We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 2

Current Research Advance on Echinococcosis

Shukun Yang, Yumin Zhao,
Don Peter McManus and YuRong Yang

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.68286

Abstract

Echinococcosis is caused by infection with larva (metacestode) of the tapeworms of the genus *Echinococcus*. Within genus *Echinococcus*, two species are known as public health concern worldwide: *Echinococcus guanulosus* causing cystic echinococcosis (CE) and *Echinococcus multilocularis* causing alveolar echinococcosis (AE). The co-evaluation due to the interaction between parasites and their hosts has been well known to be able to allow tolerating to maintain parasitism as long as possible. With many research advanced findings, scientists have been much interested in using either those molecules from parasites producing due to invading and surviving or those cytokines from hosts responding due to defenses to carry out immunotherapeutic practice that is not only against parasitic infection but also for cancer or other immunological related disorders. Taken advance of knowledge on *Echinococcus* genome research outcomes, recent attentions regarding the discoveries of targeting antiparasitic drug and/or vaccine were extensively discussed in this review.

Keywords: *Echinococcus* species, parasitism, interactions between parasites and hosts, immunotherapy agents, drug and vaccine discoveries

1. Introduction

The echinococcosis in human occurs as a result of infection by the larval stages of taeniid cestodes of the genus *Echinococcus*. Originally, four species have been recognized as the public health concern: *Echinococcus granulosus* [agent of cystic echinococococcosis (CE)], *Echinococcus multilocularis* [agent of alveolar echinococcosis (AE)], and *Echinococcus vogeli* and *Echinococcus oligarthrus* [both are the agents of polycystic echinococcosis (PE)] [1]. Recently, two new species have been identified: *Echinococcus shiquicus* [2] in small mammals from the Tibetan plateau and *Echinococcus felidis* [3] in African lions though these two new species infective to

human are still unknown [4]. A couple of studies have provided augments that these diseases are an increasing public health concern and showing emerging or re-emerging diseases [4, 5].

Among recognized four public health concerned species, *E. multilocularis* and *E. granulosus* are important for human health and economic welfare [4]. The disease occurs in most areas of the world, and currently about 4 million people are infected and another 40 million people are at risk [4, 6, 7]. The economic cost of the disease is estimated to be around 3 billion USD a year. It is classified as a neglected tropical disease [4].

The knowledge on the geographical distribution of the environmental factors for the persistence of the lifecycle is scarce [8, 9]. Studies to improve the knowledge on epidemiological risk factors should be encouraged to enable risk-based sampling. *Echinococcus* notification should always be done at species level in order to discriminate between the more severe alveolar and the cystic echinococcosis [10, 11]. Updated knowledge on the *Echinococcus* parasitism was also discussed for the potential application in immunotherapeutic against parasites and other immune disorders.

2. Transmission

The life cycle of *Echinococcus* species requires a predator-prey relationship between the definitive and intermediate hosts.

E. granulosus is adapted to an environment in which livestock farming plays a central role, completing its cycle through dogs or wild carnivorous animals (as definitive host) and a variety of livestock species, mainly sheep, cattle, pigs, horses, goats, and camels as well as the several wild ungulate species serve as intermediate hosts for the different lineages of the *E. granulosus* species complex [12]. In contrast, several wild rodent species (typically rodents of the families *Arvicolidae* and *Cricetidae*) are the natural intermediate host for *E. multilocularis* [12, 13].

The intermediate hosts become infected through ingestion of eggs in contaminated food or water [12]. The host digestive enzymes dissolve the egg's shell, releasing the oncosphere, which burrows through the host's gut wall and is transported via blood or lymph to the target organ of liver for AE, but mainly liver and lungs, as well other organs for CE [14]. While the life cycle of *E. multilocularis* is completed after a fox or canine consumes a rodent infected with alveolar echinococcosis [8]. Once again adults begin to release a new gravid proglottid, which usually carries some 1500 eggs [15], to be passed to the outside environment with their feces. The adult worms are hermaphroditic. *E. granulosus* becomes prepatent in 32–80 days in the definitive hosts [16], this period varies with the species or strain. While *E. multilocularis* usually becomes prepatent in foxes or dogs in 28–35 days [17], the life cycle of *E. multiloculcaris* is predominantly sylvatic [18].

Humans can serve as an aberrant intermediate host, acquiring the infection by accidental ingestion of eggs, due to handling of infected animals or ingesting contaminated food, vegetable, and water. Except in rare cases, where infected humans are eaten by canines [19], humans are a deadend for *Echinococcus* species, which means that this kind of intermediate host does not allow transmission to the definitive host [20].

Briefly, the disease is spreading when food or water contains the eggs of the parasite, which may be eaten by intermediate animals (such as sheep for *E. granulosus* and rodents for *E. multilocularis*),

or due to close contact with an infected definitive animal (carnivorous animals, e.g., dogs, foxes), while the definitive animals, to become infectious, they must eat the organs of an intermediate animal that contains the valid cysts.

3. The parasitism establishment

Generally, selective pressure between host and parasite (parasitism relationship) provides chance for coevolution [21, 22]. A constant adaptation occurs in both populations due to an accumulation of the genetic changes that results in the development of new parasitic strategies and new host defenses [21].

Parasites with complex life cycles often behave differently in their intermediate and definitive hosts [1, 23]. *Echinococcus* species presents strongly affected its intermediate hosts (moose or and small mammals, and rodents) due to high virulence but low virulence in the definitive hosts (such as wolf, fox, or dog). The strong effect makes the intermediate hosts to be more severe sick and easily be captured/hunted by the carnivorous animals [9, 18], thus, benefit parasitic life-cycle and increase transmission dynamics.

The relationship between *Echinococcus* species and their intermediate hosts leads to the necessity for the pathogen to have the virulent alleles to infect the organism and for the host to have the resistant alleles to survive parasitism. Variation in the pathogenicity of strains/species of *Echinococcus* is well known to influence the prognosis in patients with echinococcosis [23]. Increasing epidemiological evidence suggests that certain strains of *E. granulosus* (such as those adapted to horses and pigs) may not be commonly infective to humans [1], and the transmission of parasite strain differs (genetically) geographically and host-adaptively [24]. Therefore, estimates of gene flow between populations in different intermediate hosts or geographic areas can have valuable epidemiological applications [1, 11]. In the genomes of cestodes, considerable gene gain and gene loss associated with the adaptation to parasitism has been found in recent genome parasitic programs [21, 22]. Although, the different morphologies of their metacestode stages caused by *E. multilocularis* and *E. granulosus* are clinically often regarded as "distinctly different entities" [25], they are highly similar concerning gene structure and gene content [22]. Salient differences were so far only observed in the *Echinococcus*-specific apomucin gene family [21]. This is presumably associated with one of the few clear morphological differences between two species of *E. multilocularis* and *E. granulosus*, the thickness of the laminated layer, since the apomucin gene family encodes important components of this structure [26].

4. Interaction between *Echinococcal* parasites and their hosts

During echinococcosis infections (including AE and CE), the distinguishing feature of the host-parasite interaction is that chronic infection coexists with detectable humoral and cellular responses against the parasite [27]. It is well known that the *Echinococcus* species can actively interact with host's both innate and acquired immune systems to maintain their survival

with successful evasion from host's immune attacks [28]. The disease spectrum is clearly dependent on the genetic background of the host, as well as on the acquired disturbances of Th1-related immunity [29], such as pregnancy [30], malnutrition [4], severe stress due to work or life [4], coinfection (e.g., HIV) [31, 32], or using immune-suppressing drugs [4, 28]; thus, this kind of circumstances can provide an opportunity to allow the pathogen invading. Human AE appears to be an example of "opportunistic infection", when you make your immunity capability weakness [28, 30]. The genetic constitution of both hosts and pathogens is involved, host genes controlling resistance or susceptibility to infection, genes of the pathogen determining characters such as virulence [23].

In order to establish a successful infection, parasite releases molecules that directly modulate the host immune responses favoring and perpetuating parasite survival in the host [33]. Recent experimental evidence suggests that parasites can not only evade immune responses actively but also exploit the hormonal microenvironment within the host to favor their establishment and growth [34]. Hormonal host parasite cross communication facilitated by the relatively close phylogenetic relationship between *E. multilocularis* and its mammalian hosts, thus appears to be important in the pathology of AE [35]. *E. multilocularis* metacestode metabolic pathway cascades can be activated by host's cell signaling [13, 36], resulting in the larvae development [37]. Conversely, the larval *Echinococcus* can also influence their host immunity response and metabolic signaling mechanisms through the secretion of various molecules [24]. Therefore, immunomodulatory activities of *Echinococcus* and pathological consequences on the host's tissues were attracted by many research concerns for decades [38].

The laminated layer could also play a role similar to that of the placenta at the materno-fetal interface [39]: ensuring parasite growth and infected tissue cell homeostasis while ensuring proper immune tolerance. Tolerance is essential to ensure growth and development of the larval stages of *Echinococcus* species in their hosts [27]. It has been recognized that a series of host-adapted species in the genus *Echinococcus* fits in nicely with observations on host range [1], life cycle, and transmission patterns in areas where echinococcosis is endemic [23]. The ability of hosts to regulate parasites through innate and adaptive immune responses is one of the most important determinants affecting levels of infection, both in the individual and the population [1]. Immunomodulation and, to some extents, immune tolerogenic role have been a great interest of researchers during echinococcosis infection both in human and in animal studies. Many reports have described the worms achieve to switch in the host's response by releasing molecules that share epitopes (and possibly functional activity) with host cytokines [40]. The high relevance for host parasite interaction mechanisms is also found that the presence of evolutionarily conserved signaling systems in *Echinococcus,* such as components of the epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor ß (TGF-ß), and insulin signal transduction cascades [40, 41], though the signaling systems in animals are also known to be primarily influenced by both factors of the genetic heritage and living environments [42].

The host-derived EGF is known to induce the *Echinococcus* mitogen-activated protein kinase (MAPK) cascade, probably through direct interaction with parasite EGF-receptors [13]. Parasitic components, and not only factors from host origin, were actually acting on hepatocyte

metabolic pathways. Recent report indicated that host insulin acts as a stimulant for parasite development within the host liver and that *E. multilocularis* senses the host hormone through an evolutionarily conserved insulin signaling pathway [13, 35].

Although both parasites and hosts benefit from the dynamic balance that grantees parasite-induced damage to hosts at a reasonable level and in turn [42], to some extent, provide parasites nutrients, in some cases of human echinococcosis, spontaneous healing of the disease was observed [20, 27]. Such abortive cases are characterized by calcified parasite lesions suggesting the generation of immune responses which are able to limit parasite growth in humans [27].

5. Disease in animal hosts

A carnivore animal is the definitive host—where the adult worms live in the intestines; and almost any mammal, including humans, can be the intermediate host—where the worms form cysts in various organs for CE but mainly in liver for AE.

5.1. Infection in definitive hosts (mainly implication for dogs)

It is much more difficult to tell when a dog is infected with *Echinococcus* compared to other tapeworms such as *Taenia* or *Dipylidium* [16, 17]. An adult *Echinococcus species* is tiny—only a few millimeters long. Dog infection generally does not show any signs of illness at all even though the hundreds or thousands of tapeworms live in its intestine. Despite the difficult differentiation of the eggs between *Echinococcus* and *Taenia* species under microscopy through fecal examinations [16, 17], the diagnosis of dog infection is an important and useful through dog-copro-DNA assays [16, 17, 43]. So, dog fecal examinations should be performed regularly.

5.2. Infections in intermediate animal hosts

For AE: the primary metacestodes are found in rodent's liver. The germinal membrane of *E. multilocularis* proliferates externally, rather than internally, to form a multilocular structure with many small cysts. These vesicles are usually 1–10 mm in diameter. Hundreds to thousands of protoscolices develop from the germinal membrane in some animal intermediate hosts (small mammals). These multilocular cysts have semisolid matrix and resemble malignant tumors. The center of lesion may be necrotic. The lesion can completely infiltrate an organ, and spread to other organs and tissues nearby. The cysts can also metastasize to distant sites. Although, the tumor-like cysts can kill rodents within a few weeks of infection, this parasite has recently evolved into an experimental model system by use of rodent species to study larval cestode development and associated host-parasite interaction mechanisms.

For CE: the intermediate hosts include a large number of domesticated and wild animals, particularly herbivores. The rate of development varies with the intermediate host and species of parasite, but the cysts usually grow slowly. Their diameter generally increases from less than 1 to 5 cm every year. The parasitic cyst comprises of two walls of an outer laminated membrane and an inner membrane called the germinal layer. All the brood capsules can be

produced from the germinal membrane. If the cyst contains protoscolices, it will be named as fertility cyst. Some cysts are sterile, since protoscolices are not produced or killed by bacterial infection. The percentage of sterile cysts varies with the different intermediate host and its susceptibility to a particular strain/species of parasite. The cysts in livestock also seem to be asymptomatic, probably due to the relatively short lifespan of these animals. Because the cyst grows slowly and the symptoms can only appear until its size can effect on adjacent tissues and organs. Occasionally, symptoms have been reported in sheep [5]. But mostly the infected livestock shows poor growth, weakness, and lameness. Therefore, the economic loss assessment modeling due to livestock infections (mainly in sheep) has attracted some extensive attentions in endemic regions and countries worldwide.

6. Disease in humans

Epidemiological studies have demonstrated that the majority of human individuals exposed to infection with *Echinococcus* spp. eggs exhibit resistance to disease as shown by either seroconversion to parasite specific antigens or the presence of "dying out" or "aborted metacestodes" [4]. Seroconversion proving infection, but lack of any lesion indicating the failure of the parasite to establish and further develop within human tissues (mainly in liver) or resistance as shown by the presence of fully calcified lesion [44]; while the developing parasite can be partially controlled by host immunity in those susceptibility individuals where infection leads to disease, as found in the AE and CE patients who experience clinical signs and symptoms approximately 5–15 years after infection [20, 30].

If untreated or uncontrolled, the hyper proliferation of the metacestode due to an impaired immune response could be resulted by immune modulation of host immunity toward energy that can be triggered by parasite metabolites [38], and/or be resulted by additional clinical conditions, such as AIDS or any other reason to induce the immune deficiencies [20, 27, 30]. The disease often starts without symptoms, and this may last for years. The symptoms and signs can occur depend on the lesion location and size for CE. While, AE usually begins in the liver but can spread to other parts of the body.

Cystic echinococcosis (CE) can cause very severe symptoms, if the cyst bursts (e.g., from sudden trauma) or even fatal. The released protoscolices can spread the parasite to other parts of the body to form many new cysts [20].

Alveolar echinococcoccis (AE) ranges in size from a sesame seed to a large melon [45]. Although, the mass lesions grow slowly, the tumor-like growth manner tends to invade neighbor organs or tissues, making treatment very difficult [30].

Fibrosis is an important component of the pathophysiology of each disease caused by *Echinococcus* species. However, this role differs markedly in CE and AE. In CE, the rapidly established periparasitic fibrosis surrounding the laminated layer contributes to the unicystic feature of the disease and to limit cyst growth [46]. In AE, the slow fibrogenesis in an extensive and partially unsuccessful periparasitic granuloma does not prevent germinal layer budding.

In the long term, it eventually leads to a dense and irreversible fibrosis, responsible for the main complications of the diseases, such as bile duct, vessel obstruction, and secondary biliary cirrhosis [47–49].

7. Human disease diagnosis

Echinococcal lesions may grow for years, depending on their location, without causing any signs of illness in people [4]. The signs of illness do occur in late stages of diseases, such as abdominal pain and jaundice due to obstruction of bile ducts (in liver), chest pain and difficulty in breathing (in lungs) [4], neurological signs, and seizures (in brain) [30]. Cysts/lesions are sometimes found occasionally when tests are performed for other reasons [4]. Generally, the clinical symptoms and image presentations, e.g., radiographs, ultrasound, CT, or MRI, need to combine the evidences from a blood test for antibodies to the parasite or biopsy for histopathological examination or PCR assay to confirm the diagnosis [4]. Screening individuals living in high-risk areas by ultrasound and serological investigation [44] can catch the infection early and can make treatment much easier and more effective [44].

Therefore, diagnosis requires a combination of tools that involve imaging, histopathology, or nucleic acid detection, and serology. The ultrasound though computer tomography (CT) or magnetic resonance imaging (MRI) may be used commonly. Serology methods for antibodies against the parasite detection can be some certain supplemental tool for imaging/clinical diagnosis. The histopathology or nucleic acid using biopsy after invading methods could provide the final confirmation [4, 20].

8. Management of echinococcosis in human

The growth of larva of *Echinococcus* spp. and the proliferation of the larva are similar to a slow-growing tumor. If the lesion occurs in liver, it can damage liver function. Sometimes, it is difficult to differentiate it from liver cancer because of invasion to biliary and vascular tissue of the liver [50]. Early diagnosis and radical surgery provide the best chance for treatment and cure. Although, treatment of AE is less effective than treatment of CE, the general approach for both types of echinococcosis treatment remains to be surgery with the purpose of complete resection of infected parts of involved organs [4]. Antiparasitic drugs cannot kill cysts if the lesions have already established. However, if untreated, patient survival time is very limited. Therefore, early detection and treatment are important ways to improve patients' survival [4, 20].

Although treatment of cystic echinococcosis by surgery to remove the hydatid cyst was always a risk that the cyst would burst during the procedure, resulting in a very severe, even fatal reaction in the patient to the spilled fluid, drug therapy alone is usually not enough to eliminate cysts, but it can help reduce lesion size and operation risks. More recently, treatment with antiparasitic drugs and drainage of the fluid from the cyst using a needle has been used to treat the disease in certain cases without surgery. Briefly, with proper care, 96–98% of CE patients survive [20].

9. *Echinococcus* species infective risk to humans

The risk of infection with *E. granulosus* or *E. multilocularis* to humans from most pets is very low, but it is higher risks for those residents living in endemic areas. Their work or recreational activities involve direct contact with contaminated water, soil, and their dogs for a long time or life time [10]. Those dogs may allow to roam, hunt, and eat raw tissues from potentially infected animals (e.g., rodents, rabbits, sheep, moose) [8].

The risks for the susceptible of infection with *Echinococcus* spp. can occur in those peoples with immune-compromised conditions (e.g., HIV/AIDS patients, transplant recipients, cancer patients) or with other complications because their immune systems cannot fight infections efficiently [20]. Mostly, ingestion of *Echinococcal* eggs occurred in early ages, if they have chance to contact with contaminated environments, but the disease may appear until they are adults [44].

10. Prevention and control program

Dogs if allowed to enter *Echinococcus*-free areas from potential endemic areas need to be treated with anthelmintic agents (e.g., Praziquantel). Routine inspection of the potential parasitic intermediate host animals before permitting for importing could also prevent the parasite into a country [15].

In endemic areas, dogs should not be allowed to eat the carcasses, particularly the viscera of potential intermediate hosts. Dogs should also be kept from hunting wild rodents and small mammals [6]. Regular examination and treatment of dogs [8] can decrease echinococcosis in domesticated livestock [14].

Prevention of *Echinococcus* species spreading is by treating dogs that may carry the disease and vaccination of sheep. Health education programs focused on echinococcosis and its agents, and improvement of the water sanitation attempt to target poor economic living condition and poor drinking water sources. Educational material should include information about proper disposal of sheep viscera in abattoirs and proximity to dogs and sources of transmission [15].

11. Parasitism perspective applications

11.1. Treatment parasitic infections

In the absence of fully effective antiparasitic chemotherapy for AE and CE, modulation of the host's immune response could be envisaged to fight against the parasite and to prevent the disease and/or its complications such as using IFN-a2a immunological treatment [28] and some parasitic antigens as potential vaccination to prevent disease occurrence such as

using Em14-3-3, Em 95, EMY162, and EmTetraspanin [24]. Additionally, current picture on *Echinococcus* signaling systems will be given and the potential to exploit these pathways as targets for antiparasitic chemotherapy [51].

11.2. Using parasite productions for cancer treatment

The presence of Tn antigen in larval and adult tissues of *E. granulosus* was reported [52], this finding is interested in cancer-associated mucin-type because this parasite produced peptides can act on the nonspecific natural killer cell to express cytokines that are effective agents against tumor growth; therefore, the family of Tn antigens might be useful targets for antitumor immunotherapy [41, 53, 54]. These evidences may contribute to the design of tumor vaccines and open new horizons in the use of parasite-derived molecules that can fight against cancer [55, 56].

Cancer vaccination is an important and promising approach in cancer immunotherapy. Obstacles for clinical success may include immune tolerance to TAAs [57], the weak antigenic nature of TAAs, and active immune evasion mechanisms employed by progressing tumors [58]. Vaccination with TAAs coming from evolutionary distant organisms (such as *E. granulosus*) should be useful to override tolerance problems encountered with human TAA-based cancer therapeutic approaches [58].

11.3. Echinococcosis diagnosis

Additionally, the high level of the O-glycosylated Tn antigens generated from larvae of *E. granulosus* are found in the sera of the patients with cystic echinococcosis (CE), providing a pathway that a series of Tn antigens might be sort as a biomarker for this parasitic disease diagnosis, but the hypothesis needs more work to verify the clinical values regarding those antigens [59].

12. Conclusions

Overall, genus *Echinococcus* can be thought an example of successful adaptation to their hosts extensively. Taken advance of recent research outcomes, the parasite immunotherapy for human echinococcosis has been discussed widely by scientific literatures, but importantly, the advanced outcomes may also be interested in terms of using parasites' productions for treatment of other diseases, including cancer.

Acknowledgments

We acknowledge financial support by the National Health and Medical Research Council (NHMRC) of Australia of a NHMRC Project Grant (APP1009539). National Science Foundation of China (NSFC) of the NSFC Project Grants (30960339 and 81460311).

Author details

Shukun Yang[1], Yumin Zhao[2], Don Peter McManus[3] and YuRong Yang[4]*

*Address all correspondence to: yangyurong@hotmail.com

1 Image Diagnosis Department, The First Peoples' Hospital of Yinchuan City, Ningxia Hui Autonomous Region (NHAR), P.R. China

2 Human Pathological Department of Guiling Medical College, Guilin City, Guangxi Province, P.R. China

3 Molecular Parasitology Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Australia

4 Human Pathology & Immunology Department, Ningxia Medical University, Yinchuan City, Ningxia Hui Autonomous Region (NHAR), P.R. China

References

[1] McManus DP, Thompson RC. Molecular epidemiology of cystic echinococcosis. Parasitology. 2003;**127**(Suppl):S37-S51

[2] Xiao N, Qiu J, Nakao M, Li T, Yang W, Chen X, Schantz PM, Craig PS, Ito A. *Echinococcus shiquicus* n. sp., a taeniid cestode from Tibetan fox and plateau pika in China. International Journal for Parasitology. 2005;**35**:693-701. DOI: 10.1016/j.ijpara.2005.01.003

[3] Hüttner M, Nakao M, Wassermann T, Siefert L, Boomker JD, Dinkel A, Sako Y, Mackenstedt U, Romig T, Ito A. Genetic characterization and phylogenetic position of *Echinococcus felidis* (Cestoda: Taeniidae) from the African lion. International Journal for Parasitology. 2008;**38**:861-868. DOI: 10.1016/j.ijpara.2007.10.013

[4] McManus DP, Gray DJ, Zhang W, Yang Y. Diagnosis, treatment, and management of echinococcosis. British Medical Journal. 2012;**344**:e3866. DOI: 10.1136/bmj.e3866

[5] Carmena D, Cardona GA. Echinococcosis in wild carnivorous species: Epidemiology, genotypic diversity, and implications for veterinary public health. Veterinary Parasitology. 2014;**202**:69-94. DOI: 10.1016/j.vetpar.2014.03.009

[6] Craig PS, McManus DP, Lightowlers MW, Chabalgoity JA, Garcia HH, Gavidia CM, Gilman RH, Gonzalez AE, Lorca M, Naquira C, Nieto A, Schantz PM. Prevention and control of cystic echinococcosis. Lancet Infectious Diseases. 2007;**7**:385-394. DOI: 10.1016/S1473-3099(07)70134-2

[7] Carmena D, Sánchez-Serrano LP, Barbero-Martínez I. *Echinococcus granulosus* infection in Spain. Zoonoses and Public Health. 2008;**55**:156-165. DOI: 10.1111/j.1863-2378.2007.01100.x

[8] Craig PS, Li T, Qiu J, Zhen R, Wang Q, Giraudoux P, Ito A, Heath D, Warnock B, Schantz P, Yang W. Echinococcosis and Tibetan communities. Emerging Infectious Diseases. 2008;**14**:1674-1675. DOI: 10.3201/eid1410.071636

[9] Pleydell DR, Yang YR, Danson FM, Raoul F, Craig PS, McManus DP, Vuitton DA, Wang Q, Giraudoux P. Landscape composition and spatial prediction of alveolar echinococcosis in southern Ningxia, China. PLoS Neglected Tropical Diseases. 2008;**2**:e287. DOI: 10.1371/journal.pntd.0000287

[10] Yang YR, Craig PS, Sun T, Vuitton DA, Giraudoux P, Jones MK, Williams GM, McManus DP. Echinococcosis in Ningxia Hui Autonomous Region, northwest China. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2008;**102**:319-328. DOI: 10.1016/j.trstmh.2008.01.007

[11] Yang YR, Rosenzvit MC, Zhang LH, Zhang JZ, McManus DP. Molecular study of Echinococcus in west-central China. Parasitology. 2005;**131**:547-555. DOI: 10.1017/S0031182005007973

[12] Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clinical Microbiology Reviews. 2004;**17**:107-135. DOI: 10.1128/CMR.17.1.107-135.2004

[13] Spiliotis M, Konrad C, Gelmedin V, Tappe D, Brückner S, Mösch HU, Brehm K. Characterisation of EmMPK1, an ERK-like MAP kinase from *Echinococcus multilocularis* which is activated in response to human epidermal growth factor. International Journal for Parasitology. 2006;**36**:1097-1112. DOI: 10.1016/j.ijpara.2006.05.008

[14] Cleary E, Barnes TS, Xu Y, Zhao H, Clements AC, Gray DJ, McManus DP, Atkinson JA, Williams GM, Yang Y. Impact of "Grain to Green" Programme on echinococcosis infection in Ningxia Hui Autonomous Region of China. Veterinary Parasitology. 2014;**205**:523-531. DOI: 10.1016/j.vetpar.2014.08.023

[15] Yang YR, McManus DP, Huang Y, Heath DD. Echinococcus granulosus infection and options for control of cystic echinococcosis in Tibetan communities of Western Sichuan Province, China. PLoS Neglected Tropical Diseases. 2009;**3**:e426. DOI: 10.1371/journal.pntd.0000426

[16] Ni XW, McManus DP, Lou ZZ, Yang JF, Yan HB, Li L, Li HM, Liu QY, Li CH, Shi WG, Fan YL, Liu X, Cai JZ, Lei MT, Fu BQ, Yang YR, Jia WZ. A comparison of loop-mediated isothermal amplification (LAMP) with other surveillance tools for *Echinococcus granulosus* diagnosis in canine definitive hosts. PloS One. 2014;**9**:e100877. DOI: 10.1371/journal.pone.0100877

[17] Ni XW, McManus DP, Yan HB, Yang JF, Lou ZZ, Li HM, Li L, Lei MT, Cai JZ, Fan YL, Li CH, Liu QY, Shi WG, Liu X, Zheng YD, Fu BQ, Yang YR, Jia WZ. Loop-mediated isothermal amplification (LAMP) assay for the identification of *Echinococcus multilocularis* infections in canine definitive hosts. Parasites & Vectors. 2014;**7**:254. DOI: 10.1186/1756-3305-7-254

[18] Yang YR, Liu TX, Bai XL, Boufana B, Craig PS, Nakao M, Ito A, Zhang JZ, Giraudoux P, McManus DP. Natural infection of the ground squirrel (*Spermophilus* spp.) with *Echinococcus granulosus* in China. PLoS Neglected Tropical Diseases. 2009;**3**:e518. DOI: 10.1371/journal.pntd.0000518

[19] Kenny JV, MacCabe RJ. Sero-epidemiology of hydatid disease in the non-intervention area of north-east Turkana. Annals of Tropical Medicine and Parasitology. 1993;**87**: 451-457

[20] Brunetti E, Kern P, Vuitton DA; Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Tropica. 2010;**114**:1-16. DOI: 10.1016/j.actatropica.2009.11.001

[21] Tsai IJ, Zarowiecki M, Holroyd N, Garciarrubio A, Sanchez-Flores A, Brooks KL, Tracey A, Bobes RJ, Fragoso G, Sciutto E, Aslett M, Beasley H, Bennett HM, Cai XP, Camicia F, Clark R, Cucher M, De Silva N, Day TA, Deplazes P, Estrada K, Fernández C, Holland PW, Hou JL, Hu SN, Huckvale T, Hung SS, Kamenetzky L, Keane JA, Kiss F, Koziol U, Lambert O, Liu K, Luo XN, Luo YF, Macchiaroli N, Nichol S, Paps J, Parkinson J, Pouchkina-Stantcheva N, Riddiford N, Rosenzvit M, Salinas G, Wasmuth JD, Zamanian M, Zheng YD; Taenia solium Genome Consortium, Cai JP, Soberón X, Olson PD, Laclette JP, Brehm K, Berriman M. The genomes of four tapeworm species reveal adaptations to parasitism. Nature. 2013;**496**:57-63. DOI: 10.1038/nature12031

[22] Zheng H, Zhang W, Zhang L, Zhang Z, Li J, Lu G, Zhu Y, Wang Y, Huang Y, Liu J, Kang H, Chen J, Wang L, Chen A, Yu S, Gao Z, Jin L, Gu W, Wang Z, Zhao L, Shi B, Wen H, Lin R, Jones MK, Brejova B, Vinar T, Zhao G, McManus DP, Chen Z, Zhou Y, Wang S. The genome of the hydatid tapeworm *Echinococcus granulosus.* Nature Genetics. 2013;**45**:1168-1175. DOI: 10.1038/ng.2757

[23] Thompson, RC and Lymbery AJ, Genetic variability in parasites and host-parasite interactions. Parasitology. 1996;**112**(Suppl):S7-S22

[24] Zhang S, Hüe S, Sène D, Penfornis A, Bresson-Hadni S, Kantelip B, Caillat-Zucman S, Vuitton DA. Expression of major histocompatibility complex class I chain-related molecule A, NKG2D, and transforming growth factor-beta in the liver of humans with alveolar echinococcosis: New actors in the tolerance to parasites? Journal of Infectious Diseases. 2008;**197**:1341-1349. DOI: 10.1086/586709

[25] Stojkovic, M and Junghanss T. Cystic and alveolar echinococcosis. Handbook of Clinical Neurology, 2013;**114**:327-334. DOI: 10.1016/B978-0-444-53490-3.00026-1

[26] Díaz A, Casaravilla C, Allen JE, Sim RB, Ferreira AM. Understanding the laminated layer of larval Echinococcus II: Immunology. Trends in Parasitology. 2011;**27**:264-273. DOI: 10.1016/j.pt.2011.01.008

[27] Vuitton DA, Zhang SL, Yang Y, Godot V, Beurton I, Mantion G, Bresson-Hadni S. Survival strategy of *Echinococcus multilocularis* in the human host. Parasitology International. 2006;**55**(Suppl):S51-S55. DOI: 10.1016/j.parint.2005.11.007

[28] Vuitton, DA and Gottstein B. *Echinococcus multilocularis* and its intermediate host: A model of parasite-host interplay. Journal of Biomedicine & Biotechnology. 2010;**2010**: 923193. DOI: 10.1155/2010/923193

[29] Brehm K *Echinococcus multilocularis* as an experimental model in stem cell research and molecular host-parasite interaction. Parasitology. 2010;**137**:537-555. DOI: 10.1017/S0031182009991727

[30] Yang YR, Vuitton DA, Jones MK, Craig PS, McManus DP. Brain metastasis of alveolar echinococcosis in a hyperendemic focus of *Echinococcus multilocularis* infection. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2005;**99**:937-941. DOI: 10.1016/j.trstmh.2005.04.020

[31] Sailer M, Soelder B, Allerberger F, Zaknun D, Feichtinger H, Gottstein B. *Alveolar echinococcosis* of the liver in a six-year-old girl with acquired immunodeficiency syndrome. Journal of Pediatrics. 1997;**130**:320-323

[32] Ran B, Shao Y, Guo Y, Yimiti Y, Aji T, Jia J, Shayiding P, Jiang T, Cheng L, Li J, McManus DP, Zhang W, Wen H. Surgical treatment of hepatic cystic echinococcosis in patients co-infected with HIV/AIDS. Journal of Helminthology. 2016;**90**:125-128. DOI: 10.1017/S0022149X15000188

[33] Coakley G, Buck AH, Maizels RM. Host parasite communications-messages from helminths for the immune system: Parasite communication and cell-cell interactions. Molecular and Biochemical Parasitology. 2016;**208**:33-40. DOI: 10.1016/j.molbiopara.2016.06.003

[34] Escobedo G, Roberts CW, Carrero JC, Morales-Montor J. Parasite regulation by host hormones: An old mechanism of host exploitation? Trends in Parasitology. 2005;**21**:588-593. DOI: 10.1016/j.pt.2005.09.013

[35] Hemer S, Konrad C, Spiliotis M, Koziol U, Schaack D, Förster S, Gelmedin V, Stadelmann B, Dandekar T, Hemphill A, Brehm K. Host insulin stimulates *Echinococcus multilocularis* insulin signalling pathways and larval development. BMC Biology. 2014;**12**:5. DOI: 10.1186/1741-7007-12-5

[36] Gelmedin V, Caballero-Gamiz R, Brehm K. Characterization and inhibition of a p38-like mitogen-activated protein kinase (MAPK) from *Echinococcus multilocularis*: Antiparasitic activities of p38 MAPK inhibitors. Biochemical Pharmacology. 2008;**76**:1068-1081. DOI: 10.1016/j.bcp.2008.08.020

[37] Brehm K, Spiliotis M, Zavala-Góngora R, Konrad C, Frosch M. The molecular mechanisms of larval cestode development: First steps into an unknown world. Parasitology International. 2006;**55**(Suppl):S15-S21. DOI: 10.1016/j.parint.2005.11.003

[38] Wang J, Zhang C, Wei X, Blagosklonov O, Lv G, Lu X, Mantion G, Vuitton DA, Wen H, Lin R. TGF-beta and TGF-beta/Smad signaling in the interactions between *Echinococcus multilocularis* and its hosts. PloS One. 2013;**8**:e55379. DOI: 10.1371/journal.pone.0055379

[39] Szekeres-Bartho, J. Immunological relationship between the mother and the fetus. International Reviews of Immunology. 2002;**21**(6):471-495

[40] Brehm K, Spiliotis M. The influence of host hormones and cytokines on *Echinococcus multilocularis* signalling and development. Parasite. 2008;**15**:286-290. DOI: 10.1051/parasite/2008153286

[41] Koziol U and Brehm K. Recent advances in Echinococcus genomics and stem cell research. Veterinary Parasitology. 2015;**213**(3-4):92-102. DOI: 10.1016/j.vetpar.2015.07.031

[42] Wang X, Ding J, Guo X, Zheng Y. Current understandings of molecular biology of *Echinococcus multilocularis*, a pathogen for alveolar echinococcosis in humans – A narrative review article. Iranian Journal of Parasitology. 2015;**10**:329-337.

[43] Liu CN, Lou ZZ, Li L, Yan HB, Blair D, Lei MT, Cai JZ, Fan YL, Li JQ, Fu BQ, Yang YR, McManus DP, Jia WZ. Discrimination between *E. granulosus* sensu stricto, *E. multilocularis* and *E. shiquicus* using a Multiplex PCR Assay. PLoS Neglected Tropical Diseases. 2015;**9**:e0004084. DOI: 10.1371/journal.pntd.0004084

[44] Yang YR, Craig PS, Vuitton DA, Williams GM, Sun T, Liu TX, Boufana B, Giraudoux P, Teng J, Li Y, Huang L, Zhang W, Jones MK, McManus DP. Serological prevalence of echinococcosis and risk factors for infection among children in rural communities of southern Ningxia, China. Tropical Medicine & International Health. 2008;**13**:1086-1094. DOI: 10.1111/j.1365-3156.2008.02101.x

[45] Vuitton DA, Benzimidazoles for the treatment of cystic and alveolar echinococcosis: What is the consensus? Expert Review of Anti-Infective Therapy. 2009;**7**(2):145-149. DOI: 10.1586/14787210.7.2.145

[46] Godot V, Harraga S, Deschaseaux M, Bresson-Hadni S, Gottstein B, Emilie D, Vuitton DA. Increased basal production of interleukin-10 by peripheral blood mononuclear cells in human alveolar echinococcosis. European Cytokine Network. 1997;**8**:401-408

[47] Godot V, Harraga S, Beurton I, Deschaseaux M, Sarciron E, Gottstein B, Vuitton DA. Resistance/susceptibility to *Echinococcus multilocularis* infection and cytokine profile in humans. I. Comparison of patients with progressive and abortive lesions. Clinical and Experimental Immunology. 2000;**121**:484-490. DOI: 10.1046/j.1365-2249.2000.01308.x

[48] Reuter S, Buck A, Manfras B, Kratzer W, Seitz HM, Darge K, Reske SN, Kern P. Structured treatment interruption in patients with alveolar echinococcosis. Hepatology. 2004;**39**:509-517. DOI: 10.1002/hep.20078

[49] Konrad C, Kroner A, Spiliotis M, Zavala-Góngora R, Brehm K. Identification and molecular characterisation of a gene encoding a member of the insulin receptor family in *Echinococcus multilocularis.* International Journal for Parasitology. 2003;**33**:301-312

[50] Garcea G, Rajesh A, Dennison AR. Surgical management of cystic lesions in the liver. ANZ Journal of Surgery. 2013;**83**(7-8):E3-E20. DOI: 10.1111/j.1445-2197.2012.06096.x

[51] Brehm K. The role of evolutionarily conserved signalling systems in *Echinococcus multilocularis* development and host-parasite interaction. Medical Microbiology and Immunology. 2010;**199**(3):247-259. DOI: 10.1007/s00430-010-0154-1

[52] Esendagli G, Abbasoglu O. Immune system in cancer and hydatid disease: Cross-reactivity vs. immune modulation. Parasite Immunology. 2015;**37**(8):427-428.DOI: 10.1111/pim.12200

[53] Turhan N, Esendagli G, Ozkayar O, Tunali G, Sokmensuer C, Abbasoglu O. Co-existence of *Echinococcus granulosus* infection and cancer metastasis in the liver correlates with reduced Th1 immune responses. Parasite Immunology. 2015;**37**:16-22. DOI: 10.1111/pim.12152

[54] Yousofi Darani H, Yousefi M, Safari M, Jafari R. Parasites and immunotherapy: With or against? Journal of Parasitic Diseases. 2016;**40**:217-226. DOI: 10.1007/s12639-014-0533-4

[55] Gundogdu SB, Saylam B, Tez M. Cyst hydatid and cancer: The myth continues. Clinical Chemistry and Laboratory Medicine. Published in Association with the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), 2016. DOI: https://doi.org/10.1515/cclm-2016-0626.

[56] Daneshpour S, Bahadoran M, Hejazi SH, Eskandarian AA, Mahmoudzadeh M, Darani HY. Common antigens between hydatid cyst and cancers. Advanced Biomedical Research. 2016;**5**:9. DOI: 10.4103/2277-9175.175242

[57] Berriel E, Russo S, Monin L, Festari MF, Berois N, Fernández G, Freire T, Osinaga E. Antitumor activity of human hydatid cyst fluid in a murine model of colon cancer. Scientific World Journal. 2013;**2013**:230176. DOI: 10.1155/2013/230176

[58] Noya V, Bay S, Festari MF, García EP, Rodriguez E, Chiale C, Ganneau C, Baleux F, Astrada S, Bollati-Fogolín M, Osinaga E, Freire T. Mucin-like peptides from *Echinococcus granulosus* induce antitumor activity. International Journal of Oncology. 2013;**43**:775-784. DOI: 10.3892/ijo.2013.2000

[59] Alvarez Errico D, Medeiros A, Míguez M, Casaravilla C, Malgor R, Carmona C, Nieto A, Osinaga E. O-glycosylation in Echinococcus granulosus: Identification and characterization of the carcinoma-associated Tn antigen. Experimental Parasitology. 2001;**98**:100-109. DOI: 10.1006/expr.2001.4620

IntechOpen