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Mitochondrial-Mediated Platelet Activation in Polymyalgia Rheumatica

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Objective. Platelet activation is thought to participate in polymyalgia rheumatica (PMR) pathogenesis. Upon platelet activation, mitochondria are expelled into the extracellular space. However, whether extracellular mitochondria are present in patients with PMR and whether they can induce platelet activation is not known.

Methods. To investigate this, we measured markers of platelet activation (thrombospondin-1 [TSP-1]), mitochondrial-derived N-formyl methionine peptide (fMET), and autoantibodies directed toward specific mitochondrial antigen mitofusin-1 (MFN1) by enzyme-linked immunosorbent assay in plasma of healthy controls (HCs, n = 30) and patients with PMR without giant cell arteritis (GCA) (n = 45) and patients with PMR with GCA (n = 9) before and after treatment with glucocorticoid therapy. Ultrapure mitochondria were opsonized with plasma from patients with PMR without GCA (n = 45) or HCs (n = 10) and were subsequently incubated with HC platelets. Platelet activation was assessed by P-selectin levels using flow cytometry.

Results. Plasma levels of anti-MFN1 IgG were elevated in patients with PMR with and without GCA before glucocorticoid therapy when compared with HCs ($P < 0.01$ for both groups). Levels of anti-MFN1 IgG significantly reduced after treatment with glucocorticoids in both groups ($P < 0.01$). Levels of fMET were also significantly higher in patients with PMR with and without GCA before glucocorticoid therapy in comparison with HCs ($P < 0.001$ and $P < 0.01$, respectively). However, the levels of fMET only dropped significantly after therapy in patients with PMR without GCA ($P < 0.001$). Plasma levels of TSP-1 were elevated in patients with PMR with and without GCA before glucocorticoid therapy when compared to HC ($P < 0.001$ for both groups). After glucocorticoid therapy, plasma levels of TSP-1 decreased significantly only in patients with PMR without GCA ($P = 0.023$). Mitochondria opsonized with plasma from patients with PMR without GCA induced higher platelet activation regardless of treatment status as compared with plasma from HCs ($P < 0.0001$ and $P < 0.01$ for pretreatment and posttreatment).

Conclusion. Our results indicate increased platelet activation and the presence of mitochondrial antigens and antibodies in the circulation of patients with PMR. Blocking mitochondrial-mediated platelet activation may reduce inflammation in patients with PMR, with potential therapeutic implications.

INTRODUCTION

Polymyalgia rheumatica (PMR) is an idiopathic inflammatory disorder that affects elderly people.[1] Although the pathogenesis is not fully understood, platelet activation has been observed early in the disease onset,[2] with thrombocytosis at baseline predicting good response to glucocorticoids among patients with PMR.[3] Exaggerated platelet activation leads to thrombosis.[4] We recently demonstrated an increased risk of thrombotic events in patients with PMR.[5] During platelet activation, mitochondria can be expelled from platelets, exposing immunogenic molecules, including mitochondrial DNA and N-formylated methionine (fMET)

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peptides. This process promotes inflammation and acts as a source of autoantigens[6–8] that contribute to the formation of antimitochondrial antibodies (AMAs).

However, although the presence of extracellular mitochondria is well established in patients with autoimmune conditions such as rheumatoid arthritis (RA)[9] and systemic lupus erythematosus (SLE),[10] whether they occur in patients with PMR, and their relationship to platelet activation, has not been determined. In this study, we explored whether patients with PMR have elevated plasma levels of thrombospondin-1 (TSP-1), an alpha granule protein of human platelets, as well as mitochondrial antigens and antibodies. We also explored whether extracellular mitochondria, when opsonized with plasma factors, could mediate platelet activation in patients with PMR.

PATIENTS AND METHODS

Demographic characteristics and source of biospecimens. A total of 54 individuals with newly diagnosed PMR at the department of rheumatology, Umea University Hospital in Sweden were observed until remission, death, or end of follow up. All the patients fulfilled the Bird et al criteria for PMR.[11] Sex, age at diagnosis, symptom duration before diagnosis, prednisolone dose, and markers of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR] levels) were recorded (Table 1). When patients presented with clinical symptoms of PMR and a biopsy confirmed pathology of the temporal artery for giant cell arteritis (GCA), they were also diagnosed with GCA. Of the 54 patients with PMR, nine patients were diagnosed with biopsy-verified GCA. EDTA plasma samples were collected from each patient before and after prednisolone treatment. The tubes were spun for 15 minutes at 1,500*g*, aliquoted, and then frozen at –80°C until analyzed. No patient was treated with glucocorticoids when the first sample was collected, all patients were newly diagnosed with PMR, and no one had a relapse. None of the patients had another rheumatic disease at the time of diagnosis. Patients were regarded as having active disease when having symptoms, such as signs of being ill, fever, weight loss, new or an increase of pain and ache in shoulders or gluteal areas, and increased ESR or CRP levels.

Healthy controls (HCs, n = 30) were recruited at the University of Washington and Bloodworks, Seattle. The study was approved by the institutional review boards at the University of Washington, Seattle (#3100) and the Ethics Committee at Umea University (§192/96, dnr 96-138). Informed consent was obtained from participants in accordance with the Helsinki Declaration.

Enzyme-linked immunosorbent assay. Recombinant mitofusin-1 (MFN1) (MyBioSource, MBS2033248) at 2 μg/mL in 0.1 *M* sodium bicarbonate buffer (Polysciences, 24094-10) was coated in medium-binding 96-well enzyme-linked immunosorbent assay (ELISA) plates overnight at 4°C. The plate was washed five times with wash buffer (0.05% Tween 20 in phosphate buffered saline [PBS]) and subsequently blocked with 10% fetal bovine serum in PBS for 2 hours at room temperature (RT). Then, EDTA plasma samples diluted 1:1,000 in blocking buffer were added to the wells and incubated for 90 minutes at 37°C. The plate was then washed and incubated with antihuman IgG-HRP (Jackson ImmunoResearch, 109-035-008) diluted 1:2,000 in blocking buffer for 90 minutes at 37°C. After washing the plate, the reaction was developed with 3,3′5,5′-Tetramethylbenzidine substrate (BioLegend, 421101). The reaction was stopped by 2N sulfuric acid. Absorbance was measured by a plate reader at 450 nm (Synergy 2, BioTek). Plasma levels of human N-formyl methionine (My BioSource Inc.) and TSP-1 (R&D Systems) were measured by ELISA according to manufacturers' instructions.

Mitochondrial isolation. Mitochondria were isolated from HepG2 cells upon 80% to 90% confluency. After trypsinization, the

Table 1. Baseline demographic characteristics of patients*

Descriptive data	All patients with PMR (n = 54)	Patients with PMR without GCA (n = 45)	Patients with PMR with GCA (n = 9)	HC (n = 30)	*P* value
Women, n (%)	40 (74.1)	33 (73.3)	7 (77.8)	21 (70)	0.688[a]
Age at inclusion, mean (SD), y	73 (8)	72 (8)	76 (7)	40 (14)	<0.001
Symptom duration before diagnosis, mean (SD), mo	2.5 (1.6)	2.7 (1.6)	1.9 (1.4)	NA	NA
First follow up, mean (SD), mo	3.7 (2)	3.7 (3)	4.2 (3)	NA	NA
Glucocorticoid dose at start, mean (SD), mg/daily	21.9 (5.6)	20.4 (3.3)	28.9 (8.9)[b]	NA	NA
ESR at start before glucocorticoids, mean (SD), mm/h	60 (23.3)	59 (22.7)	62 (27.5)	Not measured	NA
CRP at start before glucocorticoids, mean (SD), mg/L	48 (36.7)	47 (35.6)	51 (44.3)	Not measured	NA
Platelets count at start before glucocorticoids, mean (SD), × 10^9	360 (92)	362 (86)	350 (127)	Not measured	NA
ESR level after glucocorticoids, mean (SD), mm/h	12 (6.5)	12 (6.5)	12 (7.4)	Not measured	NA
CRP level after glucocorticoids, mean (SD), mg/L	11 (3.1)	11 (2.6)	12 (5.3)	Not measured	NA
Platelet count after glucocorticoids, mean (SD), × 10^9	267 (61)	266 (62)	273 (61)	Not measured	NA

**P* values calculated using the Mann-Whitney U test comparing both groups of patients with PMR with HCs. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; HC, healthy control; NA, not applicable; PMR, polymyalgia rheumatica.
[a]Calculated using Pearson chi-square test.
[b]Patients with PMR with GCA versus patients with PMR without GCA calculated using Mann-Whitney U test. $P < 0.001$.

cells were resuspended in homogenization buffer (525 mM mannitol, 175 mM sucrose, 12.5 mM Tris-HCL pH 7.5, and 2.5 mM EDTA pH 7.5) and subjected to homogenization using Dounce homogenizer. The homogenized material was centrifuged at 700*g* for 10 minutes at 4°C twice to remove debris, followed by centrifugation at 3,000*g* for 10 minutes at 4°C. Isolated mitochondria were subjected to treatment with DNase (10 mg/mL, dilution 1,50, Roche) for 60 minutes at 37°C, and stored at −80°C until use in functional assays.

Platelet-rich plasma isolation. Blood from a healthy individual was drawn, using a 21G needle without a tourniquet, in sodium citrate vacutainers and centrifuged at 200*g* for 15 min at RT to obtain platelet-rich plasma (PRP). PRP was then used immediately for functional studies.

Platelet activation assay with extracellular mitochondria by flow cytometry. In brief, 10,000 mitochondria/well were incubated with patient (n = 45, PMR) or HC (n = 10) plasma (6% diluted in Tyrode's buffer) in a 96-well round bottom plate for 30 min at 37°C with 5% CO_2, and then centrifuged at 3,000*g* for 10 minutes at 4°C. Supernatants were discarded and opsonized washed mitochondria were incubated with fluorescein isothiocyanate-conjugated anti-CD41 antibodies, phycoerythrin-conjugated anti-CD62P (P-selectin) antibodies, and PRP (6%) anticoagulated with corn trypsin inhibitor at 50 μg/mL in Tyrode's buffer with Ca^{2+} and Mg^{2+}. Platelets were fixed with paraformaldehyde (2%) after 20 minutes and assessed for activation by flow cytometry.

Statistical analysis. The Mann-Whitney U test, Wilcoxon signed-rank test, and Spearman's correlation were used as applicable, and Pearson chi-square test was used for categorical data. Data analysis was performed in GraphPad Prism (GraphPad Software Inc.) and considered statistically significant at $P < 0.05$.

RESULTS

Demographic characteristics of the study population. The mean (SD) age of the patients with PMR at the time of diagnosis was 73 ± 8 years old (Table 1), and 74.1% of the patients were women. The mean (SD) symptom duration before diagnosis of PMR was 2.5 ± 1.6 months. At diagnosis of PMR, the patients had been diagnosed with the following comorbidities: diabetes Type II (n = 2), stroke (n = 2), previous myocardial infarction or angina pectoris (n = 15), osteoporosis (n = 3), and cancer treatment (n = 4). Eighteen patients were being treated with low doses of aspirin (ASA), and among these patients, seven of them reported concurrent treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). Three patients were only treated with warfarin. The mean (SD) daily dose of prednisolone at disease onset was 21.9 ± 5.6 mg. The mean (SD) ESR level was 60 ± 23 mm/hr, whereas the mean (SD) CRP level was 48 ± 37 mg/L before the initiation of therapy with glucocorticoids, fairly similar for both patient groups (patients with PMR with and without GCA). After treatment, the mean (SD) ESR level dropped to 12 ± 6.5 mm/hr, whereas the mean (SD) CRP level decreased to 11 ± 3.1 mg/L, with a similar trend for patients with PMR with and without GCA. The platelet counts decreased significantly from baseline before initiation of therapy until after treatment for both groups (patients with PMR without GCA, $P = 0.021$; patients with PMR with GCA, $P < 0.001$; Table 1).

Mitochondrial components as biomarkers of disease activity in patients with PMR. Plasma levels of anti-MFN1 IgG in patients with PMR with and without GCA with active disease before the initiation of glucocorticoid therapy had a median of 0.43 (interquartile range [IQR] 0.28–0.71) arbitrary unitis (AU) and 0.83 (IQR 0.32–0.83) AU, respectively, which was significantly higher compared with the levels of HCs that had a median of 0.22 (IQR 0.15–0.25) AU ($P < 0.01$ for both; Figure 1A). After glucocorticoid therapy, levels of anti-MFN1 IgG dropped significantly for both patient groups ($P < 0.01$, Figure 1A), with the median concentrations being 0.38 (IQR 0.24–0.50) AU and 0.41 (IQR 0.19–1.0) AU.

As shown in Figure 1B, plasma levels of fMET were significantly elevated in patients before glucocorticoid therapy with active disease compared with healthy individuals. The median concentration of fMET in patients with active disease in patients with PMR without GCA before glucocorticoid therapy was 18.6 (IQR 16.2–19.9) ng/mL, and in patients with PMR and GCA was 17.9 (IQR 17.2–19.4) ng/mL, which was significantly higher ($P < 0.001$ and $P < 0.01$, respectively) compared with HCs (median 11.31 [IQR 7.1–16.3] ng/mL). Plasma levels of fMET decreased significantly after glucocorticoid therapy in patients with PMR without GCA (median 11.2 [IQR 4.8–15.9]; $P < 0.001$ ng/mL), but not in patients with PMR with GCA (median 15.0 [IQR 14.1–18.4] ng/mL; Figure 1B). The plasma levels of fMET after glucocorticoid therapy was significantly higher in patients with PMR with GCA compared with patients with only PMR ($P < 0.05$). Plasma levels of fMET in the group with PMR without GCA correlated with ESR levels ($r_s = 0.33$, $P < 0.05$), CRP levels ($r_s = 0.52$, $P < 0.01$), and platelet count ($r_s = 0.37$, $P < 0.05$) in samples before prednisolone treatment. None of these correlations were found in patients with PMR and GCA.

Platelet marker TSP-1 as a biomarker of disease activity in patients with PMR. The median concentration of TSP-1 in patients with PMR with active disease before glucocorticoid therapy was 27 (IQR 17.5–34.5) μg/mL, and for patients with PMR with GCA the median concentration of TSP-1 was 23.2 (IQR 15.8–31.1) μg/mL (Figure 1C), which was significantly higher ($P < 0.001$ for both groups) when compared with HCs (median 8.9 [IQR 4.8–11.6] μg/mL). After glucocorticoid therapy, plasma

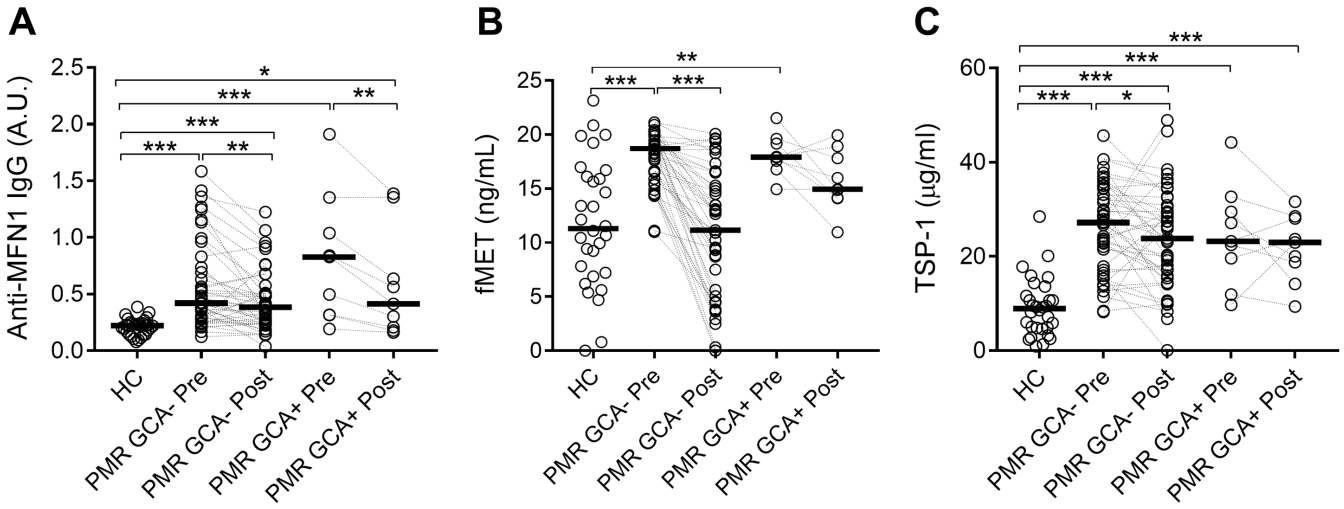

Figure 1. Levels of anti-MFN1, fMET, and TSP-1 in patients with PMR. Plasma levels of (A) anti-MFN1, (B) fMET, and (C) TSP-1 were measured by ELISA in HCs (n = 30), and patients with PMR before (n = 54) and after treatment with glucocorticoid therapy (n = 54), stratified based on overlapping disease with GCA (PMR GCA+, n = 9) or without GCA (PMR GCA–, n = 45). Statistical analyses were performed using Mann-Whitney U test and Wilcoxon signed-rank test. Statistical analyses were compared with HCs unless stated otherwise. Each circle represents an individual sample with the bar representing the median of the group. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. AU, arbitrary units; ELISA, enzyme enzyme-linked immunosorbent assay; fMET, N-formylated methionine; GCA, giant cell arteritis; HC, healthy control; MFN1, mitofusin-1; PMR, polymyalgia rheumatica; TSP-1, thrombospondin-1.

levels of TSP-1 decreased significantly in the group with PMR without GCA to a median concentration of 23.8 (IQR 15.7–30.6) µg/mL ($P = 0.023$), whereas in the group with PMR with GCA, there was nonsignificant reduction to a median concentration of 23.0 (IQR 16.5–28.3) µg/mL (Figure 1C). Levels of TSP-1 correlated with the platelet count ($r_s = 0.38$, $P < 0.05$) at baseline. Of note, there was no significant difference in the levels of TSP-1 between individuals treated with aspirin (n = 18) and individuals without aspirin treatment (n = 36) before or after prednisolone intake in our cohort with PMR (Supplementary Table 1). No difference was observed among individuals treated with aspirin that used NSAIDs (n = 7) compared with individuals treated with aspirin not using NSAIDs (n = 11) (Supplementary Table 2).

Regulation of mitochondria by platelets. Mitochondria were capable of inducing platelet activation (dotted line, Figure 2C), whereas pre-opsonization of mitochondria with plasma from healthy individuals reduced this capacity. Interestingly, pre-opsonization of mitochondria with plasma from patients with PMR increased the ability of mitochondria to promote platelet activation as compared to plasma from HCs ($P < 0.0001$, Figure 2A–C). The ability of plasma to support mitochondrial-mediated platelet activation was not associated with disease activity in patients with PMR.

DISCUSSION

Although mitochondrial abnormalities have been observed in the skeletal muscles of patients with PMR,[12–13] it is unknown whether mitochondrial components are extruded into the extracellular space contributing to the propagation of inflammation. We recently demonstrated the presence of extracellular mitochondrial-derived fMET in systemic vasculitis.[7] Herein, we were able to show that patients with PMR also have increased levels of fMET in circulation. Plasma levels of fMET not only differed between patients with PMR and HCs but were also reduced after treatment with glucocorticoids, suggesting that this mitochondrial component could be used as a biomarker of disease activity in patients with PMR. Importantly, levels of fMET correlated with markers of inflammation, similarly to what we have previously demonstrated in patients with systemic vasculitis.[7] Although the mean age of HCs at inclusion was approximately 30 years younger than the age of patients with PMR, there was no association of fMET, anti-MFN1, and TSP-1 levels with age in the cohort with PMR or among HCs (data not shown).

Extracellular mitochondria are immunogenic and serve as a source of autoantigen leading to formation of AMAs. Indeed, the presence of AMAs, including against the mitochondrial component cardiolipin, has been reported in patients with PMR.[14] However, it is unknown whether other AMAs are seen in patients with PMR. We demonstrated in this study the presence of circulating anti-MFN1 IgG antibodies in patients with PMR. Anti-MFN1 IgG antibodies have been detected in patients with SLE[15] and patients with RA, identifying seronegative patients developing erosive disease.[16] The presence of autoantibodies targeting mitochondria supports our hypothesis of extracellular mitochondrial components being present in patients with PMR, stimulating the immune response toward the mitochondrial autoantigens.

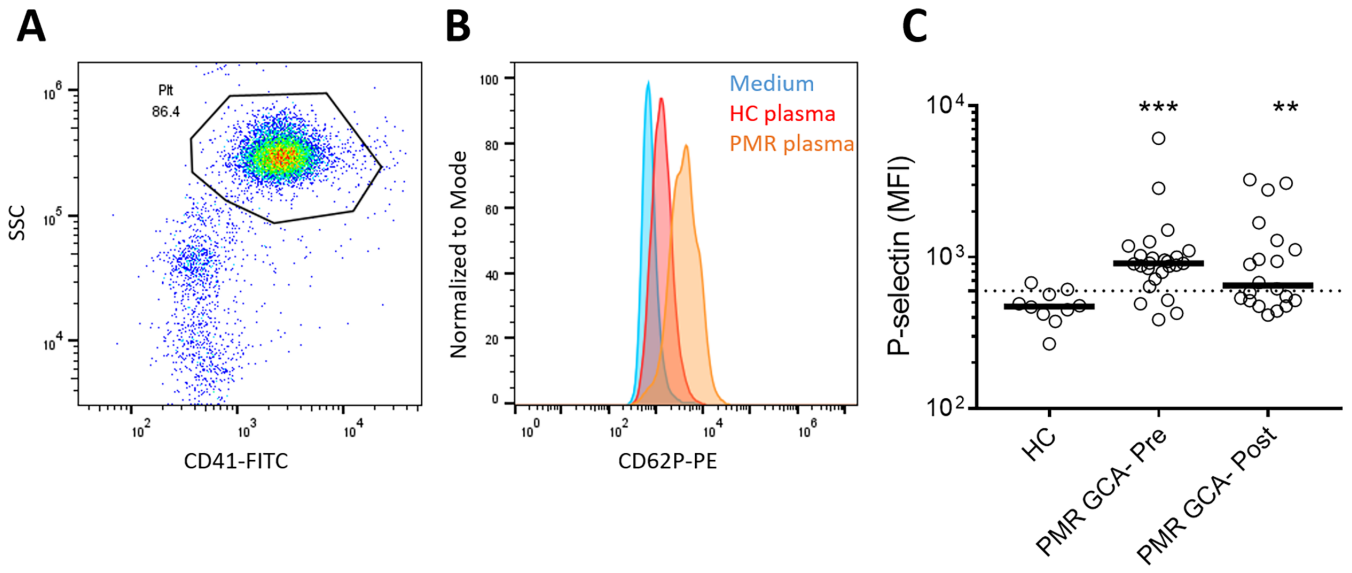

Figure 2. Mitochondrial-induced platelet activation in patients with PMR. (A) Representative SSC plot demonstrating a distinct population of platelets (CD41) as measured by flow cytometry. (B) Representative histogram illustrating platelet activation (CD62P) as measured by flow cytometry upon incubation with mitochondria opsonized with medium control (blue), plasma from HCs (red), or plasma from patients with PMR (orange). The histograms are normalized to mode with 100 being equal to peak levels for visualization. (C) PRP from a healthy individual was exposed to mitochondria opsonized with plasma from patients with PMR GCA– before treatment (n = 25) and after treatment (n = 20) or HC (n = 10). Results are shown as the MFI. The dotted line represents the induction of P-selectin by nonopsonized mitochondria. Statistical analyses were done using the Mann-Whitney U test. Each circle represents an individual sample, with the bar representing the median of the group. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. FITC, fluorescein isothiocyanate; GCA, giant cell arteritis; HC, healthy control; MFI, mean fluorescence intensity; PE, phycoerythrin; PMR, polymyalgia rheumatica; PRP, platelet-rich plasma; SSC, side scatter.

The potential clinical usage of this novel autoantibody in patients with PMR needs to be determined in larger multicenter studies.

Extracellular mitochondria can bind to platelets, resulting in the release of reactive oxygen species and induction of a procoagulant platelet phenotype.[17,18] In the current study, we were able to demonstrate that mitochondria were able to activate platelets, with up-regulation of cell surface marker P-selectin, making extracellular mitochondria a novel target for antiplatelet therapies. Plasma factors from patients with PMR amplified the capacity of mitochondria to promote platelet degranulation. This phenomenon persisted after treatment with glucocorticoid therapy, suggesting a state or a potential of chronic platelet activation. Similarly, in one of our recent studies, we demonstrated that when mitochondria were opsonized by plasma factors from patients with GCA, they acquired the capacity to regulate platelet activation.[19]

We further found that levels of TSP-1 were significantly elevated in patients with PMR. Importantly, although decreasing upon treatment, levels of TSP-1 were still markedly elevated as compared with TSP-1 levels observed in healthy individuals, which was consistent with chronic platelet activation despite disease status. The role of this platelet activation in the disease progression in patients with PMR is unknown. However, we recently demonstrated increased platelet activation in patients with systemic vasculitis, with levels of TSP-1 levels being significantly higher in patients with granulomatosis with polyangiitis with a history of thromboembolic events.[20] Whether platelet activation in patients with PMR similarly can reflect thrombotic disease is yet to be determined.

Our study has some limitations. The sample blood plasma that was prepared by centrifugation in this cohort might have produced platelet-low plasma, and plasma filtration or a second centrifugation was not performed to remove all of the platelet content.[21] The sources of TSP-1 and fMET could not be firmly established in this study. Despite platelets being a major source of TSP-1, TSP-1 can also be stored in Weibel-Palade bodies of endothelial cells.[22] Although mitochondria are the sole source of mitochondria in humans, bacterial infections may also contribute to fMET levels.[23] However, none of the patients were diagnosed with any clinical infection, reducing the likelihood of a bacterial source. Finally, although we were able to identify a novel and interesting dysregulation in the interaction between opsonized mitochondria and platelet counts in patients with PMR, we were unable to highlight the specific factors contributing to the impaired clearance and subsequent exaggerated platelet activation. Further studies are warranted to explore the mechanisms promoting mitochondrial-mediated inflammation and clearance in patients with PMR.

In conclusion, we found evidence of mitochondrial extrusion and platelet activation in patients with PMR corresponding to

disease activity. Further, PMR-derived plasma factors enabled enhanced mitochondrial-mediated platelet activation. The identity of those factors is yet to be determined. Suppressing mitochondrial extrusion may reduce platelet activation and thrombotic complications, possibly relevant for several autoimmune diseases and could be used as a new target for the development of antiplatelet drug therapy.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Lood confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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