

Myopathogenesis and Myoredifferentiation in Trichinosis

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Abstract

Despite the seemingly inhospitable nature of the vertebrate striated muscle cell as an environment for intracellular parasites, infective L₁ larvae of the genus *Trichinella* target this type of cell exclusively to support their growth, development and long term survival. However, the parasite must dramatically modulate the architecture, biochemistry and biosynthetic capabilities of the muscle cell in order to establish a suitable niche for itself. The end result of these parasite-induced perturbations in host cell structure and function is the formation of the nurse cell, a unique structure designed to protect and nurture the enclosed larva. Current knowledge on this intriguing host-parasite relationship is presented in this review, with emphasis on the nature and sequence of events in the process of *Trichinella*-induced muscle cell redifferentiation, the impact on the host of these perturbations in infected myofibers, the strategies employed by *Trichinella* which enable it to survive for long periods of time in host muscle and the benefits derived by the parasite from the altered host cell.

Key words: myopathogenesis, myoredifferentiation, *Trichinella*, parasitic myopathy.

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Most intracellular parasites alter to some degree the structure and biochemistry of the cells they invade in order to create a niche that fulfils their needs. Muscle cells are structurally and biochemically dedicated to the function of contraction, an activity that generates high variability in the chemical and physical environment within the cell. Thus, the muscle cell exhibits characteristics that would seem to place it among the least desirable cells to serve as a niche for intracellular parasites. The infective larval stage of one group of metazoan parasites, members of the genus *Trichinella*, are not only able to grow and develop within this seemingly inhospitable environment, but may reside herein for the life of the host. Not surprisingly, in order for the parasite to accomplish this it must induce heroic changes in the structure, biochemistry and biosynthetic capabilities of the vertebrate striated muscle cell.

Members of the genus *Trichinella* exhibit broad geographic distribution [39], infecting a wide range of mammals and several species of birds [13, 22]. Although controversy surrounds the number of species within this genus, there is general agreement on the existence of at least two species, *Trichinella spiralis* and *Trichinella pseudospiralis*. The former species and its geographic variants are characterized by the presence of a collagenous capsule surrounding the muscle stage larva, while the latter species resides in muscle without a capsule. The information

presented below on the relationship between *Trichinella* and vertebrate striated muscle comes primarily from studies on *T. spiralis* (swine isolate). Where available, related information on *T. pseudospiralis* is provided.

The infective L₁ larval stage is an intracellular parasite of vertebrate striated muscle (Figure 1 and 2). Following consumption of infected host muscle and exposure to conditions encountered in the vertebrate stomach, the L₁ larva is released from host muscle tissue and, in the case of *T. spiralis*, from the collagenous capsule [75] surrounding the parasite. The free larva rapidly takes up residence as an intramulticellular parasite within columnar epithelial cells of the host small bowel wherein it undergoes four molts within a period of 24-30 hr [18].

After attaining sexual maturity, adult worms begin to mate (Figure 3 and 4). Shedding of live newborn larvae (Figure 5) by adult female worms begins around day 5 postinfection (PI). The newborn larvae migrate throughout the host's body via the lymphatic and circulatory systems, entering and exiting a variety of cell-types, but taking up long-term residence only in striated muscle cells [18]. Other than perhaps the electrical properties of contracting striated muscle [30], no specific stimuli appear to orient newborn larvae towards their preferred host cell. However, since they grow and develop exclusively within striated muscle fibers, the parasite must encounter some important

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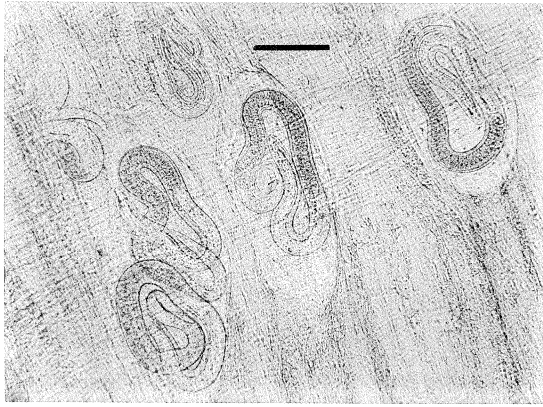


Figure 1. Compression between two microscope slides of a piece of diaphragm muscle from a mouse infected for 40 days with *Trichinella spiralis* reveals several larva/nurse cell complexes, each surrounded by a capsule. Bar = 100 μm .

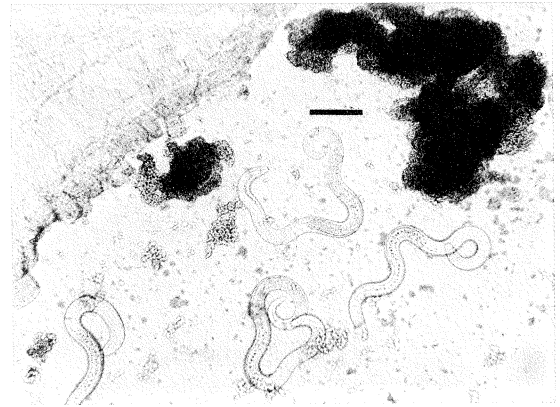


Figure 2. Compression between two microscope slides of a piece of diaphragm muscle from a mouse infected for 40 days with *Trichinella pseudospiralis* has forced several unencapsulated muscle stage larvae out of the severed ends of muscle fibers. Bar = 100 μm .

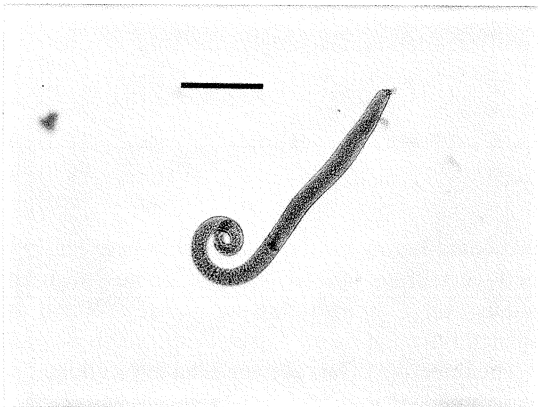


Figure 3. Adult male *Trichinella spiralis* isolated from the small intestine of a mouse at 48 hr postinfection. Bar = 100 μm .

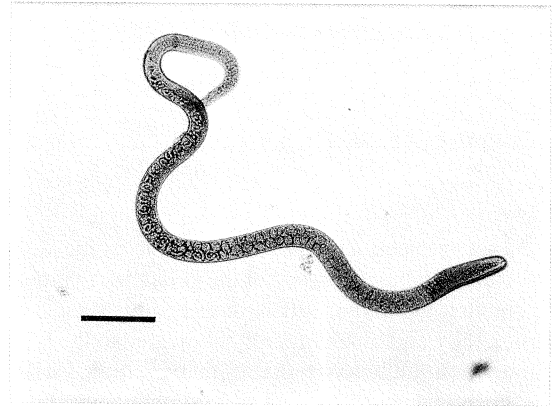


Figure 4. Adult female *Trichinella spiralis* isolated from the small bowel of a mouse at 48 hr postinfection. Bar = 100 μm .

cues upon entering this cell-type. These cues trigger the larva to grow and develop and to initiate a series of molecular interactions with the host cell that result in the production of a dramatic and complex cascade of changes in the host muscle cell.

There appear to be at least two predisposing factors that support a high level of infection of muscle by *Trichinella* larvae: (a) the higher the activity of a muscle, the higher the worm burden (see [18]); and (b) muscles situated cranial to the caudal margin of the rib cage have greater burdens of larvae than do those located caudal to the rib cage [61]. Both of these factors may be related to the vascular system; the more active muscles have greater vascularization and would receive a greater burden of

larvae, and the first muscles encountered as larvae leave the thoracic duct for the general circulation might be expected to be more heavily infected. Indeed, fewer larvae become established in muscle that has been denervated 4 wk prior to infection, a treatment that results in decreased vascularization in muscle [19]. In the mouse host, the newborn larvae of *Trichinella spiralis* preferentially invade slow-twitch striated muscle fibers, while those of *Trichinella pseudospiralis* are found in both slow- and fast-twitch fibers [4]. Ochoa and Pallis [48] reported that in a human case of trichinosis, larvae were found in both types of fibers, but the species of *Trichinella* infecting this patient was not identified.

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During the process of penetration, the newborn larva aligns with, attaches to and causes an indentation in the sarcolemma of the target cell. Penetration is accomplished in about 10 min by primarily mechanical means and is evidenced by a tear in the membrane of the muscle cell [17]. After it enters the sarcoplasm, the larva immediately moves beneath the sarcolemma away from the site of entrance, leaving an open path behind it that collapses to isolate the larva from the external environment [17].

The larva will undergo a period of exponential growth and development over the next 2 weeks, increasing its volume by 40% per day [20]. It is during this window of time that the *Trichinella* larva provokes incredible pertur-

bations in the biochemistry, microarchitecture and biosynthetic capabilities of the host muscle cell in which it resides. The end result of these changes is to create a cell that is structurally and functionally no longer recognizable as a vertebrate muscle cell. This new cell-type has been designed to house, protect and nurture the *T. spiralis* larva, and has been named the "Nurse cell" (Figure 6; [49]). All of the encapsulating isolates of *Trichinella* appear to form this nurse cell complex [8]. On the other hand, while *T. pseudospiralis* does induce some of the same changes seen in muscle cells infected by *T. spiralis* [32, 15], it does not form a nurse cell complex as described below. However, since *T. pseudospiralis* migrates rapidly within and be-

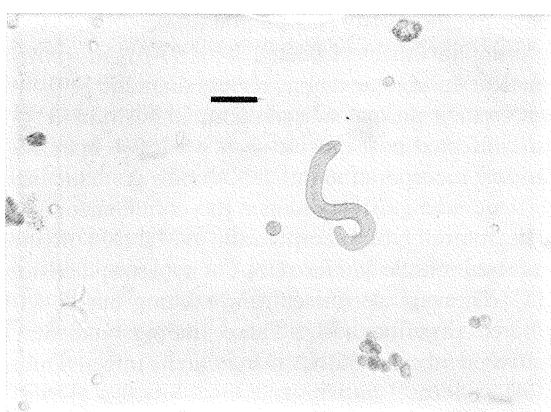


Figure 5. Newborn larva of *Trichinella spiralis*. Bar = 100 μ m.

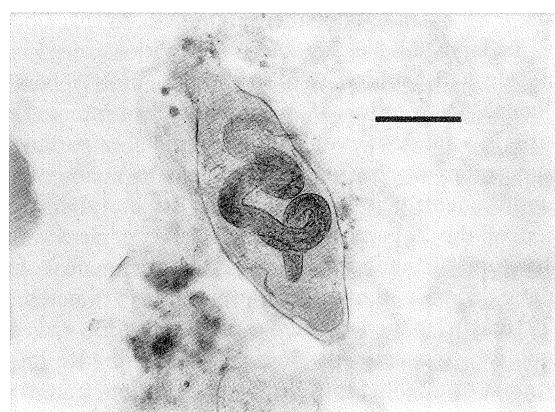


Figure 6. A Nurse cell (modified portion of the muscle fiber and a larva enclosed within a collagenous capsule) of *Trichinella spiralis* isolated by trypsin treatment of muscle from a mouse infected for 40 days. Bar = 100 μ m.

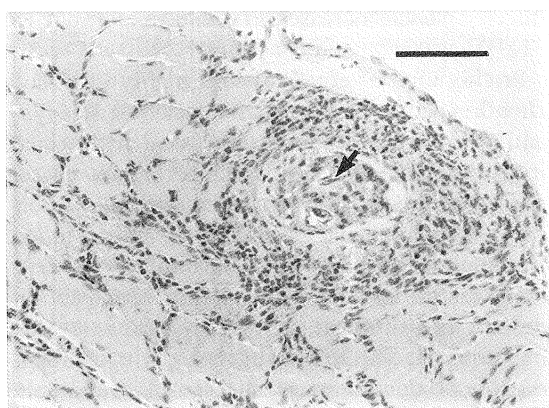


Figure 7. Dramatic influx of inflammatory cells against an encapsulated *Trichinella spiralis* larva in muscle from a Chinese hamster infected for 25 days. Note also diffuse myositis. Arrow denotes larva within capsule. Bar = 100 μ m.

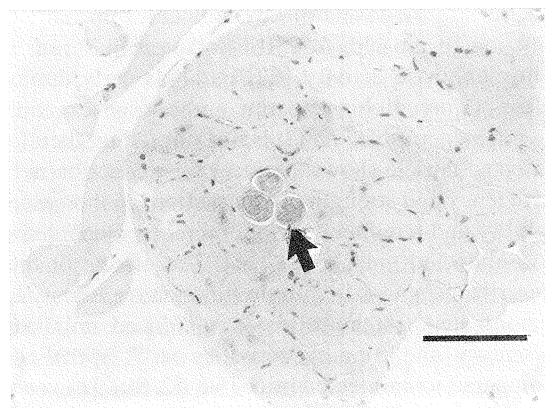


Figure 8. Note the absence of focal or diffuse inflammation at day 25 postinfection in this section of Chinese hamster diaphragm muscle housing a muscle-stage larva of *Trichinella pseudospiralis* (arrow). Bar = 100 μ m.

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