***Supplemental materials and methods***

*Antibodies used for immunofluorescent staining and immuno-blotting*

The following antibodies were used in this study: anti-AQP1, sc-25287, mouse monoclonal, (Santa-Cruz Biotechnology); anti-AQP2, sc-515770, mouse monoclonal, (Santa-Cruz Biotechnology); anti-Lipocalin-2/NGAL, Ab63929, rabbit polyclonal, (Abcam); anti- SQSTM1, MBL PM045, rabbit polyclonal, (MBL International Corporation); anti-PGC-1 α, Ab54481, rabbit polyclonal, (Abcam); anti-PINK1, Ab23707, rabbit polyclonal, (Abcam); anti-SIRT1 (D1D7), #9475, rabbit monoclonal, (Cell signaling technology); anti-TOMM20, Ab78547, rabbit polyclonal, (Abcam); Alexa Fluor, #A21206, 488 donkey anti-rabbit, (Invitrogen, Thermo Fisher Scientific); Alexa Fluor, #A10038, 680 donkey anti-mouse, (Invitrogen, Thermo Fisher Scientific)

*Determination of Gb3 in cells and conditioned culture medium*

As stated in the main part, the concentrations of Gb3 were determined by LC-MS/MS according to a published procedure with modifications [27]. Conditioned culture medium was used without additional treatment. Cells were harvested by trypsinization, washed with PBS, and stored at -80°C until further processing. Cell lysates were prepared by resuspending the cell pellets with 150 μL of lysis buffer (PBS supplemented with 1% of protease inhibitor cocktail, product No. P8340-5ML) and subjecting the cell suspension to three cycles of freeze-thawing in dry-ice/room temperature. Samples were prepared by mixing 20 μL of conditioned culture medium or cell lysate with 200 μL of extraction solvent (0.1% formic acid in methanol) containing the deuterated internal standards. The sample was subjected to centrifugation at 9447 × g for 5 min at room temperature. The supernatants were transferred into HPLC vials and subjected to LC-MS/MS analysis on a Nexera X2 UPLC system (Shimadzu) coupled to a QTRAP Sciex6500+ mass spectrometer (Sciex). Gb3 was separated on a Kinetex 5μm, C18 100 Å, 150 x 4.6 mm column (Phenomenex) using a gradient of solvent A (0.1% FA in H2O) and solvent B (0.1% FA in MeOH). The gradient was as follows: 0-2 min 5% B; 2-2.5 min 100% B, 2.50-12.5 min 100% B, 12.5-13 min 5% B and 13-15 min 5% B. Quantification was carried out using a calibration curve of Gb3 0-1 μM with D3-Gb3 (2.5 μM) as internal standard. A quality control was included to evaluate the performance of Gb3 determination under our experimental conditions (Control Special Assays in Serum, European Research Network for the evaluation and improvement of screening, Diagnosis and Treatment of Inherited Disorders of Metabolism (ERNDIM) IQCS, SAS-02.1 and SAS-02.2 from MCA Laboratories, Winterswijk, Netherlands). The concentration of Gb3 in cells and conditioned culture media were normalized by the total concentration of protein in the cell lysate determined using the bicinchoninic acid (BCA) assay (Pierce, Thermo Fisher Scientific).

*Analysis of amino acids in cell lysates*

Amino acid profiles were determined using a standardized diagnostic protocol, using a Biochrom 30 amino acid analyzer (Biochrome). One T-75 flask of confluent cells was harvested by trypsinization, washed with PBS and stored at -80° C until further processing. Frozen cell pellets were then thawed and resuspended with 250 μL of lysis buffer (PBS supplemented with 1% protease inhibitor cocktail). Cell suspensions were lysed by performing three cycles of freeze-thawing in dry-ice followed by sonication. The homogenate was centrifuged at 9447 × g for 15 min at 4° C. 200 μL of cell lysate was subjected to a standardized sample preparation protocol available at the Laboratory of Clinical Biochemistry and Metabolism, Metabolic Center Freiburg. All amino acid concentrations were normalized by the total concentration of protein in the cell lysate, determined using the BCA assay (Pierce, Thermo Fisher Scientific).

*Targeted analysis of metabolites*

The concentrations of creatinine and glutathione metabolites were determined as described [23] and stated in the main part. The concentrations of TCA cycle metabolites, lactate, malonate, methylmalonate and itaconate were determined as reported for one-carbon metabolites [23] except that an isocratic chromatography run of 50% solvent B was applied. Internal standards for TCA intermediates and related organic acids included: D4-succinate (Sigma), 13C1-lactate (Sigma), D3-methylmalonic acid (CDN isotopes), and 13C5-itaconate (Sigma). D3-methylmalonate was used as a generic internal standard for metabolites for which isotopes were not available in our laboratory. All above metabolite measurements were carried out by LC-MS/MS on a Nexera X2 UPLC system (Shimadzu) coupled to a QTRAP Sciex6500+ mass spectrometer (Sciex).

For acylcarnitine profiling cells were harvested by trypsinization, washed with PBS and stored at -80 oC until further processing. Cell lysates (from one confluent T-75 cell culture flask) were prepared by resuspending the cells with 150 μL of the lysis buffer described above, subjecting the cell suspension to three-cycles of freeze-thawing in dry-ice/room temperature followed by three cycles of sonication. An aliquot of 20 μl cell lysate was set aside for protein quantification by the BCA assay (Pierce, ThermoFisher Scientific), and the remainder of the cell lysate was stored at -80 oC until further processing. Acylcarnitines were isolated by methanol extraction starting with 50 μL of cell lysate. Samples were processed according to standard operating practices for the determination of acylcarnitine profiles in plasma (Laboratory of Clinical Biochemistry and Metabolism, Center of Metabolism Freiburg). Acylcarnitines were determined via flow-injection analysis into an MS/MS (Quattro Premier XE, Waters) coupled with an ultra-performance liquid chromatography (Acquity UPLC, Waters). Graphical analysis and comparison of acylcarnitine abundance was simplified by pooling the species according to their acyl group chain length, as follows: short chain (C-C5), medium chain (C6-C12) and long chain (C12-C18).

All metabolite concentrations were normalized by the total concentration of protein in the cell lysate, determined using the BCA assay.