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Beyond Platelet Molecular Catalogues: A Phenotype-Anchored Framework for Multi-Omics Interpretation

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ABSTRACT

Platelet omics has established that anucleate platelets contain diverse RNAs, proteins, post-translationally modified proteins, lipids and metabolites, yet molecular detection alone does not establish platelet phenotype or haemostatic function. This critical narrative review applies a phenotype-anchored framework to evaluate representative genomic, transcriptomic, proteomic, phosphoproteomic, lipidomic and metabolomic studies in greater depth. Platelet-specific interpretation is required because measured signals are shaped by megakaryocyte inheritance, absent nuclear transcription, limited RNA content, platelet age, rapid activation, extracellular exchange and disproportionate effects of leucocyte contamination. Foundational transcriptomic studies demonstrated conserved RNA repertoires, activation-dependent pre-mRNA splicing and signal-dependent translation, but isolation studies show that preparation methods alter both transcriptomic and functional outputs. Quantitative proteomics and phosphoproteomics define effector machinery and activation-state signalling, although abundance or phosphorylation remains mechanistically incomplete without agonist-matched functional testing. Lipidomic and metabolic studies connect membrane remodelling and bioenergetics to secretion, procoagulant activity and thrombus formation, but bulk measurements obscure platelet subpopulations. Sepsis and tumour-educated platelet studies illustrate how disease classification may be clinically promising while remaining ambiguous regarding altered thrombopoiesis, inflammation, activation and causality. The review distinguishes molecular detection, biomarker association and mechanism; critically appraises how representative studies meet or fail platelet-specific criteria; and proposes integration using matched multi-layer sampling, functional assays, latent-factor models and supervised multi-omics methods. Through critical synthesis of existing evidence, the review identifies the remaining limits to robust phenotype-level inference. Platelet omics is most defensible when molecular findings are interpreted through purity, activation, age, function and clinical context, thereby converting catalogues into reproducible haemostatic and thrombotic phenotypes.

Keywords: Platelets; Multi-Omics; Transcriptomics; Proteomics; Lipidomics; Metabolomics; Immature Platelet Fraction; Platelet Phenotype; Haemostasis; Thrombosis

Introduction: Why Platelet Omics Now Needs Interpretation

Platelet omics has moved beyond establishing that platelets contain molecular information. Platelets carry diverse RNAs, proteins, post-translational modifications, lipids, metabolites, mitochondria and extracellular-vesicle cargo that support rapid haemostatic, thrombotic, immune and inflammatory responses [1-4]. The interpretive problem is now more difficult than the descriptive one: an RNA, protein, lipid or metabolite measured in a platelet preparation is not automatically a platelet phenotype. It is a signal obtained from an anucleate, activation-prone and short-lived cell whose molecular state depends on megakaryocyte origin, platelet age, pre-analytical handling, disease context and functional reactivity [1,4].

Existing reviews have mapped platelet genomics and transcriptomics [2,3], transcriptomic variability [4], transcriptome-proteome integration [5], multi-omics methods [6,7], proteomics and phosphoproteomics [8,9], cardiovascular platelet omics [10], databases [11] and proteomic standardisation [12]. Those contributions are foundational. The remaining gap is not another molecular inventory but a critical account of when existing omics evidence supports

inference about platelet state, haemostatic function, thrombosis or clinical disease. This review therefore retains the original phenotype-anchored structure but strengthens it in three ways. First, it examines representative studies for their molecular results and mechanisms rather than citing them only as examples. Second, it evaluates whether those studies control platelet-specific threats to inference: cellular contamination, ex vivo activation, platelet age and turnover, and discordance between molecular layers. Third, it identifies analytical tools that can integrate matched omics data with platelet function. The central question is: when does a molecular signal justify a claim about platelet phenotype?.

Review Approach

Using a critical narrative approach, representative studies were selected because they established reference datasets, demonstrated platelet-specific mechanisms, tested methodological sources of bias, integrated more than one molecular or functional layer, or advanced clinical translation. They are appraised against six criteria: platelet purity; control of activation and pre-analytics; consideration of platelet age or turnover; concordance across molecular layers; independent functional anchoring; and proportionality of the biological or clinical claim. Table 1 makes explicit whether selected studies exemplify strong practice, reveal a common pitfall or remain limited against the proposed framework.

Table 1: Critical appraisal of representative platelet-omics studies against the phenotype-anchored framework.

Representative study/design	Strength against the framework	Remaining limitation	Interpretive lesson
[22]: GWAS of platelet count/volume with cross-species functional testing	Large discovery population and functional follow-up moved selected loci beyond association.	Primarily count and volume phenotypes; European-ancestry predominance; limited inference about acute reactivity.	Genomics defines inherited architecture, not the immediate state of circulating platelets.
[13]: multisite STRIDE comparison of three isolation techniques	Directly assessed site, preparation, RNA-seq and platelet function; strong reproducibility design.	No isolation method is biologically neutral; purity and preserved reactivity may trade off.	Isolation method is part of the biological measurement and must be reported.
[14]: experimental contamination analysis	Demonstrated how few leucocytes or erythrocytes can distort low-input platelet RNA.	Focused on a controlled technical question rather than disease phenotype or function.	Purity is a prerequisite for transcriptomic inference, not a routine descriptive detail.
[25] and [26]: quantitative proteome and activation-state phosphoproteomics	Established effector inventories and activation-linked phosphorylation changes.	Bulk abundance and phosphorylation do not identify causal sites or subpopulation-specific function.	Proteomic state requires agonist-, time- and function-matched validation.
[28]: murine lipidome with human validation and activation analysis	Cross-species validation and activation response brought lipid species closer to mechanism.	Bulk lipidomics cannot resolve the platelet subset or release pathway producing a change.	Lipid abundance should be linked to mediator generation, membrane remodelling or procoagulant function.
[33]: sorted reticulated platelets with ultrastructure, RNA-seq and secretion	Integrated molecular, structural and functional evidence in the same biological comparison.	Sorting-defined reticulation does not map exactly onto routine immature platelet fraction; manipulation may activate cells.	A model of phenotype anchoring, with a remaining translation gap to clinical indices.
[36] and [37]: sepsis RNA, translation and turnover analyses	Cross-layer evidence and explicit assessment of high turnover challenged single-cause explanations.	Sepsis heterogeneity, medications and platelet-leucocyte interactions remain difficult to separate.	Disease RNA reflects interacting megakaryocyte, turnover and circulating-state processes.
[38] and In't [39]: tumour-educated platelet classifiers	Independent development extended disease classification and tested broader tumour coverage.	Specificity fell with symptomatic disease controls; causal origin of discriminatory RNA remains unresolved.	Comparator selection determines clinical validity; classification is not mechanism.
[27]: integrated human-mouse transcriptome, proteome and trait resource	Demonstrated actual cross-layer integration and highlighted stronger protein than transcript conservation.	Cross-species conservation and trait linkage do not prove causal platelet function.	Integrated resources prioritise mechanisms that still require platelet perturbation and functional testing.

What this Review Adds

The central proposition is that platelet omics becomes clinically useful only when molecular findings are interpreted through five constraints: inherited genomic background, megakaryocyte-derived platelet formation, platelet age and subpopulation structure, activation and pre-analytical state, and independent functional phenotype. This is more than a generic call for good omics practice. These constraints are unusually consequential in platelets because they lack nuclear transcription, contain little RNA, are easily activated during isolation, circulate as age-heterogeneous populations and can be materially distorted by very small numbers of nucleated-cell contaminants [4,13,14]. Three operational definitions guide the argument. An omics signal is any measured DNA variant, RNA abundance, protein abundance, post-translational modification, lipid species or metabolite concentration. A platelet phenotype is an observable platelet

property, including count, size, immature platelet fraction, aggregation, secretion, receptor activation, procoagulant activity, clot retraction, thrombus formation, bleeding or thrombotic risk. Functional anchoring connects an omics signal to an independent biological readout rather than interpreting it from statistical association alone. The framework treats platelet omics as a chain of inference: molecular detection, biological-state assignment, functional validation and clinical interpretation. Weakness at any step reduces the evidential strength of the final claim. Figure 1 presents this phenotype-anchored model, and Table 2 demarcates it from existing review and resource literatures.

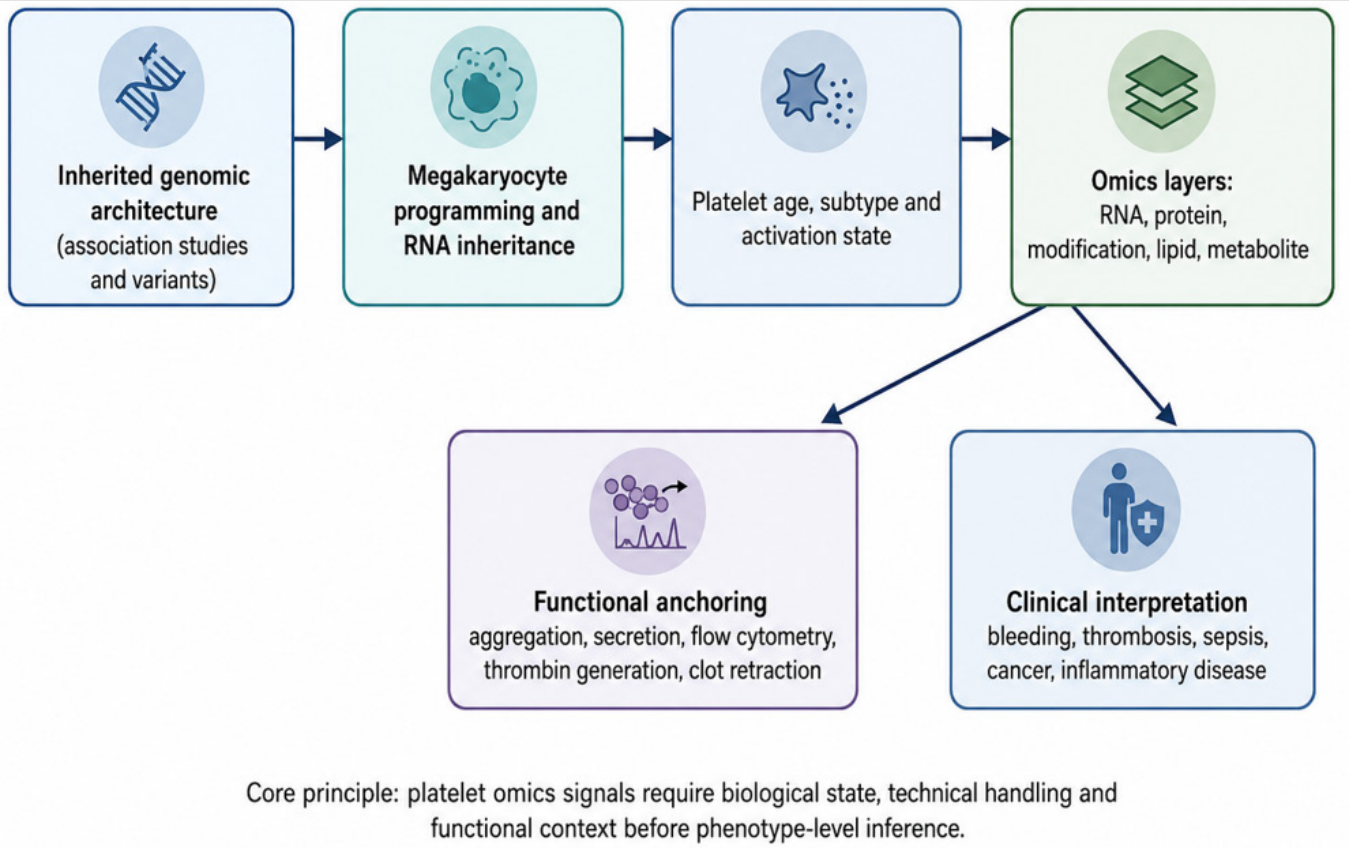

Figure 1: Phenotype-anchored framework for platelet omics interpretation. Molecular signals are interpreted through inherited architecture, megakaryocyte origin, platelet age and activation state, omics layer, and functional and clinical anchoring before phenotype-level inference.

Table 2: Demarcation from existing review papers and resources.

Existing literature focus	Typical contribution	Additional focus of this review
Layer-specific reviews	Summarise genomics, transcriptomics, proteomics, phosphoproteomics or lipidomics.	Interprets how each layer relates to platelet origin, state and phenotype [2-6,8,9].
Technology-centred multi-omics reviews	Describe platforms, discovery potential and integration strategies.	Defines platelet-specific biological constraints before phenotype-level inference [6,7].
Database/resource papers	Aggregate platelet genes, transcripts, proteins, drugs and diseases.	Distinguishes data linkage from mechanism and clinical validation [11,27].
Disease-specific platelet omics	Identify signatures in sepsis, cardiovascular disease or cancer.	Critically tests representative studies against purity, age, function and comparator selection [10,36-40].

Platelets as a Distinctive Omics System

Platelets lack nuclei but are not molecularly inert. They inherit RNA, proteins and organelles from megakaryocytes, retain translational machinery, splice selected pre-mRNAs after activation and exchange RNA-containing vesicles with other cells [2,3,14,15-21]. Genome-wide association studies (GWAS) identify inherited determinants of platelet count and volume [22], whereas RNA sequencing (RNA-seq) maps the molecular history and current state of circulating platelets [23,24]. These are different biological levels and should not be merged conceptually. Mechanistic studies show why platelet RNA cannot be treated as passive residue. Denis et al. identified spliceosome components in platelets and demonstrated signal-dependent interleukin-1 beta pre-mRNA splicing after receptor and integrin engagement [15]. Schwertz et al. then linked Cdc2-like kinase 1-dependent tissue-factor pre-mRNA splicing to accumulation of bioactive tissue factor and increased procoagulant activity [16]. Thrombin-induced Bcl-3 synthesis was inhibited by translational, phosphatidylinositol 3-kinase and mammalian target of rapamycin pathway inhibitors, establishing regulated translation rather than simple release of preformed protein [17,18]. These experiments are strong phenotype anchors because perturbation of a defined molecular process altered protein production or procoagulant function. Their limitation is scope: a small set of inducible transcripts does not establish that bulk platelet mRNA abundance generally predicts protein abundance. RNA attribution is further complicated by intercellular transfer. Platelet-like particles transferred labelled and functional RNA to monocytic and endothelial cells in vitro, with in vivo evidence of transfer to leukocytes [19]. Activated platelet microparticles can also deliver Argonaute 2-microRNA complexes to endothelial cells [20]. Accordingly, platelet RNA is best classified as megakaryocyte-inherited, platelet-state-modified, extracellularly exchanged or contaminating RNA, not as evidence of de novo platelet transcription.

Genomics and Transcriptomics: Inherited Architecture Versus Circulating RNA State

Genomics and transcriptomics require different interpretive restraints. Gieger et al. analysed up to 66,867 individuals, identified 68 loci associated with platelet count or volume and used expression networks and cross-species perturbation to functionally test candidate genes [22]. This study moved beyond association by validating regulators of blood-cell formation, but its platelet phenotypes were count and volume rather than immediate platelet activation. Genomic architecture therefore supports inherited predisposition and megakaryopoiesis; it does not by itself define the current functional state of circulating platelets. Rowley et al. mapped polyadenylated human and mouse platelet transcriptomes and demonstrated both conserved and species-specific expression, including differences consistent with known receptor biology [23]. Bray et al. subsequently used deep sequencing of leucocyte-depleted platelets to identify coding, non-coding and mitochondrial RNAs, but also showed that ribosomal RNA depletion altered relative transcript estimates [24]. Together, these studies established platelet RNA as biologically rich while exposing platform dependence and the difficulty of translating transcript abundance directly into function. Preparation is not a secondary detail. The prospective multisite STRIDE study compared three platelet-isolation methods and showed that the selected technique influenced genome-wide transcriptional and functional assay outputs [13]. This is exemplary methodological work because it tested reproducibility across sites and paired RNA measurements with function; it also demonstrates that a method chosen to increase purity can itself alter platelet responsiveness. Chebbo et al. showed that small amounts of leucocyte or erythrocyte contamination can substantially change apparent platelet transcriptomic profiles [14]. That study is principally a pitfall analysis: it does not invalidate platelet transcriptomics, but it makes cellular purity a prerequisite for interpreting low-input RNA. A changed platelet RNA profile in sepsis, cancer or cardiovascular disease may therefore reflect altered megakaryopoiesis, increased immature platelet fraction, selective RNA decay, activation-dependent processing, medication exposure, extracellular transfer or contamination. The appropriate question is not only whether RNA differs between groups, but which platelet or non-platelet process generated the difference and whether the signal corresponds to protein, function or clinical outcome.

Proteomics, Phosphoproteomics and Effector Machinery

The platelet proteome is closer to effector capacity than RNA abundance, but it is not self-interpreting. Burkhart et al. identified almost 4,000 unique proteins and estimated copy number for more than 3,700, creating a major quantitative reference for receptors, signalling proteins, cytoskeletal components and granule machinery [25]. Its strength is breadth and quantitative depth; its limitation is that a reference proteome from carefully prepared platelets cannot by itself explain disease-state reactivity, compartmental localisation or rapid activation. Phosphoproteomics is functionally proximal because platelet responses unfold within seconds to minutes through receptor-proximal signalling, phosphorylation, secretion and cytoskeletal reorganisation. Schmidt et al. reported quantitative phosphorylation differences linked to platelet activation and inhibition [26]. Such data can discriminate signalling states more directly than transcriptomics, but phosphorylation remains mechanistically ambiguous when agonist, timing, subcellular localisation or downstream function is not matched. A site may be associated with activation without being necessary for aggregation, secretion or procoagulant activity. Transcript-protein integration remains incomplete. Comparison of platelet transcriptomes and proteomes is constrained by low-abundance proteins, incomplete receptor and channel detection, annotation differences and modest transcript-protein concordance [5]. Huang et al. integrated human and mouse transcriptomes and proteomes for 3,474 genes with haemostatic or platelet traits, finding stronger cross-species conservation for proteins than transcripts [27]. This is

an important example of actual multi-omics integration rather than a proposed future design. Nevertheless, cross-species concordance and database association prioritise hypotheses; they do not establish causal platelet function. The 2025 Scientific and Standardisation Committee communication on platelet proteomics is therefore directly relevant. It identifies collection, isolation, storage, mass-spectrometry acquisition, data processing and reporting as sources requiring concerted standardisation [12]. In platelet proteomics, technical harmonisation and functional testing are not competing priorities: both are required before abundance or phosphorylation can be interpreted as phenotype.

Lipidomics, Metabolomics and Biochemical State

Lipidomics and metabolomics extend platelet omics into membrane organisation, mediator generation, procoagulant potential and bioenergetics. Peng et al. quantified nearly 400 lipid species in murine platelets, validated selected findings in human platelets and showed that activation altered a minority of the lipidome, particularly arachidonic-acid-containing species [28]. The cross-species validation and connection to activation are strengths, although bulk lipid measurements cannot determine which platelet subpopulation generated a change. Heimerl et al. quantified major lipid classes in resting and thrombin-activated human platelets and demonstrated activation-dependent release enriched for cholesterol- and phospholipid-related species [29]. This supports dynamic lipid remodelling, but release into the supernatant does not alone distinguish secretion, membrane shedding and extracellular-vesicle formation. Metabolic studies show that individual platelet functions can depend differently on energy pathways. Platelets retain metabolic flexibility and increase glycolytic use during activation [30]. Kulkarni et al. found mitochondrial adenosine triphosphate generation essential for granule secretion but dispensable in their system for aggregation and procoagulant activity [31]. Ghatge et al. linked glycolytic and one-carbon metabolites to glycoprotein VI-stimulated activation [32]. These studies are informative because they move from metabolite measurement toward perturbation and function. They also warn against a single global label such as 'metabolically activated platelet': secretion, aggregation and phosphatidylserine exposure may have distinct energetic requirements. Lipid and metabolic signals should therefore be anchored to the proposed mechanism: thromboxane generation, phosphatidylserine exposure, secretion, thrombin generation, clot retraction or flow-dependent thrombus formation. Static abundance alone is insufficient.

Platelet Age, Immature Platelets and Subpopulation Structure

Platelet age is a major source of omics heterogeneity. Reticulated or immature platelets are generally larger and richer in RNA and may be more reactive than older platelets. Hille et al. combined flow sorting, ultrastructure, RNA-seq and functional assays, identifying structural differences, 1,212 upregulated transcripts in reticulated platelets and greater agonist-induced P-selectin expression [33]. This is one of the strongest examples of phenotype-anchored platelet omics because molecular differences were tested against morphology and function. Its limitation is translation: sorting-defined reticulation is not identical to routine immature platelet fraction measurement, and preparation may alter activation. Allan et al. used proteomic and functional analyses to show progressive loss of platelet proteins and functional capacity with circulatory ageing [34]. The study supports ageing as a biological process rather than a simple time label, but age-separated populations remain operationally defined and may overlap with clearance-prone or activated platelets. In inflammatory settings, proposed procoagulant, aggregatory, secretory and immature subtypes can also overlap [35]. Bulk omics therefore averages across platelet age, activation, granule content and survival states. Immature platelet fraction, platelet count, mean platelet volume and turnover kinetics should be treated as interpretive metadata when disease or thrombocytopenia changes platelet production. Their absence does not automatically invalidate a study, but it limits confidence that a molecular difference reflects intracellular regulation rather than altered population composition.

Disease-State Examples: Promise and Ambiguity

Disease-associated platelet omics is attractive because platelets circulate at the interface of haemostasis, vascular injury, inflammation and malignancy. It is also where association is most easily overinterpreted. In sepsis, Middleton et al. integrated platelet RNA-seq with ribosome profiling and experimental models, identifying extensive transcriptomic and translational remodelling [36]. The combination of RNA abundance with translation is stronger than differential-expression analysis alone and supports disease-conditioned platelet biology. However, sepsis is heterogeneous, and thrombocytopenia, drugs, organ failure and platelet-leucocyte interactions remain potential confounders. Nührenberg et al. specifically examined high platelet turnover, finding altered RNA patterns that were not fully explained by increased immature platelet fraction [37]. Read together, the studies argue against both extremes: sepsis-associated RNA changes should not be dismissed as turnover alone, but neither should they be called a single intrinsic activation mechanism without matched protein and functional evidence. Tumour-educated platelet RNA illustrates the difference between classification and mechanism. Best et al. showed that platelet RNA-seq could distinguish cancer from healthy controls and classify tumour types in a proof-of-principle cohort [38]. In 't Veld et al. extended platelet RNA-based detection across 18 tumour types, but specificity was lower when symptomatic controls with inflammatory, cardiovascular or benign disease were used rather than asymptomatic controls [39]. The later design is more clinically stringent and demonstrates that comparator selection materially changes apparent diagnostic performance. These studies support platelet RNA as a candidate liquid biopsy, but do not establish that every discriminatory transcript is tumour-derived or mechanistically involved in cancer.

Altered thrombopoiesis, systemic inflammation, medication and platelet activation remain plausible contributors [40]. Cardiovascular omics has analogous constraints. A molecular pattern associated with arterial disease may reflect platelet hyperreactivity, vascular inflammation, antiplatelet exposure or recurrent platelet production. Claims should therefore be connected to aggregation, secretion, flow cytometry, thrombin generation, flow-based thrombus formation or prospective clinical outcomes [1,9,10].

Functional Anchoring and Translational Logic

The central distinction is between molecular detection, biomarker association and mechanism. A molecule may be present in platelets and differ between patient groups without explaining platelet behaviour. Conversely, a low-abundance phosphorylation event, lipid mediator or metabolite may be decisive if perturbing it changes an agonist-specific response. Diagnostic, prognostic, mechanistic and therapeutic claims therefore require different evidential thresholds. Functional assays should test the inference being made. Aggregation claims require light-transmission or impedance aggregometry, or flow-based thrombus formation. Secretion claims require alpha- or dense-granule readouts. Receptor activation should be examined with appropriate flow-cytometric markers. Procoagulant claims require phosphatidylserine exposure, thrombin generation or relevant clotting assays. Bleeding and thrombosis claims ultimately require clinical phenotype. Not every study must perform every test; the assay must be biologically matched to the claim. This discipline also clarifies study quality. Hille et al. linked RNA, ultrastructure and secretion and therefore approached phenotype. Chebbo et al. demonstrated a technical threat but did not make a functional claim. Tumour-educated platelet classifiers may be valid diagnostic associations even when their causal biology remains unresolved. Explicitly naming the evidential level prevents a useful biomarker study from being overpromoted as mechanism and prevents a mechanistic perturbation study from being judged by diagnostic criteria.

Analytical Tools for Platelet Multi-Omics Integration

Matched multi-layer data require more than juxtaposed heat maps. Unsupervised latent-factor methods such as Multi-Omics Factor Analysis can identify sources of variation shared across, or specific to, RNA, protein, lipid and metabolite layers [41]. Supervised sparse methods such as Data Integration Analysis for Biomarker discovery using Latent components can select correlated cross-omics features that discriminate prespecified phenotypes [42]. Network-based approaches can then test whether selected features converge on receptor, secretion, cytoskeletal, procoagulant or metabolic modules rather than isolated molecules. These tools are useful only when the input layers refer to biologically comparable samples. Platelet count, immature platelet fraction, residual leucocyte and erythrocyte contamination, activation markers, medication, processing time and batch should be incorporated as covariates or sensitivity analyses. Models should be trained and validated in separate cohorts, and feature stability should be reported. Integration must not normalise away genuine platelet-age or activation effects, nor create apparent concordance by combining unmatched individuals or differently processed preparations. Computational integration is therefore an extension of phenotype anchoring, not a substitute for it.

A Phenotype-Anchored Reporting Framework

A platelet omics study should begin by stating whether it addresses inherited architecture, circulating platelet state, activation response, drug response, disease classification or mechanism. Pre-analytical reporting should include the anticoagulant, venepuncture conditions, processing interval, temperature and storage conditions [43,44]. Centrifugation, washing, gel filtration and other platelet-isolation procedures should be specified because the selected isolation technique can alter both transcriptomic and functional outputs [13]. The leucocyte-depletion strategy and residual leucocyte and erythrocyte contamination should be reported because even low-level cellular contamination can substantially distort platelet transcriptomic profiles [14]. Platelet count and baseline activation markers should also be documented when functional outputs are assessed [13,44]. Relevant medication, inflammation, thrombocytopenia and transfusion should be recorded. The study should then state its evidential level. Molecular detection requires analytical validity. Biomarker association additionally requires appropriate controls, independent replication and assessment beyond established clinical variables. Mechanism requires perturbation of the molecule or pathway with a reproducible change in platelet function. Table 3 summarises layer-specific anchors, and Table 4 provides minimum reporting requirements. Multi-layer studies should preferentially use matched samples from the same individuals. RNA-seq may be paired with proteomics and aggregation; phosphoproteomics with agonist-specific flow cytometry; lipidomics with phosphatidylserine exposure and thrombin generation; metabolomics with secretion or clot retraction; and disease-associated RNA with platelet count and immature platelet fraction kinetics. Such designs can distinguish a marker of production, a marker of activation, an effector mechanism and a downstream consequence of systemic disease.

Table 3: Practical interpretation of platelet omics layers.

Layer	Primary information	Main interpretive hazard	Required anchor
Genomics	Inherited platelet-trait architecture and disease variants.	Variant association mistaken for current platelet mechanism.	Phenotype definition, ancestry control and functional validation [3,7].
Transcriptomics	Megakaryocyte-inherited and platelet-state RNA.	Contamination, activation, age, turnover and platform effects.	Purity metrics, platelet-age data and protein/function correlation [4,13,14].
Proteomics/phosphoproteomics	Effector repertoire and signalling state.	Preparation artefact or phosphorylation interpreted without causality.	Standardised mass spectrometry and agonist-matched platelet assays [8,12,25,26].
Lipidomics/metabolomics	Membrane, mediator and bioenergetic state.	Static catalogue or bulk release interpreted as activation mechanism.	Activation markers, standards, perturbation and functional readouts [28-32,47,48].
Single-cell approaches	Potential platelet heterogeneity and subpopulations.	Low RNA, aggregates, mitochondrial-read dominance and annotation error.	Strict purity, doublet controls and independent functional validation [44,45].

Table 4: Practical interpretation of platelet omics layers.

Domain	Minimum requirement	Reason
Sampling	Anticoagulant, venepuncture, processing time, temperature, centrifugation and medication exposure.	Handling can alter platelet activation and molecular state [43,44].
Purity	Isolation method, platelet count, residual leucocyte and erythrocyte contamination.	Nucleated cells contain far more RNA and protein than platelets [13,14].
Activation	Baseline activation markers, agonist exposure, timing and inhibitors used during preparation.	Activation changes RNA processing, secretion, phosphorylation and lipid release [15,16,26,29].
Platelet age	Immature platelet fraction, reticulated platelets, platelet count and turnover markers when relevant.	Young platelets can disproportionately influence RNA-rich bulk signals [33,37].
Integration	Matched individuals, batch structure, covariates, model specification and held-out validation.	Computational concordance can otherwise reflect processing, contamination or overfitting [41,42].
Validation and translation	Orthogonal molecular assay, claim-matched functional test and relevant clinical comparator groups.	Detection, association, mechanism and clinical utility require different evidential standards [1,38-40].

Use of Databases and Cross-Species Resources

PlateletBase integrates genomic, transcriptomic, proteomic, disease, drug and pathway information [11], while cross-species resources link orthologous genes to haemostatic and platelet traits [27]. These resources increase efficiency and can expose convergence across layers. They should nevertheless be treated as hypothesis-generating instruments. A locus associated with platelet count, a transcript detected in a platelet preparation and a protein identified by mass spectrometry may occupy different biological levels. Co-occurrence, pathway membership and cross-species conservation do not establish causality. Database prioritisation should lead to purification checks, orthogonal molecular confirmation, platelet-functional testing and patient-level validation.

Future Priorities

The most immediate priority is not a larger catalogue but better adjudication of existing and newly generated signals. Studies should use matched multi-layer samples, standardised purity and activation metrics, platelet-age metadata and functional assays selected before analysis. Shared reference materials and cross-site benchmarking, as demonstrated by STRIDE and proposed for proteomics, would make replication more meaningful [12,13]. Single-cell and single-particle methods may resolve platelet subpopulations, but current evidence remains preliminary. A pilot single-cell RNA-seq study identified platelet-enriched clusters while also illustrating limited RNA content, high mitochondrial-read proportions, sensitivity to handling and annotation uncertainty [45]. Preprint-level datasets extend this possibility but require independent validation [46-48]. The relevant advance will not be the number of clusters alone; it will be whether a cluster is reproducible, technically distinct from aggregates or contaminants, and linked to a haemostatic function. Clinically, platelet omics should address defined decisions: diagnosis of inherited platelet disorders, prediction of antiplatelet response, discrimination of inflammatory from malignant disease, risk stratification in sepsis or cardiovascular disease, and monitoring of platelet production. Utility requires external cohorts, relevant disease controls and evidence that the omics result adds information beyond platelet indices, functional tests and standard clinical variables.

Conclusion

Platelet omics has created a substantial molecular foundation for modern platelet biology. The next phase should build on, not devalue, molecular catalogues. Genomics defines inherited platelet-trait architecture; transcriptomics captures megakaryocyte-inherited and dynamically processed RNA states; proteomics and phosphoproteomics approach effector machinery; lipidomics and metabolomics describe membrane, mediator and bioenergetic state. No layer is sufficient alone. The published literature already contains examples of strong phenotype anchoring, including genomic association followed by functional perturbation, activation-dependent RNA processing linked to protein or procoagulant activity, multisite testing of isolation effects, combined structural-transcriptomic-functional analysis of immature platelets and cross-layer sepsis studies. It also contains recurrent limitations: contamination, preparation effects, bulk-population averaging, weak transcript-protein concordance and clinical classifiers tested against inadequate comparators. A phenotype-anchored framework makes those strengths and limitations explicit. Platelet omics becomes biologically and clinically defensible when molecular findings are assigned to origin and state, tested against function and interpreted proportionately in haemostatic, thrombotic and vascular context.

Highlights

- Phenotype anchoring strengthens platelet omics interpretation.
- Platelet RNA signals require purity, age and activation controls.
- Proteomic and lipidomic signals need functional platelet assays.
- Functional anchoring links omics signals to haemostatic phenotype.
- Reporting standards support reproducible platelet phenotyping.

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Authorship Contribution

U.A. conceived the review, identified and critically appraised the literature, developed the phenotype-anchored framework, drafted the manuscript, revised it critically and approved the final version.

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Ethics Approval and Consent to Participate

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Data Availability

No new data were generated or analysed for this review article.

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