Vitreous proteomics in rhegmatogenous retinal detachment and proliferative vitreoretinopathy

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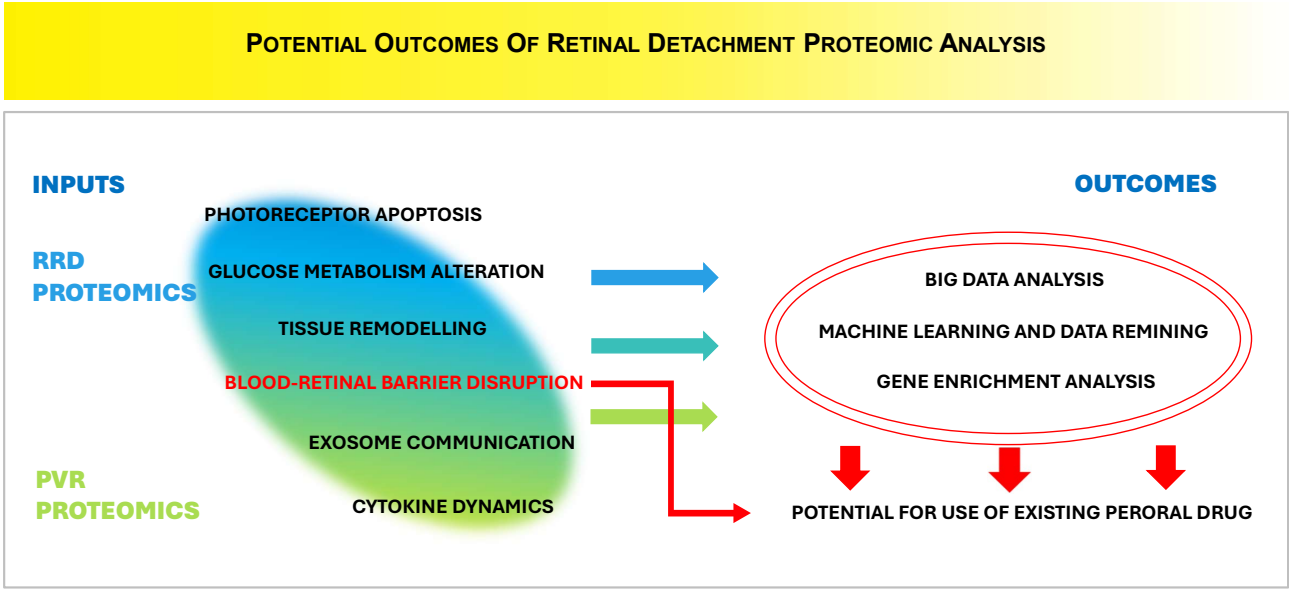
Rhegmatogenous retinal detachment (RRD) is a serious ophthalmic condition that, if untreated, can result in significant vision loss. Proliferative vitreoretinopathy (PVR) often complicates RRD and is the leading cause of surgical failure. Proteomic analysis of the vitreous has emerged as a powerful tool for elucidating the molecular mechanisms underlying RRD and PVR. This article reviews proteomic findings related to these conditions. A comprehensive literature search on PubMed was conducted, focusing on studies of vitreous proteomics in RRD and PVR published between 1988 and August 2024. Relevant findings on protein expression, metabolic pathways, and therapeutic targets were synthesized. Proteomic studies reveal significant alterations in photoreceptor-specific proteins, such as rhodopsin and Monocyte Chemoattractant Protein-1 (MCP-1), associated with apoptosis and inflammation during RRD. Metabolic dysregulation is evidenced by changes in glycolytic enzymes and antioxidants, including downregulation of peroxiredoxin-2 and ascorbic acid, suggesting impaired energy production and oxidative stress. Elevated cytokines, complement proteins, and matrix metalloproteinases highlight the role of inflammation and extracellular matrix remodelling in disease progression. Cytokine expression in PVR demonstrates distinct temporal patterns, with early stages marked by T-cell activation and mTOR pathway-related cytokines, and advanced stages characterized by monocyte chemoattractants associated with chronic inflammation. Currently, the potential of pharmacologic interventions in RRD and PVR remains limited. In contrast, proteomics offers critical insights into molecular mechanisms, identifying potential biomarkers and therapeutic pathways. The adoption of single-molecule and top-down proteomics, along with the integration of advanced technologies with artificial intelligence and bioinformatics, holds promise for accelerating progress toward precision medicine. These developments represent a promising avenue for future research and clinical application.



Machine learning and big data analysis may pinpoint an already existing drug to treat PVR.

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INTRODUCTION

Retinal detachment

Retinal detachment (RD) is a potentially blinding ophthalmic condition. In RD, the highly organized multilayer neurosensory retina separates from the underlying retinal pigment epithelium (RPE), a single-cell layer of cuboidal polarised cells located at the posterior part of the eye. Retinal detachments can be classified as rhegmatogenous (resulting from a break in the retina) or non-rhegmatogenous, due to the accumulation of subretinal fluid under the retina (exudative retinal detachment) or the traction exerted by scar tissue on the retina (tractional retinal detachment). They can also manifest as a combination of these factors. Rhegmatogenous retinal detachment (RRD) represents the most prevalent form of retinal detachment, with an estimated annual incidence rate of 6.3–17.9 per 100,000 individuals[1].

The interconnection between the retinal pigment epithelium (RPE) and the photoreceptor cells is of paramount importance to the maintenance and optimal functioning of the photoreceptor cells[2]. Following a retinal detachment, the supply of nutrients to the photoreceptor cells is disrupted, resulting in their rapid deterioration (within hours or a few days) due to apoptosis and programmed cell death[3]. Subsequently, the RPE cells and fibroblasts will undergo abnormal and ectopic proliferation, resulting in irreversible damage to visual function. In addition to structural alterations in the retina, intricate biomolecular processes initiated following RD may also contribute significantly to its pathogenesis. It is evident that a plethora of cytokines, pro-inflammatory, and growth factors are released into the vitreous during retinal detachment[4]. It has been proposed that these molecules play a pivotal role in the injury-induced wound-healing process and apoptosis of retinal photoreceptors in the context of RD (ref.[5,6]).

Currently, the only available treatment for RRD is surgical. However, in the future, the combination of this with a new therapeutic agent may prove beneficial in improving the visual outcome following surgery and preventing proliferative vitreoretinopathy.

Proliferative vitreoretinopathy (PVR)

Proliferative vitreoretinopathy (PVR) is currently the most significant factor contributing to surgical failure in the treatment of retinal detachment (RD). The precise pathophysiology remains unclear. However, it is generally accepted that PVR represents a counterproductive wound-healing response, involving multiple intraocular cell types and inflammatory mediators. Abnormal cellular proliferation leads to the formation of contractile membranes on the inner and outer surfaces of the retina, exerting traction and ultimately causing re-detachment. Studies suggest that severe PVR can complicate approximately 10% of surgical cases for RD, resulting in failure or necessitating re-operation[6].

Proteomics of vitreous

Proteomics, the comprehensive study of proteins, plays a crucial role in understanding the molecular mechanisms underlying various biological processes. The vitreous, due to its direct contact with the retina, its biological permeability even for large protein molecules and its accessibility and expendability, presents an ideal medium for proteomic studies[7]. These characteristics allow the vitreous to offer valuable insights into the pathophysiology of ocular diseases, particularly those affecting the retina and vitreoretinal interface. A key technique employed in vitreous proteomics is mass spectrometry, which enables the precise identification and quantification of proteins within complex biological samples[8].

Mass spectrometry begins with the collection and preparation of vitreous humour, where proteins are enzymatically digested into smaller peptides. These peptides are then analyzed by the mass spectrometer, which measures their mass-to-charge ratios, generating a spectrum for each peptide. These spectra are compared against theoretical spectra derived from protein databases using specialized algorithms. The matching process identifies the most likely proteins present in the sample, allowing researchers to compile a list of identified proteins for further analysis.

From the beginning of proteomic research, most studies were focused on identification of differently expressed proteins (DEP) in two or more study groups[9,10], while studies aiming to describe physiological vitreous proteome in healthy eyes were not so numerous[7]. Since the mass spectrometry is a very efficient high throughput method, the number of total identified proteins could be in thousands and the number of significant DEPs could easily reach hundreds, which makes interpretation of acquired data very challenging.

DETAILED ANALYSIS OF PROTEOMICS IN RETINAL DETACHMENT

Inner retinal layers are nourished via retinal arteries while photoreceptors and outer layers are nourished strictly by diffusion from choriocapillaris through retinal pigment epithelium[11]. Separation of neurosensory retina from RPE thus inevitably leads to ischemic stress for photoreceptors, which, if not terminated, continues into tissue remodelling and potentially into cascade of proliferative events affecting whole eye[8]. Proteomic studies support this assumption on various levels, elucidating many possible pathways taking part.

Photoreceptor apoptosis

In 1988, Newsome et al. measured the concentration of interphotoreceptor retinoid-binding protein (IRBP), a photoreceptor-specific protein involved in the visual cycle, in the subretinal fluid of patients with rhegmatogenous retinal detachment (RRD). The study found that IRBP concentrations were highest in patients with recent onset of RRD and decreased as the duration of the detachment

increased. This pattern suggests that IRBP levels may decline as photoreceptor cells are lost over time, though it remains unclear whether the loss of photoreceptors drives the decline in IRBP or if the decrease in IRBP contributes to photoreceptor degeneration[12]. Santos et al. found the accumulation of photoreceptor proteins such as rhodopsin, phosducin, S-arrestin, retinaldehyde-binding protein 1, retinal phosphodiesterase subunits and transducing subunits in the vitreous of RRD patients. This suggests that photoreceptor degeneration occurs during RRD, contributing to visual impairment and highlighting the need for therapeutic strategies targeting photoreceptor survival[13].

One possible way of promoting survival of retinal photoreceptors might be by inhibition of MCP-1 protein, which attracts monocytes in vicinity of injured retinal areas. Nakazawa et al. studied relation between monocyte chemoattractant protein 1 (MCP-1) and photoreceptor apoptosis in murine model of RRD. Both MCP-1 RNA concentration and MCP-1 vitreous concentration were elevated in RRD group. MCP-1 knockout mice and mice with injected antibodies against MCP-1 have developed far lesser extent of photoreceptor apoptosis than the wild type mice after RRD. This finding suggests potential role of MCP-1 in mediating photoreceptor apoptosis in RRD (ref.[14]). Similar results exhibiting promotion of photoreceptor survival were observed in glial fibrillary acidic protein (GFAP) and vimentin deficient mice, compared to the wild type mice[15].

Glycolytic enzymes

In addition to the finding of directly photoreceptor specific proteins as proof for their stress, differential expression of glycolytic enzymes and glucose transporters in the vitreous were also found, indicating that energy metabolism is also significantly altered in RRD. Retinal cells, especially photoreceptors, are highly dependent on ATP as source of energy. In a healthy human retina, the main source of ATP is oxidative phosphorylation, while in various pathological conditions, where lack of oxygen occurs from various reasons, anaerobic glycolysis is the alternative to produce ATP to cover cellular metabolic demands[16]. The difference of expression of glycolysis-related pathways suggesting changes in mechanisms of energy production to cope with the metabolic demands during detachment and repair processes were proven by various authors.

Mandal et al. have observed increase in alpha-enolase, enzyme directly involved in glycolysis, in rabbit RRD group. On the other hand, fructose-bisphosphate aldolase A, another glycolytic enzyme, was found downregulated by the same research group[17]. Possible explanation for this downregulation might be the loss of photoreceptor cells by their degeneration, or the ability of aldolase A to affect retinal cell structure and substance movement by binding interactions with actin in the cytoskeleton[18]. Öhman et al. have found highest enrichment of glycolytic pathway counting in total 21 significantly overexpressed enzymes playing role in enzymatic processes almost all the way from glucose to final product pyruvate. Upregulation of amino acid metabolism and citrate cycle compounds were also observed[19]. Though upregulation of glycolytic enzymes is the most common finding in proteomic studies in RRD, the situation is significantly different with progression towards PVR, where downregulation and total disappearance prevails, and also when RRD is complicated by choroidal detachment[20-22].

Antioxidants

Stress of retinal tissue induced by RRD might be expressed by the downregulation of antioxidants in vitreous. Peroxidoxin 2 is a member of the family of peroxidoxins, which are considered antioxidants, thus playing an important role in maintaining tissue homeostasis. Mandal et al. have proved a significant downregulation of peroxidoxin 2 in a study group of RRD compared to controls, implying the consumption of peroxidoxin 2 by a stress induced increase of free radicals[23]. This finding is in accordance with the results of a study of Takano et al., who have observed a decrease of vitreous levels of another important antioxidant, ascorbic acid, in patients with PVR and PDR, in comparison with less severe pathologies such as IMD and ERM (ref.[24]). The imbalance in retinal homeostasis as expressed by decreased levels of antioxidants in the vitreous, may by itself induce further damage by the incompetence of retinal tissues to cope with free radicals.

Chaperons

It has been already proven in other retinal diseases that chaperon proteins, especially heat shock proteins (HSP), play an essential role in the regeneration of diseased retina and in the maintenance of retinal homeostasis[25]. Proteomic analysis revealed an increased expression of heat shock proteins and proteins related to the inflammatory response in the vitreous of RRD patients. These proteins are involved in cellular stress responses and inflammation, suggesting that RRD triggers a protective response in retinal cells to cope with stress and damage[26]. Kayama et al. observed elevated HSP70 levels following RD in mice and rats, which correlated with phosphorylated Akt, preventing its dephosphorylation and subsequent activation of apoptotic pathways[27]. The increase of HSPs in vitreous in RRD group was also observed by Santos et al.[13].

Plasma proteins

Current proteomic studies are suggesting, that apart from the primary mechanism of alteration of outer retina by ischemia, the process of retinal detachment is associated with alteration of the inner blood-retinal barrier. The complement and coagulation cascades are significantly upregulated in the vitreous of RRD patients, indicating that immune responses and blood coagulation play crucial roles in the pathogenesis of RRD. This activation could lead to inflammation and tissue remodelling, contributing to disease progression and complications like PVR. Luo et al. have observed that the concentrations of complement component C2 and CFD were significantly increased in the vitreous humour of the RRD group, as compared to the control group[28]. These findings were even more pronounced in cases of complicated RRD

with choroidal detachment (RRDCD) and in cases of PVR (ref.[22,29]). On the other hand, Santos and al. have observed significant decrease in almost a whole cluster of plasma apolipoproteins (APOA4, APOC2, APOC3), while the only upregulated members were the components of C1 (C1QC, C1R), the first component of the serum complement system[13].

Matrix metalloproteinases

As stated above, ischemic conditions of RRD trigger the activation of proliferative process, leading to formation of PVR in some cases. On the other hand, there are also studies suggesting upregulation of matrix metalloproteinase activity in the vitreous to mitigate proliferative tendencies. Symeonidis et al. studied levels of various MMPs and its tissue inhibitors (TIMPs) in patients with RRD compared to controls. The highest increase in concentration was found in MMP-3, with concentration 45 times higher in the study group. Among studied TIMPs, TIMP-1 was found to be of greater variance between groups with a 2.5-fold increase in the study group. The general trend was that greater extent of retinal detachment was correlated with higher levels of MMPs and TIMPs detected. With respect to duration of RRD before surgery, concentrations of various MMPs peaked within the first month, while the peak of concentration of TIMP-1 was found to be 2 months after onset of RRD (ref.[30]). Mandal at al have found downregulation of another inhibitor of proteolytic enzymes, F isoform of alfa-1-antiproteinase, in a rabbit model of RRD. Same as for human alfa-1-antiproteinase, the F isoform of rabbit alfa-1-antiproteinase is susceptible to oxidation of the methionine residue site by ROS, rendering the enzyme inactive[23]. This mechanism may play role in a relatively ROS rich environment in the vitreous of patients with RRD.

Cytokine dynamics of early and advanced PVR

When attempting to describe molecular pathogenesis and pathways in PVR, it is important to stress the heterogeneity of molecular processes involved in PVR pathogenesis, especially regarding the timeframe and the severity of the whole process. In an attempt to depict the cytokine expression dynamics, at least two completely different molecular processes were described, one in early (grade A and B) and the second in advanced PVR (grade C and more) (ref.[6,31]). Similar differences were observed by another independent research group, comparing the whole vitreous or exosomal proteome of moderate and severe PVR, and suggesting differences in time and process dynamics as not being restricted only to cytokine expression[20,32].

In the study by Roybal and colleagues, comparing vitreous samples of various PVR severity and high-throughput cytokine screen measuring expression of 200 cytokines, the vitreous with early PVR exhibited increased levels of T-cell markers, pro-fibrotic cytokines, and mTOR pathway-related cytokines (IL-2, IL-6, and IL-13), while in the late PVR, cytokines promoting monocyte activity and stem-cell recruitment (such as SDF-1) were predominant. The T-cell activating pathways, significantly upregulated in early PVR samples, contained CTACK, I-TAC, lymphotactin, TSLP, MCP-4, MPIF-1, MIG and TARC. The observed chemokines were specific for both Th1- (I-TAC and MIG) and Th2-cells (TARC). Six fibrosis-inducing cytokines were also observed in this group. By further pathway analysis, 16 significantly elevated downstream effectors of the mTOR pathway were reported. When comparing advanced PVR to controls, none of early PVR cytokines were present. Amongst the 11 significantly upregulated cytokines, the monocyte chemo-attractants were most abundant, which is typical for chronic inflammation[31].

Nair and colleagues have studied proteins contained in exosomes in RRD, various stages of PVR and control groups. Thus, when performing proteomic analysis, only the pre-separated exosome particles obtained by ultracentrifugation were analyzed. By hierarchical clustering, the Kininogen-1 and EFEMP-1 pathways were found to be upregulated in the PVR group, as compared to non PVR patients. Interestingly, the m-TOR pathway was not detected at all, indicating that its promotion occurs through mechanisms other than the exosomal pathway. Specifically, in the subgroup of severe PVR, upregulated proteins included tissue remodeling factors (e.g., SPP1, CLU, VCAN, COL2A1, SEMA7A), which align with known PVR pathways, such as cell proliferation, inflammation, and gliosis[32]. In addition, the Kininogen-1 pathway was reported as upregulated in PVR vitreous samples as reported by Yu and colleagues[20].

Glycolysis and plasma proteins in PVR

As stated above, levels of glycolytic enzymes tend to be rather elevated in uncomplicated RRD (ref.[17,19]). Regarding the glycolytic pathway contained enzymes, Li and colleagues have observed upregulation of glycerate in both RRD and PVR group, with even significantly higher upregulation in the PVR group. D-glyceraldehyde upregulation was observed only in the RRD group, with return to levels similar to those in the control group, in the PVR cohort[21]. Yu et al. have studied proteome of eyes with moderate PVR, severe PVR and compared those to a control group of donor eyes. His research group have found that in total 19 enzymes were involved in the glycolysis of donor eyes. Many of them were significantly decreased in moderate PVR and even disappeared in severe PVR. This indicated that glycolysis process was obviously affected when PVR occurred[20]. Upregulation of serum proteins was also reported in this study which was further confirmed by the same research group in subsequent research. They observed an increase in serum proteins, specifically hemopexin, alpha2-HS–glycoprotein, alpha1B-glycoprotein, members of the serpin family, and complement components, in the PVR group compared to controls[29]. Apart from cellular signalling aimed to promote inflammation, as discussed above, these findings suggest that important metabolic changes, along with disruption of BRB, are also taking place.

Therapeutic targets, biomarkers and their implications

Despite the fact that various definite pathways triggering PVR progression have been described, the results of

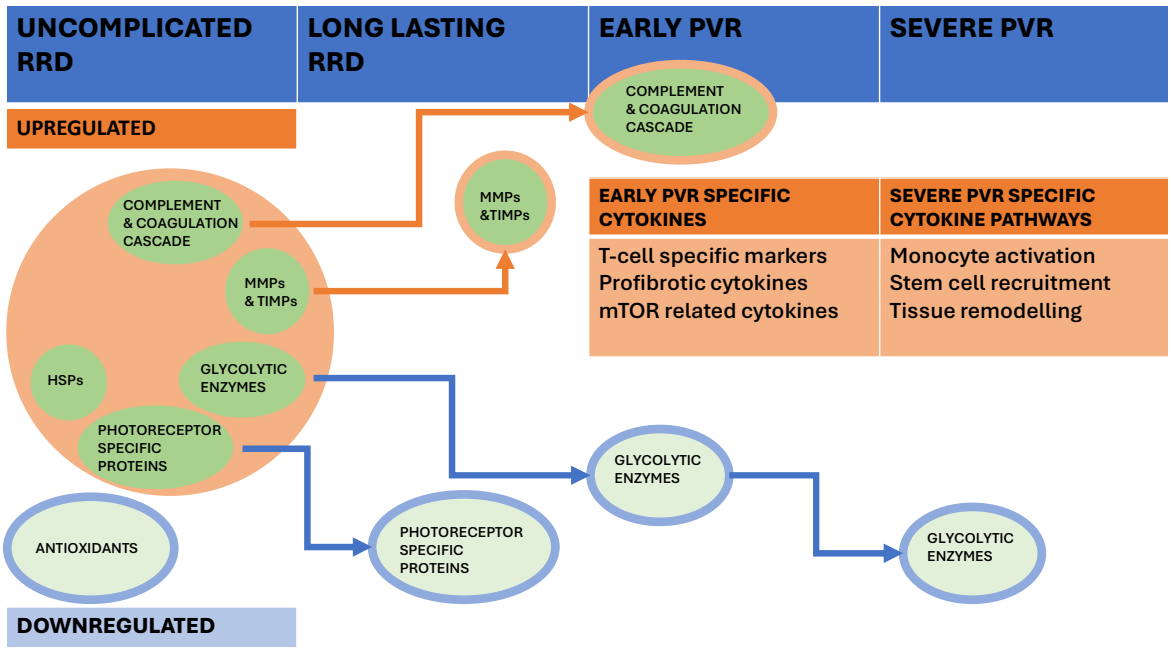

Fig. 1. Overview of proteomic changes with respect to RRD duration and PVR severity.
HSPs, Heat Shock Proteins; MMPs & TIMPs, Matrix Metalloproteinases and Tissue Inhibitors of Matrix Metalloproteinases; mTOR, Mechanistic Target of Rapamycin.

clinical trials aimed at pharmacological mitigation have not yet been satisfactory. One reason might be, that none of above-mentioned pathways is directly influenced by corticosteroids or 5-FU, which target different sites in the inflammatory response[33,34]. In addition, more comprehensive approach that addresses multiple pathways simultaneously may be needed to effectively combat PVR (ref.[35,36]). As a result of exosome proteome analysis, a promising idea of inhibition of exosome signalling pathways as a potential treatment for PVR has emerged. However, a more detailed understanding of exosome signalling is still required[32].

Contradictory findings and gaps in our knowledge

Despite significant advances in vitreous proteomics related to retinal detachment, numerous controversies and gaps in our understanding remain unresolved. Many conflicting findings arise from methodological variations and the absence of standardized protocols for vitreous collection and analysis, making it difficult to compare results across studies. Different analytical platforms (e.g., DIA, iTRAQ, exosomal proteomics) yield only partially overlapping results, reflecting considerable methodological heterogeneity.

Furthermore, the field remains heavily skewed toward proteomic research, with metabolomic and lipidomic analyses being notably underrepresented. Only a few studies have addressed these complementary approaches, resulting in a somewhat biased perspective on the molecular events underlying RRD and PVR (ref.[37]).

Translational discrepancies between animal models and human disease also persist. Numerous molecular mechanisms described in rodent models of RRD and PVR are not consistently replicated in human tissue studies, and therapeutic interventions that prove effective in experimental settings often fail to yield clinical benefits[38].

A clear example of a clinical inconsistency lies in the variable survival time of photoreceptors in different types of retinal detachment. In RRD, photoreceptor apoptosis is reported to begin within hours of separation from the RPE due to subretinal fluid accumulation[39]. In contrast, conditions such as central serous chorioretinopathy (CSC), characterized by choroidal-derived subretinal fluid, show prolonged photoreceptor survival lasting weeks to months[40]. This observation challenges the hypothesis of ischemia-induced photoreceptor death as the primary mechanism. Only a limited number of studies have specifically addressed this discrepancy. For example, Kowalczuk et al. investigated differential expression of proteins and metabolites, mainly related to glycolytic pathways, in RRD and CSC. However, their study was limited by the inclusion of only a single patient in the CSC group, highlighting the need for more robust comparative studies[41].

FUTURE PERSPECTIVES

From around 2012, data-independent acquisition (DIA) has transformed the field by enabling consistent, reproducible, and high-throughput analysis of complex vitreous proteomes. DIA methods such as SWATH-MS provide unparalleled sensitivity and accuracy, allowing the quantification of thousands of proteins and enabling detailed exploration of the molecular mechanisms underlying diseases like retinal detachment and PVR, many of them being already discussed in this review[42]. Looking ahead, single-molecule proteomics holds immense promise for vitreous proteome studies. Its ability to detect ex-

tremely low-abundance proteins, such as cytokines and signalling molecules, could uncover novel biomarkers which are critical for early diagnosis and targeted interventions in PVR. Additionally, this technique minimizes the need for extensive sample preparation, preserving the integrity of fragile vitreous proteins[43]. Top-down proteomics, with its focus on analyzing intact proteins, presents another exciting frontier. By preserving post-translational modifications and structural nuances, this approach has the potential to uncover protein isoforms and molecular details that are missed in conventional bottom-up workflows. Such insights could be pivotal in understanding the complex protein networks driving PVR pathophysiology[44].

Engagement of bioinformatic platforms capable to deal with huge datasets such as ToppGene, and systematic re-mining of proteomic data repositories, can revolutionize the identification of druggable targets. Gene set enrichment analysis of existing datasets could reveal key pathways in PVR, such as inflammation or extracellular matrix remodelling, and guide the discovery of compounds capable of interfering with these processes, possibly by using existing drugs with well-known safety profiles[45]. Another promising field is the integration of deep learning algorithms like AlphaFold, which can predict the spatial structure of proteins and thereby aid in identifying potential interactions and interferences, although practical applications of this in complex biological systems are unlikely to materialize in the near future[46]. This multi-faceted approach, leveraging advanced analytical tools and artificial intelligence, holds the potential to accelerate the development of precision medicine strategies for vitreoretinal diseases.

CONCLUSION

Proteomic analysis has emerged as a vital tool in unravelling the complex molecular mechanisms underlying rhegmatogenous retinal detachment (RRD) and proliferative vitreoretinopathy (PVR). By leveraging advanced techniques like mass spectrometry, researchers have identified key pathways, including those involved in inflammation, extracellular matrix remodelling and energy metabolism, which are central to the pathophysiology of these conditions. Despite significant advancements, challenges remain in translating these findings into effective clinical interventions. Future research must focus on integrating emerging technologies such as data-independent acquisition (DIA), single-molecule proteomics, and top-down proteomics to deepen our understanding of disease mechanisms. Additionally, artificial intelligence tools like AlphaFold and bioinformatics platforms capable of re-mining proteomic data can drive the discovery of new therapeutic targets. These innovations offer promising opportunities to identify novel druggable pathways, such as those involved in PVR progression, potentially enabling the repurposing of existing therapies or the development of targeted treatments. By combining these cutting-edge approaches, the field is poised to make transformative strides toward precision medicine, ultimately improving the outcomes for patients with vitreoretinal diseases.

SEARCH STRATEGY AND SELECTION CRITERIA

Our research strategy focused on gathering the current state-of-the-art knowledge on vitreous proteomics in rhegmatogenous retinal detachment (RRD) and proliferative vitreoretinopathy (PVR). While several review articles have addressed vitreous proteomics, none have explored the proteome of RRD and PVR in significant detail, as these topics have often been treated as subtopics within broader review scopes. We conducted a comprehensive PubMed search, selecting relevant scientific articles published between 1988 and August 2024 that focused on proteomic findings in RRD and PVR. The search terms included “vitreous proteomics retinal detachment,” “vitreous proteomics proliferative vitreoretinopathy,” “retinal detachment biomarkers,” and “proliferative vitreoretinopathy biomarkers.” Only articles published in English were included in our review.

ABBREVIATIONS

Akt, Protein Kinase B; APOA4, Apolipoprotein A-IV; APOC2, Apolipoprotein C-II; APOC3, Apolipoprotein C-III; ATP, Adenosine Triphosphate; BRB, Blood-Retinal Barrier; C1QC, Complement Component 1, Q Subcomponent; C1R, Complement Component 1, R Subcomponent; CCL2, C-C Motif Chemokine Ligand 2; CFD, Complement Factor D; CLU, Clusterin; COL2A1, Collagen Type II Alpha 1 Chain; CSC, Central Serous Chorioretinopathy; CTACK, Cutaneous T-cell Attracting Chemokine; DIA, Data-Independent Acquisition; DEP, Differentially Expressed Proteins; EFEMP-1, Epidermal Growth Factor-Containing Fibulin-Like Extracellular Matrix Protein 1; GFAP, Glial Fibrillary Acidic Protein; HSP, Heat Shock Protein; IL, Interleukin; IMD, Idiopathic Macular Degeneration; IRBP, Interphotoreceptor Retinoid-Binding Protein; MCP-1, Monocyte Chemoattractant Protein-1; MIG, Monokine Induced by Gamma Interferon; MMP, Matrix Metalloproteinase; mTOR, Mechanistic Target of Rapamycin; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; PDR, Proliferative Diabetic Retinopathy; PVR, Proliferative Vitreoretinopathy; RD, Retinal Detachment; ROS, Reactive Oxygen Species; RRD, Rhegmatogenous Retinal Detachment; SEMA7A, Semaphorin 7A; SDF-1, Stromal Cell-Derived Factor 1; SPP1, Secreted Phosphoprotein 1 (Osteopontin); SWATH-MS, Sequential Windowed Acquisition of All Theoretical Fragment Ion Mass Spectra; TARC, Thymus and Activation-Regulated Chemokine; TIMPs, Tissue Inhibitors of Metalloproteinases; TSLP, Thymic Stromal Lymphopoietin; VCAN, Versican.

Author contributions: JH, MS: study design; JH, ML, JT: literature research; JH, MS, VK: data interpretation; JH, ML, JT, VK, MS: critical reading; JH, VK, MS: manuscript writing.

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