Effect of the host gut microbiota on prion-induced neurodegeneration

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Introduction

Neuropathological damage induced by prions within the CNS is a characteristic hallmark of prion diseases. Along with prion deposition and neuronal loss, striking changes in glial activation occur. Studying these changes within scrapie-infected mouse models reveals a tractable model to investigate the mechanisms of neurodegeneration. Recently there have been numerous reports that gut microbiota influence neurodegeneration via modulation of the CNS microglial population. Indeed studies in naive mice have suggested that lack of gut microbiota results in a reduction of microglial activation state and subsequent severity of CNS innate immune responses when subjected to stimulation by lipopolysaccharide (LPS). We therefore determined whether the host commensal microbiota may influence CNS prion disease pathogenesis and susceptibility.

Methods

Germ-free mice were used to investigate the influence of the host microbiota on CNS prion disease pathogenesis and susceptibility. Germ-free mice and conventional mice (control) were injected with 22C mouse-passaged scrapie strains by the intracerebral or intraperitoneal routes. Following exposure, survival times were recorded and brains collected at the terminal stage of disease for histopathology, image and morphometric analysis techniques.

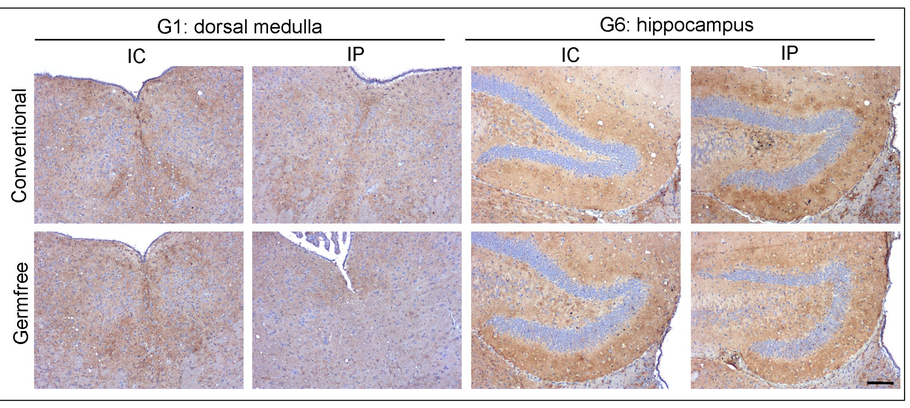

Figure 1. Absence of the commensal gut microbiota in germfree mice did not influence the distribution of disease-specific PrP within the brain.
Sections were immunostained to detect PrP (brown) and counterstained with haematoxylin (blue), scale bar, 100 µm

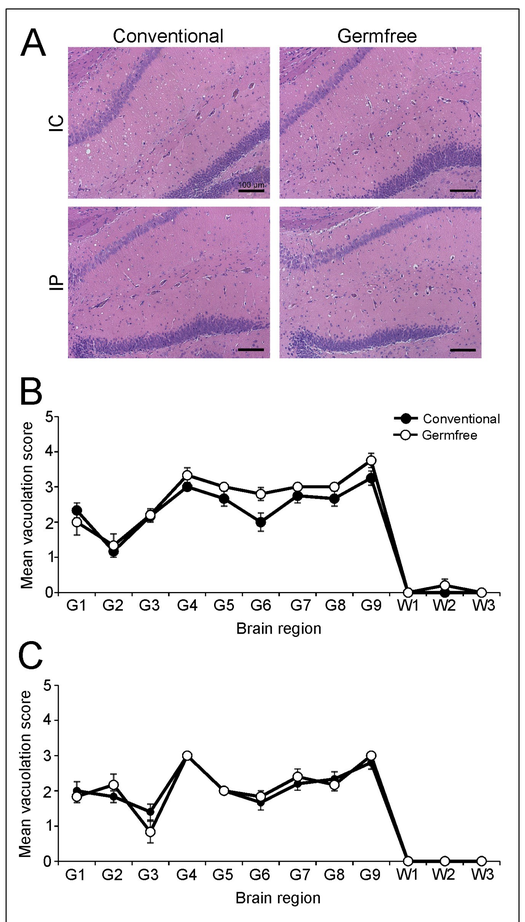

Figure 2. The commensal gut microbiota does not influence the magnitude or distribution of the prion-induced vacuolation within the brain at the terminal stage of prion disease.
A) H&E stained brain sections used for vacuolation scoring, each brain was scored on a scale of 1–5 in nine grey matter areas: G1, dorsal medulla; G2, cerebellar cortex; G3, superior colliculus; G4, hypothalamus; G5, thalamus; G6, hippocampus; G7, septum; G8, retrosplenial and adjacent motor cortex; G9, cingulate and adjacent motor cortex from mice were infected with prions by the IC (B) or IP (C) routes.

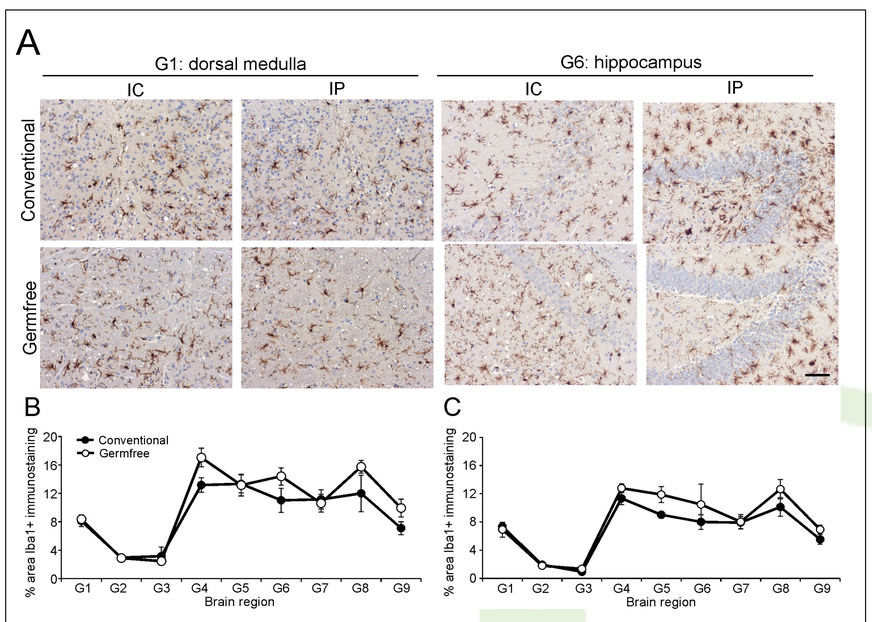

Figure 3. Absence of the commensal gut microbiota in germfree mice did not influence the distribution of microglia within the brain.
A) Sections were immunostained to detect Iba1+ cells (brown) and counterstained with haematoxylin (blue) in the brains of clinically-affected conventionally-housed and germfree mice infected with prions by the IC (B) or IP (C) routes. n = 6 mice/group, scale bar, 100 µm.

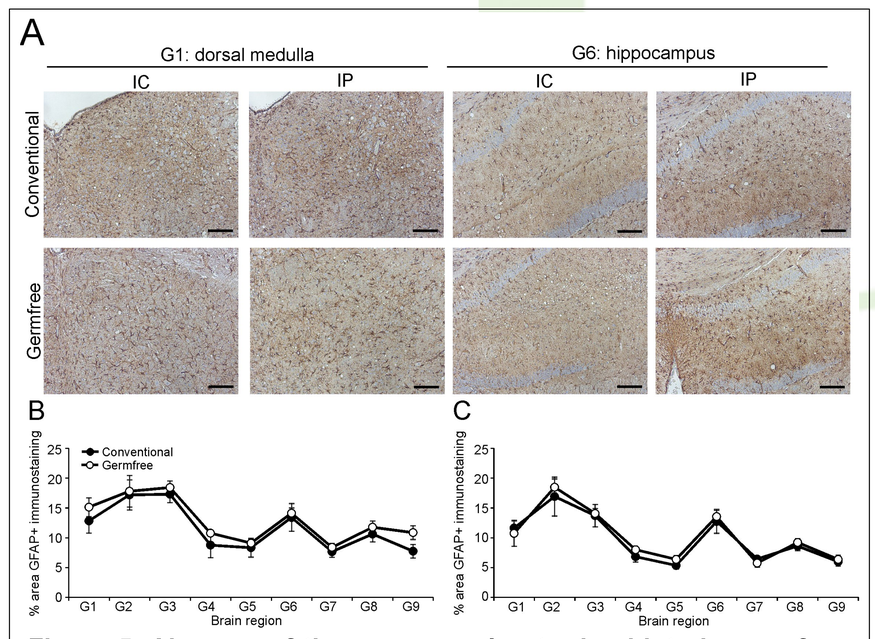

Figure 5. Absence of the commensal gut microbiota in germfree mice did not influence the distribution of microglia within the brain.
A) Sections were immunostained to detect astrocytes (GFAP+ cells, brown) and counterstained with haematoxylin (blue), scale bar, 100 µm. Analysed as above (Figure 3).

Results

Our data show that the host commensal microbiota did not influence prion disease duration or susceptibility, as survival times, disease incidences and neuropathological changes were identical in germ-free and conventional mice when infected with the same strain of prion disease agent via the same route.

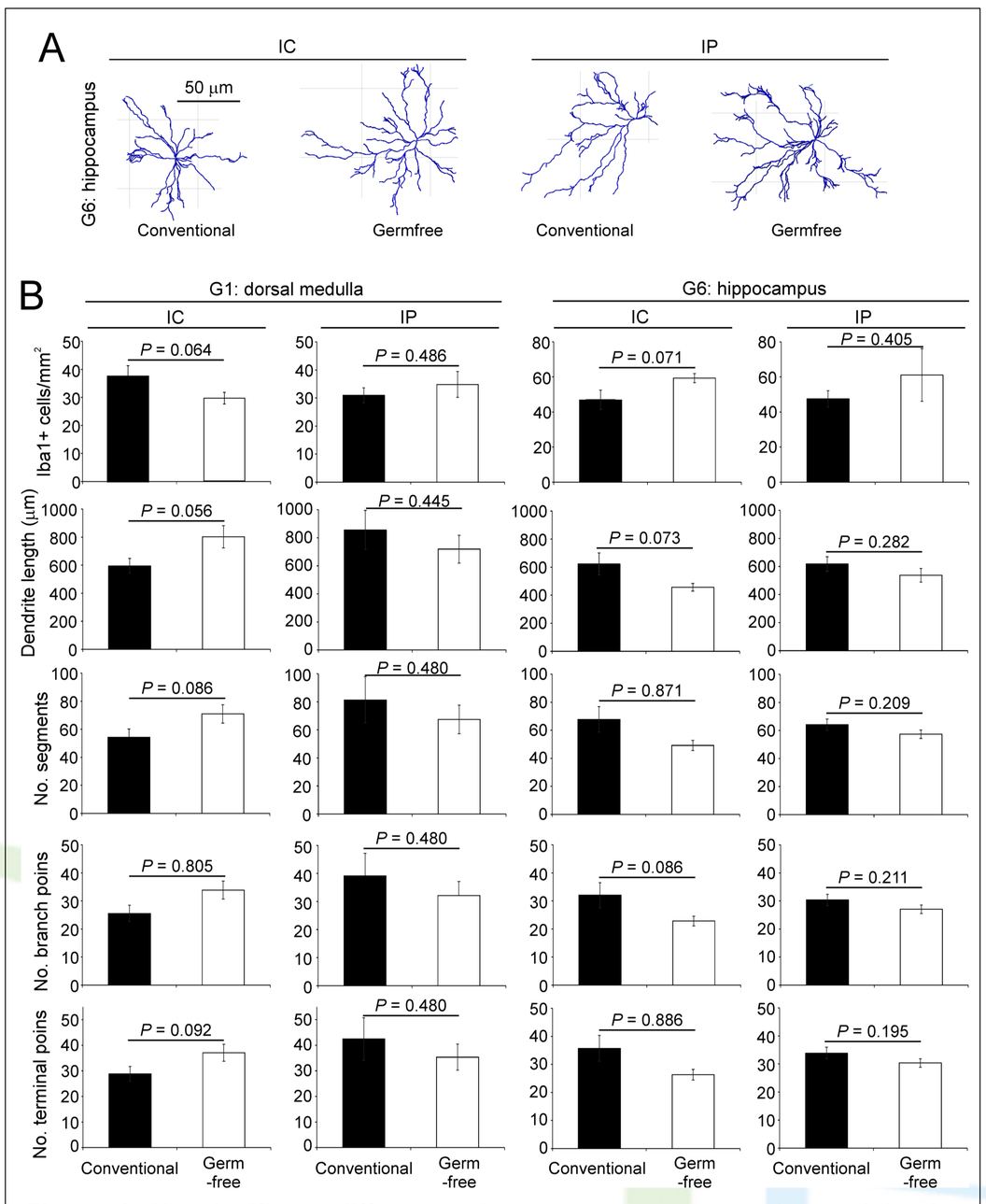

Figure 4. No significant differences between groups were observed in the number of microglia within regions, or in the length of dendrites, number of segments, branching points or terminal points on individual microglia.
A) Imaris-based reconstructions of Iba1+ microglia in the hippocampus region. B) Imaris-based quantitative cell morphometry of Iba1+ microglia in the dorsal medulla (left-hand panels) and hippocampus (right-hand panels) regions. From each group, six individual mice were sampled, and data were collected from at least 25 individual Iba1+ microglia within each brain region. Solid bars, conventionally-housed mice; open bars, germfree mice.

Conclusions

Germ-free mice have been shown to have altered microglial morphology in the naïve state when compared to those from conventional mice. However, our data show that at the terminal stage of prion disease, the neuropathological changes and microglial morphology were indistinguishable in brains from germ-free and conventional mice. Our data show that the presence or absence of the host commensal microbiota does not significantly influence the development of disease-associated PrP deposition, prion-induced vacuolation microglial activation and astrocyte activation, affecting neither targeting nor intensity of each neuropathological hallmark within the CNS during prion disease.

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