Helmintos parásitos de importancia veterinaria: regulación de la respuesta inmunitaria del portador y su uso potencial para el tratamiento de enfermedades inflamatorias

Parasitic helminths of veterinary concern: host immune response regulation and potential use for the treatment of inflammatory diseases

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Abstract

In recent years, a new alternative for the treatment of human inflammatory diseases, such as Crohn's disease, by oral administration of eggs from the swine parasitic nematode *Trichuris suis* has attracted attention, based on the capacity of helminths to polarize T helper cells (Th) to Th2 type which inhibits inflammation. In the present review the mechanisms used by parasitic helminths to modify the host immune response are analyzed and their potential use for the treatment of a variety of inflammatory diseases is discussed.

Key words: PARASITIC HELMINTHS, TH1 AND TH2 RESPONSES, INFLAMMATORY DISEASES.

Resumen

En años recientes ha llamado la atención una nueva alternativa para el tratamiento de enfermedades inflamatorias de humanos, como la enfermedad de Crohn, por medio de la administración oral de huevos del nematodo parásito de cerdos *Trichuris suis*, con base en la capacidad que tienen los helmintos de polarizar la respuesta de las células T cooperadoras (Th) a una de tipo Th2 que inhibe la inflamación. En la presente revisión se analizan los mecanismos que utilizan los helmintos parásitos para modificar la respuesta inmunitaria del portador y se discute su uso potencial para el tratamiento de una variedad de enfermedades inflamatorias.

Palabras clave: HELMINTOS PARÁSITOS, RESPUESTAS Th1 Y Th2, ENFERMEDADES INFLAMATORIAS.

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Introduction

Mechanisms of induction of the innate and acquired immune responses

The mammals' immune response is stimulated by foreign substances (antigens) which are recognized by molecules and immunocompetent cells. The protective immunity against microorganism is mediated, for example, by the opportune reactions of the innate immune response and the subsequent responses of the acquired immunity which also provoke an inflammatory response.[1,2] The innate immunity is stimulated by common structures present in groups of microorganisms, while the acquired immunity is specific for different antigens (microbial or not microbial) and it increases by repeated exposure to such antigens;[3] however, the immune system not only can protect a human or animal, but also, under certain circumstances, it can cause damage by immunopathologic or autoimmune mechanisms.[4,5]

Parasitic helminths' immune response modulator mechanisms

In general, the parasitic helminths polarize the immune response of their hosts to a one of Th2-type, evading the Th1-type response which should occur under normal conditions. The Th2-type immune response is characterized by an increase of T CD4+ cells which secrete cytokines such as IL-4, IL-5, IL-9, and IL-13; besides the eosinophils, mast cells and basophils increase in the blood and in the infection site. It is worth noting that the main characteristic is the great amount of IgE that is detected in sera of humans and animals infected by helminths. [6]

With respect to the mentioned cytokines, the IL-4 is the main stimulus for IgE production and for the development of Th2 cells from T CD4+ virgin cells.[7] The IL-5 is an activator of eosinophils and it also functions as a link between T cell activation and the eosinophilic inflammation.[8,9] The IL-13 is a cytokine similar to the IL-4 and carries out an important role in the immune response against helminths.[3] The IL-10 is a cytokine which acts on macrophages and dendritic cells inhibiting IL-12 production, the expression of co-stimulators and of Class II molecules of the main complex of histocompatibility (MCH).[3,10]

In different parasitic infections it has been documented in lesser or greater degree such a response. For example, it has been observed in the following natural or experimental infections: *Heligmosomoides polygyrus*,[11] *Fasciola hepatica*[12] and *Nippostrongylus brasiliensis*[13] in mice; *Strongyloides ratti*[14], *Fasciola hepatica*[15] and *Hymenolepis diminuta*[16] in rats; *Opistorchis viverrini*[17]

Introducción

Mecanismos de inducción de las respuestas inmunitarias innata y adquirida

La respuesta inmunitaria de los mamíferos es estimulada por sustancias extrañas (antígenos) que son reconocidas por moléculas y células inmunocompetentes. La inmunidad protectora contra microorganismos, por ejemplo, es mediada por las reacciones oportunas de la inmunidad innata y las respuestas posteriores de la inmunidad adaptativa que propician una respuesta inflamatoria.[1,2] En este contexto, aquélla es estimulada por estructuras comunes en grupos de microorganismos, mientras que esta última es específica para diferentes antígenos (microbianos o no) y se incrementa por la exposición repetida a dichos antígenos;[3] sin embargo, el sistema inmunitario no solamente puede proteger a un individuo, humano o animal, sino que también, bajo ciertas condiciones, puede causarle daño mediante mecanismos inmunopatológicos o autoinmunes.[4,5]

Mecanismos inmunomoduladores de helmintos parásitos

Los helmintos parásitos polarizan la respuesta inmunitaria de sus portadores a una de tipo Th2, evadiendo la respuesta Th1 que debiera ocurrir bajo condiciones normales. La respuesta inmunitaria tipo Th2 se caracteriza por aumento de células T CD4+ que secretan citocinas como la IL-4, IL-5, IL-9 e IL-13; además, los eosinófilos, células cebadas y basófilos, se incrementan en la sangre y en el sitio de infección. Cabe destacar que la característica principal es la gran cantidad de IgE que se detecta en el suero de humanos y animales infectados por helmintos.[6]

En cuanto a las citocinas señaladas, la IL-4 constituye el principal estímulo para la producción de IgE y para el desarrollo de células Th2 a partir de células cooperadoras vírgenes T CD4+.[7] La IL-5 es un activador de eosinófilos y también funciona como enlace entre la activación de células T y la inflamación eosinofílica.[8,9] La IL-13 es una citocina similar a la IL-4 y desempeña un papel importante en la respuesta inmunitaria contra helmintos.[3] La IL-10 es una citocina que actúa sobre macrófagos y células dendríticas que inhibe la producción de IL-12, la expresión de coestimuladores y de moléculas de clase II del complejo principal de histocompatibilidad (CPH).[3,10]

En diferentes infecciones parasitarias se ha documentado en mayor o menor grado dicha respuesta. Así, por ejemplo, se ha observado en infecciones naturales o experimentales: *Heligmosomoides polygyrus*,[11] *Fasciola hepatica*[12] y *Nippostrongylus brasiliensis*[13] en rato-

and *Ancylostoma ceylanicum*[18] in hamsters; *Ascaridia galli* in chicken;[19] *Toxocara canis*[20] and *Dirofilaria immitis* in dogs;[21] *Toxocara cati* in cats;[22] *Ascaris suum*,[23] *Trichuris suis*[24] and *Schistosoma japonicum* in swine;[25] *Haemonchus contortus*[26] and *Trichostrongylus colubriformis*[27] in sheep; *Fasciola hepatica*,[28-30] *Dictyocaulus viviparous*[31] and *Ostertagia ostertagi* in bovines;[32] *Strongylus vulgaris* in horses;[33] *Trichinella spiralis* and *T. britovi* in humans.[34]

To explain the regulation exerted by parasitic helminths (PH) on the host immune response, it has been proposed that it is due to the multiple and different components of such organisms that interfere with antigen processing; modulate to the antigen presenting cells (for example, dendritic cells —DC—); mimic cytokines and interfere with host cytokines.[35] It has been suggested that the PH regulate the production of Th2 type cytokines at the digestive tract and induce the production of regulatory T cells that can control auto reactive T cells, which from the functional point of view, might limit inflammation.[36]

The PH and their products may modify to the dendritic cells (DC) in different ways that oscillate from influencing DC maturation to affecting activation signals inside these cells (activation of Toll like receptors —TLR—, induction of ERK kinase).[37] Similarly, it has been demonstrated that they favor the increase of alternative activated macrophage (AAM).[38] The AAM are cells stimulated by IL-4, IL-13, IL-10 and IL-21 and they show high expression levels of markers such as arginase-1, CD206 mannose receptor, and IL-4 receptor α (IL-4Rα), including increased expression of IL-10.[39,40] It has been suggested that the AAM functionally carry out three main activities: immune response regulation, wound healing and resistance to parasitic invasion.[40]

Hygiene hypothesis and diseases mediated by the immune system

In developed countries, the incidence of allergic and autoimmune diseases or diseases mediated by the immune system of man, is constantly augmenting —it is estimated that up to date there are more than 40 different diseases that affect to more than 10% of the population in the developed countries—,[41] in contrast with the underdeveloped countries. To explain this fact the hygiene hypothesis has been proposed, where it is established that children from developed countries which have access to vaccines, hygiene and antibiotics —"high hygiene"— present a low exposure to pathogens giving rise to a weak immune response net that in turn provokes an increase of allergic and autoimmune diseases. On the contrary, children from underdeveloped countries which are exposed to frequent helminthic infections and other pathogen

nes; *Strongyloides ratti*,[14] *Fasciola hepatica*[15] e *Hymenolepis diminuta*[16] en ratas; *Opistorchis viverrini*[17] y *Ancylostoma ceylanicum*[18] en hámsteres; *Ascaridia galli* en gallinas;[19] *Toxocara canis*[20] y *Dirofilaria immitis* en perros;[21] *Toxocara cati* en gatos;[22] *Ascaris suum*,[23] *Trichuris suis*[24] y *Schistosoma japonicum* en cerdos;[25] *Haemonchus contortus*[26] y *Trichostrongylus colubriformis*[27] en ovinos; *Fasciola hepatica*,[28-30] *Dictyocaulus viviparous*[31] y *Ostertagia ostertagi* en bovinos;[32] *Strongylus vulgaris* en caballos;[33] *Trichinella spiralis* y *T. britovi* en humanos.[34]

Para explicar la regulación que ejercen los helmintos parásitos (HP) sobre la respuesta inmunitaria, se ha propuesto que se debe a que los múltiples y disímiles componentes de dichos organismos interfieren con el procesamiento de antígeno; modulan a las células presentadoras de antígeno (por ejemplo, células dendríticas-CD); mimetizan citocinas del portador e interfieren con citocinas de éste.[35] Se ha sugerido que los HP regulan la producción de citocinas Th2 en el tracto digestivo e inducen la producción de células T reguladoras que pueden controlar células T autorreactivas, lo que, desde el punto vista funcional, puede limitar la inflamación.[36]

Los HP y sus productos pueden modificar a las células dendríticas (CD) de diferentes maneras que oscilan entre influenciar la maduración de las CD hasta afectar las señales de activación dentro de estas células (activación de receptores tipo Toll-TLR-, inducción de la quinasa ERK).[37] Asimismo, se ha demostrado que favorecen el incremento de macrófagos activados alternativamente (MAA).[38] Los MAA son células estimuladas por IL-4, IL-13, IL-10 e IL-21 que muestran niveles altos de expresión de marcadores como arginasa-1, receptor CD206 de manosa y receptor α de IL-4 (IL-4Rα), incluyendo la expresión incrementada de IL-10.[39,40] Funcionalmente se ha sugerido que los MAA desempeñan al menos tres actividades principales: regulación de la respuesta inmunitaria, cicatrización de heridas y resistencia a la invasión parasitaria.[40]

Hipótesis de la higiene y enfermedades mediadas por el sistema inmunitario

En los países centrales la incidencia de enfermedades alérgicas y autoinmunes o enfermedades mediadas por el sistema inmunitario en el hombre, va en constante aumento —se estima que actualmente hay más de 40 diferentes enfermedades que en conjunto afectan a más del 10% de la población en los países centrales—,[41] a diferencia de los países periféricos o semiperiféricos. Para explicar este fenómeno se ha propuesto la hipótesis de la higiene, donde se establece que los niños de los países centrales que tienen acceso a vacunas, higiene y antibióticos —"higiene alta"— presentan una baja exposición a patógenos,

infections —"low hygiene"— develop a strong regulatory immune response and, as a consequence, they hardly suffer from allergic and autoimmune diseases.[36-38,40,42-45]

Parasitic helminths used for the treatment of some diseases mediated by the immune system

Diverse autoimmune and allergic diseases have been experimentally treated with parasitic helminths (PH) and their products (Table 1), on the grounds that the PH, as previously indicated, modify the host immune response in such a way that they inhibit the inflammatory response (Figure 1).

Use of parasitic helminths or their fractions for the treatment of autoimmune diseases in the future

Up to date, the available information indicates that: *a*) the prevalence of diseases mediated by the immune system (DMIS) in humans increases in areas where strict hygiene practices are carried out; *b*) these practices eliminate the natural exposure to parasitic helminths; *c*) parasitic helminths may prevent DMIS by

ello propicia una red reguladora inmunitaria débil que provoca incremento de enfermedades alérgicas y autoinmunes. Por el contrario, los niños de los países semiperiféricos que se exponen a infecciones helmínticas frecuentes y en los que además ocurre alta exposición a patógenos —"higiene baja"— desarrollan una red reguladora inmunitaria sólida y, por consecuencia, casi no se presentan enfermedades alérgicas y autoinmunes.[36-38,40,42-45]

Helmintos parásitos utilizados para el tratamiento de algunas enfermedades mediadas por el sistema inmunitario

Diversas enfermedades autoinmunes y alérgicas han sido tratadas experimentalmente con helmintos parásitos (HP) y sus productos (Cuadro 1), con base en las observaciones de que los HP, como ya se indicó, para sobrevivir modifican la respuesta inmunitaria de su portador de tal forma que inhiben la respuesta inflamatoria (Figura 1).

Cuadro 1

HELMINTOS UTILIZADOS PARA EL TRATAMIENTO DE ENFERMEDADES AUTOINMUNES Y ALÉRGICAS

HELMINTHS USED FOR THE TREATMENT OF AUTOIMMUNE AND ALLERGIC DISEASES

Helminth	*Used to*	*Reference*
Ascaris suum	Suppress lung inflammation in mice (human asthma model). Protect against eye allergic inflammation in mice (human ocular allergy model)	46-48
Dirofilaria immitis	Inhibit T1D development in NOD mice (human diabetes model)	49
Heligmosomoides polygyrus	Prevent T1D in NOD mice (human diabetes model)	50, 51
Schistosoma mansoni	Prevent type 1 diabetes (T1D) in NOD mice (human diabetes model)	52
	Reduce respiratory tree inflammation in mice (human asthma model)	53
	Lessen the inflammatory activity of autoimmune encephalitis in mice (human multiple sclerosis model)	54
Trichinella spiralis	Prevent T1D in NOD mice (human diabetes model)	50, 51
Trichuris suis	Reduce the inflammatory activity in human bowel inflammatory diseases	41, 55-58

modulating immune responses; *d*) exposure to parasitic helminths may be useful for the treatment of some DMIS in humans (for example, inflammatory bowel diseases, asthma, type 1 diabetes and multiple sclerosis) and probably too in DMIS of domesticated animals.[5]

Due to current success of treating human DMIS with parasitic helminths, these must fulfill the following ideal characteristics for their therapeutic use in humans;[54] *a*) to have negligible or no pathogenic potential; *b*) no capacity of multiplication in the host; *c*) unable to diffuse directly upon close contacts; *d*) produce self-limited colonization in humans; *e*) generate an asymptomatic colonization in humans; *f*) do not alter the behavior in patients with depressed immunity; *g*) not to be affected by common use medicaments; *h*) be eradicated by anthelmintic drugs; *i*) be isolates free of other potential pathogens; *j*) be isolates produced in great quantities; *k*) be stabilized for transport and to store; *l*) be easily administrated.

Discussion

Parasitic helminths, besides producing parasitic diseases with diverse morbidity and mortality, may have a deleterious effect on their hosts, as for example, cause immunosupression to thymus-dependent antigens[59] where the immune response to vaccinal[60,61] and diagnostic antigens is affected, as is the case of the response to diagnostic tuberculosis tests in bovines infec-

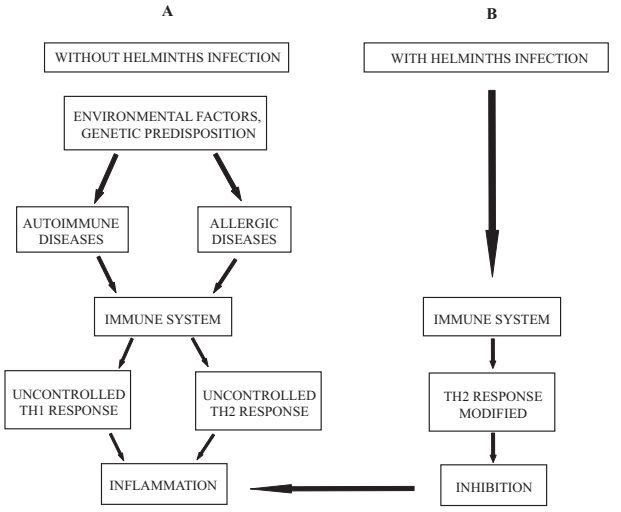

Figura 1: Efecto de los helmintos sobre las respuestas inmunitarias inducidas por enfermedades inflamatorias. A. Respuestas alteradas por enfermedades autoinmunes y alérgicas, sin presencia de helmintos; B, Inhibición de la respuesta inflamatoria en presencia de helmintos.

Figure 1: Effect of helminths on the immune responses induced by inflammatory diseases. A. Responses altered by autoimmune and allergic diseases, without the presence of helminths; B, Inhibition of the inflammatory response in the presence of helminths.

Futuro del uso de helmintos parásitos o sus fracciones para el tratamiento de enfermedades autoinmunes

La información disponible actualmente indica que: *a*) la prevalencia de enfermedades mediadas por el sistema inmunitario (EMSI) en humanos se incrementa en las áreas que practican una atención meticulosa a la higiene; *b*) estas prácticas eliminan la exposición natural a los helmintos parásitos; *c*) los helmintos parásitos pueden prevenir las EMSI por medio de la modificación de las respuestas inmunitarias; *d*) la exposición a helmintos parásitos puede servir para el tratamiento de algunas EMSI de humanos (por ejemplo, enfermedades inflamatorias del intestino, asma, diabetes tipo 1 y esclerosis múltiple) y probablemente también en ESMI de animales domésticos.[5]

Debido al éxito del tratamiento de EMSI con helmintos parásitos hasta la fecha, se han propuesto las siguientes características ideales que deben reunir éstos para su uso terapéutico en humanos;[54] *a*) tener poco o nulo potencial patogénico; *b*) no tener capacidad de multiplicación en el portador; *c*) no difundirse directamente a contactos estrechos; *d*) producir colonización autolimitada en humanos; *e*) producir colonización asintomática en humanos; *f*) no alterar el comportamiento en pacientes con inmunidad deprimida; *g*) no ser afectado por medicamentos de uso común; *h*) ser erradicados con un fármaco antihelmíntico; *i*) ser aislados libres de otros patógenos potenciales; *j*) ser aislados o producidos en grandes cantidades; *k*) ser estabilizados para transporte y almacenamiento; *l*) administrarse fácilmente.

Discusión

Los helmintos parásitos, además de producir parasitosis con morbilidades y mortalidades diversas, pueden tener un efecto perjudicial sobre sus portadores; por ejemplo, causar inmunosupresión a antígenos timodependientes[59] en donde se afecta la respuesta inmunitaria hacia antígenos vacunales,[60,61] y de diagnóstico, como es el caso de la alteración de la respuesta de bovinos infectados con *F. hepatica* a pruebas de diagnóstico de tuberculosis.[62] Sin embargo, existen estudios cada vez más detallados de utilidad de la respuesta inmunitaria del portador contra los helmintos,[63-69] y sus antígenos[70] como terapias alternativas de enfermedades autoinmunes en el humano.[71-73]

El conocimiento de que los helmintos evaden las respuestas de tipo Th1 ha propiciado nuevas estrategias de control de dichos parásitos[74-80] basadas en la estimulación inespecífica de las respuestas Th1 mediante sustancias inmunoestimuladoras.[81-84] Asimismo, se ha indicado que la caracterización de moléculas deriva-

ted with *Fasciola hepatica*.[62] However, there are detailed studies on the usefulness of the host immune response against parasitic helminths,[63-69] and their antigens[70] as alternative therapies of autoimmune diseases in the human being.[71-73]

The knowledge that the parasitic helminths evade Th1 type responses prompted new control strategies against these parasites[74-80] based on the non-specific stimulation of Th1 responses by immunostimulant substances.[81-84] Similarly, it has been indicated that the characterization of molecules derived from helminths which interact with Toll-like receptors and co-receptors that stimulated an anti-inflammatory response might be used for designing new drugs and vaccines[37] and it also might be possible to modulate and selectively induce kinases, such as EKR —involved in the induction of Th2 type responses—, whose absence is related with an increase of autoimmune disease, by analyzing signal pathways stimulated by molecules derived from helminths. [37,86]

Conclusions

The natural or experimental exposure of different host species to parasitic helminths or to their products reduces the harmful immune responses of autoimmune (Th1-type) and allergic (Th2-type) diseases.

There is the possibility of using parasitic helminths (or products derived from them) of domesticated animals as an alternative for the treatment of human autoimmune and allergic diseases.

The study of the diverse host immune mechanisms which act against parasitic helminths will allow the designing of better strategies for the control of these as well as the use of molecules (natives or recombinant) derived from parasitic helminths for the treatment of diseases of man and of his domesticated animals.

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das de los helmintos que interaccionan con receptores tipo Toll y correceptores que estimulan una respuesta antiinflamatoria podría utilizarse para el diseño de nuevos fármacos y vacunas[37] y también sería posible modular e inducir quinasas selectivamente, como la ERK– involucrada en la inducción de respuestas Th2–, cuya ausencia está relacionada con aumento de enfermedad autoinmune,[85] analizando los patrones de señalización estimulados por las moléculas derivadas de helmintos.[37,86]

Conclusiones

La exposición natural o experimental de diversas especies de portadores a helmintos parásitos o a sus productos reduce las respuestas inmunitarias dañinas de las enfermedades autoinmunes (tipo Th1) y alérgicas (tipo Th2).

Existe la posibilidad de utilizar helmintos parásitos (o productos derivados de éstos) de animales domésticos como alternativa viable para el tratamiento tanto de enfermedades autoinmunes como de enfermedades alérgicas del ser humano.

El estudio de los diversos mecanismos que operan la respuesta inmunitaria del portador contra helmintos parásitos permitirá diseñar mejores estrategias para el control de éstos y también la utilización de moléculas (nativas o recombinantes) para el tratamiento de afecciones del hombre y sus animales domésticos.

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