IMMATURE PLATELETS IN DOGS

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Introduction

- Immature platelets, also called reticulated platelets by analogy to reticulocytes, are the youngest form of platelets present in the bloodstream.
- They contain messenger ribonucleic acid (mRNA) and they use it to synthesize proteins.
- Platelets have many functions other than hemostasis and their relation with inflammation and the immune system is of great importance.
- In veterinary medicine, particularly in dogs, the correlation between an increase of immature platelets and some inflammatory conditions, where platelets may be highly active, is being studied at the moment.

Objectives

The aims of this bibliographical review are to:

- Assimilate general characteristics of immature platelets including their formation and their analysis.
- Update on the recent studies of platelet functions, emphasizing in the relation with inflammatory diseases.
- Research on the current diagnostic and clinical utility of immature platelets in veterinary medicine and study the possible use in the future.

Thrombopoiesis

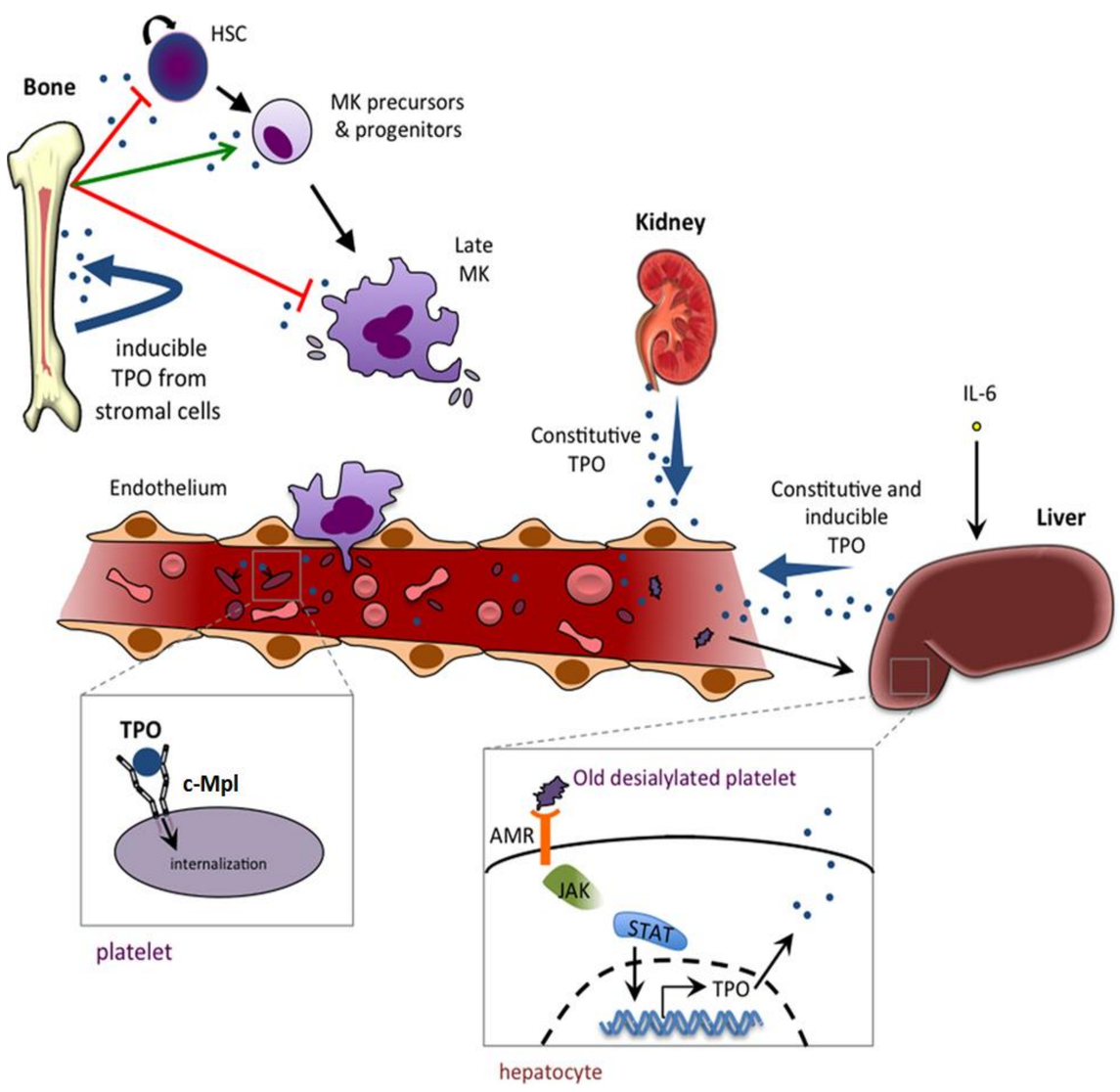

Figure 1. Thrombopoietin (TPO) production, function and homeostasis (Varghese et al. 2017) Modified

Mechanisms of platelets in inflammation and immunity

Table 1. Principal platelet mechanisms that modulate inflammation and immunity (Thomas and Storey 2015)

Mechanism	Action
Platelet α-granules release	Multiple mediators of inflammation have important pro-inflammatory effects.
Platelet P-selectin expression	Interacts with leukocyte P-selectin glycoprotein ligand-1 (PSGL-1), essential for platelet-leukocyte aggregates and also forms cross-links between leukocytes and endothelium facilitating adhesion.
Platelet-leukocyte aggregate formation	Upregulates many pro-inflammatory leukocytes functions, including release of pro-inflammatory cytokines, reactive oxygen species, phagocytosis and endothelial adhesion.
Platelet expression of cluster of differentiation 40 ligand (CD40L)	Interacts with leukocyte cluster of differentiation 40 (CD40) and induce monocyte expression of tissue factor and activation of the coagulation system. It also influences some important T cell function like antigen presenting cell activation.
Platelet toll-like receptor 4 (TLR4)-mediated NET formation	Has an important role in neutrophil extracellular traps (NETs) formation, which aid the clearance of bacteria.
Platelet P-selectin-mediated activation of the complement system	As chondroitin sulfate is released by platelets, it helps in the clearance of bacteria and contributes in vascular inflammation.
Platelet release of high mobility group box 1 (HMGB1)	It is a potent inflammatory stimulus that activates mitogen-activated protein (MAP) kinases and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), it also has an effect on the formation of NETs by neutrophils when HMGB1 is presented.
Platelet activation in response to binding of Glycoprotein Ib (GPIb) and Glycoprotein IIb/IIIa (GPIIb/IIIa) by bacteria	Aggregates in response to bacteria directly or indirectly binding.
Platelet expression of triggering receptor expressed on myeloid cells 1 (TREM1) ligand	Mediates leukocyte activation and the engagement of leukocyte TREM1 induces the secretion of some cytokines.
Platelet release of microparticles	Presents Interleukin 1 beta (IL-1β) and Regulated upon activation normal T cell expressed and secreted (RANTES) to the endothelium. It also acts signalling between platelets and the innate immune system.

Automated hematology analyzers

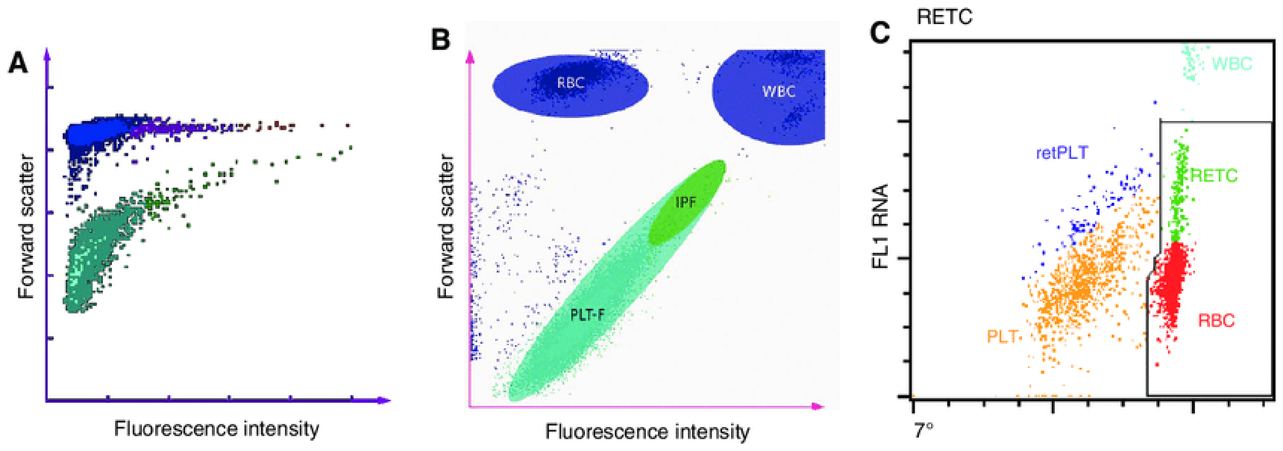

Figure 3. Scatterplots of the automated assays of immature and reticulated platelets currently available. A) Sysmex XE-series B) Sysmex XN-series C) Abbot CELL-DYN (Hoffman 2014)

Clinical utility

Immature platelets act as a megakaryopoietic activity marker in the bone marrow, useful to differentiate central or peripheral origin of thrombocytopenia in dogs.

Many other applications have been studied in humans, such as:

- Risk assessment in patients with cardiovascular diseases
- Verification of the effect of platelet transfusion
- Differentiation between chronic hepatitis and cirrhosis
- Control the increased thrombotic risk in thrombocytosis
- Evaluation of the response to antiplatelet drugs
- Prediction of sepsis in critical ill patients

Conclusions

- Immature platelets are more reactive than mature platelets.
- Thrombopoiesis is mainly regulated by thrombopoietin (TPO). Inflammatory conditions increase the production.
- Many of the inflammatory mediators secreted by activated platelets come from α-granules, the major storage.
- There is solid evidence on the correlation between some inflammatory diseases and an increase of immature platelets in human medicine, therefore targeting platelets could be a proper approach for inflammatory response manipulation.
- Due to lack of standardization of flow cytometry, immature platelets are measured by automated hematology analyzers based on RNA fluorescent dye detected by an argon laser.
- Immature platelet fraction (IPF) is a useful clinical tool for thrombocytopenia in dogs and there are many other application for immature platelets in humans, they can be used as a diagnostic, prognostic and monitoring tool.

References

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3. Thomas MR, Storey RF. 2015. The role of platelets in inflammation. Thromb Haemost. 114(3):449–458.