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Тропомиозины гельминтов: формирование сенсибилизации и связь с аллергической патологией

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АННОТАЦИЯ

Рост аллергических заболеваний явился своего рода драйвером развития технологий в аллергологии: за последние два десятилетия значительный прогресс в области биохимии и молекулярной аллергологии способствовал изучению компонентов аллергенов и развитию компонентной аллергодиагностики. Так, выделены клинически значимые семейства аллергенов, среди которых тропомиозин, способный вызывать широкий спектр перекрёстных IgE-опосредованных реакций. Одним из факторов риска формирования сенсибилизации являются гельминтозы, которые распространены в разных регионах мира, что имеет особую актуальность для населения эндемичных районов. Глобальное распространение гельминтозов остаётся высоким: по оценкам Всемирной организации здравоохранения, 1,5 млрд человек во всём мире хронически инвазированы по крайней мере одним гельминтом.

Цель настоящего обзора — анализ современных исследований, направленных на определение взаимосвязи гельминтных инвазий и развития сенсибилизации к тропомиозину гельминтов, а также клинического течения аллергических заболеваний.

Выполнен анализ научных публикаций, опубликованных за период с 1 января 2000 года по 31 декабря 2021 года. Поиск статей проводился в электронно-поисковой системе PubMed.

Ключевые слова: тропомиозин; гельминтозы; перекрёстные аллергические реакции.

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Tropomyosins of the helminthes: Sensitization and association with allergic diseases

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ABSTRACT

The increase in the prevalence of allergic diseases has been a driver of the development of new technologies. Over the past two decades, significant progress in biochemistry and molecular allergology has contributed to the study of the structure of allergens and development of component-resolved diagnostics. Specifically, clinically significant families of allergens have been identified, including tropomyosin, which can cause various cross-IgE-mediated reactions. One of the risk factors for sensitization development is helminthiasis, which is common in different regions and population of endemic areas. The global prevalence of helminthiasis remains high. Approximately 1.5 billion people worldwide have chronic infections with at least one helminth.

This review aimed to analyze current studies determining the relationship between helminth infections and the development of sensitization to helminth tropomyosin and clinical course of allergic diseases.

The analysis of scientific publications described the relationship between helminth tropomyosin and the development of allergic diseases and sensitization in patients with parasitic infection. The PubMed database was used for the review. The review included original articles published between January 1, 2000, and December 31, 2021.

Keywords: tropomyosin; helminthiasis; cross-allergic reactions.

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INTRODUCTION

The high prevalence of allergic diseases over the past two decades has led to significant progress in the field of biochemistry and molecular allergology, in-depth study of the components of allergens, and development of component allergy diagnostics [1, 2]. This method made it possible to identify clinically significant families of allergenic components, among which tropomyosin is a panallergen capable of inducing several IgE-mediated cross-reactions [3–5]. A high degree of homology among tropomyosins from various invertebrates, such as crustaceans, mollusks, house dust mites, and insects, has been established, which is the molecular basis for cross-reactivity to these allergens [3–5].

In accordance with the nomenclature of allergenic components[1], the most studied tropomyosins to date are found in the following groups of allergens: food (*Pena 1* and *Penm 1*), insects (*Blag 7* and *Aeda 10*), and house dust mites (*Derp 10* and *Derf 10*) [6–11].

In recent years, studies have indicated the possibility of the formation of sensitization to tropomyosins in individuals following helminth invasion. An association has been established between *Anisakis simplex* invasion and the formation of sensitization to *Anis 3* tropomyosin [12, 13]. Tropomyosins of other helminths have also been studied, such as *Onchocerca volvulus* and *Ascaris lumbricoides* (tropomyosin *Ascl 3*) [14–17].

Currently, according to the Committee of Experts of the World Health Organization (WHO), up to 24% of the world's population have parasitic infection [18]. The global prevalence of helminthiases remains high: according to WHO estimates, 1.5 billion people worldwide are infected with at least one helminth [19].

According to official data, a high prevalence of parasitoses is recorded in some regions of the Russian Federation, and up to 86.7% of all parasitic diseases are recorded in children aged <17 years [20]. Regarding biohelminthiases, opisthorchiasis accounted for 79.9%; diphyllobothriasis, 16.7%; dirofilariasis, 0.5%; echinococcosis, 1.9%; alveococcosis, 0.3%; teniasis, 0.1%; teniarhynchosis, 0.1%; clonorchiasis, 0.4%; and trichinosis, 0.2%. According to a recent study, the prevalence of *Opisthorchis felineus* infestation in Western Siberia is 60.2%, including 17.6% among children [21].

This review intends to analyze current studies aimed at determining the relationship between helminthic invasions and the development of sensitization to helminth tropomyosins, as well as the clinical course of allergic diseases.

DATA SOURCES

Studies that present the relationship between helminthic invasions and the development of sensitization to helminth tropomyosins, as well as the clinical course of allergic diseases, were analyzed. The literature search was conducted in PubMed. The review included original articles published between January 1, 2000, and December 31, 2021. During the analysis, the authors used the following algorithm.

Stage 1. In the primary search for publications, the keywords "helminths"/"tropomyosins" were used. Studies corresponding to the listed terms were from the referenced literature sources. At this stage, 304 publications have been analyzed.

Stage 2. Publications' abstracts were analyzed. An additional search criterion was the availability of data on sensitization to helminth tropomyosins and cross-allergic reactions between helminth tropomyosins and tropomyosins of house dust mites, insects, and seafood. Studies that do not have the indicated data (228 publications) were excluded. Articles that aimed at solving different problems, such as genetic research (n=14) and description of the conformational structures of tropomyosins (n=32 publications), were excluded.

Stage 3. The authors carried out a detailed analysis of the full text of 31 publications. At this stage, 11 review publications, 3 clinical cases, and 1 consensus paper were excluded.

RESULTS

Fifteen publications that met the inclusion criteria and represented the results of original research were included in the analysis. The results of studies conducted between 2000 and 2021 are presented in Table 1.

At present, studies have published data on tropomyosin sensitization to pathogens of anisakiasis, ascariasis, schistosomiasis, trichuriasis, ankylostomiasis, filariasis, and toxocariasis. Studies were carried out in various geographical regions endemic to parasitic invasions, namely, South America, Southeast Asia, Mediterranean region, and Norway [12,17, 22–24, 26, 28, 32].

Characterization of tropomyosins

Tropomyosins are proteins included in the composition of muscle fibers of mollusks, crustaceans, arthropods, and helminths and is an α-helix dimer forming a left-handed superhelix [1, 34, 35]. Highly thermostable tropomyosins are the main allergens in crustaceans and mollusks, making them a significant food allergen worldwide. A comparison of 2712 allergen protein molecules with helminth proteins revealed that 217 of them belong to the tropomyosin family [29].

Several studies have analyzed the amino acid sequences of tropomyosins [36–38]. For example, the anisakide allergen *Anis 3* showed the highest level of homology with tropomyosins of other species (46%–75% identity, 61%–89% similarity) [31]. Experimental studies have indicated that sensitization to house dust mite allergens is interrelated with sensitization to helminth proteins due to the molecular structural similarity between homologous tropomyosins [30].

[1] Allergen Nomenclature, WHO/IUIS Allergen Nomenclature Sub-Committee. Financial contribution from IUIS, EAACI, and AAAAI organizations. Access mode: www.allergen.org.

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Table 1. Studies of sensitization to tropomyosin

Country, year	General sample	Diagnosis of allergies/ helminthiases	Investigated tropomyosin	Results
Colombia, 2015 [22]	*n*=356 (asthma), *n*=435 (control) 7–59 years	ISAAC questionnaire; EIA/EIA: sIgE *A. lumbricoides*	*Derp 10*, *Blot 10*, *Ascl 3*	sIgE levels to all allergens in the blood serum are higher in the asthma group than in the control group (123 vs. 47.2 kU/l, p <0.001); sensitization to any of the tropomyosins (*Derp 10*, *Blot 10*, *Ascl 3*) increases the risk of asthma (OR=1.67, 95% CI 0.99–2.84, p=0.05) and at 39–59 years (OR=1.82, 95% CI 1.05–3.17, p=0.03)
Brasil, 2020 [23]	*n*=40 (asthma, AR), *n*=10 (control) 12–75 years	EIA, ImmunoCAP-ISAC, SPT/EIA: sIgE *A. lumbricoides*	*rPera 7*, *rAscl 3*, *Blag 7*, *Anis 3*	SPT results and sIgE measurements (EIA and component allergy diagnostics) showed agreement on k-indices ranging from 0.66 (95% CI 0.42–0.91) to 0.95 (95% CI 0.84–1.0)
Indonesia, 2017 [24]	*n*=1674 (schoolchildren), 5–15 years	ImmunoCAP-ISAC, SPT/stool microscopy, PCR	*rDerp 10*, *Blag 7*, *Anis 3*	The incidence of helminthiasis is 93% (hookworms, *A. lumbricoides,* and *T. trichiura*) with high levels of total IgE (geometric mean 2816 IU/mL). The reactivity in SPT is significantly lower than the sensitization assessed with IgE
Spain, 2000 [12]	*n*=10 (anisakiasis), *n*=62 (sensitization to *A. simplex*), *n*=16 (insect allergy)	Immunoblotting and *in vitro* testing of tropomyosin in *A. simplex*. EIA, SPT/EIA	Cockroach tropomyosin *P. americana*, *Anis 3*, *rDerp10*	None of the 10 sera from patients with anisakiasis responded to *A. simplex* tropomyosin on immunoblotting. With the serum inclusion criterion, sIgE to *A. simplex*, the prevalence increased to 13% (8/62)
Spain, 2020 [25]	*n*=95 (urticaria), *n*=55 (chronic urticaria), *n*=40 (acute urticaria). Control, *n*=305; no urticaria (*n*=182, respiratory allergy; *n*=123, no allergy)	Questionnaire, SPT, component allergy diagnostics, EIA, immunoblotting/immunoassay using whole antigens of *A. simplex* larvae	*Anis 3*	The incidence of sensitization to *Anisakis* or *Toxocara* is 22.70% in healthy controls, 39% in patients with allergy without urticaria, and 53.60% in patients with urticaria. The highest incidence of sensitization is in patients with acute urticaria (60%). The presence of IgE and/or IgG in *Anis 3* may help distinguish between patients with and without urticaria (p <0.001)
Italy, 2017 [26]	*n*=294 (sensitization to *Derm. pter*), 1–18 years	SPT, EIA/EIAsIgE *A. simplex*	*nis 3*, *Derp 10*, *Pena 1*	The prevalence of sensitization to *A. simplex* was 13.43% in patients with sensitization to *Derm. pter* 13.43% and patients without sensitization to *Derm. pter* 3.80% (13.43 vs. 3.80%, p=0.019). A higher prevalence is associated with cross-reactivity with *Derp 10* (OR=8.86, 95% CI 4.33–40.74); (2) patients with shrimp sensitization, 8.63%; patients without shrimp sensitization, 83, and 33% (8.63 vs 83.33%; p <0.0001) of patients with sensitization to *Pena 1* than without sensitization (46.67 vs 7.37%, p <0.0001)

Table 1. Continuation

Country, year	General sample	Diagnosis of allergies/ helminthiases	Investigated tropomyosin	Results
Italy, 2005 [27]	*n*=3 (1 patient with asthma, 2 healthy controls)	SDS-PAGE analysis, immunoblotting, EIA (sIgE *Derm. pter* 18.9 IU/mL, sIgE *A. simplex* 13.7 IU/mL in patients with asthma)/microscopy	*Anis 3*, *Derp 10*	Tropomyosin is not involved in the formation of cross-reactivity. Cross-sensitization is associated with metabolic and somatic proteins with molecular weight ranges of 35–50 kD and >100 kD
USA, 2011 [15]	*n*=126 (21 without filariasis and without atopy; 37 without filariasis and with atopy; 19 with filariasis and without atopy; 49 with filariasis and with atopy)	EIA/ medically verified diagnosis	*OvTrop* and *Derp 10*	The highest levels of IgE and IgG to *Derp 10* were registered in persons infested with filaria, compared with noninfested persons. A relationship was observed between levels of sIgE, IgG, and IgG4 to *OvTrop*- and *Derp 10* (p <0.0001; r >0.79). The amino acid sequence identity between *OvTrop* and *Derp 10* tropomyosins was 72% (87% similarity). Amino acid sequence homology among tropomyosins in which the full-length sequence was available, ranging from 67% to 98% identity (10^{-97} до 10^{-167})
Colombia, 2011 [28]	*n*=345 (with positive sIgE to ascarids: 175 with asthma; 170 without asthma control group from the same areas)	EIA: total IgE, sIgE (⩽0.156 positive), ELISA, SPT, 2D electrophoresis and mass spectrometry, immunoblotting/microscopy	*Derp 10*, *Blot 10*, *Ascl 3*, *rAscl 3*	The amino acid sequence identity was 73%–74% with house dust mites, 71%–74% with crustaceans, 69% with cockroaches, 58% with *S. mansoni*, and <57% with vertebrate tropomyosins. A significant relationship between IgE levels to *rAscl 3* and *A. lumbricoides* (r=0.47, p=0.02) and IgE levels to *rBlot 10* (r=0.80, p=0.001) was observed. The rate of sensitization to *rAscl 3* was higher in patients with asthma than in controls (OR=1.78, 95% CI 1.12–2.83, p=0.01)
USA, 2015 [29]	*n*=372 (plasma donors infected with schistosomiasis), 6–40 years	EIA/tool samples (the Kato-Katz method)	*Betv 1*-like protein (*SmBv1L)* of *S. mansoni*	1389 of 2712 allergenic molecules (~51%) are members of 20 protein domain families. Among these families, tropomyosin (Access No. Pfam:PF00261) makes up 217 allergenic molecules (~8% of all allergens)
Brasil, 2008 [17]	*n*=112 (asthma, AR, cockroach sensitization), 2–52 years); *n*=119 (from *A. lumbricoides* endemic area, 3–6 years); *n*=4 (control group)	EIA (ImmunoCap class ⩾2), SPT/microscopy	*rPera 7*, *Ascl 3*	A correlation was found between the levels of sIgE to *A. lumbricoides* and *P. americana* tropomyosins in the serum of patients and the serum of children from the endemic focus (p <0.0001). *A. lumbricoides* tropomyosin showed 69%–98% sequence identity with other invertebrate tropomyosins. The 284-amino-acid protein sequence showed 90%–98% identity with tropomyosins of other parasites, including *A. simplex and* 74% and 69% identity with house dust mite and cockroach tropomyosins, respectively

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Table 1. Ending

Country, year	General sample	Diagnosis of allergies/ helminthiases	Investigated tropomyosin	Results
USA, 2021 [30]	Mice: sensitized to *Derm. pter* without ascariasis; sensitized to *Derm. pter* with ascariasis; without sensitization to *Derm. pter* with ascariasis; without sensitization to *Derm. pter* without ascariasis	EIA/microscopy	Tropomyosin *Ascaris*, *Derp 10*, *OvTrop*	Sensitization to aeroallergens stimulates the production of reactive helminth antibodies due to the molecular and structural similarities between *Derm. pter* and *Ascaris*. The sequence analysis of 3D structural models showed a high level of homology between *Ascaris* and *Derm. Pter (Derp 10)* tropomyosins with a similarity of 73.94%. Cross-reactivity between *Derm. pter* and helminth antigens (e.g., *Derp 10* and *OvTrop*) may exacerbate Th2/Th17 mixed-allergic lung inflammation
Italy, 2007 [31]	*n*=5598 (Entrez Protein amino acid sequence data bases)	-	*Anis 3*	*Anis 2* and *Anis 3* showed significant homology with 19 known allergens, among them 16 tropomyosins. *Anis 3* (*A. simplex* tropomyosin) showed the highest homology with tropomyosins (46%–75% identity; 61%–89% similarity)
Australia, 2017 [32]	Patients with crustacean allergy, 32±10.5 years; *n*=1 (healthy human serum)	SDS-PAGE, immunoblotting; *A. pegreffii* isolated from flathead tigerfish (*Neoplatyc ephalusrichardsoni*), SSCP sequencing	Recombinant tropomyosin *A. pegreffii*	DNA encoding *A. pegreffii* tropomyosin is 99% similar to *A. simplex*
Colombia, 2015 [33]	*n*=313 (asthma), 8–70 years	EIA/and EIA microscopy	*Ascl 3*, *Derp 10*, *Blot 10*	Sensitization to tropomyosins *Ascl 3* and *Derp 10* is associated with asthma symptoms requiring emergency call more than four times a year (OR=2.23, 95% CI 1.10–4.50, *p*=0.02) (OR=2.44, 95% CI 1.19–4.98, *p*=0.01)

Note: *AR* allergic rhinitis; *EIA* enzyme immunoassay; *ELISA* enzyme-linked immunosorbent assay; ImmunoCAP allergy chip (112 allergen components); *PCR* polymerase chain reaction; SDS-PAGE sodium dodecyl sulfate-polyacrylamide gel electrophoresis; *SSCP* single-stranded conformational polymorphism; *SPT* skin prick tests.

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Formation of sensitization to tropomyosins following helminth invasions

Latent sensitization to house dust mites was established in patients with ascariasis [28]. Tropomyosin *Ascl 3* is an allergen that binds to specific IgE, induces the release of mediators from effector cells, and cross-reacts with house dust mite tropomyosins. Moreover, IgE-dependent reactivity to this allergen is often found in patients with asthma and patients sensitized to total ascaris allergens [28].

Molecular studies have found the cockroach tropomyosin peptide *Blag 7*, which exhibits IgE-dependent cross-reactivity with a similar roundworm tropomyosin molecule (*Ascl 3*) [8]. A significant correlation was also established between the levels of IgE to *rAscl 3* and *rBlot 10* in patients with helminthiasis [8, 17, 28].

A study conducted in Spain revealed a low incidence of sensitization to anisakis allergens in infected patients. Following this finding, a hypothesis has been proposed that exposure to high doses of allergens is necessary for the formation of sensitization, which is not observed with this type of helminthiasis (due to the low concentration of tropomyosins in the cuticle of the parasites) [12]. The prevalence of sensitization to anisakis is higher in patients with sensitization to house dust mites than in individuals without house dust mite sensitization (13.4% vs. 3.8%), which may be due to cross-reactivity to the mite allergen *Der 10* [26].

A study involving patients with anisakidosis caused by *Anisakis pegreffii* established that the tropomyosin of this helminth is not recognized by a monoclonal antibody to crustacean tropomyosins. Moreover, polyclonal antibodies to crustaceans are reactive to *A. pegreffii* tropomyosin [32]. Similar data were obtained in a study using the blood serum of a patient with asthma and sensitization to the house dust mite *Dermatophagoides pteronyssinus* and anisakis allergens based on the assessment of IgE levels. The results of sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis of the patient's serum and control samples revealed that tropomyosins are not involved in the formation of cross-reactivity during sensitization to house dust mites and anisakis. Cross-sensitization in this situation is associated with metabolic and somatic proteins with molecular weights in the range of 35–50 kDa and >100 kDa [27].

Allergological and parasitological examinations of schoolchildren (Indonesia, *n*=1674) revealed that the overall prevalence of various helminthiases was 93% (ankylostomiasis, ascariasis, and trichuriasis). Moreover, a higher prevalence of sensitization to the studied allergens (house dust mites, shrimp, cockroaches, and peanuts) was determined in children with infection according to the enzyme immunoassay compared with the prevalence of sensitization according to the results of skin prick testing. When comparing the results of enzyme immunoassay with those of skin prick testing in individuals with invasion, the intensity of a positive skin reaction is significantly lower than the level of specific IgE [24].

A high identity of the amino acid sequence of roundworm tropomyosins and tropomyosins of *A. simplex* (98%) and filarial parasite *O. volvulus* (95%) was reported. The identity of the amino acid sequence of roundworm tropomyosins with tropomyosins of other species was also determined: the highest identity was found with house dust mites and crustaceans (up to 74%), and the lowest was with vertebrate tropomyosins (<57%) [15, 28].

Several studies have shown the cross-reactivity of helminth tropomyosins with proteins of a similar family of other allergen groups. For example, in a study [15] conducted in the USA (*n*=126), a higher level of IgE to *Derp 10* was detected in patients with filariasis than in individuals without helminthiasis. The identity of the amino acid sequences of *O. volvulus* and *Derp 10* tropomyosins was 72%, and a relationship was also found between the levels of specific antibodies to *O. volvulus* and *Derp 10* tropomyosins.

Clinical significance of sensitization to helminth tropomyosins

Several studies have examined the relationship between sensitization to helminth tropomyosins and characteristics of the clinical course of allergic diseases [22, 23, 25, 33].

A study conducted in Columbia involving patients with ascariasis [28] (Columbia, *n*=345) found that sensitization to recombinant tropomyosin *Ascl 3* is a risk factor for the development of asthma. Thus, the prevalence of sensitization to *Ascl 3* allergen in patients with asthma was 74.9%, whereas it was 62.4% in persons without asthma.

In another study conducted in Columbia [22] (*n*=356, a sample of patients with asthma aged 7–59 years, *n*=435, control sample), tropomyosin sensitization to house dust mites (*D. pteronyssinus* and *Blomia tropicalis*) and *A. lumbricoides* increases the risk of asthma. For example, sensitization to ascaris occurs in 15.4% of patients with asthma (including sensitization to tropomyosin *Ascl 3* in 47.7%), sensitization to house dust mite *B. tropicalis* in 10.6% (including sensitization to tropomyosin *Blot 10* in 41.0%), and sensitization to *D. pteronyssinus* in 28.7% (including sensitization to tropomyosin *Derp 10* in 34.6%). Simultaneous sensitization to both allergens (house dust mite allergens and roundworm allergens) causes an increase in the frequency of asthma symptoms. According to the enzyme immunoassay, the incidence of asthma associated with tropomyosin sensitization (*Ascl 3, Blot 10,* and *Derp 10*) was higher than that of asthma associated with ascaris sensitization (18.2% vs. 15.4%). Thus, sensitization to ascaris and house dust mite tropomyosins is associated with the symptoms of asthma in people living in tropical regions, which has potential clinical significance in the diagnosis and treatment [22].

Conclusive evidence shows that the presence of sensitization to key molecules of the tropomyosin family (*Ascl 3, Derp 10*) makes an important contribution to the severity of asthma. For example, sensitization to *Ascl 3* and *Derp 10* is associated with asthma symptoms and requires emergency medical care more than four times a year [33].

In a study conducted in Brazil, which involved patients with asthma and allergic rhinitis [23] (*n*=40), *A. lumbricoides* tropomyosin increases the reactivity of homologous allergens when inhaled or ingested, causing symptoms and increasing the severity of these diseases.

Another study in Brazil [17] analyzed a sample of allergological clinic patients with asthma or allergic rhinitis and sensitization to cockroach allergens and a sample of children who attended a kindergarten in an endemic area for *A. lumbricoides*. No difference was found in the severity of asthma or allergic rhinitis symptoms between tropomyosin IgE-positive patients and individuals not sensitized to tropomyosins. This study revealed no differences in the frequency of wheezing and lung pathology between children without sensitization and children with ascaris invasion who had high levels of IgE to tropomyosins.

In the available literature, a study explored the relationship between tropomyosin sensitization in the presence of anisakidosis and the nature of the clinical course of urticaria (Spain, *n=95* patients with urticaria, *n=305* individuals without urticaria, among which 182 suffered from allergic diseases and 123 were healthy volunteers) [25]. For example, the incidence of sensitization to tropomyosins evaluated based on the levels of IgE to total extracts of anisakis allergens was 33.7% in individuals with urticaria and 4% in healthy volunteers. The authors put forward recommendations on the possibility of detecting sensitization to *Anis 3* tropomyosin in the diagnosis of acute and chronic urticaria.

CONCLUSION

The results of recent studies aimed at characterizing the relationship between helminth invasions and the development of sensitization to helminth tropomyosins revealed that the data obtained are important for assessing the pathogenesis and clinical course of allergic diseases. Given the widespread prevalence of helminthiases, this problem is of a large scale. The variety of helminthic invasions has led to the development of sensitization in the host organism to parasite tropomyosins. In many studies, the identical amino acid sequences of proteins of the tropomyosin family have made it possible to register cross-reactivity between tropomyosins of helminths and other species (house dust mites, mollusks, etc.).

Based on the results of epidemiological studies, accumulating data have indicated the relationship between sensitization to helminth tropomyosins and the risk of developing allergic diseases and the severity of these pathologies, such as asthma.

Considering several natural foci of helminthiases in the Russian Federation, the study of tropomyosin sensitization in the population of endemic regions is of potential clinical significance for the development of programs for the prevention and treatment of allergic diseases.

ADDITIONAL INFORMATION

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