Supplementary Methods:

Isolation of primary macrophage

Resident peritoneal macrophages were harvested from 8-12 week old mice by lavage with ice cold PBS without divalent cations then separated from other contaminating cells by differential adhesion to tissue culture treated plastic. Cells were confirmed to be > 95% macrophages by staining with F4/80 antibodies and uptake of DiI AcLDL.

Amyloid-β

Amyloid-β1-42 peptide and control peptide, with identical amino acid composition but reverse sequence (revAβ), were obtained from American Peptide Company (Sunnyvale, California) or from Biosource International (Amarillo, California) and prepared as described[12,49].

Measurement of ROS production

ROS production was measured by Nitro blue Tetrazolium (NBT) reduction assay. Briefly, peritoneal macrophages were plated on multi-spot glass slides and stimulated with HBSS containing 1 mg/ml BSA alone or HBSS/BSA + Aβ (0.2μg/μl) for 10 min at 37 °C. NBT 1 mg/ml was added to each spot and cells were incubated at 37 °C for 1h. ROS production correlates with formation of cell-associated dark blue colored insoluble formazan deposit. The number of cells positive for formazan deposition were quantified by microscopy and the Scion image analysis software, as described[12].

Aβ binding assay

Aβ peptide was labeled with Fluorescein Isothiocyanate (FITC) (Molecular probes, OR) according to the manufacturer's instructions. Unbound FITC was removed by dialysis overnight in cold PBS. To measure binding of FITC-Aβ to microglia, fresh brain cell preps from adult WT or *Ccr2*$^{-/-}$ mice were incubated with RPMI medium containing 1% lipoprotein deficient serum and 5μg/ml FITC-Aβ, at 37^{o}C for 2 hours. Unbound FITC-Aβ was washed away with 3 rinses and the cells stained with APC labeled anti Cd11b antibodies or control antibodies. The amount of cell-associated Aβ in Cd11b+ cells was quantified by flow cytometry. Each flow cytometry figure represents data from microglia isolated from a single mouse and is representative of similar results obtained from 4-5 mice per group.

Immunofluorescence staining for F4/80.

20 μm frozen sections from WT or *Ccr2*$^{-/-}$ mice were stained for 1 hour at 25^{o}C with 1 nM DAPI (Molecular probes, OR) and 10 μg/ml FITC labeled F4/80 monoclonal antibody (Serotec, Raleigh NC). For quantitation of the number of recruited microglia to sites of microinjection, 5 serial sections from each site of injection were visualized by fluorescence microscopy (4 X and 40 X magnifications) and digitally photographed. The fluorescence intensity of FITC-labeled microglia at each microinjection site was then quantified using Scion's image analysis software and used as a measure of the density of microglial.

Immunohistochemistry for IB4.

10μm thick frozen brain sections from WT, *APP*, *Ccr2*$^{-/-}$ and *APP-Ccr2*$^{-/-}$ mice were fixed in acetone and incubated for 2 hours with PBS alone or PBS containing 2μg/ml

peroxidase-coupled IB4 from *Griffonia Simplicifolia* (Sigma, St Louis MO). The slides were then processed using the Vectastatin Elite ABC kit (Vector laboratories, Burlingame CA) according to the manufacturer's instructions, counterstained with hematoxylin, and visualized by brightfield microscopy and digitally photographed.

Analysis of cell proliferation

WT or *Ccr2*$^{-/-}$ mice were injected with BRDU intraperitoneally (IP) (1mg/mouse). Twenty four hours later, the mice were injected IP with LPS (1μg/mouse). The mice were sacrificed 24 hours following LPS injection, and perfused with 30 ml of through their left ventricle, and one hemisphere of their brains processed for cell isolation the other hemisphere was fixed in 4% paraformaldehyde then placed in 30% sucrose for cryopreservation. For analysis of cell proliferation in the brains of APP mice, 65 day old WT and *APP* mice were injected with 1mg/mouse BRDU intraperitoneally and the injection repeated after three and six days. On day seven, the mice were sacrificed and perfused with 30 ml of through their left ventricle, and one hemisphere of their brains processed for cell isolation. The other hemisphere was fixed in 4% paraformaldehyde then placed in 30% sucrose for cryopreservation. Brain cells were then stained with FITC-labeled anti-BRDU antibodies and APC labeled anti-Cd11b antibodies using a commercially available BRDU flow cytometry kit (BD pharmingen) according to the manufacturer's instructions. Frozen sections from the other hemispheres and from the thymus were also stained with anti-BRDU staining antibodies using a commercially available BRDU in situ detection kit (BD pharmingen) according to the manufacturer's instructions and developed using the Vectastatin Elite ABC kit (Vector laboratories) counterstained with hematoxylin, and visualized by brightfield microscopy and digitally photographed.

Quantitative Real Time PCR

2 μg of total RNA from each sample was reverse transcribed using multiscribe reverse transcriptase (Applied Biosystems). Oligonucleotide primers were designed using Primer Express software 1.0 (PE Biosystems) (**Supplementary Table 1**). A series of standards was prepared by performing ten-fold serial dilutions of full-length cDNAs in the range of 20 million copies to two copies per PCR reaction. Subsequent analysis was performed on the data output from the MX4000™ software (Stratagene) using Microsoft Excel XP. Relative quantification of mRNA expression was calculated by the comparative cycle method described by the manufacturer (Stratagene).

Stereotaxic brain microinjection.

Two-three month old adult mice were anesthetized with intraperitoneal injection of 2.5 mg of ketamine and 0.5 mg of xylazine. After mice were immobilized in a Kopf stereotaxic apparatus, a linear skin incision was made over the bregma, and a 1-mm burr hole was drilled in the skull 1 mm anterior to and 2 mm lateral to the bregma on both sides. 2 μl of Aβ containing solution (1 mg/ml) was inoculated on the right side using a 5 μl Hamilton syringe. 2 μl of revAβ was inoculated at the same depth and stereotaxic coordinates on the left side of the brain, providing a control inoculation in the same animal. 48 hours later, the mice were anesthetized and perfused by an intracardiac infusion of ice cold PBS containing 4% neutral paraformaldehyde (PFA-PBS). The brains were removed, placed in 4% PFA–PBS overnight at 4 °C, and then transferred to 30% sucrose in PBS and stored at 4°C until sectioning.