**Supplementary methods**

**Sample preparation for ELISA measurements and protein array**

Cultured cells were lysed in lysis buffer containing 20 mM Tris (pH 7.5), 150 mM NaCl, 2 mM EDTA, 2 mM MgCl2, 10% glycerol, protease and phosphatase inhibitors, 0.5% Triton-X and 0.5% NP40. The lysates were kept on ice for 30 min. and centrifuged (16000x*g*, 15 min.) and the supernatant was used for ELISA measurements and western blot analyses. Conditioned cell culture medium was centrifuged (16000x*g*, 15 min.) and the supernatant was used for ELISA measurements.

Brains after dissection were frozen at -40°C in 2-methylbutane with dry ice. During tissue sectioning, sections for immunostainings were collected along with tissue samples for biochemical analyzes from each brain. Brain tissue was homogenized in 20 mM Tris buffer (pH 7.5) supplemented with 150 mM NaCl, 2 mM EDTA, 2 mM MgCl2, 10% glycerol and protease and phosphatase inhibitors. The lysate was kept on ice for 20 minutes and centrifuged (1000x*g*, 10 min.) and the supernatant was supplemented with 0.5% Triton-X and 0.5% NP40 and rotated for 1 h at 4°C. Next, the lysate was centrifuged (16000x*g*, 15 min.) and the supernatant was used for ELISA measurements and western blot analyses. Mouse blood was collected from the cheek vein to tubes containing citrate and centrifuged (15 min., 1000 x *g*) to obtain plasma.

**Immunostaining of primary cells and mouse brain samples**

Astrocytes were plated on gelatin-coated coverslips and fixed with PFA. After blocking in 5% normal serum and 0.3% Triton™ X-100 in PBS, cells were incubated with antibodies recognizing GFAP (Millipore, MAB360, 1:100) and SorCS2 (R&D Biosystems, AF4237, 1:100).

Frozen brains were sectioned to obtain 25 µm coronal cryosections mounted on glass slides. Sections were fixed with PFA and blocked in 1% horse serum in PBS prior to incubation with primary antibodies. Lectin-labeled, PFA-perfused brains were sectioned to obtain 40 µm free‑floating sections, which were blocked in 1% horse serum in PBS prior to incubation with primary antibodies.

For analysis of SorCS2 expression patterns in neurons and astrocytes in naive mouse brains and in ischemic brains at 1 or 3 days after MCAo, animals were perfused with 4% PFA and 50 µm free-floating sections were cut after cryoprotection of the tissue in sucrose.

Primary antibodies were diluted in PBS with 1% BSA, 1% donkey serum and 0.3% TritonX ‑100 in PBS.

**Immunohistochemistry on human brain samples**

Human brain tissue was fixed in 10% buffered formalin and embedded in paraffin. Paraffin‑embedded tissue was sectioned at 5 µm, mounted on pre-coated glass slides (Star Frost, Waldemar Knittel, Braunschweig, Germany) and processed for immunohistochemical staining. Sections were deparaffinated in xylene, rinsed in ethanol (100%, 96%, 70%) and incubated for 20 minutes in 0.3% hydrogen peroxide diluted in methanol. Antigen retrieval was performed using a pressure cooker in 10 mM sodium citrate, pH 6.0 at 121°C for 10 minutes. Slides were washed with phosphate-buffered saline (PBS, pH 7.4) and incubated overnight with the primary antibody (rabbit anti-SorCS2, Lifespan Biosciences, LS-C501334, 1:450) in Normal Antibody Diluent (Immunologic, Duiven, the Netherlands) at 4°C. For single labelling, sections were, after washing with PBS, stained with a polymer based peroxidase immunohistochemistry detection kit (Brightvision plus kit, ImmunoLogic, Duiven, the Netherlands) according to the manufacturer’s instructions. Staining was performed using Bright DAB substrate solution (1:10 in 0.05 M Tris-HCl, pH 7.6; ImmunoLogic, Duiven, the Netherlands) with 0.015% H2O2. Sections were dehydrated in alcohol and xylene and coverslipped.

For double-labelling, sections were incubated with anti-SorCS2 and anti-GFAP (monoclonal mouse, Sigma, 1:4000) or anti-NeuN (mouse, Millipore, 1:2000) primary antibodies overnight at 4°C. After washing with PBS, sections were incubated with fluorescently labelled secondary antibodies (1:200, Invitrogen) for two hours at room temperature, washed in PBS and coverslipped. Fluorescent microscopy was performed using a confocal microscope (SP8‑X, Leica).