Induction and protection of autoimmune rheumatic diseases. The role of infections

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ABSTRACT

It is thought that in genetically predisposed individuals, autoimmune diseases can be promoted and/or exacerbated by viruses, bacteria, or parasitic infectious agents. Pathogens can activate innate immune response interacting with Toll-like receptors that recognize pathogen-associated molecules. As a consequence of infections, a prolonged inflammatory response may occur leading to chronic inflammation with activation of adaptive immune response. In addition, the defective clearance of apoptotic infected cells, which progress- es to secondary necrosis, can foster the autoimmune reactions.

Although numerous data from humans and/or animal models support the hypothesis of a direct contribution of pathogens to the induction of the disease, some infectious agents are able to prevent autoimmune disorders.

In this review, data on the innate and adaptive immune response induced by pathogens are summarized, focusing on the possible protective or non-protective role of infections in the development of autoimmune diseases.

Introduction

Rheumatic autoimmune diseases induced by viral/and or bacterial infections have been observed in genetically predisposed individuals (1-5).

The hypothesis by which infections may trigger these disorders has been supported by several evidences such as the disease seasonal onset (2), and the isolation of viral genomic DNA/RNA from affected tissues of patients once the disease gets started (6, 7), suggesting that the disease can be considered the consequence of an altered immune response to infections.

Different mechanisms by which pathogens might be responsible for autoimmunity have been postulated (2-10):

the microorganism could interact in the host with cellular proteins inducing changes in the proteins which are no longer recognized as "self" by the host immune system; it could induce the production of human antibodies carrying pathogenic idiotypes (anti-idiotypic antibodies); or it could have antigenic sites that "mimic" aminoacid sequences in the normal host proteins (molecular mimicry hypothesis).

These abnormalities can occur as a consequence of a prolonged inflammatory response, due to infection, in genetically predisposed individuals leading to chronic inflammation and localized tissue damage.

Inflammation is a key feature of several rheumatic autoimmune diseases (11, 12) and the pivotal role of immune-inflammatory response in the initiation, progression and perpetuation of these diseases has been largely demonstrated (13).

Inflammatory response is mediated by the release of pro-inflammatory cyto-kines which are also responsible for limiting the diffusion of microbial agents in the host. However, in individuals with immune-regulatory dysfunctions, a heightened inflammatory response can contribute to the autoimmune pathogenesis of the disease.

In recent years, Toll-like receptors (TLRs) have received growing attention as mediators of the adaptive autoimmune response (14-18). In animal models of lupus nephritis, some TLRs (i.e., TLR3, TLR9) have been specifically immunolocalized in the kidney, suggesting their pivotal role in the induction of immune-inflammatory response which characterizes the disease.

B cells and TLRs are directly linked, because after the activation of B cell receptor, B lymphocytes upregulate TLRs which, in turn, contribute to the proliferation, expansion and isotype switch of

B cell clones. In addition, the combined activation of some TLRs (*i.e.,* TLR3 and 7/8) results in an enhanced production of inflammatory mediators which self sustain the immune-inflammatory disease.

An important immune-inflammatory response can also be induced as the consequence of the physiological cell death known as apoptosis (19, 20), when the clearance of apoptotic bodies is not efficient, leading to the progression of apoptosis to secondary necrosis. In some autoimmune diseases, such as SLE, a defective clearance of apoptotic bodies *in vitro* has been demonstrated, and this phenomenon has been suggested to trigger the autoimmune response in these patients (21, 22).

Among the pro-inflammatory cytokines, the recently discovered interleukin (IL)-17 seems to play an important role in the pathogenic inflammatory response to microbial agents such as fungi, activating a Th17 pathway associated to defective pathogen clearance and inhibition of fungicidal activity by the host immune system. During fungal infections, TLR4 seems to be responsible for the inhibition of Th17 pathway, preventing the pathogenetic inflammatory response and promoting Th1 antifungal resistance.

Besides the theory of the direct involvement of the infectious agents in the induction of autoimmune diseases (23), the hypothesis for a protective role of some infectious agents which are able to prevent autoimmune diseases has also been postulated. Some microbes have co-evolved with the host immune system and have developed strategies for down-modulating the host immune response, but the protective or non-protective role of pathogens in the development of some rheumatic auto-immune diseases such as RA is still debated (24).

Understanding the different immune-inflammatory pathways activated by infectious agents may be important, not only to elucidate their role in the induction of autoimmunity in genetically predisposed individuals, but also to generate therapeutic strategies which target specific molecules responsible for chronic inflammation and autoantibody-mediated damage.

Infections, BCR activation and autoimmunity

Once an infectious agent enters the human being, the innate immune system generally clears away the agent by adopting different strategies according to the molecular characteristics of the agent. In particular few molecular structures unique to viruses are known to induce immune activation of cells of the innate system (25). Among the molecules involved in the innate recognition of foreign viruses and bacteria, Toll-like receptor 2, 3, 6, 7 and 9 are of fundamental importance. Many viruses are made of dsRNA genomically or become such during viral replication as full or partial structures. The mammalian receptor for dsRNA is Toll-like receptor 3 (TLR3), a member of the Toll-like receptors (TLR 1-11) family (Table I). It is well known that TLR 3 leads dendritic cells to express and synthesize Interferon alpha/beta and chemokines which attract other immunological cells to the site of the infection. For example in the lung, TLR3 can be activated by dsRNA, but also by influenza virus A, to involve mitogen-activated protein kinases, phosphatidylinositol 3-kinase/Akt signaling, and the TLR3-associated adaptor molecule TRIF. This signal transduction elicits an epithelial response that includes the secretion of IL-8, IL-6, RANTES (regulated on activation normal T cell expressed and secreted), and interferon-beta and the up-regulation of the major adhesion molecule ICAM-1 (26).

Experimental evidences show that the MRL/lpr mice which spontaneously develop a proliferative glomerulonephritis

in the context of an SLE-like disease, express TLR3 mRNA in kidneys at comparable levels as in the spleen, while all other TLRs are expressed at low levels in the kidney. Immuno-staining for TLR3, TLR7 and Toll like receptor 9 (TLR9) revealed their expression by F4/80-positive infiltrating macrophages in 20-week-old nephritic MRL[lpr/lpr] mice. In addition, TLR3 localized to glomerular mesangial cells. Stimulation of both cell types with ligands induced IL-6 production and TNF-α and IFN-γ enhanced ligand-induced IL-6 production (27). All these data suggest that in a predisposed setting, a TLR3 activation may create the biological milieu capable of inducing the occurrence of a chronic self-maintaining inflammatory disease. This is, in fact, the case since only renal cells are necessary to maintain the inflammatory tissue reaction in the absence of B or T cells.

In another model of lupus nephritis, the NZB/NZW mice, TLR9 expression (which links unmethylated CpG-DNA, the bacterial DNA rich in CpG island, the natural ligand) is present in the tubular cells, and correlates with proteinuria, while in human lupus nephritis, TLR9 has been shown to be induced by DNA-Immune complexes formed with specific autoantibodies (28).

Could the innate immune response and B cells, directly be involved in amplifying the immune response and in inducing autoimmunity?

The current dogma under B cell engagement is that B cell activation initiates with the binding of antigen (Ag) to the B cell receptor (BCR) (signal 1),

Table I. Toll-like receptor family.

Receptor	Cell type
TLR1	Ubiquitous
TLR2	DCs, PMLs, and monocytes
TLR3*	DC and NK cells, B cells, upregulated on epithelial and endothelial cells
TLR4	Macrophages, PMLs, DCs, ECs, but not on lymphocytes
TLR5	Monocytes, immature DCs, epithelial, NK, and T cells
TLR6	High expression in B cells, lower on monocytes and NK cells
TLR7	B cells, plasmacytoid percursor DCs
TLR8	Monocytes, low in NK cells and T cells
TLR9	Plasmacytoid percursor DCs, B cells, macrophages, PMLs, NK cells, and microglial cells
TLR10	B cells, plasmacytoid precursor DCs
TLR11	Not determined

that at the immunologic synapse with T cells, the B cell receives T cell help via CD40-CD40 ligand interaction and cytokines (signal 2) which is sufficient to drive B cells towards proliferation and differentiation into antibody secreting cells, which however die after a few divisions. Data have been provided that after BCR activation, B cells upregulate TLRs, while it has been shown that memory human B cells express TLR2, 6, 7, 9 and 10, but not TLR4. This means that human memory B cells can be readily activated in the absence of BCR ligation by bystander T cell help, while naive B cells need BCR activation to undergo proliferation and subsequent differentiation. The most recent experimental data actually show that TLR9 ligation synergize with BCR triggering and T cell help in inducing naive B cell proliferation. Another important discovery has been that upon BCR triggering, extensive B cell proliferation occurs once agonists of TLR2 and 9 are concomitantly present, and that cytokines such as IL6 and IL12 have synergistic activity. This suggests that a variety of microbial products acting directly on TLR expressed by B cells or cytokines can contribute to the proliferation and expansion of B cell clones (signal 3).

Of major importance to the understanding of B cell role in autoimmune chronic inflammatory diseases (ACIDs) is class switch recombination (CSR) occurring after B the cell specific activation. It has been shown that TLR9 activation exerts a powerful synergistic effect along with BCR ligation and T cell help in determining CSR and maturation of naive B cells up to the final step of antibody-secreting cells. The conclusion is that TLR stimulation exerts a fundamental role in inducing isotype switch and B cell differentiation. This 3rd signal sustains the proliferation, differentiation, class switch recombination and isotype switch of B cells, events that are known to be part of the function of antibody secreting cells in the long-term.

Is there any evidence that BCR ligation and TLR activation occur in human diseases?

In RA synovium, TLR-3 and TLR-7 have been found to be highly expressed.

All TLR ligands elicited phenotypic DC maturation equally between DCs from RA patients and those from healthy controls. Remarkably, both TLR-3 and TLR-7/8 stimulation resulted in a skewed balance toward IL-12. Intriguingly, the combined stimulation of TLR-4 and TLR-3-7/8 resulted in a marked synergy with respect to the production of inflammatory mediators (IL6, IL12) (29).

In SLE, tubular cells of nephritic kidney obtained from patients, express TLR9 which are also expressed in B cells and plasmacytoid dendritic cells and exposure to higher order CpG-DNA ligands or to immune complexed self-RNA, triggers activation of autoreactive B cells and plasmacytoid dendritic cells. Surprisingly, experiments with chromatin-containing immune complexes in lupus sera were capable of inducing proliferation of rheumatoid factor-specific B cells (AM14-transgenic B cells) and DNA-specific B cells (3H9-transgenic B cells). This proliferation was sensitive to treatment with DNAse and required unmethylated CpG sequences. Data suggest that DNA isolated from serum immune complexes in lupus contains disproportionably more guanosine/cytosine nucleotides than adenine/thymine residues and as such can indeed stimulate simultaneously BCR and TLR9 activation (30).

Therefore the 3rd signal provided by TLR activation can indeed play an important role in inducing persistent BCR activation, anti-auto antibody synthesis by plasma cell in tissues of ACIDs patients (31).

Clearance deficiency – a potential link between infections and autoimmunity

1. Cell death: apoptosis vs. necrosis

Cell death plays an immense role in our lives and for our health. Apoptosis, the programmed form of cell death, is a physiological process and is necessary for embryogenesis, development and normal tissue homeostasis of multicellular organisms. When cells are meant to die, they undergo cell shrinkage, loss of contact to neighbouring cells, chromatin condensation, DNA cleavage, and plasma membrane "blebbing".

During the whole process, the plasma membrane of apoptotic cells remains intact and ion selective. Intracellular material gets packed in apoptotic bodies followed by their swift and efficient uptake by neighbouring cells or professional phagocytes. Usually apoptotic cells are removed silently without provoking inflammation or immune responses (32). They rather show immunosuppressive behaviour since they induce the release of anti-inflammatory cytokines (33).

If apoptosis fails its program and dying cells do not get cleared in time, they are prone to progress to the violent form of cell death: necrosis referred to as secondary necrosis. During necrosis the cytoplasm swells finally resulting in the loss of membrane integrity. Eventually, the cell ruptures and releases intracellular autoantigens, nuclear material, proteins, and non-fragmented DNA into the microenvironment. Since many of these autoantigens are modified during the process of apoptosis, they are not considered as "self" by the immune system. Consequently the putative "non-self" or "cytotoxic" material may be taken up by antigen presenting cells provoking an immune response against "altered-self". This form of cell death is no longer silent, but pro-inflammatory instead. Therefore, a clearance defect of dying cells may lead to a chronic autoimmune disease such as systemic lupus erythematosus (SLE) (34).

2. Find-me and eat-me signals

On the one hand, apoptotic cell removal is achieved by attracting professional phagocytes via secreted soluble "find me"-signals such as lysophosphatidylcholine (35). On the other hand, the apoptotic cells expose "eat me" signals for efficient recognition and engulfment by phagocytes. Exposed and oxidised phosphatidylserine (PS) belong to the early "eat me" signals on the surfaces of apoptotic cells. A plethora of phagocyte receptors (CD36, oxLDL receptor, Mer Kinase, etc.) binds to PS via several adaptor molecules (Gas6, MFG-E8, Annexin-V (AxV), etc.). PS exposure induces the induction of the anti-inflammatory cytokines IL-10 and TGF-β and the downregulation of the

pro-inflammatory IL-1β, TNF-α, and IL-12.

During late apoptosis the glycosylation pattern of the cells' surfaces changes. C1q, C-reactive protein (CRP), the long pentraxin (PTX-3), and the surfactant protein A and D (SP-A and -D) now bind to the altered surface of the apoptotic cells *in vivo* (36). In addition, the lectins *Griffonia simplificolia III* (GSL II), *Narcissus pseudonarcissus* (NPn), and *Ulex europaeus I* (UEA I) show increased binding to the dying cells *in vitro* (37). These very late "back up-eat me" signals result from an increased exposure of ER-resident lipids, proteins, and immature glycoproteins. The loss of plasma membrane due to membrane blebbing seems to be substituted by internal membranes, partially derived from the ER (38). However, if clearance is deficient, apoptosis may progress even further and the cells enter the stage of secondary necrosis, spilling out putative cytotoxic constituents, that challenge immune tolerance (39, 40).

3. Clearance deficiency – SLE
The chronic autoimmune disease SLE is a multifactorial disease. Environmental factors (like UV radiation or infections) as well as genetic predispositions are involved in its etiopathogenesis. A serological hallmark of SLE is the existence of anti-double-stranded DNA (anti-dsDNA) autoantibodies.

We have shown that monocyte-derived macrophages from patients with SLE have a reduced phagocytic activity for the uptake of autologous apoptotic material *in vitro* (39). Lymph node biopsies from SLE patients showed an accumulation of apoptotic material and a strongly reduced number of tangible-body macrophages (TBM) in their germinal centers. Apoptotic debris was even associated with the surface of follicular dendritic cells (40). If these potential autoantigens cannot be removed by TBM, they may serve as maturation and survival signals for autoreactive B cells in the germinal centers of secondary lymphoid organs. Finally self-tolerance may break, leading to severe systemic immune dysregulation of SLE. In whole blood assays, we detected a significantly impaired uptake of beads

coated with albumin or IgG, apoptotic and necrotic cells by macrophages and granulocytes of a subgroup of patients with SLE (our and other works reviewed in 41). In contrast, degraded nuclear fragments of necrotic cells were only taken up by the patients' blood-borne phagocytes since this process requires antinuclear autoantibodies to be present. The uptake of this material into the phagocytes does induce a robust production of pro-inflammatory cytokines. An increased apoptosis without an efficient clearance of dying and dead cells may thus lead to the release and an accumulation of nuclear autoantigens in certain tissues. Thus, we coined the hypothesis that a defect in the clearance of apoptotic cells plays a key role in induction and maintenance of this autoimmune disease.

Exploring and exploiting microbial regulatory T cells for the control of inflammation and autoimmunity
Direct proof that infection establishes persistent autoimmunity remains lacking, although it may provoke a prolonged inflammatory response when occurring on a susceptible immunological background. Because microbial degradation products, and even bacterial DNA, are present at sites of autoimmunity, this has led to the speculation that the continuous seeding of bacterial products from the gut may eventually favour, on a permissive genetic background, onset of inflammatory autoimmunity.

It is well known that an imbalance between pro- and anti-inflammatory cytokine activities favours the induction of autoimmunity, chronic inflammation and thereby localized tissue damage. Chronic diseases, such as inflammatory bowel diseases and rheumatoid arthritis, are characterized by a robust immune response resulting in unresolved inflammation. Inflammation is mediated by proinflammatory cytokines; recently, a novel subset of T-helper (Th) cells was identified that plays a crucial role in inflammation and autoimmune disease. This population secretes several proinflammatory cytokines, including the novel cytokine interleukin (IL)-17, and, hence, has been termed "Th17" (42). Inflammatory cytokines

are implicated in the progression of localized chronic infections as well as in serious systemic pathologies, such as diabetes, chronic obstructive pulmonary disease, and cardiovascular disease. Therapeutics that antagonize inflammatory cytokines ameliorate inflammation and may have implications in local and systemic diseases in which inflammation and autoimmunity predominate (43).

Recent evidence has helped to accommodate fungi, either commensals or ubiquitous, within the immune homeostasis and its dysregulation. Inflammation is a key feature of fungal infections and diseases. The inflammatory response to fungi may serve to limit infection but an overzealous or heightened inflammatory response may contribute to pathogenicity, as documented by the occurrence of severe fungal infections in patients with immunoreconstitution disease or primary immunodeficiencies associated with hightened immune reactivity (44). These patients may experience intractable fungal infections despite the occurrence of pathogen-specific immunity. IL-12, by initiating and maintaining Th1 responses, was thought to be responsible for overreacting immune and autoimmune disorders. This was also the case in fungal infections where immunoregulation proved to be essential in fine-tuning inflammation and uncontrolled Th1/Th2 antifungal reactivity. Recent evidence has shown that it is the Th17 pathway – and not the uncontrolled Th1 response – which is associated with defective pathogen clearance, failure to resolve inflammation and to initiate protective immune responses. Both IL-17 and IL-23 inhibited fungicidal activity (45) and subverted the inflammatory program of neutrophils even in the presence of IFN-gamma, a finding which suggests that the Th17 effector pathway prevails over the Th1 pathway. Protective Th1 and non-protective Th17 were crossregulated in experimental models of mucosal candidiasis or pulmonary aspergillosis. Cross-regulation occurred at different levels, including the production of directive cytokines (such as IL-12 or IL-23, for Th1 or Th17, respectively) by dendritic cells. TLR4 appeared to play a major role in controlling the balance

between protective and non-protective immune responses to fungi, through its ability to both promote (via MyD88) and inhibit (via TRIF) Th17 development (46). This suggests that conditions of high-threat inflammation may represent a local environmental factor that predispose to Th17 activation in fungal infections (47). In this scenario, unrestricted fungal growth will result from the activation of not only pathogenic Th17 cells but also non-protective Th2 cells, whose activation is strictly dependent on fungal burden. Blockade of IL-17/IL-23 prevented pathogenic inflammatory responses, ameliorated infections and restored protective Th1 antifungal resistance, thus causally linking pathogenic inflammation to Th17 development.

The capacity of regulatory T cells (Tregs) to inhibit aspects of innate and adaptive antifungal immunity, including functional Th17 antagonism, is required for protective tolerance to fungi (48). The circumstances in which protective or tissue-damaging T cell responses to fungi are affected by the activity of Treg are becoming clearer. The relationships range from situations in which the Treg response seems to contribute to immune dysfunction to those that minimize tissue damage caused by immunoinflammatory cell reactions. Diverse types of Treg cells, with disparate and multiple functions, are induced in fungal infections (49). By dampening Th1 immunity, Tregs producing IL-10 and expressing membrane-bound TGF-beta and Foxp3 prevented sterilization of *Candida albicans* from the gastrointestinal tract and maintained equilibrium to ensure fungal persistence, minimal tissue damage and immunity to re-infection. In aspergillosis, distinct Treg populations capable of mediating anti-inflammatory effects or respiratory tolerance were co-ordinately induced after exposure to the fungus. Thyptophan catabolites contribute to such a homeostatic condition by providing the host immune defence with mechanisms adequate for protection, without necessarily eliminating fungal pathogens – which would impair immune memory – or causing an unacceptable level of tissue damage (50).

Despite the recognized importance of Tregs in the homeostatic regulation of immune responses, our understanding of their significance and interplay with other pathway of immunity and autoimmunity is still limited. We have evidence that, through bystander effects and molecular mimicry, Tregs activated in fungal infections could be exploited for the control of inflammation and autoimmunity in experimental models of inflammatory and autoimmune diseases. Thus, microbial Tregs could be successfully exploited to prevent inflammation and maintain immune homeostasis.

Together, our study highlights the "double-edged" sword nature of the host/fungus interaction. If the ability of fungi to subvert the inflammatory program through the activation of the IL-23/IL-17 axis may eventually lead to immune dysregulation, their ability to activate Tregs, an integral and essential component of antimicrobial immunity, may represent a mechanism whereby dysregulated immunity is prevented. As fungal recognition and fungal-mediated inflammatory and anti-inflammatory responses occurs through distinct Toll-like receptors, Toll-like receptor agonists and antagonists will be promising candidates endowed with the ability of limiting inflammatory and allergic responses associated with infectious diseases.

Could infections protect against autoimmune rheumatic diseases?

Autoimmune disease arises when tolerance to self-tissue breaks down resulting in the development of pathology. Although there are some rare autoimmune diseases that result from single gene mutations, most autoimmune diseases are influenced by multiple genetic loci and by environmental factors. A role for environment in the development of most autoimmune diseases is indicated by the less than 100% concordance for disease development in monozygotic twins. Furthermore, the incidence of some autoimmune diseases such as T1D and SLE has been increasing dramatically in the developed world at a rate faster than can be accounted for by genetic change. In the case of T1D, which is a T helper 1 (Th1) mediated

autoimmune disease of juvenile onset, this is particularly interesting as it was lethal until Banting and Best discovered insulin in the 1920s (51). The development of T1D is governed by many genes, suggesting that we have retained potentially lethal genes either because they have conferred a strong selective advantage or through linkage disequilibrium. The concordance rate for diabetes development in monozygotic twins is only around 40%, emphasizing an important role for environmental modifiers. In terms of thinking about what such an environmental modifier might be there have been suggestions that diet or infection might play a precipitating role in diabetes development. The proposal that infection might play a role in initiating T1D was fuelled not only by the observed seasonal onset of diabetes in humans but also by finding that certain viruses such as coxsackie B, Reovirus or Encephalomyocarditis virus were able to induce diabetes in certain strains of mice. However, with a greater understanding of the aetiology of this autoimmune disease and the identification of key islet antigens it has been shown in humans that there is evidence of beta cell specific immune responses years before diabetes onset. This, coupled with the lack of evidence of a consistent viral association with the human disease suggested that there might be an alternative explanation which would bring together infection and autoimmunity. This other view suggested that while the increased incidence in T1D could be attributed to exposure to a novel environmental agent *e.g.*, virus, it is more probable that, given the historical lethality of T1D, it is due to a lack of infection that had hitherto dampened diabetes onset.

This hypothesis that a relative absence of infection is responsible for the observed increased incidence of autoimmunity has been gaining ascendancy over recent years and is paralleled by observations in the allergy field where it has been called "the hygiene hypothesis" (52). This, of course, does not mean that some autoimmune conditions are not precipitated by exposure to infectious agents (53). In support of this hypothesis there are now many examples

of both spontaneous and experimental models of human autoimmune diseases where infection with a given microbe inhibits the onset of autoimmune pathology (54). There are several ways in which such infections might be expected to impact on autoimmunity and it is important to consider the fact that an ideal response against a pathogen would be one which did not inflict collateral damage to host tissue. This raises the issue of immune modulation which would be advantageous both to the microbe and to the host and which could be the end result of the co-evolution of the host immune system with some infectious agents over millions of years (55).

Whether the same ideas which have been developed to explain the increased incidence of autoimmune diseases such as T1D can be applied uniformly to other autoimmune conditions such as rheumatoid arthritis (RA) is debatable. There are some considerable differen-ces between RA and some of the auto-immune conditions shown to be inhibited by infection. The concordance rate for development of RA in identical twins is much lower (12-15%) than that observed for multiple sclerosis and T1D (56). Microbial infections have been directly linked to the onset of some arthritic conditions. Gram negative bacteria such as *Yersinia, Salmonella* and *Shigella* as well as the organism *Chlamydia trachomatis* are associated with the development of reactive arthritis in some patients (57). Viral infections have also been linked to arthritis with acute arthritis being associated with the mosquito borne alphaviruses such as the Sindbis virus (58). With regard to RA itself, a significant number of patients (around 10-20%) have been reported to have serological markers suggesting recent exposure to infective agents although no one common agent was identified (59). Therefore, although there is clear evidence that arthritis can be associated with certain infections, the role of infection in precipitating onset of RA remains unclear. Evidence for the ability of infections to inhibit onset of arthritis comes largely from studies using a model system of murine collagen induced arthritis (54). In this model, there is evidence not only that

certain bacterial or parasitic infections can inhibit arthritis development, but also that ES-62 a product of a filarial nematode is able to inhibit not only the onset of disease but also influence disease progression (60).

To establish whether, indeed, some infections can inhibit autoimmune rheumatic diseases requires further epidemiological studies. Even if there is no evidence that they can inhibit autoimmune rheumatic diseases there is accumulating information regarding the ways that certain infectious agents modulate host immune responses and identification of microbial biomodulators. Some of these biomodulators may provide novel therapeutic approaches for the treatment of inflammatory diseases.

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