

Trichinella spiralis immunomodulation: an interactive multifactorial process

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Many epidemiological data support the postulate that infection with helminths might provide some protection against allergic and autoimmune diseases. Hence arises the concept that helminths strongly influence the immune system and enable protective pathways against these hyperimmune-associated disorders. This review discusses how *Trichinella spiralis* can make the immune system smarter in dealing with hyperimmune-associated disorders. *T. spiralis* possesses the capacity to direct the immune system towards a mixed Th1/Th2 phenotype with predominance of Th2 response, or it may interfere with dendritic cell maturation, induce the alternatively activated macrophages and elicit the regulatory arm of the immune response via Treg or regulatory B cells.

KEYWORDS: alternatively activated macrophages • dendritic cells • immunomodulation • regulatory B cells • Treg • *Trichinella spiralis*

In 1989, David P Strachan proposed the so-called ‘hygiene hypothesis’, according to which the decreased incidence of infections with parasites and bacteria in developed countries may be the underlying cause for immune system deregulation and consequential development of allergic and autoimmune diseases [1,2]. Epidemiological data support the postulate that infection with helminths, whether acute or chronic, might provide some protection against these diseases. Hence arises the concept that helminths strongly influence the immune system and enable protective pathways against these hyperimmune-associated disorders [3].

Helminths can infect humans for many years and in order to maintain their life cycles, helminths have to modulate the host immune response so that it tolerates the parasite via selective suppression or downregulation of the immune system and initiation of a regulatory environment [1,4]. Over the past two decades, it has become increasingly clear that helminths exert strong immunomodulatory effects in their hosts [5]. One of the most important parasites in this field is *Trichinella spiralis*.

T. spiralis is a unique parasite in which the adult inhabits the small intestine and the larvae encyst in the muscles of the same host. During the intestinal phase, the immune response is mixed Th1/Th2 with initial predominance of the Th1 response and subsequent predominance of the Th2 response [6]. Once a *T. spiralis* adult worm occupies a niche within enterocytes of the jejunum, a well-characterized type 2 cytokine response (IL-4, IL-5, IL-9 and IL-10) orchestrated by CD4⁺ T cells is elicited in the mesenteric lymph nodes, which is subsequently recruited to the gut mucosa [7,8]. Furthermore, the long-lasting infection of muscles with *Trichinella* reflects successful immunomodulation of the immune response, mainly characterized by a Th2 phenotype [9]. Th2 responses to helminths are generally beneficial for the host by repairing or preventing tissue damage caused by the parasite, provided that this response is well controlled [10].

Many experimental results have shown that *Trichinella* spp. infection can ameliorate some immune-mediated diseases (TABLE 1) such as allergic [11] and autoimmune diseases, for example,

Table 1. *Trichinella spiralis* as a new therapeutic era for hyperimmune-associated disorders in experimental studies.

Study (year)	Human disease	Experimental animal model	Ref.
Park <i>et al.</i> (2011)	Asthma and allergic disorders	Ovalbumin-induced experimental allergic airway inflammation	[11]
Khan <i>et al.</i> (2002)	Crohn's disease	Dinitrobenzene sulfonic acid colitis	[12]
Du <i>et al.</i> (2011)		Trinitrobenzene sulfonic acid colitis	[68]
Cho <i>et al.</i> (2012)	Ulcerative colitis	Dextran sulfate sodium colitis	[18]
Ashour <i>et al.</i> (2013)		Acetic acid colitis	[13]
Gruden-Movsesijan <i>et al.</i> (2010)	Multiple sclerosis	Experimental autoimmune encephalomyelitis	[15]
Saunders <i>et al.</i> (2007)	Type 1 diabetes	NOD mouse	[14]

NOD: Non-obese diabetic.

Crohn's disease [12], ulcerative colitis [13], Type 1 diabetes [14] and autoimmune encephalomyelitis [15]. The interpretation of most of these studies depends on the induced Th2 immune response. Skewing of the immune response by most helminths toward Th2 while blocking Th1 response was suggested to attenuate Th1-driven inflammatory responses in the host [12,16]. However, some of those inflammatory disorders ameliorated by *T. spiralis* are characterized by enhanced Th2 response, for example, allergic disorders and ulcerative colitis. These findings suggest that modulation of immune responses by helminth infection may not be restricted to skewing the immune response to a type 2 response. This concept highlighted the possible role of other alternative mechanisms through which helminth infections can regulate the host immune response, for example, induction of Treg, regulatory B cells (Breg), alternatively activated macrophages (AAMs) and modulation of dendritic cells (DCs).

This review will provide a framework for a better understanding of the immunomodulatory role played by *T. spiralis* in order to overcome those hyperinflammatory disorders.

Immunomodulatory mechanisms induced by *T. spiralis*

Regulatory T cells

Helminths can downregulate the immune response via the induction of Treg or the anti-inflammatory cytokines, for example IL-10 and TGF- β , that can regulate both Th1 and Th2 responses [17]. The immunomodulatory effect of *T. spiralis* infection has recently been shown to occur during acute and chronic phases of infection in experimental models of autoimmune and allergic diseases and both phases were associated with increased Treg production, however the amelioration of diseases was stronger during the chronic phase [13,18,19]. *T. spiralis* antigens from all of the parasite's stages induce a network of different mediators that increase Treg populations in the infected host [6]. This immunomodulation is hypothesized to be beneficial to both the human host and the parasite, as it could protect helminths from being eradicated by the excessive immune response and, at the same time, protect the host from excessive inflammatory responses that may lead to organ damage [20].

There are a number of studies that demonstrate the importance of *T. spiralis*-induced Treg in remodeling the immune response [15]. Treg were proven to control Th2-dominated diseases such as

allergy [21]. It is well established that both IL-10 and TGF- β are regulatory cytokines that perform crucial functions in cases of intestinal and muscle trichinellosis in mice [22]. Moreover, IL-10 modulates the function of APCs, reinforces Treg and inhibits cytokine production by Th1 and Th17 cells [23,24].

Th17 cells, which express high levels of IL-17, were found to participate in the progression of many autoimmune diseases. *T. spiralis* was proven to inhibit Th17 cells and downregulate the expression of IL-17 during all stages of infection. *T. spiralis*-induced Treg are able to suppress Th17 cell differentiation through the interaction between Foxp3 and ROR γ t, which are transcription factors of both types of cells, respectively [25,26]. Taken together, Treg have immunosuppressive properties and are characterized by secretion of IL-10 and TGF- β and may act through inhibition of Th17 cells. However, *T. spiralis*-derived products were shown to regulate the immune response without an increase in the Treg population via induction of bone marrow-derived DCs [27].

Regulatory B cells

In addition to immunoglobulin secretion and their role as APCs, B cells have been demonstrated to be capable of cytokine production [28,29]. B cells are able to produce regulatory cytokines such as IL-10. Such cells are called IL-10-producing B cells or Breg. They generate the regulatory immune response via B-cell receptors, CD40 and possibly Toll-like receptor (TLR) signaling [30]. B cells are also able to exert a regulatory function through the production of TGF- β [31] and even via induction or recruitment of Treg [32]. Other mechanisms may involve impairment of DC antigen processing and presentation [33]. Another antibody-mediated mechanism exerted by Breg is to switch to IgG4 production. IgG4 is one of the anti-inflammatory antibody isotypes as it is unable to activate complement. IgG1 also exhibits potent anti-inflammatory activity [34]. Helminth-induced polyclonal IgG production might also serve to restrict excessive inflammatory responses during chronic infection [35].

Cytokines produced by B cells have been described to modulate the differentiation of CD4⁺ T cells toward either Th1 or Th2 cells [29]. Breg are required for polarization of Th cell response toward Th2 phenotype [36]. The effect of Breg on the immunopathology of autoimmune diseases has been studied [37,38]. Breg participate in the suppression of experimental autoimmune

encephalomyelitis [39]. Interestingly, even in rheumatoid arthritis, in which autoantibodies are responsible for the development of the disease, Breg can ameliorate the arthritis by controlling the proinflammatory Th1-type response [38]. Breg have the ability to suppress the progression of chronic intestinal inflammation by enhancing IL-10 production [37]. The suppressive ability of Breg is not restricted to Th1 immune responses associated with autoimmunity as they can also suppress Th2 allergic diseases [35].

Helminth infections may be of particular value in induction of Breg, for example *Schistosoma mansoni* [40] and *Heligmosomoides polygyrus* [41]. Breg have also been described in mice infected with other parasites, for example, *Leishmania major* [36]. Although studies on the regulatory role for helminth-induced Breg have been limited to those few parasites, Breg may represent a broad mechanism of immune modulation by parasites. The exact role of *T. spiralis* infection in the induction of Breg and the exact molecules involved still have to be elucidated.

Regulatory DCs

DCs represent a very important link between innate and adaptive immunity, and they are influenced by various pathogens to orchestrate the immune response [42]. Development of specific immune responses are largely mediated by DCs via antigen presentation and signals that determine polarization of T cells. This immune response is generated in peripheral tissues, then migrated to draining lymph nodes to activate naive T cells [43].

Following exposure to helminths or their products, key changes are observed in the innate immune system of the host, including modification of DCs. DCs are essential in directing the immune response towards activating a pathway via various families of pattern recognition receptors such as TLRs and C-type lectin receptors, which are broadly expressed on DCs and represent the main targets for parasites [44]. Different studies revealed that DCs exposed to helminth antigens lack the conventional characteristics of DC maturation [45]. TLR-mediated activation is inhibited when DCs are costimulated with a broad variety of helminths or their products [46,47]. Helminths can suppress TLR signaling via an increase in the production of IL-10, which contributes to the overall suppressive effects [48]. *S. mansoni* products were found to induce IL-10 production, which has a direct anti-inflammatory effect on the DCs by controlling TLR ligand-induced DC maturation [49]. However, enhanced production of immunoregulatory factors (e.g., IL-10, TGF- β) are not the only mechanism involved. DC populations are being recognized for their potent regulatory ability to limit inflammation [50]. They regulate immune responses through other potential mechanisms, such as suppression of proinflammatory mediator production (e.g., IL-12, TNF- α and IL-6), or increased expansion and/or differentiation of Treg [51,52].

DCs stimulated by *T. spiralis* excretory/secretory (ES) products secreted greatly elevated amounts of IL-10 and TGF- β [53]. At the same time, DC activation in response to TLR ligands was dramatically suppressed by *T. spiralis* ES products, which indicates the potential of *T. spiralis*-stimulated DC to provoke regulatory responses resulting in the generation of a regulatory DC phenotype [54]. This regulatory function proceeds in a generalized manner

irrespective of their Th1 or Th2 phenotypic affiliation [46,54,55]. Moreover, Gruden-Movsesijan *et al.* demonstrated that the application of *T. spiralis*-sensitized DC successfully induces an immune response that was maintained for 30 days after their intraperitoneal injection [56]. This is a promising tool to avoid application of live parasites for the treatment of various autoimmune and allergic diseases.

Alternatively activated macrophages

Peripheral blood mononuclear macrophages can be differentiated according to macrophage polarization into two phenotypes in tissues: classically activated macrophages and AAMs [57]. Classically activated macrophages are activated by Th1 cytokines of the infected host, for example, IL-12 and IFN- γ , and enhance the immune responses resulting in tissue injury; whereas AAMs are activated by Th2 cytokines, IL-4 and IL-13, with increased levels of IL-10 and TGF- β that can control excessive immune responses and restructure the injured tissues [58,59]. Helminth infections have been suggested to induce the alternatively activated phenotype [60]. AAMs are recruited by a range of different helminth infections, for example, *H. polygyrus* [61] and *Brugia malayi* [62]. AAMs have the ability to suppress T-cell responses via production of regulatory cytokines such as TGF- β and IL-10 and driving the T cell toward a Treg activity [63,64]. Moreover, helminths molecules may also activate macrophages directly, independently of effects on T cells, for example chitin, a helminth structural molecule, which has been demonstrated to induce the alternatively activated phenotype [65].

ES products from different stages of *T. spiralis* can modulate macrophage function *in vitro* toward the alternative phenotype by inhibiting proinflammatory cytokine production, for example, TNF- α , IL-1 β , IL-6 and IL-12, resulting in reduction of the severity of inflammatory diseases [66]. Tissue repair produced by AAM mainly occurs through the increased arginase-1 (Arg1) activity, which results in increased levels of L-ornithine and urea being produced via L-arginine hydrolysis. This drives the production of polyamines, which in turn induce proline synthesis required for collagen deposition [67]. Du *et al.* demonstrated that *T. spiralis* ES products evoked AAM bias *in vivo* [68]. However, whether those AAMs are induced through direct action on macrophages or through other immune cells such as DCs is still to be elucidated.

The influence of helminth products on the innate immune system is not just restricted to DCs and macrophages. NK cells have two key functions, namely cytotoxicity and cytokine secretion, through which they can direct the immune response in an appropriate direction [69]. Mallevaey *et al.* provided evidence that NK cells are important players in the acquired immune response during helminth infection [70]. It was suggested that NK cell activity is stimulated during migration and early muscle phases of *T. spiralis* infection [71]. However, it was found that the intestinal epithelial cells during *T. spiralis* infection respond directly to the NK cell-derived IL-13, which is responsible for the intestinal tissue restructuring associated with *T. spiralis* infection [72].

Nielsen *et al.* have proven that NK cells play a role in regulation of autoimmune diseases via modulation of T-cell responses [73]. They found that NK cells efficiently killed activated, but

Box 1. How far have we got in helminth therapy using *Trichinella spiralis*?

- Many experimental studies have proven the role of *Trichinella spiralis* in amelioration of many allergic and autoimmune diseases [11–15].
- It is clear that the administration of live *T. spiralis* larvae carries potential risks. Thus, it became the focus of current research to characterize the active molecules of *T. spiralis*.
- Some experimental studies tried to make use of *T. spiralis*-derived molecules or sensitized cells and they have achieved the same immunomodulatory effect:
 - Motomura *et al.* [80] used crude muscle larval antigens via rectal submucosal administration.
 - Du *et al.* [68] used recombinant 53-kDa protein of *T. spiralis* via subcutaneous injection.
 - Sofronic-Milosavljevic *et al.* [53] used dendritic cells stimulated with ES larval products of *T. spiralis* muscle larvae via intraperitoneal injection.

ES: Excretory/secretory.

not resting, CD4⁺ T cells. Moreover, it was demonstrated that depletion of NK cells is linked with dramatic increases in colonic damage, leukocyte infiltration and proinflammatory profiles in induced colitis in mice [74]. With regard to the role played by helminth-induced NK cells, Zacccone *et al.* [75] demonstrated that infection with *S. mansoni* inhibits the development of Type 1 diabetes in mice and that this protective effect could be due to NK cell activation. Taken together, it is possible that the immunomodulation of *T. spiralis* infection could be in part interpreted by the role of NK cells.

IgE blocking hypothesis

This mechanism is suggested for the downregulation of allergic diseases by helminths. Helminths induce Th2 response that produce high levels of IL-4, IL-5, IL-9 and IL-13. These cytokines mediate immune response characterized by increased levels of circulating IgE antibodies [76]. Helminths, including *T. spiralis*, produce large amounts of polyclonal nonspecific IgE for their protection from mast cell or basophil degranulation by saturating the IgE binding sites on these cells, thereby inhibiting the binding of allergen-specific IgE [77]. Because IgE against allergens and parasites bind competitively with the Fcε receptors of mast cells or basophils, parasite-specific or non-specific IgE might block the inflammatory mediator release from mast cells and consequently, allergic responses could be ameliorated [11]. Moreover, Wang *et al.* [78] showed that high levels of total serum IgE induced by helminth infection could suppress the synthesis of antigen-specific IgE in the lungs.

Another proposed mechanism is that helminth infections are correlated with high levels of IgG4, and it has been shown that parasite-specific IgG4 antibodies can inhibit IgE-mediated degranulation of effector cells [79].

Expert commentary

T. spiralis causes the immune system to act more 'smartly' in dealing with hyperimmune-associated disorders. It possesses the capacity to direct the immune system towards the mixed Th1/Th2 phenotype with a predominance of Th2 response, or it may interfere with DC maturation, induce the AAMs and elicit the regulatory arm of immune response via Treg or Breg. Future investigations may provide a better insight into the mechanisms involved in immunomodulation by helminths in general and *T. spiralis* in particular.

Five-year view

Trials with live helminth therapy are encouraging, however it may be psychologically hard to accept by some patients and it may have some drawbacks. Therefore, it is expected that the identification and purification of helminth-derived molecules to exploit highly purified safe helminth products will proceed in order to prevent allergic and autoimmune diseases. Antigens from all life stages of *T. spiralis* could be involved in the immunomodulatory process, so different antigens from the different stages could be investigated; these could include, for example, crude adult or muscle larvae antigens, ES products of adult or muscle larvae and newborn larvae antigens (Box 1).

Key issues

- *Trichinella spiralis* has been shown to ameliorate some inflammatory disorders such as allergic and autoimmune diseases in animal models, for example Type 1 diabetes and inflammatory bowel disease.
- Skewing of the immune response by *T. spiralis* toward Th2 while blocking Th1 response was the suggested hypothesis to attenuate Th1-driven inflammatory responses in the host.
- *T. spiralis* induces Treg, which have immunosuppressive properties and are characterized by the secretion of IL-10 and TGF-β and inhibition of Th17 cells.
- *T. spiralis* inhibits TLR-mediated activation of dendritic cells, which is associated with increased production of the anti-inflammatory cytokines (IL-10 and TGF-β).
- *T. spiralis* induces the production of alternatively activated macrophages that have the ability to suppress T-cell responses via production of regulatory cytokines such as TGF-β and IL-10 and driving the T cell toward a Treg activity.
- Regulatory B cells and NK cells may have a role in downregulating the immune response during *T. spiralis* infection. Regulatory B cells are capable of increased production of regulatory cytokines (IL-10 and TGF-β) and may act via induction of Treg. NK cells act via killing of activated CD4⁺ T cells.

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References

Papers of special note have been highlighted as:

• of interest

- 1 Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science* 296(5567), 490–494 (2002).
- 2 Strachan DP. Family size, infection and atopy: the first decade of the “hygiene hypothesis”. *Thorax* 55(Suppl. 1), S2–S10 (2000).
- 3 Weinstock JV, Summers RW, Elliott DE, Qadir K, Urban JF Jr, Thompson R. The possible link between de-worming and the emergence of immunological disease. *J. Lab. Clin. Med.* 139(6), 334–338 (2002).
- 4 Belkaid Y, Blank RB, Suffia I. Natural regulatory T cells and parasites: a common quest for host homeostasis. *Immunol. Rev.* 212, 287–300 (2006).
- 5 Maizels RM, Balic A, Gomez-Escobar N, Nair M, Taylor MD, Allen JE. Helminth parasites—masters of regulation. *Immunol. Rev.* 201, 89–116 (2004).
- 6 Ilic N, Gruden-Movsesijan A, Sofronic-Milosavljevic L. *Trichinella spiralis*: shaping the immune response. *Immunol. Res.* 52(1-2), 111–119 (2012).
- Focuses on the ability of *Trichinella spiralis* to polarize the immune response toward Th2 and regulatory mode *in vitro* and *in vivo* and its ability to modulate autoimmune disease.
- 7 McDermott JR, Grecis RK, Else KJ. Leucocyte recruitment during enteric nematode infection. *Immunology* 103(4), 505–510 (2001).
- 8 Helmbj H, Grecis RK. IFN- γ -independent effects of IL-12 during intestinal nematode infection. *J. Immunol.* 171(7), 3691–3696 (2003).
- 9 Bruschi F, Chiumiento L. *Trichinella* inflammatory myopathy: host or parasite strategy? *Parasit. Vectors* 4, 42 (2011).
- 10 Wilson MS, Mentink-Kane MM, Pesce JT, Ramalingam TR, Thompson R, Wynn TA. Immunopathology of schistosomiasis. *Immunol. Cell Biol.* 85(2), 148–154 (2007).
- 11 Park HK, Cho MK, Choi SH, Kim YS, Yu HS. *Trichinella spiralis*: infection reduces airway allergic inflammation in mice. *Exp. Parasitol.* 127(2), 539–544 (2011).
- 12 Khan WI, Blennerhasset PA, Varghese AK *et al.* Intestinal nematode infection ameliorates experimental colitis in mice. *Infect. Immun.* 70(11), 5931–5937 (2002).
- 13 Ashour DS, Othman AA, Shareef MM, Gaballah HH, Mayah WW. Interactions between *Trichinella spiralis* infection and induced colitis in mice. *J. Helminthol.* doi:10.1017/S0022149X13000059, 1–9 (2013) (Epub ahead of print).
- 14 Saunders KA, Raine T, Cooke A, Lawrence CE. Inhibition of autoimmune type 1 diabetes by gastrointestinal helminth infection. *Infect. Immun.* 75(1), 397–407 (2007).
- 15 Gruden-Movsesijan A, Ilic N, Mostarica-Stojkovic M, Stosic-Grujicic S, Milic M, Sofronic-Milosavljevic L. Mechanisms of modulation of experimental autoimmune encephalomyelitis by chronic *Trichinella spiralis* infection in Dark Agouti rats. *Parasite Immunol.* 32(6), 450–459 (2010).
- 16 Liu Q, Sundar K, Mishra PK *et al.* Helminth infection can reduce insulinitis and Type 1 diabetes through CD25- and IL-10-independent mechanisms. *Infect. Immun.* 77(12), 5347–5358 (2009).
- 17 Freeman CM, Chiu BC, Stolberg VR *et al.* CCR8 is expressed by antigen-elicited, IL-10-producing CD4⁺CD25⁺ T cells, which regulate Th2-mediated granuloma formation in mice. *J. Immunol.* 174(4), 1962–1970 (2005).
- 18 Cho MK, Park MK, Kang SA, Choi SH, Ahn SC, Yu HS. *Trichinella spiralis* infection suppressed gut inflammation with CD4⁺CD25⁺Foxp3⁺ T cell recruitment. *Korean J. Parasitol.* 50(4), 385–390 (2012).
- 19 Aranzamendi C, de Bruin A, Kuiper R *et al.* Protection against allergic airway inflammation during the chronic and acute phases of *Trichinella spiralis* infection. *Clin. Exp. Allergy* 43(1), 103–115 (2013).
- 20 Grainger JR, Smith KA, Hewitson JP *et al.* Helminth secretions induce *de novo* T cell Foxp3 expression and regulatory function through the TGF- β pathway. *J. Exp. Med.* 207(11), 2331–2341 (2010).
- 21 McKay DM. The therapeutic helminth? *Trends Parasitol.* 25(3), 109–114 (2009).
- 22 Beiting DP, Gagliardo LF, Hesse M, Bliss SK, Meskill D, Appleton JA. Coordinated control of immunity to muscle stage *Trichinella spiralis* by IL-10, regulatory T cells, and TGF- β . *J. Immunol.* 178(2), 1039–1047 (2007).
- 23 Mills KH, McGuirk P. Antigen-specific regulatory T cells—their induction and role in infection. *Semin. Immunol.* 16(2), 107–117 (2004).
- 24 Liu B, Tonkonogy SL, Sartor RB. Antigen-presenting cell production of IL-10 inhibits T-helper 1 and 17 cell responses and suppresses colitis in mice. *Gastroenterology* 141(2), 653–662, 662.e1 (2011).
- 25 Chen Z, Lin F, Gao Y *et al.* FOXP3 and ROR γ t: transcriptional regulation of Treg and Th17. *Int. Immunopharmacol.* 11(5), 536–542 (2011).
- 26 Elliott DE, Weinstock JV. Helminth-host immunological interactions: prevention and control of immune-mediated diseases. *Ann. N. Y. Acad. Sci.* 1247, 83–96 (2012).
- 27 Ilic N, Worthington JJ, Gruden-Movsesijan A, Travis MA, Sofronic-Milosavljevic L, Grecis RK. *Trichinella spiralis* antigens prime mixed Th1/Th2 response but do not induce *de novo* generation of Foxp3⁺ T cells *in vitro*. *Parasite Immunol.* 33(10), 572–582 (2011).
- 28 Pape KA, Catron DM, Itano AA, Jenkins MK. The humoral immune response is initiated in lymph nodes by B cells that acquire soluble antigen directly in the follicles. *Immunity* 26(4), 491–502 (2007).
- 29 Harris DP, Haynes L, Sayles PC *et al.* Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nat. Immunol.* 1(6), 475–482 (2000).
- 30 Fillatreau S, Sweeney CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. *Nat. Immunol.* 3(10), 944–950 (2002).
- 31 DiLillo DJ, Matsushita T, Tedder TF. B10 cells and regulatory B cells balance immune responses during inflammation, autoimmunity, and cancer. *Ann. N. Y. Acad. Sci.* 1183, 38–57 (2010).
- 32 van der Vlugt LE, Labuda LA, Ozir-Fazalikhani A *et al.* Schistosomes induce regulatory features in human and mouse CD1d(hi) B cells: inhibition of allergic inflammation by IL-10 and regulatory T cells. *PLoS ONE* 7(2), e30883 (2012).

- 33 Everts B, Adegnika AA, Kruize YC, Smits HH, Kremsner PG, Yazdanbakhsh M. Functional impairment of human myeloid dendritic cells during *Schistosoma haematobium* infection. *PLoS Negl. Trop. Dis.* 4(4), e667 (2010).
- 34 Anthony RM, Nimmerjahn F, Ashline DJ, Reinhold VN, Paulson JC, Ravetch JV. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. *Science* 320(5874), 373–376 (2008).
- 35 Husaarts L, van der Vlugt LE, Yazdanbakhsh M, Smits HH. Regulatory B-cell induction by helminths: implications for allergic disease. *J. Allergy Clin. Immunol.* 128(4), 733–739 (2011).
- 36 Ronet C, Hauyon-La Torre Y, Revaz-Breton M *et al.* Regulatory B cells shape the development of Th2 immune responses in BALB/c mice infected with *Leishmania major* through IL-10 production. *J. Immunol.* 184(2), 886–894 (2010).
- 37 Mizoguchi A, Mizoguchi E, Takedatsu H, Blumberg RS, Bhan AK. Chronic intestinal inflammatory condition generates IL-10-producing regulatory B cell subset characterized by CD1d upregulation. *Immunity* 16(2), 219–230 (2002).
- 38 Mauri C, Gray D, Mushtaq N, Londei M. Prevention of arthritis by interleukin 10-producing B cells. *J. Exp. Med.* 197(4), 489–501 (2003).
- 39 Wolf SD, Dittel BN, Hardardottir F, Janeway CA Jr. Experimental autoimmune encephalomyelitis induction in genetically B cell-deficient mice. *J. Exp. Med.* 184(6), 2271–2278 (1996).
- 40 Hernandez HJ, Wang Y, Staderker MJ. In infection with *Schistosoma mansoni*, B cells are required for T helper type 2 cell responses but not for granuloma formation. *J. Immunol.* 158(10), 4832–4837 (1997).
- 41 Wilson MS, Taylor MD, O’Gorman MT *et al.* Helminth-induced CD19⁺CD23^{hi} B cells modulate experimental allergic and autoimmune inflammation. *Eur. J. Immunol.* 40(6), 1682–1696 (2010).
- 42 Lipscomb MF, Masten BJ. Dendritic cells: immune regulators in health and disease. *Physiol. Rev.* 82(1), 97–130 (2002).
- 43 Kapsenberg ML. Dendritic-cell control of pathogen-driven T-cell polarization. *Nat. Rev. Immunol.* 3(12), 984–993 (2003).
- 44 Duez C, Gosset P, Tonnel AB. Dendritic cells and toll-like receptors in allergy and asthma. *Eur. J. Dermatol.* 16(1), 12–16 (2006).
- 45 MacDonald AS, Maizels RM. Alarming dendritic cells for Th2 induction. *J. Exp. Med.* 205(1), 13–17 (2008).
- 46 Segura M, Su Z, Piccirillo C, Stevenson MM. Impairment of dendritic cell function by excretory-secretory products: a potential mechanism for nematode-induced immunosuppression. *Eur. J. Immunol.* 37(7), 1887–1904 (2007).
- 47 Ferret-Bernard S, Curwen RS, Mountford AP. Proteomic profiling reveals that Th2-inducing dendritic cells stimulated with helminth antigens have a ‘limited maturation’ phenotype. *Proteomics* 8(5), 980–993 (2008).
- 48 Barton GM, Medzhitov R. Control of adaptive immune responses by Toll-like receptors. *Curr. Opin. Immunol.* 14(3), 380–383 (2002).
- 49 Kane CM, Cervi L, Sun J *et al.* Helminth antigens modulate TLR-initiated dendritic cell activation. *J. Immunol.* 173(12), 7454–7461 (2004).
- 50 Pulendran B, Tang H, Manicassamy S. Programming dendritic cells to induce T(H)2 and tolerogenic responses. *Nat. Immunol.* 11(8), 647–655 (2010).
- 51 Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. *Annu. Rev. Immunol.* 21, 685–711 (2003).
- 52 Klaver EJ, Kuijk LM, Laan LC *et al.* *Trichuris suis*-induced modulation of human dendritic cell function is glycan-mediated. *Int. J. Parasitol.* 43(3–4), 191–200 (2013).
- 53 Sofronic-Milosavljevic L, Radovic I, Ilic N, Majstorovic I, Cvetkovic J, Gruden-Movsesijan A. Application of dendritic cells stimulated with *Trichinella spiralis* excretory-secretory antigens alleviates experimental autoimmune encephalomyelitis. *Med. Microbiol. Immunol.* doi:10.1007/s00430-012-0286-6 (2013) (Epub ahead of print).
- **Demonstrates that even dendritic cells stimulated by *T. spiralis* antigen could ameliorate autoimmune diseases.**
- 54 Langelaar M, Aranzamendi C, Franssen F *et al.* Suppression of dendritic cell maturation by *Trichinella spiralis* excretory/secretory products. *Parasite Immunol.* 31(10), 641–645 (2009).
- 55 Ilic N, Colic M, Gruden-movsesijan A, Majstorovic I, Vasilev S, Sofronic-Milosavljevic Lj. Characterization of rat bone marrow dendritic cells initially primed by *Trichinella spiralis* antigens. *Parasite Immunol.* 30(9), 491–495 (2008).
- 56 Gruden-Movsesijan A, Ilic N, Colic M *et al.* The impact of *Trichinella spiralis* excretory-secretory products on dendritic cells. *Comp. Immunol. Microbiol. Infect. Dis.* 34(5), 429–439 (2011).
- ***T. spiralis* antigens induce partial maturation of dendritic cells that elicit regulatory responses.**
- 57 Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. *Front. Biosci.* 13, 453–461 (2008).
- 58 Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 macrophages and the Th1/Th2 paradigm. *J. Immunol.* 164(12), 6166–6173 (2000).
- 59 Brown BN, Valentin JE, Stewart-Akers AM, McCabe GP, Badylak SF. Macrophage phenotype and remodeling outcomes in response to biologic scaffolds with and without a cellular component. *Biomaterials* 30(8), 1482–1491 (2009).
- 60 Horsnell WG, Brombacher F. Genes associated with alternatively activated macrophages discretely regulate helminth infection and pathogenesis in experimental mouse models. *Immunobiology* 215(9–10), 704–708 (2010).
- 61 Reynolds LA, Filbey KJ, Maizels RM. Immunity to the model intestinal helminth parasite *Heligmosomoides polygyrus*. *Semin. Immunopathol.* 34(6), 829–846 (2012).
- 62 Semnani RT, Mahapatra L, Moore V, Sanprasert V, Nutman TB. Functional and phenotypic characteristics of alternative activation induced in human monocytes by interleukin-4 or the parasitic nematode *Brugia malayi*. *Infect. Immun.* 79(10), 3957–3965 (2011).
- 63 Loke P, MacDonald AS, Allen JE. Antigen-presenting cells recruited by *Brugia malayi* induce Th2 differentiation of naïve CD4⁺ T cells. *Eur. J. Immunol.* 30(4), 1127–1135 (2000).
- 64 Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nat. Rev. Immunol.* 5(12), 953–964 (2005).
- 65 Reese TA, Liang HE, Tager AM *et al.* Chitin induces accumulation in tissue of innate immune cells associated with allergy. *Nature* 447(7140), 92–96 (2007).
- 66 Bai X, Wu X, Wang X *et al.* Regulation of cytokine expression in murine macrophages stimulated by excretory/secretory products from *Trichinella spiralis* *in vitro*. *Mol. Cell. Biochem.* 360(1–2), 79–88 (2012).
- ***T. spiralis* excretory/secretory products regulate host immune response through**

induction of macrophages toward the alternative phenotype.

- 67 Hesse M, Modolell M, La Flamme AC *et al.* Differential regulation of nitric oxide synthase-2 and arginase-1 by type 1/type 2 cytokines *in vivo*: granulomatous pathology is shaped by the pattern of L-arginine metabolism. *J. Immunol.* 167(11), 6533–6544 (2001).
- 68 Du L, Tang H, Ma Z *et al.* The protective effect of the recombinant 53-kDa protein of *Trichinella spiralis* on experimental colitis in mice. *Dig. Dis. Sci.* 56(10), 2810–2817 (2011).
- **Demonstrated that *T. spiralis* ES protein (TsP53) is an effective agent to prevent experimental colitis. However, it may cause possible adverse effects such as allergic reaction. Therefore, there are many practical questions that should be solved in the next few years.**
- 69 Strowig T, Brilot F, Münz C. Noncytotoxic functions of NK cells: direct pathogen restriction and assistance to adaptive immunity. *J. Immunol.* 180(12), 7785–7791 (2008).
- 70 Mallevaey T, Fontaine J, Breuilh L *et al.* Invariant and noninvariant natural killer T cells exert opposite regulatory functions on the immune response during murine schistosomiasis. *Infect. Immun.* 75(5), 2171–2180 (2007).
- 71 Bany J, Janiak MK, Budzynski W. Activity of natural killer (NK) cells in the course of experimental trichinellosis in mice. *Wiad. Parazytol.* 38(3–4), 117–126 (1992).
- 72 McDermott JR, Humphreys NE, Forman SP, Donaldson DD, Grecis RK. Intraepithelial NK cell-derived IL-13 induces intestinal pathology associated with nematode infection. *J. Immunol.* 175(5), 3207–3213 (2005).
- 73 Nielsen N, Ødum N, Ursø B, Lanier LL, Spee P. Cytotoxicity of CD56(bright) NK cells towards autologous activated CD4⁺ T cells is mediated through NKG2D, LFA-1 and TRAIL and dampened via CD94/NKG2A. *PLoS ONE* 7(2), e31959 (2012).
- 74 Hall LJ, Murphy CT, Quinlan A *et al.* Natural killer cells protect mice from DSS-induced colitis by regulating neutrophil function via the NKG2A receptor. *Mucosal Immunol.* doi:10.1038/mi.2012.140 (2013) (Epub ahead of print).
- 75 Zaccane P, Fehérvári Z, Jones FM *et al.* *Schistosoma mansoni* antigens modulate the activity of the innate immune response and prevent onset of Type 1 diabetes. *Eur. J. Immunol.* 33(5), 1439–1449 (2003).
- 76 Oettgen HC, Geha RS. IgE regulation and roles in asthma pathogenesis. *J. Allergy Clin. Immunol.* 107(3), 429–440 (2001).
- 77 Erb KJ. Helminths, allergic disorders and IgE-mediated immune responses: where do we stand? *Eur. J. Immunol.* 37(5), 1170–1173 (2007).
- 78 Wang CC, Nolan TJ, Schad GA, Abraham D. Infection of mice with the helminth *Strongyloides stercoralis* suppresses pulmonary allergic responses to ovalbumin. *Clin. Exp. Allergy* 31(3), 495–503 (2001).
- 79 Hussain R, Poindexter RW, Ottesen EA. Control of allergic reactivity in human filariasis. Predominant localization of blocking antibody to the IgG4 subclass. *J. Immunol.* 148(9), 2731–2737 (1992).
- 80 Motomura Y, Wang H, Deng Y, El-Sharkawy RT, Verdu EF, Khan WI. Helminth antigen-based strategy to ameliorate inflammation in an experimental model of colitis. *Clin. Exp. Immunol.* 155(1), 88–95 (2009).

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