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Current status and future prospective of vaccine development against *Echinococcus granulosus*

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ABSTRACT

Cystic echinococcosis (CE) is one of the most important zoonotic parasite diseases in human, livestock, and wildlife worldwide. Development of effective vaccines against CE appears to be the most promising strategy to control this infectious disease. Use of potential livestock and canine vaccines against the larval and adult stage of *E. granulosus* life cycle may be the key to the production of powerful vaccines. Some progress has been accomplished in the development of vaccines against hydatidosis using empirical approaches, while such immunotherapies often fail to induce adequate immune responses. Therefore, it is of great interest to identify antigens (Ags) with high immunogenicity and develop effective vaccines and adjuvant constructs against CE. To this end, various tools can be applied, including immune-based genomics and proteomics, immunoinformatics, systems vaccinology and mathematical/computational modeling. In this review, we aimed to provide comprehensive insights upon the current status of vaccination trials against *E. granulosus,* and also articulate some perspectives on the production of novel anti-CE vaccines. Use of novel prospective technologies is also discussed to highlight the importance of development and advancement of the next generation vaccines against *E. granulosus.*

1. Introduction

The hydatid disease (HD) or echinococcosis (the so-called hydatidosis and echinococcal disease) is one of the most important zoonotic parasitic diseases in the human worldwide. *Echinococcus*-mediated infection is mainly caused by the cystic and alveolar echinococcosis. It represents a considerable burden on the public health. According to the World Health Organization (WHO) report, the cost for controlling HD is over 3 billion US$ annually, while the number of infected cases is substantially growing worldwide every year [1].

A number of studies have been conducted to control the life cycle of the parasite (i.e., from dogs to human or to livestock) [2], in large part by use of the anthelmintic drugs and promotion of slaughter hygiene and health education. However, pharmacotherapy of the disease may be associated with some inevitable side effects. For example, some of these drugs may remain in the meat or milk of livestock, resulting in inadvertent health problems. Further, the repeated low doses and long-term use of same antiparasitic drugs may lead to an inadvertent drug resistance. In comparison with pharmacotherapies, advanced vaccines may provide much more effective therapies against this infection. Nevertheless, unlike other types of infection, few immunotherapy approaches have been carried out against this infectious disease [3]. By far, a number of vaccine candidate antigens (VCAs) have been used for the immunization against *E. granulosus*, while there are some inconsistencies in terms of their clinical outcomes. Thus, greater emphasis should be given to the development of multifunctional vaccines against *E. granulosus* serotype and genotypes.

In this study, we will discuss the key VCAs regarding their biochemical and immunological properties and potentials for vaccine construction against *E. granulosus*. We also provide some insights on the new generation of vaccines and design strategies that are established through computational modeling approaches.

2. *E. granulosus* life cycle and transmission

The human HD is caused by *E. granulosus,* whose life cycle depends

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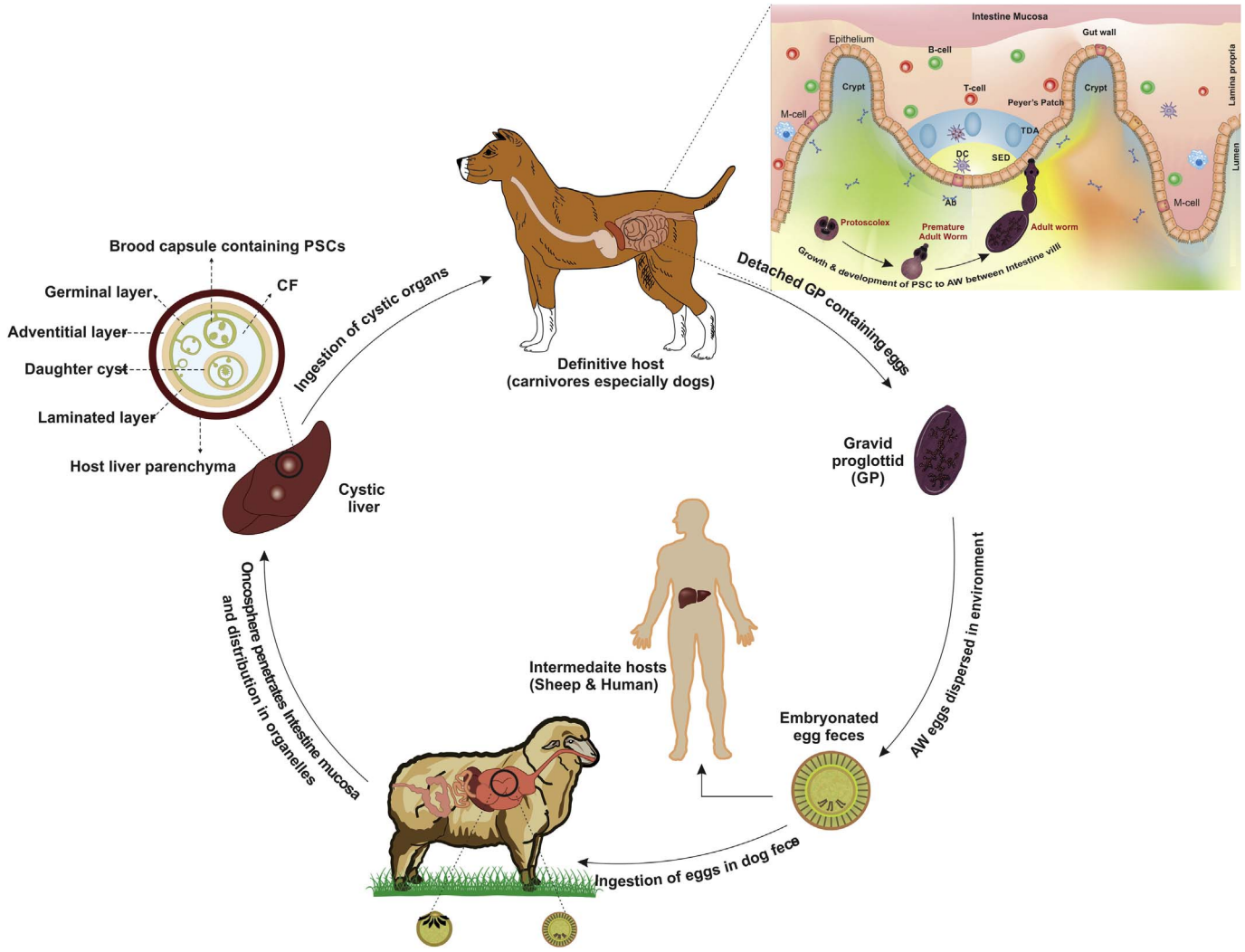

Fig. 1. Schematic representation of the life cycle and different developmental stages of *E. granulosus*. The definitive host (dog) produces GP that can become AW and infect the intermediate hosts (sheep and human). CF: Cyst fluid; GP: Gravid proglottid; PSC: Protoscolex; AW: Adult worm; SED: Subepithelial dome; TDA: Thymus-dependent area; DC: Dendritic cell; Ab: Antibody. Note: Not drawn to scale.

on interplay between predator and prey (Fig. 1).

The definitive hosts include canids and hyenids. The parasite lives in different parts of the carnivores small intestine and its herbivore prey can also be as the intermediate hosts. Likewise, these hosts, including human, may accidentally ingest infective eggs, which might result in the development of the parasite's metacestode stage and progression of HD [4]. Dogs are infected via feeding the cysts from livestock viscera while dogs' feces contain the parasite eggs. Morphogenesis of protoscolex (PSC) from the cystic viscera into scolex occurs in the small intestine and then this head-like structure attaches to the intestinal mucosa, and develop into the adult stage. Defecates of an infected dog contaminates the environment by the *E. granulosus* eggs, by which human cases are directly infected by the diseased dogs or indirectly contaminated by the ingestion of vegetables, fruits or water [5]. Once ingested by an intermediate host, their oncospheres are hatched and released in the small intestine, penetrate into the intestinal crypts and then disseminated to different organs by blood circulation. If resisting the immune system, the oncosphere loses its hooklets, undergoes central vesiculation and grows towards developing cyst and infection spread to the liver (~60–70%) and other organs like lungs.

3. Control strategies: definitive and/or intermediate hosts?

Development of the prophylactic treatments (e.g., vaccine) seems to be one of the most effective strategies in tackling this infection. The crucial prerequisite step appears to be the exploration of different VCAs against *E. granulosus* to find the most suitable VCAs for development of much more effective immunotherapies. Due to some cross-reactivity issues, the gene-based vaccines can be more effective than the crude traditional Ags [6]. As detailed in Table 3, VCAs are expressed and localized at the different developmental stage of the parasite. Therefore, the target host should be specified as the main factor in designing vaccines [7].

E. granulosus is one of those organisms that can infect more than one species of hosts via the cross-species transmission. Therefore, an ideal vaccine should be able to prevent the evolution of oncosphere to hydatid cysts (HC) in sheep and human, and thus stop the development of adult gravid tapeworms in the dog. At the first glance, the selection of vaccination strategy seems to be a dilemma. Nonetheless, it should be noted that dogs are the main host for the prevalence of HD, and hence their vaccination may provide better clinical outcomes. Because of the lower population of dogs and that the gravid proglottid (GP) of canids intestinal worms produce thousands of eggs daily [8], in fact, vaccination of dogs might be much more plausible and economical [9]. Apart from the problems of experiments on dogs such as maintaining experimental canids, a canine vaccine could be an efficacious approach for terminating the life cycle of *E. granulosus*. On the other hand, the population of homeless stray dogs is not controlled in many countries