Sci Parasitol 20(1-2):5-11, August 2019
ISSN 1582-1366

REVIEW ARTICLE

The oncogenic and oncostatic action of *Trichinella* spp. in animals

Zsolt Boros[1]✉, Călin Mircea Gherman[1], Menelaos Lefkaditis[3], Vasile Cozma[1,2]

1 – Department of Parasitology and Parasitic Diseases, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine, Calea Mănăştur 3-5, 400372 Cluj-Napoca, Romania.
2 – Academy of Agricultural and Forestry Sciences Gheorghe Ionescu-Sişeşti (A.S.A.S), 61 Mărăşti Boulevard, Bucharest 011464, Romania.
3 – Department of Parasitology and Parasitic Disease, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine, Trikalon 224, 43100, Thessalia, Greece.
Correspondence: Tel. 0040 264596384, Fax 0040264593792, E-mail zsolt.boros@usamvcluj.ro

Abstract. Trichinosis (Trichinellosis) is a cosmopolitan disease of warm-blooded animals caused by several species of *Trichinella.* During their stay in the host body the larvae migrate, causing negative effects and diseases to the hosts, especially to humans.

Establishing an association between a neoplastic disease and helminth infestation represents a problem because of the long latency period between the two diseases. Several case reports show the oncogenic potential of *Trichinella spiralis* in animals but also in humans. It was observed that *Trichinella* spp. can potentiate the carcinogenic effects of some chemicals. A few authors suggest that, the modulation of the hosts immune system, irritation and inflammation may trigger specific humoral and cellular responses in the hosts body during this parasitic infestation, that may finally lead to tumor development.

It's suspected that each developmental stage of *T. spiralis* may have an antitumor action through specific and active substances. Crude extracts obtained from the adults and newborn larvae, can also reduce the progression of tumors in some animals. Excretory–secretory proteins (ESPs) from muscle larvae could contain antitumor-substances. The antitumor action of *T. spiralis* was detected to be stronger during the intestinal stage of the infestation. *Trichinella pseudospiralis* infestations in mice can suppress inflammatory responses. *T. britovi* can also have an oncostatic action in some types of tumors (Walker carcinosarcoma) but not as strong as *T. spiralis.*

Keywords: *Trichinella* spp.; Tumors; Mice; Rats.

Acţiunea oncogenă şi oncostatică a *Trichinellei* spp. la animale

Rezumat. Trichineloza este o boală cosmopolită a animalelor cu sânge cald. Boala este cauzată de mai multe specii de *Trichinella.* În timpul parazitismului în organismul gazdă, larvele migrează, provocând efecte negative şi boli grave la unele gazde, în special la oameni.

Stabilirea unei asocieri între o boală neoplazică şi o infestaţie parazitară reprezintă o problemă. Mai multe studii pun în evidenţă capacitatea oncogenică a nematodului *Trichinella spiralis* la animale şi la om. S-a observat că *Trichinella* spp. are capacitatea de a potenţa efectele carcinogene ale unor substanţe chimice. Unii autori sugerează că modularea sistemului imunitar al gazdei, iritarea şi inflamaţia pot declanşa răspunsuri umorale şi celulare specifice, care pot duce în final la apariţia formaţiunilor tumorale.

Fiecare etapă de dezvoltare a *T. spiralis* poate avea o acţiune antitumorală. Extractele brute obţinute din larvele pot, de asemenea, să reducă progresia tumorilor la unele specii de animale. Proteinele excretoare şi secretoare (ESP) din larvele musculare pot să conţină substanţe antitumorale. Acţiunea antitumorală a *T. spiralis* a fost detectată ca fiind mai puternică în timpul fazei intestinale a parazitismului. Infestaţiile cu *Trichinella pseudospiralis* la şoareci pot avea efect antiinflamator. *T. britovi* poate avea acţiune oncostatică în unele tipuri de tumori (Walker carcinosarcoma), însă această acţiune nu este la fel de puternică comparativ cu *T. spiralis*.

Cuvinte cheie: *Trichinella* spp.; Tumori; Şoareci; Şobolani.

Received 15.03.2019. Accepted 23.04.2019.

Introduction

Trichinosis or Trichinellosis is a cosmopolitan disease of warm-blooded animals caused by several species of *Trichinella.* This parasite can also infest human beings, causing different digestive symptoms (Meyer and Olsen, 1975). *Trichinella* spp*.* are parasitic organisms that live in the intestines and in the muscle tissues of humans and animals. Both the adults and the larvae have parasitic behavior and live in the same host. During their stay in the host body the larvae migrate, causing negative effects and diseases to the host, which may culminate in death, especially in humans (Şuteu and Cozma, 2012). Helminthes have been involved in the etiology of different types of neoplasms (Herrera and Ostrosky-Wegman, 2001). Trichinellosis in association with neoplastic conditions has rarely been reported in human and veterinary literature (Restucci et al., 1991). Today, there is no doubt that some species of *Trichinella* can induce neoplasm formation in animals and in humans (Herrera and Ostrosky-Wegman, 2001). Several studies were also performed to observe the oncostatic actions of these parasites in animal hosts. *Trichinella spiralis* and *Trichinella britovi* have been recognized as helminths that can negatively influence tumor growth and prolong the life span of their hosts (Pocock and Meerovitch, 1982).

The aim of this article is to present in retrospective the most important findings from several researchers regarding the oncogenic and oncostatic action of *Trichinella spiralis* and other species from the genus *Trichinella* in different animal species*.*

The oncogenic action in animals

Helminths to induce tumor development in their host's body require many years of infestation. During this time they cause chronic inflammation of the tissues which in many cases is an essential step in tumor formation (Vennervald and Polman, 2009). Establishing an association between a neoplastic disease and helminth infestation represents a problem because of the long latency period between the two diseases. First, the time between the exposure, which is represented by the initial parasitic infestation and the outcome meaning the initial tumor development is almost unidentifiable. The interesting part is that in some cases by the time the tumor appears the helminths might not be in the host body any more (Vennervald and Polman, 2009; Machicado and Marcos, 2016).

A few studies show that *Trichinella* spp. can cause tumor development in some conditions, for instance in a 10-year-old male shorthair cat after one month of absents from home, a small mass was found in the subcutaneous tissue at the rostro-ventral surface of the left mandible. Histopathologic examination revealed chronic inflammation. After surgical excision and staining with hematoxylin and eosin (HE), the authors observed the presents of *Trichinella spiralis* larvae between the neoplastic squamous cells (Moisan et al., 1998). It was also observed that *Trichinella* spp. can potentiate the carcinogenic effects of some chemicals. A good example in this case is the experimental study that combined the infestation of *T. spiralis* larvae with the inoculation of chemical carcinogens in rats. The combination induced the formation of laryngeal carcinoma in rats more frequently than either of them alone (Gawish, 1975).

The oncogenic mechanism for *T. spiralis* and for other species from the genus *Trichinella* are not well known. Some suggest that the up regulation or down regulation of some apoptotic factors in skeletal muscle cells may represent an adaptive mechanism that helps the parasite to survive (Babal et al., 2011). However, a number of reports suggested that, the modulation of the hosts immune system, irritation and inflammation may trigger specific humoral and cellular responses in the hosts body during this parasitic infestation, that may finally lead to tumor development (Moisan et al., 1998; Čvorović et al., 2005; Kristek et al., 2005; Lichiardopol et al., 2010; Alva et al., 2015; Shirazi et al., 2015).

The oncostatic action in animals

Several species from the genus *Trichinella* have an inhibitory effect against certain types of tumors. Most studies regarding the anti-tumor potential of *T. spiralis* showed that this parasite can influence the immune system of the host (Wang et al., 2009). Secretory and excretory products of *T. spiralis* can induce immune modulations that can influence the course of some malignant diseases such as melanoma or myeloma (Sofronic-Milosavljevic et al., 2015). To understand the presence of myeloma-associated antigens in *Trichinella spiralis* and their possible anti-tumor effects, the authors in this case used cross-immune responses between antigens of myeloma cell SP2/0 versus positive sera to *T. spiralis,* and antigens of *T. spiralis* versus positive sera to myeloma cell SP2/0 in mice. They found that tropomyosin in this case may play a role in inducing cross-protective immunity (Gong et al., 2011). In an experimental study, the mice infested with *Trichinella spiralis* had successfully reduced tumor growth. It's suspected that each developmental stage of *T. spiralis* may have an antitumor effect possibly due to some anti-tumor active substances and/or tumor-associated antigens (Duan et al., 2011). These antigens may trigger outer caspase-dependent apoptotic pathways and inhibit the survival of some tumor cells, like melanoma (Vasilev et al., 2015; Pocock and Meerovitch, 1982). *Trichinella spiralis* excretory/secretory proteins may have an inhibitory effect on NCI-H446 small cell lung cancer by reducing the levels of protein C-myc and Bcl-2 mRNA (Chang et al., 2014), but excretory–secretory proteins (ESPs) from muscle larvae may also contain antitumor-substances. ESPs successfully inhibited the growth of small cell lung cancer cultures (Luo et al., 2017). Lot of ESP of *Trichinella spiralis* muscle larvae have unknown identities but six anti-tumor relevant proteins (histone H2A, tropomyosin, cleavage and polyadenylation specificity factor unit 2, armadillo segment polarity protein and eukaryotic initiation factor 4A ,serine proteinase inhibitor Kazal-type 4) were determined from 63 identified proteins (Luo et al., 2016). *T. spiralis* protein A200711 induced apoptosis in H7402 (human hepatoma) cells by increasing their susceptibility to apoptosis (Wang et al., 2013). The proliferation of HepG2 (Human hepatocellular carcinoma) cells was inhibited thanks to the excretory/secretory proteins. The inhibition was dependent on the administered dose. The apoptotic cells and necrotic ones occupied 17.9% and 6.6%, respectively (Liu et al., 2015). It can influence the cell-mediated immune responses as shown by Wing et al., in 1979. They demonstrated that macrophages from *T. spiralis* infested mice had the ability to kill EL-4 (the mouse tumor cell lines) tumor cells. The antitumor action of *T. spiralis* was detected to be stronger during the intestinal stage of the infestation. During this stage the production of

mast cells and lymphocytes was higher than usual (Ruitenberg et al., 1982). *Trichinella pseudospiralis* infestations in mice can suppress inflammatory responses. This parasite reduced T lymphocyte activity in P91 mast cell tumor development. Down regulation of cell-mediated reactions are accompanied by migratory larvae (Stewart et al., 1991).

The duration of the infestation also plays an important role in tumor inhibition. Here we can mention the findings of Kang et al., in 2013. They found that long infestation with *T. spiralis* can have a stronger antineoplastic effect in mice with B-16 melanoma. The main tumor and the lung metastases in these mice were significantly reduced.

The administration of only the crude extracts obtained from the adults and newborn larvae, can also reduce the progression of tumors in experimentally infested mice, for instance the rough extracts from adult *Trichinella* spp. could have in *vitro* anti-proliferative effect on hepatoma H7402 cell line (Wang et al., 2009). Most of the time by the end of each experiment the size and the weight of the tumors were smaller than in the control groups (Zhang et al., 2009).

The molecular mechanism of growth suppression in Balb/c mice in a SP2/0 myeloma model was observed. Genes encoding RpL41, NKTR, Rbbp4 and ANXA2 were enriched and were involved in tumor growth inhibition (Deng et al., 2013).

Even the time of infestation is important regarding tumor development. If mice are infested with *T. spiralis* 28 days prior to sarcoma cells implantation, they significantly increase the survival period of the host, but do not affect the clinical phase of the tumor. These results indicate that *T. spiralis* infestation may temporarily alter the host response to some types of sarcomas (Molinari and Ebersole, 1977). *T. spiralis* inhibited the growth of A549 lung cancer in mice when the cancer cells were inoculated 11 days after *T.spiralis* infestation (Gong et al., 2008). *Trichinella* spp. inhibited the growth of HCT-8 (Human Colorectal Carcinoma) tumor cells in BALB/c mice when the infestation with this parasite accrued before the inoculation of HCT-8 tumor cells (Li et al., 2008). The infestation dose with this parasite is also important, anti-tumor effects were more efficient in huge infestations then in small ones (Wu et al., 2005).

Some authors decided to test the potential oncostatic action of *Trichinella* spp. in rats as well.

Oltean et al., in 2012 based on their results in experimentally infested rats came to the conclusion that *T. spiralis* had a stronger protective effect against Walker 256 carcinosarcoma (solid form) then *Trichinella britovi*. Another study shows that different doses of BAS (thermostable biologically active substances) can have different effects on cell viability in Graffi myeloid, HeLa (human cervical carcinoma) and T-24 (human transitional cell bladder carcinoma) tumor cell cultures. The strongest inhibitory effect was on Graffi myeloid tumor cells (13.80%), treated with BAS that was isolated from *T. spiralis* infested rats in a dose of 1000 μg/ml (Tsocheva-Gaytandzhieva et al., 2016).

Not all studies yielded positive results regarding the oncostatic potential of *T. spiralis*. In one study *T. spiralis* antigens did not reveal any anti-tumor activity against murine colon cancer (Eissa et al., 2018).

Discussion

Hulland (1993) considered that the inflammatory and neoplastic processes in *T. spiralis* infestations were independent, especially because the larvae that he identified were located in the myofibers of the diaphragm, where no neoplastic change were found. *Trichinella* spp. infestation's could behave only as co-carcinogens and only play a part in some tumor developments, like laryngeal carcinoma in humans (Čvorović et al., 2005). Constant irritation by the presence of this parasite may be responsible for the development of some types of tumors. It is suspected that *Trichinella* spp. may up regulate the Vascular Endothelial Growth Factor (VEGF) and might also modify the external kinase and nucleotide metabolizing enzymes, and by doing so might modulate multiple host functions including the host's

immunity against tumors (Capo et al., 1998). The detection of the parasite in the tumors and in the vicinity of them gives credibility to its carcinogenic potential and not merely to a co-incidental finding (Cheung et al., 1997). Kristek et al. (2005) came to the conclusion that in case of *T. spiralis* the cysts around the larvae act as a protective barrier during tumor formation in human breast carcinoma. Chronic trichinellosis induces in the host connective tissue mast cell hyperplasia and the production of cytokines and chemokines which are necessary for pathogen clearance (Skin et al., 2008). Future research which includes case-control studies would be beneficial in resolving the association between this parasitic infestations and malignancy (Čvorović et al., 2005).

The ancient idea that parasitic organisms and their products can be used as an alternative to tumor treatment has gradually gained interest over the last few years (Liao et al., 2018). Using regular treatments and prevention we can reduce parasitic infestations or re-infestations. This way we lower the risk of tumor development in animals (Vennervald and Polman, 2009). The beneficial effects of some parasites on tumorgenesis vary from induction of apoptosis, modification of immune responses, altering metastasis and angiogenesis, to the regulation of inflammation that promotes cancer development (Callejas et al., 2018). Several animal models have shown that some parasite species or parasite products were able to inhibit or slow down tumor growth (Darani and Yousefi, 2012). Some nematodes for example can provide resistance against the development of some murine tumors (Molinari and Ebersole, 1977; Tsocheva-Gaytandzhieva et al., 2016). Scientific evidence indicate that a few *Trichinella* spp. can induce antitumor activity against certain types of neoplasms in mice and rats (Darani and Yousefi, 2012). These modifications can be observed in tumor cells when tumors and parasite infestations coincide or even more when the infestation precedes tumor development (Vasilev et al., 2015). Recent results indicate that protection against tumors is more efficient when both innate and adaptive antitumor responses are involved (Noya et al., 2013). Crude *Trichinella* spp. antigens can also have an inhibitory effect against some types of tumors, for example SP2/0 myeloma. These types of antigens can be found in adults, in new born larvae and in muscle larvae (Wu et al., 2007). *Trichinella spiralis* cDNA expression library was obtained from muscle larvae RNA and screened with sera from Balb/C mice which were injected with Sp2/0 myeloma cells to obtain novel antigen genes. These antigens can possibly be used for a future anti-tumor vaccine (Duan et al., 2013). The parasites larval somatic proteins could inhibit the proliferation and may induce the apoptotic activity of H446 cells (small cell lung cancer) and its effects may be related to the up-regulated expression of Apaf-1 and Cyt-C (Li et al., 2018). Another study showed that A200711 protein from this parasite had an inhibitory effect on H7402 (human liver cancer) cells proliferation (Li et al., 2012). CK-1 of *T. spiralis* was expressed in prokaryotic liver tumor cells (Zuo et al., 2014) and Tsp06172 gene was expressed and cloned in A549 lung cancer cells (Gao et al., 2013). *Trichinella spiralis* infestation can also induce the expression of cancer suppressor genes like RB genes in breast MCF-7 tumor cells (Li and Zhang, 2009). These findings laid the foundation for further studies on the anti-tumor effect of this parasite (Zuo et al., 2014).

Conclusions

Based on several case reports and studies we can conclude that *Trichinella spiralis* in some situations can cause or at least act as a co-cancerigen agent in some tumor formations. The oncogenic potential of other *Trichinella* spp. are not well known and future research is needed.

In the last few years several researchers observed that *T. spiralis, T. britovi* and their extracts could have an inhibitory action against some tumor formations in mice and rats.

The exact mechanism by which these parasites induce or inhibit tumor development in animals or in humans is not well known. A few more years of research is needed to clarify the questions regarding the two types of mechanisms.

References

Alva S., Saha A., Dhanalakshmi A.R., Kariappa T.M. 2015. Parotid Gland – A unique habitat for *'Trichinella Spiralis'*. Int. J. Appl. Res. 1:143-145.

Babal P., Milcheva R., Petkova S., Janega P., Hurnikova Z. 2011. Apoptosis as the adaptation mechanism in survival of *Trichinella spiralis* in the host. Parasitol. Res. 109(4):997-1002.

Callejas B.E., Martínez-Saucedo D., Terrazas L.I. 2018. Parasites as negative regulators of cancer. Biosci. Rep. 38(5):BSR20180935.

Capo V.A., Dissckson D.D., Ramola I.P. 1998. *Trichinella spiralis*: Vascular Endothelial Growth Factor is upregulated within the nurse cell during the early phase of its formation. J. Parasitol. 84(2):209-214.

Chang H.M., Zhao L., Wang X.J., Fang Y.H., Li D., Luo J.M., Du L.Y. 2014. Effect of the excretory/secretory proteins from *Trichinella spiralis* on apoptosis of NCI-H446 small-cell lung cancer cells. Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 32(4):299-303.

Cheung L.K., Yeung R.W., Leung S.Y., Samman N. 1997. Trichinosis associated with carcinoma of the tongue: case report. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 84(1):32-34.

Čvorović L., Milutinović Z., Kiurski M. 2005. *Trichinella spiralis* and laryngeal carcinoma: a case report. Eur. Arch. Otorhinolaryngol. 262(6):456-458.

Darani H.Y., Yousefi M. 2012. Parasites and cancers: parasite antigens as possible targets for cancer immunotherapy. Future Oncol. 8(12):1529-1535.

Deng B., Gong P., Li J., Cheng B., Ren W., Yang J., Zhang X. 2013. Identification of the differentially expressed genes in SP2/0 myeloma cells from Balb/c mice infected with *Trichinella spiralis*. Vet. Parasitol. 194(2-4):179-182.

Duan L., Li J., Cheng B., Lv Q., Gong P. T., Su L. B., Zhang X. 2013. Identification of a novel gene product expressed by *Trichinella spiralis* that binds antiserum to Sp2/0 myeloma cells. Vet. Parasitol. 194(2-4):183-185.

Duan L. X., Guan X. M., Zhang C. S., Rui P., Ni J., Su Y. M., Zhang X. C. 2011. Research progress on anti-tumor mechanism of *Trichinella spiralis*. Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 29(2):142-146.

Eissa M.M., Ismail C.A., El-Azzouni M.Z., Ghazy A.A., Hadi M.A. 2018. Immuno-therapeutic potential of *Schistosoma mansoni* and *Trichinella spiralis* antigens in a murine model of colon cancer. Invest. New Drugs. 1-10.

Gao J.M., Xu X.F., Lv M., Zuo S.Z., Gong P.T., Yang J., Zhang X.C. 2013. Cloning and prokaryotic expression of the Tsp06172 gene of *Trichinella spiralis* in A549 lung cancer cells. J. Path. Bio. (3):15.

Gawish N. 1975. Parasites and cancer. Egypt J. Bilharz. 2:131-136.

Gong P.T., Zhang X.C., LI J.H., Zhang G.C., Yang J., Cao L.L., Zhang J.Z. 2008. Observation of anti-tumer effect of *Trichinella spirialis* in mice on A549 lung cancer cell [J]. J. Path. Bio. 3:200-202.

Gong P., Zhang J., Cao L., Nan Z., Li J., Yang Zhang X. 2011. Identification and characterization of myeloma-associated antigens in *Trichinella spiralis*. Exp. Parasitol. 127(4):784-788.

Herrera L.A., Ostrosky-Wegman P. 2001. Do helminths play a role in carcinogenesis? Trends Parasitol. 17(4):172-175.

Hulland T.J. 1993. Muscle and tendon. *In:* Pathology of domestic animals, ed. Jubb K.V.F., Kennedy P.C., Palmer N., 4th ed., Academic Press. vol. 1. pp. 253-255.

Kang Y.J., Jo J.O., Cho M.K., Yu H.S., Leem S.H., Song K.S., Ock M.S. Cha H.J. 2013. *Trichinella spiralis* infection reduces tumor growth and metastasis of B16-F10 melanoma cells. Vet. Parasitol. 196(1-2):106-113.

Kristek J., Marjanović K., Dmitrović B., Krajinović Z., Šakić K. 2005. *Trichinella spiralis* and breast carcinoma – a case report. Coll. Antropol. 29(2):775-777.

Liao C., Cheng X., Liu M., Wang X., Boireau P. 2018. *Trichinella spiralis* and tumors: cause, coincidence or treatment? Anti-Cancer Agents Med. Chem. 18(8):1091-1099.

Lichiardopol C., Osman I., Enache S. D., Foarfă C., Comănescu V., Ghiluşi M., Popescu M. 2010. Thyroid regional metastasis from a giant cell malignant fibrous histiocytoma of the larynx in a patient with history of trichinellosis and tuberculosis. Rom. J. Morphol Embryol. 51(2):359-363.

Li H.P., Liu X., Zhang X.Y. 2012. Effect on proliferation of H7402 cell treated with A200711 protein from *Trichinella spiralis* by prokaryotic expression and purification. Chin. J. Lab. Diag. 2.

Liu Y.J., Xu J., Huang H.Y., Xu G.Q. 2015. Inhibitory Effect of the Excretory/Secretory Proteins of *Trichinella spiralis* on Proliferation of Human Hepatocellular Carcinoma HepG2 Cell line. Zhongguo ji sheng chong xue yu ji sheng chong bing za zhi. 33(4):315-317.

Li X., Zhang G.C., Zhang X.C., Li J., Yang J., Gong P., Xu P. 2008. Effect of *Trichinella* on Growth of Human Colorectal Caricinoma HCT-8 Cells in BALB/c Mice [J]. Chin. J. Biol. 4.

Li X., Zhang X. 2009. Change of gene expression in breast cancer MCF-7 cells induced by *Trichinella spiralis* infection in mice. Chin. J. Biol. 22(12):1183-1186.

Li Y.U., Men S.U., Guang-cheng X.I.E., Dan L.I., Yu-yan B.I.N.G., Yan-hui F.A.N.G., Luan-ying D.U. 2018. Effect of the somatic proteins from *Trichinella spiralis* muscle larvae on apoptosis of H446 small cell lung cancer cells. Chin. J. Zoonoses (2):6.

Luo J.M., Cheng L.Y., Guan X.D., Li D., Yu L., Du L.Y. 2016. LC-MS/MS Analysis on the Components of Excretory-secretory Protein of *Trichinella spiralis* Muscle Larvae. Zhongguo ji sheng chong xue yu ji sheng chong bing za zhi. 34(1):53-57.

Luo J., Yu L., Xie G., Li D., Su M., Zhao X., Du L. 2017. Study on the mitochondrial apoptosis pathways of small cell lung cancer H446 cells induced by *Trichinella spiralis* muscle larvae ESPs. Parasitology 144(06):793-800.

Machicado C., Marcos L.A. 2016. Carcinogenesis associated with parasites other than *Schistosoma*, *Opisthorchis* and *Clonorchis*: A systematic review. Int. J. Cancer. 138(12):2915-2921.

Meyer M.C., Olsen O.W. 1975. Order Trichinellidae. *In:* Essentials of parasitology. William C. Brown, Dubuque, IA, pp. 178-182.

Moisan P.G., Lorenz M.D., Stromberg P.C., Simmons H.A. 1998. Concurrent trichinosis and oral squamous cell carcinoma in a cat. J. Vet. Diagn. Invest. 10(2):199-202.

Molinari J.A., Ebersole J.L. 1977. Antineoplastic effects of long-term *Trichinella spiralis* infection on B-16 Melanoma. Int. Arch. Aller. A. Imm. 55:444-448.

Noya V., Bay S., Festari M.F., García E.P., Rodriguez E., Chiale C., Ganneau C., Baleux F., Astrada S., Bollati-Fogolín M., Osinaga E. 2013. Mucin-like peptides from *Echinococcus granulosus* induce antitumor activity. Int. J. Oncol. 43(3):775-784.

Oltean M., Sevastre B., Györke A., Gherman C.M., Irimie A., Tăbăran F., Cozma V. 2012. The anti-tumor potential of *Trichinella* experimental infection. *In:* Program & Abstract Book of XI European Multicolloquium of Parasitology, 352.

Pocock D., Meerovitch E. 1982. The anti-neoplastic effect of trichinellosis in a syngeneic murine model. Parasitology 84:463-473.

Restucci B., De Vico G., Maiolino P. 1991. Rare case of a palpebral melanoma associated with trichinellosis in a dog. Acta. Med. Vet. 37:107-112.

Ruitenberg E.J., Kruizinga W., Steerenberg P.A., Elgersma A., De Jong W.H. 1982. Cimetidine amplifies the anti-neoplastic effect of *Trichinella spiralis* in mice. Br. J. Cancer. 45(2):314.

Shirazi N., Bist S.S., Ahmad S., Harsh M. 2015. *Trichinella spiralis*: Mere Co-Existence or Carcinogenic Parasite For Oral Squamous Cell Carcinoma? J. Clin. Diagn. Res. JCDR. 9(10), ED03.

Skin K., Watts G.F.M., Oettgen H.C., Friend D.S., Pemberton A.D., Gurish M.F., Lee D.M. 2008. Mouse mast cell tryptase mMCP-6 is a critical link between adaptive and innate immunity in the chronic phase of *Trichinella spiralis* infection. J. Immunol. 180(7):4885-4891.

Sofronic-Milosavljevic L., Ilic N., Pinelli E., Gruden-Movsesijan A. 2015. Secretory products of *Trichinella spiralis* muscle larvae and immunomodulation: implication for autoimmune diseases, allergies, and malignancies. J. Immunol. Res. 14.

Stewart G.L., Niederkorn J.Y., Kennedy R.R., Mayhew E. 1991. Effect of acute versus chronic *Trichinella pseudospiralis* infections on systemic cell-mediated immunity. Int. J. Parasitol. 21(8):935-940.

Şuteu I., Cozma V. 2012. Parazitologie clinică veterinară. Vol. 2. [Clinical veterinary parasitology] [in Romanian]. Editura Risoprint, Cluj-Napoca, Romania, Pp 133.

Tsocheva-Gaytandzhieva N., Toshkova R., Gardeva E., Yossifova L., Petkova S., Nanev V. 2016. Antiproliferative activity against tumour cells of biologically active substances isolated from livers of healthy and *Trichinella spiralis* infected rats. C.R. Acad. Bulg. Sci. 69(11).

Vasilev S., Ilic N., Gruden-Movsesijan A., Vasilijic S., Bosic M., Sofronic-Milosavljevic L. 2015. Necrosis and apoptosis in *Trichinella spiralis*-mediated tumour reduction. Cent. Eur. J. Immunol. 40(1):42.

Vennervald B.J., Polman K. 2009. Helminths and malignancy. Parasite Immunol. 31(11):686-696.

Wang X.L., Fu B.Q., Yang S.J. 2009. *Trichinella spiralis* – a potential anti-tumor agent. Vet. Parasitol. 159:249-252.

Wang X.L., Liu M.Y., Sun S.M., Liu X.L., Yu L., Wang X.R., Wang F. 2013. An anti-tumor protein produced by *Trichinella spiralis* induces apoptosis in human hepatoma H7402 cells. Vet. Parasitol. 194(2-4):186-188.

Wing E.J., Krahenbuhl J.L., Remington J.S. 1979. Studies of macrophage function during *Trichinella spiralis* infection in mice. Immunology 36(3):479.

Wu T., Zhang X.C., Li J.H., Liu Q., Yin J.G., Yang J. 2005. Observation of anti-tumer effect of *Trichinella* on sp2/0 myeloma in mice [J]. Chin. J. Parasitic Disease Control 6.

Wu T., Zhang X.C., Li J.H., Zhang G.C., Yang J., Gong P.T. 2007. Observation on antitumous effect of crude *Trichinella* antigen to SP2/0 myeloma in mice [J]. J. Pathogen Biology 4.

Zhang Y., Gong P., Zhang X., Li J., Ju Y., Zhang G. 2009. Anti-tumoral effect of *Trichinella spirialis* on Hepa 1-6 hepatoma carcinoma cell in the C57BL/6 mice. Zhongguo Bingyuan Shengwuxue Zazhi/J. Path. Bio. 4(1):24-26.

Zuo S.Z., Zhang T.J., Chang L., Yang B.T., Gong P.T., Li J.H., Zhang X.C. 2014. Prokaryotic expression and identification of liver cancer cells-associated CK-1 gene of *Trichinella spiralis*. Chin. J. Biol. (4):9.