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Intestinal mastocytosis and goblet cell hyperplasia in BALB/c and C3H mice infected with *Neodiplostomum seoulense*

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Abstract: Mucosal mast cell (MMC) and goblet cell (GC) responses were observed in the small intestine of two strains of mice (BALB/c and C3H) infected with *Neodiplostomum seoulense*, and their roles in the host defense and worm expulsion were studied. From day 3 to 28 post-infection (PI) with 200 metacercariae, the worm recovery rate from BALB/c mice was consistently and remarkably higher than that from C3H mice. In the duodenum of both strains of mice, the main habitat of the flukes, mastocytosis was pronounced on day 7 PI but quickly diminished thereafter. Similar kinetics were observed in the jejunum and ileum, although the extent of mastocytosis was lesser in the ileum than other two areas. These MMC kinetics were not different between the two strains of mice. Moreover, the extent of mastocytosis was stronger in BALB/c mice than in C3H mice. GC hyperplasia was remarkable in the duodenum of BALB/c mice throughout the course of infection except day 14 PI, whereas it was recognizable only in the jejunum and ileum of C3H mice on day 7 PI. Mucin activation was evidently demonstrated in both strains of mice throughout the course of infection, but more marked in BALB/c than in C3H mice. The results strongly suggest that mastocytosis and GC hyperplasia are local immune responses against *N. seoulense*, however, they play a minor role in the host defense and worm expulsion.

Key words: *Neodiplostomum seoulense*, worm expulsion, mucosal mast cells, goblet cells, mucin alteration, worm recovery rate, C3H mice, BALB/c mice

INTRODUCTION

Neodiplostomum seoulense (Digenea: Neodiplostomidae) is an intestinal trematode of humans and rodents in Korea (Seo, 1990; Hong and Shoop, 1995). The first human infection was reported from a man who consumed raw viscera of undercooked snakes (Seo *et al.*, 1982), and twenty six more cases were found thereafter (Hong *et al.*, 1984 & 1986). House rats are the natural final host, and laboratory mice and rats are experimental final hosts (Hong, 1982: Cho *et al.*, 1983; Hong *et al.*, 1983). The major habitat of *N. seoulense* in the final host is the duodenum, and flukes descend down to the jejunum and ileum when worm burden is increased (Hong, 1982; Hong *et al.*, 1983).

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Like intestinal nematodes such as *Nippostrongylus brasiliensis* (Jarrett *et al.*, 1968), *N. seoulense* is spontaneously expelled from the host intestine after day 7 post-infection (PI) (Hong, 1982). Similar phenomena were observed in other trematodes such as *Metagonimus yokogawai* (Chai *et al.*, 1993) and *Echinostoma trivolvis* (Fujino *et al.*, 1996). However, little information has been available concerning the expulsion mechanisms of trematodes.

On the other hand, extensive studies have been performed to clarify the expulsion mechanisms of nematodes. A review of these studies has drawn a conclusion that intestinal mucosal mast cells (MMCs), goblet cells (GCs), secretory IgA, and various kinds of cytokines are major effectors (Wakelin, 1993). Importance of each effector is, however, different depending on the species of parasites and genetic backgrounds of hosts (Nawa *et al.*, 1994). For example, MMCs but not GCs play a vital role for expulsion of *Strongyloides ratti*, whereas GCs but not MMCs play an essential role for expulsion of *N. brasiliensis* (Miller *et al.*, 1981; Abe *et al.*, 1992 & 1993). Important roles of GCs but not MMCs in the worm expulsion were also reported in a trematode model, *E. trivolvis* (Fujino *et al.*, 1993).

In *N. seoulense* infection, mucosal mastocytosis was reported in rats (Kho *et al.*, 1990), but their role in the worm expulsion has not yet been verified. Studies on GCs and their roles in the worm rejection are unavailable. In a preliminary study with *N. seoulense*, we observed that BALB/c mice retained significantly more worms than C3H mice up to 28 days PI. In the present study, we observed MMC and GC responses of these two strains of mice to know their roles in the expulsion of *N. seoulense*.

MATERIALS AND METHODS

Animals and experimental infection with *N. seoulense*

Two strains of mice, BALB/c and C3H, were used for this study. Each strain was composed of 60 male mice, 2-3 months old and 20-25 g in body weight. Each mouse was fed 200 metacercariae of *N. seoulense* through a gavage needle. The metacercariae were isolated from the mesentery and omentum of the snake, *Rhabdophis tigrina lateralis*, using artificial digestion technique. Three mice each were fed physiological saline and used as uninfected controls.

Worm recovery

Five mice of each strain were sacrificed on days 3, 7, 14, 21 and 28 PI by cervical dislocation, and larval or adult flukes were recovered using Baermann's apparatus (Beaver *et al.*, 1984). Briefly, the abdomen of mice was opened, and their small intestine resected. The intestine was cut into several segments, longitudinally opened in petri dishes containing physiological saline solution, and transferred to the top of the apparatus. The flukes were collected from the bottom of the tube equipped in the apparatus. After incubation intestinal segments were returned to petri dishes to search for residual flukes under stereomicroscopy.

Observation of MMC responses

For this purpose, 5 mice each were sacrificed on days 3, 7, 14, 21 and 28 PI by cervical dislocation. Their abdomen was opened, and intestinal segments, about 2 cm in length, were taken from the middle portion of the duodenum, jejunum, and ileum. The segments were washed with saline two or three times and fixed in Carnoy's fixative for 4 to 6 hrs. The fixed tissues were embedded in paraffin and sectioned at about 4 μm thickness. MMC staining was done as described by Strobel *et al.* (1981). Briefly, the samples were stained with 1% alcian blue (pH 0.3, Sigma) and counterstained with 0.5% safranin (Merck, Germany). MMCs were counted in the defined regions of 10 villus-crypt units (VCU) (Miller and Jarret, 1971) for each stained sample.

Observation of GC responses

The intestinal tissue samples prepared as above were stained for GCs with periodic acid Schiff (PAS). Briefly, the samples were oxidized with 1% periodic acid (Lancaster) for 5 min, and reacted with Schiff reagent to produce a colored end product. They were counterstained

with hematoxylin (Sigma). GC numbers were counted per 10 VCU using the method described by Miller and Jarret (1971).

Lectin histochemistry for GC mucins

In order to observe functional status of GCs, lectin histochemistry was performed using *Helix pomatia* agglutinin (HPA), which specifically recognizes the terminal GalNAc residue on altered GC mucins (Hammarstrom and Kobat, 1969). The procedure was as described by Ishikawa *et al.* (1994). Briefly, paraffin sections were rehydrated, and endogenous peroxidase was blocked by 0.3% H_2O_2 in methanol. They were incubated in phosphate-buffered saline (PBS) supplemented with 1% bovine serum albumin to prevent non-specific binding of proteins. Then they were incubated in PBS containing 25 μg/ml of biotinylated HPA for 1 hr, followed by treatment with streptavidin-horseradish peroxidase conjugate (Gibco BRL, Gaithersburg, USA) at a dilution of 1:300 in PBS for 30 min. The coloring agent used was 0.02% diaminobenzidine dissolved in 0.05 M Tris-HCl (pH 7.6). Cells stained as dark brown color were regarded positive. The values were expressed as the number of HPA positive cells per 10 VCU.

Statistical test

Values were expressed as the mean ± standard deviation of data from 5 mice. In the case of histological sections 3 samples were prepared for each group. Statistical significance between groups was tested by the Students' *t*-test.

RESULTS

Worm recovery rate

On day 3 PI, the worm recovery rate (WRR) was similar between BALB/c (71.3 ± 18.7%) and C3H (71.9 ± 12.6%) mice (Table 1). But on day 7 PI, the WRR became significantly higher ($p<0.05$) in BALB/c (66.4 ± 16.9%) than in C3H mice (37.0 ± 7.2%). The same pattern was observed on day 14 PI; BALB/c (64.8 ± 27.2%) and C3H mice (37.0 ± 16.3%). Thereafter the difference in WRR became more pronounced as infection progressed until day 28 PI (Table 1). It was evident that C3H mice expelled *N. seoulense* more rapidly than BALB/c mice.

MMC responses in the small intestine

In uninfected controls, MMCs in the duodenum, jejunum and ileum were very small in numbers; only 2.0 ± 1.3, 5.3 ± 2.4, and 1.2 ± 0.7 per 10 VCU, respectively, in BALB/c, and 2.3 ± 1.1, 1.6 ± 0.7, and 2.4 ± 1.0, respectively, in C3H mice (Fig. 1). But they began to increase significantly ($p<0.05$) on day 3 PI in the duodenum of BALB/c mice, 11.5 ± 9.0, while not in their jejunum and ileum, 4.8 ± 4.9 and 1.0 ± 1.0, respectively. In C3H mice, their numbers on day 3 PI were 1.1 ± 1.6 ($p>0.05$), 2.1 ± 2.4 ($p>0.05$), and 7.1 ± 9.5 ($p<0.05$), respectively, in three portions of the small intestine. After then they increased significantly ($p<0.05$) in all of the three portions reaching a peak on day 7 PI (Fig. 1); 174.5 ± 38.3 (Fig. 2), 161.5 ± 82.2, and 54.6 ± 28.8, respectively, in BALB/c, and 69.8 ± 60.3, 57.3 ± 25.0, and 11.7 ± 16.5, respectively, in C3H mice. Then they decreased quickly on day 14 PI; 10.4 ± 12.6, 18.2 ± 17.4, and 6.2 ± 8.6 in BALB/c, and 2.3 ± 1.3, 3.6 ± 0.3, and 3.3 ± 1.7 in C3H mice. By day 21 (Fig. 3) and day 28, mastocytosis was completely normalized in all of the three portions of both strains of mice (Fig. 1).

Summarizing the above results, the extent of mastocytosis was more pronounced in BALB/c mice (30-87 fold increase) than in C3H mice

Table 1. Comparison of the WRRs from BALB/c and C3H mice infected with *N. seoulense*

Mouse strain	WRR (%)[a] by time post-infection				
	day 3	day 7	day 14	day 21	day 28
BALB/c	71.3 ± 18.7	66.4 ± 16.9	64.8 ± 27.2	61.7 ± 8.8	58.3 ± 7.4
C3H	71.9 ± 12.6	37.0 ± 7.2	37.0 ± 16.3	13.3 ± 3.2	7.2 ± 2.5

[a]Worm recovery rate; mean ± SD of data from 5 mice.

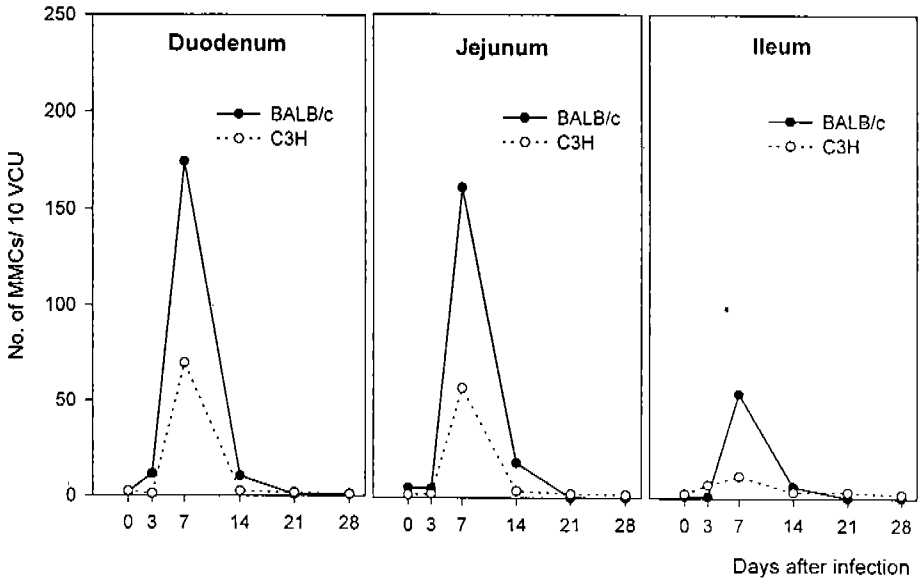

Fig. 1. Comparison of mucosal mast cell (MMC) numbers per 10 villus-crypt unit (VCU) in the small intestine of BALB/c and C3H mice infected with *N. seoulense*. Values represent the mean of data from 5 mice each consisting of three samples on each day. Standard deviation rarely exceeded the mean value.

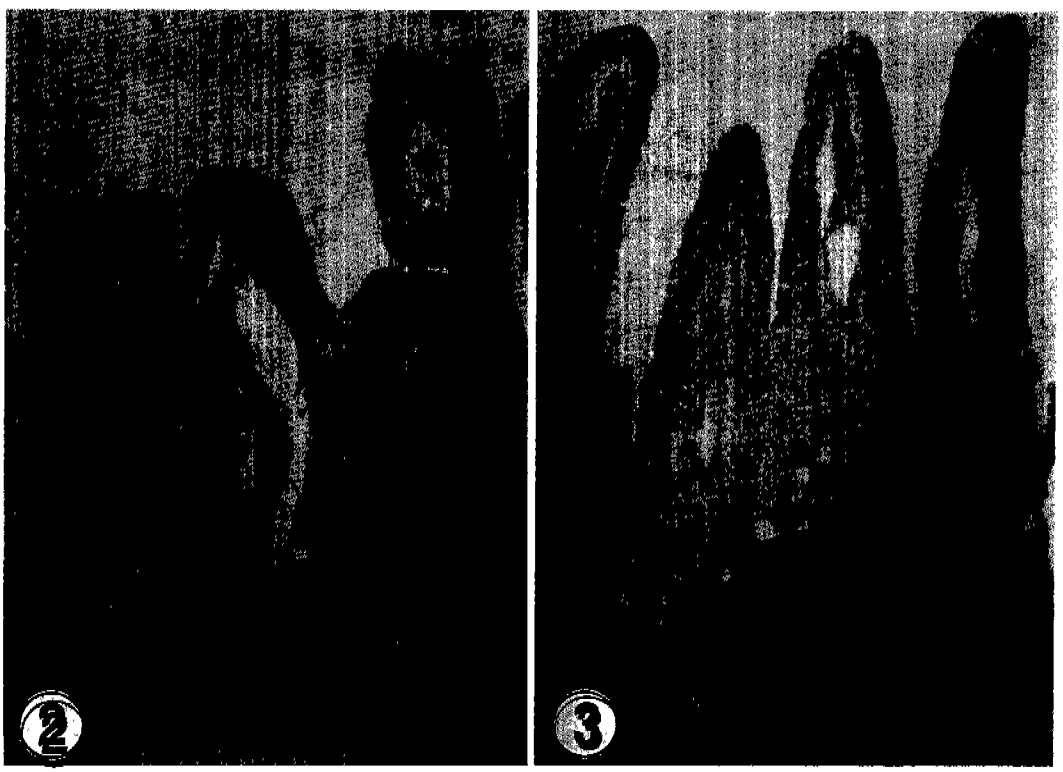

Fig. 2. Mucosal mastocytosis in the duodenum of a BALB/c mouse infected with *N. seoulense*, day 7 PI. Blue spots represent MMCs. Stained with alcian blue and safranin. × 500. **Fig. 3.** Decreased number of MMCs to nearly normal level on day 21 PI in the duodenum of a BALB/c mouse infected with *N. seoulense*. × 500.

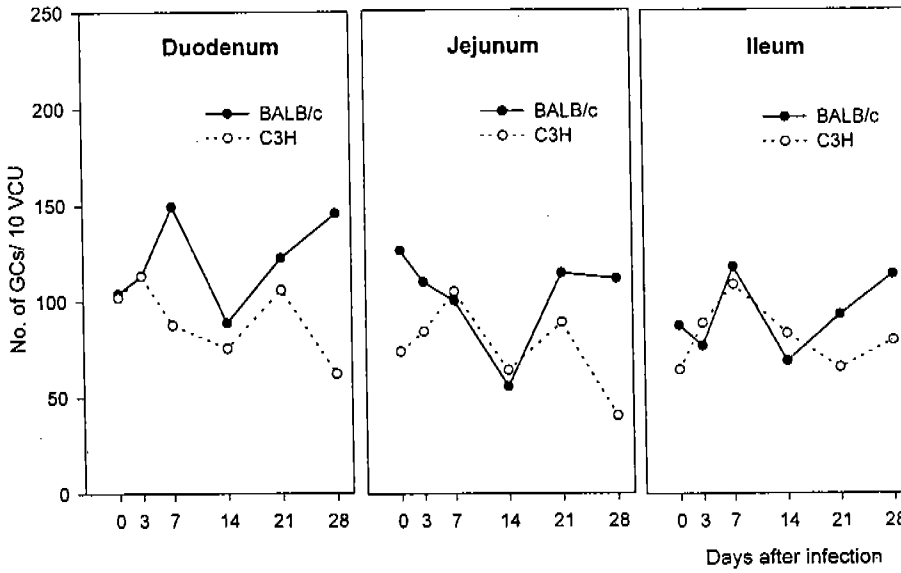

Fig. 4. Comparison of goblet cell (GC) numbers per 10 villus-crypt unit (VCU) in the small intestine of BALB/c and C3H mice infected with *N. seoulense*. Values represent the mean of data from 5 mice each consisting of three samples on each day. Standard deviation never exceeded the mean value.

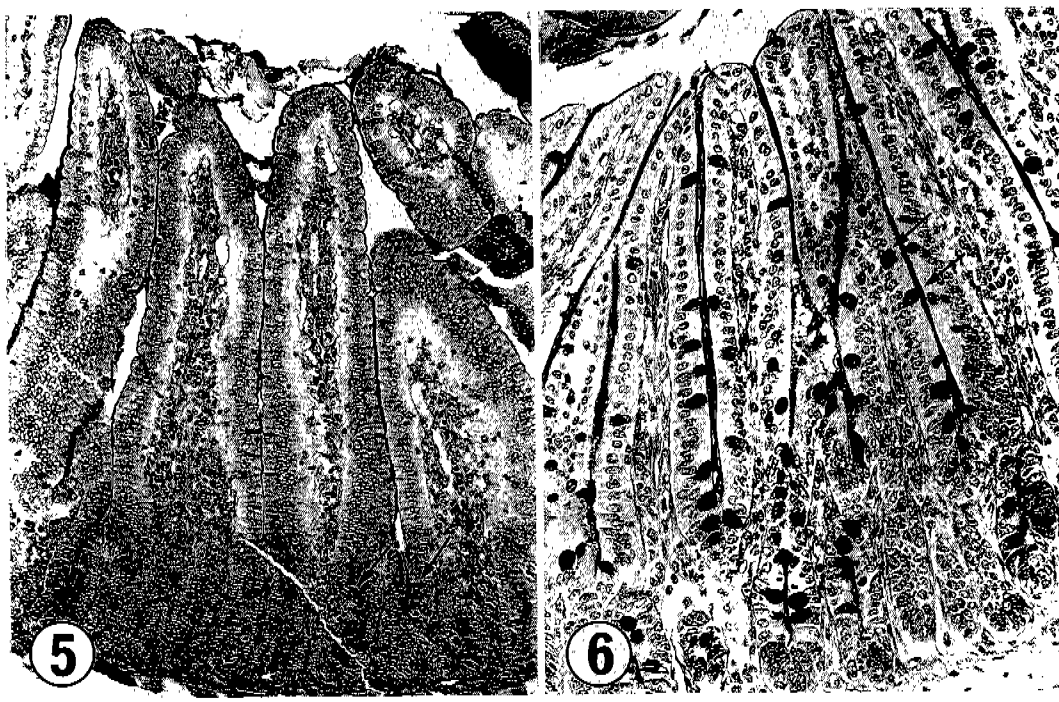

Fig. 5. The duodenum of a normal BALB/c mouse showing only a small number of GCs (arrows). Stained with PAS, and counterstained with hematoxylin. × 500. **Fig. 6.** Marked GC hyperplasia in the ileum of a BALB/c mouse infected with *N. seoulense*, day 28 PI. Dark spots (arrows) represent GCs. × 650.

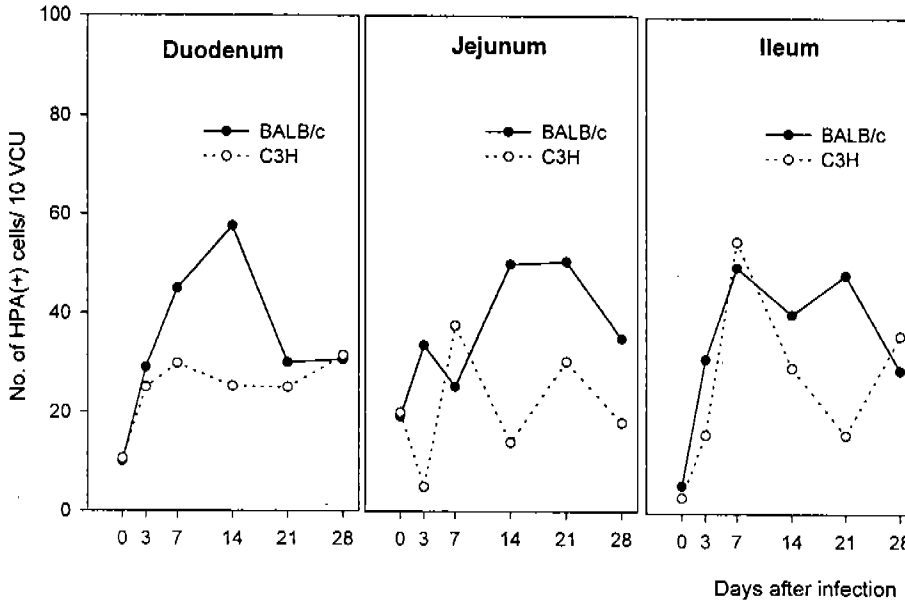

Fig. 7. Comparison of *Helix pomatia* agglutinin (HPA) positive cell numbers per 10 villus-crypt unit (VCU) in the small intestine of BALB/c and C3H mice infected with *N. seoulense*. Values represent the mean of data from 5 mice each consisting of three samples on each day. Standard deviation never exceeded the mean value.

(5-36 fold increase), and in both strains of mice mastocytosis was more remarkable in the duodenum and jejunum than in the ileum (Fig. 1).

GC responses in the small intestine

In the duodenum of normal BALB/c mice, GC numbers were 104.0 ± 38.2 per 10 VCU (Figs. 4 & 5). But in *N. seoulense*-infected BALB/c mice, they began to increase on day 3 PI (113.4 ± 20.1), reached a peak on day 7 PI (149.5 ± 20.6), then decreased remarkably on day 14 PI (72.0 ± 30.7). GC numbers were increased again on day 21 PI (122.6 ± 62.3) and further increased on day 28 PI (145.7 ± 31.7) (Fig. 4). These changes were, however, statistically insignificant ($p>0.05$) compared with uninfected controls. Similar patterns of GC kinetics were observed in the ileum of BALB/c mice (Fig. 4); 87.0 ± 2.8 (controls), 76.3 ± 13.8 (day 3 PI), 117.3 ± 23.9 (day 7 PI; $p<0.05$), 61.8 ± 15.5 (day 14 PI), 92.3 ± 32.6 (day 21 PI), and 113.3 ± 29.0 (day 28 PI; $p>0.05$; Fig. 6), but not in the jejunum, where GC depletion was marked on day 14 PI (55.3 ± 11.3; $P<0.05$) compared with controls (126.0 ± 1.0).

In C3H mice, GC hyperplasia was not recognizable in the duodenum throughout the course of infection (Fig. 4); 102.0 ± 1.4 (controls), 113.3 ± 27.5 (day 3 PI), 87.7 ± 3.7 (day 7 PI), 75.5 ± 1.3 (day 14 PI), 106.0 ± 31.1 (day 21 PI), and 62.0 ± 0.0 (day 28 PI). Slight but significant GC hyperplasia was observed on day 7 PI in the jejunum (104.6 ± 10.6; $p<0.05$) (uninfected controls; 73.6 ± 21.7) and ileum (108.0 ± 0.0; $p<0.05$) (controls; 64.0 ± 5.6) of C3H mice (Fig. 4).

The extent of GC hyperplasia on day 7 PI was most pronounced in the ileum of C3H mice (69% increase) than in the duodenum (44% increase) and ileum (35% increase) of BALB/c mice, or in the jejunum (42% increase) of C3H mice (Fig. 4).

Results of lectin histochemistry

Compared with uninfected controls (Figs. 7 & 8), the number of HPA positive cells, *i.e.* GCs with altered mucins, began to increase in both strains of mice on day 3 PI. In the duodenum, for example, the number of HPA positive cells was 10.2 ± 3.8 and 10.7 ± 1.5 in uninfected BALB/c and C3H mice, respectively. However, it was increased significantly ($p<0.05$) to 29.0

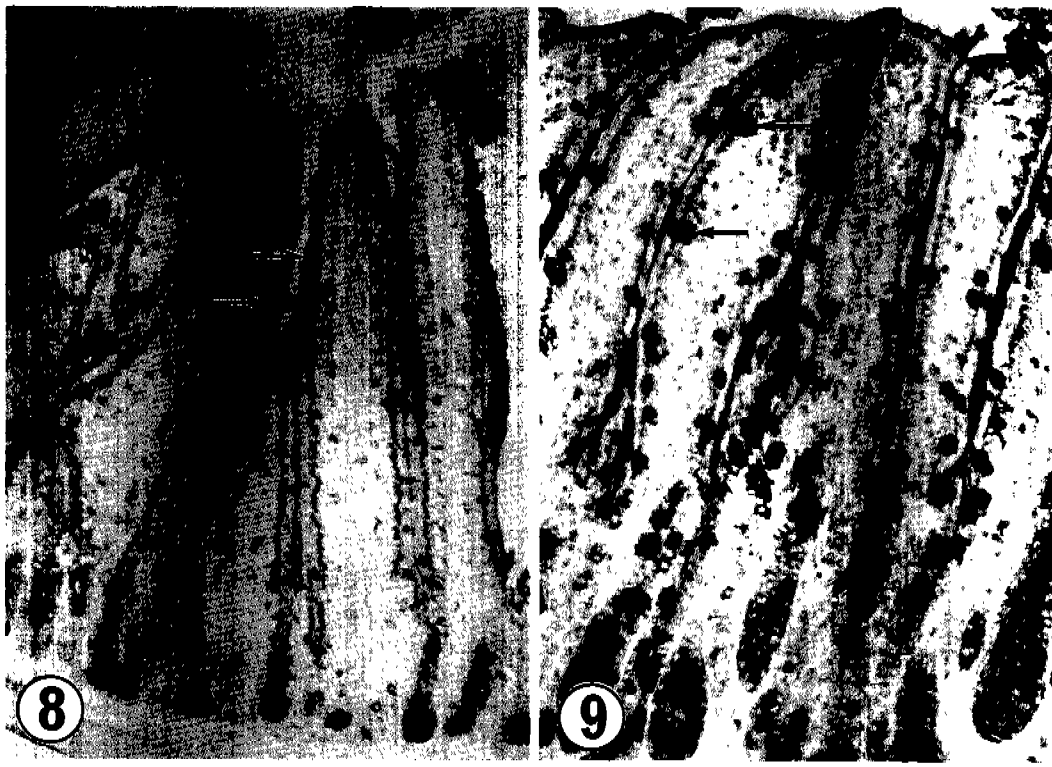

Fig. 8. The duodenum of a normal BALB/c mouse showing only a small number of activated GCs (arrows) in which altered mucins around GCs are stained dark brown. Lectin histochemistry was performed using *Helix pomatia* agglutinin (HPA) which specifically recognizes the terminal GalNAc residue on altered GC mucins. × 500. **Fig. 9.** HPA positive GCs (arrows) in the ileum of a BALB/c mouse infected with *N. seoulense*, day 28 PI. Lectin histochemistry was performed by the same procedure as in Fig. 8. × 650.

± 4.2 and 25.0 ± 0.0, respectively, on day 3 PI (Fig. 7). The increase was also remarkable in other two portions of the small intestine, except in the jejunum of C3H mice (increased on day 7 PI; 37.6 ± 14.2) (Fig. 7).

In both strains of mice, hyperplasia of altered GCs persisted throughout the course of infection (Fig. 7). A peak value was observed on day 7-21 PI; in BALB/c mice, 57.7 ± 10.7 (day 14) in the duodenum, 50.6 ± 31.6 (day 21) in the jejunum, and 49.8 ± 10.4 (day 7) in the ileum, and in C3H mice, 29.8 ± 5.9 (day 7) in the duodenum, 37.6 ± 14.2 (day 7) in the jejunum, and 55.0 ± 0.0 (day 7) in the ileum. On day 28 PI, the number was decreased a little in the jejunum (35.0 ± 11.0) and ileum (29.0 ± 27.2; Fig. 9) than the figures of day 21 PI in BALB/c mice, but increased a little in the duodenum (31.5 ± 27.5) and ileum (36.0 ± 6.0) of C3H mice.

The extent of altered GC hyperplasia on day 7-21 PI was most pronounced in the ileum of C3H mice (16.7 fold increase) than in the ileum (8.7 fold), duodenum (5.7 fold), and jejunum (2.6 fold) of BALB/c mice, or in the duodenum (2.8 fold) and jejunum (1.9 fold) of C3H mice.

DISCUSSION

It is well known that susceptibility of the host to parasitic infections is variable by species and strains of host animals. For example, dogs infected with *M. yokogawai* retained worms more than 6 weeks (Kang *et al.*, 1983). The results were different from another study using rats, in which worm expulsion of *M. yokogawai* occurred within 4

weeks PI (Chai, 1979). Different susceptibility to *M. yokogawai* infection was reported in several strains of mice, with the highest WRR of 18.9% from KK mice and the lowest WRR of 1.2% from CBH mice on day 7 PI (Chai *et al.*, 1984).

In the present study, the WRR of *N. seoulense* was much higher in BALB/c mice than in C3H mice from day 7 to day 28 PI. The WRR from BALB/c mice was about 60% even on day 28 PI. Therefore, BALB/c mice are regarded as a highly susceptible host, whereas C3H mice are not. One of the important reasons for this difference is the capacity of the host to expel worms. As candidates for effector mechanisms, mastocytosis and GC hyperplasia were observed in the small intestine of both strains of mice. However, the results suggested that both MMC and GC responses play a minor role in the expulsion of *N. seoulense*.

As for the MMC responses, their kinetics revealed no correlation with the worm expulsion, and the degree of proliferation had no relationship with the susceptibility of the two strains of mice. BALB/c mice showed a strong MMC reaction on day 7 PI but they could not expel worms until day 28 PI. The MMC reaction of BALB/c mice on day 7 PI was stronger than that of C3H mice in all of the three portions of the small intestine. Furthermore, it was stronger in the duodenum and jejunum, the preferred habitats of *N. seoulense* in mice (Hong *et al.*, 1983), than in the ileum. Therefore, proliferation of MMCs in these two strains of mice had better be regarded as a local host response rather than a responsible effector for worm expulsion. A similar result supporting this conclusion was observed. The WRR of *N. seoulense* from mast cell-deficient W/W^v mice was rather lower than their normal littermates +/+, suggesting that MMCs are not essential for expulsion of worms (Kook, 1997).

However, a contradicting result was also reported for *N. seoulense* infection using a rat model (Kho *et al.*, 1990). A peak level of mastocytosis was observed in the small intestine of Sprague-Dawley (SD) rats on day 21 PI when the WRR of *N. seoulense* began to decrease (Kho *et al.*, 1990). They suggested a significant relationship between the mastocytosis and worm expulsion. Similarly, in rats infected with *Trichinella spiralis*, the peak level of mastocytosis occurred just after the expulsion of worms (Woodbury *et al.*, 1984). Another similar pattern of mastocytosis was reported in rats infected with *S. ratti* (Mimori *et al.*, 1982). Therefore, the importance of MMCs in the expulsion of parasites seems to be different between mice and rats. However, other than the number of MMCs, the activity of rat mast cell protease II which is secreted during the expulsion process of worms was suggested to be very important (Woodbury *et al.*, 1984). In this regard, the importance of MMCs in the expulsion of *N. seoulense* from SD rats needs further investigation.

GC hyperplasia has drawn much attention as an important effector mechanism for the expulsion of nematodes, especially *N. brasiliensis* (Uber *et al.*, 1980; Koninkx *et al.*, 1988; Nawa *et al.*, 1994), which is induced by T-cell dependent mechanism (Ishikawa *et al.*, 1994). Important roles of GCs were also reported in the expulsion of a trematode, *E. trivolvis* (Fujino *et al.*, 1993). In the present study, GC hyperplasia was marked in the duodenum of BALB/c mice throughout the course of infection except day 14 PI but never observed in the duodenum of C3H mice. Only a low grade GC hyperplasia was observed in the jejunum and ileum of C3H mice on day 7 PI. Thus, the results were hardly correlated with the WRR of *N. seoulense* from BALB/c and C3H mice. Interestingly, GC depletion was observed in the duodenum and jejunum of C3H mice on day 14 PI. Whether GCs were used up during day 3 and day 14 PI is unclear. Further studies are required to elucidate the significance of GC depletion.

Other than an increase in number, functional status of GCs has also been paid attentions as an important factor for the expulsion of helminths. Functional activation of GCs, which could be expressed as alterations of terminal sugars of GC mucins and stained as HPA positive spots, was found around the time of expulsion of *N. brasiliensis* in rats (Ishikawa *et al.*, 1994). In the case of mice, there is a report describing that all

(100%) of the small intestinal GCs of normal C57BL/6 mice were strongly HPA positive before infection with *N. brasiliensis* (Ishikawa. 1994), suggesting little significance of HPA positive GCs in mice. In the present study, where BALB/c and C3H mice were used, however, only 5-27% of GCs were HPA positive before infection with *N. seoulense*, and after infection a significant increase of altered GCs was seen in all of the three portions of the small intestine in both strains of mice. This discrepancy, between C57BL/6 (Ishikawa, 1994) and BALB/c and C3H mice (this study), is difficult to explain and needs further clarification.

Anyhow, in the present study, the number of HPA positive cells and WRR of two strains of mice showed no significant correlations. Especially in the duodenum, the number of HPA positive cells was much more in BALB/c mice than in C3H mice during day 7-14 PI, contradicting the worm kinetics in the two strains of mice.

Conclusively, the MMC, GC responses, and alteration of GC mucins, observed in BALB/c and C3H mice, are considered local immune responses to *N. seoulense* infection rather than important effectors for expulsion of worms.

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=초록=

서울주걱흡충 감염 BALB/c 및 C3H 마우스에서 장점막 비만세포 및 배세포의 증식

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서울주걱흡충 (*Neodiplostomum seoulense*)에 감염된 BALB/c 및 C3H 마우스의 소장에서 비만세포 및 배세포 반응 양상을 관찰하고, 이들 반응이 숙주 방어기전 및 충체 배출에 영향을 줄 수 있는지 알아보았다. 마우스 1마리당 피낭유충 200개씩을 감염시킨 후 28일까지 충체회수율을 관찰한 바 BALB/c 마우스가 C3H 마우스에 비해 월등히 높은 충체회수율을 보였다. 그러나, 마우스 주에 관계없이 충체의 주 기생부위인 십이지장에서 감염 7일에 비만세포수가 최고에 달하였고 곧바로 감소하였다. 이러한 비만세포수의 반응 양상은 공장 및 회장에서도 비슷하게 나타났으며, 반응의 강도는 십이지장이나 공장이 회장에 비해 높았다. 또한, 비만세포수의 최고치는 BALB/c 마우스에서 C3H 마우스보다 오히려 높게 나타났다. 배세포 증식은 BALB/c 마우스의 경우 감염 14일을 제외하고는 십이지장에서 뚜렷이 관찰되었고, C3H 마우스의 경우에는 감염 7일에 공장 및 회장에서 관찰되었다. 배세포의 점액 (mucin) 활성은 BALB/c 및 C3H 마우스 모두에서 인정되었으나, 그 강도는 BALB/c 마우스에서 더욱 뚜렷하였다. 이상의 결과를 종합할 때, 이들 마우스의 장점막 비만세포 및 배세포 반응은 서울주걱흡충 감염에 대한 국소적인 면역반응으로 나타나지만 숙주 방어나 충체 배출에의 관여도는 낮을 것으로 추측되었다.

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