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RESEARCH ARTICLE

Structural Mechanisms of Protection of Parasitic Larvae from the Host's Immune Factors in the *Triaenophorus nodulosus* (Cestoda)–Perch System

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Abstract—A structural aspect of the parasite–host interactions in the *Triaenophorus nodulosus*– European perch system was studied; a number of structural mechanisms involved in the parasite's protective reaction against the host's immune response were identified. Plerocercoids are localized in the liver of the intermediate fish host. In response to invasion, a parasitic granuloma is formed from the host tissues forming a closed capsule around the parasite. It was demonstrated that the capsule wall is multilayered and consists of several cell types. The outer layer (fibrous) is represented by fibroblasts and connective tissue fibers. The inner layer is formed by several rows of flattened epithelioid cells tightly adjacent to each other and connected by desmosomes. Individual macrophages exhibiting a phagocytic activity were found on the inner surface of the capsule wall. Structural diversity of the cellular elements of the granuloma wall depends on time elapsed since infection and physiological state of the host. Phagocytosis of apical parts of microtriches and tumuli by granuloma macrophages was described for the first time. Crystal-like structures of unknown origin were also found for the first time in the capsule cavity. The plerocercoid is located freely in the capsule cavity and has formed hooks that (unlike the intestinal stage) are covered with the tegument cytoplasm. The tegument secretes a thick layer of filamentous matrix, extracellular vesicles, and vacuolized microtriches onto the surface. Terminals of specialized cells secrete three types of secretory products: secretion of frontal glands, secretion of tumuli, and neurosecretion of cup-shaped terminals. Universal structural adaptations common to all stages of parasite development and specialized ones common to tissue plerocercoids were detected. Vacuolized microtriches belong to the specialized structures that arise in response to the host immunity.

Keywords: Bothriocephalidea, glands, secretory–excretory products, tegument, parasitic capsule, parasite–host interface

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INTRODUCTION

Tapeworms (Cestoda) are highly specialized parasites of human and animals. Fish are final and intermediate hosts for representatives of many cestode orders. Cestode plerocercoids (larvae of the second stage) live in the tissues of different organs and in body cavity of the hosts (fish), through which the infection of final hosts (predatory fish, in which the parasite lives in the intestines) occurs. The life of a plerocercoid in the tissues of the intermediate host is associated with adaptations to parasitism and formation of protection mechanisms against the host's immune response.

Molecular mechanisms of evasion of the host's immune response include molecular mimicry, the ability to evade the host humoral immunity, suppression of immune cell proliferation and induction of apoptosis, and immunomodulation due to a change in the secretion of the host's immune factors (such as cytokines and interleukins) [1, 2].

The space between the parasite and host tissues (parasite–host interface) is a place of entry for cellular and humoral components of the host immunity as well as immunomodulatory and immunosuppressive substances of the parasite [3]. The structure and physiology of border tissues mediate the nature and dynamics of parasite–host interactions, the study of which is an important factor in the development of medical and veterinary means of protection against parasites. Only few studies consider the structure of a parasite–host contact comprehensively, paying attention to the border tissues of both sides of the parasite–host interactions [4–6].

It is known that substances (or parasitic factors) secreted by cestodes into the environment (that is, into the host) have a biological activity aimed at reducing

and changing the host's immune response [2, 7]. Secretory–excretory products (SEP) of plerocercoids can have immunomodulatory properties [8, 9] and anti-inflammatory effect [10]. A secretion of parasitic factors can be conducted in different ways. SEP can be secreted by the tegument [11], frontal glands [12, 13], free nerve endings of neurosecretory neurons [14] or excretory system. A complex of substances secreted by tapeworms into the host is a complex mixture of a variety of molecules, including many proteins, neuromodulators, and immunomodulators that affect the nervous and endocrine systems of the host [15].

The host's immune response (*Perca fluviatilis* perch) to the effect of the pathogen (*Triaenophorus nodulosus* (Bothriocephalidea) parasite) is manifested by the formation of a granuloma in the form of a capsule around the plerocercoid with the involvement of the perch's immune system cells [16]. The aim of the present study was to investigate the ultrastructure of *T. nodulosus* cestode larvae encapsulated in the perch liver and to comprehensively describe the border tissues of the parasite and the host, as well as the interface between them, in fixed intact parasitic capsules.

MATERIALS AND METHODS

The material was collected in February 2021 at the Rybinsk Reservoir. A total of 15 European perch individuals were caught. Before autopsy, the perches were anesthetized in ice at 0°C. The granulomas caused by a parasitic *T. nodulosus* infection were removed from the liver with a small amount of intact tissue and fixed in 2.5% glutaraldehyde solution on 0.1 M phosphate buffer, postfixed in 1% OsO_4 solution on the same buffer, and dehydrated in a series of ethyl alcohol solutions of increasing concentration and pure acetone, after which they were impregnated and poured into epoxy resin (Fluka, Germany) and polymerized at 37°C and 60°C according to the protocol for cestodes [17]. The structure of capsules was studied on semithin (2 μm) sections stained with 1% solution of methylene blue using a Leica DM5000 B light microscope (Leica, Germany).

Electron microscopy. Ultrathin 60–80-nm-thick sections were obtained on a Leica EM UC7 ultratome (Leica, Germany) using a diamond knife, mounted on formvar coated slots, contrasted with 4% uranyl acetate at 37°C and 0.4% lead citrate. The ultrastructure was studied using JEM-1011 and JEM-1400 Flash transmission electron microscopes (JEOL, Japan). For scanning electron microscopy, samples fixed and dehydrated in acetone were placed into the drying facility in a critical point in liquefied CO_2, then mounted on tables, and coated with a Pt–Pd mixture in the sputter coater chamber. Images were obtained on a JSM-6380LA (JEOL, Japan).

RESULTS

Structure of the parasitic capsule wall. Plerocercoids of *T. nodulosus* in the perch liver are surrounded by modified host tissues that form a closed multilayer capsule (granuloma) (Fig. 1). The outer layer of granuloma, bordering the liver parenchyma, is loose and composed of flattened fibroblasts with multiple processes that form a network on the capsule surface (Fig. 1a). Their nuclei have an irregular shape and contain heterochromatin. Fibroblasts secrete collagen fibers into the intercellular space. In addition, granulocytes similar to mast cells (containing multiple electron-dense round granules in the cytoplasm) were found in the outer loose layer. These cells are found regularly but form no continuous layer (Fig. 1c).

Several rows of flattened cells with oval, light nuclei are located deeper; the nuclei contain a small amount of dense heterochromatin on the inner side of the nuclear membrane and were called "epithelioid cells" [18]. They are connected to each other by multiple desmosomes (Figs. 1e, 1f). Under the plasmalemma of these cells, there is a reinforced cytoskeleton of short fibrils (Figs. 1c, 1d). The rows of epithelioid cells become denser over time so that the deeper layer consists of flat, electron-dense cells with elongated, flattened nuclei (Fig. 1d).

The innermost layer of the capsule wall contacts with the plerocercoid tegument or with electron-light contents of the parasitic capsule cavity. Individual macrophages were found on the inner surface of the capsule wall (Figs. 1b, 1e, 2a, 2b). They form no desmosomes and are loosely associated with the epithelioid cells. The nucleus of macrophages is irregular in shape and small compared with the cytoplasm volume. The cytoplasm is electron-dense and filled with large light vacuoles with fibrous content that have a density similar to the content of the capsule cavity. Phagosomes in the cytoplasm of macrophages have different sizes and content, including the apical parts of microtriches. A macrophage can capture the tegument region or detached tumulus, forming a phagocytic vacuole around it (Fig. 2a). At the same time, the content of the macrophage light vacuoles is poured into a large phagocytic vacuole, inside which the utilization of secretory products of *T. nodulosus* occurs. Disintegrating macrophages filling the cavity with degrading organoids were regularly observed (Fig. 2b).

Interface ultrastructure. The space between the larval tegument and inner layer of the granuloma is filled with an electron-light gel with multiple inclusions (Figs. 2c, 2d): filaments of different length and different diameter, fragments of microtriches, crystal-like structures, network of plerocercoid glycocalyx, fragments of membranes, extracellular vesicles, and electron-dense granules. Spherical accumulations of crystal-like noncellular material larger than 2 μm in size consist of needle-like structures oriented radially from a homogeneous center (Fig. 2d). Vacuolized micro-

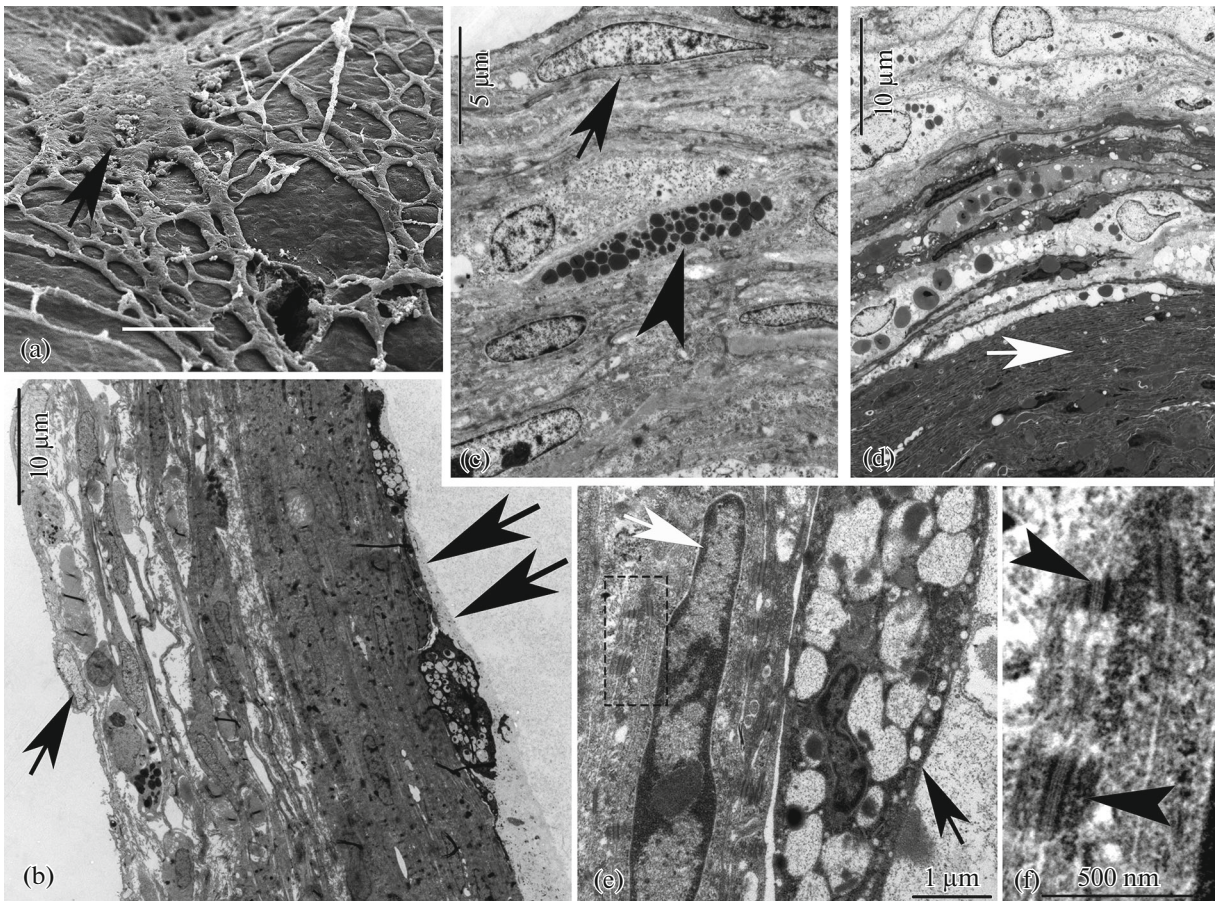

Fig. 1. Ultrastructure of the wall of parasitic granuloma in the perch liver. (a) Fibroblast on the outer surface of parasitic granuloma in the perch liver (arrow) (scale bar 100 μm); (b) granuloma wall in section; macrophages (double arrow) and dense middle and loose outer layer with fibroblasts (single arrow) are demonstrated; (c) epithelioid cell (arrow) and granulocyte (arrowhead) in the composition of the wall of parasitic granuloma; (d) inner layer of epithelioid cells (white arrow) with a typical electron-dense cytoplasm; (e) ultrastructure of epithelioid cells (white arrow) and macrophages (black arrow); (f) enlarged part of Fig. 1e (rectangle); arrowheads demonstrate desmosomes between the epithelioid cells.

triches were regularly observed in the capsule cavity. Tumuli detached from the larval surface in the form of conglomerates of dense granules and light vesicles (derivatives of glandular cells) are an important component of the interface.

Structure of the cytoplasm and tegument SEP. Inside the capsule, the plerocercoid has a formed scolex armed with two pairs of hooks. Unlike sexually mature worms in the pike intestine, the hooks of plerocercoid inside the capsule are still covered with a tegument with microtriches (Figs. 3a, 3b). In the zone of contact with the capsule wall, a distal part of the tegument is vacuolized and can peel away from the basal plate.

Microtriches cover the entire plerocercoid surface. The morphological differentiation of the plerocercoid microtriches corresponds to that in adult worms. The surface membrane of microtriches and tegument is covered with glycocalyx. The vacuoles of distal cytoplasm, a flocculent content of which is poured out in a merocrine manner and forms a filamentous basis of the gel between microtriches, contact with the surface membrane. Light vacuoles enter the distal part of the tegument from tegumental cytones immersed under the muscle layers via cytoplasmic processes (Fig. 3f). The glycocalyx threads form a three-dimensional meshwork, at the nodes of which electron-dense globular structures were noted (Figs. 2e, 2f).

In addition to a flocculent secretion, membrane-bound extracellular vesicles are secreted into the capsule. Some of the vesicles are released in the composition of multivesicular bodies found in the tegument cytoplasm; some vesicles are pinched off directly from the membrane of microtriches. Round vesicles 45–65 nm in diameter were found between microtriches, which corresponds to the size of exosomes (Fig. 2g). In addition, light vacuoles of the tegument cytoplasm (300 nm) are embedded in the basal part of microtriches and break away from the surface, forming vacuolized microtriches (Fig. 2h). Vacuolized micro-

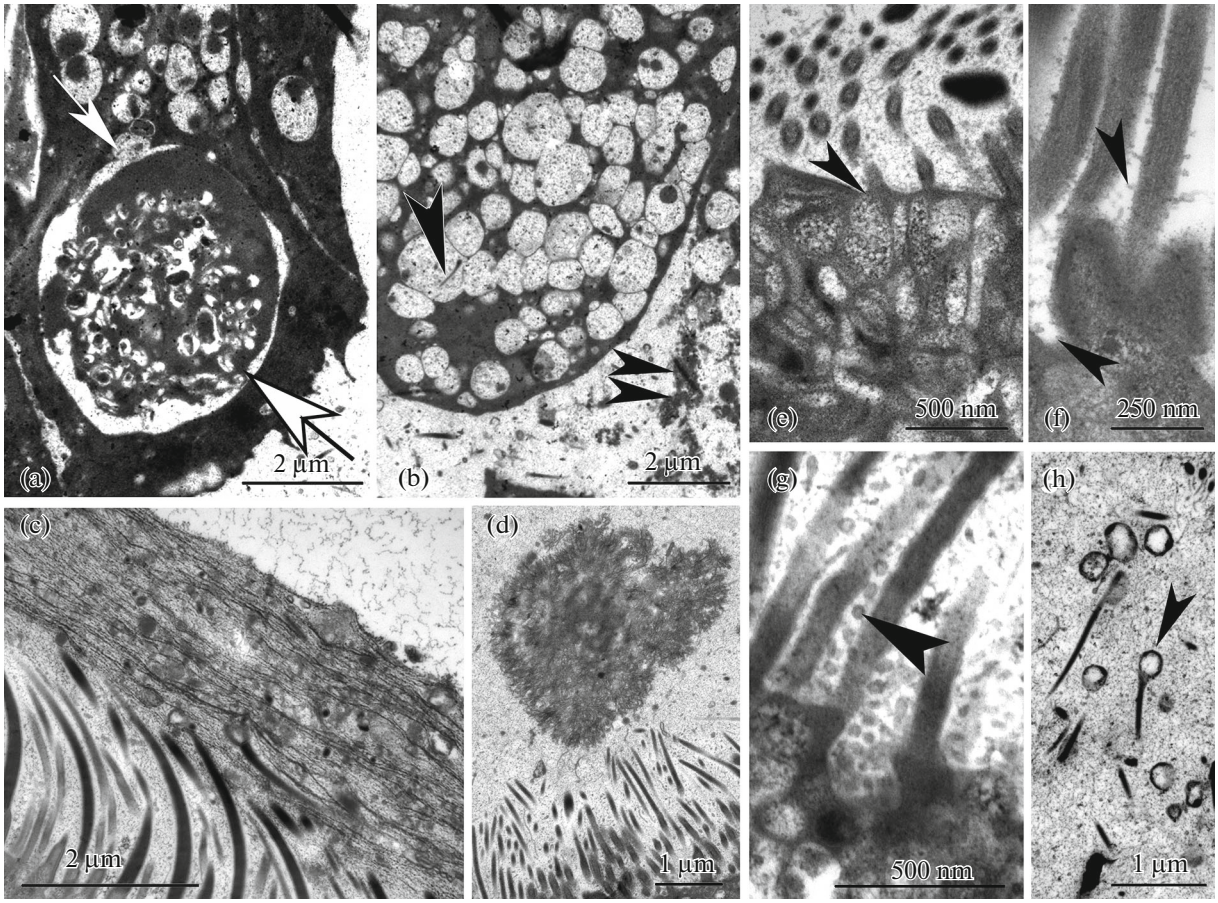

Fig. 2. Ultrastructure of the interface zone of encapsulated *T. nodulosus* larvae. (a) **M**acrophage region with a phagocytic vacuole (large arrow) containing tumulus components; the content of light vacuoles of the macrophage is poured into a large phagocytic vacuole (small arrow); (b) disintegrating macrophage in the capsule cavity (double arrowhead) and vacuole in the macrophage cytoplasm with apical part of microtriches (single arrowhead); (c) compacted glycocalyx layer on the surface of microtriches of the encapsulated plerocercoid contains a filamentous matrix, dense granules, light vesicles, and vacuolized microtriches; (d) spherical accumulation of crystal-like structures near microtriches; (e) secretion of glycocalyx (arrowhead) from the vacuoles of the plerocercoid tegument; (f) structure of glycocalyx on the surface membrane of microtriches (arrowheads); (g) release of extracellular vesicles (45–65 nm) from the tegument surface (arrowhead); (h) vacuolized microtriches and filamentous matrix within the granuloma interface (arrowhead).

triches are a component of the interface; they were often observed on the inner surface of the capsule wall.

SEP of specialized glands of plerocercoid. Three types of specialized glandular cells secrete SEP on the tegument surface into the capsule cavity.

The first type of the cells forms specialized secretory outgrowths (tumuli) rising above the microtrichial border (Figs. 3b, 3c). On the scolex, tumuli are numerous (up to 220 per 100 μm^2 of surface); on the body, there are 26 outgrowths per 100 μm^2 on average. The tumuli contain electron-dense granules with the size up to 200 nm and light vacuoles (Fig. 3e). The secretory granules enter from the secretory cell via a cytoplasmic process, which protrudes into the distal cytoplasm of the tegument together with the basal plate (Figs. 3d, 3h). In the terminal zone, the process is surrounded by electron-dense layer of basal matrix along its entire length, forming a supporting funnel. The secretory cells themselves were found in a deep parenchyma (Fig. 3g). Their perikaryons are characterized by a process-like shape and are filled with electron-dense granules with the size 230 nm and light vacuoles (130 nm). The expanded part of the process (filled with the secretory granules) breaks off and enters the capsule cavity, where it is exposed to degradation.

The second type of glandular cells is known as frontal glands of eccrine type. The plerocercoid in the capsule has developed frontal glands located in the central part of the scolex (Appendix). The cells of frontal glands send processes (strengthened by peripheral microtubules) to the distal cytoplasm of the tegument, through which the secretion comes to the tegument surface. Terminals with a diameter of 600–1000 nm penetrate the distal layer of the cytoplasm, and their membranes form a ring-shaped septate con-

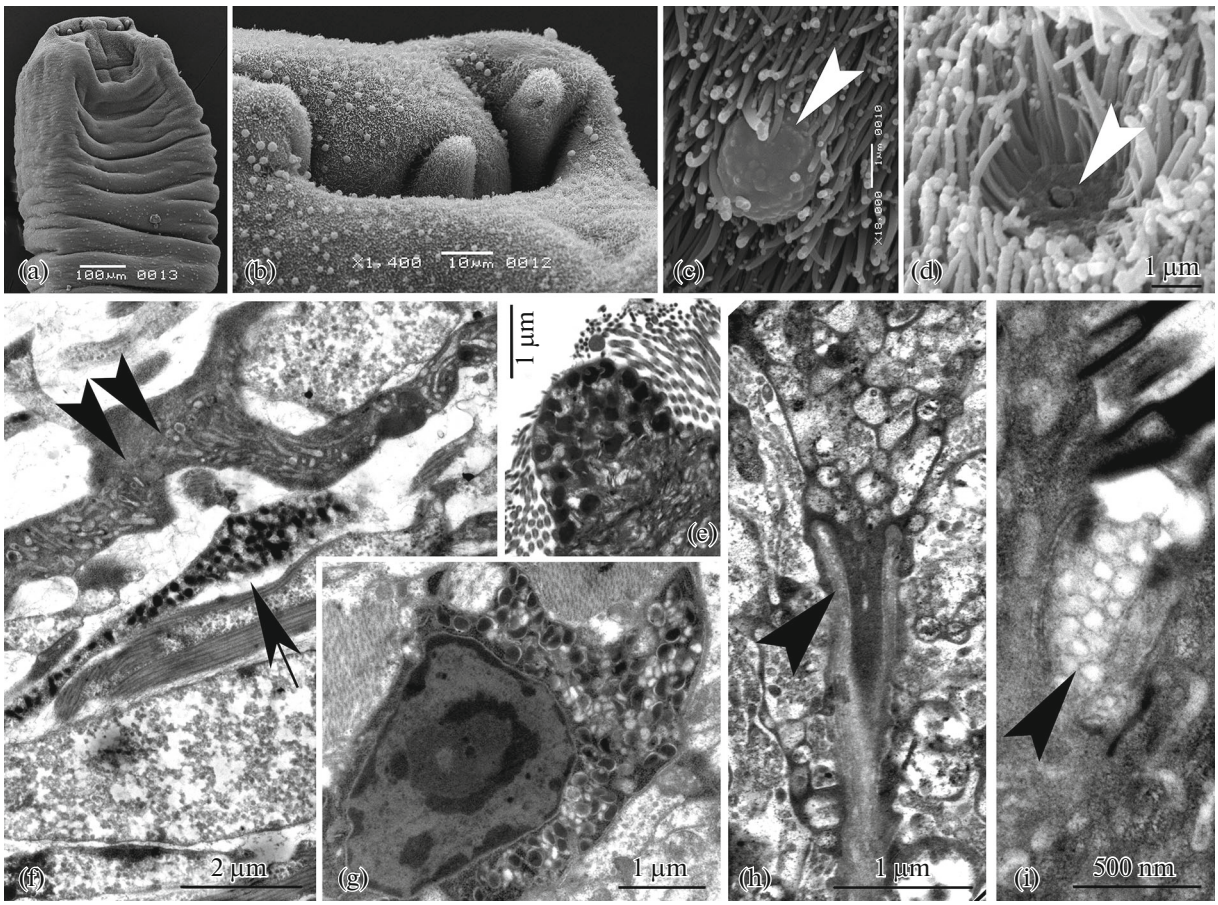

Fig. 3. Ultrastructure of the *T. nodulosus* tegument components involved in protecting the plerocercoid from the perch's immune cells (a–d, SEM; e–i, TEM). (a, b, c) Appearance of the scolex extracted from the plerocercoid capsule. The hooks covered with (b) tegument and (c) rounded glandular outgrowths (tumuli) rising above microtriches are demonstrated; (d) the surface area after the tumulus detachment; the arrowhead indicates the remaining outgrowth of the glandular cell forming the secretory outgrowth; (e) ultrastructure of the secretory content of the tumulus, cross-section; electron-dense granules and light vesicles are visible; (f) two types of processes in the subtegument of the scolex: a neurosecretory process (arrow) and a process of the tegumental cell (double arrowhead) with organoids of the distal cytoplasm; (g) perikaryon of a glandular cell forming tumuli with electron-dense and light vesicles; (h) terminal zone of a glandular cell process (arrowhead) surrounded by electron-dense layer of the basal matrix forming a supporting funnel; (i) isolation of light vesicles from the surface of a free nerve ending in the tegument of encapsulated plerocercoid (arrowhead).

tact with the tegument plasmalemma, which is reinforced by a single electron-dense supporting ring. The size of the secretory granules of frontal glands reaches 500 nm in diameter.

The third type of the cells releasing a secretion on the tegument surface probably belongs to peripheral neurosecretory neurons. Thin, free terminals with a cup-shaped expansion in the apical part with a diameter of 450–500 nm penetrate the tegument. The membranes of the terminal process and tegument form a ring-shaped septate contact, underlain by a single supporting ring from the side of the process. These terminals are filled with light rounded vesicles with a diameter up to 150 nm (Fig. 3i) that are released from their surface and enter the capsule cavity. Thin processes filled with such vesicles were detected in the subtegument.

DISCUSSION

At the time of migration from the intestine to the abdominal cavity and further to the liver, the plerocercoid is exposed to the host's immune response. Cestodes developed a number of adaptations allowing them to avoid or minimize the effect of immunity (for example, the secretion of SEP by the tegument and glands). A change in the activity of secretion of the plerocercoid tegument under the effect of the host (fish) blood serum was experimentally demonstrated [11, 19, 20]. In our study, the secretion of a thick layer of filamentous matrix, release of extracellular vesicles and vacuolized microtriches, and separation of tumuli and release of secretion of the frontal glands were observed in encapsulated plerocercoids of *T. nodulosus*. Previously, a thick layer of glycocalyx in the plerocercoid of *T. nodulosus* was noted [19]. We believe that the fila-

mentous matrix plays a role of a mechanical barrier for the perch's immune cells. It is known that the glycocalyx also contributes to a membrane digestion using the enzymes absorbed on it [21]. A flocculent secretion from light vacuoles of the tegument is apparently a source for the formation of the glycocalyx on the surface of the *T. nodulosus* tegument. A high activity of the synthesis of the glycocalyx layer is probably also associated with its involvement in antigen masking, as was demonstrated for the plerocercoids of *Ligula intestinalis*, in which a complete renewal of the glycocalyx occurs in 12–24 h [22].

Previously, lymphocytes covered with the fragments of microtriches were detected on the tegument surface of the plerocercoid of *T. nodulosus*, and adhesion of the apical parts of microtriches on the surface of leukocyte cells was observed [19]. We established that, in the capsule, the plerocercoid partially sheds microtriches by their vacuolization that are found in the capsule cavity and are detected on the surface of macrophages or inside the phagocytic vacuoles. Previously, vacuolized microtriches were noted in the composition of the protective layer in plerocercoids of *L. intestinalis* from the abdominal cavity of breams [20]. Their number increased during incubation of the plerocercoids with the host blood serum. In *L. interrupta*, vacuolized microtriches are involved in the formation of the protective layer after 12 h of incubation [11]. Apparently, vacuolized microtriches represent a special protective mechanism for the tissue larval stage of cestodes. The discarded microtriches and extracellular vesicles can presumably be involved in the sequestration of host immunoglobulins in the zone remote from the tegument. Probably, immunoglobulin deactivation occurs in this way, and they do not reach the larval. The possibility of such a process was demonstrated for the plerocercoids of *L. intestinalis* from the roach, in which it was possible to visualize immunoglobulins in the zone of microtriches [23].

Extracellular vesicles can carry noncoding RNA and proteins that can play a role of immunomodulators [25]. We detected multiple membrane-bound vesicles with a diameter up to 65 nm in the plerocercoid of *T. nodulosus* between microtriches, on their surface, and in the capsule cavity. The size of detected vesicles corresponds to that for exosomes [24].

The secretory tumulus outgrowths [26] filled with electron-dense secretory granules of a certain type are a unique feature of representatives of the Bothriocephalidea order. For *T. nodulosus*, specialized glandular cells forming the outgrowths with secretory granules were described at the stages of procercoid, plerocercoid, and adult worm [27]. We observed detached tumuli in the capsule cavity and in phagocytic vacuoles of macrophages of the inner layer of the granuloma. In the zone of forming tumulus, no specialized contacts similar to those in the terminals of frontal glands and nerve endings were found, which indicates some specialization of these structures. We demonstrated that, in the plerocercoid extracted from the capsule, the number of tumuli per unit area on the scolex is almost ten times larger than on the body. These data correlate with data of other authors and are similar to the distribution of tumuli in adult intestinal parasites, representatives of the Bothriocephalidea order [19, 27]. The role of SEP tumuli is interpreted as a response to the effect of the host immunity. In *T. nodulosus*, the number of the outgrowths and glandular cells themselves decreases as the capsule formation is completed. During repeated implantation of the plerocercoid from the formed capsule into the perch body cavity, the number of tegumental outgrowths increased significantly [19]. It is possible that the concentration of tumuli on the plerocercoid scolex in the capsule is a structural preadaptation to the adult stage, when the scolex invades the intestinal tissues and experiences an intensive host's immune response.

Free, cup-shaped endings secreting light vesicles (that we found in encapsulated plerocercoids) were previously described in earlier larvae at the stage of procercoid living in cyclops and in mature *T. nodulosus* from the pike intestine [28]. Similar endings are known in representatives of different orders of cestodes, for example, Cyclophillidea [29], Diphyllobothriidea [30, 31], and Trypanorhyncha [32]. The studies in recent years [14] prove the involvement of peripheral neurosecretory neurons of cestodes in the exocrine secretion, including in the release of FMRFamide-like IR neuropeptides and prostaglandins into the host. At the same time, an increase in the secretion of free endings of neurosecretory neurons in response to the effect of the blood serum of the host fish was demonstrated, which confirms the involvement of the nervous system in the parasite–host interactions [14]. Prostaglandins found in the composition of secretory terminals in plerocercoids of *D. dendriticum* and *L. intestinalis* can play the role of immunomodulators [32, 34].

Our data on the structure of parasitic granuloma in the perch liver are consistent with earlier results [16]. The plerocercoids are located in the cavity, which is surrounded by modified host tissues that form the capsule wall. The cells of the dense layer are connected by multiple desmosomes and are comparable to epithelioid cells [18]. The formation of a capsule around the parasite by the host tissues is recognized as a universal method for isolating the parasite [1, 2], despite the fact that the capsule wall does not prevent the absorption of nutrients from the host organism by a parasite. Granulocyte infiltration to the parasite also appears to be a universal immune response of vertebrates to the presence of a pathogen in the tissues [34].

CONCLUSIONS

According to the results of ultrastructural studies of encapsulated plerocercoids, we were able to detect

several structural mechanisms involved in the protective response of a parasite inside the granuloma.

The tegument secretes on the surface (a) the content of light vacuoles, forming a thick layer of glycocalyx; (b) exosomes; and (c) vacuolized microtriches, the role of which is still unknown. Specialized secretory cells have free terminals in the tegument and secrete SEP of three types: (a) secretion of the frontal glands, (b) secretion of tumuli, and (c) neurosecretion.

In addition to vacuolized microtriches, all the above-mentioned structures are found in the tegument of adult *T. nodulosus* from the pike intestine, which indicates a universality of these structural adaptations. Vacuolized microtriches are a newly discovered mechanism of protection of tissue plerocercoids from the host immunity. We noted for the first time phagocytosis of the apical parts of microtriches and tumuli by granuloma macrophages. In addition, we detected for the first time crystal-like radially oriented needle-like structures in the granuloma interface. The nature of these is unknown. A structural diversity of cellular elements of the granuloma wall (observed in different specimens) depends on the time elapsed from the moment of infection: the wall can be represented by a large number of capsule layers and by the parasite necrosis in the case of prolonged invasion.

SUPPLEMENTARY INFORMATION

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The experiments were carried out in compliance with all ethical standards for working with animals. In accordance with Chapter 1, paragraph 3 of Directive 2010/63/EU of September 22, 2010, on the protection of animals used for scientific purposes, bioethical requirements do not apply to tapeworms.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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