Anti-autoimmune effect of the parasites: the microbial immunomodulation

Naveen Dhingra

School of Life Science, Devi Ahilya University,
Khandwa Road, Takshashila Campus, Indore- 452001,
Madhya Pradesh, India

LK Dwivedi*

Institite of Biomedical Sciences, Bundelkhand University,
Jhansi-284128, Uttar Pradesh, India
E-mail: lavkush_dwivedi2002@yahoo.co.in
Mob: +91-9452888176

ABSTRACT

Parasites with their ability to vibrate our immune system are known as potent immunomodulators. In the course of life struggle of parasites within host body, they induce our immune system to produce immunosuppressive cytokines like IL-4 and IL-10 by the immune cells to create parasite friendly environment within host body. Co-incidentally, several autoimmune and inflammatory disorders of the host body, if existed get also relax from self aggression of the immune cells. Various recent reports have proven the relieving effects of parasitic infection among the people suffering from discriminative failure of the immune system between self and non-self. Few of those reports, on the basis of their detailed mechanism of action are critically reviewed in the present article to find out if they can be clinically employed for the treatment of billions of people across the world suffering from immune aggression.

Keywords: Parasitic infection, Autoimmune diseases, Immunosuppressive cytokines, Immune aggression, Immunomodulators.

1. Introduction

Human Immune system works on the two basic parameters of self resistance and non-self reactivity (Singh et al., 2011). Any organic material not belonging to host body is treated as antigen and cleared from the body by strong immune action. Depreciation in this ability of immune system by any way either by natural or induced way generate an immunocompromised i.e. favourite conditions for the microbial organisms to survive and multiplicate with almost zero hindrance in host body (Sfriso et al., 2010). Several parasites update themselves with the ability to suppress the immune system by inducing the secretion of immunosuppressive cytokines like IL-4 & 10 from immune cells, and hijacking the expression of regulatory genes like SOCS (Suppressor of Cytokine Signalling) and others (Dwivedi et al., 2012; 2013). However, it helps in other ways by suppressing the immune aggression of self sensitive T-cells in autoimmune diseases like Diabetes, Multiple Sclerosis (MS), Arthritis and Encephalomyelitis (Dhingra et al., 2013). In recent studies, the pathogens such as virus, bacteria, helminth (nematode (round worm) and platyhelminthes (flatworm) due to their immunosuppressive nature have been reported helpful in fighting, neutralizing, retracting or precipitating the effect of autoimmune diseases (Sfriso et al., 2010; Saunders et al., 2010; Akdis et al., 2011; He et al., 2010).

However, the parasites are chief culprit of marked morbidity, mortility and disability of more than two billion people in the world but with their immunogenic effect they are good immunomodulators also. Encouragingly, several accomplished works in this area have suggested the lasting protection of parasitically infected hosts from pre-existing autoimmune and inflammatory diseases. Thus, the application of helminth for suppressing the immune response of self targeting T-cells can be a fruitful approach in immunotherapeutics of the autoimmune and/or inflammatory diseases. Few of the recent approaches in this area and future prospects are critically reviewed and discussed in the present article.

2. Mechanism of microbial immunomodulation

2.1 Soluble worm and Soluble Egg Antigen (SWA & SEA) induced immunomodulation

Interaction between host and parasites always create alterations in host immunity for persisting the disease or clearing the pathogens from host body. There are increasing evidences that immune mechanisms are involved in the pathogenesis of many parasitic infections. This hyporesponsiveness to antigen-specific and polyclonal stimuli in chronic parasitic infections could be related to immunosuppressive cytokines like IL-10 and TGF-β which are secreted from antigen presenting cells (APCs) and regulatory T cells (Treg cells) after the parasitic infections. Several parasite products like egg and worms act as immunomodulators and induce the aforesaid cells to produce cytokines which could suppress the host immunity and encounter the autoimmune diseases

along with development of a suitable environment for the growth of parasites (Malky et al., 2011). In a study done by He et al., 2010 on Non-obese diabetic (NOD) mice, the soluble antigens like SWA-(Soluble worm antigen) and SEA- (soluble egg antigen) isolated from Schistosoma mansoni were observed inducing the anti-dibetogenic Th2 immune response by the production of Natural Killer T- Cells (NKT) in CD-1 dependent manner which prevented the onset of T1D in NOD mice. Besides, modulation of C-type lecithin receptor (CLT), Treg cell, APC (antigen presenting cell) and up regulation of TGF-Beta was also recorded after the administration of SEA in those mice. Similarly in another study by Malky et al., 2011, the immunomodulatory agents of Heligmosomoides polygyrus and Dirofilaria immitis (rDiAg) have completely reduced the expression of T1D in NOD mice by inducing the sparkling activation of Th2 response with accumulation of IL-10, $Foxp3^+$, Treg and macrophage, and blocking the Ag specific Th1 response.

Hence, as per the above reports, the parasite-derived immunomodulatory molecules induces the activation of host immune cells to secrete such polarized cytokines which can develop the immunosuppressive atmosphere for smooth survival of the parasites and also minimize the risk autoimmune reactions in host cells. Further detailed investigations on identification and application of such parasite derived immunomodulatory agents may provide new paradigm for the immunotherapy of autoimmune diseases.

2.2 Parasite driven blockade of cytokines like IL-12

Cytokines are the initiator, developer and regulator of the immune response. They critically coordinate to develop required immune reaction for resolving the bacterial and viral assault on immune system. In particular, the IL-12 family of cytokines are key players in the regulation of T cell responses. They are produced primarily by monocytes, macrophages, dendritic cells (DCs), and B cells. With the major functions like induction of the production of IFN-ϒfrom natural killer (NK) & T cells, enhancement of cytotoxity of NK and cytotoxic T cells (CTL), and differentiation of naïve T cells into Th1 effectors, the IL-12 is suggested to play a key role in the development of cell-mediated immunity (CMI) (Manetti et al., 1993; McKnight et al., 1994).

IL-12, first described as NK stimulating factor is a heterodimer that consists of a 35-kd light chain (p35) and a 40-kd heavy chain (p40). It is produced by activated monocytes, macrophages, neutrophils, microglia, and DCs. IL-12 mediates development and maintenance of Th1 cells by inducing the production of IFN-. It indirectly activates the antimicrobial, antiparasitic, and antitumor activity of macrophages and promotes cytolytic activity of NK cells and lymphokine-activated killer cells (Testa et al., 2002). Reduced production of IL-12 impairs Th1 responses and increases susceptibility to infection with intracellular pathogen (Ebner et al., 2002; Testa et al., 2002; Munitz et al., 2006) and that's what helminth parasites tries to do with the IL-12. Reports described that they inhibit to the production of IL-12 from macrophages and other cells (Figure-1) to develop an immunocompromised and parasite friendly environment in the host body which simultaneously suppresses to the autoimmune aggression too.

2.3 Induction of Th2-type immune response

Infections caused by helminth elicit both innate and adaptive response to generate polarized Th2 response for a fast and effective response which is characterized by elevated level of interlukin (IL 4, IL 5, IL 10, IL 13, IL-17, IL 21), serum IgE titer, and activation of dendrite & macrophages cells (Fukumoto et al., 2009; Walsh et al., 2009; Malky et al., 2011; Smits et al., 2010; Akdis et al., 2011). The helminthic infections evoke early step of Th2 cell response at the prerequisite site of infection and induce the production of Thymic Stromal Lymphopoietin (TSLP) from intestinal epithelial lining. High affinity receptor of TSLP is composed of TSLPR and IL-7R chains, responsible for activation of Th2 response through IL-12 (Fukumoto et al., 2009). Dendritic cells are actively involved in activation of Th2 response by inducing the activation of antigen specific adaptive Treg cells (Walsh et al., 2009). The Treg cells (CD 4+, CD 25+, Foxp3+) works as a hub of immune network for both allergy and autoimmune disease by regulating the depreciation of immune response and activating the helminth infection (Astier and Hafler, 2007) (Figure-2).

Hence, considering the experimental and epidemical data, it is conclusive that the helminthic infections have a unique property to modulate Th2 response either by stimulating DCs to provoke immunity or by secreting adjuvant for shooting up Th2 activity, which in turn provide protection against the autoimmune diseases.

3. Effect of Parasitic Infections on autoimmune and inflammatory diseases

3.1 Type 1 Diabetes

Type 1 Diabetes (T1D) is an autoimmune disease where the immune system destroys the body's pancreatic beta cells. It is on the increase in developed countries which coincides with a decrease in helminth infection (Gale, 2002). Autoimmune diabetes affects approximately 1 in 300 children and is of considerable cost to health care systems (Brown, 1998; Malky et al., 2011). The role of Th1 and Th2 cytokines in the development of autoimmune diabetes has been paradoxical. The Th1 response has been found responsible for the development of diabetes in NOD mice by Th1-mediated destruction of insulin-producing pancreatic beta cells, while Th2 response fade to the destructive effect Th1. As per the previous reports, Th2 response induced by T. Spiralis and H. Polygyrus infection have protected the mice from Th1-mediated beta cell destruction which indicates that the

induction of Th2 type responses by the helminths such as Schistosoma mansoni, Heligmosomoides polygyru, Litomosoides sigmodontis, and Trichinella spiralis have potential to cure T1D (Bach, 2005; He et al. 2010).

3.2 Collagen Induced Arthritis

The collagen-induced arthritis (CIA) mouse model is the most commonly studied autoimmune model of rheumatoid arthritis that is widely used to address questions of disease pathogenesis and to validate therapeutic targets. Schistosoma mansoni infection has been found reducing the severity of autoimmune arthritis through systemic and local suppression of pro-inflammatory mediators, which indicates towards the potential of parasite-derived materials to be used as therapeutic agents against rheumatoid arthritis (Osada, 2009).

3.3 Multiple Sclerosis (MS)

MS is an inflammatory demyelinating state that affects central nervous system by inculcating myelin injury. It is also known as "disseminated sclerosis" or "encephalomyelitis disseminata", where the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelisation and scarring as well as a broad spectrum of signs and symptoms.

In 2007, Dr. Jorge Correale et al. had studied the effects of parasitic infection on Multiple Sclerosis (MS) by comparing the MS patients infected with or without the parasitic infection. In the course of 4.6 years of their study Correale et al concluded that the MS patients who were infected with parasites experienced far less effects of MS than the non-infected MS patients. Interestingly, patients with parasitic infection impart protection from disease alleviation with induction of Treg cell which in turn secretes suppressive cytokines like IL-10, TGF β along with activation of $CD4^+$ $CD25^+$ Fox $P3^+$ T cells. Therefore, inducing the production of inhibitory cytokines like IL-10, IL-4 and TGF β may be a novel approach for reducing the malignancies of MS. Role of parasites in that induction can be an area of interest for further study.

3.4 Encephalomyelitis (EAE)

The inflammatory process in both EAE and multiple sclerosis (MS) has been traditionally considered to be a consequence of activation of a Th1-type cytokine cascade (Begolka and Miller, 1998, Malky et al., 2011). Also, a major role for Th17 cells, in the pathogenesis of EAE, has been suggested (Komiyama et al., 2006). In a study done by Malky et al 2011, the Soluble egg antigens (SEA) of helminths have been observed preventing the experimental autoimmune encephalomyelitis (EAE) in Myelin oligodendrocyte glycoprotein 35–55 amino acid peptide (MOG35–55) induced animal models of MS (Malky et al., 2011). Furthermore, the SEA immunization after EAE induction have effectively delayed the disease onset and reduced the severity of disease. $CD4^+CD25^+$ Treg cells also were implicated to mediate the protective mechanism against MS as well as other autoimmune disorders (Astier & Hafler, 2007).

4. Conclusions and future prospective

Development of autoimmune diseases has been the result of self aggression of immune system and failure of immune regulatory cells like T-reg cells. Th1 responses have been found responsible for induction and alleviation of self aggressive T lymphocytes while Th2 cell response have shown the opposite effect. Helminths infection, with the ability of induction of Th2 response and secretion of immune regulatory cytokines like IL-10, IL-4 and TGF β have been helpful in the suppression of immune self aggression during autoimmune diseases like Diabetes, Rheumatoid Arthritis (RA), Multiple Sclerosis (MS) and Encephalomyelitis (EAE). The animal models infected with helminthic parasites were showing better resistance against the onset and expansion of autoimmunity in them. Therefore, the immunomodulatory potential of helminths can be exploited for the immunosuppression of self specific T-cell response in autoimmune diseases.

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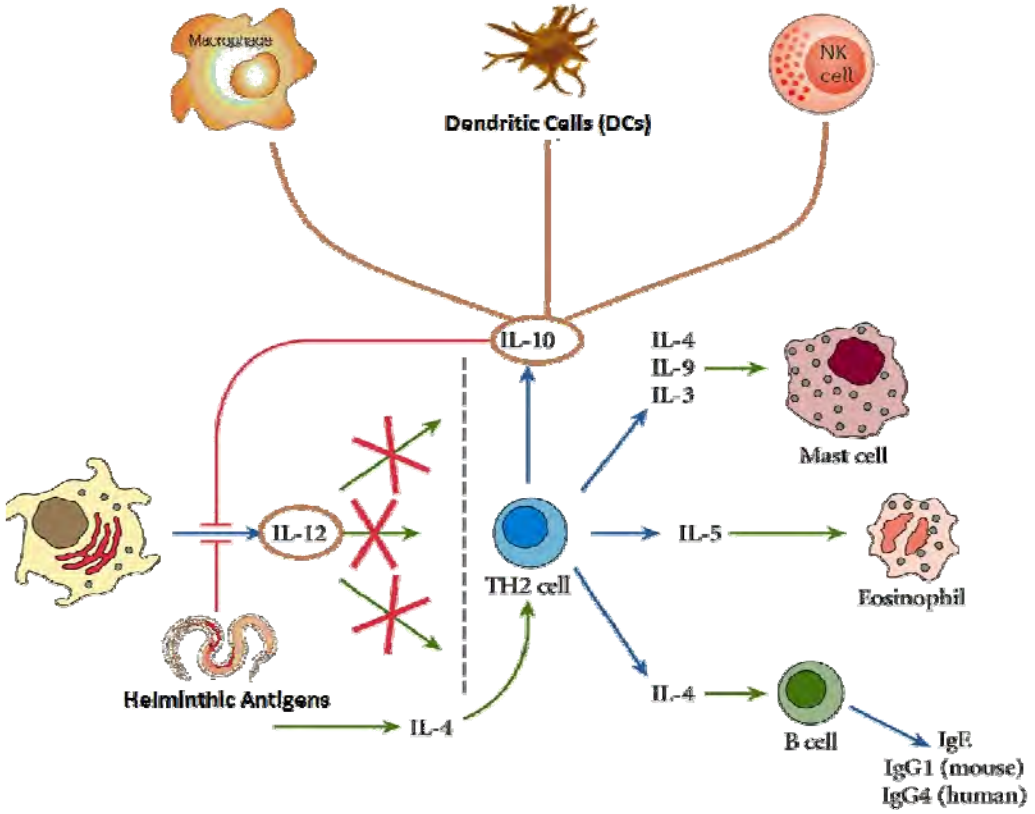

Figure 1: Inhibition of the production of IL-12 from macrophages by helminthic antigens and IL-10 secreted from macrophages, Dendritic Cells (DCs) and NK Cells. It influences to the activation of TH2 cells and development of a strong immune response against the pathogen.

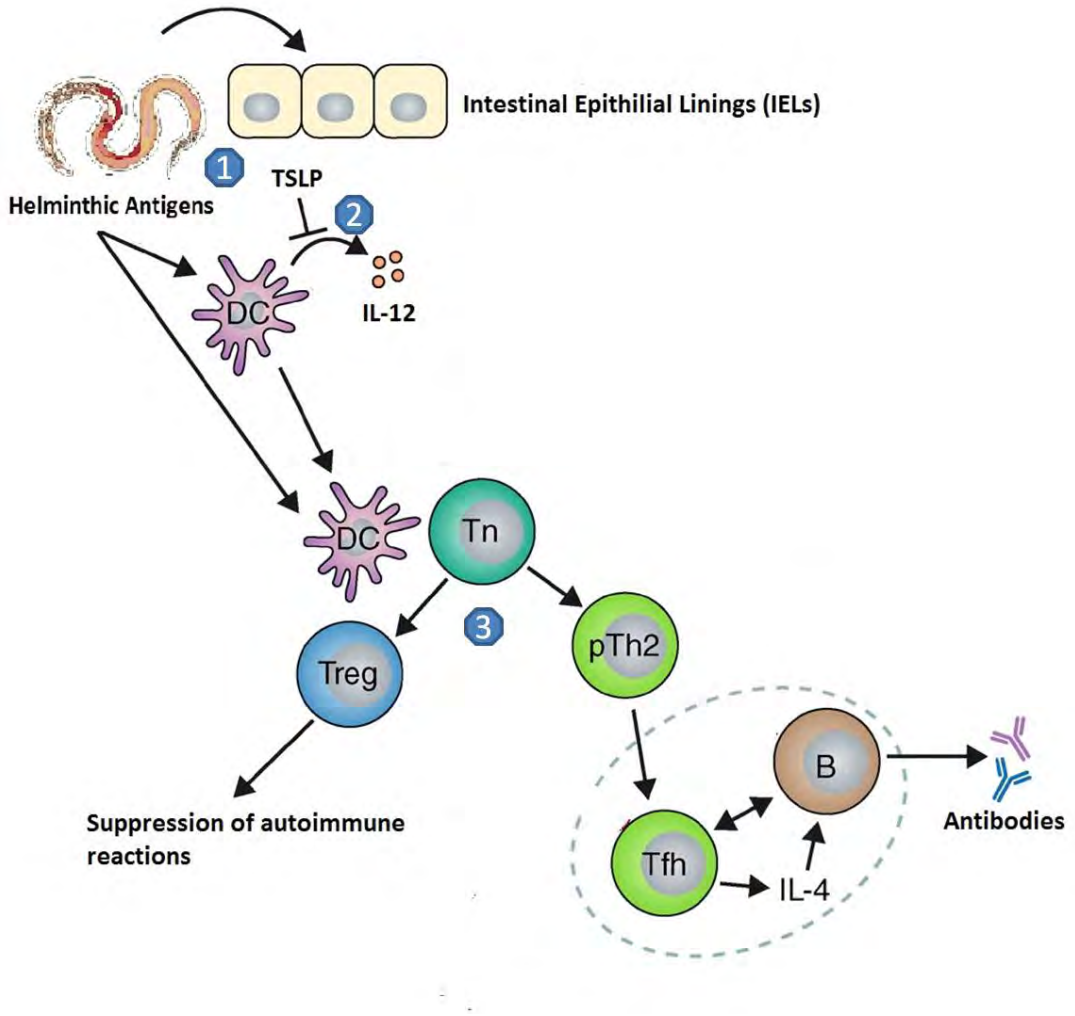

Figure 2: (1) Helminthic antigens induced production of IL-12 and TSLP from Dendritic Cells (DCs) and Intestinal Epithilial Linings (IELs) respectively. (2) Blockage of production of IL-12 from DCs by TSLP. (3) The DCs induced activation and differentiation of Tn cells into Treg and Th2 cells. The Treg cells regulate to the autoimmune and allergic reactions while Th2 cells lead to the development of humoral immune response by increasing the antibody level in blood.