The role of macrophage scavenger receptor 1 (Msr1) in prion pathogenesis

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Abstract
The progression of prion diseases is accompanied by the accumulation of prions in the brain. Ablation of microglia enhances prion accumulation and accelerates disease progression, suggesting that microglia play a neuroprotective role by clearing prions. However, the mechanisms underlying the phagocytosis and clearance of prion are largely unknown. The macrophage scavenger receptor 1 (Msr1) is an important phagocytic receptor expressed by microglia in the brain and is involved in the uptake and clearance of soluble amyloid-β. We therefore asked whether Msr1 might play a role in prion clearance and assessed the scavenger function of Msr1 in prion pathogenesis. We found that Msr1 expression was upregulated in prion-infected mouse brains. However, Msr1 deficiency did not change prion disease progression or lesion patterns. Prion deposition in Msr1 deficient mice was similar to their wild-type littermates. In addition, prion-induced neuroinflammation was not affected by Msr1 ablation. We conclude that Msr1 does not play a major role in prion pathogenesis.

Key messages
• Msr1 expression is upregulated in prion-infected mouse brains at the terminal stage
• Msr1 deficiency does not affect prion disease progression
• Msr1 does not play a major role in prion clearance or prion pathogenesis
• Microglia-mediated phagocytosis and clearance of Aβ and prion may adopt distinct molecular pathways

Keywords Prion disease · Microglia · Macrophage scavenger receptor 1 · Phagocytosis · Neuroinflammation

Introduction
Prion diseases are transmissible and fatal neurodegenerative disorders that affect both human and animals. This disease category comprises Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), Gerstmann-Sträussler-Scheinker syndrome (GSS) in humans, scrapie in sheep and goat, bovine spongiform encephalopathy (BSE) in cattle, and chronic wasting disease (CWD) in cervids [1]. Prion diseases are thus far incurable. The infectious agent mainly consists of scrapie prion protein (PrPSc), which is a misfolded isoform of the host-encoded cellular prion protein (PrPC). PrPSc acts as a propagon, which can seed a self-perpetuating reaction to recruit and convert PrPC to an aggregated conformation. The deposition of PrPSc in the central nervous system (CNS), together with neuronal loss, spongiform changes (or termed vacuolization), astrogliosis and conspicuous microglial activation, constitutes the characteristic molecular pathology of prion disease [2].

Microglia are the primary innate immune cells and phagocytes of the CNS, exerting a neuroprotective role in prion pathogenesis [3]. We have reported that pharmacogenetic removal of microglia greatly enhances PrPSc accumulation in prion-infected cultured organotypic cerebellar slices (COCS) and in mice [4, 5]. However, the molecular mechanisms underlying prion clearance by microglia are largely unknown [1]. Lack of milk-fat globule EGF factor VIII (Mfge8) was reported to enhance prion pathogenesis in a mouse strain-
dependent manner, suggesting that Mfge8 can facilitate engulfment of PrP\textsuperscript{Sc} aggregates by microglia [6, 7]. Developmental endothelial locus1 (Del-1) is a structural and functional homolog of Mfge8 and therefore was a further candidate modifier of prion removal. However, Del-1 deficiency neither changed prion deposition nor prion pathogenesis in mice, suggesting that Del-1 does not complement Mfge8 in prion clearance [8]. Also triggering receptor expressed on myeloid cells 2 (TREM2), a phagocytic receptor expressed on microglia, modulates prion-induced microglial activation but does not contribute to prion clearance [9]. Hence, the molecules that are involved in prion clearance are complex and require further study.

Microglia express various receptors that facilitate sensing and phagocytosis of pathogens and misfolded protein aggregates; these include toll-like receptors (TLRs), scavenger receptors (SRs), Fc receptors, complement receptors, triggering receptor expressed on myeloid cells-2 (TREM2), myeloid cell surface antigen CD33, and others [10]. Importantly, variants of the TREM2 and CD33 genes are risk factors for Alzheimer’s disease (AD) [11–13], probably due to impaired uptake and clearance of amyloid-β (Aβ) [14, 15]. Although TREM2 is not a main transducer of prion clearance [9], the role of other microglial receptors in prion pathogenesis merits further investigations.

Msr1, also known as scavenger receptor a1 (Scara1), is a type II transmembrane glycoprotein mainly expressed by microglia in CNS [16]. Msr1 has been involved in many macrophage-associated physiological and pathological conditions such as neurodegenerative diseases [17]. As an important phagocytic receptor, Msr1 can mediate uptake of fibrillar amyloid β (Aβ) in vitro [18–20]. Msr1 deficiency in a mouse model of AD markedly accelerates Aβ accumulation and disease progression, whereas pharmacological upregulation of Msr1 leads to enhanced Aβ clearance. These results collectively suggest that Msr1 is essential for clearing soluble Aβ [21, 22]. Since both Aβ and prion are extracellular misfolded protein aggregates, they may share similar molecular pathways by which microglia take up and degrade the protein aggregates.

In this study, we aimed to investigate whether Msr1 may have a similar function in prion clearance and pathogenesis. We first determined the Msr1 expression in a mouse model of prion disease and found Msr1 expression was significantly increased in prion-infected mouse brain. After prion inoculation, we then observed that Msr1\textsuperscript{+/–} mice showed disease progression similar to their hemizygous (Msr1\textsuperscript{+/-}) and wild-type (Msr1\textsuperscript{+/-}) littermates. Besides, prion deposition and seeding dose were not altered by Msr1 deficiency, suggesting that Msr1 is not involved in prion clearance. Furthermore, Msr1 deficiency did not affect prion-induced neuroinflammation. We therefor conclude that Msr1 is not a major player in prion clearance and does not influence prion pathogenesis.

### Material and methods

#### Ethical statement

All animal experiments were carried out in strict accordance with the Rules and Regulations for the Protection of Animal Rights (Tierschutzgesetz and Tierschutzverordnung) of the Swiss Bundesamt für Lebensmittelsicherheit und Veterinärwesen and were pre-emptively approved by the Animal Welfare Committee of the Canton of Zürich (permit # 41/2012).

#### Animals

Msr1\textsuperscript{-/-} mice were generated by inserting a neomycin cassette into the EcoRI site in exon 4, which encodes the alpha helical coiled-coil structure essential for the formation of functional trimeric receptors ([23]; JAX stock #006096). Msr1\textsuperscript{+/–} mice were first backcrossed to C57BL/6 J mice to obtain Msr1\textsuperscript{+/-} offspring, which were then intercrossed to generate Msr1\textsuperscript{+/-} (wild type), Msr1\textsuperscript{+/-} and Msr1\textsuperscript{-/-} mice for experiments described here. All animals were maintained in high hygienic grade facility under a 12 h light/12 h dark cycle (from 7 am to 7 pm) at 21±1 °C and fed with diet and water ad libitum.

#### Prion inoculation

Mice were intracerebrally (i.c) inoculated with 30 μl of brain homogenate diluted in PBS with 5% BSA and containing 3 × 10\textsuperscript{5} LD50 units of the Rocky Mountain Laboratories scrapie strain (passage 6, thus called RML6). Mice were monitored and actions were taken to minimize animal suffering and distress according to details described previously [24]. Scrapie was diagnosed according to clinical criteria (ataxia, limb weakness, front leg paresis and rolling). Mice were sacrificed by CO\textsubscript{2} inhalation on the day of appearance of terminal clinical signs of scrapie (specific criteria referred to [24]), organs were taken and then were either snap-frozen for biochemical analysis or fixed in 4% formalin for histological assessment. The time elapsed from prion inoculation to the terminal stage of disease was defined as incubation time for the survival study.

#### Quantitative real-time PCR (qRT-PCR)

Total RNA from was extracted using TRIzol (Invitrogen Life Technologies) according to the manufacturer’s instruction. The quality of RNA was analyzed by Bioanalyzer 2100 (Agilent Technologies). RNAs with RIN > 8 were used for cDNA synthesis. cDNAs were synthesized from ~ 1 μg total RNA using QuantiTect Reverse Transcription kit (QIAGEN) according to the manufacturer’s instruction. Quantitative real-time PCR (qRT-PCR) was performed using the SYBR Green
To detect PrP C in the mouse brains, one hemisphere of each
Western blot analysis

Immunohistochemistry

Prion-infected brain tissues were harvested and fixed in formalin, followed by treatment with concentrated formic acid for 60 min to inactivate prion infectivity and embedded in paraffin. Paraaffin sections (2 μm) of brains were stained with hematoxylin/eosin (HE) to visualize prion-induced lesions and vacuolation. For the histological detection of partially proteinase K-resistant prion protein deposition, deparaffinized sections were pretreated with formaldehyde for 30 min and 98% formic acid for 6 min, and then washed in distilled water for 30 min. Sections were incubated in Ventana buffer and stains were performed on a NEXES immunohistochemistry robot (Ventana instruments, Switzerland) using an IVIEW DAB Detection Kit (Ventana). After incubation with protease 1 (Ventana) for 16 min, sections were incubated with anti-PrP SAF-84 (1:200, SPI bio, A03208) for 32 min. Sections were counterstained with hematoxylin. To detect astrogliosis and microglial activation, brain sections were deparaffinized through graded alcohols, anti-GFAP antibody (1:300; DAKO, Carpinteria, CA) were applied for astrogliosis, and anti-AIF1 antibody (1:1000; Wako Chemicals GmbH, Germany) was used for highlighting activated microglial cells. Stainings were visualized using DAB (Sigma-Aldrich), and hematoxylin counterstain was subsequently applied. Sections were imaged using a Zeiss Axiophot light microscope. Quantification of SAF-84 staining was performed on acquired images. Regions of interest were drawn, and the average signal density was quantified using Image J software (National Institutes of Health).

Western blot analysis

To detect PrP C in the mouse brains, one hemisphere of each brain was homogenized with RIPA buffer. Total protein concentration was determined using the bicinchoninic acid assay (Pierce). Samples were adjusted to 20 μg protein in 20 μl and digested with 25 μg ml -1 proteinase K for 30 min at 37 °C. PK digestion was stopped by adding loading buffer (Invitrogen) and boiling samples at 95 °C for 5 min. Proteins were then separated on a 12% Bis-Tris polyacrylamide gel (NuPAGE, Invitrogen) and blotted onto a nitrocellulose membrane. POM1 and horseradish peroxidase (HRP)-conjugated goat anti–mouse IgG were used as primary and secondary antibodies, respectively. Blots were developed using Luminata Crescendo Western HRP substrate (Millipore) and visualized using the FUJIFILM LAS-3000 system. To detect GFAP and AIF1 in prion-infected brains by Western blot, 20 μg of total brain protein were loaded and anti-GFAP antibody (D1F4Q) XP Rabbit mAb (1:3000; Cell Signaling Technology, 12389), anti-AIF1 antibody (1:1000; Wako Chemicals GmbH, Germany, 019-19741) and horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG (1:10,000, Jackson ImmunoResearch, 111-035-003) were used as primary and secondary antibodies, respectively. Actin was used as the loading control.

Real-time quaking induced conversion assay (RT-QuIC)

RT-QuIC assays of prion-infected mouse brain homogenates were performed as previously described [8, 25]. Briefly, recombinant hamster full-length (23–231) PrP was expressed in Rosetta2(DE3)pLysS E. coli competent cells and purified by affinity chromatography using Ni2+-nitrilotriacetic acid Superflow resin (QIAGEN). In the RT-QuIC assay, recombinant HaPrP was used as substrate for PrP C-catalyzed conversion. RT-QuIC reactions containing HaPrP substrate protein at a final concentration of 0.1 mg mL -1 in PBS (pH 7.4), 170 mM NaCl, 10 μM EDTA, and 10 μM Thioflavin T were seeded with 2 μL of serially diluted brain homogenates in a total reaction volume of 100 μL. NBH- and RML6-treated brain homogenates were used as negative and positive controls, respectively. The RT-QuIC reactions were amplified at
mouse brain homogenate containing 3 × 10^5 LD50 (50% lethal dose) units of RML6 (a prion strain originating from the Rocky Mountain Laboratory, serially passaged to No. 6, hence termed RML6) into C57BL/6 J mice. C57BL/6 J littermates inoculated with noninfectious brain homogenate (NBH) were used as control. Prion-inoculated mice were euthanized and brains were collected when they showed severe scrapie sign and reached the terminal stage of disease. NBH-inoculated control mice were sacrificed after the same incubation time. Since we could not commercially obtain a sensitive and specific antibody detecting the Msr1 protein in mouse brains, we intracerebrally (i.c) inoculated 30 μl of diluted CD1 mouse brain homogenate containing 3 × 10^5 LD50 (50% lethal dose) units of RML6 into C57BL/6 J mice. C57BL/6 J littermates inoculated with noninfectious brain homogenate (NBH) were used as control. Prion-inoculated mice were euthanized and brains were collected when they showed severe scrapie sign and reached the terminal stage of disease. NBH-inoculated control mice were sacrificed after the same incubation time. Since we could not commercially obtain a sensitive and specific antibody detecting the Msr1 protein in mouse brains, we intracerebrally (i.c) inoculated 30 μl of diluted CD1 mouse brain homogenate containing 3 × 10^5 LD50 (50% lethal dose) units of RML6 into C57BL/6 J mice. C57BL/6 J littermates inoculated with noninfectious brain homogenate (NBH) were used as control. Prion-inoculated mice were euthanized and brains were collected when they showed severe scrapie sign and reached the terminal stage of disease. NBH-inoculated control mice were sacrificed after the same incubation time. We found that mRNA levels of various microglia markers including Aif1, CD68, and Itgax were almost simultaneously induced in prion-inoculated mice from 16 weeks post-inoculation on (supplemental Figs. 2b–d), when Msr1 mRNA was not significantly altered yet [30]. Moreover, a cell-type-specific ribosomal profiling using CX3CR1-Cre^ER mice revealed that Msr1 was indeed upregulated in microglia only at the terminal stage (supplemental Figure 2E) [31]. Therefore, these results suggest that upregulation of Msr1 expression was not merely an effect of increased microglia number after prion infection, but displayed unique pattern and dynamics.

Prion disease progression, lesion pattern, or PrP^Sc accumulation are not altered by Msr1 deficiency

To assess the function of Msr1 in prion pathogenesis, we next tested whether Msr1 ablation could affect prion disease progression and alter prion-mediated lesion pattern in mouse brains. We intracerebrally (i.c) inoculated 30 μl of RML6 prions into Msr1^+/+, Msr1^+/–, and Msr1^-/- littermates. RML6-inoculated mice were checked and monitored every other day for scrapie symptoms. Mice were euthanized and brains were collected when they showed severe scrapie sign and reached the terminal stage of disease. Incubation times were calculated as the time from initial prion inoculation until terminal disease stage. We observed that all Msr1^+/+, Msr1^+/–, and Msr1^-/- mice succumbed to prion disease at a similar progression rate (median survival: 179 dpi for Msr1^+/+ mice (n = 17), 186 dpi for Msr1^+/– mice (n = 25) and 183.5 dpi for Msr1^-/- mice (n = 14), p = 0.99) (Fig. 2a). The above results indicate that Msr1 ablation does not overtly influence progression of prion disease.

We then analyzed and compared the histology of brain sections collected and prepared from RML6-inoculated terminally sick Msr1^+/+, Msr1^+/–, and Msr1^-/- mice. The classical histological characteristics of prion disease, especially the spongiform changes (or vacuolation), were observed in all mice in different groups. Lesion pattern analysis also failed to show any qualitative distinctions between different groups.
genotypes (Figure 2B). These results suggest that lack of Msr1 does not obviously affect prion-caused lesion profile in mouse brains.

If Msr1 contributed to prion clearance as it does to Aβ, Msr1+/+ mice would accumulate more PrPSc deposits in their brains. We therefore first performed PrPSc staining on brain sections prepared from RML6-inoculated terminally sick Msr1+/+, Msr1+/-, and Msr1−/− mice. Unexpectedly, we observed a similar PrP Sc deposition level and pattern in mouse brains with the different genotypes (Fig. 2b). We next performed Western blot to detect and assess proteinase K (PK)-resistant PrPSc levels in brains of terminally sick mice. We again found a similar PrPSc accumulation level in Msr1+/+, Msr1+/-, and Msr1−/− mouse brains (Fig. 2c, d). These results suggest that lack of Msr1 does not obviously affect prion-caused lesion profile in mouse brains.

Prion-induced neuroinflammation is not affected by Msr1 deficiency

Msr1 is a scavenger receptor that could modulate immune response in CNS [34–36]. To test whether Msr1 exhibits an anti-inflammatory function in prion pathogenesis, we analyzed and compared astrogliosis and microglial activation in prion-infected terminally sick Msr1+/+, Msr1+/-, and Msr1−/− mice. First, histology and Western blots did not identify obvious differences in GFAP (glial fibrillary acidic protein), an
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study showed that upregulation of Msr1 was not merely due to increased microglia number. Although both analyses were based on brain tissue containing a mixture of various cell types, a cell-type specific ribosomal profiling again found that Msr1 was significantly upregulated in microglia only at the terminal stage. Orthogonal methodologies, such as cell sorting followed by RNA-seq, would be required to confirm the microglia-specific Msr1 expression pattern along the prion progression. Nevertheless, the late upregulation of Msr1 may explain that Msr1 have little impact on the prion pathogenesis. The varied temporal pattern and magnitude of changes of Msr1 expression between prion disease and AD may explain its different functional roles in these diseases.

We performed prion infection experiments with an appropriate number of animals (n=14–25 mice per group) and conclude, with a high degree of confidence, that Msr1 deficiency did not overtly affect progression of prion disease. We randomly divided the samples into subgroups for either biochemical analysis or histology encompassing a relatively small number of samples (n = 3–5 mice per group). Because of the increased stochasticity inherent to such subgroups, we observed some variations in these analyses. Notwithstanding these limitations, our results point towards the same direction and are congruent with our conclusion that Msr1 does not play a major role in prion pathogenesis.

Conclusion

Collectively, these results indicate that Msr1 does not play a major role in prion pathogenesis. Together with the discrepant observations of TREM2 in AD and prion disease[9, 14], this study suggests that microglia-mediated phagocytosis and clearance of Aβ and prion may adopt distinct molecular pathways. Further studies are needed to investigate molecular mechanisms underlying microglial uptake and clearance of prions.

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Author’s contributions C. Zhu and A. Aguzzi conceived the project and designed the experiments; B. Li, M. Chen, and C. Zhu conducted the experiments and acquired data. All authors contributed to data analysis.

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Availability of data and material The authors confirm that the data and material supporting the findings of this study are available within the article and its supplementary materials.

Code availability Not applicable.

Declarations

Ethics approval All animal experiments were carried out in strict accordance with the Rules and Regulations for the Protection of Animal Rights (Tierschutzgesetz and Tierschutzverordnung) of the Swiss Bundesamt für Lebensmittelsicherheit und Veterinärwesen and were preemptively approved by the Animal Welfare Committee of the Canton of Zürich (permit # 41/2012).

Consent to participate Not applicable.

Consent to publication Not applicable.

Conflict of interest The authors declare that they have no conflict of interest.
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