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.

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

Gene Peñaflor Ables

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

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*^{r} 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*^{r} congenic peritoneal

macrophages was generally higher than that of *Nramp 1*^{s} congenic macrophages after stimulation by IFN-γ, LPS or TNF-α alone or in combination. *Nramp 1* mRNA expression in both *Nramp 1* congenic macrophages was constitutive notwithstanding cytokine stimulation. During infection with *S. typhimurium* strain 6203, *Nramp 1*^{r} macrophages produced a lower amount of NO due to an initial strong reaction and unsustained iNOS gene expression as compared with *Nramp 1*^{s} macrophages. An inhibitory effect of the *Nramp 1*^{r} gene on bacterial replication was also observed during the early stage of *S. typhimurium* infection, while the effect of TNF-α occurred later. NO production and iNOS expression in TNF-α$^{-/-}$macrophages were not detected from the start of the bacterial infection or at 24 h post-infection. It was also observed that S. typhimurium strain 6203 grew more vigorously without TNF-α, especially in *Nramp 1*^{s} macrophages. These data therefore demonstrate that there is cooperation of the *Nramp 1* and *Tnfa* genes in NO production and an inhibitory effect in response to *S. typhimurium* infection.

In the second part of the study, after IFN-γ and LPS stimulation, the strains NZB/N, DBA/2N, AKR/N and A/J showed significantly lower NO production, NJL, 129/J, MOG, SJL/J, CBA/N and NOD/Shi had moderate amounts, and C3H/He and SPR had higher levels as compared to the other mice. The F1 progeny of A/J×C3H/He and AKR/N×C3H/He showed significantly higher NO production, whereas the F1 progeny of DBA/2N×C3H/He produced a relatively low amount. Furthermore, the backcross progeny from F1 showed variations in NO production, and it was therefore speculated that the regulation of NO production is polygenic. Genetic typing experiments related to NO production in the backcross progeny demonstrated significant deviations to some genetic microsatellite markers. Sequencing of the iNOS promoter regions of the *Nramp 1*^{r} strains to examine the relationship with NO production revealed that MOG and SPR strains had substitutions within the NF-κB and the γ-IRE, respectively.

These experiments therefore suggest that there are several factors involved in NO production and its function against infection. The use of more comprehensive experiments is suggested to further elucidate the main factors responsible for NO production and its activity against other infectious organisms.

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Differential effect of the combination of *Kit*^{W} or *Kit*$^{W\text{-}v}$ mutant Allele and the *Kit*^{S} allele derived from *Mus spretus* on male hybrid sterility

Samir Ahmed Mohamed El-Shazly

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

Sterility in interspecific hybrids usually affects the heterogametic sex. This is known