Targeting the Laminated Layer of *Echinococcus multilocularis* as a Potential Therapeutic Strategy

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Alveolar echinococcosis (AE) caused by *Echinococcus multilocularis* is among the most lethal helminthic diseases, but current therapeutic strategies are suboptimal due to poor parasitocidal efficacy and toxicity [1, 2]. Upon accidental ingestion of parasite eggs originating from feces of carnivore hosts (e.g., fox and dogs), eggs hatch and subsequently larval oncospheres penetrate the intestinal lining. Following migration primarily to the liver, they develop into vesiculated cysts, which are thick-wall protected and continuously proliferate by external budding. Larvae can secondarily also develop in extrahepatic tissues (such as lungs and brain), resulting in a complicated course of disease, particularly in immunocompromised individuals [3], or patients remaining untreated. The *E. multilocularis* vesicles/microcysts are protected from physiological and immunological host responses by a carbohydrate-rich laminated layer (LL), mainly composed of evolutionary conserved core-1 and 2 mucin-type O-glycans, and an elongated core 2 structure with a terminal α -linked galactose (α -Gal) cap [4, 5].

In this issue of *Pharmacology*, Wang et al. [6] demonstrate that enzymatic digestion of the LL of *E. multilocularis* may offer a novel therapeutic approach. Treatment of cultured *E. multilocularis* metacystodes (clone H95)

with either α 1-3,4,6 or β 1-3 galactosidases both resulted in the collapse of vesicles starting after 1 day and the destruction of intravesicular structures 5 days posttreatment. Intraperitoneal injection of untreated parasite vesicles in mice resulted, as expected, in multivesiculated tumor-like structures. By contrast only small calcified lesions and significantly reduced parasite weight was observed upon pre-treatment of the vesicles with either α - or β -galactosidase, which indicates the importance of the LL for parasite survival. Although treatment by both enzymes resulted in an “abortive” course of infection, differences in the subsequent immune response were observed, including lower numbers of intrahepatic IL-10⁺ CD4⁺ T cells upon treatment with β -galactosidase.

The mechanistic roles of glycans within the LL in parasite survival are uncertain. In humans, α -Gal structures, which are frequently found in pathogens, induce anti- α -Gal antibodies and are common in the serum of healthy individuals [7]. Whether the remarkable reduction of anti- α -Gal antibodies in immunodeficient patients [8], or in some healthy individuals [9], may influence the incidence or course of AE remains to be studied. While β -galactosidase treatment, as used in the experiments by Wang et al. [6], might digest the core structures of the *E.*

multilocularis LL, the removal of the α -Gal cap appeared to be similarly effective, yet resulted in an altered immune response. While the destruction of the LL may help to overcome a major barrier of resistance, future studies will be required to investigate the subsequent host-pathogen responses and interactions, which may necessitate additional and personalized therapeutic approaches [3, 10], in light of the importance of the hosts' genotype in AE susceptibility and resistance [2, 11].

Conflict of Interest Statement

The author declares no conflicts of interest.

Funding Sources

The authors did not receive any funding.

Author Contributions

S.V.G. and R.D.G. wrote the manuscript.

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