


# Functional Diversity of Primed Platelets—Powered by Machine Learning

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## Effects of Platelet Agonists and Priming on the Formation of Platelet Populations

Heterogeneity of platelet activity is well known when collagen plus thrombin-stimulated platelets form a distinct subpopulation, exposing phosphatidylserine and a “coat” of procoagulant proteins.<sup>1</sup> The sensitivity of the initial platelet response can be decreased and increased by primers, e.g., prostacyclin, nitric oxide (negative priming), and adrenaline (positive priming).<sup>2</sup> In this issue of *Thrombosis and Haemostasis*, Veninga et al provided new insights into how priming affects subpopulations of human platelets with suboptimal activation via glycoprotein VI (GPVI), protease-activated receptor 1 (PAR-1), and P2Y<sub>1</sub>/P2Y<sub>12</sub> receptors.<sup>3</sup> Multiparameter flow cytometric analysis revealed agonist-specific patterns of platelet  $\alpha$ IIb $\beta$ 3 integrin activation (PAC-1),  $\alpha$ -granule (P-selectin, TLT-1), dense granule, and lysosome (CD63) secretion. Sophisticated unsupervised clustering tools sensitized the discrimination of three platelet populations with distinct intermediate activation profiles (solely activated  $\alpha$ IIb $\beta$ 3 [PAC-1<sup>+</sup>]; solely degranulated [CD62P<sup>+</sup>, TLT-1<sup>+</sup>, and CD63<sup>+</sup>]; activated  $\alpha$ IIb $\beta$ 3 plus  $\alpha$ -granule secreting [PAC-1<sup>+</sup>, CD62P<sup>+</sup>, and TLT-1<sup>+</sup>]) in addition to resting and fully activated platelets. Adenosine and succinate, elevated in ischemic heart disease, have been implicated to suppress and enhance platelet activation by raising and reducing intracellular cAMP levels, respectively. Adenosine mediated a dose-dependent decrease of fully activated platelets in response to CRP-XL, TRAP-6, and ADP, while positive priming with succinate

enlarged this population. Notably, priming did not significantly affect populations with intermediate platelet activation patterns. PAR-1-mediated platelet activation was most sensitive to adenosine, whereas platelet activation via GPVI showed the highest sensitivity to succinate. This interesting study identified receptor-specific signatures of subpopulations related to platelet activity, which are differentially modulated by priming. It remains exciting to elucidate the complexity of platelet functional subpopulations in the presence of a primer “cocktail.” Driving progress in machine-learning-based analysis of multiple platelet function markers, covering also coagulation, chaperon, scavenger, and death functions, is promising to precisely identify the definition of pathological platelet reactivity in immuno-thrombotic diseases with potential diagnostic purpose.

### Conflict of Interest

None declared.

### References

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