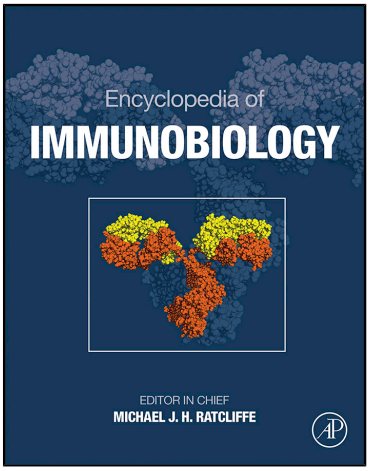

From Ito, A., 2016. Immunology in Cestode Infections. In: Ratcliffe, M.J.H. (Editor in Chief), Encyclopedia of Immunobiology, Vol. 4, pp. 159–165. Oxford: Academic Press.

Immunology in Cestode Infections

Akira Ito, Asahikawa Medical University, Asahikawa, Hokkaido, Japan

Glossary

Eucestode Eucestodes, which can infect humans, are divided into two orders, Cyclophyllidea and Pseudophyllidea. Most pathogenic cestodes are in the order Cyclophyllidea, including *Echinococcus* spp., *Taenia solium*, and *Hymenolepis nana*.

Helminths Helminths utilizing humans as intermediate host, paratenic host (where developmental progression does not occur), or definitive host are represented by the roundworms (phylum Nematoda), flukes (Digenea), and tapeworms (Eucestoda). The latter two belong to the phylum Platyhelminthes. All Platyhelminthes are hermaphroditic, except for blood flukes (Schistosomes), which are dioecious.

Life cycle Cestode parasite requires two or more host species to complete their life cycle. This includes one or two species as the intermediate host and one as the definitive host. The life cycle is maintained by the predator–prey interactions.

Metacestode A larval stage of cestodes established in parenteral tissues of the intermediate host, which is generally highly pathogenic.

Oncosphere Embryo in egg shell of cyclophyllidean cestode which is highly immunogenic in the mammalian intermediate host. Eggs of cyclophyllidean cestodes, produced in the adult tapeworm's gravid proglottids, are the infective stage and ready to infect when they are inoculated into suitable susceptible intermediate host animals.

Tapeworm Adult stage of cestodes established in the intestinal lumen of the definitive host and generally benign in terms of pathology. However, eggs produced in tapeworms can directly cause autoinfection in the same host individuals, causing massive or disseminated metacestodiases. Such autoinfection is well known in *Taenia solium* and *Hymenolepis nana*.

Vaccine Intermediate mammalian host animals become completely immune to reinfection with eggs within a few days of the primary infection with eggs. Therefore, vaccines against the establishment of metacestodes are most promising and effective across all parasitic infections. The target stage is the oncosphere.

Abstract

There is a dynamic balance between host-protective and parasite-protective defense mechanisms from the beginning of infection until the parasite is killed or expelled, or the host dies. In cestode infections of mammals, including humans, and especially when they acquire infection with eggs as the intermediate host, they become immune to reinfection with eggs. Simultaneously, these eggs are highly pathogenic and cause zoonotic metacestodiases including cysticercosis and echinococcosis. In contrast, when mammals, including humans, become the definitive hosts, the extent of immunity to adult tapeworms in the intestine is not always clear, and the pathogenicity of adult tapeworms is generally low. Zoonotic cestode infections are maintained by predator–prey interactions. Among these zoonotic cestodes, there are two exceptional species, which can complete their whole life cycles within a single mammalian host (*Hymenolepis nana* and *Taenia solium*). Among-other zoonotic cestodes, *Echinococcus* spp. are notable, since their definitive hosts are exclusively carnivores. However, such carnivorous definitive hosts may become accidental intermediate hosts in some circumstances. Immunity to cestode infections is differentiated as parenteral tissue immunity in the intermediate host and enteral immunity in the definitive host.

Introduction

Eucestodes (Cestoda) and trematodes (Digenea) are major fauna of parasitic platyhelminths. Eucestodes are unique parasites which complete the whole life cycle in two or more host animals by predator–prey interactions. Predators, either carnivores or omnivores, are the definitive hosts which are parasitized with adult tapeworms after ingestion of uncooked or undercooked meat contaminated with larval stage of cestodes in prey animals of omnivores or herbivores. However, omnivores or even carnivores which usually function as the definitive host may accidentally become the intermediate host. Table 1 briefly summarizes the main cestodes which can infect humans. Both *Hymenolepis nana* and *Taenia solium* are two exceptional species which can normally complete their whole life cycle in one mammalian host. Carnivores, which are normally the definitive hosts, accidentally become unusual intermediate hosts of *Echinococcus* spp. (Ito, 2015a,b). Details of cestode life cycles can be found on the Centers for Disease Control and Prevention website (see Relevant Website).

Eggs with oncospheral embryos inside, infective for the intermediate host (Cyclophyllidea) or not (Pseudophyllidea),

Table 1 Major cyclophyllidean cestodes which require mammalian hosts for the completion of the life cycle and known to be zoonotic

Family and species	*Intermediate host*	*Definitive host*
Taeniidae		
Taenia solium[a]	Human, pig, dog	Human
Taenia saginata	Cattle, reindeer	Human
Taenia asiatica	Pig, cattle	Human
Taenia crassiceps	Rodent, (human)	Dog, fox
Taenia ovis	Sheep, (human)	Dog
Taenia hydatigena	Pig, sheep, goat, (human)	Dog
Taenia pisiformis	Rabbit, (human)	Dog, fox
Taenia taeniaeformis	Rodent, (human)	cat
Taenia coenurus	Sheep, rabbit, (human)	Dog, cat, wolf
Taenia serialis	Rabbit, rodent, (human)	Dog, fox, wolf
Taenia martis	Rodent, (human)	Dog, fox
Echinococcus granulosus s.s.	Sheep, goat, human, (cat)	Dog
Echinococcus canadensis	Pig, camel, moose, human	Dog, wolves
Echinococcus multilocularis	Rodent, human, primate, (fox, dog)	Fox, dog, wolf
Echinococcus vogeli	Paka, human	Bush dog
Echinococcus oligarthra	Agoutis, human	Wild felids
Hymenolepididae		
Hymenolepis nana[a]	Rodents, humans	Rodents, humans
All other species	Beetles	Rodents, humans

Eggs of *Echinococcus* spp. may rarely infect the definitive host animals (Ito, 2015a).
[a] Whole life cycle may be completed in a single host from eggs to metacestodes and from metacestodes to adult worms (*H. nana*) or from metacestodes to adult worms and from eggs to metacestodes (*T. solium*). However, in the latter, metacestodes developed in human body have no chance to contribute for further development without cannibalism (Ito, 2015a). In these species, autoinfection occurs (Ito, 2015a,b).
Modified from Nakao, M., Lavikainen, A., Yanagida, T., Ito, A., 2013. Phylogenetic systematics of the genus *Echinococcus* (Cestoda: Taeniidae). Int. J. Parasitol. 43, 1017–1029; Ito, A., Yanagida, T., Nakao, M. Recent advances and perspectives in molecular epidemiology of *Taenia solium* cysticercosis. Infect. Genet. Evol. http://dx.doi.org/10.1016/j.meegid.2015.06.022, in press; additional data from Ntoukas et al., 2013. Cerebellar cysticercosis by larval *Taenia crassiceps* tapeworm in immunodeficient woman. Emerg. Infect. Dis. 19, 2008–2011; and Brunet, J., Benoilid, A., Kremer, S., et al., 2015. First case of human cerebral *Taenia martis* cysticercosis. J. Clin. Microbiol. 53, 2756–2759.

or proglottids full of eggs represent an exceptional developmental stage of cestodes which can remain outside of the host after shedding by defecation. All other stages are established in the host body to develop and differentiate to the next developmental stage. Oncospheral embryos hatch in the small intestine of suitable herbivores or omnivores or sometimes carnivores, and invade the intestinal tissue and migrate into parenteral tissues including brain, liver, lungs, bone, etc., and develop into larval stage (=metacestodes). These stages are highly pathogenic and often fatal to the host (Arme et al., 1983). Almost all metacestodes except *H. nana* survive for long periods in parenteral tissues of the intermediate host until they are ingested by the definitive host. When definitive hosts ingest the intermediate hosts contaminated with metacestodes, these metacestodes develop into mature tapeworms in the small intestine and release eggs. The longevity of adult tapeworms is highly variable among the cestode species.

Key questions in cestode biology that might be understood from both immunological and developmental biology viewpoints (Ito, 2015a) include:

1. What determines host specificity?
2. What are the mechanisms of tissue or organ tropism?
3. What mechanisms allow long-term survival of metacestodes in the intermediate host?
4. What mechanisms determine the life span and fecundity of adult tapeworms?
5. What mechanisms allow for intermediate host shifting from invertebrates to vertebrates in *H. nana* infection?

Primary Infection in an Intermediate Host

Host specificity is usually fixed with either a wide or narrow host range. For example, the intermediate hosts of *Taenia saginata* are cattle and reindeer, whereas those of *T. solium* are pigs, dogs, and humans. What determines the innate resistance to oncospheral hatching in the intestinal lumen of different animal species, with complete failure of invasion of intestinal tissue in resistant host species, is currently unknown. However, it is well known that a susceptible host becomes completely resistant or immune to reinfection with eggs within a few days of oral egg inoculation and that this reinfection immunity lasts until the host dies. No other parasite induces such a crucial and critical resistance to reinfection with eggs, and this fact underpins why highly efficient vaccines have been developed against zoonotic cestode infections (Mitchell et al., 1977; Rickard and Williams, 1982; Williams, 1983; Rickard, 1983; Johnson et al., 1989; Lightowlers et al., 2003; Gauci and Lightowlers, 2003). Indeed, there are no other parasites for which such complete resistance to reinfection can be demonstrated by vaccination.

The Mechanism Involved in Resistance to Reinfection with Eggs

Passive transfer of serum from resistant host animals is well documented, providing the basis for antibody-based vaccines targeting the oncosphere. Historically, booster immunizations were required to generate high antibody titers following immunization and given the role of T cells in generating secondary antibody responses, some effort has been made on identifying the nature of those T cells that contribute to antibody formation.

The mechanism assessed after several weeks of primary infection but challenged with secondary inoculation with eggs was identified early on as being thymus-dependent acquired immunity (Okamoto, 1968; Okamoto and Koizumi, 1972; Mitchell et al., 1977; Asano and Okamoto, 1991). Therefore, congenitally athymic nude mice or rats are susceptible to secondary infection or reinfections with eggs in *H. nana*/mouse or rat system and *Taenia taeniaeformis*/mouse or rat system (Mitchell et al., 1980; Ito, 1997, 2015a).

In these cestode infections, the importance of T-helper 1/T-helper 2 (Th1/Th2)-cell balance and IFNγ has been reported (Asano and Muramatsu, 1997; Ma et al., 2014). Newer studies have involved the traditional complement of gene-deficient and mutant mice to study this response in more detail, including NOG and NOD/shi-*scid*, and TLR2 knockout (KO) mice.

All studies on reinfection immunity have demonstrated this to be thymus dependent, as assessed after >2 weeks of the primary infection (Mitchell et al., 1977; Ito, 1977), yet complete resistance to reinfection with eggs is induced within a few days of the primary egg inoculation. Even a single oncospheral invasion is sufficient to induce this rapid resistance (Ito and Yamamoto, 1976). The underlying mechanism of this rapid resistance has not yet been identified, since the very early stage of the onset of the resistance to reinfection cannot be explained by antibody responses. Therefore, it remains as an unsolved challenge to understand the rapid onset of resistance. Furthermore, the assay system for evaluation of reinfection immunity is not well suited for assessing early resistance mechanisms and there might be some discrepancy between the real mechanisms of protection and those so far described (Ito, 2015a). What is the real mechanism of the rapid resistance evoked within a few days? It is most likely that the effector mechanism reflects an innate resistance to reinfection but not to a primary infection, implying some degree of remodeling of the innate response during primary infection. Nevertheless, it is clear that there is a late-acting component, as assessed by thymus-dependent and antibody-dependent assays.

What Mechanism(s) Regulate Long-Term Survival of Metacestodes in the Intermediate Host?

Metacestodes may be found selectively in brain, liver, muscle, abdominal cavity, or in multiple sites. For example, *Taenia pisiformis* and *Taenia hydatigena* develop in the liver but escape from the liver into the abdominal cavity to grow up to mature metacestodes, whereas *T. solium* and *Echinococcus* spp. may develop in the brain. There are several different types of parasite strategy for metacestode survival in the intermediate host. (1) Metacestodes can develop into adult tapeworms in the same individual's intestine as shown for *H. nana* in the mouse or human system with no additional step of survival in the mammalian intermediate host tissue (Ito, 2015a). This is rather rare or exceptional. (2) Metacestodes can survive for a long time to be ingested by the definitive predator host, as typical in *Echinococcus* spp. infections and some other species, which may cause metacestodiases such as cysticercosis caused by *T. solium* and sparganosis by *Spirometra erinacei*. Among these parasites, *Echinococcus multilocularis* is unique, since the metacestode causes chronic progressive hepatic damage through continuous proliferation of metacestode. Other unique parasites are *Taenia* species which result in long survival of the cysticercus and coenurus in mammalian intermediate hosts. The cysticercus of *T. solium* is unique among them, since it causes neurocysticercosis (NCC), a potentially lethal disease characterized by the late onset of seizures.

Taenia solium is unique, since it can infect humans via eggs released from the human tapeworm carrier or via metacestodes derived from pigs. Metacestodes of this parasite can survive longer than 10–30 years in the human brain with no symptoms (Yanagida et al., 2010). Cysticerci of *T. solium* cause cysticercosis including the most potentially lethal NCC. There is some unique mechanism to keep the host-parasite balance during the asymptomatic stage, where minimal inflammatory response occurs. This represents a crucial difference from almost all other helminthic infections, where eosinophilia dominates. When host-protective mechanisms become stronger than the regulatory ones that favor parasite survival, sudden edema is triggered and inflammatory responses with eosinophilia become clear. The metacestodes of this parasite excrete and secrete antigen B (AgB) family proteins, potent anti-inflammatory substances (Laclette et al., 1989). A similar parasite-protective mechanism has been analyzed in *Taenia crassiceps* infections in mice (Spolski et al., 2000; Reyes et al., 2011). AgBs are common components in metacestodes of *Taenia* and *Echinococcus* and facilitate the parasite's differentiation and long-term survival.

The cysticercus of *T. solium* is vesicular and less than 1 cm in diameter in immunocompetent hosts. Avesicular, racemose, or giant cysts, crucially different types of cysticercus, may, however, develop in immunodeficient patients. Thus far, there is no animal model for avesicular cysticercus in experimental animals. As avesicular, racemose, or giant cysticerci are exclusively found in patients with immunodeficiency, this implies that some immune mechanism contributes to maintaining vesicular cysticerci in immunocompetent hosts, but such mechanism(s) have not been determined.

Taenia crassiceps is unique in another way, since metacestodes of this parasite can be reproduced by budding of the mother metacestode. The mechanism of budding is unknown (Ntoukas et al., 2013). Other taeniid parasites (Brunet et al., 2015) are also highly variable in aspects of their developmental biology, including coenurus and echinococcus.

The most important echinococcoses are caused by *Echinococcus granulosus* sensu lato, mainly *E. granulosus* sensu stricto (G1) and *Echinococcus canadensis* (G6/7) which cause cystic echinococcosis (CE) and by *E. multilocularis* which causes alveolar echinococcosis (AE). *Echinococcus granulosus* s.s. and *E. multilocularis* are relatively well analyzed, since these diseases are chronic and AE, like hepatic cancer, can result in death of the host including humans (Gottstein et al., 1994). Kizaki et al. (1993a,b) reported $CD8^+$ T cell–mediated immunosuppression by protoscoleces of *E. multilocularis*, but further work is required to define the source of target antigens, given that the majority of AE lesions are not fertile, but sterile without protoscoleces (Ito et al., 2001). *Echinococcus* cysts, mainly *E. multilocularis*, are well known to be fertile in highly susceptible hosts but sterile in less susceptible hosts. This appears to be a genetically controlled mechanism in humans and in rodents with experimental secondary echinococcosis (Gottstein et al., 1994; Nakaya et al., 1997). T cell–mediated immune responses provide a crucial control of proliferation of this parasite, but the parasite counters with modulation of the T cell immune response for its longer survival (Vuitton et al., 2006; Graichen et al., 2007; Nono et al., 2014).

Susceptibility versus Resistance to Oncospheral Invasion into the Intestinal Tissue and Differentiation into Metacestodes in Parenteral Tissue* (*Exception: *Hymenolepis nana*)

What is the factor to control the host specificity for oncospheral invasion into the mammalian intermediate host? **Table 1** clearly indicates that the host species are rather rigid for each cestode species. However, this host specificity is maintained only when eggs are orally inoculated into different host species. Experimental inoculation of hatched oncospheres into the abdominal cavity, subcutaneous tissue, or other tissue can

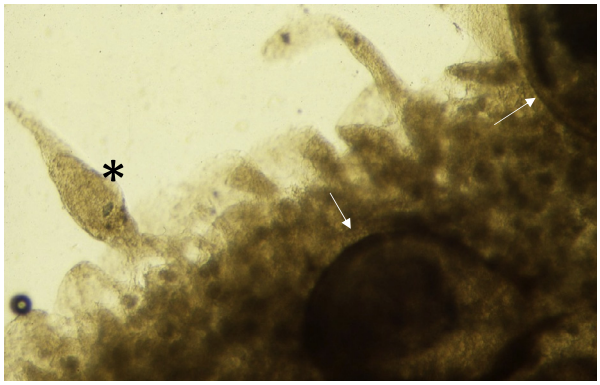

Figure 1 Abnormal balloon-like cysticercoids of *Hymenolepis nana* in a nude mouse 14 days after a primary egg inoculation and a normal cysticercoid (*) of 4 days after challenge inoculation. Cysticercoid developed in immunocompetent mice within 4 days of egg inoculation differentiate into mature adult tapeworm within 12 days. However, as shown in this figure, some of such cysticercoids remain in the intestinal tissue. This may be pathogenic in immunodeficient hosts including humans (Olson et al., 2003).

establish metacestodes in resistant host species (Ito et al., 1997; Nakaya et al., 2006).

Although all cysticercoids of *H. nana* developed in the intestinal tissue (within 4 days of egg inoculation), some escape into the lumen where maturation occurs within 12 days of egg inoculation. However, some cysticercoids in nude mice cannot escape into the lumen and remain in the intestinal tissue to become balloonlike giant cysticercoids (**Figure 1**; Ito and Kamiyama, 1984), even though the majority develop into mature tapeworms in the same host. Such abnormal cysticercoids have also been reported in immunodeficient patients (Olson et al., 2003). These studies may suggest some level of immune control over the process of luminal invasion.

Vaccines against the Establishment of Metacestodes in the Intermediate Host Species

As the intermediate host becomes immune to reinfection with eggs of these cestodes, vaccine development against zoonotic cestode species has been the most promising and feasible of all parasitic vaccine development programs (Gauci et al., 2006). Antifecundity vaccines are alternative vaccine candidates in other parasite infections (Bergquist et al., 2005; Diemert et al., 2008; Schneider et al., 2011). In contrast, vaccines against larval cestode infections are expected to induce almost 100% protection (Johnson et al., 1989; Lightowlers, 2003; Jayashi et al., 2012; Gauci et al., 2013), and highly efficient vaccines against cysticercosis and echinococcosis have been developed. Two doses appear to be necessary, but a single dose may be sufficient.

Primary Infection in a Definitive Host

Susceptibility versus Resistance to Establishment and Differentiation of Juveniles into Adult Worms in the Intestinal Lumen

As the majority of cestodes which mature in the mammalian definitive host require omnivorous and carnivorous species, it is difficult to analyze the mechanism. Therefore, most studies have been carried out using *Hymenolepis* species which usually matures in rodents and humans after ingestion of metacestodes (=cysticercoids) developed in arthropods (mainly small flour beetles such as *Tribolium* spp.). In experimental infection in rodents, cysticercoids isolated from beetles are orally inoculated. Three species have been relatively well studied: *Hymenolepis diminuta*, *H. nana*, and *Hymenolepis microstoma*. However, these three species have their own unique strategies for survival in permissive (mouse) and nonpermissive (rat) hosts (Ito, 2015a). Among these three hymenolepidid species, *H. diminuta* is ideal for studying immunity to adult tapeworms in the small intestine without any other influence from eggs, which may occur by autoinfection in the *H. nana*/mouse system (Ito and Smyth, 1987; Ito, 2015a). *Taenia* spp. and *Echinococcus* spp. have also been studied in laboratory animal models.

Hymenolepis diminuta survives for longer than 1 year in the rat host but cannot mature in the nonpermissive mouse. There are many reports on the mechanism of resistance in the mouse (McKay and Khan, 2003; Persaud et al., 2007; Reyes et al., 2015), and long-term survival has been attributed to parasite-produced immunosuppressive factor(s) (Johnston et al., 2010). Infection with helminths evokes in general a Th2-cell response in mammalian hosts. Interleukin (IL)-4 and IL-13 are known to be important in the rapid expulsion of parasitic nematodes (Artis, 2006). In the *H. diminuta* model, only STAT-6 KO mice harbored adult worms. Neither gravid adult nor stunted *H. diminuta* were found in infected IL-4 KO or IL-13 KO mice, 12 days or longer postinoculation with cysticercoids (Mckey and Khan, 2003; Persaud et al., 2007; Johnston et al., 2010; Reyes et al., 2015). McKey and colleagues proposed that increased mucin production is an important part of the host response to tapeworm infection and that functional STAT-6 signaling may be an absolute requirement for the rejection or expulsion of intestinal cestodes and thus, helminth parasites in general. There are no reports, however, on mechanisms that regulate how juveniles escape from the cysticercoid wall, and their development into mature worms in permissive but not in nonpermissive host species.

Hymenolepis nana survives for shorter periods compared with other species, just 2 weeks in some strains of mice. The size of the adult worms becomes smaller over this time course and stunted worms disappear within 1 month. In contrast, in other strains of mice *H. nana* can survive up to 6 months. IgE production and mast cell development have been reported to be involved in worm expulsion and/or stunted development (Watanabe et al., 1994). This parasite is exceptional among almost all other cestodes, since it can complete its whole life cycle within a single mammalian host, either mice or humans (Ito and Smyth, 1987; Ito, 1997, 2015a). This parasite-mouse system may be the only model in which (1) immunity to reinfection with eggs in the intermediate host and that to reinfection with cysticercoids in the definitive host and (2) direct comparative studies on the tissue phase in the intermediate host and the lumen phase in the definitive host can be analyzed without considering any influence from different host species (Ito and Smyth, 1987; Conchedda et al., 1997; Ito, 2015a). The establishment of adult tapeworms in nonpermissive host

species may be modified by corticosteroid injection throughout the expected growing period either in immunocompetent or congenitally athymic nude rats (Ito and Kamiyama, 1984; Ito, 1997, 2015a). The mechanism of resistance to the establishment of adult worms in the intestinal lumen is, however, unknown.

Hymenolepis microstoma can survive for longer than 1 year in the mouse host. It parasitizes the bile duct but not the small intestine. The different mast cell populations in the bile duct (tissue mast cells) and in the small intestine (mucosal mast cells) may affect survival. When adult tapeworms were established in the bile duct, whole worms are located inside the bile duct. However, after 6 months of infection, posterior worm bodies come out of the bile duct and hang down into the small intestine, again suggestive of an intricate link between immunity and parasite development.

Experimental Models of *Taenia* spp. and *Echinococcus* spp. Infection

Taenia spp. and *Echinococcus* spp. can survive in rodents but only during corticosteroid treatment, even in immunodeficient animals. Therefore, the effect of steroid may not only be due to immunosuppression but might be on growth hormones that affect parasite development (Ito and Kamiyama, 1984; Ito, 2015a). Recent studies on the development of adult tapeworms of *T. solium* in hamsters as a laboratory animal model of human infection have shown an intense IFNγ response, as well as upregulation of IL-4 as early as 3 days postinfection, persistance of IL-10 until the end of the experiment, and downregulation of IL-12 (Cruz-Rivera et al., 2014). Intense IFNγ responses, as well as upregulation of IL-4 as early as 3 days postinfection may be suggestive of a mechanism for the rapid onset of reinfection immunity to eggs discussed above.

Immunity to Reinfection in the Definitive Host

Reinfection immunity to adult cestodes has been studied using laboratory animal models including *Hymenolepis* spp. It is clear that model animals become resistant to reinfection as shown in *H. diminuta*/mouse (Hopkins, 1980) and *H. nana*/mouse models (Ito and Smyth, 1987). Similarly, it is clear that in mice inoculated with cysticercoids, which develop immature adult worms but which are expelled naturally from mice (*H. diminuta*) or following chemotherapy (*H. nana*), there is resistance to reinfection with cysticercoids. The mechanism(s) preventing juveniles from establishing and maturating in the intestinal lumen remain undefined.

Vaccine against the Establishment of Adult Tapeworms in the Definitive Host

There are several reports on vaccines against *Echinococcus* spp. in dogs, but reproducibility has proved an issue, with control dogs often showing similar pseudoeffects (Zhang and McManus, 2008; Ito, 2015a). New approaches for vaccine screening are therefore necessary to support future vaccine development (Kouguchi et al., 2013).

The Unique Direct Life Cycle in *Hymenolepis nana*/Mouse (or Human) and *Taenia solium*/Human

These two species are exceptional in that they can complete their whole life cycle in a single host. In *H. nana* infection, it is common to complete the whole life cycle from egg to metacestode (cysticercoid) in the intestinal tissue, and from metacestode to adult tapeworm in the intestinal lumen of the same host individual. Eggs produced by adult worms cannot infect to the same individual unless it is immunodeficient. Therefore, only one generation is established in mice or humans from a direct cycle of egg inoculation. In contrast, when mice or humans were inoculated with cysticercoids, they grow into mature tapeworms and eggs released from adult worms can infect the same individuals (autoinfection) and two adult generations may be established in the intestinal lumen (Ito and Smyth, 1987; Ito, 2015a). In contrast, in *T. solium* infection in humans, the whole life cycle may be completed from ingestion of metacestodes. Cysticerci develop to mature tapeworms that release eggs, which can infect to the same individual. Massive metacestodes may develop in parenteral tissue and organs and cause cysticercosis (Ito, 2015b).

Conclusions

Each cestode species has a unique biology in the intermediate and definitive mammalian hosts, and even a single mammalian host may serve as both intermediate and definitive host (*H. nana*, *T. solium*). For example, *E. multilocularis* has a unique larval development with continuous proliferation of metacestodes mainly in the liver. Cysticerci of *T. solium* can survive more than 10 years without any damage or any inflammatory responses. In contrast, cysticercoids of *H. nana* have no such stage, and a juvenile developed in the cysticercoid escapes into the intestinal lumen of the same individual immediately and continues to mature to produce eggs in immunocompetent host. A very small portion of cysticercoids remain in the small intestine or other tissue and become balloonlike giant cysticercoids in immunodeficient host, although almost all juveniles escape into the intestinal lumen and mature as in the immunocompetent host.

In the susceptible definitive host, how long-term tapeworms survive in the intestine is highly variable among the species. Adult tapeworms mature and become senescent or can be suddenly expelled (Ito and Budke, 2014).

In the resistant host, metacestodes cannot grow into adult tapeworms, except following immunosuppressive treatment (Ito and Kamiyama, 1984; Maravilla et al., 1998, 2011). However, this is not simply attributed to immunosuppression but might be due to growth hormone regulation (Ito, 2015a) which is affected by the IFNγ response (Cruz-Rivera et al., 2014).

Due to the difficulty in maintaining highly pathogenic cestodes in the laboratory, immune mechanisms in cestode infections still remain poorly understood. Immunological research on cestode infections needs to be based on a critical understanding of each parasite's unique life cycle (Bergquist et al., 2005).

Acknowledgments

The studies on cestode infections carried out by Ito and colleagues were supported by Grants-in-Aid for international collaboration research funds from the Japan Society for the Promotion of Science (JSPS) (April 1994–March 2015), by JSPS-Asia/Africa Scientific Platform Fund (April 2006–March 2012), the Special Coordination Fund for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT) (April 2003–March 2006, April 2011–March 2014), and the MEXT-Translational Research Fund (April 2007–March 2012).

See also: **Cells of the Innate Immune System:** Eosinophils; Mast Cells in Allergy, Host Defense, and Immune Regulation. **Cytokines and Their Receptors:** IL-10; The Cellular and Molecular Network of IL-4 and IL-13; The IL-12/IL-23 Cytokine Family. **Development of T Cells and Innate Lymphoid Cells:** Orchestration of T Cell Development by Common γ Chain Cytokines. **Immunity to Bacterial, Parasitic and Fungal Infections:** Immunology of Schistosomiasis. **MHC Structure and Function:** Genetic Associations of the Major Histocompatibility Complex (MHC) with Infectious Disease. **Molecular Aspects of Innate Immunity:** The Mucins.

References

Arme, C., Bridges, J.F., Hoole, D., 1983. Pathology of cestode infections in the vertebrate host. In: Arme, C., Pappas, P.W. (Eds.), Biology of the Eucestoda, vol. 2. Academic Press, London, pp. 499–538.

Artis, D., 2006. New weapons in the war on worms: identification of putative mechanisms of immune-mediated expulsion of gastrointestinal nematodes. Int. J. Parasitol. 36, 723–733.

Asano, K., Muramatsu, K., 1997. Importance of interferon-gamma in protective immunity against *Hymenolepis nana* cysticercoids derived from challenge infection with eggs in BALB/c mice. Int. J. Parasitol. 27, 1437–1443.

Asano, K., Okamoto, K., 1991. Murine T cell clones specific for *Hymenolepis nana*: generation and functional analysis *in vivo* and *in vitro*. Int. J. Parasitol. 21, 891–896.

Bergquist, N.R., Leonardo, L.R., Mitchell, G.F., 2005. Vaccine-linked chemotherapy: can schistosomiasis control benefit from an integrated approach? Trends Parasitol. 21, 112–117.

Brunet, J., Benoilid, A., Kremer, S., et al., 2015. First case of human cerebral *Taenia martis* cysticercosis. J. Clin. Microbiol. 53, 2756–2759.

Conchedda, M., Bortoletti, G., Gabriele, F., Wakelin, D., Palmas, C., 1997. Immune response to the cestode *Hymenolepis nana*: cytokine production during infection with eggs or cysts. Int. J. Parasitol. 27, 321–327.

Cruz-Rivera, M., Caughan, G., Mendlovic, F., et al., 2014. Cytokine expression at the anchor site in experimental *Taenia solium* infection in hamsters. Vet. Parasitol. 200, 299–302.

Diemert, D.J., Methony, J.M., Hotez, P.J., 2008. Hookworm vaccines. Clin. Infect. Dis. 46, 282–288.

Gauci, C., Lightowlers, M.W., 2003. Molecular cloning of genes encoding oncosphere proteins reveals conservation of modular protein structure in cestode antigens. Mol. Biochem. Parasitol. 127, 193–198.

Gauci, C., Jayashi, C., Lightowlers, M.W., 2013. Vaccine development against the *Taenia solium* parasite. Bioengineered 4, 343–347.

Gauci, C., Verastegui, M.R., Gilman, R.H., Lightowlers, M.W., 2006. *Taenia solium* and *Taenia ovis*: stage-specific expression of the vaccine antigen genes, TSOL18, TSOL16, and homologues, in oncospheres. Exp. Parasitol. 113, 272–275.

Gottstein, B., Wunderlin, E., Tanner, I., 1994. *Echinococcus multilocularis*: parasite-specific humoral and cellular immune response subsets in mouse strains susceptible (AKR, C57Bl/6J) or 'resistant' (C57Bl/10) to secondary alveolar echinococcosis. Clin. Exp. Immunol. 96, 245–252.

Graichen, D.A.S., Gottstein, B., Matsumoto, J., et al., 2007. Expression and diversity of *Echinococcus multilocularis AgB* genes in secondarily infected mice: evaluating the influence of T-cell immune selection on antigenic variation. Gene 392, 98–105.

Hopkins, C.A., 1980. Immunity and *Hymenolepis diminuta*. In: Arai, H.P. (Ed.), Biology of the Tapeworm *Hymenolepis diminuta*. Academic Press, New York, pp. 551–614.

Ito, A., 1977. The mode of passive protection against *Hymenolepis nana* induced by serum transfer. Int. J. Parasitol. 7, 67–71.

Ito, A., 1997. Basic and applied immunology in cestode infections: from *Hymenolepis* to *Taenia* and *Echinococcus*. Int. J. Parasitol. 27, 1203–1211.

Ito, A., 2015a. Basic and applied problems in developmental biology and immunobiology of cestode infections: *Hymenolepis*, *Taenia* and *Echinococcus*. Parasite Immunol. 37, 53–69.

Ito, A., 2015b. Beyond the conceived concepts. Parasite Immunol. 37, 430–431.

Ito, A., Budke, C.M., 2014. Culinary delights and travel? A review of zoonotic cestodiases and metacestodiases. Travel Med. Infect. Dis. 12, 582–591.

Ito, A., Kamiyama, T., 1984. *Hymenolepis nana*: worm recovery from congenitally athymic nude and phenotypically normal rats and mice. Exp. Parasitol. 58, 132–137.

Ito, A., Smyth, J.D., 1987. Adult cestodes. Immunology of the lumen-dwelling cestode infections. In: Soulsby, E.J.L. (Ed.), Immune Responses in Parasitic Infections: Immunology, Immunopathology, and Immunoprophylaxis, vol. 2. CRC Press, Boca Raton, pp. 115–163.

Ito, A., Yamamoto, M., 1976. The mode of active protection against *Hymenolepis nana* reinfection in mice inoculated with different does of shell-free eggs. Jpn. J. Parasitol. 25, 247–253.

Ito, A., Kanazawa, T., Nakao, M., et al., 2001. Comparison of the antigenicity of protoscoleces and microvesicles of *Echinococcus multilocularis* prepared from rats. J. Helminthol. 75, 355–358.

Ito, A., Ma, L., Sato, Y., 1997. Cystic metacestodes of a rat-adapted *Taenia taeniaeformis* established in the peritoneal cavity of scid and nude mice. Int. J. Parasitol. 27, 903–905.

Ito, A., Yanagida, T., Nakao, M. Recent advances and perspectives in molecular epidemiology of *Taenia solium* cysticercosis. Infect. Genet. Evol. http://dx.doi.org/10.1016/j.meegid.2015.06.022, in press.

Jayashi, C.M., Gonzalez, A.E., Neyra, R.C., et al., 2012. Characterisation of antibody responses in pigs induced by recombinant oncosphere antigens from *Taenia solium*. Vaccine 30, 7475–7480.

Johnson, K.S., Harrison, G.B., Lightowlers, M.W., et al., 1989. Vaccination against ovine cysticercosis using a defined recombinant antigen. Nature 338, 585–587.

Johnston, M.J.G., Wang, A., Catarino, M.E.D., et al., 2010. Extracts of the rat tapeworm, *Hymenolepis diminuta*, suppress macrophage activation *in vitro* and alleviate chemically induced colitis in mice. Infect. Immun. 78, 1364–1375.

Kizaki, T., Ishige, M., Bingyan, W., et al., 1993a. Generation of $CD8^+$ suppressor T cells by protoscoleces of *Echinococcus multilocularis*. Immunology 79, 412–417.

Kizaki, T., Ishige, M., Bingyan, W., et al., 1993b. Interleukin-1-dependent mutagenic responses induced by protoscoleces of *Echinococcus multilocularis* in murine lymphocytes. J. Leukoc. Biol. 53, 233–239.

Kouguchi, H., Matsumoto, J., Nakao, R., et al., 2013. Characterization of a surface glycoprotein from *Echinococcus multilocularis* and its mucosal vaccine potential in dogs. PLoS One 8, e69821.

Laclette, J.P., Rodriguez, M., Landa, A., Arcos, L., et al., 1989. The coexistence of *Taenia solium* cysticerci and the pig: role of the antigen B. Acta Leiden. 57, 115–122.

Lightowlers, M.W., 2003. Vaccines for prevention of cysticercosis. Acta Trop. 87, 129–135.

Lightowlers, M.W., Gauci, C.G., Chow, C., et al., 2003. Molecular and genetic characterisation of the host-protective oncosphere antigens of taeniid cestode parasites. Int. J. Parasitol. 33, 1207–1217.

Ma, X., Wang, L., Zhao, H., et al., 2014. Th17 cells are associated with the Th1/Th2-cell balance during *Echinococcus multilocularis* infection. Mol. Med. Rep. 10, 236–240.

Maravilla, P., Avila, G., Cabrera, V., Aguilar, L., Flisser, A., 1998. Comparative development of *Taenia solium* in experimental models. J. Parasitol. 84, 882–886.

Maravilla, P., Garza-Rodriguez, Z., Gomez-Diaz, B., et al., 2011. *Chinchilla laniger* can be used as an experimental model for *Taenia solium* taeniasis. Parasitol. Int. 60, 364–370.

McKay, D.M., Khan, W.I., 2003. STAT-6 is an absolute requirement for murine rejection of *Hymenolepis diminuta*. J. Parasitol. 89, 188–189.

Mitchell, G.F., Goding, J.W., Rickard, M.D., 1977. Studies on the immune response to larval cestode in mice. I. Increased susceptibility of certain mouse strain and hypothymic mice to *Taenia taeniaeformis* and analysis of passive transfer of resistance with serum. Aust. J. Exp. Biol. Med. 55, 165–186.

Mitchell, G.F., Rajasekariah, G.R., Rickard, M.D., 1980. A mechanism to account for mouse strain variation in resistance to the larval cestode, *Taenia taeniaeformis*. Immunology 39, 481–489.

Nakao, M., Lavikainen, A., Yanagida, T., Ito, A., 2013. Phylogenetic systematics of the genus *Echinococcus* (Cestoda: Taeniidae). Int. J. Parasitol. 43, 1017–1029.

Nakaya, K., Nakao, M., Ito, A., 1997. *Echinococcus multilocularis*: mouse strain difference in hydatid development. J. Helminthol. 71, 53–56.

Nakaya, K., Mamuti, W., Xiao, N., et al., 2006. Usefulness of severe combined immunodeficiency (scid) and inbred mice for studies of cysticercosis and echinococcosis. Parasitol. Int. 55, S91–S97.

Nono, J.K., Lutz, M.B., Brehm, K., 2014. EmTIP, a T-cell immunomodulatory protein secreted by the tapeworm *Echinococcus multilocularis* is important for early metacestode development. PLoS Negl. Trop. Dis. 8, e2632.

Ntoukas, V., Tappe, D., Pfütze, D., Simon, M., Holzmann, T., 2013. Cerebellar cysticercosis by larval *Taenia crassiceps* tapeworm in immunocompetent woman, Germany. Emerg. Infect. Dis. 19, 2008–2011.

Okamoto, K., 1968. Effect of neonatal thymectomy on acquired resistance to *Hymenolepis nana* in mice. Jpn. J. Parasitol. 17, 53–59.

Okamoto, K., Koizumi, M., 1972. *Hymenolepis nana*: effect of antithymocyte serum on acquired immunity in mice. Exp. Parasitol. 32, 56–61.

Olson, P.D., Yoder, K., Dajardo, L.-G.L.F., et al., 2003. Lethal invasive cestodiases in immunosuppressed patients. J. Infect. Dis. 187, 1962–1966.

Persaud, R., Wang, A., Readon, C., McKey, D.M., 2007. Characterization of the immune-regulatory response to the tapeworm *Hymenolepis diminuta* in the non-permissive mouse host. Int. J. Parasitol. 37, 393–403.

Reyes, J.L., González, M.I., Ledesma-Soto, Y., Satoskar, A.R., Terrazas, L.I., 2011. TLR2 mediates immunity to experimental cysticercosis. Int. J. Biol. Sci. 7, 1323–1333.

Reyes, J.L., Wang, A., Fernando, M.R., et al., 2015. Splenic B cells from *Hymenolepis diminuta*-infected mice ameliorate colitis independent of T cells and via cooperation with macrophages. J. Immunol. 194, 364–378.

Rickard, M.D., 1983. Immunity. In: Arme, C., Pappas, P.W. (Eds.), Biology of the Eucestoda, vol. 2. Academic Press, London, pp. 539–579.

Rickard, M.D., Williams, J.F., 1982. Hydatidosis/cysticercosis: immune mechanisms and immunization against infection. Adv. Parasitol. 21, 229–296.

Schneider, B., Jariwala, A.R., Victoria Periago, M., et al., 2011. A history of hookworm vaccine development. Hum. Vaccin. 7, 1234–1244.

Spolski, R.J., Corson, J., Thomas, P.G., Kuhn, R.E., 2000. Parasite-secreted products regulate the host response to larval *Taenia crassiceps*. Parasite Immunol. 22, 297–305.

Vuitton, D.A., Zhang, S.L., Yang, Y., et al., 2006. Survival strategy of *Echinococcus multilocularis* in the human host. Parasitol. Int. 55, S51–S55.

Watanabe, N., Nawa, Y., Okamoto, K., Kobayashi, A., 1994. Expulsion of *Hymenolepis nana* from mice with congenital deficiencies of IgE production or of mast cell development. Parasite Immunol. 16, 137–144.

Williams, J.F., 1983. Cestode infections. In: Cohen, S., Warren, K. (Eds.), Immunology of Parasitic Infections. Blackwell Scientific Publications, Oxford, pp. 676–714.

Yanagida, T., Yuzawa, I., Joshi, D.D., et al., 2010. Neurocysticercosis: assessing where the infection was acquired from. J. Travel Med. 17, 206–208.

Zhang, W., McManus, D.P., 2008. Vaccination of dogs against *Echinococcus granulosus*: a means to control hydatid disease? Trends Parasitol. 24, 419–424.

Relevant Website

http://www.cdc.gov/parasites/az/index.html – Centers for Disease Control and Prevention, Life Cycle Diagrams for the Major Cestode Parasites of Humans.