Parkinsonism and Related Disorders 143 (2026) 108155

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

SGK1 downregulation co-occurs with leukocyte oligomeric α-synuclein accumulation in Parkinson's disease

Federica Veltri [a,1], Giulia Maria Sancesario [b,1], Marco Rosina [c,1], Davide Mascioli [a,d,1], Jacopo Bissacco [a,d], Matteo Conti [a,d], Henri Zenuni [a], Valentina Nesci [e], Daniela Maftei [d], Veronica Buttarazzi [a,d], Maria Mancini [a,d], Clara Simonetta [a], Ermanno Berlizzi [a,f], Aikaterini Andradi [a,f], Federica Todaro [a], Valerio Chiurchiù [g,h], Alberto Ferri [e,g], Cristiana Valle [e,g], Alessandro Stefani [a,d], Nicola Biagio Mercuri [a,d,i], Alfonso Bellia [a,f], Davide Lauro [a,f], Tommaso Schirinzi [a,d,*]

[a] Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy
[b] Clinical Neurochemistry Unit and Biobank, IRCCS Fondazione Santa Lucia, European Centre for Brain Research, Rome, Italy
[c] Italian National Institute of Health (ISS), Department of Neuroscience, Rome, Italy
[d] Unit of Neurology, Fondazione PTV – Tor Vergata University Hospital, Rome, Italy
[e] Laboratories of Neurochemistry and of Molecular and Cellular Neurobiology, IRCCS, Santa Lucia Foundation, Rome, Italy
[f] Unit of Endocrinology and Diabetology, Fondazione PTV – Tor Vergata University Hospital, Rome, Italy
[g] Institute of Translational Pharmacology (IFT), National Research Council (CNR), Rome, Italy
[h] Laboratory of Resolution of Neuroinflammation, IRCCS Santa Lucia Foundation, Rome, Italy
[i] Laboratory of Experimental Neuroscience, IRCCS Santa Lucia Foundation, Rome, Italy

ARTICLE INFO

Keywords:
Parkinson's disease
SGK1
α-synuclein
PBMCs
Neuroinflammation
Biomarker

ABSTRACT

Background: Serum and glucocorticoid-inducible kinase 1 (SGK1) is a ubiquitous kinase with cytoprotective and immune-specific functions. Parkinson's disease (PD) animal models disclosed interactions between SGK1 and the critical pathogenic pathways of the disease, whereas human-based evidence is lacking. We investigated the SGK1 contribution to the biological dynamics of PD *ex vivo,* at immune and systemic level.

Methods: Thirty-two well-phenotyped PD patients and 34 controls were enrolled. Peripheral blood mononuclear cells (PBMCs) and serum were obtained. PBMCs levels of SGK1, α-synuclein total and oligomeric forms ($\alpha\text{-syn}^{tot}$, $\alpha\text{-syn}^{olig}$) were measured by Western blot and ELISA, respectively. SGK1 levels were tested in the serum by ELISA. Group differences were assessed using age-adjusted, rank-based linear regression models; ROC analysis was performed using age-adjusted PBMC SGK1 residuals and a Youden-derived cutpoint; associations with clinical variables were tested using age-adjusted regressions.

Results: PD PBMCs exhibited lower SGK1 ($p < 0.001$) and higher $\alpha\text{-syn}^{olig}$ levels than controls ($p = 0.026$). SGK1 serum levels were also lower in PD patients ($p = 0.040$). ROC analysis showed that PBMC SGK1 significantly discriminated PD from controls (AUC = 0.85,[95 % CI 0.75–0.95],$p < 0.001$). The optimal cutpoint yielded a sensitivity of 1.00 and a specificity of 0.60. No significant correlations were found between biological and clinical parameters.

Conclusions: In PD patients, SGK1 was downregulated in both PBMCs and serum. Given the preliminary nature of these findings and the co-occurrence of $\alpha\text{-syn}^{olig}$ accumulation in leukocytes, common mechanistic pathways might be supposed, although pending confirmation. Nevertheless, SGK1 emerged as a potential target in PD, for both biomarker and therapeutic purposes.

* Corresponding author. Unit of Neurology, Department of Systems Medicine, Tor Vergata University of Rome, Via Montpellier, 00133, Rome, Italy.
E-mail addresses: t.schirinzi@yahoo.com, tommaso.schirinzi@uniroma2.it (T. Schirinzi).
[1] These authors equally contributed as first authors.

https://doi.org/10.1016/j.parkreldis.2025.108155
Received 13 October 2025; Received in revised form 4 December 2025; Accepted 13 December 2025
Available online 14 December 2025
1353-8020/© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder responsible for a progressive motor and non-motor syndrome. Neuropathology hallmarks are the loss of dopaminergic nigral cells and the intraneuronal accumulation of α-synuclein (α-syn)-positive Lewy bodies. PD pathogenesis is complex and arises from the impairment in multiple cellular pathways [1], but the immune system activation also provides a critical contribution [2,3]. In this regard, there is solid evidence on central neuroinflammation, whereas knowledge on peripheral immunity is still emerging. Circulating leukocytes rearrange their subpopulations in PD patients, shaping a systemic inflammatory state [4,5] and undergo molecular reprogramming consistent with a direct participation in the disease mechanisms. Moreover, peripheral blood mononuclear cells (PBMCs) recapitulate key PD pathology features, including the accumulation of pathological α-syn species and the impairment of main cellular systems, supporting their use in translational frameworks [6,7].

Serum and glucocorticoid-inducible kinase 1 (SGK1) is a ubiquitously expressed phosphorylation-activated kinase. Several hormones, inflammatory and metabolic mediators, promote the expression of SGK1 that, in turn, modulates ion channels and pumps, glucose metabolism enzymes, and transcription factors involved in a cytoprotective signaling network [8–10]. In addition, SGK1 exerts specific regulatory activity on different immune cell subtypes, tuning their differentiation and activity [10].

This functional profile underlies SGK1 involvement in chronic conditions, such as diabetes, cancer, cardiovascular, inflammatory, and neurological diseases, including PD [8–10]. Indeed, SGK1 steers those pathways classically linked to PD pathogenesis, which encompass α-synuclein aggregation dynamics, mitochondrial dysfunction, oxidative stress, and neuroinflammatory signaling [11–14]. However, most of the evidence on the role of SGK1 in PD basically derives from animal models, whereas there are still no data from living patients.

Taking into consideration the relevance of peripheral immune cells to the pathogenic mechanisms of PD, as well as their ability to reflect primary disease hallmarks [6,7], we evaluated SGK1 levels and their correlations with PBMC α-syn species in well-phenotyped PD patients and controls. Since PBMC α-syn species are emerging peripheral markers of synucleinopathy, we also compared their levels between groups to assess whether SGK1 downregulation aligns with altered α-syn handling. We then examined the relationship between leukocyte SGK1 expression and PD clinical-pathological features. Finally, by measuring SGK1 in serum as a readout of systemic expression, we provided a first overall assessment of SGK1's potential as a novel disease target in PD.

2. Materials and methods

2.1. Study population

We conducted a case–control study at Tor Vergata University Hospital (Rome, Italy), from 2022 to 2024, involving 32 PD patients and 34 healthy controls with a similar age and sex distribution. PD was diagnosed following MDS 2015 Postuma's criteria [15]. Controls were healthy volunteers without a history or clinical signs of neurological diseases. Individuals with main acute/chronic infectious/inflammatory/systemic diseases, immunosuppressive/immunomodulatory therapies, recent vaccination, and other neurological diseases were excluded. A flowchart summarizing the selection process is shown in Supplementary Fig. 1.

For each subject, we collected demographic, anthropometric, and medical history data. PD patients were assessed using the MDS-UPDRS part III, Non-Motor Symptoms Scale (NMSS), Mini-Mental State Examination (MMSE), adjusted for age and educational level, and the levodopa equivalent daily dose (LEDD) calculation. The assessment was performed within one week of the blood sampling, in "on" state (under the effect of dopaminergic therapy).

2.2. Blood sampling and PBMCs isolation

All participants received a venous blood sampling (15 mL) in the morning, after overnight fasting, for PBMCs extraction and serum separation. PBMCs extraction was performed as previously described [16]. Briefly, the blood sample was processed to separate PBMCs by density gradient centrifugation with Ficoll– Hypaque (GE Healthcare Life Sciences, Milano, Italy), according to standard procedures. Samples were then diluted 1:1 with phosphate-buffered saline and stratified on Ficoll–Hypaque (0.7 vol in respect to diluted blood). PBMCs were carefully frozen in cryoSFM medium (Merck KGaA, Darmstadt, Germany) and stored in liquid nitrogen and subsequently thawed for bioenergetics and immunoblot analyses (2 x 10 7 cells/mL). Cell viability was assessed with Try-pan Blue staining before cryopreservation and after thawing. All PBMCs experiments have been run within 1 year of collection. All operators involved in the experimental procedures were blinded to the patient's clinical diagnoses. All serum and PBMC samples were randomly analyzed using ELISA techniques to detect and quantify specific proteins and analytes.

2.3. PBMCs protein quantification and SGK1 western blot assay

SGK1 Western blot assay was conducted on lysed PBMCs by using the following primary antibodies: rabbit anti SGK1 (Cell Signaling, #D27C11), GAPDH (AB Clonal, #AC002); and secondary antibody: Goat Anti-Mouse IgG, Goat Anti-Rabbit IgG. For immunoblot analysis, cells were lysed in RIPA buffer (50 mM Tris-base, 150 mM NaCl, 1 % NP-40, 0.5 % sodium deoxycholate), supplemented with 1 mM sodium orthovanadate, 1 mM NaF, and a protease inhibitor cocktail (1 × , Sigma-Aldrich, Cat. No. P3840). Lysates were incubated on ice for 30 min, followed by centrifugation at 16,000×*g* for 30 min at 4 °C to remove insoluble material.

Protein quantitation was assessed with Bradford Bio-Rad Protein Assay Dye Reagent Concentrate 5 × . After protein dosage, the supernatant was treated with Sample Buffer 4 × (Tris base 125 mM, 4 % of Sodium dodecyl sulphate, 20 % of Glycerol, 0.004 % of bromophenol blue, 10 % of beta-mercapto-ethanol) and incubated for 10 min at 96 °C. 30 μg of proteins were loaded onto SDS-polyacrylamide gel and subjected to electrophoresis with 1 × tris-glycine-SDS running buffer and blotted overnight (4 °C for 16 h) at 30V in immersion transfer system loaded with 20 % v/v methanol tris-glycine transfer buffer. The correct protein transfer was evaluated through 1 mg/ml in 5 % v/v acetic acid Ponceau S solution. Membranes were washed 3 times for 10 min with TBS-0.1 % v/v Tween 20 (TBS-T) until completely clear and blocked with 5 % non-fat dry milk in TBS-T for 1 h at RT. Primary antibodies were incubated overnight at 4 °C in appropriate buffer and dilutions: rabbit anti SGK1 (1:1000 v/v in 5 % w/v milk/TBS-T, Cell Signaling, #D27C11), and GAPDH (1:10000, in 5 % w/v BSA/TBS-T, AB Clonal, #AC002). The day after, membranes were washed 3 times with TBS-T for 10 min and incubated for 1 h at RT with secondary antibody: Goat Anti-Mouse IgG (1:3000 v/v in 2 % w/v milk/TBS-T), Goat Anti-Rabbit IgG (1:3000 v/v in 2 % w/v milk/TBS-T). Membranes were washed 3 times with TBS-T for 10 min. For protein detection, the chemiluminescence was acquired with an iBright CL Imaging System (Applied Bioscience) using ClarityTM Western ECL Substrate. Densitometric analysis of the immunoreactive bands was performed using ImageJ (NIH) analysis Software. SGK1 protein levels were normalized against the respective GAPDH.

2.4. α-syn PBMC quantification by ELISA

Total α-syn (α-syn^{tot}) and oligomeric α-syn (α-syn^{olig}) levels were assessed using ELISA kits from Invitrogen (KHB0061) and MyBioSource (MBS730762), respectively, on proteins derived from PBMCs. For both

ELISA kits 10 μg of protein were loaded. Unknown samples were derived from standard curve fitting with a 4-parameter logistic (4-PL) algorithm. All samples (blanks, standards, and unknowns) were read in duplicate. A unique 96-well ELISA plate was sufficient to run all samples analyzed in the present study. All samples were in the standard curve range. The Optical density (O.D.) was determined at 450 nm using a microplate reader Victor3V (PerkinElmer).

2.5. SGK1 serum quantification by ELISA

Serum concentration of SGK1 was measured using Human SGK1 ELISA Kit (Invitrogen, Thermofisher). The protocol was previously validated to assess the reproducibility and accuracy by serial dilution. All samples (100 μL) were diluted 2x and analyzed in duplicate. Colorimetric reactions were measured by reading the absorbance at 450 nm after the addition of a stop solution, using Varioskan LUX Multimode Microplate Reader (Thermo Fisher). Unknown concentrations in the samples were determined by plotting absorbance values on the corresponding standard curve, using a 4-parameter logistic (4-PL) algorithm (GraphPad software).

2.6. Statistical analysis

Between-group comparisons (PD vs controls) of continuous biological variables (PBMC and serum SGK1, PBMC α-syn^{tot} and α-syn^{olig}) were examined using age-adjusted, rank-based linear regression models, with group as the main predictor and age as a covariate. Unadjusted ranks are shown in Fig. 1 for descriptive and visualization purposes. Categorical variables were compared using the χ^2 test. Receiver operating characteristic (ROC) analysis was used to evaluate PBMC SGK1 discrimination between PD and controls. For ROC analysis, residuals from a linear regression models with PBMC SGK1 as the dependent variable and age as the only predictor (computed in the pooled sample) were used. The optimal cutpoint was defined using Youden's J statistic. Within-group associations between biomarkers (SGK1, α-syn) and demographic variables (age, sex) were evaluated using rank-based linear regression models, while associations with clinical variables (MDS-UPDRS III, H&Y stage, NMSS, MMSE scores) were assessed using age-adjusted rank-based models. Analyses were performed using SPSS 29 (Armonk, NY). All analyses were two-sided and were performed with a significance level set at $P < 0.05$.

2.7. Sample size and power

An a priori power analysis was performed using G*Power. Since the primary comparisons were performed using ANCOVA with two covariates, we conducted a power calculation based on this model (F-test, fixed effects, main effects and interactions). Assuming a large effect size ($f = 0.40$; $\eta^2 = 0.14$), a two-sided $\alpha = 0.05$, and 80 % statistical power, the required total sample size for two groups was $N = 52$. Our final sample size (32 patients with PD and 34 controls; total $N = 66$) exceeded this a priori requirement, ensuring adequate power for the planned analyses.

3. Results

Table 1 summarizes demographics, clinical and biological parameters of the study population.

3.1. SGK1 levels

Rank-transformed PBMC SGK1 levels were significantly lower in PD patients compared with controls after adjustment for age ($\beta = -19.33$, 95 % CI -27.64 to −11.02, $p < 0.001$). Also, serum SGK1 levels showed lower values in PD than in controls ($\beta = -8.62$, 95 % CI -16.77 to −0.47, $p = 0.04$) (unadjusted ranks are shown in Fig. 1). ROC analysis based on

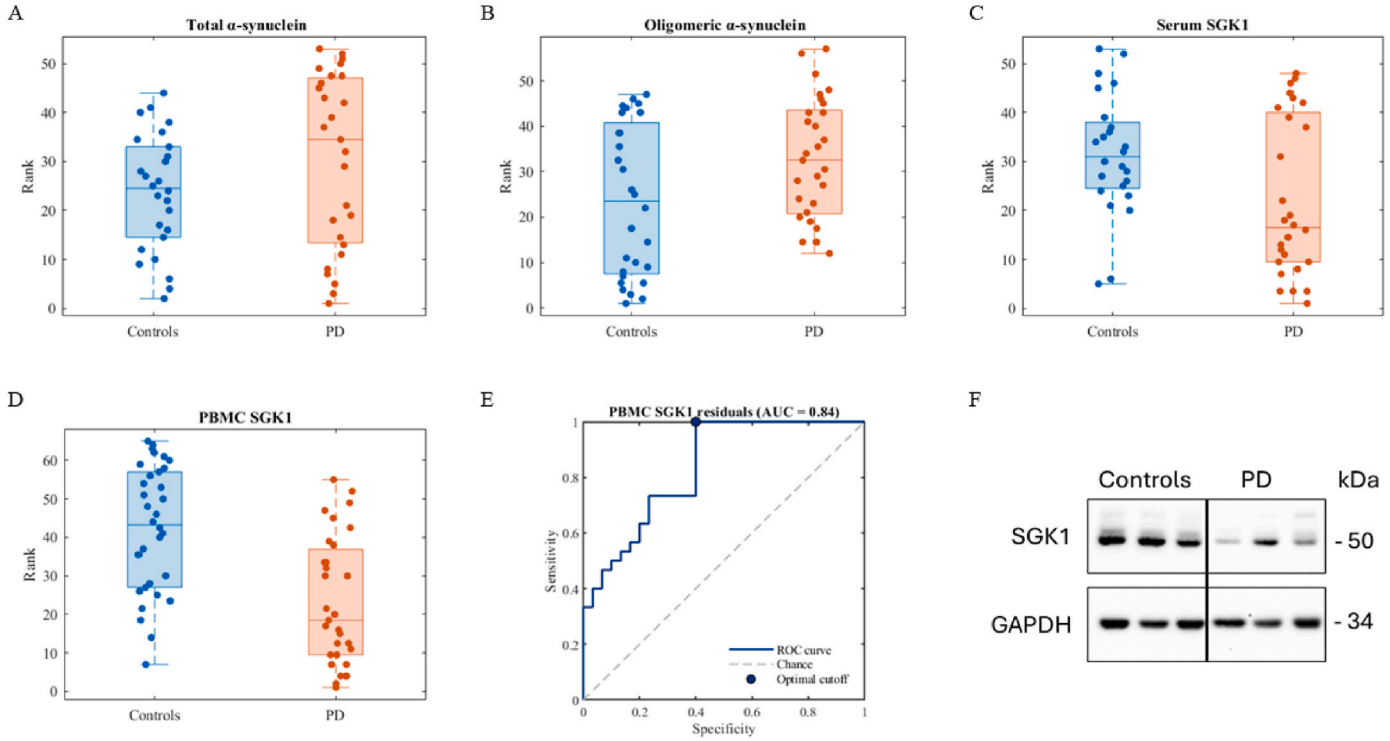

Fig. 1. PBMC and serum SGK1 and PBMC α-synuclein in PD and controls.
Box-and-dot plots display unadjusted ranks of PBMC α-synuclein total (**A**) and oligomeric (**B**), and serum (**C**) and PBMC SGK1 (**D**), and a representative Western blot gel (**F**). ROC analysis (**E**) shows the discriminative performance of age-adjusted PBMC SGK1 (regression residuals) (AUC, optimal Youden's J cutoff with sensitivity and specificity).

Table 1
Demographic and clinical characteristics of the study population.

Variable	PD patients (n = 32)	Controls (n = 34)
Age (y)	66.3 ± 9.7 (49.0–83.0)	63.7 ± 8.0 (48.0–78.0)
Sex (m/f)	19/13 (40.6 % f)	20/14 (41.2 % f)
BMI	28.15 ± 2.18 (24.4–32.7)	27.65 ± 2.02 (24.1–31.2) *(n=28)*
PBMC SGK1 *(ng/ml)*	0.3 ± 0.3 (0.01–1.1)	0.8 ± 0.6 (0.06–2.7)
Serum SGK1 *(ng/ml)*	8.5 ± 9.2 (0.4–25.8)	9.7 ± 9.8 (2.00–32.6)
Total α-synuclein *(ng/ml)*	2.2 ± 1.3 (0.09–4.9)	1.7 ± 0.7 (0.3–3.0)
Oligomeric α-synuclein *(ng/ml)*	2.5 ± 0.2 (2.2–3.2)	2.3 ± 0.3 (1.8–2.8)
Disease duration (y)	4.0 ± 3.4 (0.5–9.5)	–
MDS-UPDRSIII	38.2 ± 14.3 (16.0–70.00)	–
NMSS	45.3 ± 38.6 (3.00–180.00)	–
MMSE	27.3 ± 2.6 (22–30.00)	–
LEDD	612.6 ± 253.5 (160.00–950.00)	–

Abbreviations: f = female, m = male, n = number; y = years; other abbreviations are spelled out in the text. Results are expressed as mean ± standard deviation (minimum - maximum) for continuous variables and as absolute counts for categorical variables.

age-adjusted PBMC SGK1 residuals yielded an AUC of 0.85 (95 % CI 0.75–0.95, $p < 0.001$). The optimal cut-point residual value (−0.322), identified by Youden's J statistic, provided a sensitivity of 0.97 and a specificity of 0.61 (Fig. 1). No significant associations were found between SGK1 levels and demographic variables (age, sex) in either PD patients or controls (Supplementary Table S1). No significant associations were found between SGK1 levels (serum or PBMC) and PBMC α-syn species (total or oligomeric), as assessed through age-adjusted rank-based regression analyses (Supplementary Table S2).

3.2. PBMC α-syn

Rank-transformed $\alpha\text{-syn}^{olig}$ levels were significantly higher in PD patients compared with controls after adjustment for age (B = 9.34, 95 % CI 1.15 to 17.53, p = 0.026). In contrast, syn^{tot} levels did not differ between groups (B = 6.25, 95 % CI -2.31 to 14.81, p = 0.149) (unadjusted ranks are shown in Fig. 1). No significant associations were found between α-syn species and demographic variables (age, sex) in either PD patients or controls (Supplementary Table S1).

3.3. Clinical correlations

In the PD group, SGK1 and α-syn species levels showed no significant associations with MDS-UPDRS III, H&Y, NMSS, or MMSE (Supplementary Table S3).

4. Discussion

Although synucleinopathy has a pivotal role in the clinical-pathological progression of PD, the disappointing results of recent anti-α-syn trials highlight the urgent need for novel targets or alternative strategies [17]. Accordingly, here we went to test the reliability in this scenario of SGK1, a factor mediating the main PD pathogenic pathways, including immune activation [8–10], directly in patients *ex vivo*. Specifically, we measured SGK1 levels in PBMCs and serum and assessed their associations with peripheral synucleinopathy markers. Of interest, we found that SGK1 was reduced in both compartments. In contrast, PBMCs α-syn species were increased (only the $\alpha\text{-syn}^{olig}$ significantly), suggesting that a SGK1 pathway downregulation may occur either at immune or systemic levels, probably in relation to α-syn pathology dynamics.

$\alpha\text{-syn}^{tot}$ reflects the total amount of α-syn monomers, including the physiological forms; $\alpha\text{-syn}^{olig}$, conversely, is pathological, representing aggregates of modified α-syn monomers that precede Lewy body fibrils and exert cytotoxic and pro-inflammatory effects [18]. The accumulation of α-syn species in PD PBMCs aligns with previous observations [19]. Indeed, leukocyte subpopulations differently express α-syn as a critical regulator of normal immune activity; as well, various environmental stimuli and systemic inflammation may trigger the overexpression in immune cells and peripheral tissues [20,21], eventually facilitating α-syn oligomerization and priming the synucleinopathy overall [21]. Therefore, the higher PBMCs content of α-syn species, especially $\alpha\text{-syn}^{olig}$, may be a consequence of the systemic inflammation classically occurring in PD [2,3,5,22]. Otherwise, leukocytes can engulf the different α-syn forms directly from the brain [23] or rather from the periphery, capturing those circulating within the exosomes [24] or picking those deposited in other tissues [25,26].

SGK1 levels, instead, were reduced in PD PBMCs. The concurrence of pathological α-syn accumulation and SGK1 downregulation was already noticed in other experimental frameworks. Specifically, different studies based on PD MPTP-mice demonstrated an inverse association between SGK1 and α-syn expression occurring in the Substantia Nigra [27], in the skeletal muscle cells [13], and in the colon tissue [12], providing a multisystem biological construct linking SGK1 reduction to synucleinopathy that we observed even in patients' blood cells.

SGK1 operates ubiquitously in the cytoprotective response and drives the differentiation and activity of leukocytes [8–10]. In addition, SGK1 negatively regulates the activation of the NLRP3 inflammasome and the production of inflammatory cytokines in immune cells [28]. NLRP3 inflammasome components are increased in PD PBMCs [29], and the inflammasome effectors enhance α-syn expression and aggregation in the CNS or peripherally [29]. Accordingly, we might hypothesize that leukocyte SGK1 downregulation reflects an inflammatory state, the same that facilitates the concurrent accumulation of α-syn species.

After investigating the blood cells, we evaluated SGK1 in the serum as a matrix mirroring the biological dynamics at a systemic level. Also, serum SGK1 was reduced in PD, suggesting a lower peripheral tissue production or a downregulation of the pathway, again in line with preclinical findings [12,13,27]. Peripheral SGK1 production depends on several triggers [8,30], one of the foremost being Klotho [31], a ubiquitous anti-gerontic and anti-inflammatory factor whose levels are reduced in PD serum [32]. Therefore, we may suppose that systemic SGK1 downregulation results from a broader impairment of cytoprotective networks, although the intermediate molecular steps have not been explored here.

Our results might, to some extent, appear in contrast with previous findings from other authors showing, for example, in PD mice, an upregulation of SGK1 at the initial stages of dopaminergic degeneration [11], or, as well, to those demonstrating similar upregulation in acute CNS injury, such as cerebral ischemia, arising from excitotoxic and inflammatory cascades [33]. However, we should remember that SGK1 exerts highly context-dependent functions in neurological disease, acting through distinct molecular pathways according to cell type, timing, and pathological environment [14]. Accordingly, we should not consider leukocyte and serum expression as direct surrogates of central SGK1 activity. Conversely, they can represent events specifically occurring in the periphery, namely within circulating blood cells and peripheral tissues, accounting for those molecular changes that make PD a sort of systemic disorder [34].

These preliminary findings must be interpreted considering several limitations. First, the relatively small sample size. Second, SGK1 levels were assessed only in the periphery, and no CSF measurements were available, which might have provided more direct insights into CNS-related dynamics. Third, we did not evaluate upstream regulators or downstream targets of SGK1. In particular, we did not quantify key phospho-substrates such as NDRG1, which would have offered a more direct readout of SGK1 enzymatic activity beyond protein abundance alone. Finally, immune–inflammatory profiling (e.g., immunophenotyping, inflammasome components, or soluble mediators) was not

performed, limiting a more comprehensive characterization of the pathway.

5. Conclusion

Although preliminary, this study translates the promising preclinical evidence on SGK1 involvement in the biological dynamics of PD to humans. SGK1 was found to be globally downregulated in PD patients, either in PBMCs or systemically, likely due to a complex dysfunction of the cytoprotective networks or immune-inflammatory activation. Notably, leukocyte SGK1 downregulation coincides with the accumulation of pathological α-syn, suggesting a common underlying mechanism that needs to be elucidated in proper, dedicated experimental frameworks. While waiting for replication in larger and longitudinal cohorts, we support the potential value of SGK1 in the scenario of the emerging targets in the PD field.

CRediT authorship contribution statement

Federica Veltri: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Giulia Maria Sancesario:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Marco Rosina:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Davide Mascioli:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Jacopo Bissacco:** Data curation. **Matteo Conti:** Formal analysis, Writing – review & editing. **Henri Zenuni:** Data curation. **Valentina Nesci:** Supervision, Data curation. **Daniela Maftei:** Supervision, Data curation. **Veronica Buttarazzi:** Data curation. **Maria Mancini:** Data curation. **Clara Simonetta:** Data curation. **Ermanno Berlizzi:** Data curation. **Aikaterini Andradi:** Data curation. **Federica Todaro:** Data curation. **Valerio Chiurchiù:** Writing – review & editing, Supervision, Data curation. **Alberto Ferri:** Supervision, Data curation. **Cristiana Valle:** Data curation. **Alessandro Stefani:** Validation, Supervision. **Nicola Biagio Mercuri:** Validation, Supervision. **Alfonso Bellia:** Validation, Supervision. **Davide Lauro:** Writing – review & editing, Validation, Supervision, Conceptualization. **Tommaso Schirinzi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Ethics approval

The study was approved by the Policlinico Tor Vergata EC in 2021 (protocol n° 16.21) and followed the principles of the Declaration of Helsinki. All participants provided written informed consent.

Financial disclosures for the previous 12 months

FV: nothing to report.
GMS: nothing to report.
MR: nothing to report.
DM: nothing to report.
JB: nothing to report.
MC: nothing to report.
HZ: nothing to report.
VN: nothing to report.
DMa: nothing to report.
VB: nothing to report.
MM: nothing to report.
CS: nothing to report.
EB: nothing to report.
AA: nothing to report.
FT: nothing to report.
VC: nothing to report.
AF: nothing to report.
CV: nothing to report.
AS: MNESYS (PE0000006) grant by the Italian Ministry of University and Research; PNRR-MAD-2022-12,376,769 Grant by the Italian Ministry of Health.
NBM: MNESYS (PE0000006) grant by the Italian Ministry of University and Research; PRIN 2022 Grant by Italian Ministry of University and Research; PNRR-MAD-2022-12376556 Grant by Italian Ministry of Health.
AB: Progetti Ricerca Scientifica di Ateneo 2021 – Università di Roma Tor Vergata" (PD-munity).
DL: nothing to report.
TS: "Progetti Ricerca Scientifica di Ateneo 2021 – Università di Roma Tor Vergata" (PD-munity); PRIN 2022 – Prot. 20222FYK9R – Grant from the Italian Ministry of University and Research; PNRR PE00000019 – HEAL ITALIA – PE6 – Grant from the Italian Ministry of University and Research.

Funding

The study was supported by the "Progetti di Ricerca Scientifica di Ateneo 2021 – Università di Roma Tor Vergata" (PD-munity to TS and AB) and by PRIN Bando 2022 (Prot. 20222FYK9R), funded by MIUR to TS.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tommaso Schirinzi reports financial support was provided by Ministry of Education and University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2025.108155.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] G.U. Höglinger, C.H. Adler, D. Berg, C. Klein, T.F. Outeiro, W. Poewe, R. Postuma, A.J. Stoessl, A.E. Lang, A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria, Lancet Neurol. 23 (2024) 191–204, https://doi.org/10.1016/S1474-4422(23)00404-0/ATTACHMENT/8F3B223F-5E1F-41B7-BC3B-120CBEA595D5/MMC1.PDF.
[2] C. Roodveldt, L. Bernardino, O. Oztop-Cakmak, M. Dragic, K.E. Fladmark, S. Ertan, B. Aktas, C. Pita, L. Ciglar, G. Garraux, C. Williams-Gray, R. Pacheco, M. Romero-Ramos, The immune system in Parkinson's disease: what we know so far, Brain 147 (2024) 3306–3324, https://doi.org/10.1093/brain/awae177.
[3] M.G. Tansey, R.L. Wallings, M.C. Houser, M.K. Herrick, C.E. Keating, V. Joers, Inflammation and immune dysfunction in Parkinson disease, Nat. Rev. Immunol. 22 (2022) 657–673, https://doi.org/10.1038/s41577-022-00684-6.
[4] L. Muñoz-Delgado, D. Macías-García, S. Jesús, J.F. Martín-Rodríguez, M.Á. Labrador-Espinosa, M.V. Jiménez-Jaraba, A. Adarmes-Gómez, F. Carrillo, P. Mir, Peripheral immune profile and neutrophil-to-lymphocyte ratio in parkinson's disease, Mov. Disord. 36 (2021) 2426–2430, https://doi.org/10.1002/MDS.28685.
[5] P. Grillo, G.M. Sancesario, R. Bovenzi, H. Zenuni, J. Bissacco, D. Mascioli, C. Simonetta, P. Forti, G.R. Degoli, M. Pieri, V. Chiurchiù, A. Stefani, N.B. Mercuri, T. Schirinzi, Neutrophil-to-lymphocyte ratio and lymphocyte count reflect alterations in central neurodegeneration-associated proteins and clinical severity in Parkinson disease patients, Parkinsonism Relat. Disorders 112 (2023) 105480, https://doi.org/10.1016/j.parkreldis.2023.105480.
[6] G. Massacci, V. Venafra, M. Zwiebel, M. Wahle, R. Cerroni, J. Bissacco, L. Perfetto, V. Michienzi, A. Stefani, N.B. Mercuri, T. Schirinzi, F. Sacco, Stage-dependent

phosphoproteome remodeling of Parkinson's disease blood cells, Neurobiol. Dis. 200 (2024) 106622, https://doi.org/10.1016/J.NBD.2024.106622.
[7] T. Schirinzi, I. Salvatori, H. Zenuni, P. Grillo, C. Valle, G. Martella, N.B. Mercuri, A. Ferri, Pattern of mitochondrial respiration in peripheral blood cells of patients with parkinson's disease, Int. J. Mol. Sci. 23 (2022) 10863, https://doi.org/10.3390/IJMS231810863/S1.
[8] X. Chen, H. Kang, Y. Xiao, The role of SGK1 in neurologic diseases: a friend or foe? IBRO Neurosci Rep 17 (2024) 503–512, https://doi.org/10.1016/J.IBNEUR.2024.12.003.
[9] D. Lauro, D. Pastore, B. Capuani, F. Pacifici, R. Palmirotta, P. Abete, M. Roselli, A. Bellia, M. Federici, N. Daniele, P. Sbraccia, F. Guadagni, R. Lauro, D. Della-Morte, Role of serum and glucocorticoid-inducible kinase (SGK)-1 in senescence: a novel molecular target against age-related diseases, Curr. Med. Chem. 22 (2015) 3765–3788, https://doi.org/10.2174/0929867322666150812145035.
[10] X. Bian, H. Xue, D. Jing, Y. Wang, G. Zhou, F. Zhu, Role of Serum/glucocorticoid-regulated kinase 1 (SGK1) in immune and inflammatory diseases, Inflammation 46 (2023) 1612–1625, https://doi.org/10.1007/S10753-023-01857-8/FIGURES/4.
[11] C.C. Stichel, B. Schoenebeck, M. Foguet, B. Siebertz, V. Bader, X.R. Zhu, H. Lübbert, *sgk1* , a member of an RNA cluster associated with cell death in a model of Parkinson's disease, Eur. J. Neurosci. 21 (2005) 301–316, https://doi.org/10.1111/j.1460-9568.2005.03859.x.
[12] M.H. Seo, D. Kwon, S.-H. Kim, S. Yeo, Association between decreased SGK1 and increased intestinal α-Synuclein in an MPTP mouse model of parkinson's disease, Int. J. Mol. Sci. 24 (2023) 16408, https://doi.org/10.3390/ijms242216408.
[13] E.-J. Heo, Y. Lee, M. Hyung Seo, S. Yeo, Association between SGK1 and α-synuclein in skeletal muscle in an MPTP-induced Parkinson's disease model, Neurosci. Lett. 814 (2023) 137464, https://doi.org/10.1016/j.neulet.2023.137464.
[14] P.G. Howard, P. Zou, Y. Zhang, F. Huang, V. Tesic, C.Y.-C. Wu, R.H.-C. Lee, Serum/glucocorticoid regulated kinase 1 (SGK1) in neurological disorders: pain or gain, Exp. Neurol. 382 (2024) 114973, https://doi.org/10.1016/j.expneurol.2024.114973.
[15] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (2015) 1591–1601, https://doi.org/10.1002/mds.26424.
[16] M. Rosina, F. Veltri, V. Nesci, J. Bissacco, R. Bovenzi, D. Mascioli, C. Simonetta, H. Zenuni, D. Maftei, M. Marano, M. Pierantozzi, A. Stefani, V. Chiurchiù, P. Longone, C. Valle, N.B. Mercuri, A. Ferri, T. Schirinzi, Immunometabolic signature and tauopathy markers in blood cells of progressive supranuclear Palsy, Mov. Disord. (2024), https://doi.org/10.1002/MDS.30009.
[17] A.J. Espay, Movement disorders research in 2021: cracking the paradigm, Lancet Neurol. 21 (2022) 10–11, https://doi.org/10.1016/S1474-4422(21)00413-0.
[18] P. Calabresi, G. Di Lazzaro, G. Marino, F. Campanelli, V. Ghiglieri, Advances in understanding the function of alpha-synuclein: implications for Parkinson's disease, Brain 146 (2023) 3587, https://doi.org/10.1093/BRAIN/AWAD150.
[19] S. Petrillo, T. Schirinzi, G. Di Lazzaro, J. D'Amico, V.L. Colona, E. Bertini, M. Pierantozzi, L. Mari, N.B. Mercuri, F. Piemonte, A. Pisani, Systemic activation of Nrf2 pathway in Parkinson's disease, Mov. Disord. (2019), https://doi.org/10.1002/mds.27878.
[20] M.M. Alam, D. Yang, X.Q. Li, J. Liu, T.C. Back, A. Trivett, B. Karim, D. Barbut, M. Zasloff, J.J. Oppenheim, Alpha synuclein, the culprit in Parkinson disease, is required for normal immune function, Cell Rep. 38 (2022) 110090, https://doi.org/10.1016/J.CELREP.2021.110090.
[21] A. Kasen, C. Houck, A.R. Burmeister, Q. Sha, L. Brundin, P. Brundin, Upregulation of α-synuclein following immune activation: possible trigger of Parkinson's disease, Neurobiol. Dis. 166 (2022) 105654, https://doi.org/10.1016/J.NBD.2022.105654.
[22] J. Bissacco, R. Bovenzi, M. Conti, C. Simonetta, D. Mascioli, R. Cerroni, G. M. Sancesario, P. Grillo, M. Pierantozzi, A. Stefani, N.B. Mercuri, M. Camacho, T. Schirinzi, Gastrointestinal dysfunction bears on the clinical-biological profile of Parkinson's disease, Mov. Disord. Clin. Pract. 12 (2025) 497–503, https://doi.org/10.1002/mdc3.14319.
[23] R.L. McFleder, A. Makhotkina, J. Groh, U. Keber, F. Imdahl, J. Peña Mosca, A. Peteranderl, J. Wu, S. Tabuchi, J. Hoffmann, A.K. Karl, A. Pagenstecher, J. Vogel, A. Beilhack, J.B. Koprich, J.M. Brotchie, A.E. Saliba, J. Volkmann, C. W. Ip, Brain-to-gut trafficking of alpha-synuclein by CD11c+ cells in a mouse model of Parkinson's disease, Nat. Commun. 14 (1) (2023) 1–13, https://doi.org/10.1038/s41467-023-43224-z, 14 (2023).
[24] S. Yan, C. Jiang, A. Janzen, T.R. Barber, A. Seger, M. Sommerauer, J.J. Davis, K. Marek, M.T. Hu, W.H. Oertel, G.K. Tofaris, Neuronally derived extracellular vesicle α-Synuclein as a serum biomarker for individuals at risk of developing parkinson disease, JAMA Neurol. 81 (2024) 59–68, https://doi.org/10.1001/JAMANEUROL.2023.4398.
[25] C. Painous, M. Fernández, J. Pérez, L. de Mena, A. Cámara, Y. Compta, Fluid and tissue biomarkers in Parkinson's disease: immunodetection or seed amplification? Central or peripheral? Parkinsonism Relat. Disorders 121 (2024) 105968 https://doi.org/10.1016/J.PARKRELDIS.2023.105968.
[26] T. Schirinzi, D. Maftei, F.M. Passali, P. Grillo, H. Zenuni, D. Mascioli, R. Maurizi, L. Loccisano, M. Vincenzi, A.M. Rinaldi, M. Ralli, S.D.G. Prof, A. Stefani, R. Lattanzi, C. Severini, N.B. Mercuri Prof, Olfactory neuron Prokineticin-2 as a potential target in Parkinson's disease, Ann. Neurol. (2022), https://doi.org/10.1002/ANA.26526.
[27] S. Yeo, B. Sung, Y.M. Hong, M. van den Noort, P. Bosch, S.H. Lee, J. Song, S. K. Park, S. Lim, Decreased expression of serum- and glucocorticoid-inducible kinase 1 (SGK1) promotes alpha-synuclein increase related with down-regulation of dopaminergic cell in the substantia nigra of chronic MPTP-induced Parkinsonism mice and in SH-SY5Y cells, Gene 661 (2018) 189–195, https://doi.org/10.1016/J.GENE.2018.03.086.
[28] D.G. Zhang, W.Q. Yu, J.H. Liu, L.G. Kong, N. Zhang, Y.D. Song, X.F. Li, Z.M. Fan, Y. F. Lyu, N. Li, H.B. Wang, Serum/glucocorticoid-inducible kinase 1 deficiency induces NLRP3 inflammasome activation and autoinflammation of macrophages in a murine endolymphatic hydrops model, Nat. Commun. 14 (1) (2023) 1–18, https://doi.org/10.1038/s41467-023-36949-4, 14 (2023).
[29] L.T.N. Nguyen, H.D. Nguyen, Y.J. Kim, T.T. Nguyen, T.T. Lai, Y.K. Lee, H. Il Ma, Y. E. Kim, Role of NLRP3 inflammasome in Parkinson's disease and therapeutic considerations, J. Parkinsons Dis. 12 (2022) 2117, https://doi.org/10.3233/JPD-223290.
[30] D. Pastore, D. Della-Morte, A. Coppola, B. Capuani, M.F. Lombardo, F. Pacifici, F. Ferrelli, R. Arriga, C. Mammi, M. Federici, A. Bellia, N. Di Daniele, M. Tesauro, G. Donadel, D. Noto, P. Sbraccia, G. Sconocchia, D. Lauro, SGK-1 protects kidney cells against apoptosis induced by ceramide and TNF-α, Cell Death Dis. 6 (9) (2015) https://doi.org/10.1038/cddis.2015.232, 6 (2015) e1890–e1890.
[31] M. Torbus-Paluszczak, W. Bartman, M. Adamczyk-Sowa, Klotho protein in neurodegenerative disorders, Neurol. Sci. 39 (2018) 1677–1682, https://doi.org/10.1007/S10072-018-3496-X/METRICS.
[32] A. Yalcin, E. Gemci, B. Yurumez, R. Yilmaz, M. Varli, V. Atmis, M.C. Akbostancı, N. Yazihan, Serum alpha klotho levels in Parkinson's Disease, Neurol. Sci. 46 (2024) 743–749, https://doi.org/10.1007/S10072-024-07809-W/FIGURES/3.
[33] C.Y.-C. Wu, Y. Zhang, L. Xu, Z. Huang, P. Zou, G.A. Clemons, C. Li, C.T. Citadin, Q. Zhang, R.H.-C. Lee, The role of serum/glucocorticoid-regulated kinase 1 in brain function following cerebral ischemia, J. Cerebr. Blood Flow Metabol. 44 (2024) 1145–1162, https://doi.org/10.1177/0271678X231224508.
[34] H.N. Costa, A.R. Esteves, N. Empadinhas, S.M. Cardoso, Parkinson's disease: a multisystem disorder, Neurosci. Bull. 39 (2023) 113–124, https://doi.org/10.1007/s12264-022-00934-6.