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Title	Pathogenesis of gastroenteropathy in <i>Taenia taeniaeformis</i> larval infections
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Citation	Japanese Journal of Veterinary Research, 50(1), 36-37
Issue Date	2002-05-31
Doc URL	https://hdl.handle.net/2115/2939
Type	departmental bulletin paper
File Information	KJ00002400423.pdf



PBMC, but the precursor IL-18 had little effect. Since IL-18 has been shown to play an important role in host defenses against pathogens, availability of porcine IL-18 cDNA and its recombinant protein may offer a new approach for investigating its role in the host defense mechanisms and pathogenesis of infectious diseases of pig.

Fifteen anti-porcine IL-18 mAbs were established and characterized. Biologically active recombinant porcine IL-18 was obtained easily from the supernatant of Tn 5 cells infected with recombinant baculovirus containing the coding sequences of porcine mature IL-18 by immunoaffinity chromatography using an anti-porcine IL-18 mAb. Furthermore, the anti-porcine IL-18 mAbs developed in this study were useful for the immunoblotting, sandwich ELISA, and immunohistochemical staining of porcine IL-18. They will become powerful tools for investigating the role of porcine IL-18 in various immune responses

and diseases of pig.

A cDNA encoding porcine ICE was successfully isolated and characterized for the first time. The kinetics of mRNA expression of ICE, IL-1 β , and IL-18 in porcine alveolar macrophages after LPS stimulation revealed that ICE transcripts were up-regulated after LPS stimulation. Moreover, IL-1 β and IL-18 mRNAs were differently expressed after LPS stimulation.

Recombinant baculovirus containing the cDNA encoding porcine ICE was constructed and successfully elicited ICE activity in insect cells. The porcine mature IL-18 was produced efficiently by co-expression of precursor IL-18 and ICE in insect cells. The large amounts of biologically active recombinant porcine mature IL-18 obtained by this method will allow us to investigate the physiological roles of IL-18 as well as its potential efficacy as a therapeutic agent or vaccine adjuvant in pigs.

Original five papers concerned with this thesis were published in *Journal of Interferon and Cytokine Research*, 19 : 1289-1296 (1999), 20 : 331-336 (2000), 21 : 125-130 (2001), *Cytokine*, 12 : 566-572 (2000), and *Journal of Immunological Methods*, 236 : 99-104 (2000).

Pathogenesis of gastroenteropathy in *Taenia taeniaeformis* larval infections

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The present study determined the epithelial cell kinetics and searched for animal models appropriate to study the pathological lesions observed during *T. taeniaeformis* larval infections. The first part was the investigations on cell proliferation and fate of epithelial cells in the gastric mucosa. Assays used for cell proliferation studies were proliferating cell nuclear antigen (PCNA) immunostain-

ing and time course bromodeoxyuridine (BrdU) labeling and immunohistochemistry.

Proliferative zone lengths and the number of BrdU labeled cells were markedly increased in gastric mucosa of infected rats. Prior or concomitant to the increase of cell proliferation was the loss of parietal cells. Massive cell proliferation associated with the loss of parietal and zymogenic cells caused ac-

cumulation of immature cells. Inhibition in maturation of zymogenic cells led to accumulation of intermediate mucous cells. Cellular kinetics was also investigated in three regions of the small intestine. An increase of proliferative zone length in infected rats was evident. BrdU labeling revealed significant increase in mean number of labeled cells. Enteropathy was also found in the colonic mucosa.

The second part studied different animal models to search for suitable host to investigate the role of larvae-derived products. *T. taeniaeformis* (mouse strain) susceptible AKR mice was investigated whether gastroenteropathy could be induced. Heavily infected immunocompetent mice developed gastroenteropathy from 6-12 months post inoculation. SCID mice inoculated with different doses and routes of *T. taeniaeformis in vitro*-hatched oncospheres and those orally inoculated with eggs resulted in different degrees of gastric hyperplasia. Surgical implantation

of larvae into the peritoneal cavity of SCID mice resulted in moderate gastric hyperplasia both in corpus and antral mucosa. SCID mice proved as an experimental animal model to study larval ES products. *In vitro* cultured *T. taeniaeformis* larval excretory-secretory (TtLES) products containing 1 mg of protein injected daily into SCID mice resulted in mild gastropathy. SCID mice injected daily with 0.5 mg of TtLES products also showed slight gastric hyperplasia. The study proved that ES products of larvae facilitated a remote pathologic effect to gastric mucosa, and that gastropathy in SCID mice could be induced by larval *in vitro* products alone.

Understanding the pathogenesis of gastroenteropathy during *T. taeniaeformis* larval infection will lead to new insights about host-parasite relationship. Moreover, this will be a good model to study the pathogenesis of similar gastroenteropathies with unknown etiology.

Original papers of this thesis appeared in *Parasitol. Int.*, 51 : 81-89 (2002) and *Jpn. J. Vet. Res.*, 49 : 273-285 (2002).

Functional studies and genetic analysis of macrophage nitric oxide production in mice

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Nitric oxide (NO) correlates with the cytotoxic effect of macrophages on neoplastic cells and in the killing of intracellular parasites (Lissner *et al.*, 1985 ; MacMicking *et al.*, 1997a). NO produced by macrophages, in response to IFN- γ or TNF- α , is known to be a potent antimicrobial agent (Nathan, 1995). This study in mice aimed to establish the roles of the *Nramp 1* and *Tnfa* genes in NO production upon cytokine activation as well as

in infection with *S. typhimurium*. Furthermore, the genetic factors associated with NO production were analyzed by using macrophages from several different *Nramp 1'* mouse strains that were theoretically expected to have relatively high NO production after cytokine stimulation.

In the first part of the study, it was confirmed that the level of iNOS-mediated NO production in *Nramp 1'* congenic peritoneal