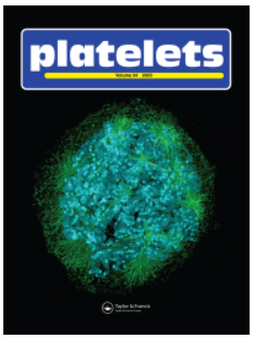

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REVIEW

Proteomics-wise, how similar are mouse and human platelets?

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Abstract

The field of proteomics and its application to platelet biology, is rapidly and promisingly developing. Platelets (and megakaryocytes) are postulated as biosensors of health and disease, and their proteome poses as a tool to identify the specific health-disease hallmarks. Furthermore, the clinical management of certain pathologies where platelets are active players demands the development of alternative treatments, such is the case in patients where the balance thrombosis-bleeding is compromised, and a proteomics approach might aid at the identification of novel targets. Hereby, the mouse and human platelet proteomes and secretomes from public databases are compared, which shows that human and mouse platelets share a highly conserved proteome, considering identified proteins, and most importantly, their relative abundance. These supports, also interspecies wise, the use of the proteomics tool in the field, substantiated by a growing number of clinically relevant studies in humans or preclinical models. While the study of platelets through proteomics seems accessible and direct (*i.e.* noninvasive blood sampling, enucleated), there are some points of concern regarding the quality control of samples for such proteomics studies. Importantly, the quality of the generated data is improving over the years, which will allow cross-study comparisons. In parallel, the application of proteomics to the megakaryocyte compartment has a promising but long journey ahead. We foresee and encourage the application of platelet proteomics for diagnostic/prognostic purposes even beyond hematopoiesis and transfusion medicine, and as a tool that will procure the improvement of current therapies and the development of alternative treatment options.

Plain Language Summary

The unbiased identification and quantitation of the protein profile (the so-called proteome) of cells, tissues, or organs, has gained attention from different fields because it gives additional valuable information to research questions. Understanding the protein building blocks of a biological system in normal physiological processes and how this may be altered in disease, may allow the discovery of biomarkers that could be used in diagnosis (early diagnosis), prognosis of disease or response to treatment. Furthermore, it may allow the identification of novel targets to develop personalized treatment options. Platelets, the anucleate cell components of the blood in charge of maintaining the body hemostasis, are postulated as biosensors of health and disease, and their proteome poses as a tool to identify health-disease hallmarks. Since platelets are in the circulation, a noninvasive blood sample is sufficient to obtain platelets from donors or patients in order to acquire information of the platelet proteome. Still, some research questions might require the use of animal preclinical models, where researchers may phenocopy human disorders, pathologies or diseases, to better understand the mechanisms behind these traits and to test potential novel treatments. How meaningful the studies in preclinical models are depends on how similar the biological systems of study are, interspecies wise. Hereby, the mouse and human platelet proteomes from available databases obtained by different research groups are compared, which shows that human and mouse platelets share a highly conserved proteome, considering identified proteins, and most importantly, their relative abundance. These supports, also interspecies wise, the use of the proteomics tool in the field, an approach with growing clinical relevance, as discussed.

Keywords

Human, interspecies, megakaryocytes, mouse, platelets, proteomics

History

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The use of mice as pre-clinical models

Although there are obvious differences between mice and humans, the use of mice as preclinical models is sufficiently justified by the conservation of physiological, anatomic, and genetic features.[1] Needless to say, preclinical models have provided essential knowledge and facilitated various clinical applications that range from surgery, and vaccine development, to diagnosis and treatment of disease, amongst others. However, there are social, scientific, and ethical concerns regarding their usage.[2] The detailed knowledge acquired so far from interspecies

studies, makes it clear that conclusions drawn from animal studies cannot be carelessly transferred to humans. Still, some studies require a living organism, which allows observation and experimental manipulation, in order to answer biological questions where multiple tissues or systems contribute to health and disease. In parallel, *in vitro* tools with increasing levels of complexity (*i.e.*, human organoids) are being developed, which can potentially substitute many *in vivo* studies.[3] All in all, many variables have to be pondered before engaging in animal studies, and always bearing in mind that, ultimately, the experimental option has to translate into a benefit for human clinical research.

While differences in the platelet formation process between mice and humans have been identified, their genetic similarity to humans and our ability to genetically/physiologically modify them, have positioned mice as a suitable model for studying human megakaryopoiesis, thrombopoiesis, and platelet function.[1,4] For example, murine preclinical models have been essential to demonstrate the function of various proteins (transcription factors, receptors, signaling molecules, hormones, cytokines …) in megakaryopoiesis and hemostasis and have aided to better understand the process of megakaryocyte differentiation.[5,6] However, whenever a murine preclinical model is used with the intention to extrapolate results into humans, either when studying normal physiological processes or when phenocopying a human disease or pathology, it is important to be aware of the differences and similarities.

Key features of megakaryopoiesis in mice and humans

Haematopoiesis is a dynamic and constant physiological process that aims at the production of all circulating blood and immune cells. It starts from a multipotent stem cell that may, by asymmetric cell division, self-renew and/or give rise to the progenitors that later commit or differentiate toward the various cell lineages.[7,8] A hierarchic idea of cell-trajectory from the multipotent hematopoietic stem cell (HSC) through committed progenitors, which give rise to mature blood cells, has been replaced by the long-lasting theory of the hematopoietic continuum,[9] recently supported by the implementation of new technologies, such as single-cell RNA sequencing, amongst others.[10,11] In fact, it seems that megakaryocytes could be located at the crossroads of this continuum, since they not only share features with HSCs but also with immune cells, myeloid cells (like their twinned erythroid progenitors), and even with neurons.[12–15] While thrombopoietin (TPO) is the main hormone regulating platelet production, it is not the only required factor, as basal platelet production occurs in its absence.[16,17] On the other hand, loss of function of MPL, the TPO receptor, affects the whole hematopoietic continuum, as it is expressed in early progenitors and HSCs.[18] In fact, megakaryocyte/platelet specific *Mpl* deletion in mice not only results in thrombocytosis, but it also associates with myeloproliferation, presumably as a consequence of ineffective TPO clearance.[19] That makes the megakaryocytic lineage a particular one, within the hematopoietic system.

Bone marrow-resident megakaryocytes release platelets into the blood circulation through a process of cell-remodeling, which appears to be conserved between mice and humans, with some species-specific particularities. While human megakaryocytes locate principally to the bone marrow, murine megakaryocytes are also present in clusters in the red pulp of the spleen, at least in the normal adult state.[4] Adding to that, murine and human megakaryocytes have also been observed within the lungs and pulmonary circulation, where they may contribute to platelet production.[4,20] Curiously, lung megakaryocytes seem to be immune-primed compared to bone marrow megakaryocytes and may exert a function at the crossroads with the immune system.[21]

Although murine and human megakaryocytes display similar ploidy distribution (modal ploidy of 16N), their density within the bone marrow is greater in mice than in humans, while the size of mature megakaryocytes appears to be significantly smaller in mice.[4] Proplatelets are formed in megakaryocytes from both species; however, human megakaryocyte proplatelets have been described as "long strands with regular constrictions (collar of pearls)," while murine megakaryocyte proplatelets are shorter and interconnected with other proplatelets.[4]

Key features of platelets in mice and humans

Mice have approximately five times more platelets in the circulation compared to humans, although murine platelets are overall smaller. Their lifespan is also shorter, around 4 d, while human platelets remain in the circulation for 8- to 12-d; the faster turnover is probably counterbalanced in mice by a constant splenic platelet production.[4,6] Schmitt et al. reported that murine platelets have an increased granule heterogeneity, although reduced in number per platelet section, and it seems that this heterogeneity affects specially the α-granules, as dense granules are quite similar morphologically between the two species.[4]

Evolutionary aspects and platelet function

Aside from the classical role that platelets play in maintaining hemostasis, the ancestral immune function of thrombocytes has not been lost through evolution, as they participate in immunomodulation and inflammation, in the separation of blood and lymphatic vessels during ontogeny, and are also active players on pathogenic processes, such as thrombo-inflammation or cancer metastasis.[22–27]

Polyploid megakaryocytes and enucleated platelets are only found in mammals (placentals, marsupials, and monotremes).[28] It seems that these acquired characteristics have resulted from the necessity to enhance the hemostatic function of platelets in detriment of their prominent immune ancestral role in other vertebrates. The fact that in mice platelets are more numerous, smaller and with a shorter lifespan, might be to cover a greater demand to protect against injury, which implies faster and more efficient clotting reactions, while facilitating, at the same time, the clearance of potential circulating pathogens.

Many other differences have already been put forward between mouse and human platelets, such as the absence of FCγRIIA[29] and PAR1 in mouse.[30] Additionally, several studies with Eltrombopag, a noncompetitive agonist of TPO, found that the juxtamembrane domain of MPL (at residue H499) is not conserved in mice, which means that it is specific to humans and nonhuman primates.[31] In this context, studies with Eltrombopag may seem intuitively useless in mice; however, this particular feature is the basis for the rationale to use mouse models to study MPL-independent mechanisms, which seem to play a role in the recovery of immune thrombocytopenia patients treated with this drug. Another example of interspecies differences is the case of the protein kinase C (PKC) isoforms, PKCδ and PKCε, whose expression levels seem to display an opposite balance between mouse and human platelets, with PKCδ being highly expressed in human platelets, while in murine platelets, it is PKCε the one expressed at higher levels.[32] However, the kinase universe of platelets is so promiscuous (or pleiotropic) that these differences do not seem to make a difference in the functional capacities between murine and human platelets.

An interspecies proteomics overview of platelets

Given the plethora of functions in which platelets are involved, in addition to the fact that they are produced differently or altered somehow by the health status,[33,34] and that they even uptake molecules from neighboring cells, and release microvesicles in the circulation, they constitute biosensors worth exploring and delineating.[35,36]

Proteomics stands as one of the most interesting tools to study platelets, due to their inherent characteristics (*i.e.*, absence of a nucleus). This tool might be used to understand disease, and to identify biomarkers for prognosis and diagnosis of pathologies of different etiology.[37–39]

In that regard, if we employ mice as preclinical models, how similar are they, proteomic-wise? Do we have a basis to claim that they represent a good model?

The platelet and megakaryocyte proteome

The comparison of the mouse and human genomes at the sequence level has revealed that, while there are striking differences, especially in non-coding regions, the protein-coding regions are evolutionary conserved, with approximately 85% identity on average,[40] driven by physiological function requirements. In order to obtain a comprehensive comparison of the platelet proteome between species, we have selected different publicly available proteomics datasets, as described in the Supplementary Methods and Tables S1 and S2.

The core platelet proteome in each species – that is, the subset of platelet proteins detected in at least half of the datasets included in this review (see Supplementary Methods, Tables S1, S2, and Figure S1a)– represents about 10% of the respective species reference proteome (Figure 1a). Additionally, the

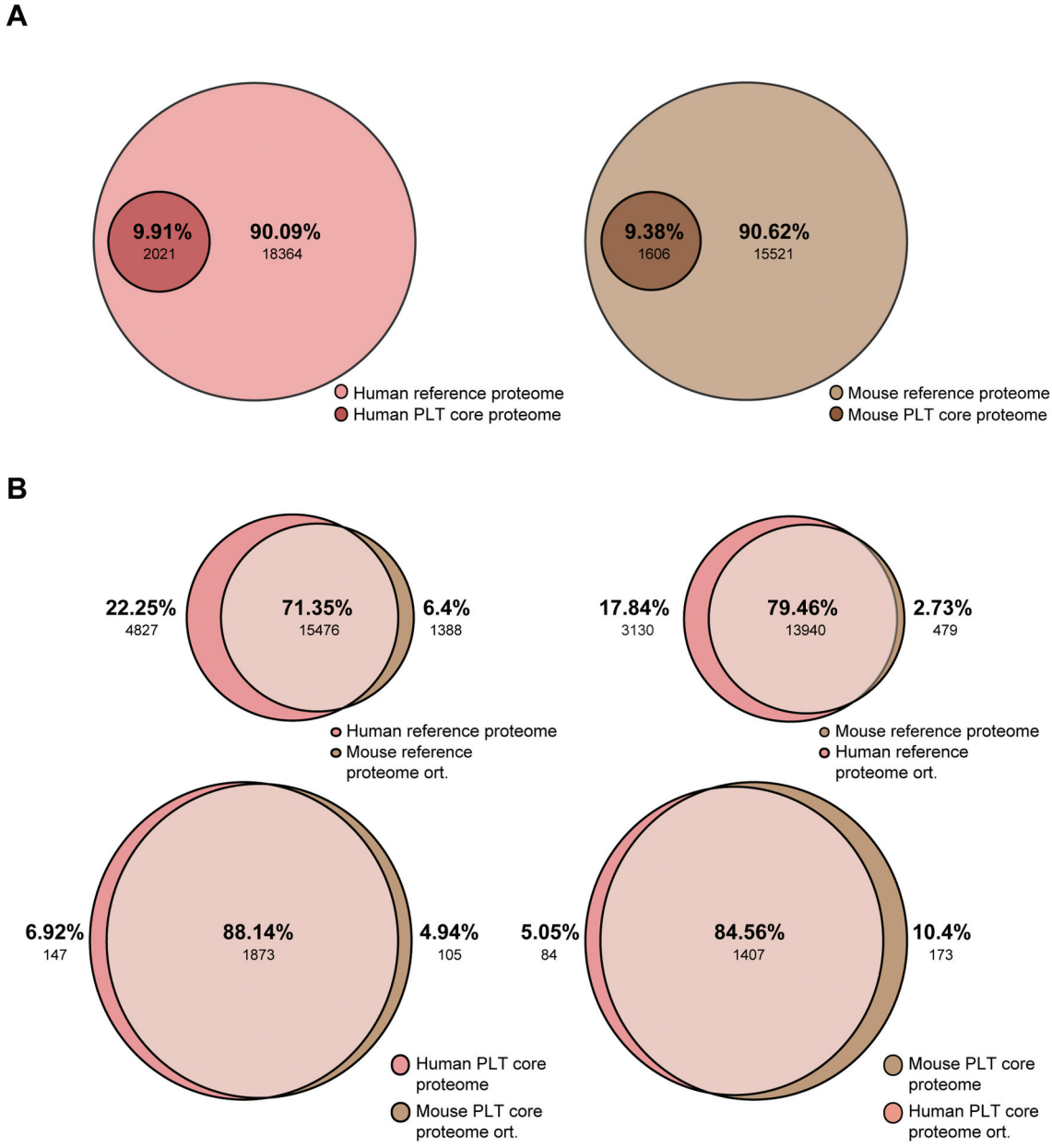

Figure 1. Interspecies comparison of the human and mouse reference and platelet core proteomes. (a) Venn diagrams showing the overlap between the human (left) and mouse (right) reference proteomes, and the respective platelet core proteome. (b) Venn diagrams showing the overlap between the reference proteomes or the platelet core proteomes, of mouse and human (top left and right, and bottom left and right, respectively), and their respective mouse and human orthologs.

comparison after bidirectional orthologue translation of the core platelet proteome protein lists confirms an overlap of approximately 85% of the identified proteins (Figure 1b). This is a very important aspect to consider, since the bidirectional orthologue translation of the reference proteome between species is 70–80% (Figure 1b), suggesting a strong function-driven evolutionary conservation in the protein content of platelets of both species.

We next compared the relative quantification distribution of the identified proteins in platelets from the respective mouse and human chosen datasets, as indicated in the Supplementary Methods. We could observe a high overlap of the highly and intermediately expressed proteins between species, while low abundant proteins differed more, suggesting that they either do not have an essential role in platelet function (*i.e.*, residual proteins, plasma/erythrocyte contamination), that they are different components of unitary functional protein-complexes (*i.e.* redundancy), and/or that the heterogeneity is subject to technical limitations in the detection, due to their low abundance expression or other protein-specific constraints[38] (Figures S2 and S3). Enrichment analysis of the protein lists based on abundance (*i.e.*, per expression slot), further supported these results, confirming conservation of function between species (Figures S2 and S3). According to this, we can suggest that human and mouse platelets share a highly conserved proteome, considering identified proteins, and most importantly, their relative abundance.

These conclusions are parallel to those extrapolated from the isolated comparison of the mouse and human platelet transcriptomes.[41] Therefore, we next set out to determine the mirroring level of the platelet transcriptome and proteome, species-wise. Both species showed a similar overlap, around 18% (suggesting that the majority of platelet RNA is either inherited residual RNA or exogenous), which constitutes 85% and 75% of the human and mouse core proteome, respectively (Figure 2a). However, they both showed a weak correlation (R ~ 0.4) in terms of relative abundance (Figure 2b), in accordance with what has been published,[42] and supporting the idea of a desynchronized protein and RNA homeostasis in platelets. Still, a multi-Omics approach (proteomics, transcriptomics) in the study of platelets and megakaryocyte progenitor cells may be determinant, especially considering that platelets contain exogenous proteins, as mentioned above. Studies that intended to identify the transcription origin of identified platelet proteins have included megakaryocyte transcriptomics in their experimental design, proving the reliability of the multi-Omics approach in this regard.[43,44]

Literature search related to the megakaryocyte proteome showed that it is scarcely studied from an unbiased perspective, and a characterization of both mouse and human primary megakaryocytes is lacking. A study focusing on mouse megakaryocytes, aimed at comparing the total proteome of embryonic stem cell-derived and fetal liver megakaryocytes.[45] As for the human studies, one of them aimed at identifying the proteome of megakaryocytes differentiated from induced pluripotent stem cells (iPSCs),[46] while the other was performed on megakaryocytes differentiated from

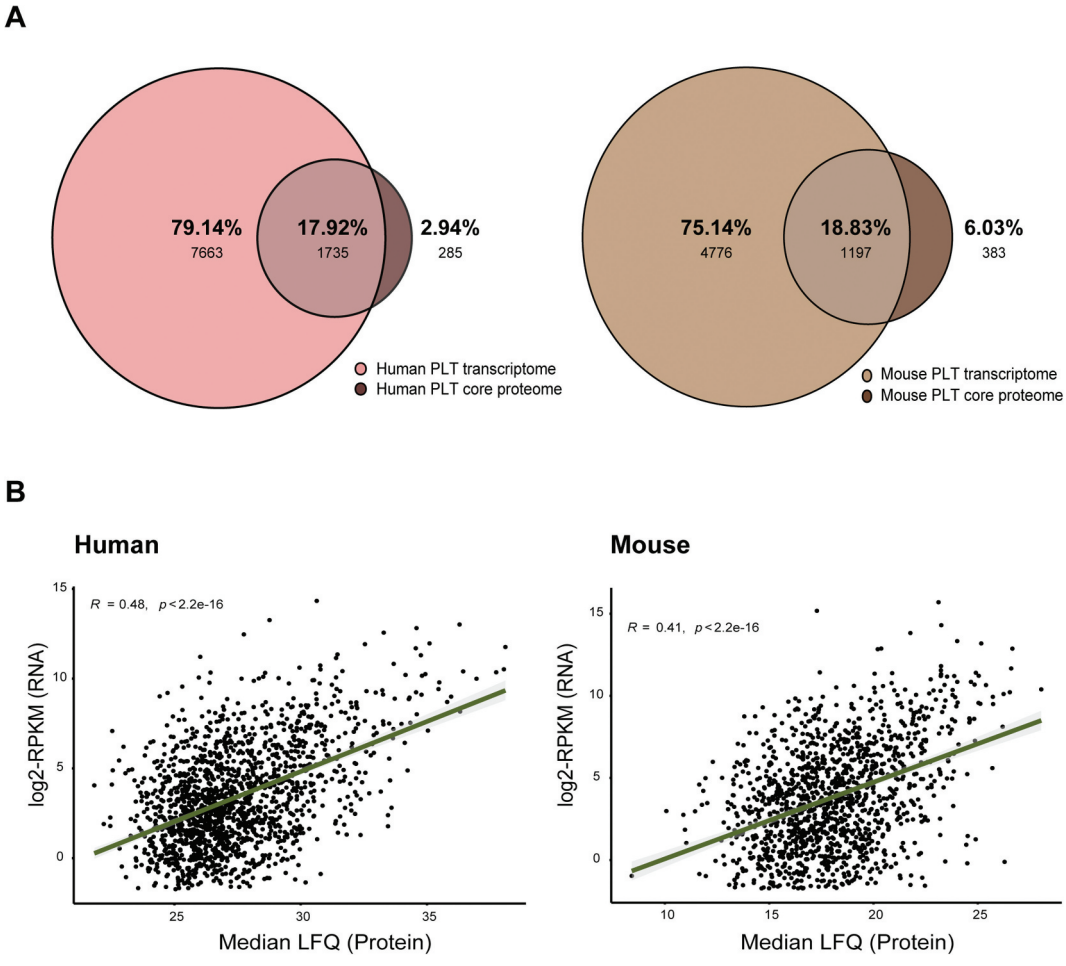

Figure 2. Interspecies comparison of the human and mouse platelet transcriptomes and core proteomes. (a) Venn diagrams showing the overlap between the human (left) and mouse (right) transcriptome and platelet core proteome. (b) Scatterplot showing the Pearson correlation between the relative transcriptomics (log2-RPKM) and proteomics (log2-LFQ) abundances both in human (left) and in mouse (right). The proteomics data belong to the x11 and x39 datasets (as in Tables S1 and S2), respectively.

DAMI cell line.[47] Additionally, no raw data was available from any of the mentioned studies. This points toward the difficulty of working with primary megakaryocytes, due to their low abundance in peripheral blood and *in vitro*, their asynchrony when differentiated from progenitor cells, and the issues regarding their isolation (*i.e.*, flow cytometry cell-sorting), evidencing that the application of proteomics to the megakaryocyte compartment has a promising but long journey ahead.[48–50]

The platelet secretome

Since platelets secrete their granule cargo upon activation, and this process is relevant in their hemostatic and non-hemostatic functions, we set out to compare the proteomic profile of platelet secretomes of mouse and human from publicly available datasets (see Supplementary Methods, Tables S1, S2, and Figure S1b). Of these, all save one were using thrombin as the stimulating agonist. The secretome constitutes around 20% of the core platelet proteome both in mouse and human (Figure 3a). Of note, the platelet secretome proteins that do not overlap with the respective core platelet proteomes (Figure 3a) are detected as part of the platelet proteome, when all the proteins of all datasets are taken into consideration (data not shown, see Supplementary Methods). The overlap of the identified secretome proteins, in bidirectional orthologue translations, is around 75% (Figure 3b).

Following the same analysis performed with the platelet core proteome, we next compared the identified proteins in the platelet secretomes from mouse and human depending on their relative abundance, in different datasets. We observed a great overlap of the highly and intermediately expressed proteins between species, while low abundant proteins showed more variation, similarly as with the platelet core proteome (Figure S4). However, the separation of the proteins that are present in the high and intermediate abundances slots did not appear as relevant, functionally, as with the platelet core proteome. Enrichment analysis of the protein lists further supported these results, confirming the conservation of function between species, and supporting the notion that the high and intermediate abundance slots constitute a functional joint fraction (Figure S4).

Clinical applications of platelet and megakaryocyte proteomics studies

The analysis of the platelet proteome and sub-proteomes (releasates/secretomes, phospho-proteome, platelet-derived extracellular vesicles, etc) poses as a promising mean not only to better understand platelet function and production but also to identify novel biomarkers for disease diagnosis and prognosis. Furthermore, the increasing demand to develop novel and more-specific anti-platelet/anti-aggregant drugs for the management of thrombosis will benefit from the rigorous dissection of platelet

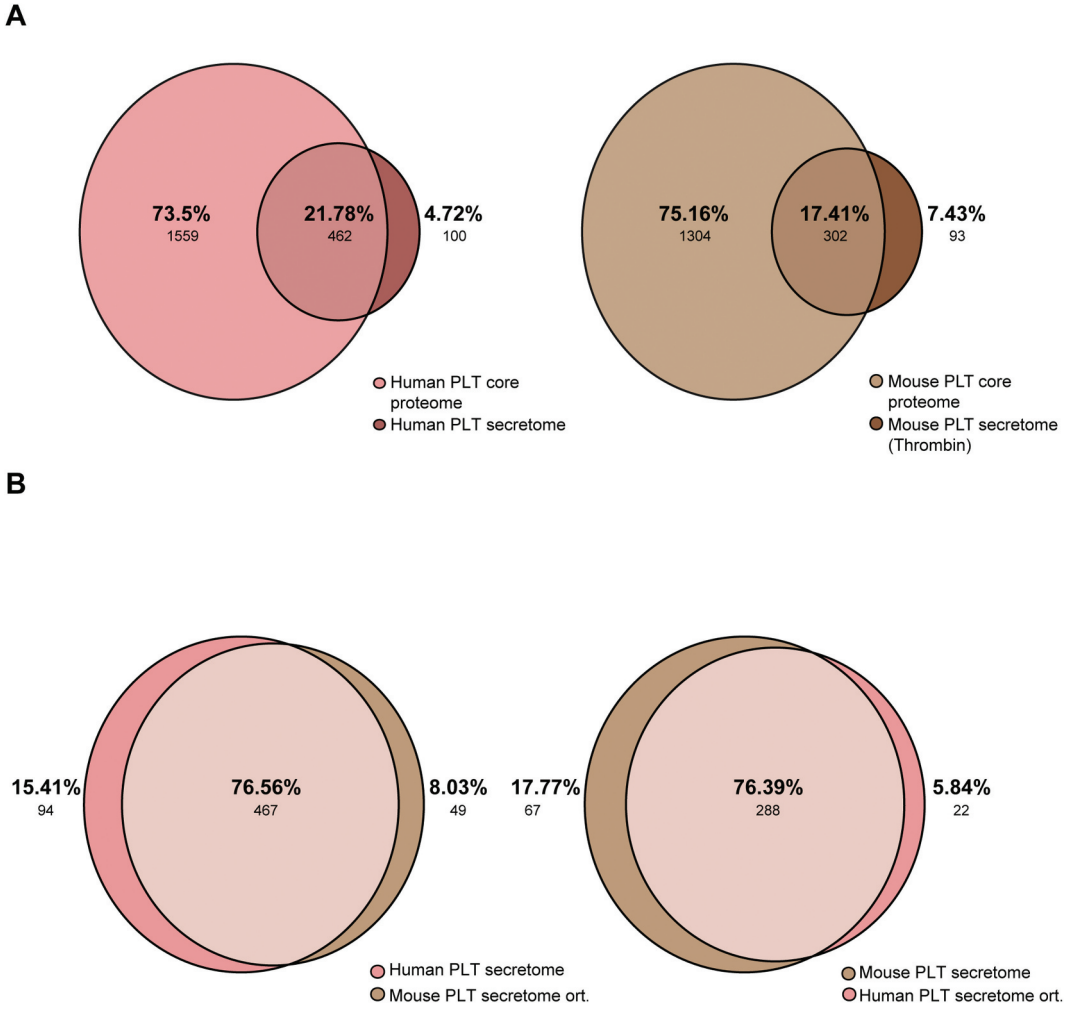

Figure 3. Interspecies comparison of the human and mouse platelet core proteomes and secretomes. (a) Venn diagrams showing the overlap between the human (left) and mouse (right) platelet core proteomes, and their respective platelet secretomes. (b) Venn diagrams showing the overlap between the platelet human (left) and mouse (right) secretomes, and their respective mouse and human orthologs.

signaling cascades, where phospho-proteomics may play a relevant role.

Platelets represent a critical factor in the onset and progression of cardiovascular diseases, which globally account for one of the top-ten leading causes of death worldwide.[51,52] A study by Maguire and colleagues identified distinct proteomic signatures in platelet releasates from patients at different stages of progression of symptomatic cardiovascular disease,[39,53] and another study by García et al. even observed differences in the proteomes of intracoronary and peripheral platelets in patients of acute myocardial infarction.[54]

Regarding genetic platelet disorders, a comprehensive quantitative proteomics analysis revealed that platelets of patients carrying individual mutations in the transcription factors GATA1, GFI1B, or RUNX1 had a distinct proteome profile, while displaying similar platelet morphological and functional abnormalities,[55] and recent data of platelet proteome profiles of inherited platelet disorders, although performed with a limited amount of samples from each condition, already shows how the platelet proteome reflects the mechanisms behind each of the genetic traits.[56]

Concerning the ability of platelets to reflect health or disease status, several studies have reported differences at the proteomic level in platelets or platelet-derived extracellular vesicles of cancer patients, which further supports the idea of platelets and their proteome as potential holders of valuable general disease diagnostics and prognostic biomarkers.[57–60]

In the field of transfusion medicine, there is a concern on how to maintain the integrity and functionality of platelets in the platelet concentrates to be transfused. The so-called platelet storage lesion (PSL), appears with more evidence in longer-stored platelet concentrates, and manifests conditioned by all the steps involved in platelet concentrate production and storage.[61,62] The application of proteomics identified a number of hallmarks that could be associated with PSL, starting from proteomic differences related to platelet apoptosis,[63] to a differential expression of proteins related to platelet degranulation or structural ones.[39,64,65] Of note, more information was gained in parallel to technology development. Another aspect of concern is the impact of pathogen reduction treatments on platelet concentrates, a safety measure to reduce the inherent risk for bacterial contamination of platelet concentrates.[66] Proteomics studies on platelet concentrates treated or not with Mirasol Pathogen Reduction Technology, also revealed specific alterations, although marginal, which were not exclusively due to an accelerated PSL, contrary to what was earlier thought.[67] Likewise, proteomics has been employed to characterize temperature-induced platelet alterations in stored concentrates.[68]

The similarity of the mouse and human platelet proteome provides a solid foundation to the studies performed on mouse models, such as our recently published study, where we characterized and compared the platelet proteome of two mouse models of immune thrombocytopenia, at the thrombocytopenic stage and after platelet count recovery. The study revealed specific dynamics in the alterations of the platelet proteomes, which could serve to develop prognostic markers, and that will be followed up in a cohort of immune thrombocytopenia patients.[69]

Interestingly, the application of proteomics in the field has allowed the exploration of the platelet proteomes and secretomes in other species, such as squirrels, rats, pigs, and dogs.[70–75] The particular physiological or pathological conditions in each model provide new knowledge with potential direct applications in evolutionary science, veterinary medicine, and importantly, with potential translation into humans. An example is the case of the study of the platelet proteomes of hibernating squirrels that reach body temperatures of 4–8°C. Physiological differences have been observed in the platelet proteome of squirrels (hibernating vs active) which might translate into developments to improve the cold storage of human platelets used for transfusion, in an effort to minimize platelet activation at the same time as relenting the storage lesion.[70]

In summary, given the function of platelets to facilitate thrombosis and hemostasis, quantitative (phospho)proteomics analyses of platelet proteomes/sub-proteomes, and of megakaryocytes, will provide molecular biomarkers for diagnosis and prognosis of platelet related pathologies or dysfunction, and even provide targets for anti-platelet drug development. On the other hand, considering the various and diverse roles of platelets during ontogeny, or in inflammation, platelet proteomics might pose a significant biomarker discovery tool in other pathologies, beyond those primarily related to platelets.[34,38,39,76–81]

Limitations and final conclusion

As it has been acknowledged by all experts in the field, there are certain issues of concern regarding the application of high-throughput proteomics to the study of platelet biology, ranging from the field-specific ones (such as blood sampling collection variables [extraction method, anticoagulant used] and sample processing), to the aspects related to mass spectrometry technological characteristics and data analysis themselves (protein detection – low abundance, modifications altering digestion, etc.). When applying proteomics to megakaryocytes, certain variables will also require to be acknowledged, such as the source (primary, or cultured *in vitro*), the homogeneity of the sample (differentiation status, contamination with other cell types, etc), to name a few. Such variables account for inter-laboratory procedural differences that might limit cross-comparison of data and extrapolation of results to the clinical setting. As of today, mass spectrometry proteomic analyses are still costly, many studies comprise a low number of samples, and data should be validated in larger cohorts; however, few institutions can afford to perform studies with an optimal number of samples that allows rigorous data analysis. As a consequence, regarding the applicability of platelet proteomics to the clinical field, there is a concern that the equipment may not be affordable by clinical institutions, and that proteomics analysis is complex and requires trained staff, precluding a globalized usage of the technique at the diagnostic clinical laboratory.[38,39,81–84]

Consider, and despite having observed experimental differences in the datasets used in this study, we have also noticed consistency and reproducibility if we consider the relative abundance of detected proteins, and the identified GO terms from the enrichment analysis (see Supplementary Figures).

Supporting our findings, Bayés et al. (2012) studied human and mouse postsynaptic membranes at the protein level, and found a ~70% overlap after orthologue translation, similarly to what we have observed with the interspecies platelet proteomes and combining data from datasets from independent experiments.[85] This suggests that it is possible to identify differences in the platelet proteome (or sub-proteome) associated with pathology, even in an interspecies-wise manner.[69,76]

In general, we propose that, for the field to move forward, common guidelines and points of concern should be established that help to improve the multi-laboratory reproducibility of platelet preparation, sample processing, and data analysis. Most importantly, all these variables should be carefully described in scientific communications, and access to raw data and/or data analysis through public repositories should be mandatory. Objectively, technological developments of mass spectrometers, with deeper detection capacities and more compact, will allow the reduction of costs for the analysis of large sample groups. The implementation of comprehensive pipelines of analysis, which are globally evolving in parallel, will also provide more robust information at the clinical level. The quality of the generated data is improving over the years, and when technical limitations and heterogeneity are overcome, cross-study comparisons will be possible, aiding in the advance of the field. While crude mass spectrometry might be as of today unthinkable in the clinical diagnostic lab, it will surely

aid biomarker discovery with potential application in the clinic, as customized protein multiplex detection assays can be designed with the information obtained from unbiased proteomic studies and implemented in the diagnostic lab. Finally, we conclude from our *in silico* analysis that platelets from mice and humans share a proteome with high identity, which portrays mouse as an optimal pre-clinical model. The same conclusion was reached by Balkenhol and colleagues on their systems biology study aimed at the *in silico* analysis of the central platelet signaling cascade and interspecies comparison.[86] Furthermore, obtaining blood samples requires noninvasive methods, and if platelets (and their proteome) should reflect the health status of a patient, the application of platelet proteomics for diagnostic/prognostic purposes could potentially invade other clinical fields beyond hematopoiesis and transfusion medicine.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All datasets used for analysis in the present manuscript belong to published manuscripts and/or have been obtained from public repositories, as indicated. The full reproducible code and datasets are freely available at https://github.com/PLT-lab/PLT-proteomics-review.

Supplementary data

Supplemental data for this article can be accessed online at https://doi.org/10.1080/09537104.2023.2220415.

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