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REVIEW ARTICLE

Parasites and immunotherapy: with or against?

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Abstract Immunotherapy is a sort of therapy in which antibody or antigen administrates to the patient in order to treat or reduce the severity of complications of disease. This kind of treatment practiced in a wide variety of diseases including infectious diseases, autoimmune disorders, cancers and allergy. Successful and unsuccessful immunotherapeutic strategies have been practiced in variety of parasitic infections. On the other hand parasites or parasite antigens have also been considered for immunotherapy against other diseases such as cancer, asthma and multiple sclerosis. In this paper immunotherapy against common parasitic infections, and also immunotherapy of cancer, asthma and multiple sclerosis with parasites or parasite antigens have been reviewed.

Keywords Immunotherapy · Parasitic diseases · Parasite · Cancer · Asthma · Multiple Sclerosis

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Introduction

Immunotherapy, which is also called biotherapy, is defined as uses of biological substances to regulate or adjust responses of human or animal's immune system to fulfill a prophylactic and/or therapeutic goals. In immunotherapy, immunomodulators or biological response regulators interfere with immune system. Therefore, immunotherapeutic agents can directly or indirectly raise bodie's natural defenses (Okwor and Uzonna 2009; Oldham 1988).

Currently two types of immunotherapy are mostly used. The first type, which is called antibody based or passive immunotherapy, is used for variety of diseases such as cancer (Noguchi et al. 2013; Tse et al. 2014; Weiner et al. 2012), cryptosporidiosis (Crabb 1998; Fayer et al. 1990; Riggs et al. 1994; Santín and Trout 2009) and malaria (Schofield et al. 1993). Another type of immunotherapy is antigen based or active immunotherapy. this method of therapy is used for cancer (Hsueh and Morton 2003), leishmaniasis (Carrero Rangel et al. 2011), autoimmune disorders(Adorini and Sinigaglia 1997; Liu 2003) and allergy (Yazdanbakhsh et al. 2002). Furthermore DNA vaccines are used not only for prophylaxis, but also for successful immunotherapy (Liu 2003, 2011). Generally, the objective of passive immunotherapy is to generate a quick and momentary protection or to sedate the existing state of disease, whilst immunization in active form will induce immune system and produce immunologic memory that results in a boost immune response to repeated exposure to the same antigen (Boulter-Bitzer et al. 2007; Casadevall 1996).

In early twentieth century, passive immunotherapy practiced for treatment of different infectious diseases (Casadevall 1996; Casadevall and Scharff 1994, 1995). By widespread growth of drug resistant pathogens and

difficulties that are faced in treatment of drug resistance infections (Grogl et al. 1992; Hadighi et al. 2006; Hyde 2007; Safari et al. 2014, 2013), immunotherapy may be considered as a good solution with fewer side effects (Badaro et al. 2006; Convit et al. 1987, 1989; Genaro et al. 1996; van der Weiden et al. 1990). So in the last century immunotherapy either passive or active forms have been practiced for control and treatment of parasitic diseases (Boulter-Bitzer et al. 2007; Chamond et al. 2002).

On the other hand, after controlling the parasitic diseases especially in developed countries, a simultaneous raise in frequency of cancer and allergy was observed. So it was hypothesized that parasitic infections may have a role in stimulation of immune system in favor of controlling such diseases (Darani and Yousefi 2012). As an example worm therapy has been presented for treatment and control of asthma (Araujo et al. 2010; Falcone and Pritchard 2005) and multiple sclerosis (Correale 2014; Fleming 2013). In this review article, parasite immunotherapy has been discussed in terms of immunotherapy against parasitic infections and also in terms of using parasites for treatment of other diseases.

Immunotherapy against parasitic infection

Leishmaniasis

Leishmaniasis is probably the parasitic disease with the most practices of immunotherapy for its treatment. In 1939 Salles-Gomesi attempted the first trial of vaccination of human against leishmaniasis using dead leishmanial promastigote preparation. He evaluated the effects of inoculation of dermotropic *Leishmania* spp., killed by phenol, on cutaneous leishmaniasis. He observed therapeutic effects of suspension of dead leishmanial promastigote preparation and suggested that this kind of vaccine may produces protection against the infection (Genaro et al. 1996; Mayrink et al. 2006).

Pessoa and his colleagues carried out the first vaccination trials against leishmaniasis in 1940s using suspension of promastigotes that resulted in reduction of 80 % in occurrence of the infection. Interestingly they recorded no side effects and Montenegro skin test remained negative after vaccination (Genaro et al. 1996). After that, Convit et al., and Mayrink et al., returned to practice immunotherapy in localized cutaneous leishmaniasis with killed promastigotes along with BCG and also in mucosal leishmaniasis using killed promastigote whole antigen, with cure rate of 76 % (Mayrink et al. 1992) to 94 % (Convit et al. 1987), respectively.

Vaccination is one of the safer, most acceptable and practical prophylactic method in American cutaneous leishmaniasis, but it could be useful for treatment of mucosal leishmaniasis in some cases too (Genaro et al. 1996). Despite the fact that these vaccines are recommended, they are unspecified mixtures, difficult to standardize and the possibility of causing noxious local or systemic unwanted effects, so it seems unlikely to be used widespread (Badaro et al. 2006; Machado-Pinto et al. 2002).

As it is experimented, the combination of a single-strain *Leishmania amazonensis* killed promastigote crude antigen vaccine along with a half dose regimen of meglumine antimoniate is impressively efficacious for the treatment of American cutaneous leishmaniasis (Machado-Pinto et al. 2002). Immunotherapy using crude preparations of *Leishmania* antigen, with or without Bacille Calmette-Guérin, is recommended and practiced successfully in treatment of mucosal leishmaniasis and dramatically showed healing in some patients with the disease (Convit et al. 1987, 1989, 2003; Genaro et al. 1996; Mayrink et al. 1992).

Vaccine therapy with a combination of define antigen, along with standard chemotherapy reported to be an effective strategy for treatment of drug-refractory mucosal leishmaniasis. This method also demonstrates mild systemic adverse effects such as: fever, headache, malaise or somnolence in the first administration. Local reactions of injection site such as redness and edema may occur and is similar to that of leishmanin skin-test induration, but vivid granulomatous reactions are absent. Local reaction happens in first, second and third dose of immunotherapy. Drug refractory mucosal leishmaniasis has successfully treated with antigens thiol-specifi antioxidant, *Leishmania major* stress inducible protein-1, *Leishmania* elongation initiation factor, and *Leishmania* heat shock protein-83, plus granulocyte–macrophage colony-stimulating factor (Badaro et al. 2006).

The effective role of *Leishmania* whole antigen in acceleration of healing of cutaneous leishmaniasis and mucosal leishmaniasis and also it's very lighter side effects has been proven and documented (Convit et al. 1987, 1989, 2003). Side effects are mostly occurs when vaccine is used together with BCG (Convit et al. 1987, 2003).

Immunotherapy is also well practiced for canine visceral leishmaniasis. The fucose mannose ligand (FML)-vaccine showed hopeful impact on treating visceral leishmaniasis of asymptomatic dogs experimentally infected by *Leishmania donovani* and *Leishmania chagasi*. Also this vaccine causes increase in CD8 lymphocytes percentage in peripheral blood of dogs (Borja-Cabrera et al. 2004). Fucose mannose ligand (*Leishmania donovani* FML)-saponin vaccine causes increase in types and subtypes of anti-FML antibodies in visceral leishmaniasis in experimentally infected murine model. The delayed type of hypersensitivity response against promastigote lysate

(DTH) and the in vitro proliferative response of ganglion cells against FML antigen also occurs. Also, decline in liver parasitic load reported in 94.7 % of FML-vaccine treated mice (Santos et al. 2003).

Immunotherapeutic effects of heat killed *Leishmania* crude antigen along with live BCG are in association with T cell responses through Th1 and production of IFNγ. T cell response through antigen-driven IFNγ production alone does not cause immunopathology in mucocutaneous leishmaniasis. Therefore, stimulation of Th1 response in patients with American cutaneous leishmaniasis does not end with immunopathology (Cabrera et al. 2000).

In conclusion, the triumphant usage of immunotherapy in treatment of cutaneous leishmaniasis made this method as a good substitute for chemotherapy in single-lesion cutaneous leishmaniasis which chemotherapy is not recommended due to occurrence of drug resistance and also in severe infections such as diffuse cutaneous leishmaniasis and/or leprosy/HIV and *Leishmania* co-infections (Genaro et al. 1996). Upregulation of Th1 profile and also the absence of Th2 response is responsible factor for being resistance to *Leishmania* infection (Barral-Netto et al. 1995; Holaday et al. 1991; Verwaerde et al. 1999). Immunotherapy is an effective, safe and inexpensive method for treatment of cutaneous leishmaniasis of man and visceral leishmaniasis in animals (Borja-Cabrera et al. 2004; Cabrera et al. 2000; Convit et al. 1987, 1989; Santos et al. 2003).

Cryptosporidiosis

Protozoan parasite *Cryptosporidium* is causative agent of cryptosporidial diarrhea in animals and human being (Fayer 2009). Cryptosporidiosis is mostly in low prevalence (Jafari et al. 2014b; 2013; Jafari et al. in press) benign infection of humans that typically lasts for two weeks, but in some special conditions it became a hostile disease. It is difficult to treat the infection in immunocompromised/immunosuppressed individuals including patients who have HIV/AIDS or organ transplantation (Fayer 2009).

Chemotherapy for cryptosporidiosis has limited efficacy in the treatment of the infection and that made researchers to develop admissible rationale for immunological studies of *Cryptosporidium* with recombinant vaccine using live or attenuated parasite (Santín and Trout 2009). Studies carried out in animals illustrated effective impact of hyperimmune bovine colostrum, paromomycin, and nitazoxanide in therapy of *Cryptosporidium* infections (Fayer and Ellis 1993; Jenkins et al. 1999a; Perryman et al. 1999; Theodos et al. 1998; Tzipori et al. 1994).

Passive and active immunotherapeutic methods are fruitful strategies for immunization against cryptosporidiosis (Boulter-Bitzer et al. 2007). Passive immunotherapy with antibody for *Cryptosporidium* infection is a method of treatment that has been practiced experimentally and clinically. Several studies on this subject have been initiated in last decades, namely on use of hyperimmune or naturally immune bovine colostrum containing colostral antibody, antibodies from chicken egg yolk, monoclonal antibodies and antibodies from human - plasma that administrated orally. Majority of studies have applied oral administration method of treating or prophylaxis of this protozoan infection. Variety of antibody preparations has been tested in animals and man and showed some degree of effectiveness (Crabb 1998).

Anti-*Cyptosporidium parvum* antibodies in hyperimmune bovine colostrum possess remedial effect on cryptosporidiosis. These antibodies distinguish sporozoite, oocyst and merozoite antigens; also they recognize stage-specific antigens. After incubation of hyperimmune antibody with sprozoites, they experience noticeable morphologic alterations, defined by oncoming production and release of sporozoite membranous surface antibody-antigen complexes. The reaction makes infectivity of sprozoites to be neutralized (Riggs et al. 1994).

In experimentally infected nude mice model, intestinal-infection score decreases when treated with neutralizing

Table 1 Some known antigens of *C. parvum*, which is identified by antibodies are suggested to play a role in host immune response(Boulter-Bitzer et al. 2007)

Antigen	Reference
Sporozoite and merozoite cell surface protein	
gp15/45/60(Cpgp40/15)	(Cevallos et al. 2000; Strong et al. 2000)
CP15	(Jenkins and Fayer 1995)
P23	(Arrowood et al. 1991; Riggs 2002)
GP25-200	(Riggs 2002)
CSL	(Riggs 1997)
CP47	(Nesterenko et al. 1999)
Cpa135	(Tosini et al. 2004)
Microneme proteins	
Gp900	(Petersen et al. 1992)
TRAP-C1	(Spano et al. 1998)
***Cryptosporidium* oocyst wall protein family**	
COWP	(Fayer et al. 2000)
Other potential antibody targets against *C. parvum* antigens	
CPS-500	(Riggs et al. 1999)
CP41	(Jenkins et al. 1999b)
100-kDa antigen of sporozoites	(Bonnin et al. 1993)

monoclonal antibodies (mAb 17.41). Neutralizing monoclonal antibodies directed to sporozoite and merozoite surface antigens, nullify the infectivity of sporozoites (Bjorneby et al. 1991), reduce oocyst shedding and lower the infection score in gall bladder (Riggs et al. 1994). Bovine immune colostrum reduces 50 % of intestinal development score of *C. parvum* in mice (Jenkins et al. 1999a). Some known antigens of *C. parvum*, which is identified by antibodies are available in Table 1.

A protection against cryptosporidiosis would be achieved by developing a vaccine against *Cryptosporidium* spp., and if done would have several useful effects, especially and most importantly on immunocompromised patients that are at risk of developing chronic infection. It is expressed that an acceptable approach in treatment of *Cryptosporidium* infection in immunocompromised individuals is passive immunotherapy using antibodies appointed against merozoites and/or sporozoites of *C. parvum,* administrated into the gastrointestinal lumen (Boulter-Bitzer et al. 2007; Petersen et al. 1992).

Malaria

Glycosylphosphatidylinositol (GPI) is a glycolipid antigen of *Plasmodium* spp., induces the overproduction of TNF-α and IL-1 and probably contributes to the malarial pathophysiology such as severe cerebral malarial. GPI derived from malaria parasite can be a good candidate to raise monoclonal antibodies to, and consequently can neutralize the toxicity of extracts of the parasite. Parasite origin GPI can be used as a target for immunotherapeutic purposes and may it would be a good solution for severe malaria (Schofield et al. 1993).

Another and most novel immunotherapeutic method for malaria and cancer is CTLA-4 blockade. Exhaustion of T cells is a usual immunoevasion mechanism in neoplastic tumors and chronic infections. T cell exhaustion recognition in malaria proposes a much needful and modern therapeutic tactics for treatment of this horrible disease of mankind. In melanoma immunotherapy, CTLA-4 blockade is approved to be used in treatment of the tumor. This method of therapy, illustrated a promising perspective for therapy of cancer and chronic infections (Freeman and Sharpe 2012).

Monoclonal Antibody 7H8 (mAb 7H8) is an IgM monoclonal antibody, which is producing by the hybridoma cell line, directed against a protein of *Plasmodium* spp. This antibody also binds to Pf93 that is an antigen unique to *P. falciparum*. MAb 7H8 is proper for immunodiagnostic tests and immunotherapy of malaria of human and other animals, which plasmodial-associated antigen expresses in and contained reactive epitopes to the monoclonal antibody (Taylor 1991).

American trypanosomiasis

Developing vaccine against the infection is a difficult and intricate task, because the parasite is able to induce a variety of mechanisms to make host immune system unable to eradicate the infection (Chamond et al. 2002; de Souza et al. 2010). Immunotherapy can help to increase the effectiveness of the anti-parasite drug and consequently decreases the severity of chronic infections such as lethal chagas' disease (Kumar and Tarleton 2001; Tarleton et al. 2000).

A desirable immunotherapy against American trypanosomiasis would encompasses such molecules that stimulate lymphocytes to act in several concordant immune responses, including antibody secretion, cytotoxic activity to trigger moieties of parasite and cytokines to modulate immune response against parasite (Camargo 2009; Chamond et al. 2002).

Trypanosoma cruzi expresses glycophosphoinositol (GPI), which is a potential stimulator of production of interleukin 12 (IL-12). During the Chagas' disease IL-12, and probably GPI, may induce NKT cells to effect a protective response. It is shown that NKT cells implicate in protective immune responses against this pathogen (Duthie et al. 2002; Wilson et al. 2002), and may be a future candidate target in the immunotherapy of infection.

For effective immunotherapy against *Trypanosoma cruzi* infection, the significance of polyclonal lymphocyte responses straight after the infections and the inefficient immune homeostasis they cause are the most limitations. It is thought that if immunotherapy against *Trypanosoma cruzi* comprises molecules that are capable of negating or inactivating nonspecific immune responses, in that way immune responses are capable to develop a durable response in its' victim (Chamond et al. 2002).

Toxoplasmosis

Toxoplasmosis is a benign infection of man and other warm-blooded animals, caused by a zoonotic protozoan *Toxoplasma gondii*, belonging to the phylum Apicomplexa (Galvan-Ramirez M de et al. 2012; Zhou et al. 2011). The prevalence rate of the infection is fairly high in most populations (Jafari et al. 2012; Rasouli et al. 2014).

In animal model, transference of the spleen or serum and lymph node cells of guinea pigs that became immune against RH strain of *Toxoplasma gondii* can results in partial protection of symptomatic infection in recipient guinea pigs. The phenomenon is according to the reduction of dissemination or multiplication of *Toxoplasma* from initiation of inoculation spot to other different organs of immunotherapy recipient. The same degree of partial immunity against disseminated toxoplasmosis happen in

animals received suspensions of cell, rich for immune T cells. However the immune cells exposed to a monoclonal antibody raised against guinea pig T cell along with complement, lose their capability to transfer resistance (Pavia 1986).

Trichomoniasis

Trichomoniasis is an infection caused by *Trichomonas vaginalis* which is the common cause of vaginitis (Schwebke and Burgess 2004). Lactobacillus vaccine, Solco Trichovac, has a therapeutic impact on trichomoniasis which is resulted of cross reaction of vaccine induced antibodies with *Trichomonas vaginalis*. Therefore serological assessment of the cross reactivity between *Trichomonas vaginalis* and lactobacilli from Solcotrichovac vaccine has failed to prove the idea (Gombosova et al. 1986).

The Solco Trichovac is a lactobacillus vaccine which dramatically showed therapeutic effect on trichomoniasis. The cure rate has been reported 90 % (Bonilla-Musoles 1984) and 80 % (Karkut 1984) in vaccine therapy. Immunotherapy of trichomoniasis has some advantages over metronidazole which are the prophylactic effect of vaccine on patients about reinfection and recurrence (Bonilla-Musoles 1984).

There is a report about metronidazole and immunotherapy resistant trichomoniasis in two cases, which the parasites were persistent after a high dose of intravenous metronidazole administration. In this case the immunotherapy using *Lactobacillus* was unsuccessful (van der Weiden et al. 1990).

Schistosomiasis

Schistosoma spp., are flatworms and causative agent of schistosomiasis, which is a parasitic disease with second public health significance after malaria. The prevalence of the disease is estimated over 200 million cases and 1,00,000 deaths, annually (Jenkins-Holick and Kaul 2013).

Granulomatous response against ova of *Schistosoma*, which are trapped in the host liver, is responsible of subsequent fibrosis. It is reported that administrating interleukin 12 (IL-12) along with *Schistosoma* egg prevents the formation of pulmonary granuloma. Administration of eggs along with IL-12 results in partial inhibition of formation of granuloma and therefore considerably reduces the tissue fibrosis persuade by natural *Schistosoma mansoni* infection. This achievement is a sample of vaccination in which the pathogenesis of infection is prevented, but not the infection itself. This is happening by substitution of Th2 cytokine response, characteristic of *Schistosoma* infection immune response, by Th1 which is induced by IL-12. Vaccination with antigen plus IL-12 in the variety of infections with tissue fibrosis can help to improve the patient's condition (Wynn et al. 1995).

Interleukin-13 has many functional similarities to IL-4 (de Vries 1998), and also it shares the same receptor subunits with IL-4. Therefore it has the same role in pathogenesis of schistosomiasis. Treatment with IL-13 inhibitor (sIL-13Rα2-Fc) remarkably reduces the formation of hepatic fibrosis in mice when infected by *S. mansoni* (Chiaramonte et al. 1999).

Treatment of experimentally infected mice by *S. mansoni* with monoclonal antibody raised against IL-4 inhibits the formation of granuloma in lung, but not formation of hepatic granuloma. Anti-IL-4 treatment notably reduces the collagen deposition of liver. IL-4 has a significant role to induce Th2 response in mice infected with *S. mansoni* and subsequently contributes to formation of hepatic fibrosis (Cheever et al. 1994; Kaplan et al. 1998).

Parasite stages or parasite antigens as targets for immunotherapy of cancer, multiple sclerosis or asthma

Hygiene hypothesis

Prolonged co-existence of parasites, especially helminthes, and their hosts has been co-evolved over many generations. The majority of parasites are adapted to the specific hosts, which resulted in reduction in pathogenesis and their better survival. This adaptation has led to the establishment of a specific immunological microenvironment. The later phenomena support the adaptability of both the host and the pathogen (Rzepecka and Harnett 2013).

During recent decades, reduction in exposure to variety of microbial organisms (Falcone and Pritchard 2005; Jafari et al. 2014a; Rzepecka and Harnett 2013) and absence of the subsequent immune response against them are responsible for the increase in occurrence of allergic disease, which is called Hygiene hypothesis. Although, the hypothesis has been questioned by some authors, because there are some evidences that suggest that some of the microbial infections may be deteriorate allergic asthma rather than subsiding (Falcone and Pritchard 2005; Rzepecka and Harnett 2013).

Asthma

The epidemiological data supports that the hookworm of human, *Necator americanus*, might ameliorate symptoms of asthma in atopic individuals (Scrivener et al. 2001). Also the human hookworm is famous for its immune-modulatory capacity (Falcone et al. 2004; Pritchard and Brown

2001). Data from experimentation on mice models clearly illustrated that parasitic worms and their products can alleviate asthma-like disease (Rzepecka and Harnett 2013).

The progress of *Trichinella spiralis* Infection from acute to the chronic phase shows increase in protective effects on experimental allergic airway inflammation in animal model. T regulatory cells may play substantial role in the amelioration of experimental allergic airway inflammation (Aranzamendi et al. 2013).

Studies have been suggested that there is a protective impact of parasites in subtracting skin test reactivity and also the alleviation of symptoms of asthma, especially in schistosomal infections (Figueiredo et al. 2012). Additionally, there is support for causal relationship between atopy and helminthic infections (Cooper 2004). Although some believe that intestinal helminthic infections, namely ascariasis and trichuriasis, are regulating the immune response and suppress the atopy, but some other intestinal helminthic infections have shown no effect or exacerbated the atopic diseases (Figueiredo et al. 2012).

Multiple sclerosis

Epidemiological studies revealed that helminth infected individuals are less likely to be affected by autoimmune diseases such as multiple sclerosis (MS). The thesis has been experimented in animal model of MS, asthma, type I diabetes and colitis. It is been observed that helminthes infected mice are resilient against the mentioned diseases. Up to now, helminth therapy with *Trichuris suis* ova and *Necator americanus* larvae have been trailed in MS. Mostly, no adverse effects have been perceived associated with helminth therapy. Studies suggest some helminth-derived immunomodulatory molecules, which are capable of altering immune responses and, hence, the term of autoimmune diseases (Correale 2014).

Helminthic infections in MS patients modulate immune responses through a retinoic acid-dependent pathway. Retinoic acid concentrations are higher in MS patients infected by helminthes comparing to healthy individuals (Correale and Farez 2013).

Soluble products of *T. suis* suppress the synthesis of the pro-inflammatory cytokines such as TNF-α, IL-12 and IL-6. Also it has been demonstrated for soluble products of other helminthes too. These attributes, along with upregulation of expression of CXCL16 and OX40L that are considered as a positive signals for polarization of Th2 cells, may allow soluble products of *T. suis* to guide monocyte-derived dendritic cells to conduct polarization to lower the inflammation at sites of the infection. On the other hand, *Trichuris suis* glycans are crucial important for their capability about suppressing the production of pro-inflammatory chemokine and cytokine of dendritic cells (Klaver et al. 2013).

Table 2 Parasites with anticancer activities in experimental animals

Row	Parasite	References
1	Hydatid cyst	(Berriel et al. 2013)
2	*Toxocara canis*	(Darani et al. 2009)
3	*Acantamoeba castellani*	(Pidherney et al. 1993)
4	*Plasmodium yoelli*	(Chen et al. 2011)
5	*Trypanosoma cruzi*	(Kallinikova et al. 2006; Mel'nikov et al. 2004)
6	*Toxoplasma gondii*	(Darani et al. 2009; Kim et al. 2007; Miyahara et al. 1992)

Cancers

Following control of parasitic diseases in developed countries a marked increase in incidence and mortality of cancers was occurred (Oikonomopoulou et al. 2013; Vineis and Wild 2014). So it was postulated that parasite somehow interferes with the tumor growth. Although the mechanisms of inhibitory effect of parasite on cancer growth are not understood, but there are raising scientific evidences to support this idea. In culture medium it has been shown that some parasites or parasite products inhibit the growth of cancer cells. Also it has been shown that parasite or parasite antigens reduce tumor growth in the experimental animals. Some of these studies were also summarized in Table 2.

Concluding remarks

As a conclusion, immunotherapy has been practiced successfully in most cases of parasitic infections (Genaro et al. 1996; Mayrink et al. 2006) and some other diseases such as cancer (Noguchi et al. 2013; Tse et al. 2014; Weiner et al. 2012) and autoimmune (Adorini and Sinigaglia 1997; Van Kaer 2004) disorders. This method has shown hopeful remarks regarding treatment of leishmaniasis (Convit et al. 1987) and trichomoniasis (Bonilla-Musoles 1984). Also it can partially reduce the pathogenesis of the infection and improve the patient's condition in cryptosporidiosis (Riggs et al. 1994), schistosomiasis (Wynn et al. 1995), malaria (Schofield et al. 1993) and American trypanosomiasis (Kumar and Tarleton 2001). In severe cases of the malaria (Schofield et al. 1993) and leishmaniasis (Convit et al. 1987, 1989), immunotherapy alone or beside chemotherapy, would be a best strategy to reduce the pathophysiology

of the infection. Another aspect which made immunotherapy as a remarkable method of treatment is drug resistance, which is increasing in parasitic infections. This phenomenon results in ineffective or less effective chemotherapy. In these cases, immunotherapy would benefit the treatment (Badaro et al. 2006).

On the other hand, interestingly parasite stages and parasite antigens are proposed for immunotherapy of asthma (Rzepecka and Harnett 2013) or cancers (Darani and Yousefi 2012), respectively. Inhibitory effects of some parasites such as *Toxoplasma gondii* (Darani et al. 2009; Kim et al. 2007; Shirzad et al. 2012), Hydatid cyst (Aref et al. 2012; Yousofi Darani et al. 2012), *Toxocara canis* (Darani et al. 2009) and *Trypanosoma cruzi* (Kallinikova et al. 2006; Mel'nikov 2004) on tumor growth has been shown in culture medium or animal model. So immunotherapy with parasitic antigens may be an interesting line of research in the future.

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