The Protective Discourse Between Infections and Autoimmunity

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Abstract

Autoimmune diseases are characterized by aberrant immune response against host own tissues. Studies have suggested that through molecular mimicry, bystander activation, and cross-reactivity, infections can trigger autoimmune diseases. However, paradoxically recent studies have highlighted the role of bacteria, viruses, and parasites in protection against autoimmune diseases. Epidemiological evidences and hygiene hypothesis also highlight the involvement of microbes in protection against autoimmune diseases. Interestingly, the data suggests increased incidence of the autoimmune diseases in developed countries. Microorganisms can protect against autoimmune diseases by antigenic competition, innate immune mechanisms, immune regulation; however, the detailed mechanisms underlying the involvement of microorganisms in protection of autoimmune diseases is unknown. The detailed understanding of mechanisms involved could lead to efficient therapeutics to treat autoimmune diseases.

Keywords

Autoimmunity · Antigenic competition · Innate immunity · Immune regulation · Infection

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4.1 Introduction

Autoimmune disease are chronic disorders characterized by loss of immune tolerance leading to aberrant immune response against hosts own tissues (Wang et al. 2015; Giri et al. 2022). The loss of immune tolerance leads to organ specific or systemic damage to the host (Janeway et al. 2001; Wang et al. 2015). Multiple factors like genetics, epigenetics, stress, environment, tobacco smoke, pharmaceutical agents, hormones, could trigger the development of autoimmune diseases (Costenbader et al. 2012). Moreover, recent studies suggest the role of infections in triggering autoimmune diseases (Arango et al. 2013). Conversely, studies have highlighted that infections can prevent or even suppress the development of autoimmune diseases (Arango et al. 2013).

According to the hygiene hypothesis, the decreased infections may lead to increase in the occurrence of allergies and autoimmune diseases (Sironi and Clerici 2010). The evidence for the hygiene hypothesis has been demonstrated worldwide (Bloomfield et al. 2006; Okada et al. 2010). Additionally, the animal model experiments have provided evidences for the hypothesis (Okada et al. 2010). Furthermore, studies suggest that the decreased rate of infections may be a likely explanation for increased incidence of autoimmune diseases in developed countries (Okada et al. 2010). Moreover, the prevalence of parasitic infections has been associated with increased risk of autoimmune disease (Strachan 2000; Arango et al. 2013). For example, the *Schistosoma mansoni* infection has been associated with protection of Type 1 diabetes mellitus (T1DM) (Cooke et al. 1999; Zaccone et al. 2003; Arango et al. 2013). Therefore, previous studies suggest that infections may be a potent immune system modulator (Arango et al. 2013).

However, the mechanism explaining the casual link between protective function of infection in development of autoimmunity is unclear. Various factors such as reduced regulatory T (Treg) cells activation, altered pro-inflammatory, and anti-inflammatory cytokine levels, changes in the microbiota may be linked with increased incidence of autoimmune diseases (Moudgil and Choubey 2011; Dwivedi et al. 2013a, 2015, 2017; Giri et al. 2020b, 2021a, 2022). Moreover, studies suggest that infections may suppress variety of autoimmune diseases by modulating immune response, non-specific to the particular pathogen (Sfriso et al. 2010). Given the role of infections in controlling aberrant immune response, this chapter focuses on the involvement of infections in protection of autoimmune diseases.

4.2 Autoimmune Diseases

Autoimmune diseases are characterized by loss of immune tolerance leading to destruction of bodies own tissues by self-reactive immune cells (Wang et al. 2015; Giri et al. 2022). The prevalence of autoimmune diseases is about 5% worldwide, and they represent a major concern of mortality and morbidity (Leslie and Hawa 1994; Wang et al. 2015). The autoimmune diseases are generally divided into two types organ specific autoimmunity, where the immune system mediated destruction

is localized to a particular organ, the other type in systemic autoimmunity, where multiple organs are involved (Janeway et al. 2001). Despite enormous research in the field there is no cure for most of the autoimmune diseases, and the current therapeutics mostly focus on symptomatic relief (Chandrashekara 2012).

The exact triggering factor is unknown but multiple factors such as environment, genetics, epigenetics, tobacco smoke, infections may be responsible for the triggering the development of autoimmune response (Giri et al. 2022). The initial trigger generally activates the innate immune cells, which leads to activation of antigen presenting cells (APCs) and increased production of pro-inflammatory cytokines (Gandhi et al. 2010; Thanapati et al. 2017; Giri et al. 2022). The activated APCs stimulate the adaptive immune response by activating self-reactive $CD4^+$ and $CD8^+$ T cells (Skapenko et al. 2005; Giri et al. 2022). The self-reactive $CD4^+$ T cells further aids in activating self-reactive $CD8^+$ T cells and B cells, which exacerbates the autoimmune response (Skapenko et al. 2005; Giri et al. 2022). Additionally, the self-reactive $CD4^+$ T cells mediate autoimmune response by FAS-FASL-mediated apoptosis (Tateyama et al. 2000; Giri et al. 2020b).

The self-reactive $CD8^+$ T cells are the major culprits of the autoimmune response that mediate autoimmunity by production of the cytotoxic granules like granzyme B and perforin, resulting in apoptosis of target cells (Janeway et al. 2001). Additionally, they exacerbate the tissue damage by production of pro-inflammatory cytokines and FAS-FASL mediated apoptosis (Tateyama et al. 2000; Giri et al. 2020b). Apart from this, autoreactive B cells produce autoantibodies, which are the hallmark of various autoimmune diseases like RA, MS, SLE, and T1DMM (Hampe 2012). The autoantibodies after binding to the cellular receptors mediate cell lysis through complement activation and antibody-dependent cellular toxicity (Hampe 2012).

The subset of $CD4^+$ T cells known as regulatory T cells (Tregs), maintains immune tolerance by suppressing such self-reactive T and B cells (Dwivedi et al. 2013a, 2015; Giri et al. 2020a, 2021c). However, studies suggest that the decreased expression of FOXP3 (the master regulator of Tregs), leads to quantitate and functional Tregs defects in various autoimmune diseases (Long and Buckner 2011; Dwivedi et al. 2013b; Giri et al. 2020a, b). Overall, the initial trigger of autoimmune response and failure of immunological tolerance leads to widespread activation of self-reactive T and B cells contributing to pathogenesis of autoimmune diseases (Giri et al. 2022).

4.3 Proposed Mechanisms for Protective Effect of Infections on Autoimmune Diseases

Compelling evidence suggest correlation between decreased incidence of infections and increase in occurrence of autoimmune diseases and allergies in developed north American and European countries (Gale 2002; Mayr et al. 2003; Joner et al. 2004; Zaccone et al. 2006; Okada et al. 2010). There is an increase in the development of T1DM and multiple sclerosis for the past decade in the Western countries (Bach 2009; Okada et al. 2010). Such trend is not observed in less developed countries.

Moreover, such high incidence cannot be attributed solely to genetic factors since such increased autoimmune disease incidence have also been observed in immigrated families (Detels et al. 1972; Leibowitz et al. 1973; Bodansky et al. 1992; Symmons 1995; Staines et al. 1997; Hammond et al. 2000; Okada et al. 2010). The mechanism of protective effect mediated by infections on autoimmune diseases is multifactorial (Okada et al. 2010). Here, we discuss certain mechanisms like antigenic competition, innate immune mechanisms, immune regulation, mediated by infections which could lead to protection against autoimmune diseases.

4.3.1 Antigenic Competition

Antigenic competition is defined by diminished immune response to one antigen in the presence of another antigen (Pross and Eidinger 1974; Liacopoulos and Ben-Efraim 1975; Bach 2001). It occurs between closely related and unrelated antigens (Fujinami and Oldstone 1989; Oldstone 1998; Bach 2001). The phenomena are well studied in multicomponent vaccines such as diphtheria–pertussis–tetanus (DPT), and *Haemophilus influenzae*-tetanus vaccines (Table 4.1) (Halperin et al. 1999; Jatana and Nair 2007). Additionally, envelope component of human immunodeficiency virus (HIV) vaccine leads to reduced $CD4^+$ T cells response against Gag/Pol antigens due to antigenic competition (Table 4.1) (Kallas et al. 2019). Moreover, similar phenomena have been observed in case of influenza virus, where the antigenic competition leads to increased immune response against hemagglutinin and decreased immune response against neuraminidase (Table 4.1) (Johansson 1988). This antigenic competition may be due to presence of multiple components or multiple antigens (Bach 2001). In some cases, the antigenic competition could lead to one antigen being dominated and other being suppressed or in other cases both the antigens can be mutually suppressed (Bach 2001).

In the cases of autoimmune diseases, the infections can lead to increased competition with self-antigens, which could result in suppressed autoimmune response (Hara and Iwasa 2020). For example, administration of *Streptococcal* and *Klebsiella* extracts significantly reduces diabetes in non-obese diabetic (NOD) mice (Toyota et al. 1986; Saï and Rivereau 1996). Moreover, the immunization against bovine serum albumin (BSA) drastically reduces thyroiditis (McMaster and Kyriakos 1970). There may be multiple underlying mechanisms through which these infections can induce antigenic competition. The activation of adaptive immune response is triggered by antigen presenting cells (APCs). The APCs through the process of phagocytosis present the antigens on their surface (Janeway et al. 2001). These phagocytosis and subsequent antigen presentation process could be subject to saturation (Fig. 4.1) (Babbitt et al. 1986; Adorini et al. 1988; Bach 2001). Moreover, Fc receptors may also be saturated due to presence of antibodies against particular pathogens (Fig. 4.1) (Babbitt et al. 1986; Adorini et al. 1988; Bach 2001). Furthermore, evidences suggest the major histocompatibility complex (MHC) may be saturated by the presence of foreign antigens (Fig. 4.1) (Babbitt et al. 1986; Adorini et al. 1988; Bach 2001). Thus, the presence of infectious pathogen through antigenic

Table 4.1 Mechanisms involved for beneficial role of infections in suppression of autoimmune diseases

Mechanism	Description/example	Reference
Antigenic competition	Immune response to one antigen leads to diminished immune response against another antigen.	Chatenoud et al. (1986), Babbitt et al. (1986), Johansson (1988), Adorini et al. (1988), Fujinami and Oldstone (1989), Adorini (1998), Oldstone (1998), Halperin et al. (1999), Bach (2001, 2005), Jatana and Nair (2007), Gaisford and Cooke (2009), Kallas et al. (2019)
	Presence of multiple components or multiple antigens can lead to saturation of antigen presentation and B cell antibody production.	
	Specific antibodies against pathogens can be more immunodominant compared to antibodies against self-antigens.	
	Pathogen specific T cells can compete with self-reactive T cells, by consumption of IL-2.	
	Response against pathogen can trigger regulatory T cells which could suppress self-reactive T and B cells.	
	HIV envelope protein reduces $CD4^+$ T cells response against Gag/Pol antigens.	
	In influenza virus infection, immune response against hemagglutinin reduces immune response against neuraminidase.	
	Multicomponent vaccines such as DPT vaccine, and *Haemophilus influenzae*-tetanus vaccine.	
Innate immune mechanisms	Infections can modulate the immune response by binding to various TLRs leading to production of vast array of cytokines including regulatory cytokines.	Zaccone et al. (2003), Bach (2005), Lang et al. (2005), Bartemes and Kita (2018)
	TLR-dependent production of IL-10 and TGF-β are crucial in regulation of autoimmunity.	
	Binding of fungi to TLR2 activates Th2 type response.	
	Soluble antigens of worm induce NKT cells which inhibit T1DM.	
	Staphylococcal enterotoxin B can suppress experimental allergic encephalomyelitis and collagen-induced arthritis by inhibiting Vβ-T cell subsets.	

(continued)

Table 4.1 (continued)

Mechanism	Description/example	Reference
Infections induced Immunoregulation	Tregs activated against antigens can suppress the autoimmune response.	Bach (2001, 2005), Alyanakian et al. (2006), Raine et al. (2006), Lee et al. (2008), Gaisford and Cooke (2009), McSorley and Maizels (2012)
	Helminths can recruit Tregs by activating IL-10, IL-13, and TGF-β.	
	Mycobacterial infections control autoreactive T cells trafficking in MS and T1DM.	
	Extract of Gram-positive bacteria can enhance TGF-β production resulting in suppression of T1DM.	
	Viruses such as LCMV and HIV infect immune cells, leading to depletion of the host immune response.	
	Viral infections can trigger IFN-β, an immunoregulatory cytokine.	

DPT vaccine diphtheria–pertussis–tetanus vaccine, *TLR* toll like receptor, *Tregs* regulatory T cells, *TGF-β* transforming growth factor-β, *T1DM* type 1 diabetes, *LCMV* lymphocytic choriomeningitis virus, *HIV* human immunodeficiency virus, *IFN-β* interferon-β

competition could lead to reduced immune response against self-antigens contributing to decreased autoimmunity (Babbitt et al. 1986; Adorini et al. 1988; Bach 2001).

Furthermore, B cells also act as APCs, and the complex procedure of processing antigens, B cell differentiation, proliferation, and antibody production could lead to antigenic competition through various mechanisms (Bach 2001). The antibody directed towards the pathogen could be more immunodominant compared to self-antigens: as it may be present in a relatively higher numbers or it may have high affinity and avidity. Moreover, B cells precursors could be present in higher numbers for the particular antigen (Adorini 1998; Bach 2001, 2005; Gaisford and Cooke 2009). Thus, the antigenic competition mediated antibody against pathogen could lead to reduced autoimmune response.

Apart from this, restriction of the activated $CD4^+$ T cells' number could also influence B cells help. The presence of pre-existing pathogen specific T cells could interfere in activation of self-reactive T cells by consumption of IL-2 (Chatenoud et al. 1986; Bach 2001). Moreover, closely related antigens can act as T cells antagonist and can inhibit the activation of T cells specific to self-antigens (Fig. 4.1) (Chatenoud et al. 1986; Bach 2001). Furthermore, immune responses against pathogens could induce Treg cells which could suppress self-reactive T and B cells (Fig. 4.1) (Bach 2001). Thus, the decreased activation of self-reactive $CD4^+$ T cells could contribute to reduced activation of self-reactive B and cytotoxic T cells leading to decreased autoimmune response.

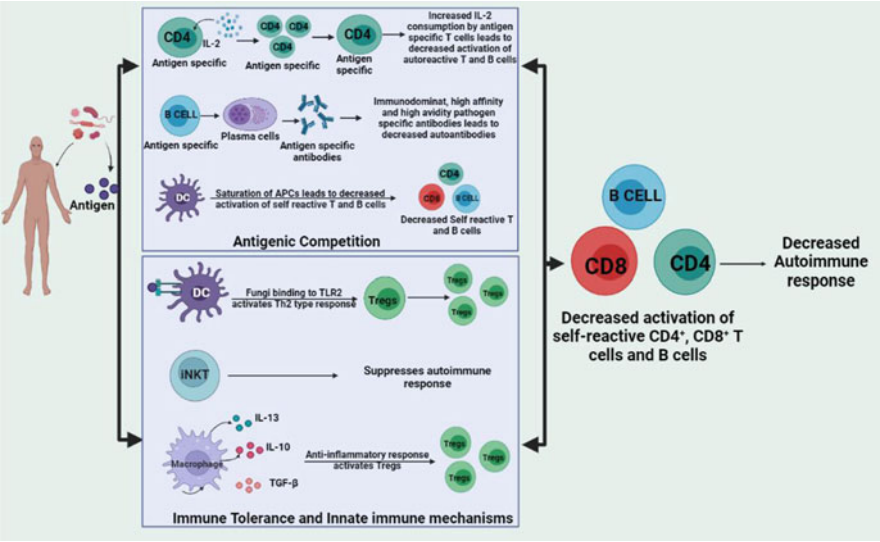

Fig. 4.1 Proposed mechanism for the beneficial role of infections in protection towards autoimmune diseases. Increased consumption of IL-2 by pathogen specific T cells, can lead to reduced activation of self-reactive $CD4^+$ T cells, which could contribute to reduced activation of self-reactive B and cytotoxic T cells leading to decreased autoimmune response. Additionally, pathogen specific antibodies can be more immunodominant compared to autoantibodies. Moreover, saturation of antigen presentation process and antibody production can lead to decreased self-reactive T and B cells response. Apart from this, the binding of fungi to TLR-2 promotes Th2 response. Additionally, soluble antigens of worm induce NKT cells which inhibit autoimmune response. Furthermore, helminths activate a subset of macrophage that produce anti-inflammatory cytokines like IL-10, IL-13, and TGF-β, which recruit Tregs. Overall pathogens through antigen competition, innate immune mechanisms and immune tolerance suppress autoimmune response

4.3.2 Innate Immune Mechanisms

Autoimmune diseases are characterized by specific adaptive immune response against the host cells; however, the role of innate immune response cannot be denied in autoimmune diseases (Waldner 2009). Specifically, studies have suggested the involvement of toll like receptors (TLRs) in development of autoimmune response, in RIP-LCMV mice where, TLR3 binding and subsequent IFN-α production is crucial in development of autoimmunity (Bach 2005; Lincez et al. 2021). However, in vivo and in vitro studies have suggested that TLR-dependent production of IL-10 and TGF-β are crucial in regulation of autoimmunity (Table 4.1) (Bach 2005; Lang et al. 2005).

Microbial infections, and commensal bacteria can modulate the immune response by binding to various TLRs (Fig. 4.1) (Bach 2005). The binding of pathogens to the TLRs could lead to production of vast array of cytokines which could include regulatory cytokines (Bach 2005). For example, the binding of fungi to TLR2 could activate Th2 type response (Table 4.1, Fig. 4.1) (Bartemes and Kita 2018).

Moreover, fungi can regulate the inflammatory response through activating Tregs and production of anti-inflammatory cytokines (Table 4.1) (Bartemes and Kita 2018). This could lead to suppression of self-reactive T and B cells leading to reduced autoimmune response. Moreover, they are known to induce Treg cells by binding to TLR2 on dendritic cells (DCs) (Fig. 4.1) (Van der Kleij et al. 2002; Oliveira-Nascimento et al. 2012). Additionally, soluble antigens of worm induce NKT cells which inhibit T1DM (Fig. 4.1) (Zaccone et al. 2003). Moreover, superantigens such as *Staphylococcal* enterotoxin B are known to suppress the pathogenesis of experimental allergic encephalomyelitis and collagen-induced arthritis by inhibiting Vβ T cell subsets (Prabhu Das et al. 1996; Bach 2001). Overall, these studies highlight the importance of innate immune mechanisms in suppression of autoimmunity.

4.3.3 Infections Induced Immunoregulation

The suppressive effect induced against a particular antigen could through bystander activation suppress the autoimmune response (Bach 2005). Therefore, the Treg cells activated in response to the particular antigen could in turn dampen the autoimmune response (Bach 2005). The mechanisms involved could be by enhancement of Th2 cells which could suppress the inflammatory response leading to protection against autoimmune diseases (Table 4.1).

Experimental evidence suggests that administration of gram-positive bacterial extract in NOD mice enhances the anti-inflammatory cytokine TGF-β production resulting in suppression of T1DM (Alyanakian et al. 2006). Furthermore, helminths activate a subset of macrophage that produce anti-inflammatory cytokines like IL-10, IL-13, and TGF-β, which recruit Tregs (Fig. 4.1) (McSorley and Maizels 2012). Furthermore, in MS, mycobacterial infections control trafficking of autoreactive T cells (Lee et al. 2008; Gaisford and Cooke 2009). Moreover, in T1DM the *Salmonella typhimurium* infection has been linked with inhibition of trafficking of autoreactive T cells trafficking to pancreas (Table 4.1) (Raine et al. 2006; Gaisford and Cooke 2009).

Several viruses have tropism towards immune cells and viral infections such as LCMV could infect the immune cells (Zinkernagel et al. 1999; Bach 2001). This could lead to reduction in autoreactive immune cells, resulting in suppression of autoimmune responses (Bach 2001). The most evident case of infection induced immunosuppression is of human immunodeficiency virus, which is known to infect $CD4^+$ T cells, leading to depletion of the host immune response (Bach 2001). Moreover, viral infections could lead to increased production of IFN-β, an immunoregulatory cytokine (Bach 2001). Additionally, the IFN-β immunomodulatory properties have been used in the treatment of multiple sclerosis (Bach 2001). Interestingly a study has highlighted that lymphocytic choriomeningitis virus (LCMV) infection in diabetic NOD mice, delayed the onset of disease (Oldstone et al. 1990; Bach 2001). This could be due to suppression of $CD8^+$ T cells by TGF-β producing Treg cells.

Overall, the studies suggest microorganisms and viruses could suppress the ongoing autoimmune diseases by suppressing pro-inflammatory Th1 response and promoting anti-inflammatory Th2 response (Fig. 4.1) (Bach 2001, 2005; Gaisford and Cooke 2009). However, detailed mechanistic studies assessing how microbes regulate the autoimmune response can lead novel therapeutics for autoimmune diseases. Additionally, studies will highlight the complex interactions between microbes and cellular signaling pathways involved in development of autoimmunity.

4.4 Epidemiological Evidence for the Protective Role of Infections in Human Autoimmune Diseases

Incidence of autoimmune diseases including MS, RA, T1DM have increased dramatically over the past few decades (Poser et al. 1989; Green and Patterson 2001; Myasoedova et al. 2010). Furthermore, this increased incidence has been observed prominently in the developed countries (Bach 2001). Epidemiological data suggests the increased incidence of MS, T1DM and Crohn's diseases in North America and Europe (Bauer 1987; Bach 1994; Kurtzke 1995; Green and Patterson 2001). The increased incidence cannot be solely linked with genetics (Okada et al. 2010). Interestingly recent evidence has suggested changes in lifestyle in the developed countries could lead to increased occurrence of allergic and autoimmune diseases (Okada et al. 2010). Moreover, according to the hygiene hypothesis the decreasing incidence of infections in developed countries could lead to increased incidence of allergic and autoimmune diseases (Okada et al. 2010). The hygiene hypothesis is supported by the fact that the autoimmune diseases have increased in immigrants from low income countries to developed countries (Okada et al. 2010).

In developing countries, the incidence of asthma, allergic rhinitis and atopic dermatitis has increased by over 15% in United Kingdom, New Zealand, and Australia (Okada et al. 2010). Moreover, there is an increased prevalence of autoimmune diseases such T1DM in European countries such as Finland (Harjutsalo et al. 2008). Furthermore, the prevalence of inflammatory bowel diseases (IBD), such as Crohn's disease or ulcerative colitis (Bach 2002) and primary biliary cirrhosis (Rautiainen et al. 2007), has increased. Interestingly, the incidence of T1DM and MS has also increased in the Asian and African immigrants in the US (Detels et al. 1972; Staines et al. 1997).

Multiple factors could explain the increased incidence of autoimmune diseases. Recent studies suggest the change in the microbiota and decreased exposure to infections in childhood could lead to autoimmune diseases, by multiple mechanisms like decreased immune regulation, antigenic completion and innate immune factors (Bach 2001, 2005; Gaisford and Cooke 2009). Moreover, studies suggest that increased exposure to farming and cowsheds in early life could prevent atopic diseases (Riedler et al. 2001; Ege et al. 2006). Moreover, exposure to endotoxin in the childhood protects against asthma and atopy (Braun-Fahrländer et al. 2002). Furthermore, *Schistosoma* infections have also been reported to protect against atopy (Flohr et al. 2006; Okada et al. 2010). Therefore, the detailed understanding of the

role of microorganisms could lead to potent therapeutics for treatment of autoimmune diseases.

4.5 Animal Model Studies for Exploring the Protective Effects of Infections on Autoimmune Diseases

Studies have suggested a strong correlation between infections and incidence of autoimmunity (Okada et al. 2010). Here, we discuss few animal model studies which suggest the role of infections towards protection of autoimmune diseases.

4.5.1 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by loss of insulin producing β-cells (Hara et al. 2013). The exact etiology is unknown, but multiple factors like genetics, autoimmunity, and environmental factors can trigger T1DM. Insulitis and elevated autoantibodies produced against β-cells lead to β-cell death (Pihoker et al. 2005). The destruction of β-cell death leads to symptoms like urination, loss of appetite, fatigue, thirst, and hyperglycaemia (Pihoker et al. 2005).

Although microorganisms are thought to be triggering factors for development of autoimmune diseases, but animal model studies suggest that T1DM is associated with sanitary conditions of animal facilities (Bach 2002). The studies suggest that lower the burden of infection, the higher the incidence of diabetes (Like et al. 1991; Okada et al. 2010). Moreover, infection of NOD mice with bacteria, viruses, and parasites prevents NOD mice from diabetes (Table 4.2) (Bach 2002). Apart from this, probiotics and microbial components also protect NOD mice from diabetes (Petrovsky 2010; Kim et al. 2020). Additionally, exposure to components like soluble worm antigen and soluble egg antigen from *Shistosoma mansoni*, OM89 and OM85 from *Escherichia coli* and ES62 from *Acanthocheilonema viteae* can protect from autoimmune diseases like T1DM, SLE, and RA (Zaccone et al. 2003; Alyanakian et al. 2006; Harnett and Harnett 2006; Toussirot et al. 2006; Gaisford and Cooke 2009).

Additionally, administration with complete Freund's adjuvant (CFA) in NOD mice has shown to protect from T1DM (Qin et al. 1993). Similarly, *Mycobacterium bovis* and *Mycobacterium avium* have shown to suppress autoimmune diabetes (Brás and Águas 1996; Inafuku et al. 2015). Interestingly, infection with viruses such as LCMV, murine hepatitis virus and LDV and *Schistosoma mansoni* parasites have shown to suppress T1DM in NOD mice (Oldstone et al. 1990; Wilberz et al. 1991; Takei et al. 1992; Bach 2002; Zaccone et al. 2009). Moreover, *Pseudomonas aeruginosa* signaling molecule, *N*-(3-oxododecanoyl)-L-homoserine lactone suppresses insulitis and controls T1DM in NOD mice (Pritchard et al. 2005). Additionally, *Salmonella typhimurium* infection generates immunomodulatory DCs which suppress T1DM in NOD mice (Raine et al. 2006). Moreover,

Table 4.2 Protective role of infections in autoimmune disorders

Autoimmune disease	Infection	Reference
Type 1 diabetes mellitus	*Mycobacterium bovis* and *Mycobacterium avium* suppresses autoimmune diabetes.	Toyota et al. (1986), Oldstone et al. (1990), Wilberz et al. (1991), Takei et al. (1992), Brás and Águas (1996), Saï and Rivereau (1996), Bach (2002), Zaccone et al. (2003), Pritchard et al. (2005), Alyanakian et al. (2006), Raine et al. (2006), Saunders et al. (2007), Zaccone et al. (2009), Petrovsky (2010), Inafuku et al. (2015), Kim et al. (2020)
	Pseudomonas aeruginosa signaling molecule, *N*-(3-oxododecanoyl)-L-homoserine lactone suppresses insulitis and T1DM in NOD mice.	
	Salmonella typhimurium induces immunomodulatory DCs, thereby suppressing diabetes in NOD mice.	
	Streptococcal and *Klebsiella* extracts suppress diabetes in NOD mice.	
	Gram-positive bacterial extract enhances TGF-β production resulting in suppression of T1DM.	
	LCMV, murine hepatitis virus and LDV protect against diabetes in NOD mice.	
	Trichinella spiralis and *Heligmosomoides polygyrus* helminths suppress autoimmune diabetes.	
	Soluble worm antigen and soluble egg antigen from *Shistosoma mansoni* can protect against diabetes.	
	Probiotics and microbial components also protect NOD mice from diabetes.	
	Bacteria, viruses, and parasites infection prevents NOD mice from diabetes.	
Rheumatoid arthritis	Bacteria and parasite infections can suppress arthirits.	Pearson and Taylor (1975), Toussirot et al. (2006), Harnett et al. (2008), Osada et al. (2009), Shi et al. (2011)
	S. mansoni can decrease autoantibodies and pro-inflammatory cytokine production in CIA.	
	E. coli extract suppresses arthritis.	
	Symphacia obvelata parasites suppress CFA arthritis is rats.	
	Acanthocheilonema viteae suppresses CIA.	
	Hymenolepis diminuta reduces CFA.	
	Bacterial extract OM-89 induce IL-10 production and suppress pro-inflammatory cytokine in RA.	

(continued)

Table 4.2 (continued)

Autoimmune disease	Infection	Reference
Multiple sclerosis	Bacterial and Helminths' infections protect against autoimmune MS in EAE model.	Lehmann and Ben-Nun (1992), Sewell et al. (2003), La Flamme et al. (2003), Gruden-Movsesijan et al. (2008), Walsh et al. (2009), Cleenewerk et al. (2020), White et al. (2020)
	S. mansoni converts Th1/Th17 response to anti-inflammatory Th2 response, thus protecting from EAE.	
	Heligmosomoides polygyrus infection protects from EAE in IL-4Rα-dependent manner.	
	Fasciola hepatica infections control EAE through TGF-β-Mediated suppression of Th17 and Th1 responses.	
	Schistosomiasis parasitic infection reduces CNS inflammation thereby suppressing EAE.	
	Trichinella spiralis infection ameliorates the EAE in dose dependent manner in Dark Agouti rats.	
	Mycobacteria infection can prevent mice from EAE.	
	Mycobacterium bovis BCG diverts self-reactive T cells from CNS in EAE.	
	Mycobacterium tuberculosis exposure protects from EAE-susceptible mice from disease.	
	Bordetella pertussis protects mice from EAE.	
	Escherichia coli, *Shigella*, and *Staphylococcus aureus* infections suppress EAE.	
Inflammatory bowel disease	Helminth's infection suppresses IBD pathology.	Khan et al. (2002), Elliott et al. (2003, 2004), Summers et al. (2005a, b), Ruyssers et al. (2008), Motomura et al. (2009), Johnston et al. (2010), McSorley and Maizels (2012), Cleenewerk et al. (2020)
	S. mansoni infection suppress IBD by macrophage and IL-10 dependent mechanism.	
	Schistosome egg, suppresses pro-inflammatory cytokines production and enhances anti-inflammatory cytokines like IL-10 and TGF-β, thereby protecting from colitis.	
	Heligmosomoides polygyrus reduces colitis in IL-10 deficient manner.	

(continued)

Table 4.2 (continued)

Autoimmune disease	Infection	Reference
	Hymenolepis diminuta infections suppress colitis pathology by suppressing macrophage activation.	
	Trichuris suis improves disease activity index of ulcerative colitis.	
	Trichuris suis controls Crohn's disease.	
	Ancylostoma hookworm products suppress colitis.	
	T. spiralis infections and antigens suppress colitis pathology.	

T1DM type 1 diabetes *NOD mice* non-obese diabetic mice, *DCs* dendritic cells, *MS* multiple sclerosis, *IL-4Rα* interleukin-4 receptor α *BCG* Bacillus Calmatte-Gurin, *CIA* collagen-induced arthritis, *CFA* complete Freund's adjuvant, *LCMV* lymphocytic choriomeningitis virus, *LDV* lactate dehydrogenase-elevating virus, *EAE* experimental autoimmune encephalomyelitis, *IBD* inflammatory bowel disease, *CNS* central nervous system

gastrointestinal helminths such as *Trichinella spiralis* and *Heligmosomoides polygyrus* inhibit autoimmune diabetes in NOD mice (Saunders et al. 2007).

Although the data suggests the involvement of infections in protection against T1DM; however, the data is currently limited to animal model of diabetes (Bach 2001; Gaisford and Cooke 2009). Moreover, the underlying mechanisms how infections could suppress such autoimmune response is unknown. Infections and microbial components through antigenic competition, innate immune factors, immunoregulation could suppress the pro-inflammatory environment, promote anti-inflammatory cytokines and induce Treg cells, which could control the ongoing autoimmune response (Fig. 4.1) (Bach 2001, 2005; Gaisford and Cooke 2009). However, future animal model studies must explore the underlying mechanisms which could lead to development of potent therapeutics for treatment of T1DM.

4.5.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease, characterized by chronic joint inflammation leading to bone and cartilage damage. RA is responsible for significant morbidity as it causes disability, discomfort, stiffness, and decreased life expectancy (Thanapati et al. 2017; Carbone et al. 2020; Giri et al. 2021b). Although the exact etiology for RA is unknown, multiple factors such as genetics, autoimmunity, environment, diet alcohol, and smoking can trigger RA development (Giri et al. 2022). Although infections are considered to trigger autoimmune RA (Mahajna et al. 2015); however, recent evidence in animal model studies suggests that infections can protect from RA (Table 4.2) (Vischer 1993).

Evidence for pathogen induced RA protection are found in type II collagen-induced arthritis (CIA) arthritis model (Harnett et al. 2008). Studies suggests *Syphacia obvelata* parasite's infection suppresses CFA arthritis in rats (Pearson and Taylor 1975). Moreover, *S. mansoni* infections reduces autoantibodies and pro-inflammatory cytokine production in CIA arthritis models (Osada et al. 2009). Additionally, tapeworm, *Hymenolepis diminuta* infections in rats induces IL-10 dependent CFA arthritis (Shi et al. 2011). Overall, animal model studies suggest parasite infections can alleviate arthritis pathology by suppressing pro-inflammatory cytokine production and inducing anti-inflammatory cytokine production (McSorley and Maizels 2012). Additionally, bacterial extract OM-89 showed inhibition of arthritis by inducing IL-10 production and suppressing pro-inflammatory cytokine production in RA patients (Toussirot et al. 2006). The above mentioned studies suggest that bacterial and parasitic infections can protect from ongoing autoimmunity in RA by promoting anti-inflammatory response and suppressing pro-inflammatory response. However, future in vitro and in vivo studies are warranted to understand the underlying mechanism for development of potent therapeutics for treatment of RA.

4.5.3 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune neurological disease, characterized by chronic inflammation and demyelination resulting in symptoms such as vision loss, cognitive defects, depression, and bowel defects (Filippi et al. 2018). The pathogenesis of MS is due to autoimmune reactions against myelin proteins and gangliosides (Prat and Martin 2002). Multiple factors such as vitamin D deficiency, intestinal dysbiosis, viral infections, a hypercaloric diet, genetics, and environmental factors can trigger MS development (Milo and Kahana 2010). Although infections, particularly viral infections are considered to trigger MS development, but animal model studies suggest certain bacterial and helminth infection can protect against autoimmune MS (Table 4.2) (Sewell et al. 2003; La Flamme et al. 2003).

Several bacterial and parasitic infections have shown disease protection in experimental autoimmune encephalomyelitis (EAE), the mouse model of MS (Lehmann and Ben-Nun 1992; Sewell et al. 2003; La Flamme et al. 2003; Gruden-Movsesijan et al. 2008). Studies suggest *Mycobacteria* infection can prevent mice from EAE (Lehmann and Ben-Nun 1992; Sewell et al. 2003). *Mycobacterium bovis* BCG diverts self-reactive T cells away from the central nervous system (CNS) which then suppresses EAE in mice (Sewell et al. 2003). Moreover, *Mycobacterium tuberculosis* exposure protects EAE-susceptible mice against induction of disease (Lehmann and Ben-Nun 1992). Moreover, *Bordetella pertussis* could also protect mice from EAE development (Lehmann and Ben-Nun 1992). Additionally, *Escherichia coli*, *Shigella*, and *Staphylococcus aureus* were found to be effective in suppressing EAE (Lehmann and Ben-Nun 1992). Moreover, *S. mansoni* parasite has shown to alleviate the EAE pathology (Cleenewerk et al. 2020). It converts the pro-inflammatory Th1/Th17 response to anti-inflammatory Th2 response

(Cleenewerk et al. 2020). Interestingly, *Heligmosomoides polygyrus* infection suppressed the EAE in IL-4Rα-dependent manner (White et al. 2020). *Fasciola hepatica* infections has been shown to control EAE through TGF-β-Mediated suppression of Th17 and Th1 responses (Walsh et al. 2009). Additionally, Schistosomiasis (a parasitic infection) reduces the inflammation in the CNS, thereby alleviating the EAE pathology (La Flamme et al. 2003). *Trichinella spiralis* infection also showed to ameliorate the clinical course of EAE in dose dependent manner in Dark Agouti rats (Gruden-Movsesijan et al. 2008).

Overall, the above mentioned studies suggest that bacterial and parasitic infections can control EAE; however, studies in this field are scarce and only limited to animal models of MS. Therefore, future in vitro and in vivo studies must be carried to identify the exact underlying mechanism to explore the role of infections in protection of MS, which will aid in the development of potent therapeutics for treatment of MS.

4.5.4 Inflammatory Bowel Disease (IBD)

Crohn's disease and ulcerative colitis are two main inflammatory bowel diseases (Seyedian et al. 2019). They are characterized by chronic inflammation in the digestive tract (Seyedian et al. 2019). The condition ulcerative colitis is characterized by chronic inflammation in the colon and rectum. Crohn's disease involves chronic inflammation in the lining of digestive tract (Seyedian et al. 2019). IBD is generally characterized by diarrhea, rectal bleeding fatigue, weight loss, abdominal pain, and cramping (Seyedian et al. 2019).

In mouse model of IBD, helminths' infections have been demonstrated to suppress disease pathology (Summers et al. 2005a, b; McSorley and Maizels 2012). For instance, *S. mansoni* infection suppressed the IBD by macrophage and IL-10 dependent mechanisms (Cleenewerk et al. 2020). Additionally, *Ancylostoma* hookworm products' administration suppressed the colitis (Ruyssers et al. 2008). *T. spiralis* infections and antigens also suppressed the colitis pathology (Khan et al. 2002; Motomura et al. 2009). Moreover, *Schistosome* egg has been shown to protect colitis by suppressing the production of pro-inflammatory cytokines as well as by inducing anti-inflammatory cytokines such as IL-10 and TGF-β (Elliott et al. 2003; McSorley and Maizels 2012). Moreover, *Heligmosomoides polygyrus* was demonstrated to dampen the colitis in an IL-10 deficient manner (Elliott et al. 2004). The *Hymenolepis diminuta* infections were also able to suppress colitis pathology by suppressing macrophage activation (Johnston et al. 2010), increased IL-10 and Tregs' production (Johnston et al. 2010; McSorley and Maizels 2012). Additionally, *Trichuris suis* improved the disease activity index of ulcerative colitis (Summers et al. 2005b). Furthermore, *Trichuris suis* was also shown to control Crohn's disease (Summers et al. 2005a).

The suppressive effects of the infections on IBD are not characterized well. However, the findings suggest that the infections suppress the ongoing infections by promoting the production of anti-inflammatory cytokines like IL-10 and TGF-β

(McSorley and Maizels 2012). Additionally it induces Tregs and suppresses Th1/Th17 associated cytokines after infection (McSorley and Maizels 2012). Thus, as shown in animal models of IBD the anti-inflammatory environment induced by infections can further lead to development of potent therapeutic strategies for IBD.

4.6 Conclusions

Infections are one of the major players which modulate the development of autoimmune diseases. Recently, compelling evidences have suggested the role of infections in protection of autoimmune diseases. However, the detailed underlying mechanisms how the infection could protect against autoimmune and allergic diseases are unclear. Therefore, in vitro and in vivo approaches studying the role of infections in suppression of autoimmune diseases are warranted. Moreover, considering ethical limitations for using infections in treatment of human autoimmune diseases, the therapeutic potentials of bacterial extracts in experimental models of autoimmune diseases must be investigated. Overall, a far better understanding for the underlying mechanisms for role of infections in protection of autoimmune diseases could pave a way to novel therapeutics for the treatment of autoimmune diseases.

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