Blocking of FcR suppress the intestinal invasion of scrapie agents


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5. Status of BSE Occurrence Abroad

Similar BSE countermeasures have been adopted world‐widely. In recent years, the number of BSE‐affected cattle in each country has decreased rapidly.

Change in the Number of BSE‐Affected Cattle around the World

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<tbody>
<tr>
<td>Overall</td>
<td>37,316</td>
<td>2,215</td>
<td>2,179</td>
<td>1,389</td>
<td>878</td>
<td>561</td>
<td>359</td>
<td>169</td>
<td>23</td>
<td>190,355</td>
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<td>Europe (excluding UK)</td>
<td>36</td>
<td>1,030</td>
<td>1,032</td>
<td>722</td>
<td>529</td>
<td>327</td>
<td>199</td>
<td>96</td>
<td>11</td>
<td>5,752</td>
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<td>UK</td>
<td>37,280</td>
<td>1,202</td>
<td>1,144</td>
<td>611</td>
<td>343</td>
<td>225</td>
<td>114</td>
<td>67</td>
<td>10</td>
<td>184,551</td>
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<td>2(*)</td>
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<td>5</td>
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<td>14(*)</td>
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*2 One of these cases was identified in the US, but the total number of confirmed cases worldwide is 190,355. (http://www.oie.int)

*3 The total number of Canadian cases includes one case of imported cow and one case firstly confirmed in the US (tested in December 2003).
Background (transmission of prion diseases)

- Oral transmissibility by PrPSc (issue in food safety)
- Invasion and dynamics in the intestines of PrPSc is little elucidated.
  - M cells on Peyer’s patches or Villous epithelium

15 day-old-SCID mice (with IgG) PrPSc uptake in intestine

The number of PrPSc-positive cells

<table>
<thead>
<tr>
<th></th>
<th>NOD</th>
<th>NOD-SCID</th>
<th>NOD-SCID (+IgG)</th>
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<tr>
<td>The number of PrPSc-positive cells</td>
<td>50</td>
<td>45</td>
<td>40</td>
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Background (function of neonatal Fc receptor)

The neonatal Fc receptor (nFcR) functions most efficiently in the neonatal period when it transports maternally derived IgG in ingested milk. IgG binds with high affinity to nFcR at an acidic pH (<6.5), but not at physiological pH (7.4).

Concept

When Fc receptors are blocked by compound, what happens in terms of incorporating PrP<sup>Sc</sup>?
Materials and Methods
(Administration and preparation of tissue specimens)

Animals
CD-1 or NOD mice (15-day-old)

Substance of administration and condition
• Z-ε-aminocaproic acid (Fc receptor blocker)
• IgG (5.0mg/ml in PBS)
• 10% brain homogenate infected with scrapie prions (Tsukuba1)
  (Under the appropriate biosafety condition)

Euthanized and extirpation of intestine and spleen
  ① duodenum, ②③ jejunum, ④⑤ ileum

Fixed by immersion in 4% paraformaldehyde

Thechnobit embedding

immunostaining

Thechnobit embedding
Materials and Methods
(Administration and preparation of tissue specimens)

<table>
<thead>
<tr>
<th>Fc receptor blocker</th>
<th>×</th>
<th>O</th>
<th>O</th>
<th>×</th>
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<tr>
<td>IgG</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>×</td>
<td>×</td>
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<tr>
<td>scrapie prions</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>O</td>
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✦: IgG or prions was administrated 2h later the administration of Fc receptor blocker

✦✦: IgG or prions was administrated with Fc receptor blocker

The number of positive cells in each microscopic visual fields was counted at five random points in the villous epithelium. Cell counts are expressed as the mean ± SD of microscopic fields viewed at x400 magnification.
Intestinal invasion of PrPSc

Intestinal invasion of IgG
Results

15 day-old NOD mice, PrP\textsuperscript{Sc} uptake in intestine

The number of PrP\textsuperscript{Sc}-positive cells

- 1: 100
- 2: 60
- 3: 30
- 4: 20
- 5: 10

*P<0.01*
The inhibitory effect was calculated as following formula

\[
\text{Percentage of ileal epithelial cells incorporating IgG or PrPSc with ZAA treatment} \\
\times 100(\%)
\]

\[
\text{Percentage of ileal epithelial cells incorporating IgG or PrPSc without ZAA treatment}
\]

FcR blocker (Z- ε -aminocaproic acid) suppresses the intestinal invasion of scrapie agents in NOD mouse
15 day-old-SCID mice (with IgG) PrPSc uptake in intestine

The number of PrPSc-positive cells

15 day-old-NOD SCID (with IgG) mice PrPSc uptake in intestine

The number of PrPSc-positive cells
The number of PrP^Sc-positive cells

FcR blocker inhibit the incorporation of PrP^Sc in the NOD mouse ileum

15 day-old-NOD mice with incorporation of IgG in the ileum
15 day-old-NOD SCID (+IgG) mice with incorporation of IgG in the ileum

The number of IgG-positive cells

FcR blocker inhibit the incorporation of IgG in the NOD mouse ileum

The number of IgG-positive cells

\[ P < 0.01 \]
Conclusion

Fc receptors were blocked by FcR blocker

The incorporation of Prion was observed in the latter part of ileum.

Neonatal Fc receptor (nFcR) was associated with the incorporation of Prion in the latter part of ileum.

One of the mechanism incorporating PrP<sub>Sc</sub>
the intestinal invasion of IgG (CD-1)

FcR blocker (Z-ε-aminocaproic acid) suppresses the intestinal invasion of IgG

(number of IgG-positive cells [cells/area]

Rate of IgG-positive cells [%]

PrPSc

FcR blocker (Z-ε-aminocaproic acid) suppresses the intestinal invasion of scrapie agents

(number of PrPSc-positive cells [cells/area]

Rate of PrPSc-positive cells [%]
Maternal Ig or neonatal Fc receptor may affect the incorporation of PrPSc during lactation period.

Ano et al. *P < 0.01