Hubs and Webs in Platelet Intracellular Signalling

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Received: 30.09.2021

Accepted: 30.09.2021

Published: 30.09.2021

DOI: 10.52455/sbpr.01.202103014

Editorial Letter

In this issue of Systems Biology and Physiology Reports, A.A. Martyanov and M.A. Pantelev suggested a review on platelet intracellular signalling network, which is a second part in the discussion on the molecular relationships between platelet activation and responses (1). The review contains seven thousands words and two hundred references and yet it is not complete, as there are still unclear parts in platelet signaling, especially in its inhibition (2–4). In an effort to comprehend the platelet activation pattern, I drew a signalling scheme based on the review and data from other authors (2,3) (Fig. 1).

One could see from the Figure that there is no clear isolated “activation sequence” or “activation cascade” from any receptor. Platelet signalling pathways tend to tightly interact with each other and cross-link on several levels. For example, both pathways from PARs and GPVI activate PLCs and PI3Ks, and cytosolic calcium regulates both PLCs. Cytosolic calcium was suggested to be the main regulator of platelet activation (5) and, indeed, it regulates most of the platelet functional responses (1). Therefore, cytosolic calcium could be called a “Hub”, which summarizes information on platelet activation (6). However, there are several other candidates for signalling hubs: all platelet GPCRs use the same Gβγ, which is crucial for platelet integrin activation (7), all platelet glycoprotein receptors activate SFK and Syk kinases, and all platelet receptors activate PI3Ks of different types. With addition of cross-regulation, these interactions form a spider-web, which is hard to analyze (Fig. 1).

While linear description could be useful for memorizing platelet signalling, it is misleading for its comprehension. The realistic description of platelet signal transduction is that of a network with several levels of intersection, with bifurcations and junctions. Any attempt to understand the mechanism of information transmission in the signalling network

should consider the system as a whole, in the entirety of its architecture.

It is not easy; moreover, it is not likely that this is something to be done mentally. Non-linear interactions, oscillations and spiking, frequency and amplitude coding/decoding could be only analyzed with the help of mathematical and computer modelling (6,8–10). I believe that this line of approach is going to be incrementally important in deciphering the meaning behind the platelet signalling design, and will hopefully lead to the development of efficient tools for diagnostics and treatment based on this understanding.

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Figure. Scheme of platelet intracellular signalling with focus on cytosolic calcium as a “Hub”. Cytosolic calcium concentration is given in the shades of red. Almost all types of platelet receptor agonists lead to activation of phospholipase C (PLC), followed by calcium release from intracellular stores (DTS). Calcium concentration is rapidly reduced by calcium-dependent ATPases (SERCA and PMCA). Also, it could be reduced by binding with some buffering proteins, including its effector-proteins (indicated with red dots). Platelet mitochondria also can function as a calcium buffer and, simultaneously, be regulated by calcium concentration. Direct activation is shown by solid green arrows, direct inhibition - by solid red arrows. Indirect interactions are shown by dashed lines. Abbreviations. AC – adenylate cyclase, $\alpha 2$ AAR – $\alpha 2$ A-adrenergic receptor, CDGEF – CalDAGGEFI, COX – cyclooxygenase, DAG – diacylglycerol, DTS – dense tubular system, Fbg – fibrinogen, IP3R – receptor for inositol-1,4,5-trisphosphate (IP3), Mit – a mitochondrion, mPTP – mitochondrial permeability transition pore, NCLX – mitochondrial sodium/calcium exchanger, OCS – open canicular system, P2Y – purinergic receptor, PAR – protease-activated receptor, PIP2 – phosphoinositol-4,5-bisphosphate, PIP3 – phosphoinositol-3,4,5-trisphosphate, PI(P)n – phosphoinositides, PKA – protein kinase A, PKG – protein kinase G, PKC – protein kinase C, PL – phospholipid, PLA2 – phospholipase A2, PMCA – plasma membrane calcium ATPase, PR – PGI₂ receptor, P-Tyr – phosphorylated tyrosine residue, SERCA – sarcoplasmic/endoplasmic reticulum calcium ATPase, sGC – soluble guanylate cyclase, TR – thromboxane A₂ (TxA₂) receptor, TRPC – transient receptor potential channel, UNI – mitochondrial uniporter, vWF – von Willebrand Factor, Y-Pase – tyrosine phosphatase.