Evaluation of ferroxidase activity. Ferroxidase activity was evaluated according to a modified Erel assay[74]. Three µl of plasma were added to 750 µl of acetate buffer solution (45 mM Na-acetate, pH 5.8), then 150 µl of substrate solution (367 µM ammonium iron(II) sulfate hexahydrate, 130 mM thiourea) were added and incubated 1 h at 37 °C. The colorimetric reaction was activated by adding 60 µl of 18 mM Ferene-S solution and absorbance measured in triplicate at 595 nm on a microplate reader (iMark, BioRad). As positive control 3 µl of 25 mM EDTA solution were used instead of plasma sample, while for negative/background control only reagents without sample were used. The activity was reported as percentages of the average of the activity evaluated in the plasma of WT mice.

Detection of anti-CP antibodies in the plasma and analysis of their neutralizing effect on CP-ferroxidase activity. The occurrence of anti-CP antibodies in the plasma of kCP-treated mice was evaluated by ELISA performed on purified human kCP. IgG fraction from mouse plasma was purified with rProtein-G-agarose beads (Invitrogen) as reported in[20] from 5 pools of 4 randomly selected sera from the same experimental group of animals (750 µg total proteins). The retention of the ability to bind human kCP by the purified IgG was tested by ELISA, using 150 ng of purified IgG from each pool of mouse plasma against 50 ng of purified human kCP. Neutralizing effect of IgG purified from mice plasma on the CP ferroxidase activity was analyzed by modified Erel assay. Purified kCP (600 ng) was incubated with 3 µg of purified IgG from each pool of mouse plasma, and ferroxidase assay was performed. kCP alone, heat-inactivated kCP (5 min at 100 °C), kCP incubated with 1 mM NaN_3 as selective inhibitor[30] or with 3 µg of a mixture (1/1/1 vol) of anti-CP commercial antibodies (Abcam: ab8813, ab48614, ab19171; SantaCruz: sc21242, sc21240) were used as controls. Oxidized iron was reported considering the absorbance of the total amount of ferrous iron present in the assay (3.2 µg) and was compared to the activity of purified kCP (1 µg).

Analysis of iron by inductively coupled plasma-mass spectrometry (ICP-MS). Concentrations of metal ions was evaluated in lyophilized specimens of brain and liver of mice, after incubation (1 h at 70 °C) in a mixture of 65% nitric acid and 30% hydrogen peroxide, by ICP-MS using an ELAN DRC II instrument (PerkinElmer Sciex) as described in[20].

Iron histochemistry. Modified Perl's staining was performed on 14 µm sagittal sections of paraformaldehyde fixed brain as described in[20]. Staining at different emission wavelength was evaluated by the Nuance® FX multiplex biomarker imaging system (PerkinElmer) in the choroid plexus of the mice. A semi-quantitative analysis of iron deposition normalized for cell staining was performed using ImageJ software (National Institute of Health, http://rsb.info.nih.gov/ij) as in ref. [20].

Purkinje cells count. A total of 14 µm sections of paraformaldehyde fixed brain were stained with toluidine blue and analyzed with a Zeiss AxioImager M2m microscope. Images were acquired with AxioCam MRc5 (Zeiss) and analyzed with ImageJ software for automated count of Purkinje body cell over a linear distance of 500 µm in the Purkinje cell layer of the cerebellum. Five different linear distance were analyzed for each mouse.

Fluorescence Immunohistochemistry. Immunohistochemistry was performed on paraffin-embedded mouse brain sagittal sections (5 µm) after deparaffinization and antigen retrieval. Triple immunostaining for NeuN+, GFAP+, IBA1+ cells was performed using a mouse anti-NeuN antibody for neurons (1:400; MAB377, Millipore), a rabbit anti-IBA1 antibody for total microglia (1:300; 016-20,001, WAKO) and a mouse anti-GFAP antibody conjugated with Alexa Fluor 488 (1:500; MAB3402X, Millipore) for astrocytes[76]. Alexa Fluor 635 anti-rabbit (1:600; Alexa Fluor 555 anti mouse antibody (1:600; A31577 and A31570, Thermo Fisher Scientific) were used as secondary antibodies.

Confocal microscopy and quantitative image analysis. Confocal scans were acquired on a LEICA TCS SP7 (Leica Microsystems CMS GmbH) equipped with 20X objective (z step 0.6 µm). Analyses were performed stacking 10 consecutive z scans with ImageJ software. Immunofluorescence of GFAP, IBA1 were detected setting a fix threshold level with ImageJ threshold tool and the positive pixels above threshold were quantified and expressed as percent positive pixels/total pixels[76]. The number of astrocytes, total microglia, NeuN+, and autofluorescent pyramidal neurons were evaluated using the multi-point tool and expressed as cells/mm^2. Autofluorescent Purkinje cells were expressed as cells/mm. The thickness of CA1 was evaluated using the line tool and expressed in µm.

Liver histological analysis. Automated hematoxylin-eosin staining was performed on 3 µm sections of paraformaldehyde fixed and paraffin embedded liver using the Leica BOND RX instrumentation at the Animal Histopathology facility, HSR. Samples were analyzed with Zeiss AxioImager microscope. Lipid microvesicles were quantified on histological images with ImageJ software. Four images for each mouse were segmented by a threshold filtration to define white lipid droplets staining, and then quantified as percentage of the pixel area covered by lipid droplets on the total of pixel area.

Leptin evaluation. Leptin level was quantified using ELISA kits (MOB00, R&D Systems) in mouse plasma samples (diluted 1:40) and plates were read in a BioRad iMark spectrophotometer. The optical density was determined by subtracting value obtained at 570 nm of wavelength from value obtained at 450 nm according to manufacturer's instructions.

Hematological parameters evaluation. Blood collected from mice at 6 and 10 months of age was analyzed for hematological parameters at the San Raffaele Mouse Clinic-Animal Biochemistry facility using ILab Aries (Instrumentation Laboratory) instrumentation for biochemistry analyses, and Idexx Procyte analyzers for hematology.

Statistics and reproducibility. Statistical analyses were performed with Prism V9.5 software (GraphPad Inc.), a two-tailed p value < 0.05 was considered significant comparing means ± standard error of the mean. Data from two groups were evaluated by unpaired Student's t-test, if they passed the normality test (Kolmogorov-Smirnov test) or were evaluated by Mann Whitney test. Differences between three groups were assessed by one-way Analysis of Variance (ANOVA) if data passed the normality test or by Kruskal-Wallis test if they don't. Post hoc test analysis was performed to compare all pairs of groups, namely Tukey's test or Newman-Keuls' test for ANOVA and Dunn's or uncorrected Dunn's test for Kruskal-Wallis. The sample size ($n = 20$ animals per group) was established using the G-Power v3.1.9.4 software (Heinrich-Heine-Universität Düsseldorf), applying a one-way ANOVA test for the comparison of means between 3 groups with alpha error of 0.05 and power of 0.8; effect size (Cohen's effect size) of 0.45 which by convention is a large effect size. The resulting number was $n = 17$ animals per group, however, we increased the number by 20% to compensate for any/possible animal

deaths which, from our previous experience[20] can occur with the animals aging up to 10 months. Multidimensional reduction analysis was done using unsupervised principal component analysis (PCA). Data were normalized by auto-scaling transformation, and the analysis was performed using MetaboAnalyst 5.0 online package (www.metaboanalyst.ca/home.xhtml). Upon PCA, the experimental groups of animals were highlighted as 95% confidence interval area automatedly defined by the software.

Reporting summary. Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The datasets of the study are available at "San Raffaele Open Research Data Repository" (ORDR) (https://ordr.hsr.it/research-data/); https://doi.org/10.17632/r2p5n38mdz.1. The mass spectrometry proteomics data have been deposited to the ProteomeXchangeConsortium via the PRIDE partner repository with the dataset identifier PXD046234.

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Conceptualization: M.A., A.Ca. Methodology: A.Z., G.D.P., I.N., C.S., M.G.G., V.C., R.M.M., P.D. Investigation: A.Z., S.R., B.F., A.Con, E.G., I.N., F.M., L.N., A.P., P.G., G.Z., G.Magh, G.T., D.L., G.Magn, L.S., L.T., C.T., C.M., A.Col, S.B., P.R. Funding acquisition: M.A., A.Ca, M.G.G. Supervision: M.A., A.Ca. Writing, original draft: M.A., A.Ca, A.Z., I.N. Writing, review & editing: M.A., A.ca, A.Z., I.N., A.G., M.G.G., D.L., C.S., V.C. All the authors discussed the results and commented on the manuscript at all stages.

Competing interests

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Additional information

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