Review

The Proteome Content of Blood Clots Observed Under Different Conditions: Successful Role in Predicting Clot Amyloid(ogenicity)

Douglas B. Kell [1,2,3,*] and Etheresia Pretorius [1,3,*]

1 Department of Biochemistry, Cell and Systems Biology, Institute of Systems, Molecular and Integrative Biology, Faculty of Health and Life Sciences, University of Liverpool, Crown St, Liverpool L69 7ZB, UK
2 The Novo Nordisk Foundation Centre for Biosustainability, Building 220, Søltofts Plads 200, Technical University of Denmark, 2800 Kongens Lyngby, Denmark
3 Department of Physiological Sciences, Faculty of Science, Stellenbosch University, Stellenbosch Private Bag X1, Matieland 7602, South Africa
* Correspondence: dbk@liv.ac.uk (D.B.K.); resiap@sun.ac.za (E.P.)

Abstract: A recent analysis compared the proteome of (i) blood clots seen in two diseases—sepsis and long COVID—when blood was known to have clotted into an amyloid microclot form (as judged by staining with the fluorogenic amyloid stain thioflavin T) with (ii) that of those non-amyloid clots considered to have formed normally. Such fibrinaloid microclots are also relatively resistant to fibrinolysis. The proteins that the amyloid microclots contained differed markedly both from the soluble proteome of typical plasma and that of normal clots, and also between the diseases studied (an acute syndrome in the form of sepsis in an ITU and a chronic disease represented by Long COVID). Many proteins in the amyloid microclots were low in concentration in plasma and were effectively accumulated into the fibres, whereas many other abundant plasma proteins were excluded. The proteins found in the microclots associated with the diseases also tended to be themselves amyloidogenic. We here ask effectively the inverse question. This is: can the clot proteome tell us whether the clots associated with a particular disease contained proteins that are observed uniquely (or are highly over-represented) in known amyloid clots relative to normal clots, and thus were in fact amyloid in nature? The answer is in the affirmative in a variety of major coagulopathies, viz., venous thromboembolism, pulmonary embolism, deep vein thrombosis, various cardiac issues, and ischaemic stroke. Galectin-3-binding protein and thrombospondin-1 seem to be especially widely associated with amyloid-type clots, and the latter has indeed been shown to be incorporated into growing fibrin fibres. These may consequently provide useful biomarkers with a mechanistic basis.

Keywords: clotting; amyloid; fibrinaloid; proteomics; cross-seeding; fibrils

1. Introduction

Blood normally clots into a thrombus in which the fibres appear like cooked spaghetti when observed in the electron microscope (e.g., [1–5]). However, a series of our own studies [6–23], as well as those of others [24–26], have demonstrated, via staining with the amyloid stain thioflavin T (or by other, label-free means [27]), that fibrinogen monomers (when exposed to thrombin) can self-assemble to form an amyloid version of (micro)clots that we refer to as fibrinaloid microclots. As with other forms of amyloid proteins, these are much more resistant to proteolysis (fibrinolysis [28]) than are the normal forms. In a recent analysis [29], we compared the proteome of blood clots seen when blood had

clotted into a known amyloid form (as judged by staining with the classical amyloid stain thioflavin T) with those clots considered to have formed normally. While the amounts of non-fibrin proteins that were trapped in the normal clots had a rough correlation with the typical contents of the soluble plasma proteome, there was little such correlation in the amyloid clots; indeed, the proteins that the amyloid microclots contained were characterised by their highly amyloidogenic potential [29]. They also differed markedly between the disease studies (viz acute sepsis in an ITU [25] vs. the chronic disease Long COVID [9], with only apolipoprotein-A2 being common to both). Notably, we there showed that the fibrinaloid microclots are associated with proteins that are very different [9,25] from those within normal, non-amyloid clots, using for the latter data from a paper by Undas and colleagues [30]. More explicitly, we argued there [29] that, in the terminology of Bondarev and colleagues [31], as illustrated in Figure 1, proteins entrapped in normal clots were likely to be 'titrated' (bound) or sequestered, while those in fibrinaloid microclots were, through their cross-β motifs, likely to be incorporated such as to be part of the amyloid fibres themselves. All of this, along with the presence of anti-fibrinolytic proteins such as α2-antiplasmin [28], served to explain the significant resistance of these microclots to normal fibrinolysis. As it happens, there are a number of other clot proteomics studies available, studying samples from a variety of diseases (e.g., [32,33]), but in which the amyloidogenic nature of the clots was not, however, measured. Since we now have access to proteomes from known, 'calibrated' systems, we can therefore here effectively ask the inverse question (Figure 2). This is: can the clot proteome tell us whether the clots associated with a particular disease plausibly contained proteins that are observed uniquely (or are highly over-represented) in known amyloid clots relative to normal clots, and thus that the clots were in fact probably amyloid in nature? The present paper sets out to answer this; in all cases where the data are available, the answer is in the affirmative, suggesting the value of testing this directly, as has very recently been performed in the case of clots removed by thrombectomy from stroke patients [34].
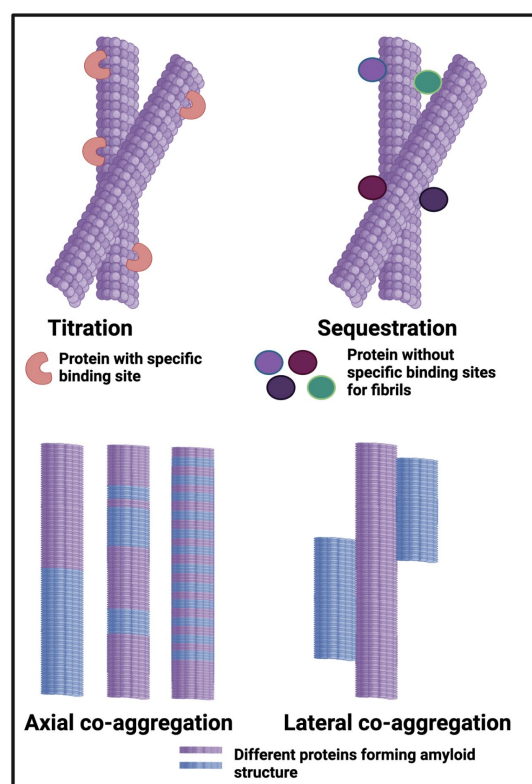

Figure 1. Different classes or types of protein co-aggregation: Titration; Sequestration; Axial and Lateral. Reprinted from the open access preprint [29], which was itself adapted from [31].

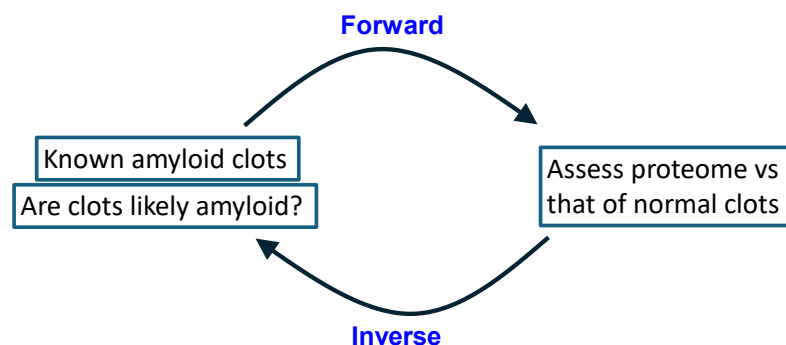## Forward and inverse strategies for amyloid clot proteomics

Figure 2. The relationship between forward and inverse strategies (as in systems biology [35]), in which here we seek to assess the normal or amyloid nature of clots as judged by their proteome. In the forward strategy, we calibrate the system by asking which proteins differ in the two cases where the amyloid nature is known [36]. In the inverse case, developed here, we use the observed protein entrapments to infer or to suggest whether the clots are likely to be amyloid in nature.

2. Results

Letunica and colleagues [32] provide a very helpful summary of clot proteome studies, and in what follows we analyse the relevant (clot) studies that they highlight, along with some other studies of clot proteomes under various circumstances.

Alonso-Orgaz and colleagues [37] studied the proteome of clots taken from individuals who had suffered an acute myocardial infarction with ST-segment elevation (STEMI patients). They used three mass spectrometric methods for proteome analysis; we here confine ourselves to the 46 proteins detected using all three methods (their Table S5). In fact, apart from fibrin(ogen), there was surprisingly little overlap with any of the proteins in the previous works [9,25,30] that we studied, with the exception of thrombospondin-1 [37]; however, thrombospondin-1 (Uniprot P07996) was present in our Long COVID study [9] but barely so (8 $\mu g \cdot g^{-1}$ clot) in the normal-clot study of Undas and colleagues [30]). This molecule thus provides a strong hint for the amyloid nature of the clots in the STEMI patients.

2.1. Venous Thromboembolism (VTE)

Stachowicz and colleagues [38] studied the proteome of clots generated from the plasma of individuals with venous thromboembolism (VTE). Interestingly, these clots were significantly resistant to trypsinolysis (they yielded about 4× more peptides using lys C), possibly providing a strong hint (as per [39]) that these clots were likely amyloid in character, albeit this was not measured. LysC + trypsin + chymotrypsin yielded the most peptides [38] (note that in *E. coli* the peptides yielded by incubation with lys C vs trypsin were largely orthogonal [40]). Of the proteins mentioned in their Table 1 [38], fibronectin, vitronectin, and antithrombin III are more typical of proteins entrapped in normal clots, while α2-antiplasmin and von Willebrand factor appear in both [29].

VTE was also studied by Bruzelius and colleagues [41]. The stand-out markers for VTE in their study were VWF and platelet-derived growth factor B (PDGFB); the latter did not make an appearance in any of our earlier studies. VWF is also very prone to changes in that it may be elevated at one stage in a coagulopathic disease's progression, but hypercoagulability can deplete it rapidly, even thereby leading to hypocoagulability [42].

Another prospective VTE study was that of Jensen and colleagues [43], who analysed the proteome of those suffering a VTE in samples obtained from a large cohort study. Most interestingly, one of their top biomarkers was Galectin-3-binding protein (LG3P), a protein

that was highly over-represented in our Long COVID study of fibrinaloid microclots [9], but that did not appear in the normal clot proteome [30]. Transthyretin, a protein well known to be prone to amyloidogenesis (e.g., [44–46], was also upregulated in those clot proteomes whose owners later went on to have a VTE [43]. Galectin-3-binding protein (LG3P) does seem like an interesting marker for <u>later</u> VTE events and is certainly amyloidogenic.

A reviewer pointed out that coagulopathies can be associated with certain cancers, and we would add that this is especially true in pancreatic cancer (e.g., [47]), where fibrosis is also a common accompaniment [48], as are neutrophil extracellular traps (NETs), a common feature of fibrinaloid microclots [49]. However, to maintain the focus of the present analysis on 'pure' amyloids, we decided not to add diseases (such as cancer) in which the coagulopathy was not seen as the main syndrome.

2.2. Pulmonary Embolism

Bryk and colleagues [50] studied the quantitative proteome of clots generated from the plasma of 20 individuals who had had a pulmonary embolism (PE) compared with that of 20 controls. They [50] used a combination of lysC and trypsin to ensure good digestion. The specific protein composition in plasma fibrin clots from acute PE patients was associated with denser clots, and proteins that were enriched in these included apolipoprotein B, a protein enriched in our own studies [9] of fibrinaloid microclots. PE is hugely exacerbated by COVID-19 [51], so it is probably not then surprising (e.g., [9,17,18,20,39,42,49,52–61]) to see amyloid-type clot markers in these clots. Bryk and colleagues also detected platelet factor 4 in their clots, a protein also detected in fibrinaloid microclots by Schofield et al. [25], but present only in minuscule amounts in both plasma and normal clots [29]. These findings suggest strongly that the clots seen with pulmonary embolism are also indeed likely to be amyloid in nature.

In an important series of studies, Ząbczyk et al. [5,62–64] analysed the 'prothrombotic fibrin clot phenotype' that they discovered to be associated with pulmonary embolisms. Recurrent PE was associated with the formation of denser fibrin networks reflected by lower permeability, with impaired fibrinolysis, and consequently with reduced maximum rate of increase in D-dimer levels in the lysis assay, despite higher plasma D-dimer levels [64]. Although seemingly not measured, these are precisely the properties of fibrinaloid microclots. The prothrombotic fibrin clot properties were associated with NETs formation [5,63] (see also [65]) as well as elevated lactate levels [63] (implying hypoxia), and most importantly of all (from our perspective) with low grade endotoxaemia [62]. Endotoxin (bacterial lipopolysaccharide) is <u>precisely</u> the trigger that we initially discovered [11] and have subsequently confirmed many times [13–16,66], that was able to catalyse the formation of fibrinaloid microclots. It is hard not to infer that these clots are amyloid in nature; hopefully those studying them will deploy the necessary tests, which are easy enough to do (e.g., [67,68]).

2.3. Deep Vein Thrombosis (DVT)

As a subset of VTE, Deep Vein Thrombosis (DVT) is seen as less likely to be fatal thanis PE, but is nonetheless a significant cardiovascular problem. In addition, post-thrombotic syndrome (PTS) is a common comorbidity (of DVT). We suspect that the two are related via fibrinaloid microclots, since the main clinical manifestation of PTS is chronic venous insufficiency [69,70]. Ramacciotti and colleagues studied the proteome of microparticles following DVT. Very strikingly, just two proteins, namely Galectin-3 Binding Protein (LG3BP) and Alpha-2 macroglobulin (a highly expressed plasma protein [71]), were overexpressed. As noted [29], the amyloidogenic LG3BP is highly over-represented in the fibrinaloid microclots of Long COVID but is invisible in normal clots. Zhang and

colleagues studied the plasma (rather than clot) proteome of individuals with various kinds of DVT [72] and again found a great many differences (Figure 3), in addition to suggesting several metabolites that might be discriminatory. Interestingly, the protein most lowered in the plasma of patients showing DVT following trauma (pt-DVT) (Figure 3) was the highly amyloidogenic [44,73] transthyretin, strongly implying that it had disappeared into amyloidogenic clots. Note that this is not simply an acute-phase response since many classical acute-phase response proteins (such as C-reactive protein) do not appear in Figure 3.
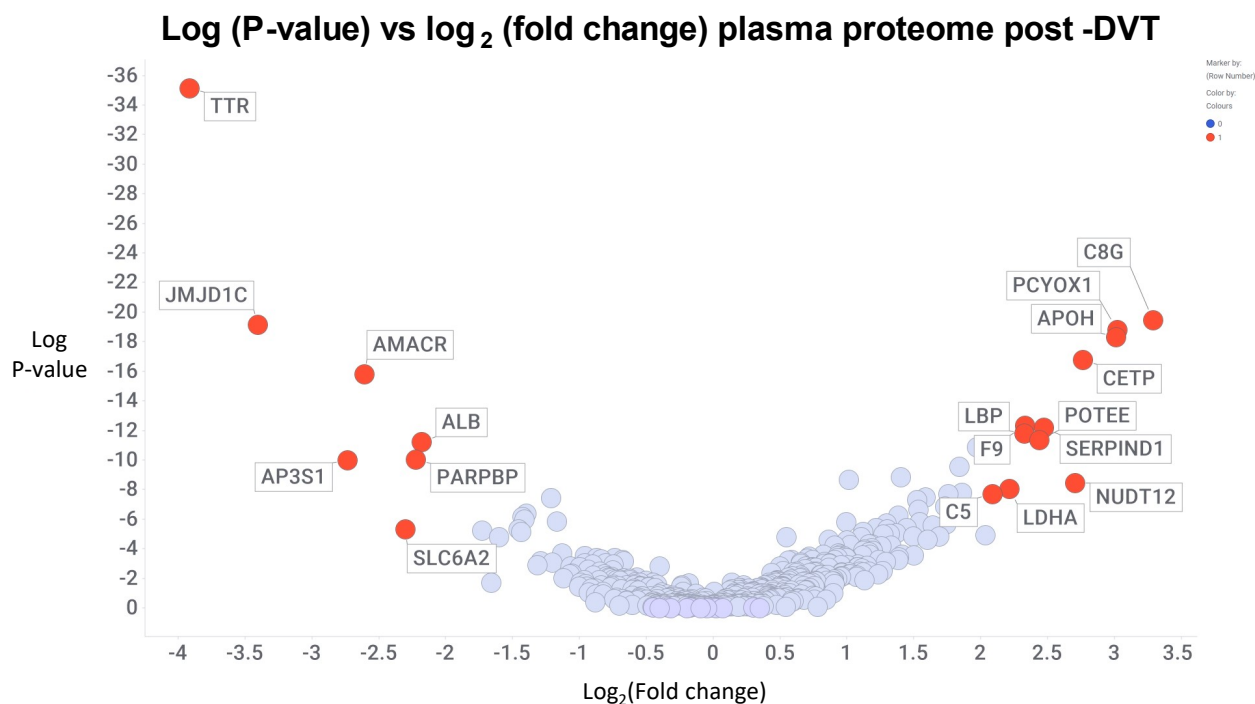

Figure 3. Changes in the plasma proteome in individuals with deep vein thrombosis after trauma. Data are taken from Supplementary Table S15 of [72] and visualised using the Spotfire program (http://spotfire.com/, accessed on 30 January 2025). Those with a log2 change of <−2 or >2 are labelled.

2.4. Post-Thrombotic Syndrome

Post-thrombotic syndrome (PTS) is a common chronic complication of deep vein thrombosis [74], occurring in up to 50% of individuals who have had a DVT [75]. It seems to involve residual clots that are not removed, in that successful therapies include catheter-directed thrombolysis and mechanical thrombectomy [75,76], as well as low-MW heparin [77]. Obviously we suspect fibrinaloid clots here, though no one seems to have looked, and part of the purpose of this article is to encourage experts to do so.

2.5. Cardioembolic and Large Artery Atherosclerotic Clots

Rossi and colleagues [78] studied the proteome of formalin-fixed paraffin-embedded cardioembolic and large artery atherosclerotic (LAA) clots, finding 1581 proteins; however, the numbers of samples were insufficient for us to draw meaningful conclusions.

2.6. Myocardial Infarction

We have been unable to find any studies in which clots were analysed following a myocardial infarction (MI). However, it is notable that serum amyloid A is a risk factor for MI [79] and is massively increased in patients who have had an acute myocardial infarction [80]. It is to be stressed that serum amyloid A has been shown to promote fibrinaloid formation [10].

2.7. Trauma-Induced Coagulopathy

A somewhat separate but closely related category is trauma-induced coagulopathy (TIC). This describes abnormal coagulation processes that are attributable to trauma [81]. In contrast to acute COVID, in which the sequence is opposite [42], TIC exhibits a hypocoagulable phase linked to haemorrhage [81–83] followed by one of hypercoagulability [81,84]. Both seem to be controlled significantly by the rates of fibrinolysis [85,86], with the hypocoagulability being attributed to hyperfibrinolysis and the hypercoagulability to hypofibrinolysis. For present purposes, our focus is on the latter, with hypofibrinolysis being explicable, at least in part, by any amyloid formation. As per the theme of this article, we next explore what is known of the proteome in the hypercoagulable phase of TIC.

Sadly, such studies of the clot proteome in TIC seem few and far between. However, Coleman and colleagues [87] found increases in both α2-antiplasmin and α1-antitrypsin (SERPINA1), both of which are increased in fibrinaloid microclots [9,36,39], are stimulated by oestradiol (that may also contribute to this phenotype [88]) and that this can contribute to the known sex dimorphism in coagulability [89]. Interestingly, thrombospondin-1 was among the most overexpressed proteins (3.84-fold; Supplementary Information to [87]), and this is one of our two most favoured markers for clots being amyloid in nature [36]. Apolipoprotein-A1 was also strongly over-represented in the clot proteomes of [87], and this too was a significant contributor to the amyloid clot proteome of Toh and colleagues [25]. Taken together, the evidence strongly favours the view that the clots produced when a patient is exhibiting hypercoagulability in TIC are indeed amyloid in nature.

2.8. Polycythemia Vera

Polycythemia vera (PV) is a myeloproliferative neoplasm associated with a haematocrit over 45% and a JAK2 mutation (mainly V617F) [90,91], with phlebotomy being the commonest treatment to lower the haematocrit in lower-risk patients. High-risk patients are treated with cytoreductive agents, where hydroxyurea and recombinant interferon-alpha are seen as first-line therapies [92]. Despite this, thromboembolic events are the major (and a common) complication of polycythemia vera [93] (and indeed the thromboembolic events may themselves lead to the diagnosis of PV) [94].

Neutrophil extracellular traps are known to be somewhat linked to thrombotic events in PV [95–97], and are associated with fibrinaloid microclots [49].

However, although there have been a few proteomic studies of PV [98–100], none seem to have involved clot proteomics. In the spirit of the above reasoning, it would seem that effecting such an analysis would be of value.

2.9. Stroke

Stroke, the second greatest cause of death worldwide [101–104], has long been associated with the production of anomalous clots [105–107] (that, as rehearsed above, we now know to be amyloid in nature).

O'Connell and colleagues [108] studied the circulating (rather than clot) proteome of individuals following an ischaemic stroke. They found a substantial gender difference in corticosteroid-binding protein that rather dominated the analyses and overwhelmed stroke effects.

Penn et al. sought proteomic biomarkers of stroke. Their first study of the clot proteome [109] found proteins involved in inflammation (47%), coagulation (40%), and atrial fibrillation (7%), among others. Atrial fibrillation is, of course, well associated with stroke risk [110], as well as a prothrombotic state [111–113]. Other studies known as SpecTRA [114,115] included the assessment of thrombospondin and VWF as part of a biomarker panel. Further validation studies showed that both thrombospondin and

apolipoprotein B contributed. Both have been recognised as amyloidogenic markers in fibrinaloid microclots, and in particular, it is to be highlighted that thrombospondin can be incorporated into fibrin fibrils themselves [116–119] (and see later).

Lopez-Pedrera and colleagues [120] analysed the thrombus proteome of stroke patients. The thrombus proteome reflected three classes or clusters of patients with varying levels of severity, prognosis, and aetiology of the stroke. Gelsolin and vinculin were among the proteins observed in the clots. Cardioembolic thrombi were enriched in proteins of the innate immune system.

Staessens and colleagues [121,122] note the prevalence of neutrophil extracellular traps (NETs) in the thrombus taken from ischaemic strokes (they were also found in cardioembolic thrombi [123]); very interestingly, NETs are also an important feature of the fibrinaloid microclots found in long COVID [49] and were found in prothrombotic clots in the studies of Ząbczyk et al. [5]. Lower levels of extracellular DNA were related to the ease of thrombectomy [124], plausibly allowing one to relate the extent of amyloid clotting to the difficulty of thrombectomy (often measured as the number of passes).

Muñoz and colleagues [125] analysed the proteome content of clots from ischaemic strokes, noting some 1600 proteins, but quantitative data were not given, and so we cannot extract meaningful conclusions for the present purposes.

Finally, Prochazka and colleagues [126] analysed clots following acute ischaemic stroke, noting the role of von Willebrand Factor and ADAMTS13.

Most pertinently, however, is that we have shown experimentally, and for the first time, that the clots thrombectomized from 8/8 individuals with ischaemic stroke were strongly amyloid in character [34], strongly validating the arguments put forward here.

Two of the proteins over-represented in fibrinaloid microclots that regularly appeared in coagulopathic diseases are illustrated in Figure 4.
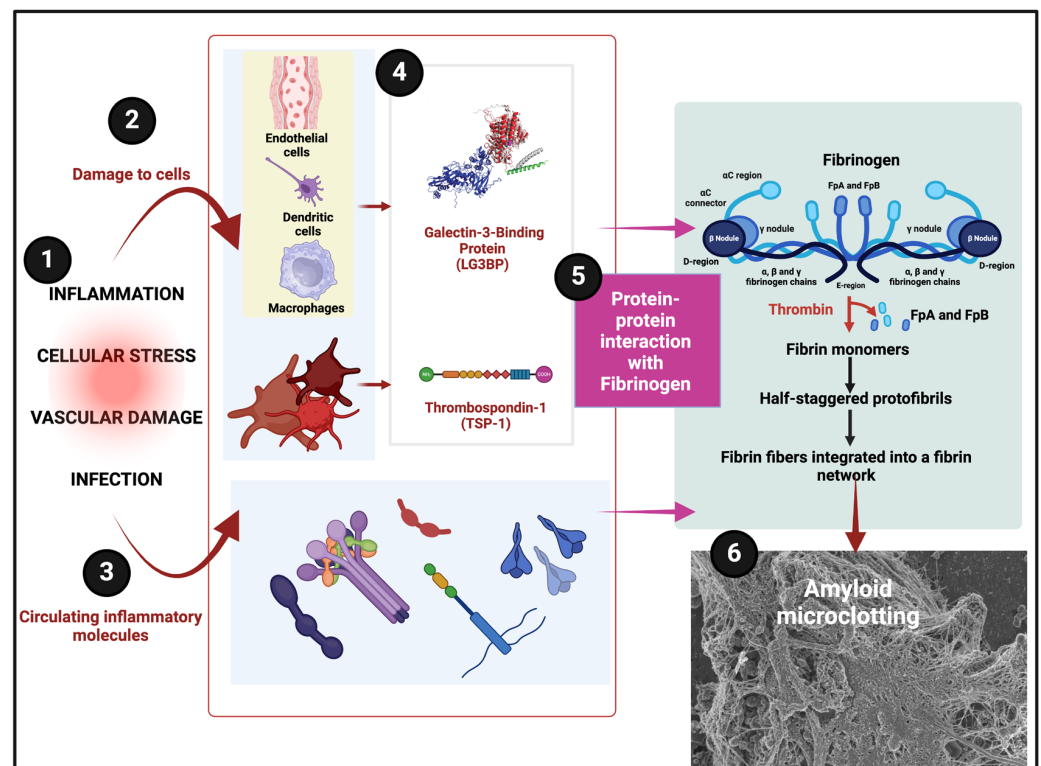

Figure 4. Illustration of the pathways from inflammation-induced cellular damage to the formation of amyloid microclots, highlighting the roles of two notably amyloidogenic proteins (LG3BP and TSP-1) in abnormal fibrinogen interactions and the resulting fibrinolysis-resistant clot structures.

(**1**) Inflammation and Cellular Stress: Triggers that initiate vascular damage, often due to infection or systemic inflammation. (**2**) Damage to Cells: Injury to endothelial cells and activation of immune cells like dendritic cells and macrophages. (**3**) Circulating Inflammatory Molecules: Release of inflammatory mediators that exacerbate vascular stress and promote clot formation. (**4**) Key Amyloidogenic Proteins: Production of Galectin-3-Binding Protein (LG3BP) and Thrombospondin-1 (TSP-1) by immune and endothelial cells. (**5**) Protein–Protein Interaction with Fibrinogen: Interaction of LG3BP and TSP-1 with fibrinogen, promoting amyloid-like fibrin formation. (**6**) Amyloid Microclotting: Formation of amyloid microclots that are resistant to fibrinolysis, contributing to disease pathology.

2.10. Galectin-3-Binding Protein (LG3BP)

LG3BP (Uniprot B4DVE1), also known as Mac-2 binding protein (Mac-2BP) or tumour-associated antigen 90K [127], is a heavily glycosylated, secreted protein whose expression is induced in viral infection and other inflammatory conditions [128–130], including metabolic syndrome [131,132] and cancer [133,134]. LG3BP appears in so many examples of the clots seen in a variety of the coagulopathic diseases under study, as well as in established fibrinaloid microclots in Long COVID [9], that it seems beyond peradventure for it not to have an aetiological role. It does not seem to be present in normal clots [30]. It has already been highlighted as a major player in the development of deep vein thrombosis [135–138], albeit detailed mechanisms are not to hand. However, the fact that it can participate in fibrinaloid microclots plausibly means that it can induce them. Certainly it is part of the deposits seen in glomerular nephritis [139], but these seemingly have not been tested for amyloid properties either. That said, renal amyloidosis is a common accompaniment to glomerulonephritis [140] and kidney damage more generally [141–146]. Galectin-3, the binding partner of LG3BP, is itself amyloidogenic [147], an inducer of fibrosis [148–151], and is a risk factor for a variety of diseases [151–153], including atrial fibrillation [154–158], something highly pertinent to this discussion [110].

Given the propensity for cross-seeding (many references, summarised in [29]), it is noteworthy that L3GBP is also capable of interacting with the precursor of the highly amyloidogenic Aβ protein [159].

2.11. Thrombospondin-1

Thrombospondin-1 (TSP-1) (Uniprot P07996) is a homotrimeric, heavily glycosylated [160], 450 kDa glycoprotein stored within the α-granules of platelets and released upon platelet activation [161]. It has significant roles in a variety of cardiovascular diseases [162–165] (including atrial arrhythmias [166]; see also [110]), lung pathologies [167], carcinomas [168,169], ageing [170], and, interestingly, stimulating platelet aggregation [171] and fibrosis [172–176], though it remains comparatively under-studied [177]. It is known to interact with Aβ [178], and, most importantly for the present analysis, it was shown nearly 40 years ago [116,118,119] that it is actually incorporated into fibrin during clot formation. Although this was not measured at the time, it seems likely that those clots were amyloid in nature, especially since—as with known fibrinaloid microclots [11]—the fibres so formed were on average both thinner and more numerous than clots formed in its absence [117].

Although thrombospondin-1 levels are comparatively low in platelet-poor plasma [161], thrombospondin-1 was highly enriched in the fibrinaloid microclots associated with Long COVID [9] but barely detectable in normal clots [30]. It seems that in clot proteomics, thrombospondin-1, along with galectin-3-binding protein, could indeed be an excellent marker of fibrinaloids, and may even induce them.

3. Discussion and Conclusions

In a previous analysis [29], we assessed the differences in the clot proteome between clots known to be normal and those measured experimentally to be amyloid in character

(fibrinaloid clots), concluding that the major difference in those proteins that were over- or under-represented in the clots was clearly correlated with the extent to which they were amyloidogenic in character. Coupled with the contrasting fact that the proteome content of normal clots was far more representative of the normal plasma proteome, this gave strong weight to the view that the 'entrapment' of the non-fibrin proteins was actually within the cross-β elements of the amyloid fibrils themselves, via so-called cross-seeding.

In the present analysis we asked what amounts to the inverse question, which is as follows: given what we know about proteins enriched in amyloid clots, could we seek to predict the amyloid nature of the clots in a variety of diseases in which it was not measured by looking at the proteome alone? The answer was a resounding yes. In particular, galectin-3-binding-protein and thrombospondin-1 seemed to be present in all the clots from the diseases studied here, and both were highly amyloidogenic (scoring over 0.86 on the amylogram server [179,180] http://biongram.biotech.uni.wroc.pl/AmyloGram/, accessed on 30 January 2025). It now seems that the polymerisation of fibrin(ogen) into an amyloid is indeed associated with a considerable number of acute as well as chronic diseases.

One reviewer asked whether events such as acute phase responses or platelet changes or differential crosslinking might account for some of the differences in clot composition, or the fact [181] that some clots are white rather than red. These are fair and interesting and potentially very important questions, but they are ones for the future. Here our purpose is merely to highlight an important basis for the different clot compositions, which is whether they are, or are likely to be, amyloid or not. Only if and when that is accepted does it become pertinent to consider the mechanistic bases for such differences. In the proteome papers that we cite, such details are anyway not made available.

Another reviewer raised a number of equally excellent questions: (1) What is the role of LG3BP and TSP-1 in forming amyloid clots? (2) How does the presence of these proteins change the nature of the fibrin fibres related to their structure and resistance to fibrinolysis? (3) Is the presence of these proteins in clots the cause or effect of amyloid clot formation? (4) How does ageing of clots (e.g., in chronic DVT) lead to amyloid clot formation? Again, they are all excellent questions for future work, but apart from (1), where the role is clearly stated to be cross-seeding [36], and (3), where the growth of amyloid fibrils implies both, are beyond the scope of the present analysis.

What is within the scope of the paper, however, is the recognition that proteomics analyses can give important information about the likelihood of clots being amyloid-containing and thus relatively resistant to normal fibrinolysis. The fact that we found in every kind of thromboembolic case studied that they were seems beyond coincidence, and consequently highly significant to the diseases themselves.

4. Materials and Methods

This was an analytical paper using literature data and bioinformatics methods; the data were obtained, and the analyses were performed precisely as described in the text.

References

1. Litvinov, R.I.; Pieters, M.; de Lange-Loots, Z.; Weisel, J.W. Fibrinogen and Fibrin. *Subcell. Biochem.* **2021**, *96*, 471–501. [CrossRef] [PubMed]

2. Pretorius, E.; Bester, J.; Vermeulen, N.; Alummoottil, S.; Soma, P.; Buys, A.V.; Kell, D.B. Poorly controlled type 2 diabetes is accompanied by significant morphological and ultrastructural changes in both erythrocytes and in thrombin-generated fibrin: Implications for diagnostics. *Cardiovasc. Diabetol.* **2015**, *134*, 30. [CrossRef] [PubMed]

3. Pretorius, E.; Swanepoel, A.C.; DeVilliers, S.; Bester, J. Blood clot parameters: Thromboelastography and scanning electron microscopy in research and clinical practice. *Thromb. Res.* **2017**, *154*, 59–63. [CrossRef] [PubMed]

4. Risman, R.A.; Belcher, H.A.; Ramanujam, R.K.; Weisel, J.W.; Hudson, N.E.; Tutwiler, V. Comprehensive Analysis of the Role of Fibrinogen and Thrombin in Clot Formation and Structure for Plasma and Purified Fibrinogen. *Biomolecules* **2024**, *14*, 230. [CrossRef]

5. Ząbczyk, M.; Natorska, J.; Janion-Sadowska, A.; Metzgier-Gumiela, A.; Polak, M.; Plens, K.; Janion, M.; Skonieczny, G.; Mizia-Stec, K.; Undas, A. Prothrombotic fibrin clot properties associated with NETs formation characterize acute pulmonary embolism patients with higher mortality risk. *Sci. Rep.* **2020**, *10*, 11433. [CrossRef]

6. de Villiers, S.; Bester, J.; Kell, D.B.; Pretorius, E. Erythrocyte health and the possible role of amyloidogenic blood clotting in the evolving haemodynamics of female migraine-with-aura pathophysiology: Results from a pilot study. *Front. Neurol.* **2019**, *10*, 1262. [CrossRef]

7. Grobbelaar, L.M.; Kruger, A.; Venter, C.; Burger, E.M.; Laubscher, G.J.; Maponga, T.G.; Kotze, M.J.; Kwaan, H.C.; Miller, J.B.; Fulkerson, D.; et al. Relative hypercoagulopathy of the SARS-CoV-2 Beta and Delta variants when compared to the less severe Omicron variants is related to TEG parameters, the extent of fibrin amyloid microclots, and the severity of clinical illness. *Semin. Thromb. Haemost.* **2022**, *48*, 858–868. [CrossRef]

8. Kell, D.B.; Laubscher, G.J.; Pretorius, E. A central role for amyloid fibrin microclots in long COVID/PASC: Origins and therapeutic implications. *Biochem. J.* **2022**, *479*, 537–559. [CrossRef]

9. Kruger, A.; Vlok, M.; Turner, S.; Venter, C.; Laubscher, G.J.; Kell, D.B.; Pretorius, E. Proteomics of fibrin amyloid microclots in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) shows many entrapped pro-inflammatory molecules that may also contribute to a failed fibrinolytic system. *Cardiovasc. Diabetol.* **2022**, *21*, 190. [CrossRef]

10. Page, M.J.; Thomson, G.J.A.; Nunes, J.M.; Engelbrecht, A.M.; Nell, T.A.; de Villiers, W.J.S.; de Beer, M.C.; Engelbrecht, L.; Kell, D.B.; Pretorius, E. Serum amyloid A binds to fibrin(ogen), promoting fibrin amyloid formation. *Sci. Rep.* **2019**, *9*, 3102. [CrossRef]

11. Pretorius, E.; Mbotwe, S.; Bester, J.; Robinson, C.J.; Kell, D.B. Acute induction of anomalous and amyloidogenic blood clotting by molecular amplification of highly substoichiometric levels of bacterial lipopolysaccharide. *J. R. Soc. Interface* **2016**, *123*, 20160539. [CrossRef] [PubMed]

12. Pretorius, E.; Mbotwe, S.; Kell, D.B. Lipopolysaccharide-binding protein (LBP) reverses the amyloid state of fibrin seen in plasma of type 2 diabetics with cardiovascular comorbidities. *Sci. Rep.* **2017**, *7*, 9680. [CrossRef] [PubMed]

13. Pretorius, E.; Page, M.J.; Engelbrecht, L.; Ellis, G.C.; Kell, D.B. Substantial fibrin amyloidogenesis in type 2 diabetes assessed using amyloid-selective fluorescent stains. *Cardiovasc. Diabetol.* **2017**, *16*, 141. [CrossRef] [PubMed]

14. Pretorius, E.; Page, M.J.; Mbotwe, S.; Kell, D.B. Lipopolysaccharide-binding protein (LBP) can reverse the amyloid state of fibrin seen or induced in Parkinson's disease. *PLoS ONE* **2018**, *13*, e0192121. [CrossRef]

15. Pretorius, E.; Page, M.J.; Hendricks, L.; Nkosi, N.B.; Benson, S.R.; Kell, D.B. Both lipopolysaccharide and lipoteichoic acids potently induce anomalous fibrin amyloid formation: Assessment with novel Amytracker™ stains. *J. R. Soc. Interface* **2018**, *15*, 20170941. [CrossRef]

16. Pretorius, E.; Bester, J.; Page, M.J.; Kell, D.B. The potential of LPS-binding protein to reverse amyloid formation in plasma fibrin of individuals with Alzheimer-type dementia. *Front. Aging Neurosci.* **2018**, *10*, 257. [CrossRef]

17. Pretorius, E.; Venter, C.; Laubscher, G.J.; Lourens, P.J.; Steenkamp, J.; Kell, D.B. Prevalence of readily detected amyloid blood clots in 'unclotted' Type 2 Diabetes Mellitus and COVID-19 plasma: A preliminary report. *Cardiovasc. Diabetol.* **2020**, *19*, 193. [CrossRef]

18. Pretorius, E.; Venter, C.; Laubscher, G.J.; Kotze, M.J.; Oladejo, S.; Watson, L.R.; Rajaratnam, K.; Watson, B.W.; Kell, D.B. Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with Long COVID/Post-Acute Sequelae of COVID-19 (PASC). *Cardiovasc. Diabetol.* **2022**, *21*, 148. [CrossRef]

19. Turner, S.; Laubscher, G.J.; Khan, M.A.; Kell, D.B.; Pretorius, E. Rapid flow cytometric analysis of fibrin amyloid microclots in Long COVID. *Preprint* 2023. *submitted*.

20. Turner, S.; Laubscher, G.J.; Khan, M.A.; Kell, D.B.; Pretorius, E. Accelerating discovery: A novel flow cytometric method for detecting fibrin(ogen) amyloid microclots using long COVID as a model. *Heliyon* **2023**, *9*, e19605. [CrossRef]

21. Visser, M.J.E.; Pretorius, E. Atomic Force Microscopy: The Characterisation of Amyloid Protein Structure in Pathology. *Curr. Top. Med. Chem.* **2019**, *19*, 2958–2973. [CrossRef] [PubMed]

22. Pretorius, E.; Nunes, M.; Pretorius, J.; Kell, D.B. Flow Clotometry: Measuring Amyloid Microclots in ME/CFS, Long COVID, and Healthy Samples with Imaging Flow Cytometry. *Res. Sq.* **2024**. Available online: https://www.researchsquare.com/article/rs-4507472/v1 (accessed on 30 January 2025). [CrossRef]

23. Nunes, J.M.; Fillis, T.; Page, M.J.; Venter, C.; Lancry, O.; Kell, D.B.; Windberger, U.; Pretorius, E. Gingipain R1 and lipopolysaccharide from *Porphyromonas gingivalis* have major effects on blood clot morphology and mechanics. *Front. Immunol.* **2020**, *11*, 1551. [CrossRef] [PubMed]

24. Dalton, C.F.; de Oliveira, M.I.R.; Stafford, P.; Peake, N.; Kane, B.; Higham, A.; Singh, D.; Jackson, N.; Davies, H.; Price, D.; et al. Increased fibrinaloid microclot counts in platelet-poor plasma are associated with Long COVID. *medRxiv* **2024**. [CrossRef]

25. Schofield, J.; Abrams, S.T.; Jenkins, R.; Lane, S.; Wang, G.; Toh, C.H. Amyloid-fibrinogen aggregates ("microclots") predict risks of Disseminated Intravascular Coagulation and mortality. *Blood Adv.* **2024**, *8*, 2499–2508. [CrossRef]

26. Okuducu, Y.K.; Boribong, B.; Ellett, F.; Hajizadeh, S.; VanElzakker, M.; Haas, W.; Pillai, S.; Fasano, A.; Irimia, D.; Yonker, L. Evidence Circulating Microclots and Activated Platelets Contribute to Hyperinflammation Within Pediatric Post Acute Sequala of COVID. *Am. J. Respir. Crit. Care Med.* **2024**, *209*, A2247.

27. Bergaglio, T.; Synhaivska, O.; Nirmalraj, P.N. 3D Holo-tomographic Mapping of COVID-19 Microclots in Blood to Assess Disease Severity. *ACS Chem. Biomed. Imaging* **2024**, *2*, 194–204. [CrossRef]

28. Risman, R.A.; Kirby, N.C.; Bannish, B.E.; Hudson, N.E.; Tutwiler, V. Fibrinolysis: An illustrated review. *Res. Pract. Thromb. Haemost.* **2023**, *7*, 100081. [CrossRef]

29. Kell, D.B.; Pretorius, E. Proteomic evidence for amyloidogenic cross-seeding in fibrinaloid microclots. *Int. J. Mol.Sci.* **2024**, *25*, 10809. [CrossRef]

30. Ząbczyk, M.; Stachowicz, A.; Natorska, J.; Olszanecki, R.; Wiśniewski, J.R.; Undas, A. Plasma fibrin clot proteomics in healthy subjects: Relation to clot permeability and lysis time. *J. Proteom.* **2019**, *208*, 103487. [CrossRef]

31. Bondarev, S.A.; Antonets, K.S.; Kajava, A.V.; Nizhnikov, A.A.; Zhouravleva, G.A. Protein Co-Aggregation Related to Amyloids: Methods of Investigation, Diversity, and Classification. *Int. J. Mol. Sci.* **2018**, *19*, 2292. [CrossRef] [PubMed]

32. Letunica, N.; Van Den Helm, S.; McCafferty, C.; Swaney, E.; Cai, T.; Attard, C.; Karlaftis, V.; Monagle, P.; Ignjatovic, V. Proteomics in Thrombosis and Hemostasis. *Thromb. Haemost.* **2022**, *122*, 1076–1084. [CrossRef] [PubMed]

33. Edfors, F.; Iglesias, M.J.; Butler, L.M.; Odeberg, J. Proteomics in thrombosis research. *Res. Pract. Thromb. Haemost.* **2022**, *6*, e12706. [CrossRef] [PubMed]

34. Grixti, J.M.; Chandran, A.; Pretorius, J.-H.; Walker, M.; Sekhar, A.; Pretorius, E.; Kell, D.B. The clots removed from ischaemic stroke patients by mechanical thrombectomy are amyloid in nature. *medRxiv* **2024**. [CrossRef]

35. Kell, D.B.; Knowles, J.D. The role of modeling in systems biology. In *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts*; Szallasi, Z., Stelling, J., Periwal, V., Eds.; MIT Press: Cambridge, UK, 2006; pp. 3–18.

36. Kell, D.B.; Pretorius, E. Proteomic evidence for amyloidogenic cross-seeding in fibrinaloid microclots. *bioRxiv* **2024**, 2024.07.16.603837. [CrossRef]

37. Alonso-Orgaz, S.; Moreno-Luna, R.; López, J.A.; Gil-Dones, F.; Padial, L.R.; Moreu, J.; de la Cuesta, F.; Barderas, M.G. Proteomic characterization of human coronary thrombus in patients with ST-segment elevation acute myocardial infarction. *J. Proteom.* **2014**, *109*, 368–381. [CrossRef]

38. Stachowicz, A.; Siudut, J.; Suski, M.; Olszanecki, R.; Korbut, R.; Undas, A.; Wisniewski, J.R. Optimization of quantitative proteomic analysis of clots generated from plasma of patients with venous thromboembolism. *Clin. Proteom.* **2017**, *14*, 38. [CrossRef]

39. Pretorius, E.; Vlok, M.; Venter, C.; Bezuidenhout, J.A.; Laubscher, G.J.; Steenkamp, J.; Kell, D.B. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. *Cardiovasc. Diabetol.* **2021**, *20*, 172. [CrossRef]

40. Wiśniewski, J.R.; Rakus, D. Multi-enzyme digestion FASP and the 'Total Protein Approach'-based absolute quantification of the *Escherichia coli* proteome. *J. Proteom.* **2014**, *109*, 322–331. [CrossRef]

41. Bruzelius, M.; Iglesias, M.J.; Hong, M.G.; Sanchez-Rivera, L.; Gyorgy, B.; Souto, J.C.; Frånberg, M.; Fredolini, C.; Strawbridge, R.J.; Holmström, M.; et al. PDGFB, a new candidate plasma biomarker for venous thromboembolism: Results from the VEREMA affinity proteomics study. *Blood* **2016**, *128*, e59–e66. [CrossRef]

42. Grobler, C.; Maphumulo, S.C.; Grobbelaar, L.M.; Bredenkamp, J.; Laubscher, J.; Lourens, P.J.; Steenkamp, J.; Kell, D.B.; Pretorius, E. COVID-19: The Rollercoaster of Fibrin(ogen), D-dimer, von Willebrand Factor, P-selectin and Their Interactions with Endothelial Cells, Platelets and Erythrocytes. *Int. J. Mol. Sci.* **2020**, *21*, 5168. [CrossRef] [PubMed]

43. Jensen, S.B.; Hindberg, K.; Solomon, T.; Smith, E.N.; Lapek, J.D., Jr.; Gonzalez, D.J.; Latysheva, N.; Frazer, K.A.; Braekkan, S.K.; Hansen, J.B. Discovery of novel plasma biomarkers for future incident venous thromboembolism by untargeted synchronous precursor selection mass spectrometry proteomics. *J. Thromb. Haemost.* **2018**, *16*, 1763–1774. [CrossRef] [PubMed]

44. Ruberg, F.L.; Berk, J.L. Transthyretin (TTR) cardiac amyloidosis. *Circulation* **2012**, *126*, 1286–1300. [CrossRef]

45. Ankarcrona, M.; Winblad, B.; Monteiro, C.; Fearns, C.; Powers, E.T.; Johansson, J.; Westermark, G.T.; Presto, J.; Ericzon, B.G.; Kelly, J.W. Current and future treatment of amyloid diseases. *J. Intern. Med.* **2016**, *280*, 177–202. [CrossRef]

46. Subedi, S.; Sasidharan, S.; Nag, N.; Saudagar, P.; Tripathi, T. Amyloid Cross-Seeding: Mechanism, Implication, and Inhibition. *Molecules* **2022**, *27*, 1776. [CrossRef]

47. Prouse, T.; Mohammad, M.A.; Ghosh, S.; Kumar, N.; Duhaylungsod, M.L.; Majumder, R.; Majumder, S. Pancreatic Cancer and Venous Thromboembolism. *Int. J. Mol. Sci.* **2024**, *25*, 5661. [CrossRef]

48. An, J.; Jiang, T.; Qi, L.; Xie, K. Acinar cells and the development of pancreatic fibrosis. *Cytokine Growth Factor. Rev.* **2023**, *71–72*, 40–53. [CrossRef]

49. Pretorius, E.; Thierry, A.; Sanchez, C.; Ha, T.; Pastor, B.; Mirandola, A.; Pisareva, E.; Prevostel, C.; Laubscher, G.; Usher, T.; et al. Circulating microclots are structurally associated with Neutrophil Extracellular Traps and their amounts are strongly elevated in long COVID patients. *Res. Sq.* **2024**. Available online: https://www.researchsquare.com/article/rs-4666650/v1 (accessed on 30 January 2025). [CrossRef]

50. Bryk, A.H.; Natorska, J.; Ząbczyk, M.; Zettl, K.; Wisniewski, J.R.; Undas, A. Plasma fibrin clot proteomics in patients with acute pulmonary embolism: Association with clot properties. *J. Proteom.* **2020**, *229*, 103946. [CrossRef]

51. Kim, H.J.; Jeong, S.; Song, J.; Park, S.J.; Park, Y.J.; Oh, Y.H.; Jung, J.; Park, S.M. Risk of pulmonary embolism and deep vein thrombosis following COVID-19: A nationwide cohort study. *MedComm* **2024**, *5*, e655. [CrossRef]

52. Kell, D.B.; Khan, M.A.; Kane, B.; Lip, G.Y.H.; Pretorius, E. Possible Role of Fibrinaloid Microclots in Postural Orthostatic Tachycardia Syndrome (POTS): Focus on Long COVID. *J. Pers. Med.* **2024**, *14*, 170. [CrossRef]

53. Kell, D.B.; Khan, M.A.; Pretorius, R. Fibrinaloid microclots in Long COVID: Assessing the actual evidence properly. *Res. Pract. Thromb. Haemost.* **2024**, *8*, 102566. [CrossRef] [PubMed]

54. Turner, S.; Naidoo, C.; Usher, T.; Kruger, A.; Venter, C.; Laubscher, G.J.; Khan, M.A.; Kell, D.B.; Pretorius, E. Increased levels of inflammatory molecules in blood of Long COVID patients point to thrombotic endotheliitis. *medRxiv* **2022**, 2022.10.13.22281055.

55. Grobbelaar, L.M.; Venter, C.; Vlok, M.; Ngoepe, M.; Laubscher, G.J.; Lourens, P.J.; Steenkamp, J.; Kell, D.B.; Pretorius, E. SARS-CoV-2 spike protein S1 induces fibrin(ogen) resistant to fibrinolysis: Implications for microclot formation in COVID-19. *Biosci. Rep.* **2021**, *41*, BSR20210611. [CrossRef]

56. Kell, D.B.; Pretorius, E. The potential role of ischaemia-reperfusion injury in chronic, relapsing diseases such as rheumatoid arthritis, long COVID and ME/CFS: Evidence, mechanisms, and therapeutic implications. *Biochem. J.* **2022**, *479*, 1653–1708.

57. Kell, D.B.; Khan, M.A.; Laubscher, G.J.; Pretorius, E. The aetiological involvement of fibrin amyloid microclots in PASC/Long COVID. *J. Thromb. Haemost.* **2023**. *submitted*.

58. Laubscher, G.J.; Lourens, P.J.; Venter, C.; Kell, D.B.; Pretorius, E. TEG®, Microclot and Platelet Mapping for Guiding Early Management of Severe COVID-19 Coagulopathy. *J. Clin. Med.* **2021**, *10*, 5381. [CrossRef]

59. Laubscher, G.J.; Khan, M.A.; Venter, C.; Pretorius, J.H.; Kell, D.B.; Pretorius, E. Treatment of Long COVID Symptoms with Triple Anticoagulant Therapy. 2023. Available online: https://www.researchsquare.com/article/rs-2697680/v1 (accessed on 30 January 2025). [CrossRef]

60. Turner, S.; Khan, M.A.; Putrino, D.; Woodcock, A.; Kell, D.B.; Pretorius, E. Long COVID: Pathophysiological factors and abnormal coagulation. *Trends Endocrinol. Metab.* **2023**, *34*, 321–344. [CrossRef]

61. Turner, S.; Naidoo, C.A.; Usher, T.J.; Kruger, A.; Venter, C.; Laubscher, G.J.; Khan, M.A.; Kell, D.B.; Pretorius, E. Increased Levels of Inflammatory and Endothelial Biomarkers in Blood of Long COVID Patients Point to Thrombotic Endothelialitis. *Semin. Thromb. Hemost.* **2023**, *50*, 288–294. [CrossRef] [PubMed]

62. Ząbczyk, M.; Kruk, A.; Natorska, J.; Undas, A. Low-grade endotoxemia in acute pulmonary embolism: Links with prothrombotic plasma fibrin clot phenotype. *Thromb. Res.* **2023**, *232*, 70–76. [CrossRef]

63. Ząbczyk, M.; Natorska, J.; Janion-Sadowska, A.; Malinowski, K.P.; Janion, M.; Undas, A. Elevated Lactate Levels in Acute Pulmonary Embolism Are Associated with Prothrombotic Fibrin Clot Properties: Contribution of NETs Formation. *J. Clin. Med.* **2020**, *9*, 953. [CrossRef]

64. Ząbczyk, M.; Plens, K.; Wojtowicz, W.; Undas, A. Prothrombotic Fibrin Clot Phenotype Is Associated with Recurrent Pulmonary Embolism After Discontinuation of Anticoagulant Therapy. *Arterioscler. Thromb. Vasc. Biol.* **2017**, *37*, 365–373. [CrossRef]

65. Bryk, A.H.; Prior, S.M.; Plens, K.; Konieczynska, M.; Hohendorff, J.; Malecki, M.T.; Butenas, S.; Undas, A. Predictors of neutrophil extracellular traps markers in type 2 diabetes mellitus: Associations with a prothrombotic state and hypofibrinolysis. *Cardiovasc. Diabetol.* **2019**, *18*, 49. [CrossRef] [PubMed]

66. de Waal, G.M.; Engelbrecht, L.; Davis, T.; de Villiers, W.J.S.; Kell, D.B.; Pretorius, E. Correlative Light-Electron Microscopy detects lipopolysaccharide and its association with fibrin fibres in Parkinson's Disease, Alzheimer's Disease and Type 2 Diabetes Mellitus. *Sci. Rep.* **2018**, *8*, 16798. [CrossRef]

67. Grixti, J.M.; Theron, C.W.; Salcedo-Sora, J.E.; Pretorius, E.; Kell, D.B. Automated microscopic measurement of fibrinaloid microclots and their degradation by nattokinase, the main natto protease. *bioRxiv* **2024**. [CrossRef]

68. Pretorius, E.; Kell, D.B. A Perspective on How Fibrinaloid Microclots and Platelet Pathology May Be Applied in Clinical Investigations. *Semin. Thromb. Hemost.* **2024**, *50*, 537–551. [CrossRef]

69. Galanaud, J.P.; Kahn, S.R. The post-thrombotic syndrome: A 2012 therapeutic update. *Curr. Treat. Options Cardiovasc. Med.* **2013**, *15*, 153–163. [CrossRef]

70. Guo, X.; Xu, H.; Zhang, J.; Hao, B.; Yang, T. A systematic review and meta-analysis of risk prediction models for post-thrombotic syndrome in patients with deep vein thrombosis. *Heliyon* **2023**, *9*, e22226. [CrossRef]

71. Kalaidopoulou Nteak, S.; Völlmy, F.; Lukassen, M.V.; van den Toorn, H.; den Boer, M.A.; Bondt, A.; van der Lans, S.P.A.; Haas, P.J.; van Zuilen, A.D.; Rooijakkers, S.H.M.; et al. Longitudinal Fluctuations in Protein Concentrations and Higher-Order Structures in the Plasma Proteome of Kidney Failure Patients Subjected to a Kidney Transplant. *J. Proteome Res.* **2024**, *23*, 2124–2136. [CrossRef]

72. Zhang, K.; Wang, P.; Huang, W.; Tang, S.H.; Xue, H.; Wu, H.; Zhang, Y.; Rong, Y.; Dong, S.S.; Chen, J.B.; et al. Integrated landscape of plasma metabolism and proteome of patients with post-traumatic deep vein thrombosis. *Nat. Commun.* **2024**, *15*, 7831. [CrossRef]

73. Suhr, O.B.; Lundgren, E.; Westermark, P. One mutation, two distinct disease variants: Unravelling the impact of transthyretin amyloid fibril composition. *J. Intern. Med.* **2017**, *281*, 337–347. [CrossRef]

74. Ten Cate-Hoek, A.J. Prevention and treatment of the post-thrombotic syndrome. *Res. Pract. Thromb. Haemost.* **2018**, *2*, 209–219. [CrossRef]

75. Baldwin, M.J.; Moore, H.M.; Rudarakanchana, N.; Gohel, M.; Davies, A.H. Post-thrombotic syndrome: A clinical review. *J. Thromb. Haemost.* **2013**, *11*, 795–805. [CrossRef] [PubMed]

76. Pikovsky, O.; Rabinovich, A. Prevention and treatment of the post-thrombotic syndrome. *Thromb. Res.* **2018**, *164*, 116–124. [CrossRef] [PubMed]

77. Hull, R.D.; Liang, J.; Townshend, G. Long-term low-molecular-weight heparin and the post-thrombotic syndrome: A systematic review. *Am. J. Med.* **2011**, *124*, 756–765. [CrossRef] [PubMed]

78. Rossi, R.; Mereuta, O.M.; Barbachan, E.S.M.; Molina Gil, S.; Douglas, A.; Pandit, A.; Gilvarry, M.; McCarthy, R.; O'Connell, S.; Tierney, C.; et al. Potential Biomarkers of Acute Ischemic Stroke Etiology Revealed by Mass Spectrometry-Based Proteomic Characterization of Formalin-Fixed Paraffin-Embedded Blood Clots. *Front. Neurol.* **2022**, *13*, 854846. [CrossRef]

79. Ji, H.; Chen, S.; Hu, Q.; He, Y.; Zhou, L.; Xie, J.; Pan, H.; Tong, X.; Wu, C. Investigating the Correlation between Serum Amyloid A and Infarct-Related Artery Patency Prior to Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction Patients. *Angiology* **2024**, *75*, 585–594. [CrossRef]

80. Časl, M.T.; Surina, B.; Glojnarić-Spasić, I.; Pape, E.; Jagarinec, N.; Kranjčević, S. Serum amyloid A protein in patients with acute myocardial infarction. *Ann. Clin. Biochem.* **1995**, *32 Pt 2*, 196–200. [CrossRef]

81. Moore, E.E.; Moore, H.B.; Kornblith, L.Z.; Neal, M.D.; Hoffman, M.; Mutch, N.J.; Schöchl, H.; Hunt, B.J.; Sauaia, A. Trauma-induced coagulopathy. *Nat. Rev. Dis. Primers* **2021**, *7*, 30. [CrossRef]

82. Chang, R.; Cardenas, J.C.; Wade, C.E.; Holcomb, J.B. Advances in the understanding of trauma-induced coagulopathy. *Blood* **2016**, *128*, 1043–1049. [CrossRef]

83. Kornblith, L.Z.; Moore, H.B.; Cohen, M.J. Trauma-induced coagulopathy: The past, present, and future. *J. Thromb. Haemost.* **2019**, *17*, 852–862. [CrossRef]

84. Fletcher-Sandersjöö, A.; Thelin, E.P.; Maegele, M.; Svensson, M.; Bellander, B.M. Time Course of Hemostatic Disruptions After Traumatic Brain Injury: A Systematic Review of the Literature. *Neurocrit. Care* **2021**, *34*, 635–656. [CrossRef]

85. Meizoso, J.P.; Moore, E.E.; Pieracci, F.M.; Saberi, R.A.; Ghasabyan, A.; Chandler, J.; Namias, N.; Sauaia, A. Role of Fibrinogen in Trauma-Induced Coagulopathy. *J. Am. Coll. Surg.* **2022**, *234*, 465–473. [CrossRef]

86. Coleman, J.R.; D'Alessandro, A.; LaCroix, I.; Dzieciatkowska, M.; Lutz, P.; Mitra, S.; Gamboni, F.; Ruf, W.; Silliman, C.C.; Cohen, M.J. A metabolomic and proteomic analysis of pathologic hypercoagulability in traumatic brain injury patients after dura violation. *J. Trauma. Acute Care Surg.* **2023**, *95*, 925–934. [CrossRef]

87. Coleman, J.R.; Moore, E.E.; Schmitt, L.; Hansen, K.; Dow, N.; Freeman, K.; Cohen, M.J.; Silliman, C.C. Estradiol provokes hypercoagulability and affects fibrin biology: A mechanistic exploration of sex dimorphisms in coagulation. *J. Trauma. Acute Care Surg.* **2023**, *94*, 179–186. [CrossRef]

88. Swanepoel, A.C.; Lindeque, B.G.; Swart, P.J.; Abdool, Z.; Pretorius, E. Estrogen causes ultrastructural changes of fibrin networks during the menstrual cycle: A qualitative investigation. *Microsc. Res. Tech.* **2014**, *77*, 594–601. [CrossRef]

89. Coleman, J.R.; Gumina, R.; Hund, T.; Cohen, M.; Neal, M.D.; Townsend, K.; Kerlin, B.A. Sex dimorphisms in coagulation: Implications in trauma-induced coagulopathy and trauma resuscitation. *Am. J. Hematol.* **2024**, *99* (Suppl. 1), S28–S35. [CrossRef]

90. Sun, T.; Zhang, L. Thrombosis in myeloproliferative neoplasms with JAK2V617F mutation. *Clin. Appl. Thromb. Hemost.* **2013**, *19*, 374–381. [CrossRef]

91. Kuykendall, A.T.; Fine, J.T.; Kremyanskaya, M. Contemporary Challenges in Polycythemia Vera Management From the Perspective of Patients and Physicians. *Clin. Lymphoma Myeloma Leuk.* **2024**, *24*, 512–522. [CrossRef]

92. Barbui, T.; Tefferi, A.; Vannucchi, A.M.; Passamonti, F.; Silver, R.T.; Hoffman, R.; Verstovsek, S.; Mesa, R.; Kiladjian, J.J.; Hehlmann, R.; et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: Revised management recommendations from European LeukemiaNet. *Leukemia* **2018**, *32*, 1057–1069. [CrossRef]

93. Kroll, M.H.; Michaelis, L.C.; Verstovsek, S. Mechanisms of thrombogenesis in polycythemia vera. *Blood Rev.* **2015**, *29*, 215–221. [CrossRef]

94. Griesshammer, M.; Kiladjian, J.J.; Besses, C. Thromboembolic events in polycythemia vera. *Ann. Hematol.* **2019**, *98*, 1071–1082. [CrossRef]

95. Schmidt, S.; Daniliants, D.; Hiller, E.; Gunsilius, E.; Wolf, D.; Feistritzer, C. Increased levels of NETosis in myeloproliferative neoplasms are not linked to thrombotic events. *Blood Adv.* **2021**, *5*, 3515–3527. [CrossRef] [PubMed]

96. Guy, A.; Favre, S.; Labrouche-Colomer, S.; Deloison, L.; Gourdou-Latyszenok, V.; Renault, M.A.; Riviere, E.; James, C. High circulating levels of MPO-DNA are associated with thrombosis in patients with MPN. *Leukemia* **2019**, *33*, 2544–2548. [CrossRef]

97. Guy, A.; Garcia, G.; Gourdou-Latyszenok, V.; Wolff-Trombini, L.; Josserand, L.; Kimmerlin, Q.; Favre, S.; Kilani, B.; Marty, C.; Boulaftali, Y.; et al. Platelets and neutrophils cooperate to induce increased neutrophil extracellular trap formation in JAK2V617F myeloproliferative neoplasms. *J. Thromb. Haemost.* **2024**, *22*, 172–187. [CrossRef]

98. Tan, G.; Wolski, W.E.; Kummer, S.; Hofstetter, M.; Theocharides, A.P.A.; Manz, M.G.; Aebersold, R.; Meier-Abt, F. Proteomic identification of proliferation and progression markers in human polycythemia vera stem and progenitor cells. *Blood Adv.* **2022**, *6*, 3480–3493. [CrossRef]

99. Kelliher, S.; Gamba, S.; Weiss, L.; Shen, Z.; Marchetti, M.; Schieppati, F.; Scaife, C.; Madden, S.; Bennett, K.; Fortune, A.; et al. Platelet proteomic profiling reveals potential mediators of immunothrombosis and proteostasis in myeloproliferative neoplasms. *Blood Adv.* **2024**, *8*, 4276–4280. [CrossRef]

100. Raman, I.; Bennett, C.; Juneja, S.; Costas, K.Y.; Indran, T.; Pasricha, S.-R. Dysregulated Complement Activation in Polycythemia Vera: A Novel Mechanism for Thrombosis in Myeloproliferative Neoplasms Uncovered By Proteomic Analysis. *Blood* **2024**, *144* (Supp. 1), 4417. [CrossRef]

101. Donkor, E.S. Stroke in the 21(st) Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Res. Treat.* **2018**, *2018*, 3238165. [CrossRef]

102. Powers, W.J. Acute Ischemic Stroke. *N. Engl. J. Med.* **2020**, *383*, 252–260. [CrossRef]

103. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* **2021**, *20*, 795–820. [CrossRef]

104. He, Q.; Wang, W.; Zhang, Y.; Xiong, Y.; Tao, C.; Ma, L.; Ma, J.; You, C.; Wang, C. Global, Regional, and National Burden of Stroke, 1990–2021: A Systematic Analysis for Global Burden of Disease 2021. *Stroke* **2024**, *55*, 2815–2824. [CrossRef]

105. Pretorius, E.; Windberger, U.B.; Oberholzer, H.M.; Auer, R.E. Comparative ultrastructure of fibrin networks of a dog after thrombotic ischaemic stroke. *Onderstepoort J. Vet. Res.* **2010**, *77*, E1–E4. [CrossRef]

106. Pretorius, E.; Swanepoel, A.C.; Oberholzer, H.M.; van der Spuy, W.J.; Duim, W.; Wessels, P.F. A descriptive investigation of the ultrastructure of fibrin networks in thrombo-embolic ischemic stroke. *J. Thromb. Thrombolysis* **2011**, *31*, 507–513. [CrossRef]

107. Pretorius, E.; Steyn, H.; Engelbrecht, M.; Swanepoel, A.C.; Oberholzer, H.M. Differences in fibrin fiber diameters in healthy individuals and thromboembolic ischemic stroke patients. *Blood Coagul. Fibrinolysis* **2011**, *22*, 696–700. [CrossRef]

108. O'Connell, G.C.; Walsh, K.B.; Burrage, E.; Adeoye, O.; Chantler, P.D.; Barr, T.L. High-throughput profiling of the circulating proteome suggests sexually dimorphic corticosteroid signaling following ischemic stroke. *Physiol. Genom.* **2018**, *50*, 876–883. [CrossRef]

109. Penn, A.M.; Saly, V.; Trivedi, A.; Lesperance, M.L.; Votova, K.; Jackson, A.M.; Croteau, N.S.; Balshaw, R.F.; Bibok, M.B.; Smith, D.S.; et al. Differential Proteomics for Distinguishing Ischemic Stroke from Controls: A Pilot Study of the SpecTRA Project. *Transl. Stroke Res.* **2018**, *9*, 590–599. [CrossRef]

110. Kell, D.B.; Lip, G.Y.H.; Pretorius, E. Fibrinaloid Microclots and Atrial Fibrillation. *Biomedicines* **2024**, *12*, 891. [CrossRef]

111. Bartus, K.; Litwinowicz, R.; Natorska, J.; Zabczyk, M.; Undas, A.; Kapelak, B.; Lakkireddy, D.; Lee, R.J. Coagulation factors and fibrinolytic activity in the left atrial appendage and other heart chambers in patients with atrial fibrillation: Is there a local intracardiac prothrombotic state? (HEART-CLOT study). *Int. J. Cardiol.* **2020**, *301*, 103–107. [CrossRef]

112. Mołek, P.; Ząbczyk, M.; Malinowski, K.P.; Natorska, J.; Undas, A. Markers of NET formation and stroke risk in patients with atrial fibrillation: Association with a prothrombotic state. *Thromb. Res.* **2022**, *213*, 1–7. [CrossRef]

113. Glowicki, B.; Matusik, P.T.; Plens, K.; Undas, A. Prothrombotic State in Atrial Fibrillation Patients With One Additional Risk Factor of the CHA(2)DS(2)-VASc Score (Beyond Sex). *Can. J. Cardiol.* **2019**, *35*, 634–643. [CrossRef]

114. Penn, A.M.; Bibok, M.B.; Saly, V.K.; Coutts, S.B.; Lesperance, M.L.; Balshaw, R.F.; Votova, K.; Croteau, N.S.; Trivedi, A.; Jackson, A.M.; et al. Validation of a proteomic biomarker panel to diagnose minor-stroke and transient ischaemic attack: Phase 2 of SpecTRA, a large scale translational study. *Biomarkers* **2018**, *23*, 793–803. [CrossRef]

115. Penn, A.M.; Bibok, M.B.; Saly, V.K.; Coutts, S.B.; Lesperance, M.L.; Balshaw, R.F.; Votova, K.; Croteau, N.S.; Trivedi, A.; Jackson, A.M.; et al. Verification of a proteomic biomarker panel to diagnose minor stroke and transient ischaemic attack: Phase 1 of SpecTRA, a large scale translational study. *Biomarkers* **2018**, *23*, 392–405. [CrossRef]

116. Bale, M.D.; Westrick, L.G.; Mosher, D.F. Incorporation of thrombospondin into fibrin clots. *J. Biol. Chem.* **1985**, *260*, 7502–7508. [CrossRef]

117. Bale, M.D.; Mosher, D.F. Effects of thrombospondin on fibrin polymerization and structure. *J. Biol. Chem.* **1986**, *261*, 862–868. [CrossRef]

118. Bale, M.D. Noncovalent and covalent interactions of thrombospondin with polymerizing fibrin. *Semin. Thromb. Hemost.* **1987**, *13*, 326–334. [CrossRef]

119. Bale, M.D.; Mosher, D.F. Thrombospondin is a substrate for blood coagulation factor XIIIa. *Biochemistry* **1986**, *25*, 5667–5673. [CrossRef]

120. Lopez-Pedrera, C.; Oteros, R.; Ibáñez-Costa, A.; Luque-Tévar, M.; Muñoz-Barrera, L.; Barbarroja, N.; Chicano-Gálvez, E.; Marta-Enguita, J.; Orbe, J.; Velasco, F.; et al. The thrombus proteome in stroke reveals a key role of the innate immune system and new insights associated with its etiology, severity, and prognosis. *J. Thromb. Haemost.* **2023**, *21*, 2894–2907. [CrossRef]

121. Staessens, S.; Francois, O.; Brinjikji, W.; Doyle, K.M.; Vanacker, P.; Andersson, T.; De Meyer, S.F. Studying Stroke Thrombus Composition After Thrombectomy: What Can We Learn? *Stroke* **2021**, *52*, 3718–3727. [CrossRef]

122. Staessens, S.; Francois, O.; Desender, L.; Vanacker, P.; Dewaele, T.; Sciot, R.; Vanhoorelbeke, K.; Andersson, T.; De Meyer, S.F. Detailed histological analysis of a thrombectomy-resistant ischemic stroke thrombus: A case report. *Thromb. J.* **2021**, *19*, 11. [CrossRef]

123. Genchi, A.; Semerano, A.; Gullotta, G.S.; Strambo, D.; Schwarz, G.; Bergamaschi, A.; Panni, P.; Simionato, F.; Scomazzoni, F.; Michelozzi, C.; et al. Cerebral thrombi of cardioembolic etiology have an increased content of neutrophil extracellular traps. *J. Neurol. Sci.* **2021**, *423*, 117355. [CrossRef]

124. Vandelanotte, S.; Staessens, S.; Francois, O.; De Wilde, M.; Desender, L.; De Sloovere, A.S.; Dewaele, T.; Tersteeg, C.; Vanhoorelbeke, K.; Vanacker, P.; et al. Association between thrombus composition and first-pass recanalization after thrombectomy in acute ischemic stroke. *J. Thromb. Haemost.* **2024**, *22*, 2555–2561. [CrossRef]

125. Muñoz, R.; Santamaría, E.; Rubio, I.; Ausín, K.; Ostolaza, A.; Labarga, A.; Roldán, M.; Zandio, B.; Mayor, S.; Bermejo, R.; et al. Mass Spectrometry-Based Proteomic Profiling of Thrombotic Material Obtained by Endovascular Thrombectomy in Patients with Ischemic Stroke. *Int. J. Mol. Sci.* **2018**, *19*, 498. [CrossRef] [PubMed]

126. Prochazka, V.; Jonszta, T.; Czerny, D.; Krajca, J.; Roubec, M.; Macak, J.; Kovar, P.; Kovarova, P.; Pulcer, M.; Zoubkova, R.; et al. The Role of von Willebrand Factor, ADAMTS13, and Cerebral Artery Thrombus Composition in Patient Outcome Following Mechanical Thrombectomy for Acute Ischemic Stroke. *Med. Sci. Monit.* **2018**, *24*, 3929–3945. [CrossRef] [PubMed]

127. Rana, R.; Chauhan, K.; Gautam, P.; Kulkarni, M.; Banarjee, R.; Chugh, P.; Chhabra, S.S.; Acharya, R.; Kalra, S.K.; Gupta, A.; et al. Plasma-Derived Extracellular Vesicles Reveal Galectin-3 Binding Protein as Potential Biomarker for Early Detection of Glioma. *Front. Oncol.* **2021**, *11*, 778754. [CrossRef]

128. Nielsen, C.T.; Lood, C.; Østergaard, O.; Iversen, L.V.; Voss, A.; Bengtsson, A.; Jacobsen, S.; Heegaard, N.H.H. Plasma levels of galectin-3-binding protein reflect type I interferon activity and are increased in patients with systemic lupus erythematosus. *Lupus Sci. Med.* **2014**, *1*, e000026. [CrossRef]

129. Loimaranta, V.; Hepojoki, J.; Laaksoaho, O.; Pulliainen, A.T. Galectin-3-binding protein: A multitask glycoprotein with innate immunity functions in viral and bacterial infections. *J. Leukoc. Biol.* **2018**, *104*, 777–786. [CrossRef]

130. Rasmussen, N.S.; Draborg, A.H.; Houen, G.; Nielsen, C.T. Human herpesvirus infections and circulating microvesicles expressing galectin-3 binding protein in patients with systemic lupus erythematosus. *Clin. Exp. Rheumatol.* **2022**, *40*, 158–161. [CrossRef]

131. Zhen, S.; Cai, R.; Yang, X.; Ma, Y.; Wen, D. Association of Serum Galectin-3-Binding Protein and Metabolic Syndrome in a Chinese Adult Population. *Front. Endocrinol.* **2021**, *12*, 726154. [CrossRef]

132. Zhen, S.; Ma, Y.; Han, Y.; Zhao, Z.; Yang, X.; Wen, D. Serum galectin-3BP as a novel marker of obesity and metabolic syndrome in Chinese adolescents. *BMJ Open Diabetes Res. Care* **2021**, *9*, e001894. [CrossRef]

133. Capone, E.; Iacobelli, S.; Sala, G. Role of galectin 3 binding protein in cancer progression: A potential novel therapeutic target. *J. Transl. Med.* **2021**, *19*, 405. [CrossRef]

134. Park, D.D.; Xu, G.; Park, S.S.; Haigh, N.E.; Phoomak, C.; Wongkham, S.; Maverakis, E.; Lebrilla, C.B. Combined analysis of secreted proteins and glycosylation identifies prognostic features in cholangiocarcinoma. *J. Cell. Physiol.* **2024**, *239*, e31147. [CrossRef]

135. DeRoo, E.P.; Wrobleski, S.K.; Shea, E.M.; Al-Khalil, R.K.; Hawley, A.E.; Henke, P.K.; Myers, D.D., Jr.; Wakefield, T.W.; Diaz, J.A. The role of galectin-3 and galectin-3-binding protein in venous thrombosis. *Blood* **2015**, *125*, 1813–1821. [CrossRef] [PubMed]

136. Nielsen, C.T.; Østergaard, O.; Rasmussen, N.S.; Jacobsen, S.; Heegaard, N.H.H. A review of studies of the proteomes of circulating microparticles: Key roles for galectin-3-binding protein-expressing microparticles in vascular diseases and systemic lupus erythematosus. *Clin. Proteom.* **2017**, *14*, 11. [CrossRef] [PubMed]

137. Peretz, A.S.R.; Rasmussen, N.S.; Jacobsen, S.; Sjowall, C.; Nielsen, C.T. Galectin-3-binding protein is a novel predictor of venous thromboembolism in systemic lupus erythematosus. *Clin. Exp. Rheumatol.* **2021**, *39*, 1360–1368. [CrossRef]

138. Hansen, E.S.; Edvardsen, M.S.; Aukrust, P.; Ueland, T.; Hansen, J.B.; Braekkan, S.K.; Morelli, V.M. Galectin-3-binding protein and future venous thromboembolism. *Res. Pract. Thromb. Haemost.* **2024**, *8*, 102311. [CrossRef]

139. Nielsen, C.T.; Ostergaard, O.; Rekvig, O.P.; Sturfelt, G.; Jacobsen, S.; Heegaard, N.H. Galectin-3 binding protein links circulating microparticles with electron dense glomerular deposits in lupus nephritis. *Lupus* **2015**, *24*, 1150–1160. [CrossRef]

140. Anupama, Y.J.; Vankalakunti, M. Rapidly progressive glomerulonephritis in a patient with renal amyloidosis: Case report and review of the literature. *Indian J. Nephrol.* **2012**, *22*, 377–380. [CrossRef]

141. Feitosa, V.A.; Neves, P.; Jorge, L.B.; Noronha, I.L.; Onuchic, L.F. Renal amyloidosis: A new time for a complete diagnosis. *Braz. J. Med. Biol. Res.* **2022**, *55*, e12284. [CrossRef]

142. Gurung, R.; Li, T. Renal Amyloidosis: Presentation, Diagnosis, and Management. *Am. J. Med.* **2022**, *135* (Suppl. 1), S38–S43. [CrossRef]

143. Ryšavá, R. AL amyloidosis: Advances in diagnostics and treatment. *Nephrol. Dial. Transplant.* **2019**, *34*, 1460–1466. [CrossRef]

144. Fedotov, S.A.; Khrabrova, M.S.; Anpilova, A.O.; Dobronravov, V.A.; Rubel, A.A. Noninvasive Diagnostics of Renal Amyloidosis: Current State and Perspectives. *Int. J. Mol. Sci.* **2022**, *23*, 12662. [CrossRef]

145. Karam, S.; Haidous, M.; Royal, V.; Leung, N. Renal AA amyloidosis: Presentation, diagnosis, and current therapeutic options: A review. *Kidney Int.* **2023**, *103*, 473–484. [CrossRef] [PubMed]

146. Leung, N.; Nasr, S.H. 2024 Update on Classification, Etiology, and Typing of Renal Amyloidosis: A Review. *Am. J. Kidney Dis.* **2024**, *84*, 361–373. [CrossRef] [PubMed]

147. Tao, C.C.; Cheng, K.M.; Ma, Y.L.; Hsu, W.L.; Chen, Y.C.; Fuh, J.L.; Lee, W.J.; Chao, C.C.; Lee, E.H.Y. Galectin-3 promotes Abeta oligomerization and Abeta toxicity in a mouse model of Alzheimer's disease. *Cell Death Differ.* **2020**, *27*, 192–209. [CrossRef]

148. Nishi, Y.; Sano, H.; Kawashima, T.; Okada, T.; Kuroda, T.; Kikkawa, K.; Kawashima, S.; Tanabe, M.; Goto, T.; Matsuzawa, Y.; et al. Role of galectin-3 in human pulmonary fibrosis. *Allergol. Int.* **2007**, *56*, 57–65. [CrossRef]

149. Li, L.C.; Li, J.; Gao, J. Functions of galectin-3 and its role in fibrotic diseases. *J. Pharmacol. Exp. Ther.* **2014**, *351*, 336–343. [CrossRef]

150. Slack, R.J.; Mills, R.; Mackinnon, A.C. The therapeutic potential of galectin-3 inhibition in fibrotic disease. *Int. J. Biochem. Cell Biol.* **2021**, *130*, 105881. [CrossRef]

151. Hara, A.; Niwa, M.; Noguchi, K.; Kanayama, T.; Niwa, A.; Matsuo, M.; Hatano, Y.; Tomita, H. Galectin-3 as a Next-Generation Biomarker for Detecting Early Stage of Various Diseases. *Biomolecules* **2020**, *10*, 389. [CrossRef]

152. Dong, R.; Zhang, M.; Hu, Q.; Zheng, S.; Soh, A.; Zheng, Y.; Yuan, H. Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review). *Int. J. Mol. Med.* **2018**, *41*, 599–614. [CrossRef]

153. Lima, T.; Perpetuo, L.; Henrique, R.; Fardilha, M.; Leite-Moreira, A.; Bastos, J.; Vitorino, R. Galectin-3 in prostate cancer and heart diseases: A biomarker for these two frightening pathologies? *Mol. Biol. Rep.* **2023**, *50*, 2763–2778. [CrossRef]

154. Clementy, N.; Benhenda, N.; Piver, E.; Pierre, B.; Bernard, A.; Fauchier, L.; Pages, J.C.; Babuty, D. Serum Galectin-3 Levels Predict Recurrences after Ablation of Atrial Fibrillation. *Sci. Rep.* **2016**, *6*, 34357. [CrossRef]

155. Clementy, N.; Garcia, B.; Andre, C.; Bisson, A.; Benhenda, N.; Pierre, B.; Bernard, A.; Fauchier, L.; Piver, E.; Babuty, D. Galectin-3 level predicts response to ablation and outcomes in patients with persistent atrial fibrillation and systolic heart failure. *PLoS ONE* **2018**, *13*, e0201517. [CrossRef] [PubMed]

156. Hara, A.; Niwa, M.; Kanayama, T.; Noguchi, K.; Niwa, A.; Matsuo, M.; Kuroda, T.; Hatano, Y.; Okada, H.; Tomita, H. Galectin-3: A Potential Prognostic and Diagnostic Marker for Heart Disease and Detection of Early Stage Pathology. *Biomolecules* **2020**, *10*, 1277. [CrossRef] [PubMed]

157. Lippi, G.; Cervellin, G.; Sanchis-Gomar, F. Galectin-3 in atrial fibrillation: Simple bystander, player or both? *Clin. Biochem.* **2015**, *48*, 818–822. [CrossRef] [PubMed]

158. Gong, M.; Cheung, A.; Wang, Q.S.; Li, G.; Goudis, C.A.; Bazoukis, G.; Lip, G.Y.H.; Baranchuk, A.; Korantzopoulos, P.; Letsas, K.P.; et al. Galectin-3 and risk of atrial fibrillation: A systematic review and meta-analysis. *J. Clin. Lab. Anal.* **2020**, *34*, e23104. [CrossRef]

159. Seki, T.; Kanagawa, M.; Kobayashi, K.; Kowa, H.; Yahata, N.; Maruyama, K.; Iwata, N.; Inoue, H.; Toda, T. Galectin 3-binding protein suppresses amyloid-beta production by modulating beta-cleavage of amyloid precursor protein. *J. Biol. Chem.* **2020**, *295*, 3678–3691. [CrossRef]

160. Houlahan, C.B.; Kong, Y.; Johnston, B.; Cielesh, M.; Chau, T.H.; Fenwick, J.; Coleman, P.R.; Hao, H.; Haltiwanger, R.S.; Thaysen-Andersen, M.; et al. Analysis of the Healthy Platelet Proteome Identifies a New Form of Domain-Specific O-Fucosylation. *Mol. Cell. Proteom.* **2024**, *23*, 100717. [CrossRef]

161. Buda, V.; Andor, M.; Cristescu, C.; Tomescu, M.C.; Muntean, D.M.; Baibata, D.E.; Bordejevic, D.A.; Danciu, C.; Dalleur, O.; Coricovac, D.; et al. Thrombospondin-1 Serum Levels in Hypertensive Patients with Endothelial Dysfunction After One Year of Treatment with Perindopril. *Drug Des. Dev. Ther.* **2019**, *13*, 3515–3526. [CrossRef]

162. Bonnefoy, A.; Moura, R.; Hoylaerts, M.F. The evolving role of thrombospondin-1 in hemostasis and vascular biology. *Cell. Mol. Life Sci.* **2008**, *65*, 713–727. [CrossRef]

163. Zhang, K.; Li, M.; Yin, L.; Fu, G.; Liu, Z. Role of thrombospondin-1 and thrombospondin-2 in cardiovascular diseases (Review). *Int. J. Mol. Med.* **2020**, *45*, 1275–1293. [CrossRef]

164. Liu, B.; Yang, H.; Song, Y.S.; Sorenson, C.M.; Sheibani, N. Thrombospondin-1 in vascular development, vascular function, and vascular disease. *Semin. Cell Dev. Biol.* **2024**, *155*, 32–44. [CrossRef]

165. Gutierrez, L.S.; Gutierrez, J. Thrombospondin 1 in Metabolic Diseases. *Front. Endocrinol.* **2021**, *12*, 638536. [CrossRef] [PubMed]

166. Liao, W.; Xu, L.; Pan, Y.; Wei, J.; Wang, P.; Yang, X.; Chen, M.; Gao, Y. Association of atrial arrhythmias with thrombospondin-1 in patients with acute myocardial infarction. *BMC Cardiovasc. Disord.* **2021**, *21*, 507. [CrossRef] [PubMed]

167. Tabary, M.; Gheware, A.; Penaloza, H.F.; Lee, J.S. The matricellular protein thrombospondin-1 in lung inflammation and injury. *Am. J. Physiol. Cell Physiol.* **2022**, *323*, C857–C865. [CrossRef] [PubMed]

168. Ohta, Y.; Shridhar, V.; Kalemkerian, G.P.; Bright, R.K.; Watanabe, Y.; Pass, H.I. Thrombospondin-1 expression and clinical implications in malignant pleural mesothelioma. *Cancer* **1999**, *85*, 2570–2576. [CrossRef]

169. Pal, S.K.; Nguyen, C.T.; Morita, K.I.; Miki, Y.; Kayamori, K.; Yamaguchi, A.; Sakamoto, K. THBS1 is induced by TGFB1 in the cancer stroma and promotes invasion of oral squamous cell carcinoma. *J. Oral Pathol. Med.* **2016**, *45*, 730–739. [CrossRef]

170. Isenberg, J.S.; Roberts, D.D. Thrombospondin-1 in maladaptive aging responses: A concept whose time has come. *Am. J. Physiol. Cell Physiol.* **2020**, *319*, C45–C63. [CrossRef]

171. Isenberg, J.S.; Romeo, M.J.; Yu, C.; Yu, C.K.; Nghiem, K.; Monsale, J.; Rick, M.E.; Wink, D.A.; Frazier, W.A.; Roberts, D.D. Thrombospondin-1 stimulates platelet aggregation by blocking the antithrombotic activity of nitric oxide/cGMP signaling. *Blood* **2008**, *111*, 613–623. [CrossRef]

172. Sweetwyne, M.T.; Murphy-Ullrich, J.E. Thrombospondin1 in tissue repair and fibrosis: TGF-beta-dependent and independent mechanisms. *Matrix Biol.* **2012**, *31*, 178–186. [CrossRef]

173. Julovi, S.M.; Sanganeria, B.; Minhas, N.; Ghimire, K.; Nankivell, B.; Rogers, N.M. Blocking thrombospondin-1 signaling via CD47 mitigates renal interstitial fibrosis. *Lab. Investig.* **2020**, *100*, 1184–1196. [CrossRef]

174. Julovi, S.M.; Trinh, K.; Robertson, H.; Xu, C.; Minhas, N.; Viswanathan, S.; Patrick, E.; Horowitz, J.D.; Meijles, D.N.; Rogers, N.M. Thrombospondin-1 Drives Cardiac Remodeling in Chronic Kidney Disease. *JACC Basic Transl. Sci.* **2024**, *9*, 607–627. [CrossRef]

175. Xu, L.; Zhang, Y.; Chen, J.; Xu, Y. Thrombospondin-1: A Key Protein That Induces Fibrosis in Diabetic Complications. *J. Diabetes Res.* **2020**, *2020*, 8043135. [CrossRef] [PubMed]

176. Kirk, J.A.; Cingolani, O.H. Thrombospondins in the transition from myocardial infarction to heart failure. *J. Mol. Cell. Cardiol.* **2016**, *90*, 102–110. [CrossRef] [PubMed]

177. Kale, A.; Rogers, N.M.; Ghimire, K. Thrombospondin-1 CD47 Signalling: From Mechanisms to Medicine. *Int. J. Mol. Sci.* **2021**, *22*, 4062. [CrossRef] [PubMed]

178. Son, S.M.; Nam, D.W.; Cha, M.Y.; Kim, K.H.; Byun, J.; Ryu, H.; Mook-Jung, I. Thrombospondin-1 prevents amyloid beta-mediated synaptic pathology in Alzheimer's disease. *Neurobiol. Aging* **2015**, *36*, 3214–3227. [CrossRef] [PubMed]

179. Burdukiewicz, M.; Sobczyk, P.; Rödiger, S.; Duda-Madej, A.; Mackiewicz, P.; Kotulska, M. Amyloidogenic motifs revealed by n-gram analysis. *Sci. Rep.* **2017**, *7*, 12961. [CrossRef]

180. Szulc, N.; Burdukiewicz, M.; Gąsior-Głogowska, M.; Wojciechowski, J.W.; Chilimoniuk, J.; Mackiewicz, P.; Šneideris, T.; Smirnovas, V.; Kotulska, M. Bioinformatics methods for identification of amyloidogenic peptides show robustness to misannotated training data. *Sci. Rep.* **2021**, *11*, 8934. [CrossRef]

181. Mereuta, O.M.; Rossi, R.; Douglas, A.; Gil, S.M.; Fitzgerald, S.; Pandit, A.; McCarthy, R.; Gilvarry, M.; Ceder, E.; Dunker, D.; et al. Characterization of the 'White' Appearing Clots that Cause Acute Ischemic Stroke. *J. Stroke Cerebrovasc. Dis.* **2021**, *30*, 106127. [CrossRef]