CURRENT OPINION

Infections as triggers of flares in systemic autoimmune diseases: novel innate immunity mechanisms

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Purpose of review
The innate immune response (IIR) has to be immediate facing pathogens, and effective to induce a long-lasting adaptive immunity and immune memory. In genetically susceptible individuals, beyond a first defense, a chronically activated by infections IIR may represent a trigger for the onset or flares in systemic autoimmune diseases. This article reviews the recent scientific literature in this regard and highlights the key issues needing investigation.

Recent findings
Thanks to its high specificity mediated by pattern recognition receptors, the IIR is not called unspecific anymore. The discovery of these increasingly accurate recognizing molecular mechanisms has also evidenced their involvement in breaking self-immune tolerance and to maintain chronic inflammation in autoimmune responses. Neutrophil extracellular traps (NETS) as the main source of antinuclear antibodies; the 'neutrophils-pDC activation loop' theory; and the Th1/Th2/Th17 misbalances induced by microbial products because of chronically activated innate immune cells, are some of the recent uncovered IIR origins involved in infectious-induced systemic autoimmune diseases.

Summary
A deeper understanding of the genetic predisposition and the pathogen-derived factors responsible to exacerbate the IIR might potentially provide therapeutic targets to counteract flares in systemic autoimmune diseases.

Video abstract
http://links.lww.com/COR/A44

Keywords
infectious-induced autoimmune diseases, innate humoral factors, innate immune cells, innate immune mechanisms

INTRODUCTION

Innate immune cells (neutrophils, eosinophils, basophils, mast cells, macrophages, natural killers, innate lymphoid cells, monocytes, dendritic cells and platelets) bear intracellular and extracellular pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), Nod-like receptors, RIG-I-like receptors, C-type lectin receptors, Absent in melanoma 2-like receptors, oligoadenylate synthase family proteins and cyclic GMP-AMP synthase, focused on recognizing conserved pathogen-associated molecular patterns (PAMPs) present in large groups of microorganisms [1]. This specialized molecular identification elicits an immediate defensive response but, to become efficient, it must also activate a long-lasting adaptive immunity and induce immune memory. The innate immune response (IIR) also involves soluble mediators (defensins, complement system, collectins/ficolins and pentraxins) that destroy and/or opsonize microbes [2]. Infections in individuals with genetic or functional alterations in any of these recognizing molecules may produce chronic activation and lead to dysfunctional changes in IIR mechanisms, representing triggers for the onset or flares in systemic autoimmune diseases.

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KEY POINTS

- The 'neutrophils-pDC activation loop' theory in antinuclear antibodies-bearing autoimmune diseases (and IFN-α as key cytokine) has emerged as a central mechanism of their immunopathology.

- NADPH oxidase inhibitors (as NETs production blockers) have been theoretically proposed as reducers of fungal and bacterial infection-induced flares in autoimmune systemic diseases; pilot studies of clinical research are desirable to evaluate their therapeutic efficacy.

- The overactivation state of the innate immune response in autoimmune patients might be because of genetic predisposition or induced by pathogen-derived factors; both likelihoods might coexist and need tight investigation.

- A direct cause–effect association between infections and many innate immune factors is very well supported; others require further research to assign them a role as inducers, witnesses or enhancers in autoimmune diseases.

NEUTROPHIL EXTRACELLULAR TRAPS: ARISING AS THE MAIN SOURCE TO INDUCE ANTINUCLEIC ANTIBODIES

NET release was described as an antimicrobial neutrophils mechanism; nevertheless, it was later found in other noninfectious conditions, such as gout, malignancy and atherosclerosis. Likewise, NET exacerbation has been described in autoimmune diseases (https://www.sciencedirect.com/topics/immunology-and-microbiology/autoimmune-diseases) including rheumatoid arthritis (RA), antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and psoriasis [3]. Neutrophils from systemic lupus erythematosus (SLE) patients have showed higher susceptibility to NET production and this effect frequently correlates with the activation state of plasmacytoid dendritic cells (pDC), allowing the emergence of the 'neutrophils-pDC activation loop' theory [4]. NET production induced by infections has been proposed as a plenteous source of neutrophil-derived self-DNA, activating pDC via TLR9 and TLR7, inducing high levels of IFN-α, and exacerbating the autoimmune disorder. This theory is supported by the evidence that IFN-α is a potent NET inducer and promotes autoantibody-secreting autoreactive B cells [5].

The higher neutrophil susceptibility to NET production might be an intrinsic genetic feature of autoimmune patients or be produced by pathogen-derived factors. In this regard, Konig *et al.* showed that *Aggregatibacter actinomycetemcomitans*,

a periodontal pathogen, induces hypercitrullination of host neutrophils, such as observed in joints from RA patients. This effect was mediated by the *A. actinomycetemcomitans*-derived leukotoxin A (LtxA) through inducing NET-like structures and releasing hypercitrullinated proteins. In addition, the effect of the RA-associated risk allele HLA-DRB1 was just observed in RA patients exposed to *A. actinomycetemcomitans* [6]. Furthermore, although RA and cystic fibrosis in common present airway inflammation and NET production has been implicated in their autoimmunity process; these diseases present different profiles of anti-NET protein antibodies. RA patients develop anticitrullinated protein autoantibodies (ACPAb) but not antibactericidal permeability-increasing protein autoantibodies (ABPIAb). In contrast, cystic fibrosis ABPIAb-positive patients showed no ACPAb. Interestingly, ABPIAb recognize the BPI C-terminus lacking posttranslational modifications and NET induction by *Pseudomonas aeruginosa* results in BPI cleavage by *P. aeruginosa* elastase. The presence of ABPIAb was associated with the detection of *P. aeruginosa* on sputum culture and with diminished lung function in cystic fibrosis patients [7]. This evidence reveals a likely involvement of this infection in autoimmunity development to NET-derived proteins in cystic fibrosis.

EOSINOPHILS FACING UP PATHOGENS: FRIENDS OR FOES IN AUTOIMMUNITY?

Activated eosinophils can produce extracellular traps (EETs) to kill pathogens too, but their contribution to release nuclear autoantigens might be minor. Their association with the autoimmune process may be owing to the tissue injury caused by their ability to bind autoantibodies recognizing self-cells and their strong cytotoxic properties [8]. Eosinophils have been identified in inflammatory infiltrates in organ-specific autoimmune diseases and the absence of eosinophils significantly reduces the disease severity in animal models of autoimmune bowel diseases and of autoimmune myocarditis [9,10].

Eosinophils are specialized cells against helminths but, paradoxically alive helminths, excretory/secretory helminths products, and helminths-derived synthetic molecules have been used to treat autoimmune diseases, such as inflammatory bowel disease (IBD), type 1 diabetes (T1D), multiple sclerosis and RA [11]. Infection with parasitic worms polarize the immune response to Th2 by avoiding chronic inflammatory responses involved in autoimmune diseases (Th1 and Th17). This effect is mediated by a differentiation of macrophages toward M2 phenotype, tolerogenic dendritic cells

and regulatory T cells, all together producing immunoregulatory molecules (IL-10 and TGFβ) [12]. Yet, recognizing helminth-purified products by the immune system does not necessarily involve eosinophil participation. Th2 polarization is a subsequent process dependent on the emitted signals during antigen presentation and some pathogenic antigens possess inherent tolerogenic properties [13]. Hence, as there is evidence supporting eosinophil participation in both tissue injury and protective Th2 polarization, their real contribution in infection-induced autoimmunity needs to be elucidated.

IN PERSISTENT INFECTIONS, BASOPHILS AND MAST CELLS CONTRIBUTE TO CHRONIC INFLAMMATION AND FLARES IN AUTOIMMUNE PROCESS

Basophils and mast cells are phenotypic and functionally related cells intensely studied as key effector cells in IgE-associated immune responses (helminths infection and allergy). But, these cells additionally play a critical role in innate immune responses to bacteria and viruses and, there is emerging evidence of their active contribution in the pathogenesis of cancer, inflammatory diseases [14,15] and, as this review discusses: infection-induced autoimmunity. Basophils are differently activated in SLE depending on the disease severity and they have been implicated in the pathogenesis of lupus nephritis [16]. As expected, activated mast cells have been found in skin autoimmune diseases, such as bullous pemphigoid and epidermolysis bullosa acquisita [17]; but surprisingly, also in systemic autoimmune diseases, such as multiple sclerosis and RA [18–20].

Basophils and mast cell activation by infections induces degranulation and secretion of stored proinflammatory mediators, such as tumor necrosis factor (TNF), histamine, serotonin, heparin, and proteases; followed by de-novo synthesis and secretion of prostaglandins and leukotrienes and, cytokines and chemokines (IL-3, IL-4, IL-5, IL-6, IL-8, and IL-13) [21]. Mast cells elicit type I interferons (IFNs) but only in response to viral infection [22]. Overall these molecules induce survival, activation and differentiation of B cells with the consequent antibodies production via BAFF, IL-4, and IL-6; mainly inducing Th2 type responses and IgE antibodies, but it would block the Th1 polarization usually associated to autoimmune responses [23]. Hence, the pathogenic role of infection-activated basophils and mast cells in systemic autoimmune disorders might be just during persistent infections and intense immune responses, mainly attributable to their contribution to the persistence of chronic inflammation as described in RA, Crohn's diseases, scleroderma, multiple sclerosis, pulmonary and hepatic fibrosis and, autoimmune heart disease [24].

THE PROINFLAMMATORY ROLE OF MONOCYTES AND MACROPHAGE INDUCED BY MICROBIAL PRODUCTS IN AUTOIMMUNE DISEASES

Monocyte and macrophage activation has reproducibly been reported in several autoimmune diseases. On the basis of clinical evidence, Epstein–Barr virus (EBV) infection is a suspected cause of relapses in RA [25]. EBV replication activates the TLR8 molecular pathway in purified systemic sclerosis monocytes. Viral interleukin 10 (vIL-10), a lytic phase protein from EBV homolog of human IL-10 (hIL-10), induces significantly lower STAT3 phosphorylation in comparison with hIL-10, and it is less efficient downregulating inflammatory genes – vIL-10 levels are significantly higher in plasma from SLE patients compared with matched unaffected controls [26▪]. On the other hand, tracking of adoptively transferred Ly6C high GFP monocytes infected with murid herpesvirus 68 (a mouse virus closely related to EBV), into arthritic CCR2-/- mice showed that this monocyte subset delivers viruses to inflamed RA joints [27▪]. This evidence indicates to vIL-10-induced monocyte activation as an EBV-related virus mechanism responsible for flares in RA.

Classically activated macrophages (M1) have been described exerting a strong microbicide activity in different autoimmune disease [28,29]. This effect is mediated by producing reactive oxygen species, nitric reactive species and pro-inflammatory cytokines (IL-1, IL-6, IL-12, IL-23, and TNF-α). M1 can be originated by in-vitro stimulation with Th1 cytokines (IFNα or TNF-α) and importantly with Gram-negative (lipopolysaccharide) and Gram-positive (lipoteichoic acid) PAMPs [30].

Regarding virus infections, human cytomegalovirus (HCMV)-positive cells were found in islets and exocrine areas from patients with fulminant T1D. This infection was accompanied with higher numbers of macrophages and, CD4+ and CD8+ T lymphocytes. Parallelly, 11 viral genes mainly associated with latent HCMV infection were identified in the PBMCs of SLE patients. A functional analysis of the *US31* gene (a human cytomegalovirus protein highly represented in SLE patients) expression could induce monocyte activation and M1 differentiation via a direct US31/NF-κB2 interaction [31]. In a T1D model, following lymphocytic choriomeningitis virus infection, macrophages accumulate near islets and in close contact to islet-infiltrating (autoimmune) CD8+ T cells. Disruption of IFNα/β

receptor signaling in macrophages resulted in restricting trafficking of autoreactive-specific T cells into the islets [32]. These evidences support and strengthen the idea of the proinflammatory M1 involvement in AD induced by microbial products.

SELF-ANTIGENS PRESENTING DENDRITIC CELLS AS INITIATORS OF AUTOIMMUNITY

Dendritic cells are a heterogeneous population of professional antigen-presenting cells that connect and modulate innate and adaptive immune responses. Dendritic cells are involved in the initiation of both immunity and immunological tolerance but, some infections may induce changes in their tolerogenic/immunogenic balance and instigate the development or flares in autoimmune diseases. Certain pathogen-derived molecular structures can *per se* emulate self-antigens (molecular mimicry); additionally, during an infection, dendritic cells capture and process foreign and self-antigens and; after trauma of immune-privileged sites, hidden antigens can be exposed and taken up by migrating dendritic cells [13]. Whatever the self-antigen source, in genetically prone individuals, processing and presentation by skewed dendritic cells may activate low-affinity autoreactive preexisting T cells and induce an autoimmune response.

The pathogenic role of dendritic cells interacting with the commensal intestinal microbiota on the tolerance loss to glycoproteins in IBD was recently shown. In this condition, more colonic dendritic cells express TLR2 and TLR4 with higher levels of CD40. In Crohn's disease, mature CCR7+ dendritic cell group with proliferating T cells and production of higher levels of IL-12 and IL-6 are associated with the disease activity. IL-6 producing intestinal dendritic cells induced by local bacteria broke T cells' regulatory activity, resulting in tolerance loss to gut self-antigens and tissue damage [33]. This idea is strengthened by the results obtained in a Toll-like receptor 7 (TLR7)-dependent mouse model of SLE, where the authors showed that a gut microbiota lactobacillus (*Lactobacillus reuteri*) induced autoimmunity by increasing plasmacytoid dendritic cells (pDC) and interferon signaling [34▪▪].

PLATELET ACTIVATION BY INFECTIONS: CAUSE OR EFFECT IN SYSTEMIC AUTOIMMUNE DISEASES

In addition to their pivotal role in hemostasis, platelets are also recognized as crucial players in innate and adaptive immunity, and growing evidence is positioning them as participants in autoimmune diseases. Platelets express functional TLRs and FcγRII. Hence, these cells can recognize microorganisms directly or opsonized [35]. Upon activation, platelets recruit immune cells to the injured site by secreting proinflammatory factors. Simultaneously, they secrete antimicrobial and hemostatic factors, such as P-selectin, beta-thromboglobulin and PF4, which are constitutively found in serum of RA, SLE and multiple sclerosis patients correlating positively with platelet activation and disease severity [36–38]. In mouse models of RA and autoimmune neuroinflammation, thrombocytopenia ameliorates inflammation [39]. In humans, anticitrullinated protein autoantibodies in RA [40] and self-immune complexes in SLE, directly stimulate P-selectin expression, soluble CD40L secretion and platelet aggregation [41]. Currently, the available discoveries indicate a likely platelet implication as both inducers and witnesses in the autoimmunity induced by infections.

NATURAL KILLER CELLS AND INNATE LYMPHOID CELLS: MUCH MORE THAN THE LYMPHOID LINEAGE INNATE IMMUNE CELLS

Natural killer cells' response to malignant transformed cells or to intracellular pathogenic invasion is modulated by activating or inhibitory receptors upon recognizing surface ligands on target cells and inflammatory cytokines. A reduced frequency and over-activated state of peripheral natural killer cells was reported in children with autoimmune hepatitis type 2. These natural killer cells displayed increased IFNγ and reduced IL-2 production [42]. Chronic liver inflammation and injury may be produced by viral infections reverting the natural killer cells' tolerance by altering their activating/inhibitory balance, cytokine profile and migratory pattern [43,44]. In the liver, natural killer cells can mediate the recruitment, activation and release of cytotoxic agents from neutrophils, thus contributing to the tissue damage. Additionally, activated natural killer cells producing high levels of IFNγ can induce strong Th17 immune responses in an autoimmune disease-like EAE mice model [45] and, in infection-induced autoimmune disease, the increased IFN-γ-mediated immune response can be even more harmful for tissues than the pathogen *per se*.

ILC lack antigen specificity but express PRRs, such as TLRs (1, 2, 4, 5, 6, 7, and 9). These cells respond to cytokines and are able to activate T cells via MHC II receptors. ILC1, ILC2, and ILC3 share transcription factors and cytokine profiles with Th1, Th2, and Th17 cells, respectively. ILCs have shown multiple beneficial effects including protection

against infections, maintenance of homeostasis, tissues repair, and mediation of normal inflammatory responses. Therefore, many studies suggests that alterations in ILC functions may contribute to the abnormal immune activation leading to autoimmunity [IBD, RA, multiple sclerosis, SLE, psoriasis, Sjögren syndrome, ankylosing spondylitis, autoimmune hepatitis (AIH), and chronic inflammatory disorders] [46]. The common pattern is that ILC1 and ILC3 increase in peripheral blood and accumulate in inflamed tissues, which promote chronic inflammation by producing IFN-γ and IL-17A, respectively [47]. ILC1 secrete IFN-γ and TNF, which are recognized as critical pro-inflammatory factors

underlying a variety of autoimmune diseases [48]. Some studies have shown that ILC3 can directly participate in intestinal pathogenesis of IBD particularly through IL-23. During an infection, the number of IL-17-producing ILC3 increases in the inflamed ileum and colon of patients with Crohn's disease [49], and GM-CSF from ILCs play a key role in the initiation of autoimmune arthritis [50]. Inversely, ILC2 in blood and tissues seem to correlate with anti-inflammatory activity, ILC2 located in lung and respiratory tract mediate allergic responses and secrete anti-inflammatory cytokines. Nevertheless, ILC2 produce cytokines such as IL-4, IL-5, and IL-13 in response to stimulation by IL-25, IL-33, and
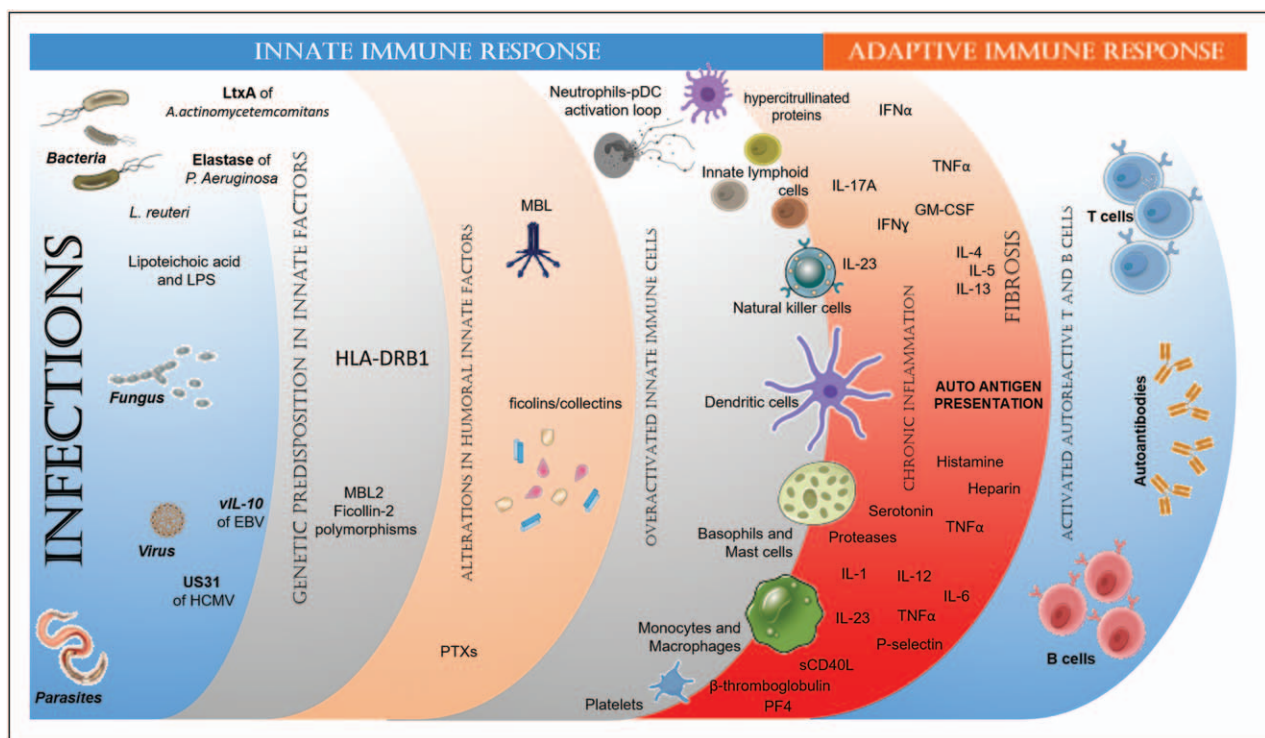
FIGURE 1. 'A series of unfortunate events' starting with an infection-induced-overactivated innate immune response. The presence of activated T and B-autoreactive cells and, autoantibodies is just the final result of several uncontrolled events. As very well known, the first undesirable event is the presence of genetic predisposition, yet the current information about innate immune factors in this regard is limited. NET induction by bacteria and fungus might represent an abundant source of neutrophil-derived self-DNA, which in turn would activate pDC via TLR9 and TLR7, inducing high levels IFN-α; this event would initiate the tolerance loss in antinuclear antibody-bearing autoimmune diseases. Humoral innate factors might be a relevant event involved in the origin or flares in pathogen-induced autoimmunity because of their high production enhancing the action of other innate and adaptive immune cells. A chronic production of proinflammatory mediators by activated innate immune cells (ILC1, ILC3, natural killer, basophils, mast cells, monocytes, and macrophages) in response to infections is an indisputable event contributing to the presentation of self-antigens by skewed dendritic cells, which might activate low-affinity autoreactive preexisting T and B cells. ILC2 contribution in isotype switch, B-cell proliferation and enhancing autoantibody production might be a key event to be evaluated. The current evidence about platelet involvement as both inducers and witnesses in infection-induced autoimmunity is an event deserving special attention. Finally, thanks to their specialized function against helminths, polarizing the immune response towards Th2 avoiding chronic inflammatory (Th1 and Th17 responses) and inducing M2macrophages, tolerogenic dendritic cells, and regulatory T cells, eosinophils are crucial innate immune cells with high potential to discover new therapeutic strategies to avoid the tragic culmination of unfortunate events in autoimmunity.

thymic stromal lymphopoietin (TSLP), and these cytokines play an important function in fibrosis in several autoimmune diseases [49]. Altogether, these evidence suggest that a chronic ILC1 and ILC3 activation by pathogenic agents might induce an overproduction of their respective proinflammatory cytokines. On the other hand, ILC2 enhances the antibodies production, isotype switch and B-cell proliferation, a pivotal aspect in some autoimmune diseases.

INNATE HUMORAL FACTORS AS ENHANCERS OF THE AUTOIMMUNE RESPONSES

In the IIR, the complement system can be activated by pathogen-derived lectins induced by collagen-like humoral pattern recognition molecules (PRMs), such as mannose-binding lectin (MBL), the ficolins/ collectins and pentraxins (PTXs). The deficiency of some complement proteins or in the control of their activity has been widely described in autoimmune diseases [51], and MBL genotypes have been associated with the risk of rheumatic fever and rheumatic heart disease (RHD) [52,53]. In two studies in patients with rheumatic fever, the results showed that polymorphism in MBL2 and *ficolin-2* genes are involved in the pathogenesis [54]. Ficolins-2 and Ficolins-3 bind DNA to clearance apoptotic cell debris by phagocytic cells to prevent autoimmunity [55]. Pentraxins (PTXs) have a crucial role in maintaining immune homeostasis; hence defects in PTX expression has been associated with increased sensitivity to some pathogens and, failing PTX-mediated apoptotic cell clearance is thought to be involved in the pathophysiology of some autoimmune diseases, such as SLE [56].

Defensins are a group of antimicrobial peptides of the IIR. α, β, and θ defensins, moreover, function as chemokines. Defensins have been involved in virus-induced autoimmunity in the central nervous system (CNS). Granulocyte-secreted defensins induce recruitment of mast cells to the luminal space followed by production of inflammatory cytokines, affecting the blood–brain barrier and, allowing access of activated T cells and invader virus; enhancing in this way, the immune-related injury. During the antiviral immune response, defensins augment the production of neutralizing antibodies associated to autoimmune events with variable neurologic involvement [57]. In summary, humoral factors of the innate immune system might be involved in pathogen-induced autoimmunity development and flares as their high production enhances the action of other innate and adaptive immune cells.

CONCLUSION

A direct cause–effect relationship between infection-activated innate immune cells and humoral factors, and autoimmunity is a little explored research field by autoimmunologists. The autoimmunity process might be the final result of 'a series of unfortunate events' starting with an infectious-induced-overactivated innate immune response (Fig. 1). The continuous discovery of new IIR mechanisms with high potential to specifically recognize and act against certain pathogens make them potential exploration targets to investigate their highly probable participation in the tolerance loss to auto-antigens and simultaneously, as latent therapeutic targets to the treatment of systemic autoimmune diseases.

Conflicts of interest

There are no conflicts of interest.

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