manifestations. Recently, HTLV-II coinfection was associated with an observable survival benefit and delay in progression to AIDS among HIV-I–infected IDUs.

While HTLV-I has been definitively proven to cause adult T-cell leukemia/lymphoma and a progressive neurodegenerative illness known as tropical spastic paraparesis/HTLV-I–associated myelopathy (TSP/HAM), a causal role for HTLV-II with either leukemia or TSP/HAM is much less well-defined and based on a handful of case reports. Long-term asymptomatic HTLV-II infection has been identified in American Indians, a group in which the virus is thought to have existed for hundreds or perhaps thousands of years with little evolutionary change.

In the absence of clinical disease, Bartman et al observed clear alterations in the hematologic parameters of HTLV-II–infected blood donors over time. The reasons for these findings are unclear. While HTLV-I has primary tropism for CD4+ T cells, HTLV-II may share differential tropism with both CD4+ and CD8+ T cells. In the present study, preliminary analysis of lymphocyte subpopulations failed to reveal any strong associations, but it is anticipated that further immunophenotypic and molecular/genetic analysis of lymphocytes from the patient population could prove fruitful in understanding the biologic basis for the clinical findings.

There are plausible explanations on a biologic level that explain the findings of Bartman et al. The transcriptional activating proteins of HTLV-I and HTLV-II, known as Tax1 and Tax2, are essential for viral replication but also modulate several key host cellular genes, such as cytokines and their receptors, antiviral chemokines, transcription factors (such as c-fos, c-sis, c-rel, c-myc, and others), proapoptotic factors, DNA repair enzymes, cell cycling pathways, growth factors, and adhesion molecules.

While the clinical consequences of HTLV-II infection remain infrequent and poorly studied, counseling and treatment of the HTLV-II–infected individual remains problematic. Confusion exists among professionals and lay people alike as to the significance of a positive HTLV-II blood testing result in the face of asymptomatic infection. Referral to an experienced hematologist or infectious disease specialist for further clinical evaluation of these patients often results in unnecessary tests and increased anxiety on the part of the affected person. Therefore, the knowledge gained from long-term observational studies, such as that published by Bartman et al, is invaluable in helping clinicians and subspecialists understand the more subtle hematologic abnormalities of chronic infection with this human retrovirus.

**Conflict-of-interest disclosure:** The author declares no competing financial interests.

## SYSTEMS BIOLOGY MEETS PLATELET BIOLOGY

**Comment on Purvis et al, page 4069**

**Michael C. Berndt and Robert K. Andrews**

In this issue of Blood, Purvis and colleagues describe a computational approach, employing 4 interlinked kinetic modules, to model platelet phosphoinositide and calcium regulation in resting platelets and after ADP-mediated P2Y1 purinergic receptor activation.

**REFERENCES**


**T**he model accurately replicates experimental findings, including the broad frequency distribution and asynchronous calcium spiking behavior in single platelets in response to adenosine diphosphate (ADP).

The P2Y1 receptor is a G-protein coupled receptor that signals through Gq and mediates ADP-induced platelet shape change and aggregation. Phospholipase Cβ2 (PLC-β2) is the major signaling molecule downstream of Gq and is responsible for transient increases in inositol 1,4,5-trisphosphate (IP3) and calcium concentration as well as the production of diacylglycerol (DAG) and protein kinase C (PKC) activation.1,2 In resting platelets, the cytoplasmic calcium concentration is actively maintained at approximately 100 nM, primarily through bulk storage of calcium within the dense tubular system (DTS). Calcium homeostasis between the cytoplasm and the DTS is regulated by inositol trisphosphate receptor (IP3R) channels, which release calcium ions from the DTS in response to IP3 and by a sarcoplasmic/endoplasmic reticulum Ca2⁺ ATPase (SERCA), which pumps calcium ions from the cytoplasmic compartment into the DTS.3

Classically, our understanding of platelet biology has come from a reductionist approach where individual events are studied under a single set of conditions. Here, Purvis et al present the first detailed and integrated “systems biology” approach to platelet signaling, modeling both phosphoinositide and calcium homeostasis in the resting platelet as well as temporal changes post-P2Y1 receptor activation. The model employs 4 interlinked kinetic modules: a calcium module, where the cytosolic and DTS compartments are separated by the DTS membrane, which contains the IP3R channels and SERCA; a phosphatidylinositol (PI) module, in which plasma membrane-bound PIs are cleaved by PLC-β2 to form diffusible inositol phosphates and DAG, which are substrates for resynthesis of PIs; a PKC module, whereby calcium and DAG activate PKC, which migrates to the plasma membrane and phosphorylates PLC-β2; and a P2Y1 module, where extracellular ADP activates P2Y1, accelerating formation of GTP-bound Gαi, and subsequent activation of PLC-β2. Each module was initially considered in isolation for optimization. For example, platelet calcium homeostasis was analyzed by
fixing the kinetic properties of the IP₃R channels and SERCA, the resting calcium concentration, the volume of the platelet from experimental measurement, and assessing combinations of values for the number of IP₃R channels per platelet, SERCA pumps per platelet and volume of the dense tubular system, using analog computation. P2Y₁ signaling was considered within the constraint that calcium influx was experimentally excluded, obviating the need to model store-operated calcium entry.⁴

This integrated model developed by Purvis and colleagues accurately accounts for known platelet behavior and replicates experimental data at both averaged platelet and single-platelet response. Stochastic simulation of the platelet model generated calcium spiking with peak-to-peak interval times favoring 6 to 8 and 11 to 13 s gaps, strikingly similar to calcium responses in video-imaged single platelets. In addition, the model allowed several novel predictions: The calcium spiking in single platelets was a consequence of the small platelet volume, the number of SERCA pumps must significantly outnumber IP₃R channels, and recovery of basal PI levels requires a negative-feedback mechanism in which PKC phosphorylation of PLC-β inhibits its hydrolytic activity. The model further explains that the reason thrombin is a more potent agonist than ADP is primarily due to differences in receptor copy number. The power of the computational approach of Purvis et al is that with continued development and experimental refinement of current variables, the model will not only accurately reflect known platelet behavior, but also predict new experimental findings, allowing a true in silico molecular and kinetic understanding of platelet biology.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES


Comment on Meyer–Bahlburg et al, page 4158, and Westerberg et al, page 4139

WASp stings mature lymphocytes

Eva Severinson STOCKHOLM UNIVERSITY

WAS is an X-linked immunodeficiency disease caused by mutations in WASp.¹ Meyer–Bahlburg and colleagues and Westerberg and colleagues in this issue of Blood have investigated lymphocyte subpopulations in WASp⁺/⁻ mice and found that WASp confers a selective advantage to the most mature T and B cells.

The Wiskott–Aldrich syndrome protein (WASp) is an important cytoskeletal regulator expressed in hematopoietic cells. WASp and its relative, the ubiquitously expressed neural WASp, participate in the regulation of actin polymerization through activation of the Arp2/3 complex. In patients with Wiskott–Aldrich syndrome (WAS), the WASP gene is mutated, leading to low or no WASP expression and varying degrees of clinical symptoms, such as immunodeficiency, eczema, and thrombocytopenia. Absence of WASp affects...
Systems biology meets platelet biology

Michael C. Berndt and Robert K. Andrews