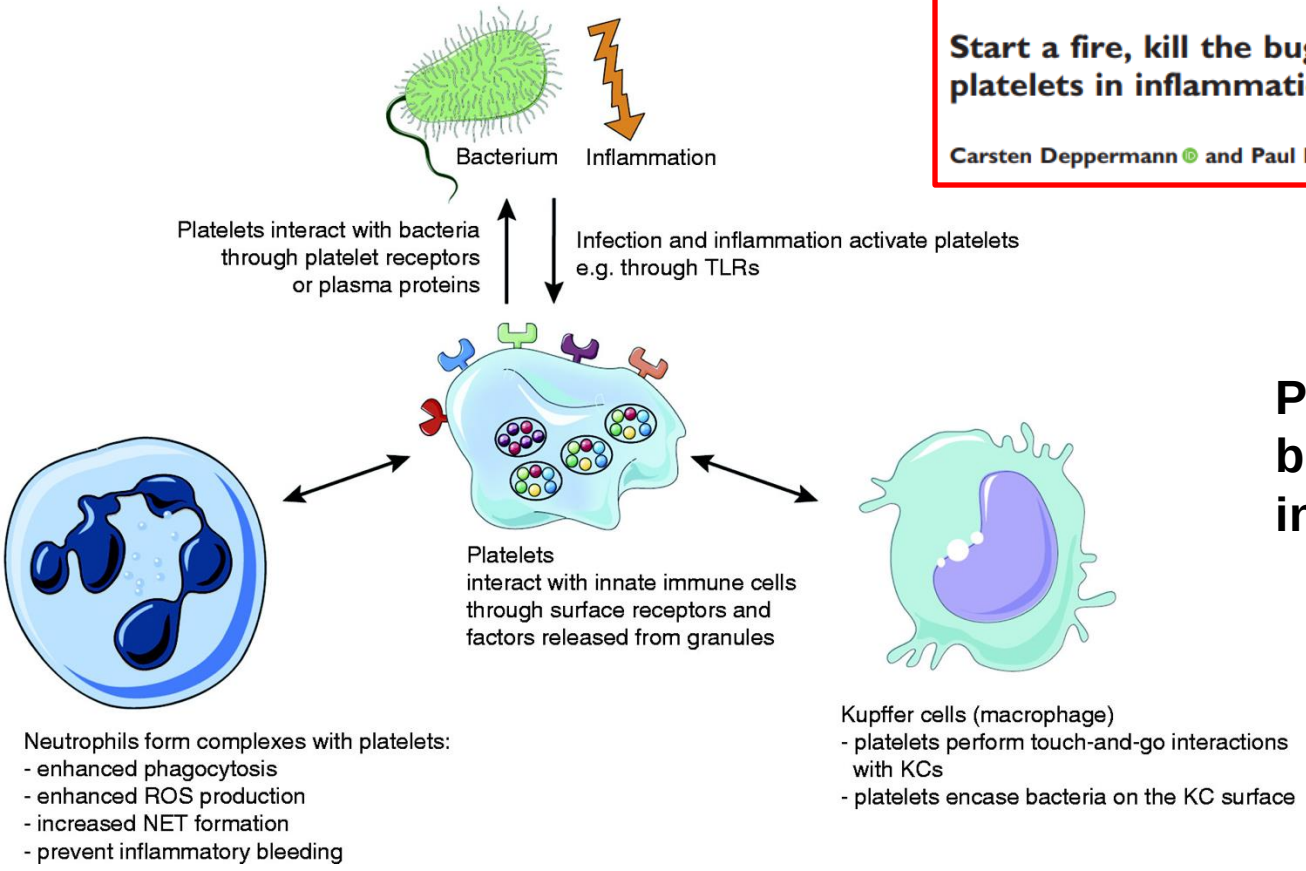
Innate Immunity

Innate Immunity
2018, Vol. 24(6) 335–348

DOI: 10.1177/1753425918789255
journals.sagepub.com/home/ini
SAGE

Start a fire, kill the bug: The role of platelets in inflammation and infection

Carsten Deppermann and Paul Kubes



Platelets interact with bacteria and cells of the innate immune system.

- **Platelets orchestrate the immune reaction to inflammation and infection by direct interactions with cells of the innate immune system (neutrophils and Kupffer cells) or through the secretion of mediators.**

- **Platelets interact with bacteria directly through their surface receptors or indirectly through plasma proteins.**

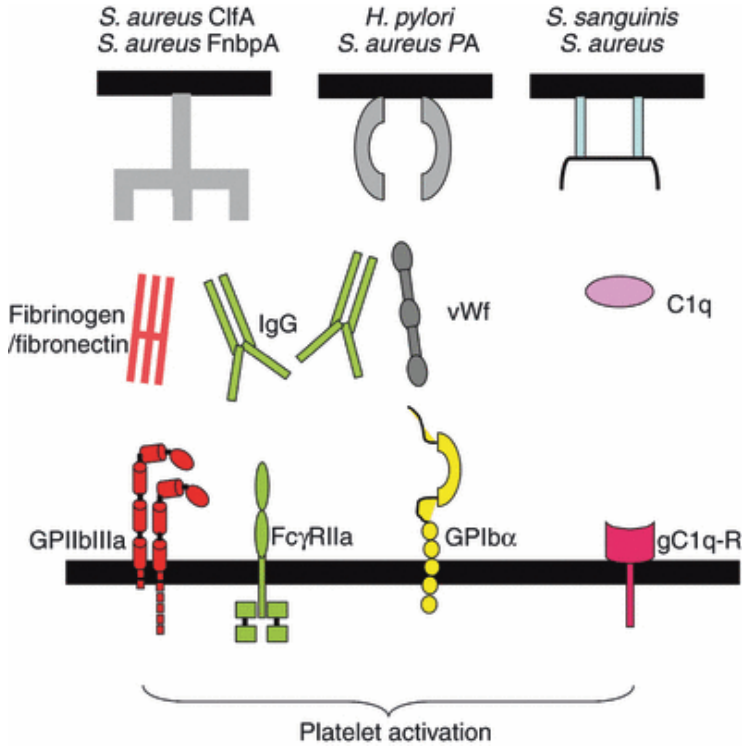
Journal of Thrombosis and Haemostasis, 9: 1097–1107 DOI: 10.1111/j.1538-7836.2011.04264.x

REVIEW ARTICLE

Platelets and the innate immune system: mechanisms of bacterial-induced platelet activation

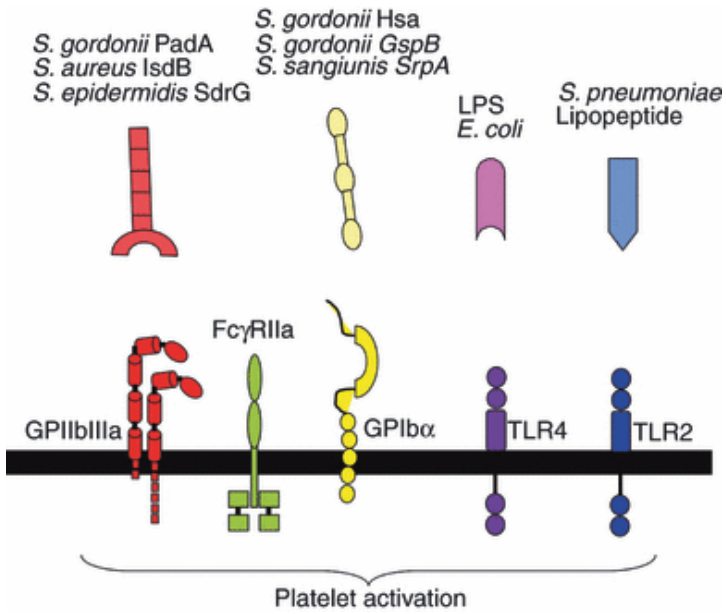
D. COX,* S. W. KERRIGAN† and S. P. WATSON‡

*Molecular and Cellular Therapeutics; †School of Pharmacy, Royal College of Surgeons in Ireland, Dublin, Ireland; and ‡Centre for Cardiovascular Sciences, University of Birmingham, Birmingham, UK



Summary of indirect interactions between bacteria and platelets.

Different species of bacteria bind different plasma proteins which bridge to their respective platelet receptors, triggering activation.



Summary of direct interactions between bacteria and platelets. Different species of bacteria contain ligand mimetic motifs that act as agonists on platelet receptors.

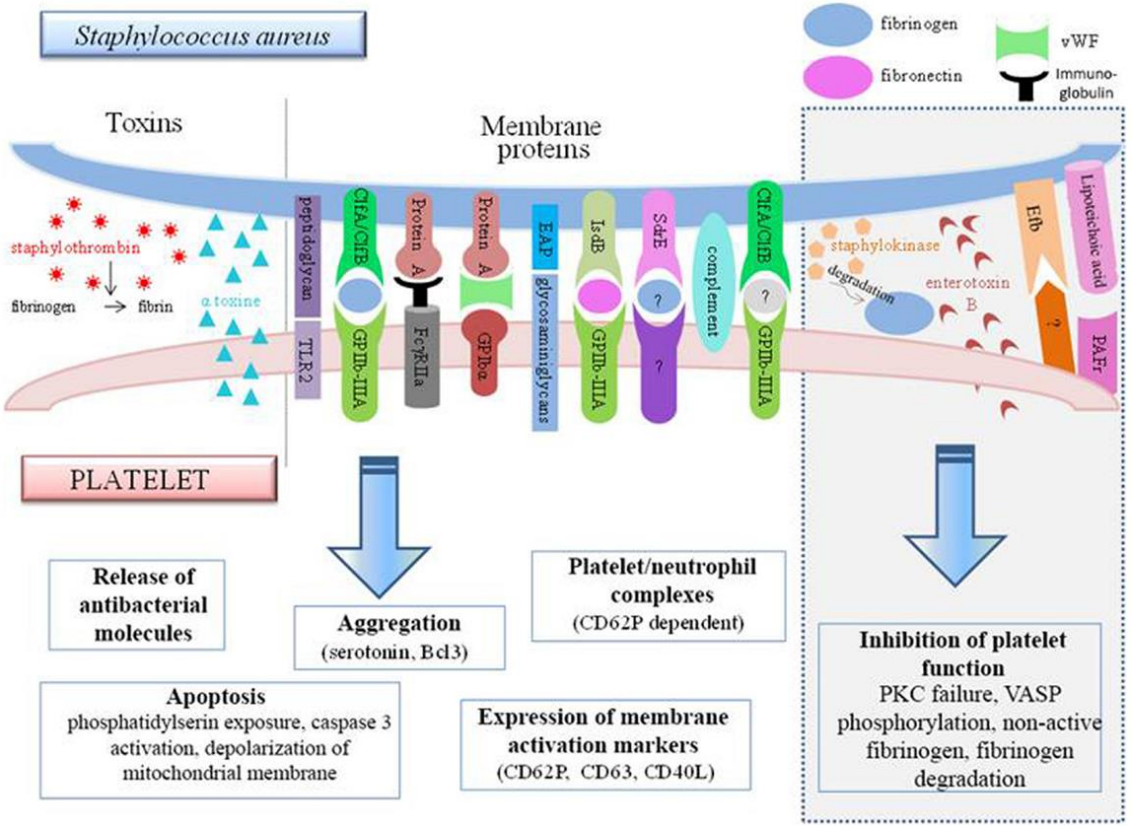
frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 26 February 2015
doi: 10.3389/fimmu.2015.00082

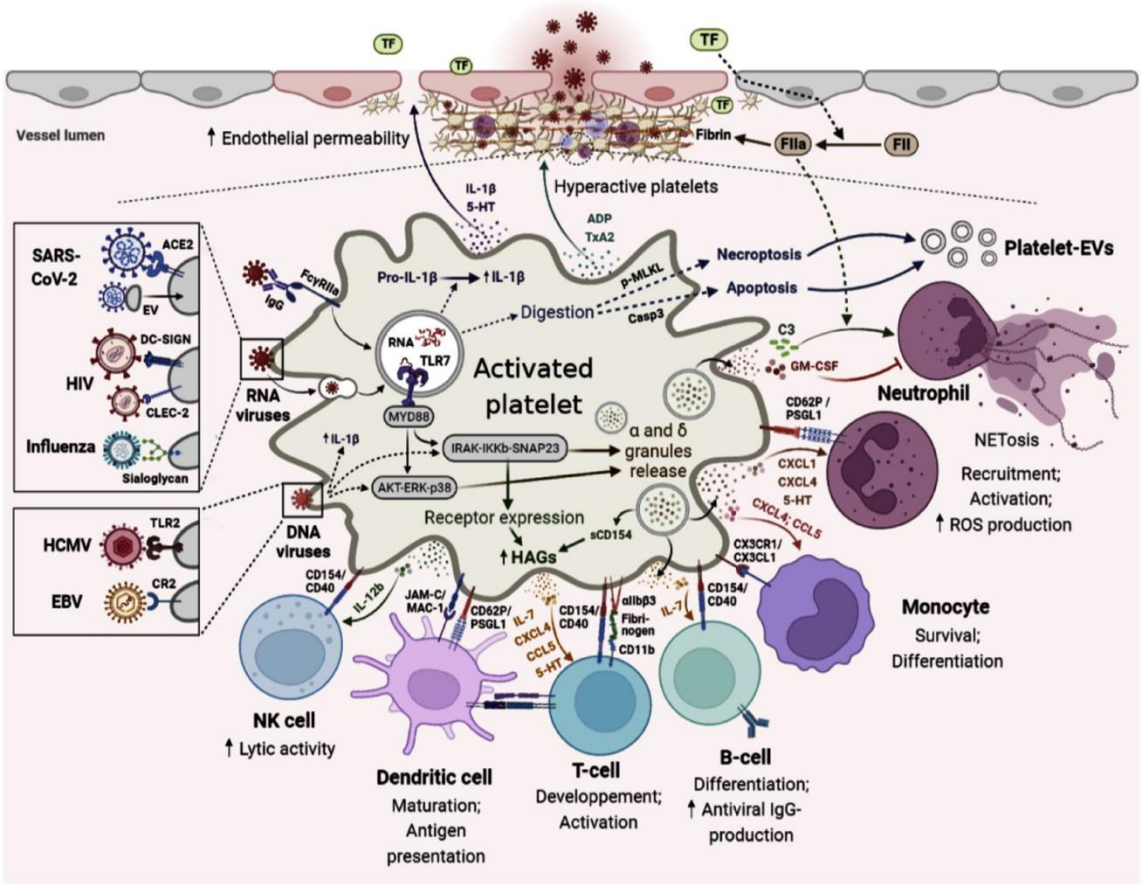
Platelets and infections – complex interactions with bacteria

*Hind Hamzeh-Cognasse[1], Pauline Damien[1], Adrien Chabert[1], Bruno Pozzetto[1], Fabrice Cognasse[1,2] and Olivier Garraud[1,3]**

[1] GIMAP-EA3064, Université de Lyon, Saint-Etienne, France
[2] Etablissement Français du Sang Auvergne-Loire, Saint-Etienne, France
[3] Institut National de la Transfusion Sanguine, Paris, France



- **Interconnections between *s. aureus* and platelets: *S. aureus* can induce platelet activation by several ways, e.g., through toxin release or by using membrane protein that bind platelet receptors either directly or indirectly and induce the activation of platelet fucntion.**
- **However, some bacterial factors induce the inhibition of platelet function**



International Journal of Molecular Sciences
Int. J. Mol. Sci. 2023, 24, 2009. https://doi.org/10.3390/ijms24032009
MDPI

Review

Dissecting Platelet's Role in Viral Infection: A Double-Edged Effector of the Immune System

Hajar El Filaly [1,†], Meryem Mabrouk [2,†], Farah Atifi [3], Fadila Guessous [4,5], Khadija Akarid [1], Yahye Merhi [6] and Younes Zaid [2,3,7,*]

Platelet immune mechanisms during viral infection:

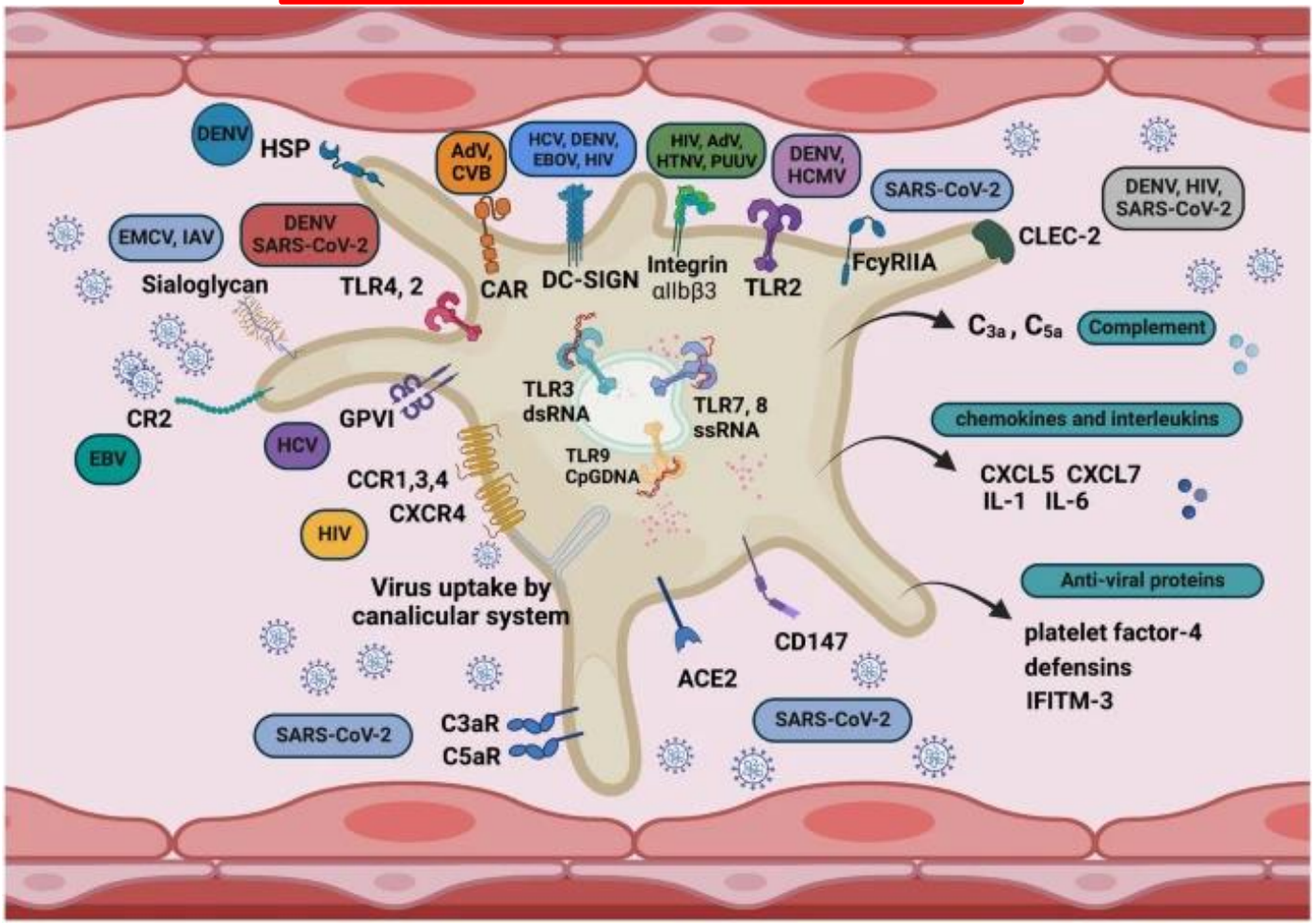
•Platelets can take up viral agents and stimulate neutrophil activation and production of antimicrobial NETs.

- **Platelets contain numerous pro- and anti-inflammatory cytokines and chemokines that are released into the extracellular space upon viral activation.**
- **Platelets contain several types of RNA that can be exported by PMPs and can then be translated into proteins.**
- **CD40L expression by platelets allows them to activate and/or inhibit different cells of the immune system and platelet content can contribute to immune cell function and modify adaptive immunity**

Platelets in COVID-19 disease: friend, foe, or both?

Marta Smęda[1] · Ebrahim Hosseinzadeh Maleki[1] · Agnieszka Pełesz[1] · Stefan Chłopicki[1,2]

Received: 24 October 2022 / Revised: 16 November 2022 / Accepted: 17 November 2022 / Published online: 3 December 2022



The non-hemostatic function of platelets likely plays an important role in responses to SARS-CoV-2, but the mechanisms involved are less understood as compared to those operating in host defense response to bacterial infections.

International Journal of *Molecular Sciences*

Int. J. Mol. Sci. **2020**, *21*, 6150; doi:10.3390/ijms21176150

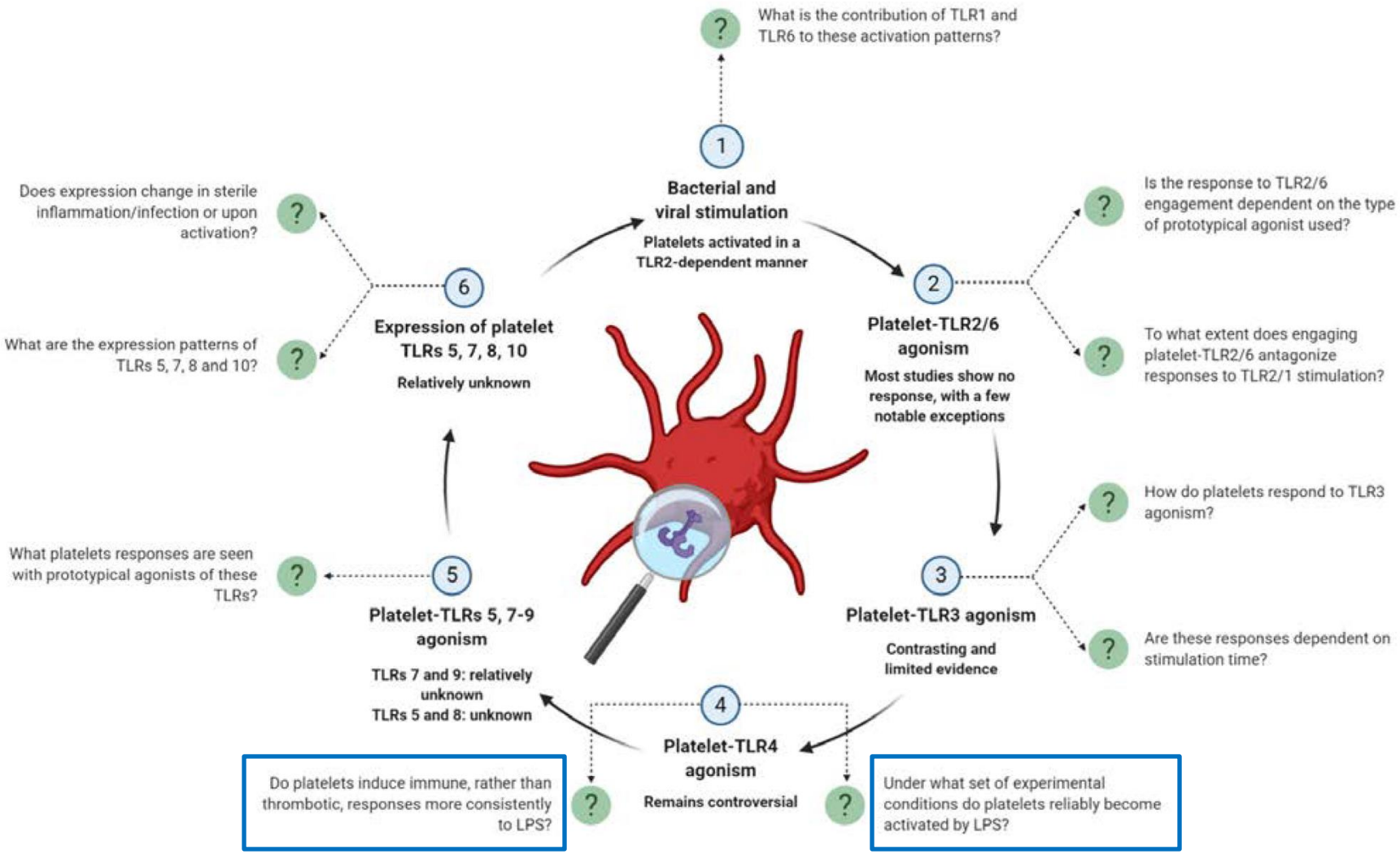
MDPI

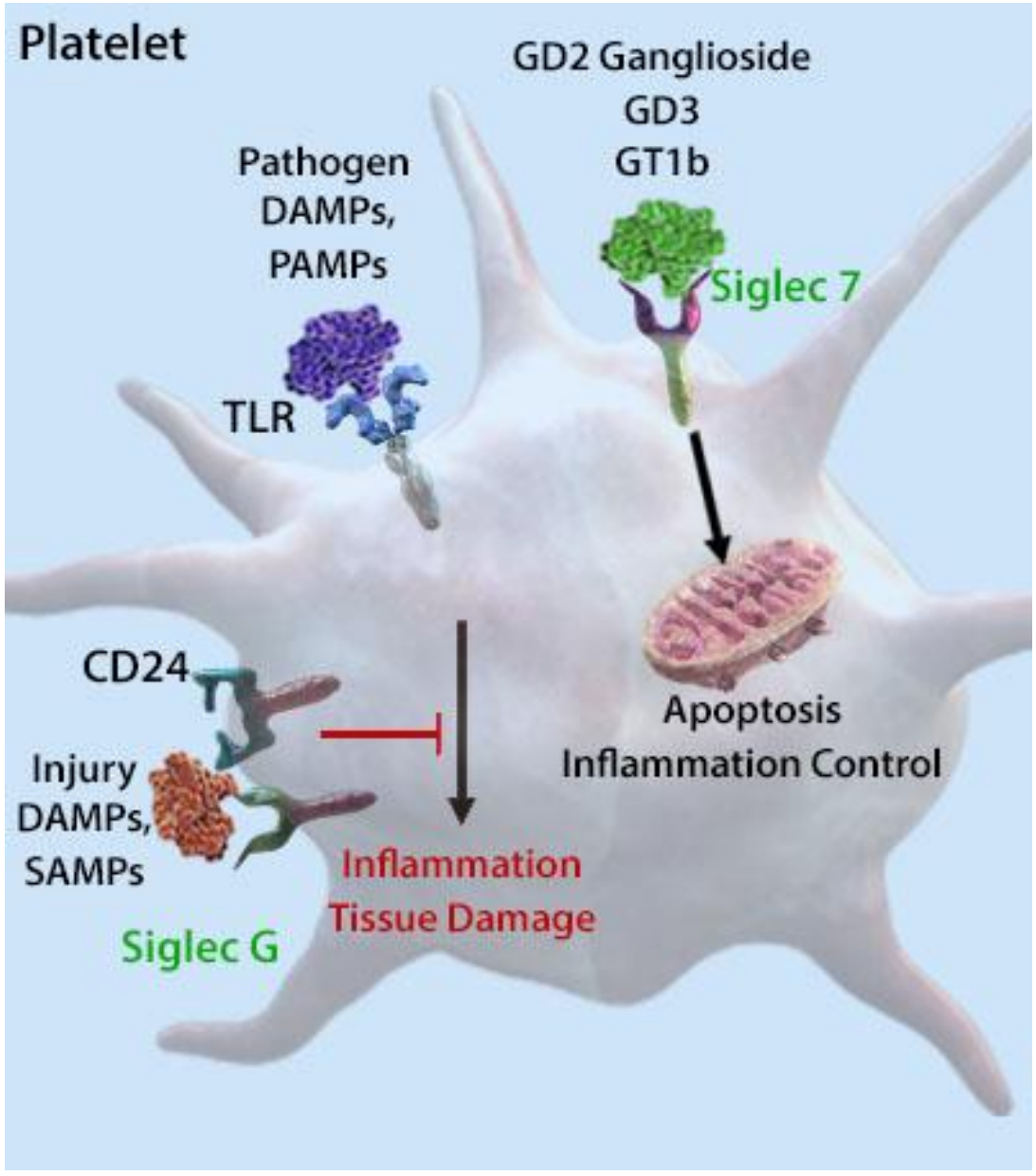
Review

Revisiting Platelets and Toll-Like Receptors (TLRs): At the Interface of Vascular Immunity and Thrombosis

Kathryn Hally [1,2,3,*], Sebastien Fauteux-Daniel [4,5], Hind Hamzeh-Cognasse [5], Peter Larsen [1,2,†] and Fabrice Cognasse [4,5,†]

Unanswered questions that remain in the field of platelet-TLR biology ?





frontiers in IMMUNOLOGY
REVIEW ARTICLE
published: 02 March 2015
doi: 10.3389/fimmu.2015.00083

The inflammatory role of platelets via their TLRs and Siglec receptors

Fabrice Cognasse[1,2], Kim Anh Nguyen[2], Pauline Damien[2], Archibald McNicol[3], Bruno Pozzetto[2], Hind Hamzeh-Cognasse[2] and Olivier Garraud[2,4]*

[1] Etablissement Français du Sang Auvergne-Loire, Saint-Etienne, France
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[3] Faculty of Health Sciences, Colleges of Pharmacy and Medicine, University of Manitoba, Winnipeg, MB, Canada
[4] Institut National de Transfusion Sanguine (INTS), Paris, France

OPEN ACCESS Freely available online
September 2014 | Volume 9 | Issue 9 | e106239
PLOS ONE

Role of Siglec-7 in Apoptosis in Human Platelets

Kim Anh Nguyen[1], Hind Hamzeh-Cognasse[1], Sabine Palle[2], Isabelle Anselme-Bertrand[3], Charles-Antoine Arthaud[4], Patricia Chavarin[4], Bruno Pozzetto[1], Olivier Garraud[1,4], Fabrice Cognasse[1,4]*

1 GIMAP-EA3064, Université de Lyon, Saint-Etienne, France, **2** 4D Multiphotonic Confocal Microscopy Platform (Hubert Curien Laboratory and UMR CNRS 5516), Université de Lyon, Saint-Etienne, France, **3** Centre de Microscopie Electronique Stéphanois - CMES–Saint Etienne, Université de Lyon, Saint-Etienne, France, **4** EFS Auvergne-Loire, Saint-Etienne. France

- **Pathogen recognition receptors (like TLRs) can induce inflammation upon the binding of their targets.**
- **Certain Siglecs are able to limit inflammation even after TLR engagement.**
- **Siglec-7 is capable of inducing platelet apoptosis *via* intrinsic and extra-mitochondrial pathways.**

These mechanisms help control tissue damage, platelet inflammatory responses, and excessive inflammatory reactions.

nature cardiovascular research

REVIEW ARTICLE

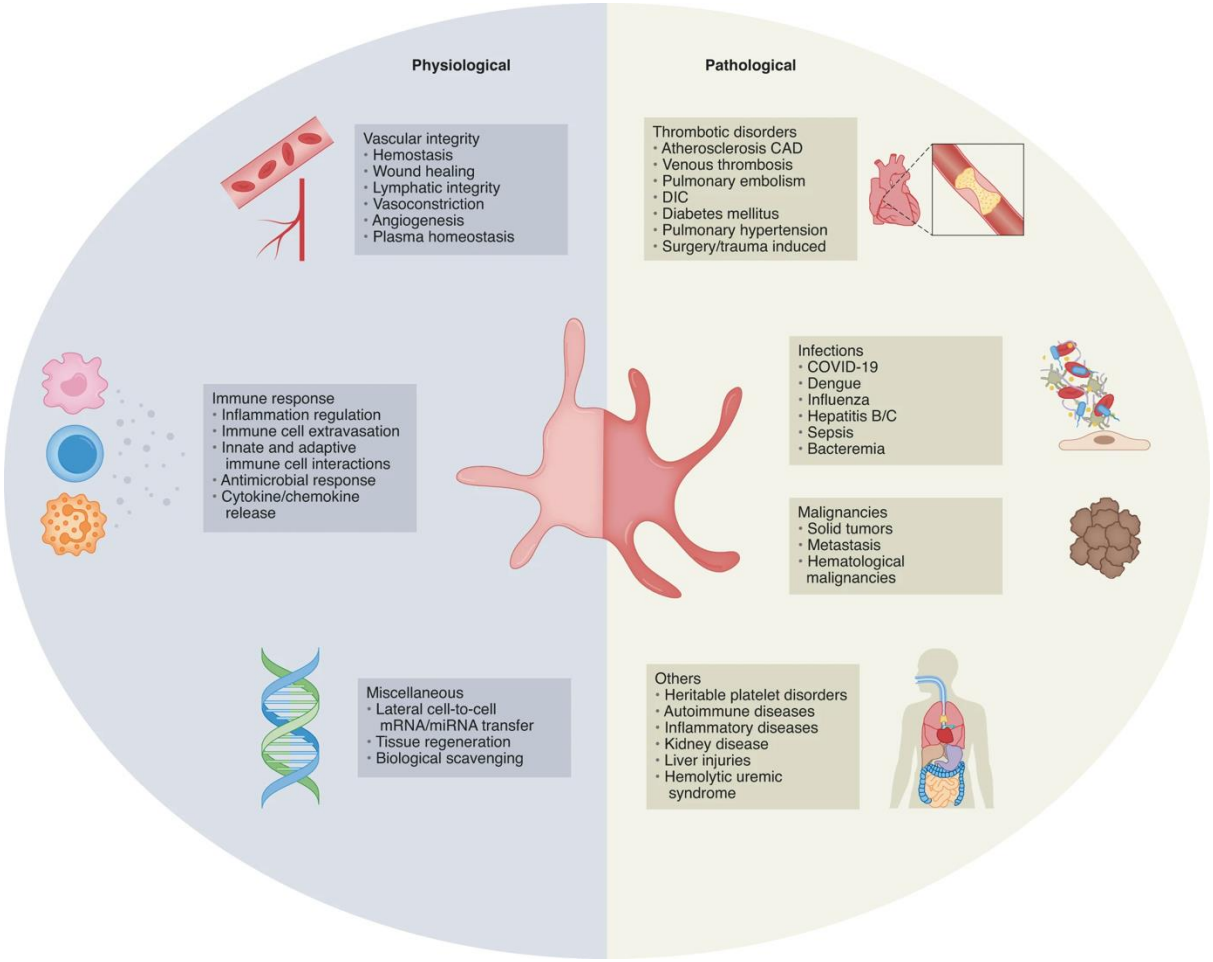
https://doi.org/10.1038/s44161-022-00021-z

Check for updates

A guide to molecular and functional investigations of platelets to bridge basic and clinical sciences

Tarun Tyagi[1,6], Kanika Jain[1,6], Sean X. Gu[1,2], Miaoyun Qiu[3], Vivian W. Gu[1], Hannah Melchinger[1], Henry Rinder[2], Kathleen A. Martin[1], Elizabeth E. Gardiner[4], Alfred I. Lee[5], Wai Ho Tang[3] and John Hwa[1]✉

NATURE CARDIOVASCULAR RESEARCH | VOL 1 | MARCH 2022 | 223-237 | www.nature.com/natcardiovascres



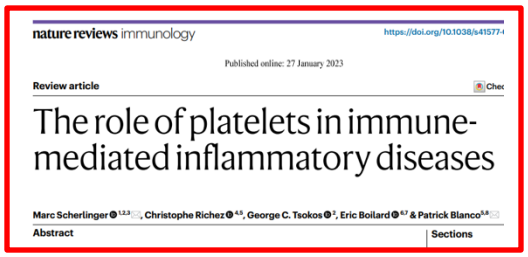
This functional diversity in both physiological and pathological contexts is unusual for a small, short-lived cell with no nucleus.

- **Platelets physiological functions include**

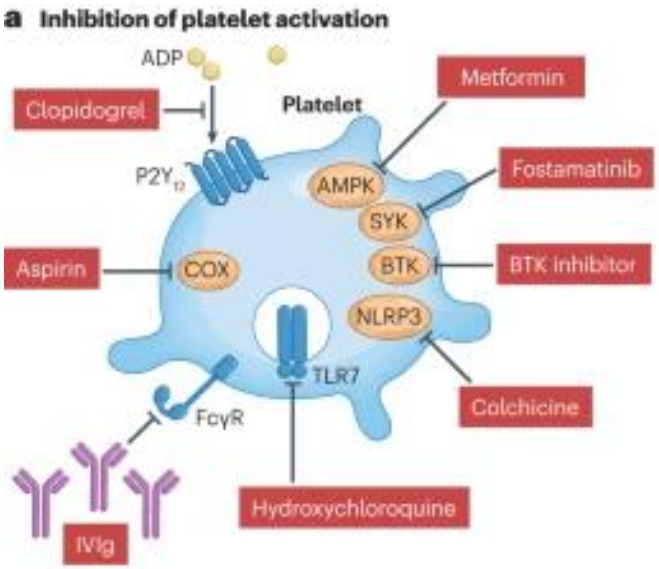
  - The maintenance of vascular integrity
  - The immune response
  - Inflammation
  - Biological scavenging
  - Tissue regeneration

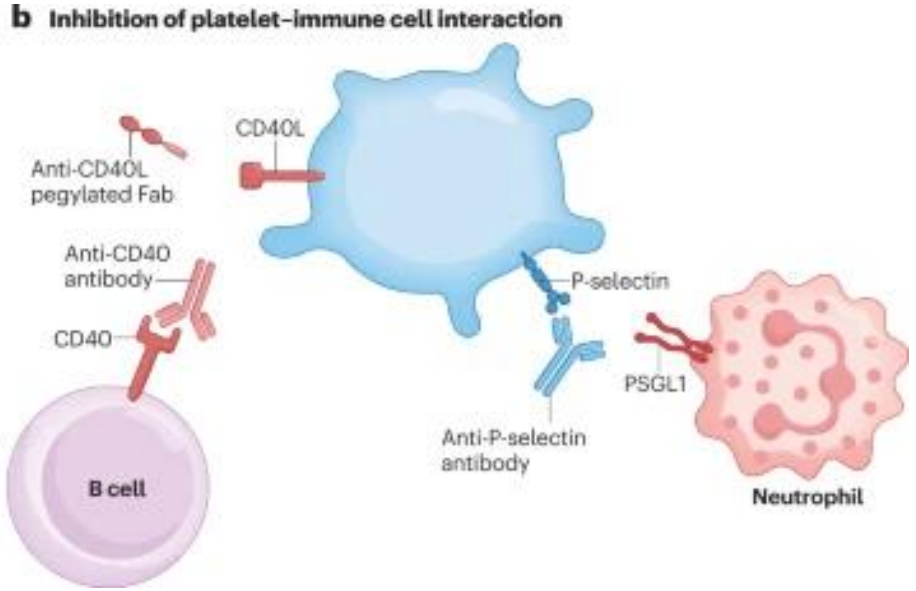
- **Platelets are well studied for their pathological roles in thrombotic disorders.**

  - Platelets have also been linked to the pathogenesis of disease states such as
  - Infections (sepsis and viral infections including COVID-19)
  - Malignancies
  - Inflammatory and autoimmune disorders
  - Liver disease and kidney disease.



Potential therapeutic strategies to target platelets in immune-mediated inflammatory disease.





Two strategies may be used to target platelets in immune-mediated inflammatory disease:

a) inhibiting platelet activation

- by blocking agonist engagement,
- inhibiting platelet cyclooxygenase activity using aspirin,
- inhibiting (TLR7) activation using hydroxychloroquine,
- Etc …

b) inhibiting the interaction between platelets and immune cells.

• antibody to P-selectin prevents P-selectin binding to P-selectin glycoprotein ligand 1 on neutrophils and other immune cells
• antibodies targeting CD40 or CD40 ligand (CD40L) prevent interaction with B cells. Fab, antigen-binding fragment.

Platelet Inflammatory Response to Stress

Fabrice Cognasse[1,2], Sandrine Laradi[1,2], Philippe Berthelot[2,3], Thomas Bourlet[2,3], Hubert Marotte[4,5], Patrick Mismetti[4,6], Olivier Garraud[2,7] and Hind Hamzeh-Cognasse[2]*

frontiers in Immunology

REVIEW
published: 28 June 2019
doi: 10.3389/fimmu.2019.01478

Journal of Thrombosis and Haemostasis, **14**: 794–796 DOI: 10.1111/jth.13262

COMMENTARY

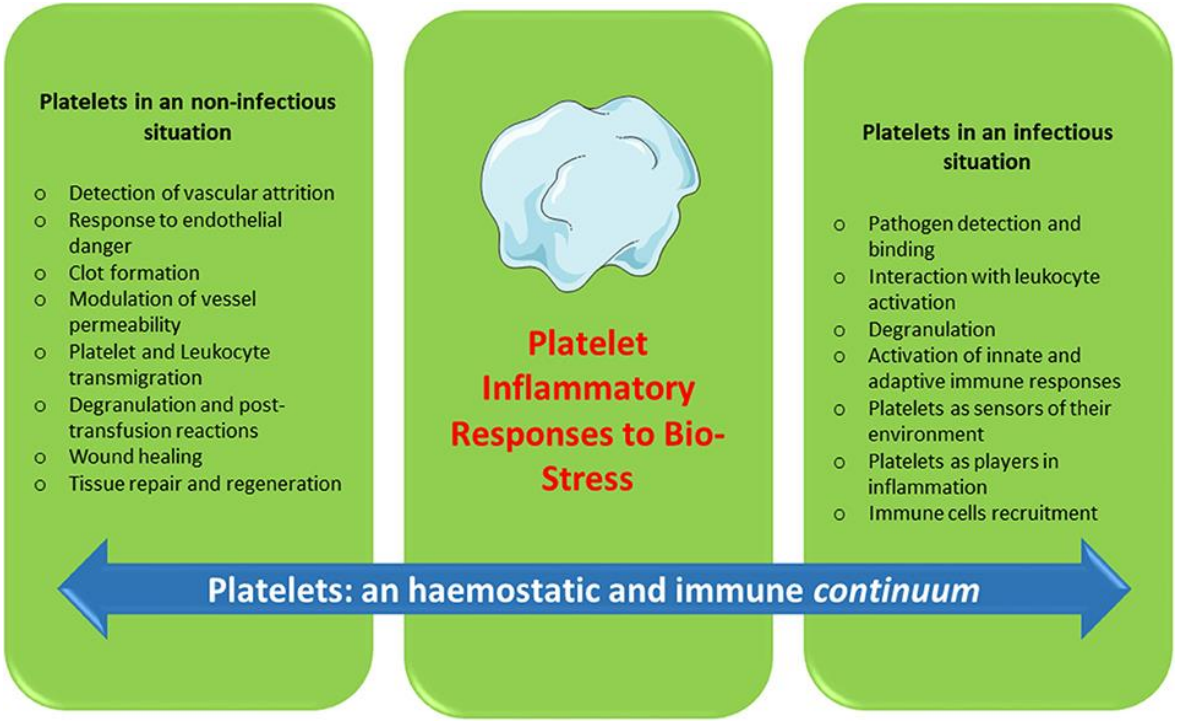
How can non-nucleated platelets be so smart?

F. COGNASSE,*† O. GARRAUD,†‡ B. POZZETTO,†§ S. LARADI*† and H. HAMZEH-COGNASSE†
*Etablissement Français du Sang Auvergne-Loire; †Groupe Immunité des Muqueuses et Agents Pathogènes, EA 3064, Université de Lyon, Saint-Etienne; ‡Institut National de la Transfusion Sanguine, Paris; and §Laboratoire des Agents Infectieux et d'Hygiène, University Hospital of Saint-Etienne, Saint-Etienne, France

- **It is now clear, that in addition to their roles in hemostasis and thrombosis, platelets have a large range of other functions (inflammatory process, immune responses, regenerative medicine and host defense against pathogens).**

- **The challenge for therapeutic intervention in pathological processes will be to identify drugs that block specific targets involved in the complex contribution of platelets to inflammation/immunity without affecting their hemostatic function**

Our future directions for research concern the critical role of platelets as an immune cell in the host immune response (non infectious *versus* infection situation)



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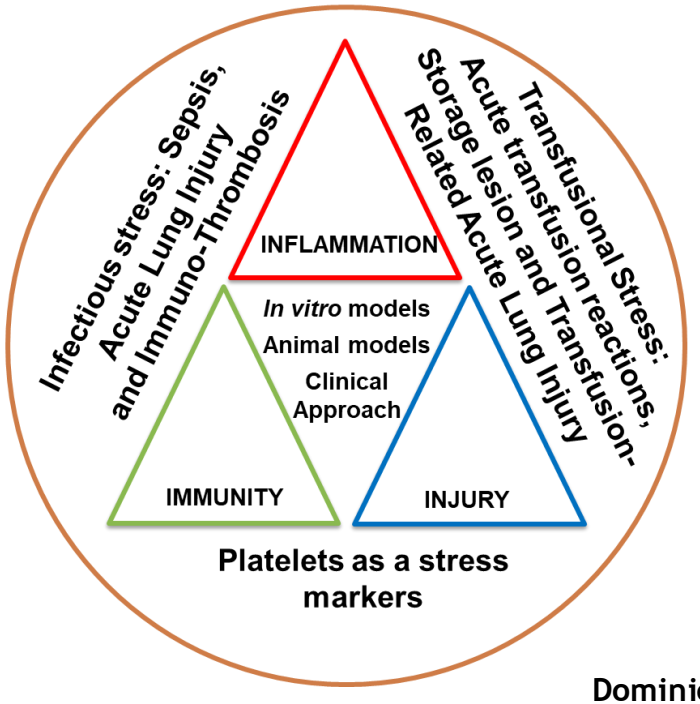
Mailys Portier (Master's student) / EFS 

Natalia Shurko «Institute of Blood Pathology and Transfusion Medicine NAMSU», Lviv, Ukrain

"Because of your generosity, lives will be saved. Thank you for your blood donation."



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