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Case report

Proteomic analysis of intermediate uveitis suggests myeloid cell recruitment and implicates IL-23 as a therapeutic target

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ABSTRACT

Purpose: To profile vitreous protein expression of intermediate uveitis (IU) patients.
Observations: We identified a mean of 363 ± 41 unique proteins (mean ± SD) in IU vitreous and 393 ± 69 unique proteins in control samples using liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of liquid vitreous biopsies collected during pars plana vitrectomy. A total of 233 proteins were differentially expressed among control and IU samples, suggesting a protein signature that could distinguish the two groups. Pathway analysis identified 22 inflammatory mediators of the interleukin-12 (IL-12) signaling pathway in IU vitreous. Upstream regulator analysis identified downstream mediators of IL-23 and myeloid differentiation primary response protein (MYD88), both of which are involved in the recruitment and differentiation of myeloid cells. Taken together, our results suggest the recruitment of myeloid cells as an upstream pathway in the pathogenesis of IU.
Conclusions: This study provides insights into proteins that will serve as biomarkers and therapeutic targets for IU. These biomarkers will help design future clinical trials using rational molecular therapeutics.

1. Introduction

Intermediate uveitis (IU), as defined by the Standardization of Uveitis Nomenclature (SUN) working group, is chronic inflammation of the ciliary body, anterior vitreous, and peripheral retina that accounts for 1.4–22% of all uveitis patients.[1,2] The onset of IU is typically insidious and presents bilaterally; however, asymmetric disease has a predilection for younger patients (15–40 years). The disease course can range from self-limiting (10%) to chronic recurrence. Clinically, IU is characterized by vitreous haze, snowball, and snow-banking along the pars plana, varying degrees of peri-phlebitis, and a quiet anterior chamber. While the etiology of IU can be infectious or non-infectious, idiopathic IU accounts for more than 70% of cases with causes that are often not well understood. Notable etiologies of IU include tuberculosis, syphilis, sarcoidosis, multiple sclerosis, and lymphoma.

Classic treatments for non-infectious uveitis, such as corticosteroids, focus on blocking common downstream inflammatory pathways. More recently developed immune modulating therapies (IMT), such as adalimumab, have been used as monotherapy to reduce the amount of steroid burden or as adjunct therapy to control recurrent and resistant uveitis. While patient responses to these medications are highly variable, corticosteroids and IMTs are associated with numerous unfavorable side effects. The search for novel therapies with improved efficacy and safety profiles is under way, and an approach that is individualized to each patient's unique disease and pathophysiology may yield the best outcomes.

Personalized proteomic analysis is becoming an attractive and powerful tool for characterizing the molecular profiles of diseased tissues.[3] Analyzing the proteome of the uveitic vitreous can uncover biomarkers for specific etiologies of ocular inflammation. Our group has used targeted proteomic platforms (e.g. multiplex cytokine ELISA) to analyze the protein signature in vitreous biopsies from uveitis patients.[4] This approach has allowed us to identify several candidate biomarkers that can reliably determine different types of uveitis;

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however, this platform was limited to analyzing a maximum of 200 cytokines and may have missed other important protein signatures.[4] In this study, we present findings from four eyes of three patients with IU at an academic tertiary-referral healthcare system and analyzed their vitreous protein content using an unbiased proteomic detection platform (mass spectrometry).

2. Methods

Study approval– The study was approved by the Stanford University and University of Iowa Institutional Review Board and adhered to the tenets set forth in the Declaration of Helsinki (IRB: 201803853). Further experimental details can be found in the Supplemental Online Content. The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD011972.

3. Findings

3.1. Case 1

A 7-year-old female was referred for evaluation of optic disc edema found in both eyes (OU) on routine examination. Since her father had similar appearing optic nerves, the patient was initially believed to have a congenital anomalous variant. A year later she reported floaters OU, which interfered with her daily activities. On fundus examination there were vitreous clumps along with snowballs and inferior snowbanks in the inferior pars plana. She was diagnosed with IU and began topical steroid therapy; however, she developed a mild steroid-induced ocular hypertension along with pseudo-papilledema and early band keratopathy. Laboratory testing was unremarkable. Diagnostic and therapeutic pars plana vitrectomy (PPV) with vitreous biopsy and subtenons triamcinolone injection was performed, after which her vision and symptoms improved. Postoperatively, she noted photopsia and was found to have a paracentral scotoma in the right eye (OD) and cystoid macular edema (CME) on optical coherence tomography (OCT) imaging (see Fig. 1) OU that was resistant to oral prednisone as well as topical ketorolac. There was no clinical or laboratory evidence to suggest a systemic inflammatory or infectious process.

3.2. Case 2

A 31-year-old male construction worker complained of floaters for 4 weeks along with pain and redness in his left eye (OS) along with back pain. On examination, best corrected visual acuity (BCVA) was 20/15 OD and 20/800 OS. In the OS, the patient had 3+ conjunctival and scleral injections, 3+ cells and 1+ flare in the anterior chamber without a hypopyon, and 2+ vitreous cells and haze with small white round vitreous opacities located inferiorly in OS. The inflammation was predominantly intermediate with anterior chamber spill over in OS. There was also epiretinal membranes and inferior snowbanks. Examination of the anterior and posterior segments of OD was normal. PPV with vitreous biopsy was performed, and the patient was initiated on oral prednisone. Six weeks later, his BCVA improved to 20/20 OS. Laboratory studies and the vitreous biopsy did not show any infectious or tumor etiology. Since neither the clinical examination nor his laboratory testing revealed any known entity, he was given a diagnosis of non-infectious idiopathic IU (see Fig. 2).

3.3. Case 3

A 31-year-old female veterinary technician was referred for floaters, pain, and redness in the OD for 2 weeks. Her past ocular history was significant for an episode of genital chlamydia infection that was successfully treated 9 months prior and blunt trauma to the OD 6 years prior without sequelae. On examination, she was found to have 1+ vitreous haze, 2+ vitreous cells, and snowballs inferiorly in the OD. OCT and fluorescein angiogram (FA) did not show any abnormal findings posteriorly OU. Laboratory testing was unremarkable. A diagnosis of IU of the OD was made, and the patient was started on oral prednisone with a tapering dose. After a few months, the patient noted intermittent flashes in OD and new floaters in OS. Examination revealed a large posterior vitreous detachment (PVD) with old vitreous opacities OD, thus a PPV with vitreous biopsy was performed. Postoperatively, her vision improved from 20/40 to 20/20 OD, but she started complaining of floaters and spots in OS without any flashes. On examination, vitreous snowballs were observed. Since neither the clinical exam nor her laboratory testing pointed to a known entity, she was given a diagnosis of non-infectious idiopathic IU. PPV with vitreous biopsy was subsequently performed in the OS. Her postoperative course was unremarkable, and her BCVA improved from 20/800 to 20/20 OS (see Fig. 3E and F).

3.4. Mass spectrometry overview

We performed a proteomics screen for candidate biomarkers of four vitreous biopsies collected from the three IU patients described above. This was compared to control vitreous biopsies obtained from patients with idiopathic macular holes (Supplemental Table 1). Shotgun proteomics utilizing liquid chromatography-tandem mass spectrometry (LC-MS/MS) approach was used for simultaneous quantitation and identification of proteins for both cohorts. We identified 393 ± 69 unique proteins (mean ± SD) in control samples and 363 ± 41 unique proteins in IU samples. Proteomics data were compared using principal component (PC) analysis, which showed a separation between IU and control samples based on protein intensities that were significantly different (Supplemental Fig. 1). To identify the difference between IU and control samples at the molecular level for potential biomarkers, further analysis was performed as described below.

3.5. Differential protein expression

Protein intensities were analyzed by 1-way ANOVA and hierarchical heatmap clustering (Fig. 4). A total of 233 proteins were differentially expressed by control and IU samples (103 upregulated, 130 downregulated; $p < 0.05$; Fig. 4). These provided an excellent reference for potential disease markers for IU. Proteins within IU samples that exhibited the greatest expression compared to controls included latent-transforming growth factor beta-binding protein 2 (LTBP2), retinoic acid receptor responding protein (RARR2), ribonuclease (RNAS1), peptidoglycan recognition protein 2 (PGRP2), ceruloplasmin (CERU), biotinidase (BTD), afamin (AFAM), anti-thrombin III (ANT3), fibronectin (FN), transthyretin (TTHY), cystatin-3 (CYTC), alpha-1B-glycoprotein (A1BG), prostaglandin-H2 D-isomerase (PTGDS; Fig. 5A). Those that exhibited the least expression compared to controls included cystatin-S (CST4), glutathione synthetase (GSS), calsyntenin 3 (CLSTN3), tryptophanyl-tRNA synthetase (WARS), prolyl 4-hydroxylase, beta polypeptide (P4HB), clusterin-like 1 (CLUL1), aspartylglucosaminidase (AGA), and 4-hydroxyphenylpyruvate dioxygenase (HPD; Fig. 5A). IU patients typically develop snowballs near the vitreous composed mainly of glial elements, Müller cells, organized collagen, and inflammatory cells.[5] The marked increase of fibronectin, which organizes extracellular matrix components and collagen, suggests it may play a role in the formation of the characteristic snowballs. Similarly, decreased glutathione synthetase (GSS) levels in IU vitreous suggest a decreased regulation of oxidative stress.

3.6. Pathway representation

Molecular pathway analysis was used to identify functionally-linked proteins in IU vitreous samples. We performed pathway analysis on differentially expressed proteins using Ingenuity Pathway Analysis

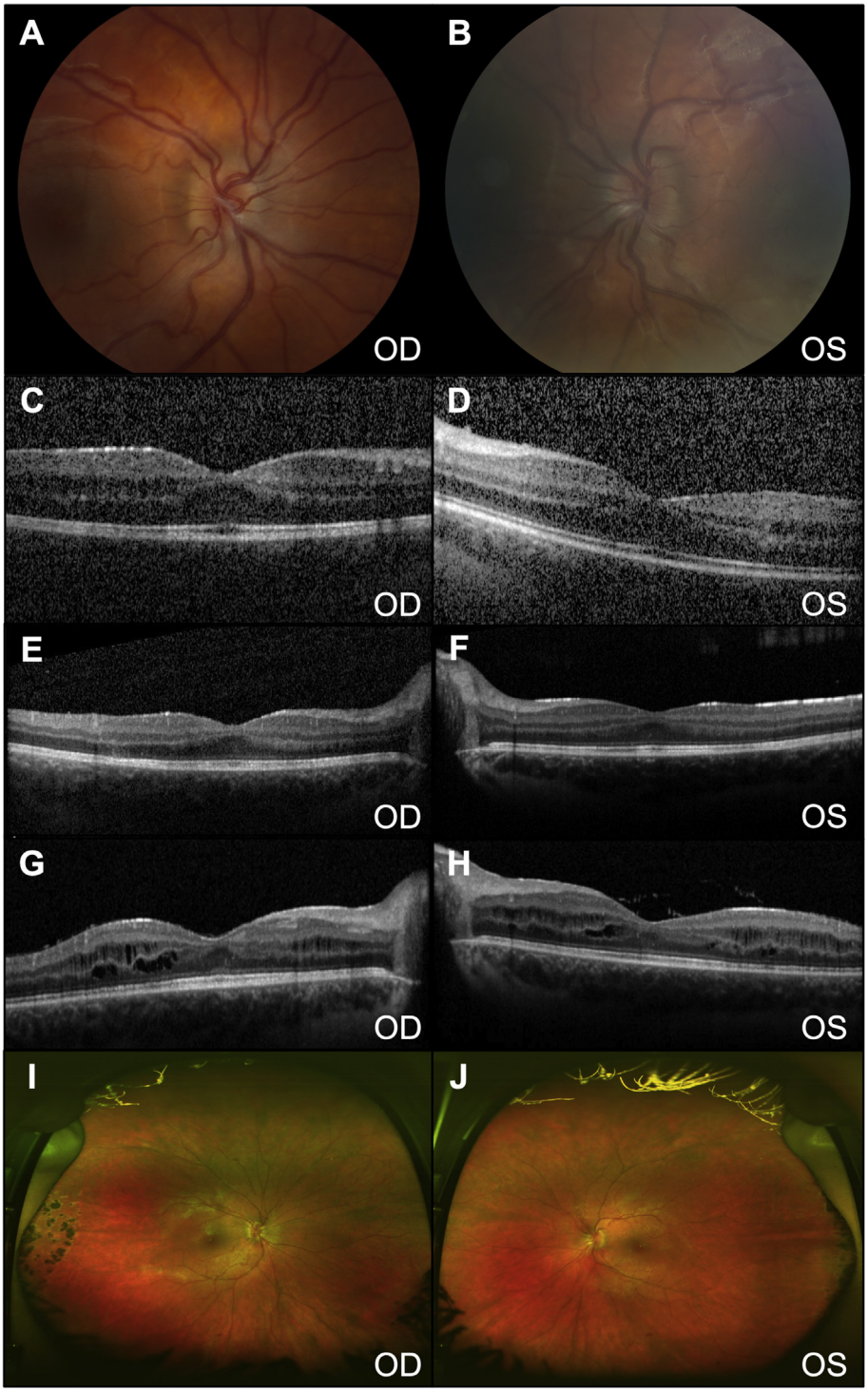

Fig. 1. Case 1: Color fundus photographs (FP) at the initial presentation show vitreous haze in OU, more severe in OS; both eyes have blurry borders of the optic disc along with vascular sheathing **(A–B)**. OCT of both eyes shows normal contour; and retinal layers show minimal disruption; however vitreous haze causes causes significant noise on the OCT **(C–D)**. OCT of both eyes after vitrectomy show that inflammation has improved; and OCT images are much clearer than initial visit **(E–F)**. OCT of both eyes demonstrated intraretinal fluid when the patient came back complaining of photopsias and paracentral scotoma in OD **(G–H)**. Ultra-widefield images in the last visit show the same findings as the initial visit but less severe; and old chorioretinal lesions temporal to the macula can be appreciated in both eyes **(J–I)**. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(IPA) software. The most represented pathways included: LXR/RXR activation, acute phase response, FXR/RXR activation, complement system, atherosclerosis signaling, coagulation system, clathrin-mediated endocytosis, intrinsic prothrombin activation, glycolysis, and IL-12 signaling in macrophages (Fig. 5B). The complement cascade has been previously implicated in the pathogenesis of uveitis, and we identified elevated levels of complement cascade effectors, including C1, C1R, C1S, and C1QS.[6] We also identified 22 IL-12 signaling mediators in IU samples: apolipoproteins (LPA, APOA1, APOA2, APOA4, APOB, APOC1, APOC2, APOC3, APOD, APOE, APOL1, and APOM), clusterin (CLU), alpha-1-antitrypsin (SERPINA1), serum amyloid A-4 protein precursor (SAA4), serum paraoxonase/arylesterase 1 (PON1), albumin, lysozyme, alpha-1-acid glycoproteins (ORM1 and ORM2), retinol-binding protein 4 (RBP4), and S100 calcium-binding protein A8 (S100A8; Fig. 5B). IL-12 is a T-cell stimulating factor produced by neutrophils, dendritic cells, and macrophages in response to antigenic stimulation[7] and promotes the differentiation of naïve CD4 T-cells along the Th1-effector pathway. The role of Th1-cells in experimental autoimmune uveitis (EAU) has been extensively studied along with Th17-cells.[8] Additionally, IL-12 can play an alternative role in suppressing autoimmune disease development by inducing the expression of interferon gamma (IFN-γ).[7,8] Taken together, these results suggest

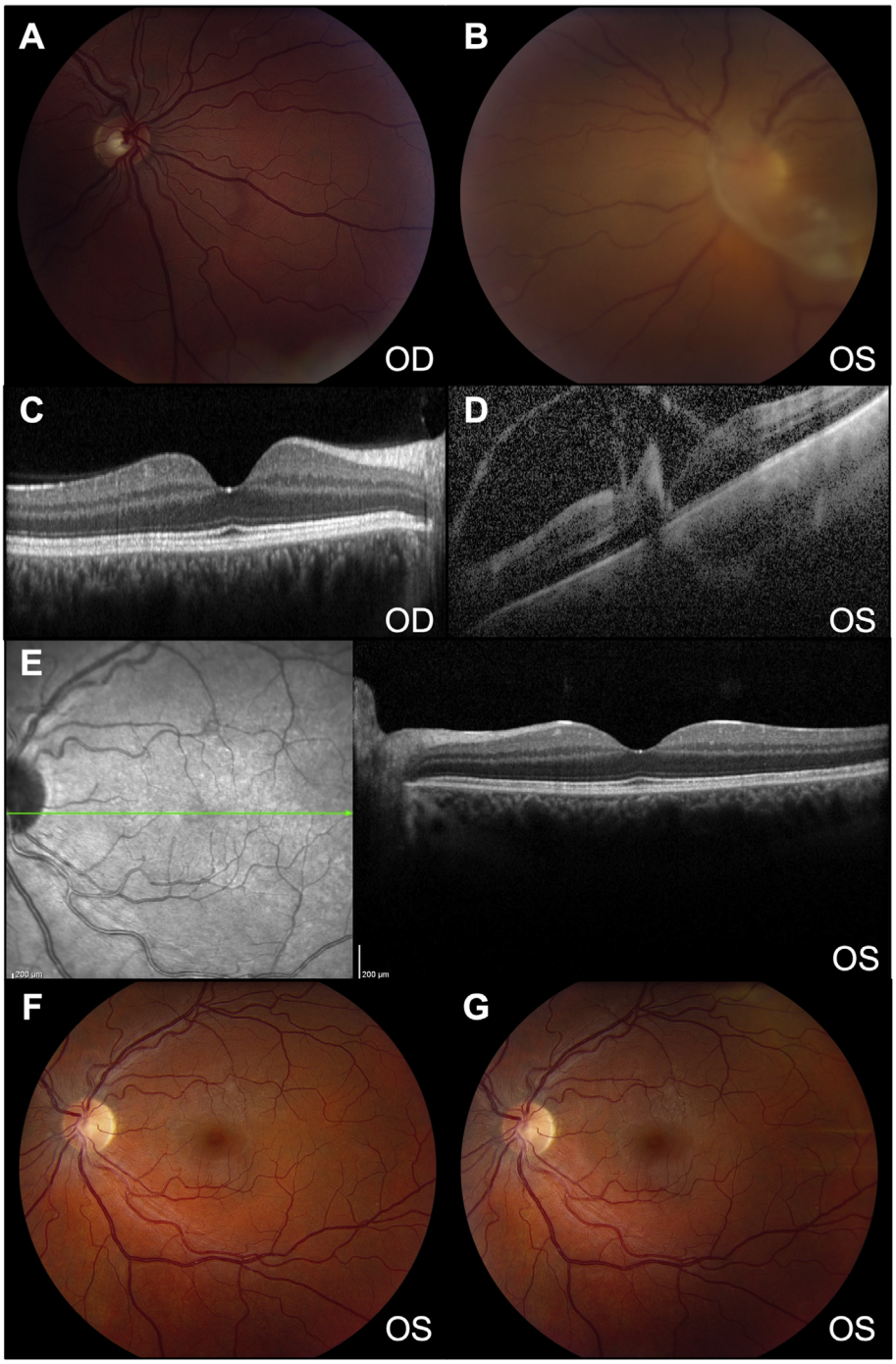

Fig. 2. Case 2: (A) Fundus photo OD at presentation shows white vitreous condensations inferiorly. **(B)** Fundus photo OS at presentation shows snowballs inferiorly and SUN 2+ vitreous haze with BCVA of 20/250. **(C)** OCT taken at presentation was normal OD. **(D)** OCT taken at presentation OS showed white vitreous opacity of the macula and disc and white condensations inferiorly. **(E)** OCT taken post-vitrectomy OS shows resolution of vitreous opacity and condensations. **(F–G)** Fundus photos taken post-vitrectomy shows resolution of vitreous haze.

the presence of both innate and adaptive immune elements in IU pathogenesis.

To identify proteins that could potentially regulate these pathways, significantly predicted upstream regulators were also identified using IPA software (Fig. 5C). This analysis is based on the expression of detected proteins within the dataset, which then predicts upstream genetic/protein factors that may regulate these proteins. The regulator with the most significant activation was myeloid differentiation primary response protein (MYD88; activation z-score = 2.842; Fig. 5C). Blockade of myeloid activation in EAU models have been previously shown to attenuate tissue damage.[9] Another significant upstream regulator was IL-23 (activation z-score = 2.0; Fig. 5B), which is secreted by macrophages and dendritic cells and regulates Th17 cell function and proliferation. The role of IL-23 in the development of EAU has been extensively studied, and we have previously reported elevated IL-23 levels in a common vitreous cytokine signature for uveitis.[10] Furthermore, single nucleotide polymorphisms (SNPs) in the *IL23R* gene have been previously associated with idiopathic intermediate and HLA-B27-associated uveitis.[11] A consequence of IL-23 signaling is increased levels of myeloid-specific proteins S100A8 and A9, both of which were

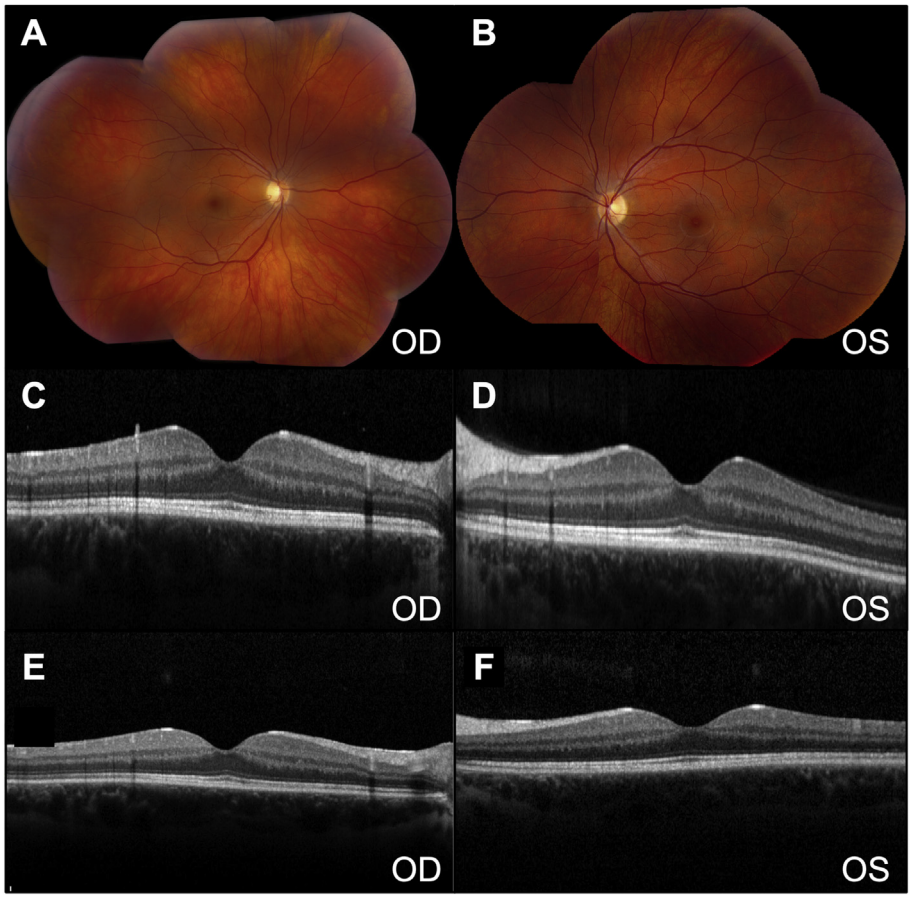

Fig. 3. Case 3: Color fundus photograph (FP) of both eyes show (+0.5) vitreous haze with minimal vascular sheathing at the initial presentation **(A–B)**. OCT of both eyes had normal foveal contour; hyper reflective micro opacities were observed in the vitreous on the OCT of the OS **(C–D)**. OCT of both eyes taken post-vitrectomy show same findings as the initial presentation **(E–F)**. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

detected in our IU samples. S100A8 promotes the infiltration and migration of inflammatory cells and has been previously associated with acute anterior uveitis (AAU) and recurrence of EAU in animal models.[12,13] Previous administration of an anti-S100A9 antibody ameliorated inflammation in a model of endotoxin-induced uveitis (EIU).[14] A protein-protein interaction network of myeloid cell recruitment proteins in IU vitreous was ascertained (Fig. 5D). Taken together, these results suggest IL-23 mediated myeloid cell recruitment is an 'upstream' pathway in IU pathogenesis.

3.7. Drug repositioning

Based on the significance of IL-23 as an upstream regulator from our pathway analysis, we explored pharmacologic treatments that could target IL-23. There are currently two IL-23-selective inhibitors that have been recently approved by the Food and Drug Administration to treat moderate to severe plaque psoriasis: guselkumab and tildrakizumab. While guselkumab is a human IgG monoclonal antibody that is an inhibitor of the p19 subunit of IL-23[15], tildrakizumab is a similar monoclonal antibody targeting IL-23p19.[16] In addition, ustekinumab is a monoclonal antibody targeting the shared p40 subunit of both IL-23 and IL-12 and was recently approved to treat severe psoriasis, psoriatic arthritis, and Crohn's Disease.[17,18] Any of these three pharmaceutical agents, particularly guselkumab and tildrakizumab, could be repurposed to treat IU.

Due to the elevated levels of C1, C1R, C1S, and C1QS in our patients, we further investigated the possibility that C1 inhibitors could also be used to treat IU. Four different C1 inhibitors that have been approved by the FDA to treat hereditary angioedema, a rare genetic disorder caused by mutations in the SERPING1 gene which results in a lack of functional endogenous C1 inhibitor.[19] Three human-derived C1 esterase inhibitors (trademarked as Berinert, Cetor, and Cinryze) and a rabbit-derived a recombinant C1 inhibitor (Ruconest) are available.[20] All C1 inhibitors bind irreversibly to C1R and C1S to inactivate the classical pathway of the complement cascade.[21] The enrichment of C1 and its associated proteins in our cohort indicates the potential utility of repurposing approved C1 inhibitors for therapeutic benefit in IU. Furthermore, there are other approved inhibitors for proteins downstream of C1 in the complement cascade, the most prominent example of which is eculizumab, a C5 inhibitor which prevents the formation of the membrane attack complex to treat paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.[22] Numerous inhibitors, each targeting various enzymes in the cascade, are in early phase clinical trials. For instance, Compstatin, a C3 blocker and antibody antigen binding fragment against Factor D, is being investigated for dry age-related macular degeneration (AMD) with intravitreal administration.[23]

4. Discussion

Patients who present with leukocytes in the vitreous humor and/or active chorioretinal inflammation without evidence of infection or known autoimmune disorder are diagnosed with idiopathic uveitis, thus targeted therapies are difficult to develop. Advancements in diagnostic approaches are needed to develop novel biomarkers and potential therapeutic targets for these diseases.

Precision medicine has allowed scientists to identify genetic risk factors for numerous diseases and personalize treatments to the individual patient. Recent technological advances allow for personalized proteomic profiling, which has many advantages over genomic profiling. In most diseases, there are no known genetic risk factors that can fully explain the pathophysiology. Furthermore, while genetic sequences are static, the disease process is characterized by dynamic protein expression that correlates with timing of signs and symptoms

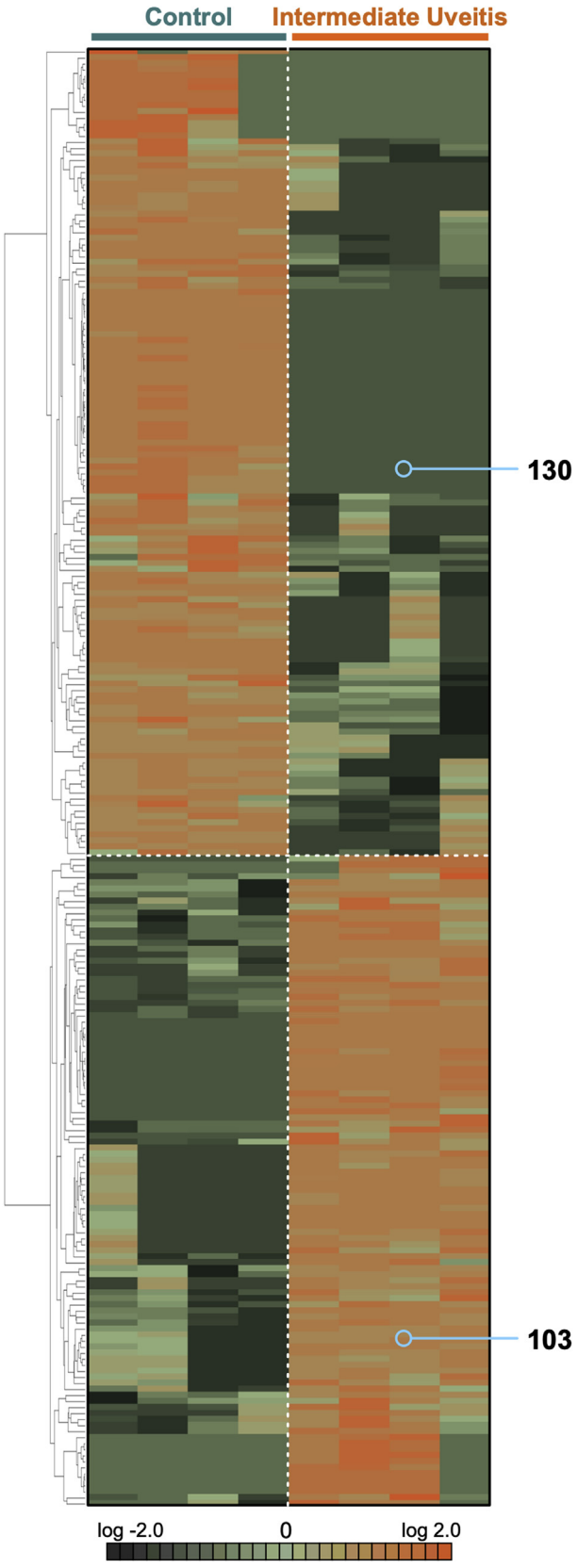

Fig. 4. Differentially-expressed proteins: Protein intensities were compared using 1-way ANOVA analysis and hierarchical heatmap clustering. Hierarchal clustering of proteins differentially expressed in our intermediate uveitis samples compared to normal controls (IMH). Results are represented as a heatmap and display protein expression levels on a logarithmic scale. Orange indicates high expression while dark green/black indicates low or no expression. A total of 103 proteins were upregulated and a total of 130 proteins were downregulated ($p < 0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and response to therapy. One may argue that there is a remote possibility that differences in the proteomic profiles of the patients and controls could be due to the difference in age of the two cohorts based on studies from plasma. However, the biomarkers that we have observed in the vitreous are predominantly from the inflammatory pathways that have not been consistently shown to be highly expressed in patients without disease of any age. Therefore, it is highly unlikely that differences in the proteomic signature of our study vs control groups could be attributed to age especially in the presence of significant clinical disease.

Another issue in the treatment of autoimmune diseases is the use of drugs with unfavorable side effect profiles. The mainstay treatment of non-infectious uveitis is corticosteroids. There are many disadvantages to corticosteroid therapy including the need to continue the therapy long-term and adverse effects such as Cushingoid features, hyperglycemia, osteopenia and osteoporosis, bone marrow suppression and insomnia. Additionally, some patients do not respond to corticosteroid therapy. Personalized proteomics can select for pharmacotherapeutics that are helpful and exclude those that are not. Cytokine therapy is used for autoimmune disease, but most drugs are not developed specifically for uveitis. Using our proteomics platform, we have identified a common cytokine signature for uveitis that may render these new medications to be crucial in any therapeutic plan. Due to the small sample size of the study, we are not able to generalize the results. However, these results do provide evidence that there may be an opportunity to manage patients with different uveitic diseases based on their individual proteomic profile and the predominant inflammatory pathway.

5. Conclusions

Proteomic profiling showed that IL-23 was upregulated in the vitreous humor of three IU patients who had similar clinical course. IL-23 induces the differentiation of naïve CD4 + T cells into IL-17 helper T cells (TH17/$TH_{IL\text{-}17}$). IL-17 enhances T cell priming and stimulates fibroblasts, endothelial cells, macrophages, and epithelial cells to produce multiple pro-inflammatory mediators, including IL-1, IL-6, TNF-alpha, NOS-2, metalloproteases thereby inducing inflammation.[24] There is substantial evidence that the IL-23/IL-17 pathway is critical for the development of multiple autoimmune diseases including psoriatic skin inflammation, inflammatory bowel disease, and experimental autoimmune encephalitis and autoimmune myocarditis.[25–27] High expression of IL-23 in the vitreous humor of these uveitis patients suggest that IL-23 may also drive pathologic processes in IU. Consequently, biologics that target IL-23 signaling may be a viable therapy for these patients.

Patient consent

Consent to publish this case series has been obtained from the patients in writing.

Author contributions

Dr. Mahajan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YS, GV, AGB, VBM. Acquisition of data: YS, GV, JY, TC, VBM. Analysis and interpretation of data: YS, GV, ASL, QDN, AGB, VBM. Drafting of the manuscript: YS, GV, ASL, VBM.

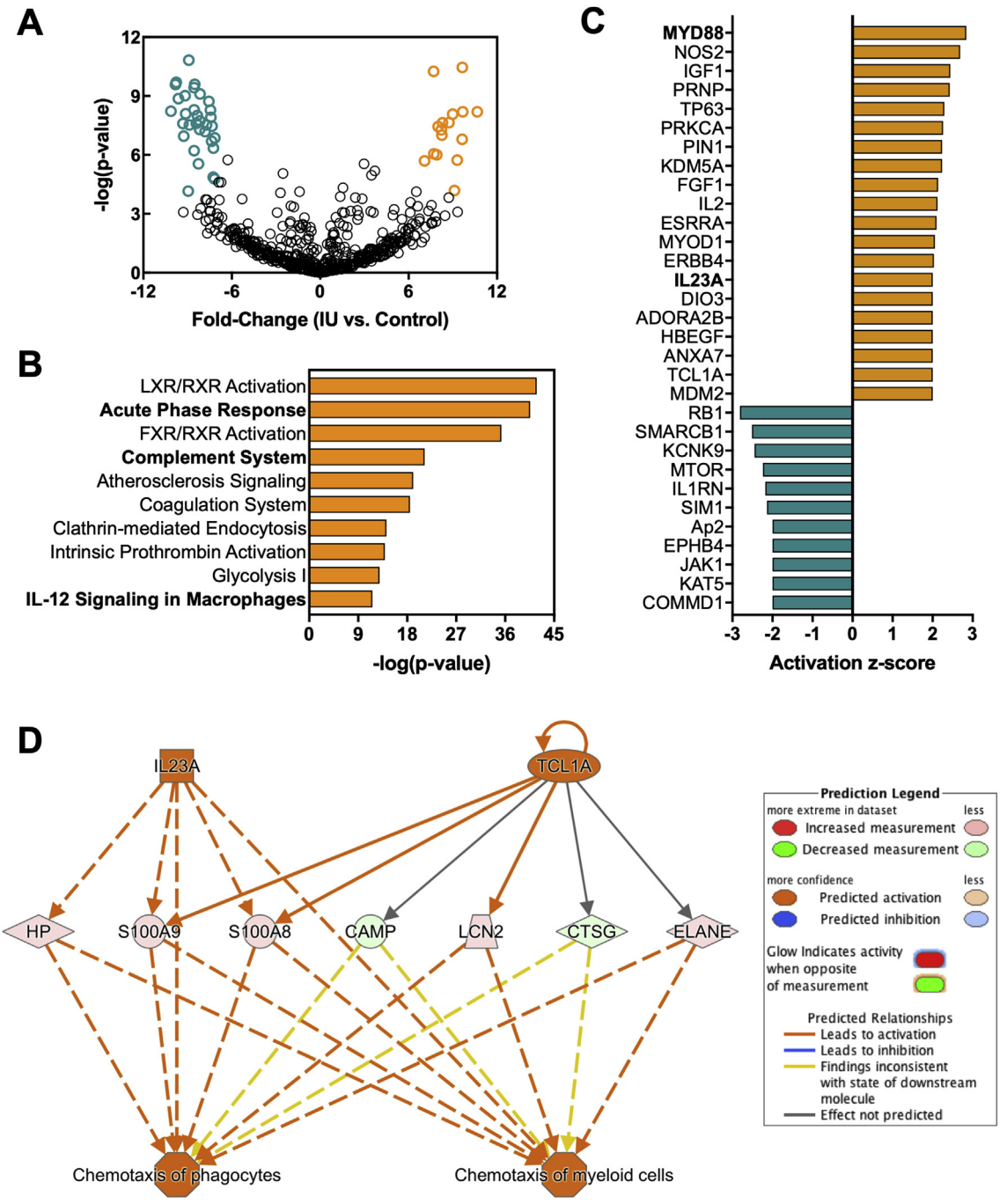

Fig. 5. Pathway representation and upstream regulators in intermediate uveitis: (A) Protein fold-changes represented as a volcano plot. The horizontal axis (x-axis) displays the log 2 fold-change value (IU vs. controls) and the vertical axis (y-axis) displays the noise-adjusted signal as the -log 10 (p-value) from the 1-way ANOVA analysis. **(B)** Top ten pathways represented in intermediate uveitis. Pathways are ranked by their -log (p-value) obtained from the right-tailed Fisher's Exact Test. **(C)** Upstream regulators predicted based on proteins that were differentially-expressed in intermediate uveitis vs. controls ($p < 0.05$). Upstream regulators are ranked by their activation z-score. Upstream regulators with significantly more "activated" predictions (positive z-score) are colored orange while regulators with significantly more "inhibited" predictions (negative z-score) are colored green. **(D)** Myeloid cell recruitment network. Results are displayed as a protein interaction network with proteins (nodes) connected by lines representing predicted or experimentally-confirmed interactions (edges). Upstream regulators are colored in orange, while experimentally-detected proteins are colored by relative expression (upregulation in red; downregulation in green). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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Role of the sponsor

The funding organizations had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of competing interest

None reported.

Acknowledgements & disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2020.100646.

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