



Title	Studies on porcine interleukin-18 and interleukin-1 converting enzyme
Author(s)	MUNETTA, Yoshihiro
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tato plants was biologically active. TNF- $\alpha$  should be a homotrimeric form to exert its functions. Successful expression of biologically active TNF- $\alpha$  in the potato plant cells indicates that recombinant products, which should be multimeric to exert their functions, can be expressed in this expression system. Furthermore, expression of HuTNF- $\alpha$  at the high levels (15 $\mu$ g/g plant tissue) revealed that cytokines could be expressed using plant expression systems at higher level (more than  $\mu$ g per g plant tissue).

Type I IFN (IFN- $\alpha/\beta$ ) possesses not only 'classical' anti-viral and tumoricidal effects, but also play a key role in the regulation of the systemic immune response. Therefore, it was examined whether orally administered HuIFN- $\alpha$  can augment natural immune response against systemic bacterial infection using *L. monocytogenes* infection model in mice. Daily (6 days) oral administration of HuIFN- $\alpha$  reduced bacterial burden in spleen and liver from *L. monocytogenes* infected mice. This protective effect was observed in the

middle phase of *L. monocytogenes* infection, but not in the early phase of the infection, it was considered that orally administered HuIFN- $\alpha$  should contribute to rapid elimination of *L. monocytogenes* from infected organs.

Finally, the potential of orally administered HuIFN- $\alpha$  expressing potato plant to enhance natural immune response was examined using *L. monocytogenes* infection model. Oral administration of extracts of the HuIFN- $\alpha$  expressing potato plant decreased *L. monocytogenes* burden in the spleen, compared with mice which were treated with control plant extracts. Even low concentration of HuIFN- $\alpha$  in the extracts (20IU/mouse/day) exerted the protective effect, compared with that achieved with PBS-diluted HuIFN- $\alpha$  when administered to mice. That may be due to 'bioencapsulation' of HuIFN- $\alpha$  by plant components.

In conclusion, this study revealed that transgenic plants expressing cytokines can be used as feed and/or feed additives in order to enhance natural immune response.

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The original papers of this thesis appeared in *J. Interferon Cytokine Res.*, 21 : 596-602 (2001) and *J. Interferon Cytokine Res.*, 22 : 371-378 (2002).

## Studies on porcine interleukin-18 and interleukin-1 $\beta$ converting enzyme.

Yoshihiro Muneta

*Immune System Section, Department of Immunology,  
National Institute of Animal Health, Tsukuba, Ibaraki, 305-0856, Japan*

In the present study, porcine interleukin-18 (IL-18) and IL-1 $\beta$  converting enzyme (ICE) were cloned and characterized, and the expression of their recombinant proteins using baculovirus expression systems was stated. The production and utilization of monoclonal antibodies to porcine IL-18 were also

described. The conclusions obtained by this study are summarized as follows.

A cDNA encoding porcine IL-18 was cloned and its recombinant protein was expressed as both precursor and mature forms by baculovirus systems. The porcine mature IL-18 induced IFN- $\gamma$  production from porcine

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 $\beta$ , and IL-18 in porcine alveolar macrophages after LPS stimulation revealed that ICE transcripts were up-regulated after LPS stimulation. Moreover, IL-1 $\beta$  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.

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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

Jose Trinipil G. Lagapa

Laboratory of Parasitology, Department of Disease Control,  
Graduate School of Veterinary Medicine, Hokkaido University, Sapporo 060-0818, Japan

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-