Parasitology

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Model systems for investigating disease processes in neurocysticercosis

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Review

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Abstract

Neurocysticercosis (NCC) occurs following brain infection by larvae of the cestode *Taenia solium*. It is the leading cause of preventable epilepsy worldwide and therefore constitutes a critical health challenge with significant global relevance. Despite this, much is still unknown about many key pathogenic aspects of the disease, including how cerebral infection with *T. solium* results in the development of seizures. Over the past century, valuable mechanistic insights have been generated using both clinical studies and animal models. In this review, we critically assess model systems for investigating disease processes in NCC. We explore the respective strengths and weaknesses of each model and summarize how they have contributed to current knowledge of the disease. We call for the continued development of animal models of NCC, with a focus on novel strategies for understanding this debilitating but often neglected disorder.

Introduction

Neurocysticercosis (NCC) is a human disease which arises when larvae of the cestode *Taenia solium* infect the central nervous system (CNS) (Mahanty and Garcia, 2010). The most common symptom of this infection is the development of epileptic seizures, which occurs in 70–90% of symptomatic NCC cases (Carpio and Romo, 2014). As such, NCC is thought to be the leading cause of acquired epilepsy. Epilepsy affects 50 million people worldwide with about 80% of cases in the developing world, constituting a critical global health concern. NCC is typically prevalent in developing countries, but with increasing migration from – and travel to – endemic countries, it is steadily becoming a global phenomenon (Burneo and Cavazos, 2014; Carpio and Romo, 2014). This is concerning as NCC not only impacts heavily on the quality of life of those infected, but also presents a significant drain on medical and economic resources (Roman *et al.*, 2000; Bhattarai *et al.*, 2011).

Despite the global impact of NCC, there is still much that is uncertain about the disorder. Precisely how, for example, cerebral infection with *T. solium* relates to the development of seizures remains unclear. Furthermore, there exists a need for additional therapeutic options for patients with epilepsy secondary to NCC, as many of these patients suffer from seizures that are refractory to currently available treatment (Burneo and Cavazos, 2014; Carpio and Romo, 2014; Mahanty *et al.*, 2015). The study of NCC also represents a unique opportunity for understanding how neuroinflammatory processes contribute to the development of seizures more generally (Nash *et al.*, 2015). As such, it is essential that we continue to develop new ways in which to study this disease. In this review, we explore the various model systems used to study NCC. We critically evaluate their relative strengths and weaknesses and summarize how they have contributed to our current understanding of disease processes. Finally, we discuss the potential for novel research strategies, which could enable progress in understanding pathogenic mechanisms in NCC.

A brief background on NCC

Taenia solium *life cycle: how does NCC come about?*

The adult worm of *T. solium* is found in the small intestine of *Homo sapiens*, the only known definitive host of *T. solium* (White, 2000) (Fig. 1). These worms can produce up to 2 00 000 and 4 00 000 infectious oncospheres (eggs) per day, which are excreted in the human feces (White, 2000). If infected feces are ingested by a pig, the oncospheres become activated/mature in the presence of bile salts and intestinal enzymes, and force their way through the gut wall and into the bloodstream (White, 2000). At blood vessel terminations, the activated oncospheres lodge in muscle, nervous, subcutaneous and ocular tissue (White, 2000). There, each mature oncosphere evolves into a vesicular larva with an invaginated scolex (also known as a cysticercus) over a period of weeks or months (White, 2000). These cysticerci have a lifespan of a few years (White, 2000). If pork meat containing a viable cysticercus is ingested by a human, the scolex of the cysticercus evaginates in the small intestine (due to

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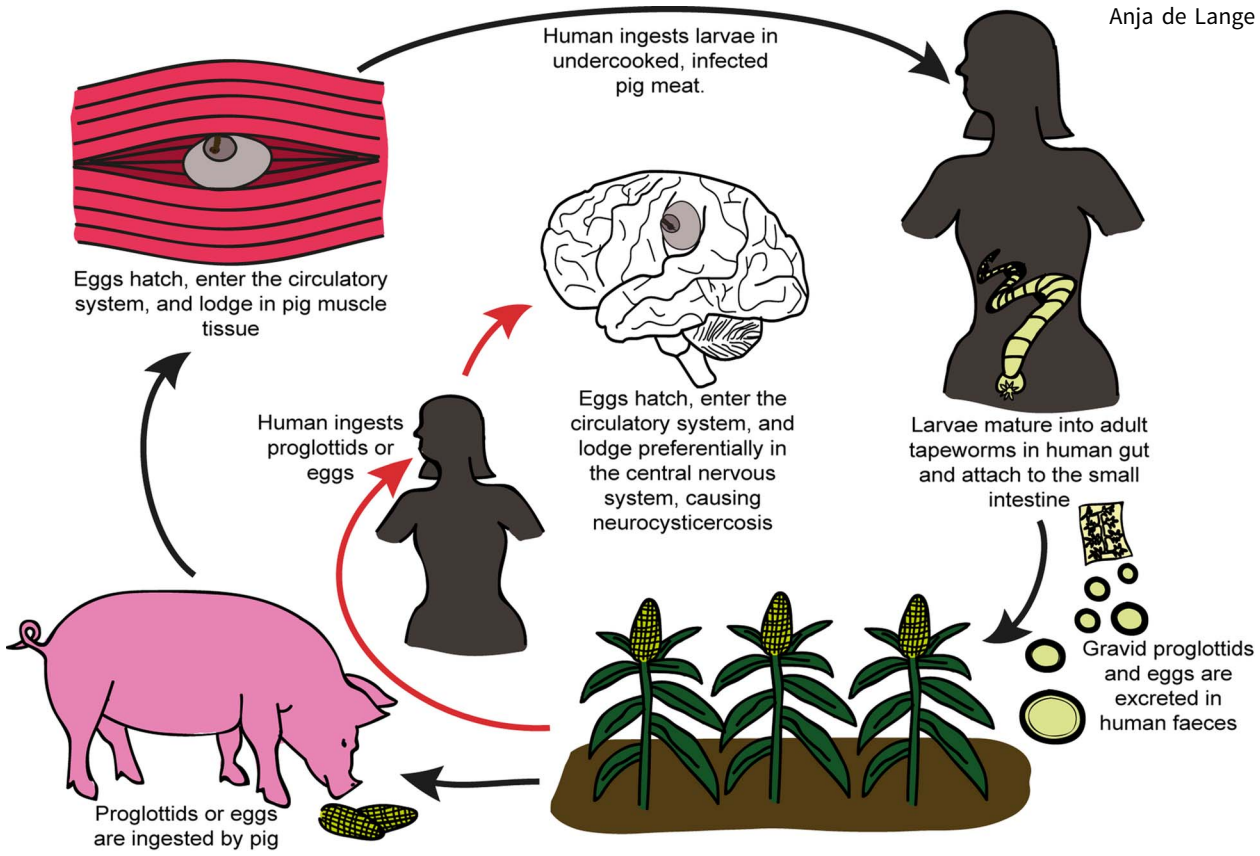

Fig. 1. Schematic representation illustrating the life cycle of *Taenia solium* and the process which results in human infection and neurocysticercosis.

a change in osmotic pressure), and attaches to the intestinal wall. Here the larva develops once more into an adult worm (White, 2000) (see Fig. 1).

NCC occurs when humans accidentally ingest the oncospheres of *T. solium* (Carpio, 2002). This may occur *via* food or water in areas where water sources are contaminated by human feces, or *via* accidental ingestion of tiny amounts of the feces of an adult tapeworm carrier in the household (Flisser, 1994). Oncospheres are also activated in the human gut as they would be in the pig gut, and are able to penetrate the gut wall and pass into the bloodstream (Carpio, 2002). The activated oncospheres may then lodge in muscle, ocular, subcutaneous or nervous tissue, with nervous system infection being of the greatest clinical concern (Carpio, 2002).

NCC disease progression and manifestation in humans

Following initial infection and the establishment of cysticerci in the brain parenchyma, sub-arachnoid space or ventricles, there is usually a lengthy period (months to years) in which the host shows little to no immune or inflammatory response to the infection and experiences no clinical symptoms (White, 2000). This may be because the viable cysticerci employ various immune modulatory mechanisms to remain largely unaffected by the host immune system (White, 2000). Viable cysticerci are also referred to as being in the vesicular stage (White, 2000). At some point, however, the cysts appear to lose their ability to control the host immune response and the cyst wall and fluid become infiltrated by host inflammatory cells. This is termed the colloidal phase. Thereafter the cyst cavity collapses and the host response progresses to surrounding the cyst with fibrosis, resiulting in the granular–nodular phase. Together, cysts in the colloidal or granular–nodular phase are often termed as transitional phase cysts. Eventually the entire cyst is replaced with fibrosis and calcifies and is then said to be in the calcific stage (White, 2000).

Manifestations of NCC are often studied and described in reference to the stage of the cyst (White, 2000; Fleury *et al.*, 2016; Gonzales *et al.*, 2016) (see Fig. 2). Cyst stages are largely determined using imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) scans, as well as post-mortem brain dissections (Carpio and Romo, 2014). A systematic review of the prevalence of different clinical manifestation of NCC reports seizures or epilepsy as the most common symptom, followed by headaches, intracranial hypertension, hydrocephalus and meningitis (Carabin *et al.*, 2011). Seizures occur more commonly in patients with calcified cysts, although this symptom of NCC is still prevalent in those with transitional/active cysts. Intracranial hypertension, hydrocephalus and meningitis seem to be much more common in patients with transitional/active cysts (see Fig. 2). There are numerous other, extremely varied, symptoms secondary to NCC that have been reported (Patel *et al.*, 2006; Mahanty and Garcia, 2010; Peon *et al.*, 2016). This diversity in symptoms has been attributed to the diversity in cyst antigens, numbers, stages, positions in the nervous system and the level of inflammation induced (Yakoleff-Greenhouse *et al.*, 1982; Fleury *et al.*, 2004).

Studying NCC disease processes in humans

NCC is most commonly studied in patients with the disease, that is, *in vivo* in humans naturally infected with *T. solium* larvae. These studies frequently make use of imaging techniques, such as CT and MRI. Such images have then been used in conjunction with clinical presentation of the disease in order to start disentangling what it is that underlies symptom development in NCC. Such studies have provided many valuable insights including that the presence of vesicular cysts may contribute to a patient remaining asymptomatic, even when other stages of cyst are present (Prasad *et al.*, 2008); that patients with calcified parenchymal cysts appear to be more susceptible to depressive symptoms (Leon

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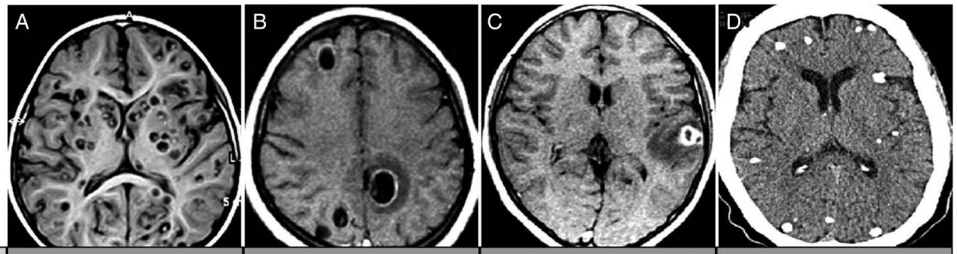

Cyst stage: (White, 2000)	Vesicular	Colloidal	Granular-nodular	Calcific
Cyst state: (White, 2000)	Viable.	Dying/transitional.		Dead.
Characterised by: (White, 2000)	Little to no inflammatory response.	Cyst is infiltrated by host inflammatory cells.	Cyst cavity collapses, onset of fibrosis.	Cyst fully fibrotic/calcified.
Common clinical manifestations: (Ndimubanzi et al., 2010)	Minimal, but can include: seizures, intracranial hypertension, hydrocephalus and meningitis.	Seizures.		Seizures.
Suspected main cause of symptoms: (Tsai et al., 2010)	Compression of the surrounding brain parenchyma and initial transient inflammatory reaction.	Acute inflammatory changes.	Perilesional gliosis.	Perilesional gliosis/oedema.
Antigens/proteins present:	Excreted/secreted and membrane presenting.	Products from cyst fluid, scolex and membrane.		Some evidence of residual cyst elements in calcific cysts (Gupta et al., 2002).
Predominant immune response: (Peon et al., 2016)	Modulated by Taenia larvae – upon infection there is a transient, inflammatory, T-helper 1 type response, which is shifted to a non-inflammatory T-helper 2 type response by larval excretory/secretory products.	Inflammatory. T-helper 1 type response.		Regulatory. Mixed T-helper 1 & 2 type response.

Fig. 2. Key differences in clinical, molecular and immune characteristics associated with *Taenia solium* cysts in neurocysticercosis [photographs sourced, with permission, from Carpio and Romo (2014)].

et al., 2015); that some cysts which appear to be inactive on an MRI scan are actually surrounded by gliosis, which may contribute to seizure recurrence (Pradhan *et al.*, 2000); and that the best drug regimens vary for different NCC presentations (Garcia *et al.*, 2014; Zhao *et al.*, 2016; Del Brutto *et al.*, 2006).

Another common way of studying disease processes in humans is through the analysis of blood serum or cerebrospinal fluid samples from NCC patients. Such studies have revealed proteins that appear to be specific to active, symptomatic NCC (Chung *et al.*, 1999; Ferrer *et al.*, 2005); that *T. solium* larvae appear to induce a regulatory T-cell response in the host, which creates an environment favourable to their survival (Arce-Sillas *et al.*, 2016); and that there appear to be certain genetic polymorphisms associated with individuals who have symptomatic *vs* asymptomatic NCC (Verma *et al.*, 2010).

More rarely, researchers may obtain brain tissue samples from NCC patients that undergo neurosurgical procedures as a part of their standard clinical care (Restrepo *et al.*, 1998; Robinson *et al.*, 2012). One such study has reported that substance *P* (a neuropeptide involved in neuropathic inflammation and possibly seizure induction) is prevalent in cells adjacent to NCC granulomas, but not in areas distant from granulomas, nor in brain tissue from individuals without NCC (Robinson *et al.*, 2012). Another examined the cellular and molecular immune response

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surrounding cysts and reported that there are at least four distinct types of immune responses in NCC (Restrepo *et al.*, 1998).

Human NCC is also studied *in vitro* utilizing normal, healthy cell culture lines of nervous system immune cells, or extracted and cultured immune cells from NCC infected patients. Such cell cultures have been utilized in conjunction with *T. solium* extracts to study immune responses in NCC (Uddin *et al.*, 2005, 2010; Amit *et al.*, 2011). Notable discoveries include that cysts treated with anti-parasitic agents elicit greater chemokine secretion in monocytes than those left untreated (Uddin *et al.*, 2010); that astrocytes play a key role in the inflammatory response to certain *T. solium* larval elements (Uddin *et al.*, 2005); that healthy human monocytes respond differently to *T. solium* brain cysts than to *T. solium* muscle cysts from pigs (Uddin *et al.*, 2010); and that different cyst elements (scolex, membrane or fluid) elicit different responses in both monocytes and lymphocytes (Uddin *et al.*, 2010; Amit *et al.*, 2011).

Challenges to NCC research in humans and the necessity for animal models

A major challenge for the study of NCC in humans is that the disease can only be studied as it occurs naturally. This means that there are large numbers of variables which cannot be controlled for in human studies, making it hard to isolate conditions which lead to symptom onset. Additionally, when patients present with symptomatic NCC, there exists an ethical obligation to start treatment as soon as possible, which also obstructs the understanding of the disease processes underlying symptom development (Cardona *et al.*, 1999). Study of the disease in humans is costly, as the only definitive diagnostic techniques are MRI or CT scans, which are typically not available in endemic areas with the highest prevalence rates. In addition, the large variability in human pathology and symptom presentation means that large sample sizes are required to obtain statistical significance. Longitudinal studies in humans are also challenging due to the lengthy time course of the disease, both in terms of symptom onset and progression of the cysts (Cardona *et al.*, 1999).

Studies using human tissue are also limited, as most rely on specimens that are collected using only minimally invasive procedures such as the collection of blood samples. Beyond that, samples of brain tissue or cerebrospinal fluid can only be sourced in cases where these are sampled out of clinical or diagnostic need. This is fairly rare, making it difficult to obtain large sample sizes (Cardona *et al.*, 1999). Taken together, these challenges greatly limit the exploration of the cellular and molecular processes underlying disease progression in NCC.

Animal models of NCC offer the potential to overcome many of these limitations: they allow for the experimental infection of animals in a controlled environment and for the study of disease progression both with and without treatment interventions. They are often much more cost-effective, as definitive infection can be confirmed post-mortem without neuroimaging, and smaller sample sizes can be used due to the controlled experimental environment. They facilitate longitudinal studies, as the time course of disease, especially in smaller animals, is much shorter and can be accelerated experimentally. Most importantly, animal models allow for unrestricted access to brain tissue and cerebrospinal fluid, thereby enabling more extensive cellular and molecular exploration. Although animal models have great utility in the study of disease processes in NCC, one should always bear in mind that findings from animal studies may not necessarily extrapolate to the human condition, as no animal model can fully recapitulate the human disease state.

In the section that follows, we review existing models of NCC, whilst describing their specific strengths and weaknesses.

Parasites utilized in animal model systems of neurocysticerosis

Model systems for studying NCC typically consist of two components: a cestode species and a host organism. In this review, we will discuss model systems involving three different cestode species.

Taenia solium

Taenia solium (*T. solium*) is the 'gold standard' organism in the study of NCC, as it is the cestode responsible for pathology in humans. Further, the genome of *T. solium* has recently been sequenced, allowing for the use of powerful genetic tools (Tsai *et al.*, 2013). However, *T. solium* has numerous practical limitations for use within the laboratory setting. It is highly infectious to humans and its experimental use requires strict biosafety measures. It is also challenging to obtain *T. solium* larvae, and extremely hard to maintain a steady experimental supply of the larvae. Larvae (or cysticerci) can be obtained in three ways: they can be harvested directly from a naturally or experimentally infected pig; they can be produced experimentally by feeding oncospheres [obtained from gravid proglottids in the stool of infected human patients, or from experimentally infected, immunosuppressed, chinchillas or hamsters (Arora *et al.*, 2017)] to a host in which they will be activated and develop naturally into cysticerci (Nguekam *et al.*, 2003); or they can be produced by activating oncospheres *in vitro* and then injecting the activated oncospheres into the brain to develop into cysts (Liu *et al.*, 2002; Verastegui *et al.*, 2015). *Taenia solium* may also not be infectious to animals utilized in animal models, thus requiring direct intracranial application, but the larvae of *T. solium* are large, and may displace most of the brain tissue in small animals.

Taenia crassiceps

Taenia crassiceps (*T. crassiceps)* is the most commonly utilized model organism for *T. solium*. The two cestodes are closely related, belonging to the same genus, and have been shown to have significant antigenic similarity (Larralde *et al.*, 1989; Sciutto *et al.*, 1990). *Taenia crassiceps* very rarely infect humans, making it a reasonably safe laboratory model, not requiring extensive biosafety measures (Willms and Zurabian, 2010). This is particularly the case for the ORF strain of *T. crassiceps*, which has entirely lost the ability to infect a definitive host and mature into adult worms, meaning that it does not present an infection risk to animals (Willms and Zurabian, 2010). A major advantage of *T. crassiceps* as a model organism for *T. solium* is that *T. crassiceps* larvae are able to rapidly asexually divide by budding in the intermediate host (usually mice), providing a simple way to maintain a steady experimental supply of the organism (Stringer *et al.*, 2003; Willms and Zurabian, 2010). The larvae are also able to survive for several weeks in *in vitro* culture.

The use of *T. crassiceps* as a model organism in the study of NCC also has its limitations. The definitive hosts for *T. crassiceps* are carnivores, most often wild canines (Willms and Zurabian, 2010), whilst that of *T. solium* is humans (see Fig. 3). *Taenia crassiceps* larvae are usually hosted by rodents and small moles (Willms and Zurabian, 2010), whilst pigs host larval *T. solium* (see Fig. 3). As a result, there must exist differences in the antigens and species-specific immune responses induced by the two organisms (Sciutto *et al.*, 2011). Another concern when utilizing *T. crassiceps* is that it has been found that many of the strains undergo morphological and genetic changes when they are maintained *via* serial intraperitoneal inoculation in mice, which may affect their immunogenicity and increase their dissimilarity to *T. solium*

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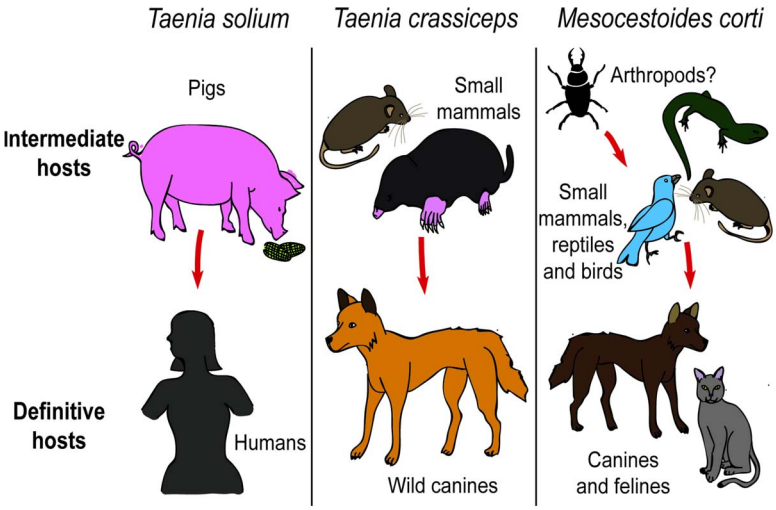

Fig. 3. The intermediate and definitive hosts of *Taenia solium*, *Taenia crassiceps and Mesocestoides corti.*

larvae (Zurabian *et al.*, 2008; Willms and Zurabian, 2010). Lastly, *T. crassiceps* are difficult to use where intracranial inoculation of small model animals is desired (e.g. mice), as the cysticerci displace most of the brain tissue (Alvarez *et al.*, 2010).

Mesocestoides corti

Mesocestoides corti (*M. corti*) is thought to infect anthropods as the initial host, small mammals, birds, reptiles and amphibians in the larval form, and carnivores, such as dogs and cats, as an adult worm (Crosbie *et al.*, 2000) (see Fig. 3). *Mesocestoides corti* is not known to infect humans, making it a safe laboratory model not requiring extensive biosafety measures. *Mesocestoides corti* asexually divides both as cysticerci in the intermediate host (Alvarez *et al.*, 2010) and as adult worms in the definitive host (Schmidt and Todd, 1978). The larvae have also been shown to be able to survive and divide under the right *in vitro* culturing conditions (Voge and Coulombe, 1966; Vendelova *et al.*, 2016). A colony of *M. corti* can therefore be experimentally produced and maintained with relative ease (Schmidt and Todd, 1978). *Mesocestoides corti* is closely related to *T. solium*, but is not of the same genus, which means that it may have greater antigenic difference to *T. solium* than does *T. crassiceps* (Alvarez *et al.*, 2010). A major advantage of *M. corti* is that the cysticerci are significantly smaller than those of *T. solium* and *T. crassiceps*, which makes it easier to use for intracranial inoculation of small model animals such as rodents (Alvarez *et al.*, 2010). However, unlike *T. solium* and *T. crassiceps*, *M. corti* has not been known to infect the CNS of any of its hosts during its natural cycle, which means that intracranial injection by the experimenter is the only way in which *M. corti* can enter the CNS (Alvarez *et al.*, 2010).

Animal model systems utilized in the study of NCC

Taenia crassiceps *in mice*

Mice are attractive model organisms for studying NCC due to their popularity across the life sciences. They are relatively cheap to maintain and have a rapid breeding cycle. Most importantly, the relative ease of modifying the mouse genome means that transgenic strains allowing molecular dissection of immunological and neurological pathways are now widely available.

NCC has been modelled in mice by intracranially injecting *T. crassiceps* larval extracts or intact early-stage larvae (Matos-silva *et al.*, 2012; Robinson *et al.*, 2012; Leandro *et al.*, 2014). Different strains of mice show differing susceptibility to *T. crassiceps* intracranial infection (Matos-silva *et al.*, 2012). There has been one report of *T. crassiceps* in the brain of a wild mouse (Kroeze and Freeman, 1982), which is suggestive that further experimentation on the oral administration of *T. crassiceps* oncospheres in mice (perhaps using immunocompromised individuals) may have potential for the development of a model somewhat more congruent to the condition in humans. One strength of this model is that intracranial injection of peritoneal granulomas can produce seizures in the host (Robinson *et al.*, 2012), although it is not known whether these seizures could persist chronically.

Intracranial administration of *T. crassiceps* in mice has provided some valuable insights: one study has shown that early-stage granuloma extracts containing substance *P* may be responsible for seizure activity; another has shown this model results in encephalitis closely resembling that in human NCC; and a third has shown that *Taenia* larvae in the brain are highly adaptable when faced with adverse conditions (Matos-silva *et al.*, 2012; Robinson *et al.*, 2012; Leandro *et al.*, 2014).

Mesocestoides corti *in mice*

Mesocestoides corti (*M. corti*) can be utilized in conjunction with cultured mouse primary microglia to explore helminth-associated immunomodulation. One study utilizing this model system elucidated an immunosuppressive mechanism that may help to explain the delay in the onset of neuroinflammation seen in human NCC (Sun *et al.*, 2014). More commonly, however, *M. corti* larvae are administered intracranially in mice (as they do not migrate to the CNS if administered orally) to model human NCC (Cardona *et al.*, 1999, 2003; Cardona and Teale, 2002; Alvarez and Teale, 2007; Alvarez *et al.*, 2010). This model presents with an initial relative lack of immune responsiveness, which is thought may be useful as a comparative model for the study of asymptomatic NCC (Cardona *et al.*, 1999). Thus far no seizures have been reported in this model system of NCC, but it has provided much insight into potential mechanisms that dictate the severity of inflammation, blood–brain barrier breakdown, parasite burden and neuronal pathology (Cardona *et al.*, 1999, 2003; Cardona and Teale, 2002; Alvarez and Teale, 2006, 2007).

Taenia crassiceps *in rats*

Extracts of *T. crassiceps* larvae have been administered intracranially in rats, but to date no studies have been performed where intact oncospheres/cysts are injected. Studies using this model have shown that the intracranial administration of early-stage granulomal extracts can induce seizures in the host (Stringer *et al.*, 2003; Robinson *et al.*, 2012). This is a very promising

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finding in terms of its potential use in the study of seizures secondary to NCC. It should be noted, however, that these studies are limited by the fact that the granulomas were produced peripherally in mice, and immune responses differ in different hosts, as well as peripherally as compared with the CNS, so the content of these granulomas may not be reflective of brain cysts. Brain activity was monitored acutely in these studies, so it is not yet known whether recurrent seizures would present in these rats.

Taenia solium *in rats*

Taenia solium does not naturally infect rodents, and as such very little research has been done using the *T. solium*–rat combination. In one study, however, activated oncospheres were intracranially injected into rats, and these were found to form cysts in roughly half of the rats after about 4 months (Verastegui *et al.*, 2015). Importantly, infection is much more successful in younger rats. The authors report that this model presents with many NCC characteristics typical of human infection and that 9% of infected rats present with chronic seizures (Verastegui *et al.*, 2015). Although this is not a very efficient model of epilepsy secondary to NCC, the induction of chronic seizures is intriguing, and it may be worth exploring whether this model could be optimized for seizure occurrence. The study further revealed diverse cyst distribution and immunopathology, similar to what is observed in humans. A major advantage of this model over other rodent models is the use of the parasite responsible for human disease.

Taenia solium *in pigs*

The study of *T. solium* NCC in pigs often involves the utilization of pigs reared for agricultural purposes that have naturally acquired the infection. Pigs can also be experimentally infected by oral administration of *T. solium* eggs to induce NCC, with between 20 and 100% of pigs dosed with high numbers of eggs developing NCC (de Aluja *et al.*, 1996; Santamaria *et al.*, 2002; Nguekam *et al.*, 2003). Older pigs appear to be more resistant to infection than younger pigs (Santamaria *et al.*, 2002). Recently, a new model of pig NCC was developed whereby activated *T. solium* oncospheres are surgically implanted into the subarachnoid space (Fleury *et al.*, 2015). All infected pigs developed brain cysts, although at very low infection efficiencies (Fleury *et al.*, 2015). This model surprisingly did not result in any neurological signs (Fleury *et al.*, 2015).

The pig model system of NCC has been extremely useful in characterizing immunopathological and proteomic changes in response to *T. solium* in the brain, both in the normal course of disease and after a vaccination or treatment protocol. Significant overlap between human and pig reactions has been found (Molinari *et al.*, 1983; Sikasunge *et al.*, 2009; Guerra-Giraldez *et al.*, 2013; Singh *et al.*, 2013; Mahanty *et al.*, 2015; Christensen *et al.*, 2016; Navarrete-Perea *et al.*, 2017). A recent study reports severe seizures in naturally infected pigs, which could be extremely valuable in aiding progress towards understanding the most common symptomatic presentation in NCC (Trevisan *et al.*, 2016). The pigs that presented with seizures in this study were much older than the others in the sample group, suggesting that a longer infection/experimental period may be necessary for neurological symptoms to present (Trevisan *et al.*, 2016). NCC in pigs also presents with great variation in the infection characteristics and antibody response, which suggests that porcine models may be able, to some extent, to recapitulate the great variation in pathology and disease progression that is observed in infected humans (Prasad *et al.*, 2006; Saenz *et al.*, 2008).

Limitations of the pig–*T. solium* model system includes that this model can prove very time and resource intensive, with *T. solium* cysts taking as long as 350 days to form in pigs (de Aluja *et al.*, 1996), pig handlers requiring training and larger animals requiring more resources to feed and keep (de Aluja *et al.*, 1996; Arora *et al.*, 2017).

Taenia solium *in rhesus monkeys*

Primate studies of neurological conditions are rare due to the significant ethical (Greene *et al.*, 2005) and legal (Fox, 2009) implications of using primates for research purposes. Many countries have laws in place either preventing primate research or restricting their use to cases where all other options have been exhausted or found unsuitable (Greene *et al.*, 2005; Fox, 2009).

Taenia solium has, however, been reported to infect several non-human primates in its larval form, although this is considered an 'accidental infection' since *T. solium* does not require infection of non-human primates to complete its life cycle (Kuntz, 1973; Johnston *et al.*, 2016). NCC can be reliably induced in rhesus monkeys by feeding them large doses of activated *T. solium* oncospheres. The infected monkeys present with seizures and clinical symptoms very similar to those in humans within a matter of days, and if not treated may eventually die from the infection (Saleque *et al.*, 1988; Chowdhury *et al.*, 2014). Symptom presentation is delayed and attenuated in monkeys receiving smaller numbers of oncospheres, which may more closely resemble the human condition (Chowdhury *et al.*, 2014). It is interesting to note that symptom onset could be induced within a matter of days, in contrast to a study reporting a case of naturally acquired NCC in an 8-year-old rhesus monkey, which presented with no symptoms (Johnston *et al.*, 2016). This could be explained by the high dosage of oncospheres used in the experimental studies and serves as a reminder of the importance of dose in eliciting disease phenotypes in models of NCC.

Future roles for animal model systems in the study of NCC

Due to the remaining uncertainty surrounding disease mechanisms in NCC and the limitations of studying the disease in humans, there is a need for continued exploration and improvement of animal models that recapitulate the human disease process. Table 1 summarizes the respective utility of currently available model systems used in NCC research and highlights the fact that there still exist many areas that remain unexplored.

One aspect of the disease that may be useful consider when designing model systems is that the disease state in humans involves a mismatch between the host and the parasite stage. Humans are not natural hosts for the larval life stage of *T. solium* (Fig. 1). Therefore, it may be worth considering using or creating model systems where this mismatch is replicated. Inducing NCC using *T. crassiceps* or *M. corti* in animals that usually act as the definitive host for these parasites (such as cats or dogs – see Fig. 3), for example. Reports exist of CNS infections by *T. crassiceps* and *T. solium* occurring naturally in cats or dogs, and although seizures are not amongst the neurological symptoms reported in these cases, they provide an encouraging precedent for experimental models in these animals (Rogers *et al.*, 1989; Crosbie *et al.*, 2000; Wünschmann *et al.*, 2003; Jull *et al.*, 2012). By recreating the host–parasite stage mismatch, models in canines offer a potential new avenue for NCC research, although this would need to be weighed against the ethical and cultural concerns of using these animals for research purposes.

Another potential avenue of exploration towards the expansion of animal model systems is the use of novel model parasites.

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Table 1. A summary of the characteristics and utilities of existing model systems for the study of neurocysticercosis

Host	Parasite	*In vivo*/ *in vitro*	Parasite material administered (if experimental)	Reflects human NCC host–parasite stage mismatch?	Enables experimental infection/ manipulation?	Useful to study immunopathology?	Presents with electrographic hyperexcitability/ seizures?	Presents with other clinical symptoms?	Useful in investigating effect of different cyst stages on disease state?	Useful to assess drug treatment? (AEDs, steroids, anthelminthics)	Common experimental techniques
Human	*T. solium*	*In vivo*	Not applicable	Yes	No	Yes	Yes[1–7]	Yes[1,3]	Yes[2,3,8]	Yes (only by repurposing existing human drugs)[6–10]	Neuroimaging[1–5] Cellular/molecular examination of blood/CSF/tissue (other than histology)[3,11–16]
Human	*T. solium*	*In vitro*	Larval/granuloma elements	Yes	Yes	Yes[17–19]	Not yet tested	No	Not yet tested	Yes[17]	Cell culture with parasite elements[17–19]
Mouse	*M. corti*	*In vitro*	Larval/granuloma elements	No	Yes	Yes[20]	Not yet tested	No	Not yet tested	Not yet tested	Cell culture with parasite elements[20]
Pig	*T. solium*	*In vivo*	Oncospheres	No	Yes[21–23]	Yes[11,23–31]	Yes[32]	Yes[32,33]	Yes[11,22,25,26,29,34]	Yes[21,27,28,31]	Neuroimaging [26,31,33] Cellular/molecular examination of blood/CSF/tissue (other than histology)[11,26] Macroscopic examination of brain[22,32–34] BBB permeability assessment[27,28,31] Histological studies [22,24,25,27,29–31,33]
Rat	*T. solium*	*In vivo*	Activated oncospheres	No	Yes[35]	Yes[35]	Yes[35]	Not yet tested	Not yet tested	Not yet tested	Cellular/molecular examination of blood/CSF/tissue (other than histology)[35] Macroscopic examination of brain[35] Histological studies[35]
Rat	*T. crassiceps*	*In vivo*	Larval elements	No	Yes[14,36]	Not yet tested	Yes[14,36]	Not yet tested	Yes[14,36]	Not yet tested	Histological studies[14] Electrophysiological recordings[14,36]
Rhesus monkey	*T. solium*	*In vivo*	Oncospheres	No	Yes[37,38]	Yes[37,38]	Yes[37,38]	Yes[37,38]	Not yet tested	Not yet tested	Macroscopic examination of brain[39] Histological studies[39] Behavioural observations[37,38]
Mouse	*T. crassiceps*	*In vivo*	Early-stage cysticerci	No	Yes[14,40,41]	Yes[14,40]	Yes[14]	Not yet tested	Yes[14]	Yes[41]	Macroscopic examination of brain[40] Histological studies[40] Electrophysiological recordings[14] Gene manipulation[14]
Mouse	*M. corti*	*In vivo*	Early-stage cysticerci	No	Yes[42–48]	Yes[42–48]	Not yet tested	Yes[44]	Yes[42]	Not yet tested	Cellular/molecular examination of blood/tissue[43,44,47,48] BBB permeability[42,45,46] Histological studies[42–48]

Table reference guide: 1 – Leon *et al*. (2015); 2 – Prasad *et al*. (2008); 3 – Fleury *et al*. (2004); 4 – Pradhan *et al*. (2003); 5 – Pradhan *et al*. (2000); 6 – Das *et al*. (2007); 7 – Garcia *et al*. (2014); 8 – Del Brutto *et al*. (2006); 9 – Zhao *et al*. (2016); 10 – Nash *et al*. (2006); 11 – Ferrer *et al*. (2005); 12 – Chung *et al*. (1999); 13 – Arce-Sillas *et al*. (2016); 14 – Robinson *et al*. (2012); 15 – Restrepo *et al*. (1998); 16 – Verma *et al*. (2010); 17 – Uddin *et al*. (2010); 18 – Uddin *et al*. (2005); 19 – Amit *et al*. (2011); 20 – Sun *et al*. (2014); 21 – de Aluja *et al*. (1996); 22 – Fleury *et al*. (2015); 23 – Nguekam *et al*. (2003); 24 – Molinari *et al*. (1983); 25 – Sikasunge *et al*. (2009); 26 – Singh *et al*. (2013); 27 – Marzal *et al*. (2014); 28 – Guerra-Giraldez *et al*. (2013); 29 – Alvarez *et al*. (2002); 30 – Christensen *et al*. (2016); 31 – Cangalaya *et al*. (2016); 32 – Trevisan *et al*. (2016); 33 – Prasad *et al*. (2006); 34 – Saenz *et al*. (2008); 35 – Verastegui *et al*. (2015); 36 – Stringer *et al*. (2003); 37 – Chowdhury *et al*. (2014); 38 – Saleque *et al*. (1988); 39 – Johnston *et al*. (2016); 40 – Matos-silva *et al*. (2012); 41 – Leandro *et al*. (2014); 42 – Cardona *et al*. (1999); 43 – Cardona *et al*. (2003); 44 – Cardona and Teale (2002); 45 – Alvarez and Teale, (2007); 46 – Alvarez and Teale, (2006); 47 – Gundra *et al*. (2011); 48 – Mishra *et al*. (2011).

Taenia taeniaeformis, for example, has been used to experimentally induce cysticercosis in rodents and been shown to have significant antigenic similarity to *T. solium* (Shukla *et al.*, 2008; Preet and Prakash, 2011). Further, another species of *Taenia*, *Taenia serialis*, has been reported to cause cerebral cysticercosis in cats, and as such may also be an interesting experimental parasite to explore (Jull *et al.*, 2012; Orioles *et al.*, 2014).

There currently exists a paucity of model systems that result in the development of seizures, and even fewer that result in recurrent seizures (refer to Table 1). One way in which research into this aspect of NCC could be relatively easily expanded is through the use of *in vitro*/*ex vivo* models using neural tissue, such as acute or organotypic brain slices (De Simoni and Yu, 2006). Whilst these model systems lack many key components necessary for fully recapitulating the disorder (e.g. adaptive immunity), brain slice models do allow for unprecedented experimental and molecular access to the tissue in ways that are difficult or impossible to accomplish *in vivo*. The expansion and optimization of *in vivo* animal models, that result in seizures would also be extremely valuable. Such a rodent model would be particularly well received, as experimental tools for observing and manipulating neural circuits and seizure activity in rodents have progressed remarkably over the past two decades. For example, wireless telemetry now enables chronic (>3 months) EEG recordings in freely moving mice and rats, which can document the development of seizures over time (Wykes *et al.*, 2012); and transgenic mouse lines can selectively knockout immunological pathways (Ndlovu and Brombacher, 2014) or allow *in vivo* calcium imaging to better understand circuit-level changes which result in seizures (Madisen *et al.*, 2010). Any animal model of NCC which results in recurrent seizures would have additional worth as a general inflammatory model of epilepsy, for which reliable animal models are still lacking (Nash *et al.*, 2015).

Whilst genetically altered mice are an underutilized resource in the study of NCC, there is also much potential for the development of molecular tools for modifying the genomes of model parasites. There is one research group who, for example, are developing a 'reporter' strain of *T. crassiceps* where larvae express fluorescent proteins (Moguel *et al.*, 2015). This could prove valuable for tracking the parasites *in vivo*. Further, genetic knock-out cestode strains could help isolate parasite functions that are crucial for disease progression, and thereby help elucidate the mechanisms of disease.

Conclusion

NCC is an important global health challenge that is still poorly understood. Whilst the study of NCC in patients has provided important insights into the disease, there exist innate limitations that can only be overcome through the use and continued development of animal models. Model systems utilizing *T. solium*, *T. crassiceps* and *M. corti* in mice, rats, pigs and even rhesus monkeys have generated invaluable knowledge on disease mechanisms in NCC. However, there is a great need for animal models of NCC which result in seizures and epilepsy. New rodent model systems of NCC would allow researchers to take advantage of the latest technological advances to explore the disease at unprecedented molecular and cellular detail. We believe that there is still huge potential that could be realized in animal model systems, and that this represents the key to ultimately unlocking a definitive understanding – and treatment of NCC.

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