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Proteomics in Thrombosis and Hemostasis

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Abstract

Proteomics, the simultaneous study of all proteins in a given cell, tissue or organism, is an innovative approach used to identify novel markers for diagnosis, prognosis and the pathophysiological mechanisms associated with diseases. Proteomic methodologies have been used in a variety of contexts such as investigating changes in protein abundance that may occur with disease presence, the response to therapeutic treatments as well as the impacts of age on the plasma proteome.

Over the last decade, significant technological advancements in proteomic techniques have resulted in an increase in the use of proteomics in thrombosis and hemostasis research, particularly in order to identify relevant and novel clinical markers associated with bleeding and thrombosis. This mini-review explores the use of proteomics in the setting of thrombosis and hemostasis from 2010-2020, across five main domains (platelets, blood clot composition, stroke, venous thromboembolism, and therapeutics), as well as provides insights into key considerations for conducting proteomic studies.

Keywords

- proteomics
- thrombosis
- hemostasis

Introduction

Proteomics represents the simultaneous study of many proteins in a given cell, tissue, or organism,[1] and is an innovative approach used in identifying novel markers for diagnosis, prognosis, and characterization of diseases, such as heart failure and cancer.[2,3] This methodological approach can be utilized to study a variety of biological fluids such as saliva, urine, and blood, specifically focusing on changes in protein abundance that may occur with disease, age, or as a response to therapeutic treatments.[1]

Proteomic techniques have evolved rapidly over the past decade, with a decrease in sample volume requirement, and a subsequent increase in data acquisition and throughput. There has also been a significant decrease in the footprint and cost of mass spectrometers, "the workhorses" of proteomics, from large stand-alone analyzers to desktop analyzers, a development that has moved proteomics significantly closer toward real-time clinical integration. Due to these technological advancements, there has been an increase in the use of proteomics in thrombosis and hemostasis research, specifically in aspects such as stroke and venous thromboembolism (VTE).[4,5] This mini-review explores the use of proteomics in the setting of thrombosis and hemostasis from 2010 to 2020, across five main domains (platelets, blood clot composition, VTE, stroke, and therapeutics), to reflect the focus of proteomics studies undertaken across this period.

Platelets

Platelets play a key role in maintaining hemostasis by helping form clots to prevent bleeding.[6] We identified

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two studies from the past decade that used proteomics to gain a better understanding of the platelet proteome.[7,8] Platelets can be modified by multiple external factors such as disease,[9] therapeutic treatments,[7] and diet.[10] Proteomics is an advantageous method to compare the effects of these modifiers. Proteomic discovery and validation studies have compared platelet proteomes between intracoronary platelets and peripheral arterial platelets from patients with ST-segment elevation myocardial infarction (STEMI). Four proteins were found differentially abundant in intracoronary platelets in comparison to arterial platelets.[8] In a population of type 2 diabetes patients with stable coronary ischemia, proteomics demonstrated that using dual-antiplatelet therapy in the form of clopidogrel in conjunction with aspirin differentially altered the abundance of several platelet proteins in comparison to aspirin alone.[7]

Blood Clot Composition

Blood clots consist of a variety of components and proteomics has been used effectively in four studies to further understand the composition of blood clots (►**Table 1**).[5,11–13] Stachowicz et al investigated the differences in plasma clot composition in patients with thrombotic antiphospholipid syndrome compared with patients with VTE.[5] In plasma clots prepared ex vivo, 63 proteins were different, with results highlighting that the underlying disease plays a crucial role in the composition and mechanism of clots in distinct clinical settings.[5] Proteomics has enabled the identification of up to 467 proteins, with several functional roles such as cell differentiation, metabolism, and adhesion in coronary thrombi extracted from STEMI patients.[11] Plasma proteomic approaches have also been used in STEMI patients to identify death-inducer obliterator 1, a proapoptotic transcription factor, as a potential marker of coronary thrombosis.[11] Two studies prepared plasma clots ex vivo, using healthy adult samples to investigate the composition of clots.[12,13] Ząbczyk et al identified 494 proteins in ex vivo prepared, plasma fibrin clot structures and demonstrated that body mass index and age have an impact on clot structure properties, such as lysis time.[13] Proteomics has also been useful in identifying specific mechanisms associated with fibrin cross-links, as well as specific substrates of FXIIIa, a protein responsible for cross-linking fibrin γ-chains in early phases of clot formation.[12] The formation of blood clots, as well as the precise balance between clotting and bleeding, is heavily regulated by thrombin. Proteomics studies have identified 54 different substrates of thrombin suggesting the need for future clinical studies of specific thrombin substrates in individuals based on age or health status.[14]

Venous Thromboembolism

VTE affects 10 million individuals globally each year and the need for novel predictive biomarkers of VTE is imperative.[15] Two studies from the past 10 years utilized proteomics to identify novel biomarkers associated with VTE incidence in adults.[16,17] A comprehensive study using plasma proteomics identified platelet-derived growth factor subunit B, a developmental protein, as a novel VTE-associated plasma protein, as well as a potential novel predictive marker of VTE.[16] Proteins ProZ, DJ-1, and transthyretin have also been identified as possible predictive biomarkers of VTE in adults.[17]

Stroke

Globally, the prevalence of stroke is increasing at an alarming rate[18] and consequently there has been an increasing focus on mechanisms leading to stroke, as well as potential protein markers of clinical outcomes associated with stroke. Three studies used proteomics to investigate mechanisms of stroke and stroke-associated clinical outcomes.[4,19,20] Corticosteroid signaling was identified as the main differentiating mechanism between female and male stroke patients. Furthermore, sex-based differences of stroke severity and outcomes were determined using the marker circulating corticosteroid-binding globulin.[20] Proteomics has also shown that transient ischemic attack (TIA) drives changes in coagulation, cell adhesion, atrial fibrillation, and inflammation, and that there are 30 proteins differentially abundant among individuals with TIA in comparison to healthy controls.[19] This finding led to the validation of a plasma protein signature in a proof-of-concept study, identifying IGFBP-3 and PON3 as specific predictors of TIA.[4]

Therapeutics

Therapeutics, and specifically blood-based therapeutics, are highly complex compounds made up of multiple plasma proteins and diverse cells, and are used to treat clotting deficiencies, such as hemophilia.[21,22] The complex process involved in producing and manufacturing these therapeutics has been shown to cause several protein variations such as degradation, posttranslational modifications (PTMs) and phosphorylation.[23] Proteomic technologies have not only been used to identify novel protein-drug targets, but also in monitoring the pharmacodynamic effects of therapeutics.[23] In the last decade, proteomics has been used to investigate commercially available recombinant factor VIII, highlighting the excess amount of plasma proteins, such as von Willebrand factor.[22] These findings are important, particularly in the context of monitoring patients undergoing therapeutic treatments.

Future of Proteomics in Thrombosis and Hemostasis

Proteomics is not only advantageous for the discovery of clinical markers and changes in protein abundance, but also for an array of additional applications, as shown in ►**Fig. 1**. The last decade has seen proteomics applied to a wide range of clinical settings from investigating commercially available therapeutics,[22] to identifying biomarkers of VTE[16,17] and understanding the mechanisms associated with ischemic stroke.[20] The use of proteomics, particularly in the clinical

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Table 1 Summary of proteomic studies in the setting of thrombosis and hemostasis

Number	Author Year Country	Focus area	Aim	Population	Comparative groups ($n =$)	Proteomic methods	Key findings
1.	Azcona et al 2012 Spain	Platelets	To compare the effect of dual-antiplatelet therapy on protein abundance of platelets in T2D patients with stable coronary ischemia	T2D patients with stable coronary ischemia	$N = 28$ (aspirin) $N = 29$ (aspirin + clopidogrel)	MS 2-DE	- PF4 was not different among the two groups - The following proteins were altered after dual-antiplatelet therapy: - Actin-binding protein isotypes 2 and 5 - Lactate dehydrogenase - Serotransferrin isotype 4 - Protein disulphide isomerase-A3 isotype 1 - Fibrinogen β chain isotype 5 - Ras-related protein Rab-7b isotypes 1 and 6 - Immunoglobulin heavy chain - T2D patients have lower platelet reactivity after dual-antiplatelet therapy treatment
2.	Vélez et al 2016 Spain	Platelets	To compare the proteome of intracoronary and peripheral arterial platelets from STEMI patients	Acute myocardial infarction adult patients	Proteomic study ($n = 10$) Validation study ($n = 11$)	2D-DIGE MALDI TOF/TOF Western Blot	- Proteins upregulated in intracoronary platelets: - Integrin aIIb - Heat shock protein HSP 90-α - Prefoldin subunit 6 - SKAP-2 - Thrombospondin-1 - Proteins downregulated in intracoronary platelets: - Actin - FXIII-a chain - Talin-1 - Vinculin - SKAP2, ITA2B, Talin-1, and TSP-1 were selected for validation studies - ITA2B and SKAP2 were upregulated in intracoronary platelets - TSP-1 and Talin-1 isoforms are differentially regulated in intracoronary platelets TSN-1 increased, Talin-1 was downregulated
3.	Alonso-Orgaz et al 2014 Spain	Blood clot	To characterize the proteome of coronary thrombus in STEMI patients	Adult STEMI patients	$N = 20$ (STEMI patients) $N = 16$ (healthy controls)	2-DE MALDI-TOF/-TOF 1-DE LC-MALDI MS/MS	- 1-DE LC-MALDI MS/MS yielded 372 proteins - LC-ESI-MS/MS yielded 467 proteins - 2-DE MALDI-TOF/TOF yielded 81

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Table 1 (*Continued*)

Number	Author Year Country	Focus area	Aim	Population	Comparative groups ($n =$)	Proteomic methods	Key findings
						LC-ESI-MS/MS Western Blot	proteins - Proteins were from seven functional groups: cell differentiation, metabolism, redox state and apoptosis, regulation and transport, immune response, structural and adhesion, and other - Further analysis was conducted for: - FERM3 - DIDO1 - NADPH - Carbonic anhydrases 1, 2, and 3 - Calreticulin - Catalase - MMRN1 - MYH9 - PARVB - RAP1B - Titin - TSP1 - FERM3 showed a moderate non-significant increase in the plasma of STEMI patients - DID01 was upregulated in plasma of STEMI patients - DID01 could potentially serve as a biomarker of thrombosis
4.	Stachowicz et al 2018 Poland	Blood clot	To investigate the protein composition of plasma clots prepared ex vivo from patients with APS-associated VTE versus those with VTE unrelated to APS and age- and sex-matched healthy controls	Thrombotic APS and VTE patients	Thrombotic APS ($n = 23$) VTE ($n = 19$) Healthy controls ($n = 20$)	LC-MS/MS	- Clots of thrombotic APS patients had decreased content of ATIII, F2, FXIII α chain, apo A-I, and HRG - Clots from APS and VTE patients: fermitin family homolog 3, multimerin-1, TREM-like transcript-1, GPIIb, GPI, GPIII, integrin-linked protein kinase, talin-1, vinculin, filamin A, GPIX, GPIbA, GPIbB, and TSP1 were overrepresented as compared with healthy controls - Increased amounts of clot-bound β2GpI in APS patients
5.	Schmitt et al 2019 Hungary	Blood clot	To develop an approach for the characterization of	Healthy adult	Not specified	LC-MS/MS	- Findings show fibrin proteins were the most abundant components followed by albumin

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Table 1 (*Continued*)

Number	Author Year Country	Focus area	Aim	Population	Comparative groups (*n* =)	Proteomic methods	Key findings
			fibrin clots to obtain molecular detail regarding the specificity of FXIIIa cross-link sites and substrates				- Substrates of FXIIIa were identified: PAI-1, THBS1, and FINC - Cellular components (hemoglobin and integrins) interact with fibrin clot - Majority of cross-links originated from α c region of fibrinogen-α - C-terminal γ–γ peptide cross-linking was determined to be higher in the in vivo thrombus compared with the whole-blood clot
6.	Zabczyk et al 2019 Poland	Blood clot	To investigate plasma clot's protein composition and its associated clot properties	Healthy adults	Healthy adult controls ($n = 20$)	LC- MS/MS	- 494 proteins identified in the plasma fibrin clot - Highest protein concentrations found in clot were three fibrinogen chains (64%) and fibronectin (13%) - Protein concentrations less than 0.1% were antithrombin, platelet factor 4 and factor V, vWF, and others. - Fibrinogen-a and -γ chains were associated with age - BMI was associated with clot bound apolipoproteins - Clot lysis time correlated with age, fibrinogen-a and -γ, and histidine-rich glycoprotein - HRG may modulate plasmin-mediated clot lysis - C-reactive protein was detected in most plasma clots
7.	Bhagwat et al 2020 India	Blood clot	To identify the substrates of thrombin using the N-terminomics-based methods	Adult healthy volunteer	$N = 1$	LC-MS/MS MALDI-TOF/TOF	- 54 substrates identified (antithrombin, C5, hemopexin, CP, Singlec-6, and AGP) - Singlec-6 and AGP were validated by cleavage with thrombin - Thrombin residues Ser (410) and Arg (413) form H-bonds with siglec-6 at Arg (193) and Arg (205), respectively - AGP activity of inhibition of platelet aggregation is countered by thrombin cleavage of AGP

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Table 1 (*Continued*)

Number	Author Year Country	Focus area	Aim	Population	Comparative groups ($n =$)	Proteomic methods	Key findings
8.	Bruzelius et al 2016 Sweden	VTE	To identify plasma protein biomarkers for VTE	Adults-VEBIOS Study (Sweden) Adults-FARIVE Study (French)	VEBIOS: $N =$ VTE cases $N = 88$ Controls FARIVE: $N = 603$ VTE cases $N = 597$ controls	LC-MS ELISA	- Main proteins identified with an association with VTE risk were: HIVEP1, GPX3, vWF, and PDGFB across both studies - Levels of GPX3 were lower in cases than controls in study - HIVEP, VWF, and PDGFB levels were significantly higher in cases, compared with controls - PDGFB as a novel VTE-associated plasma protein worthy of further research
9.	Jensen et al 2018 United States	VTE	To discover predictive biomarkers for incident VTE	Adults	$N = 100$ (VTE) $N = 100$ (controls)	LC-MS3	- 681 proteins identified - 46 proteins ($p < 0.5$) were considered for biomarker panel - FIX, galectin-3 binding protein S1000A8/9 were differentially expressed in cases and controls - Transthyretin was the strongest biomarker candidate (increased in VTE subjects) followed by ProZ and DJ-1 - Subjects who developed VTE later had an upregulation in ProZ
10.	O'Connell et al 2018 United States	Stroke	To profile sex-associated differences in the plasma proteomes of a small group of ischemic stroke patients during the acute phase of care	Adult ischemic stroke patients	Female stroke patients ($n = 4$) Male stroke patients ($n = 6$) Female controls ($n = 18$) Male controls ($n = 19$)	LC-ESI-MS ELISA	- 297 proteins identified using mass spec. - CBG was expressed 16-fold higher in women compared with males - CBG levels were lower in male stroke patients compared with male controls in the validation cohort - Circulating CBG levels are directly responsive to stroke pathology in men, in women it's absent or attenuated
11.	Penn et al 2018 Canada	Stroke	To confirm that MS platforms yield useful information and provide preliminary candidates of	Adult stroke patients	Stroke patients ($n = 20$) Controls ($n = 20$)	LC/ MRM-MS ELISA kits	- 30 significant proteins identified, which are involved in: coagulation, inflammation, cell adhesion, and atrial fibrillation - Prothrombin was highly correlated

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Table 1 (*Continued*)

Number	Author Year Country	Focus area	Aim	Population	Comparative groups (n =)	Proteomic methods	Key findings
			protein biomarkers for TIA				with plasminogen and vitamin K-dependent protein C - MS platforms are useful for yielding info for the diagnosis of stroke
12.	Penn et al 2018 Canada	Stroke	To validate previously developed 16 plasma-protein biomarker panels to differentiate between TIA and non-cerebrovascular ED patients.	Adult stroke patients enrolled in the SpecTRA Study	Cohort 2a ($n = 575$) Cohort 2b ($n = 528$)	LC/MRM-MS	- LSEL, ApoB100, F9, and TSP-1 are potentially important predictors of TIA status - IGFBP-3 and PON3 were significant univariate predictors of TIA - Univariate analysis indicated that many of the panel proteins that were significant in the cohort 2A dataset (LSEL, ApoB100, F9, and TSP-1) were not significant in the cohort 2B dataset
13.	Timperio et al 2010 Italy	Therapeutics	To investigate other proteins in commercially available FVIII products which may stimulate immune responses in patients	Commercially available recombinant FVIII (rFVIII)	Emoclot (Aventis Behring) Beriate (Kedrion)	SDS-PAGE RP-nanoHPLC mass spec.	- 9 proteins identified in Beriate - 16 proteins identified in Emoclot - vWF is the most predominant protein identified in both commercially available FVIII, followed by fibrinogen, fibronectin, and IgM heavy chain - FVIII concentrates contain excess of plasma proteins which could influence the function of cellular components of the immune system

Abbreviations: β2GpI, anti-β2 glycoprotein I; 1-DE, one-dimensional electrophoresis; 2D-DIGE, two-dimensional gel electrophoresis; 2-DE MALDI-TOF/TOF, 2-dimensional electrophoresis matrix-assisted laser desorption/ionization-tandem time of flight mass spectrometry; 2-DE, 2 dimensional electrophoresis; AGP, alpha-1-acid glycoprotein; Apo A-I, apolipoprotein A-I; ApoB100, apolipoprotein B-100; APS, antiphospholipid syndrome; C5, complement C5; CBG, corticosteroid- binding globulin; CDC42hs, cell division control protein 42 homolog; CP, ceruloplasmin; DIDO1, death-inducer obliterator 1; DJ-1, Parkinson disease protein 7; ED, emergency department; ELISA, enzyme-linked immunosorbent; F2, factor 2 (prothrombin); FERM3, fermitin family homolog 3; FINC, fibronectin; FIX, factor 9; FXIIIa, factor XIIIa (Laki–Lorand factor); GPI, integrin beta-1; GPIIb, integrin alpha-IIb; GPIII, integrin beta-3; GPIX, platelet glycoprotein IX; GPX3, glutathione peroxidase 3; HIVEP1, zinc finger protein 40; HRG, histidine-rich glycoprotein; IGFBP-3, insulin-like growth factor-binding protein 3; IgM, immunoglobulin M; ITA2B, integrin alpha-IIb; LC/ MRM-MS, liquid chromatography/multiple reaction monitoring- mass spectrometry; LC-ESI-MS/MS, liquid chromatography-electrospray ionization-tandem mass spectrometry; LC-MALDI MS/MS, liquid chromatography matrix-assisted laser desorption/ionization-tandem mass spectrometry; LC-MS3, liquid chromatography triple mass spectrometry; LSEL, L-selectin; MMRN1, Multimerin-1; MRM-MS, multiple reaction monitoring-mass spectrometry; MS, mass spectrometry; NADPH, flavin reductase; PAI-1, plasminogen activator inhibitor 1; PARVB, beta-parvin; PDGFB, platelet-derived growth factor subunit-B; PF4, platelet factor 4; platelet glycoprotein Ib α and β chain (GPIbA, GPIbB); PON3, serum paraoxonase/lactonase 3; ProZ, protein Z, vitamin K dependent plasma glycoprotein; RAP1B, Ras-related protein Rap-1b; rFVIII, recombinant FVIII; RP-nanoHPLC mass spec, reversed phase-nano high-performance liquid chromatography mass spectrometry; SDS-PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis; SKAP-2, Src kinase-associated phosphoprotein 2; STEMI, ST-segment elevation myocardial infarction; SWATH-MS, sequential window acquisition of all theoretical mass spectra-mass spectrometry; T2D, type 2 diabetes; THBS1, thrombospondin-1; TIA, transient ischemic attack; TSP1, thrombospondin-1; VTE, venous thromboembolism; vWF, von Willebrand factor.

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Fig. 1 Applications of proteomics.

setting, is crucial for precision and personalized medicine,[24] enhancing the ability to identify patient-specific therapeutic targets such as proteins and antibodies, and ultimately improving patient outcomes.[25]

With increasing use of proteomics, the discovery of relevant and novel clinical markers associated with diseases or predicting clinical outcomes (e.g., thrombosis or bleeding) is made possible and can be easily and practically translated into the clinical setting. Proteomics can also be used to aid in early-onset disease diagnosis, disease management, and monitoring of therapeutic interventions.[25]

The use of proteomics in the setting of thrombosis and hemostasis poses many advantages. With technological and methodological advancements, the shift from bench to bedside can be achieved to translate proteomic research findings into the clinical setting and to improve patient outcomes.

Key Considerations for Proteomics Studies

Similarly to any study, a well-designed proteomics study requires definition of a clear research question and a specific rationale for statistical analysis.[26] Proteomics studies also require a carefully selected population of interest. Proteomes change with age, sex, race, and disease, therefore selecting the most appropriate population prior to undertaking a proteomics study is crucial for accurate interpretation of the proteomic data. Considerations for sample size, specifically for clinical marker studies, should be dependent on the phase of proteomics study being undertaken.

Additionally, the type of sample to be analyzed must be carefully considered when executing a proteomics study. Understanding differences between plasma and serum is critical in choosing which sample type to use. Serum preparation involves activation of coagulation which in turn results in changes in the abundance of not only coagulation proteins, but also proteins involved in inflammation, and as such plasma is the preferred sample of choice for proteomics studies in the setting of hemostasis. By utilizing citrated plasma, it is possible to combine the results of proteomics analysis with functional coagulation assays.

Typical proteomics-based blood marker studies are conducted in three phases: discovery, verification, and validation. The discovery phase requires a small sample size ($n = 10–50$) and focuses on hundreds to potentially thousands of proteins in an untargeted manner (e.g., SWATH-MS). When it comes to the discovery phase, techniques such as the two-dimensional gel electrophoresis represent an outdated methodology that requires extensive multistep protocols from the sample itself to the generation of mass spectrometry data and have almost exclusively been replaced by liquid chromatography/mass spectrometry (LC/MS) and LC tandem MS (LC/MS/MS) approaches. LC/MS and LC/MS/MS approaches are associated with minimal preanalytical sample processing and maximized protein detection, and are used extensively in proteomics studies, especially in the setting of plasma proteomics. LC/MS/MS allows identification of approximately 500 proteins in a single run, as well as protein isoforms and PTMs.[27]

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Verification is then conducted using a more targeted approach (e.g., MRM-MS) with a larger sample size ($n = 50$–100), focusing on several proteins of interest. Validation studies represent the last phase of clinical proteomics studies and are typically conducted using immunoassays, with a much larger sample size ($n = 100$–1,000), focusing on a small number of candidate proteins.[28]

These fundamental considerations ensure that results of proteomics studies can be efficiently translated into patient-specific benefits.

When it comes to clinical application of proteomics, recent advances have enabled extremely fast data acquisition. Specifically, plasma proteomes are able to be analyzed across a 1-minute gradient, resulting in identification of 180 proteins, a dataset that includes 47 Food and Drug Administration-approved biomarkers.[29] Combined with the fact that mass spectrometers already have a place in clinical laboratories and are utilized in clinical practice (e.g., newborn screening), it is only a matter of time before proteomics becomes a part of routine practice in the setting of thrombosis and hemostasis.

Conflict of Interest
None declared.

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