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Bystander activation and autoimmunity

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ABSTRACT

The interaction over time of genetic, epigenetic and environmental factors (i.e., autoimmune ecology) increases or decreases the liability an individual would have to develop an autoimmune disease (AD) depending on the misbalance between risk and protective effects. Pathogens have been the most common antecedent events studied, but multiple other environmental factors including xenobiotic chemicals, drugs, vaccines, and nutritional factors have been implicated into the development of ADs. Three main mechanisms have been offered to explain the development of autoimmunity: molecular mimicry, epitope spreading, and bystander activation. The latter is characterized by auto-reactive B and T cells that undergo activation in an antigen-independent manner, influencing the development and course of autoimmunity. Activation occurs due to a combination of an inflammatory milieu, co-signaling ligands, and interactions with neighboring cells. In this review, we will discuss the studies performed seeking to define the role of bystander activation in systemic and organ-specific ADs. In all cases, we are cognizant of individual differences between hosts and the variable latency time for clinical expression of disease, all of which have made our understanding of the etiology of loss of immune tolerance difficult and enigmatic.

1. Introduction

Autoimmune diseases (ADs) are characterized by a loss of immunological tolerance to self-antigens. ADs can be organ-specific or systemic chronic diseases influenced by genetic and environmental factors [1]. Three major mechanisms have been offered to explain the development of autoimmunity:

(i) Molecular mimicry, which describes the structural similarity between self and non-self-epitopes, which trigger activation of cross-reactive B and/or T cells [2,3].
(ii) Epitope spreading, which is a secondary autoimmune response generated after a release of neo-self-antigens caused by an inflammation [4].
(iii) Bystander activation is a heterologous activation of non-antigen-specific lymphocytes. This activation is mediated by indirect signals that favor an inflammatory milieu such as ligands of co-signaling receptors, cytokines, chemokines, pathogen-associated molecular patterns, and extracellular vesicles with microbial particles [5].

The immune system presents different control and checkpoint mechanisms to avoid the destruction of host tissue by deploying an immune response against an infection [6,7]. However, a robust immune response to an invading microorganism can alter this regulation and trigger autoimmunity [8]. Failure in such responses could be mediated by damage in peripheral and central tolerance, as observed in primary immunodeficiencies [9–11]. Diverse pathogens (viruses, bacteria, and parasites) are implicated in the triggering or propagation of auto-reactive immune responses [8].

Bystander activation was first described in 1996 by Tough et al. [12] in an attempt to understand the massive clonal T-cell expansion that occurs after a heterologous viral infection. Indeed, they hypothesized that T cells could proliferate and expand in a non-specific, T cell receptor (TCR)-independent manner. They demonstrated that type I interferons (IFNs) could act as an adjuvant and could induce T-cell

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Abbreviations

AD	autoimmune disease
AIH	autoimmune hepatitis
AITD	autoimmune thyroid disease
APCs	antigen-presenting cells
CFA	complete Freund's adjuvant
cGAMP	cyclic guanosine monophosphate-adenosine monophosphate
CMV	cytomegalovirus
CNS	central nervous system
Cx	connexins
DC	dendritic cells
Der p 2	recombinant protein of *Dermatophagoides pteronyssinus* group 2
DMARDs	disease-modifying anti-rheumatic drugs
EAE	experimental autoimmune encephalomyelitis
EBV	Epstein-Barr virus
GD	Graves disease
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hPG	human proteoglycan
HSV	herpes simplex virus
HT	Hashimoto thyroiditis
IDO1	indoleamine-2,3-dioxygenase-1
IFA	incomplete Freund's adjuvant
IFN	interferon
IL	interleukin
JIA	juvenile idiopathic arthritis
LCMV	lymphocytic choriomeningitis virus
LKM1	liver kidney microsomal type 1
LPS	lipopolysaccharide
MCMV	murine CMV
MHC	major histocompatibility complex
MICA/B	MHC class I chain-related protein A and B
MS	multiple sclerosis
NKG2D	natural killer group 2D
NK	natural Killer
NKT	natural killer T
NO	nitric oxide
PBMCs	peripheral blood mononuclear cells
pDC	plasmacytoid DC
RA	rheumatoid arthritis
SLE	systemic lupus erythematosus
SS	Sjögren syndrome
T1D	type 1 diabetes
T4SS	type IV secretion system
TCR	T-cell receptor
Tg	thyroglobulin
TGF	transforming growth factor
Thmem	T helper memory
TLR	Toll-like receptor
TNF	tumor necrosis factor
TRIM-21	tripartite motif 21
VV	vaccinia virus

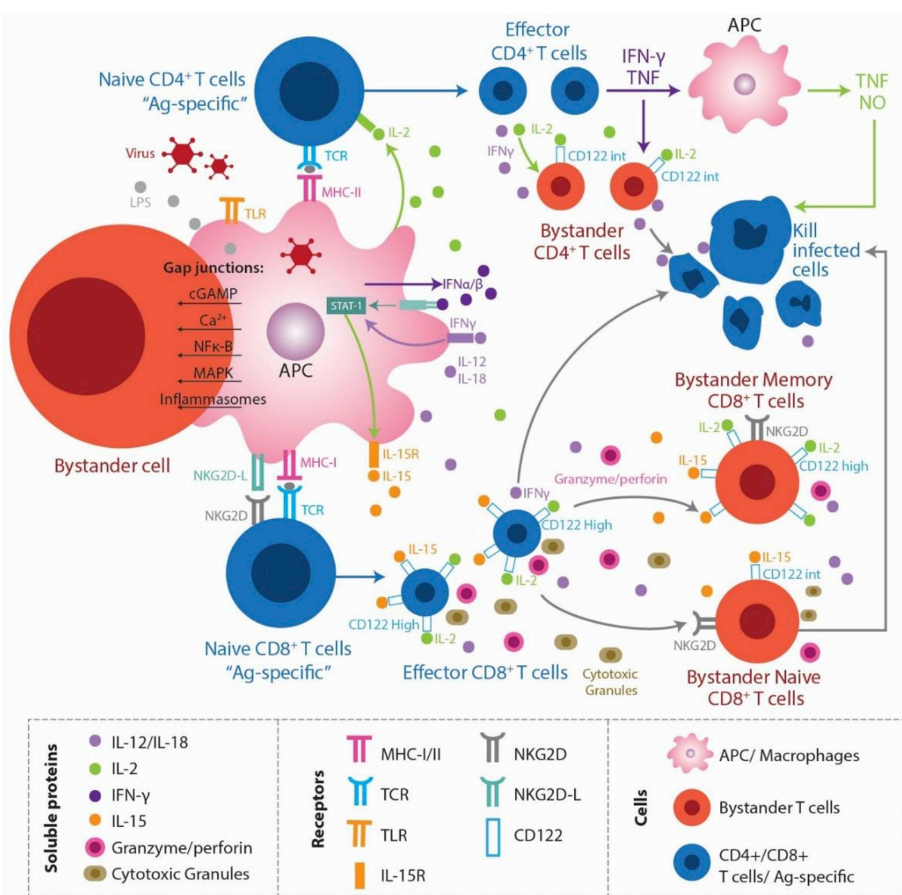

Fig. 1. Bystander activation mechanisms mediated by pathogen infections. Infected cells by virus or bacteria can induce activation of uninfected-cells through soluble signals (cytokines), co-receptor expression (NKG2D, CD122, TLR) and intercellular communication (gap junctions). Ag: antigen; APC: antigen-presenting cells; cGAMP: cyclic guanosine monophosphate-adenosine monophosphate; IFN: interferon; IL: interleukin; LPS: lipopolysaccharide; MHC: major histocompatibility complex; NKG2D: natural Killer group 2D; NO: nitric oxide; TCR: T cell receptor; TLR: Toll-like receptor; TNF: tumor necrosis factor.

proliferation with no-TCR involvement. Nevertheless, this concept has been tempered, as several authors note that the majority (but not all) of the T cells activated by infections are antigen-dependent [5,13,14]. Herein, a review about the mechanisms associated with bystander activation is presented.

2. Mechanisms of bystander activation

Classical T- and B-cell activation is mediated mainly by engagement of the TCR or BCR, respectively, which promotes several signaling cascades that induce cytokine production, proliferation, differentiation, and/or apoptosis [15,16]. It was previously thought that self-reactive T cells were deleted in the thymus before migrating to the periphery [17]. Nevertheless, there is evidence demonstrating that a considerable amount of self-reactive naïve lymphocytes avoids central tolerance [18,19].

Even though auto-reactive cells have normally been associated with pathogenesis, the fact that healthy individuals constitutively harbor such type of cells could indicate that they have a protective role. Indeed, B cells able to produce natural antibodies recognizing self-epitopes are described to be beneficial in the clearance of apoptotic bodies [20], B-cell development [21], and B-cell homeostasis [22,23]. Thus, stringent mechanisms might exist to restrict auto-reactive cell stimulation and allow lymphocyte activation under external cognate antigen stimulation. Unspecific activation of T and B cells has been called bystander activation, and is characterized by the stimulation of lymphocyte function independently of TCR/BCR specificity (Fig. 1).

2.1. Virus

2.1.1. Memory T cells are prone to bystander activation

Viral infections induce the activation of antigen-presenting cells (APCs) as well as auto-reactive T cells, favoring the development of ADs [24]. Furthermore, virus-specific T cells stimulate other immune cells when migrating to zones of infection, in which the infected cells present viral peptides through major histocompatibility complex (MHC) class I. $CD8^+$ T cells release cytotoxic granules that cause the death of infected cells. In this inflammatory environment, the release of tumor necrosis factor (TNF)-α, lymphotoxin, and nitric oxide (NO) causes the death of infected cells [25]. Several studies have described that $CD8^+$ T memory cells with high levels of CD44 can be activated by bystander activation [12]. In this process, non-antigen-specific $CD8^+$ T cells are activated by inflammation, producing IFN-γ and granzyme B, similar to a classical antigen-dependent cytotoxic response. Other ways of inducing bystander activation of memory $CD8^+$ T cells are through soluble mediators such as IL-12, IL-15 and IL-18. For instance, IL-15 promotes memory $CD8^+$ T-cell activation in cells that express high levels of the β subunit of the receptors for IL-2 and IL-15 (CD122). Thus, memory $CD8^+$ T cells are highly sensitive to IL-15 stimulation when compared to naïve $CD8^+$ T cells. Less expression of CD122 on naïve $CD8^+$ T cells turn them less sensitive to IL-15 and/or IL-2 bystander activation after viral infection [26,27].

Bystander activation of $CD4^+$ T cells is less efficient than in $CD8^+$ T cells. This decreased efficiency of activation is due to a moderate expression of CD122 ($CD122^{int}$) [28]. In addition, heterologous $CD4^+$ T cells expressing high levels of CD25 (IL-2Rα) and intermediate levels of CD122 can be activated by IL-2 produced by activated, antigen-specific $CD4^+$ T cells. These cells are able to respond to IL-2 through the IL-2 receptor comprised of the α, β, and γ subunits [29].

Other soluble signals involved in bystander activation were demonstrated in a mouse model inoculated with the natural killer T (NKT)-cell ligand (α-galactosylceramide). Proliferation of memory $CD8^+$ and $CD4^+$ T cells, but naïve ones, was induced in the mouse spleen and liver in response to NKT cell activation, in an IFN-γ- and IL-12-dependent pathway [30].

2.1.2. Intercellular communication promotes bystander effect

In addition to soluble signals, contact between bystander and infected cells can induce heterologous activation. Although little is known about this intracellular space-time interaction, detection of a pathogen's nucleic acids is important for activation of type I IFN signaling during anti-viral innate immune responses. After binding to DNA, cyclic GMP-AMP synthase (cGAS) generates cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), which binds to STING and leads to activation of interferon regulatory transcription factor 3 (IRF3) and consequent production of type I IFNs [31]. One study demonstrated that microbial DNA induces activation of innate immune responses not only on pathogen-infected cells but also in neighboring cells via gap junctions, which are oligomeric proteins that form channels between adjacent cells. Indeed, they used an IRF3-driven GFP reporter to demonstrate that transfection of DNA into cells generated IRF3-dependent GFP expression in neighboring untransfected cells. In addition, both cells generated antiviral cytokines, including IFN-β and TNF-α [32]. Also, Ablasser et al. [33] demonstrated in an *in-vitro* experiment of vaccinia virus (VV) infection that cGAMP produced by infected cells could be transferred intercellularly to adjacent cells, acting as a secondary intermediate that triggers STING in bystander cells and activated them. Additionally, cGAMP can be packed into extracellular vesicles and viral particles and then transferred to neighboring cells [34].

Another possible mechanism of bystander activation mediated by cell-to-cell interaction has been demonstrated by Dreux et al. [35]. They found that exosomes derived from hepatocytes containing hepatitis C virus (HCV) RNA are absorbed by neighboring DCs. Furthermore, human plasmacytoid DCs (pDCs) were activated by exosomal transfer of HCV in a Toll-like receptor (TLR)-7-dependent manner [36]. This pDC activation led to the secretion of type I IFNs. The latter was confirmed by Takahashi et al. [37], demonstrating that HCV-infected hepatocytes co-cultured with uninfected pDCs lead to a robust type I IFN production by pDCs.

2.1.3. Bystander activation by heterologous virus infection

Mechanisms of multiple bystander activation by virus-specific infection have been described by Doisne et al. [38], who studied bystander activation in heterologous virus-specific $CD8^+$ T cells during primary human immunodeficiency virus (HIV) infection. They found that in HIV patients, $CD8^+$ T cells specific for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and influenza present activation markers such as CD38 and HLA-DR, and proliferate in absence of cognate antigenic stimulation. This bystander activation can partially explain the over-activation and over-expansion of $CD8^+$ T cells during the acute phase of HIV infection contributing to its pathophysiology.

2.2. Bacteria

2.2.1. Bystander activation induced by cell co-receptors

Studies have demonstrated that bacterial lipopolysaccharide (LPS) can activate non-antigen-specific T cells [39]. In addition, LPS can activate other cells of the immune system such as DCs by up-regulation of CD86 and production of IFN-γ [40]. In turn, innate immune mediators such as DCs and NK cells induce bystander activation of T cells in response to TLR agonists through the production of IFN-α/β/γ [41]. In general, microbial receptors (i.e., TLRs) and soluble signals (i.e., cytokines) are necessary for bystander activation of T cells. Signals coming from neighboring cells or the inflammatory microenvironment can determine co-receptors expressed in these cells.

For instance, natural killer group 2D (NKG2D) is an activating receptor highly expressed on NKs, and less frequently expressed on some subsets of $CD8^+$ and $CD4^+$ T cell. Recent studies have implicated the receptor NKG2D in bystander activation of T cells [42]. Signaling by NKG2D induces similar effects to those of TCR signaling such as phosphorylation of ZAP70 and Syk. For example, bystander-activated memory $CD8^+$ T cells control infection by *Listeria monocytogenes* through NKG2D [43].

2.2.2. Gap junction intercellular communication promotes bystander effect

In some bacterial infections, infected cells can use gap junctions to transmit pathogen recognition signals to bystander cells. Gap junctions are constituted by connexin (Cx), which forms channels that allow transfer of low molecular weight molecules between adjacent cells. In *Pseudomonas aeruginosa* infection of the respiratory airway, TLR-2 expressed on epithelial cells can activate MAPK signaling, which produces Ca^{2+} flux and NF-κB translocation that induces expression of cytokines and chemokines such as CXCL8, resulting in neutrophil recruitment. According to Martin et al. [44], this Ca^{2+} flux can be transmitted to neighboring bystander cells via the gap junctions (Cx43), which increases the production of epithelial CXCL8.

In another example, *Shigella flexneri*-infected cells activate the signaling cascade of MAPK (ERK, JNK and p38), and this cascade can be propagated to bystander uninfected cells through the gap junctions, increasing their production of IL-8 [16].

2.2.3. Bystander activation to control bacterial infection by soluble mediators

Legionella pneumophila is able to successfully infect cells by use of a type IV secretion system (T4SS), which injects complexes of bacterial proteins into the host cytosol and inhibits host protein synthesis among other functions. However, in infected macrophages and neighboring cells, IL-1α and IL-1β evade this inhibition through MyD88 signaling [17]. Unlike infected cells, uninfected bystander cells are able to produce IL-6, TNF, and IL-12 necessary in host protection. Moreover, lack of IL-1 receptor signaling decreases the production of bystander cytokines, demonstrating that the bystander activation is mediated by the initial secretion of IL-1α and IL-1β [19]. This bystander mechanism allows generation of an effective immune response by evading the effects of pathogen-derived effector proteins delivered by the T4SS.

Another example of bystander innate activation occurs with *Chlamydia trachomatis.* In this infection, IFN-γ has a pivotal role in the anti-bacterial immune response, as this cytokine upregulates indoleamine-2,3-dioxygenase-1 (IDO1) production which catalyzes host cell tryptophan elimination. Tryptophan is necessary for *Chlamydia trachomatis* survival, but is also necessary for T-cell proliferation. In order to circumvent this anti-bacterial immune response, bacteria are able to block IFN-γ production via inhibition of STAT1 translocation into the nucleus, resulting in an inability to induce IDO1. Bystander cells will play an important role in restricting bacterial spread, by supplementing the lack of IFN-γ and subsequent IDO1 production and tryptophan catabolism [45].

2.2.4. Bystander activation by exchange of particles

Macrophages infected with Bacillus Calmette-Guérin or *Mycobacterium tuberculosis* (*M. tuberculosis*) release exosomes that have bacterial proteins and promote cytokine production in naïve macrophages [46]. Additionally, extracellular vesicles released from *M. tuberculosis*-infected macrophages induce TLR-2 signaling and stimulate cytokine production by non-infected macrophages, which help with bacterial clearance [47].

Some studies have demonstrated that bystander cells can internalize active inflammasome complexes produced by infected cells. Microbial substances activate inflammasome sensors such as AIM2 or NLRP3, promote the polymerization of the ASC adapter, and the formation of an ASC speck. This multimeric complex contributes to innate immune responses through the stimulation of caspase-1, production of IL-1β and subsequent death cells by pyroptosis. ASC specks released from the infected cells accumulate in the extracellular spaces, where they are phagocytosed by bystander macrophages, generating lysosomal damage and IL-1β secretion in neighboring cells [48]. In this manner, IL-1β will promote the rapid clearance of bacteria spread by bystander activation of macrophages.

2.3. Parasites

There is bystander activation in infections with intracellular parasites. *Leishmania braziliensis* (*L. braziliensis*) infections are characterized by immune responses associated with high levels of IFN-γ and TNF-α.

Table 1
Bystander activation in autoimmunity.

Disease	Mechanism	Impact on disease	References
JAI	Expression of CD31 on CD28⁻ $CD8^+$ T cell inducing IL-2, IL-17, IL-10, IFN-γ and granzymes.	Increase T cell cytotoxicity favoring the inflammation.	[76,77]
RA	LPS from bacteria generates vicious cycle of cytokines storm mediated by monocytes and T cells.	Perpetuation of inflammation.	[63,66]
RA	Expression of NKG2D in $CD28^-$ $CD4^+$ T cells. MICA/B trigger NKG2D activation leading to IL-5 and TNF-α secretion in synovia.	Auto-reactive T cells stimulation and joint disease perpetuation.	[67]
RA	α-fodrin antigens induce unrelated type II collagen-specific T cells activation, encourage Th1 response and impair T cells apoptosis pathways.	Exacerbation of RA in SS mouse model.	[68]
RA	LPS induces proinflammatory cytokines in $CD8^+$ T cells overexpressing TLR-4.	Increase severity of the disease.	[72]
RA	DMARDs can induce bystander activation.	No data - *in vitro* model.	[74]
SLE	Expression of NKG2D in $CD4^+$ T cells induces immunosuppressive responses through IL-10 and TGF-β.	Attenuating SLE activity.	[84]
SLE	House dust mites allergen induces IL-1β, IL-6, IL-8, CXCL5 and TRIM-21 up-regulation in B cells.	Production of autoantibodies (anti-TRIM-21) and inflammation.	[86]
T1D	Coxsackievirus and rotavirus infections induce bystander activation by inflammation.	T1D development.	[99,100,103]
MS	Activation of quiescent auto-reactive T cells by proinflammatory cytokines, which induce calcium influx pathway in T cells.	Development and/or exacerbation.	[112–114]
MS	Molecular mimicry following bystander activation (Re-activation of auto-reactive T cells prime by first viral infection).	Onset of the disease.	[117]
EAE	LPS induce activation of auto-reactive T cells.	Exacerbation of the disease.	[118]
AIH	$CD8^+$ T cells accumulation in the liver inducing hepatocytes apoptosis, IFN-γ, TNF-α release and tissue damage.	Liver damage in mouse model.	[128,130]
AITD	CD40 expression on T cells increases cytokines response and bystander activation of neighboring T cells.	Increase in the production of autoantibodies.	[135,136]
AITD	Viral infection induces production of IL-8, which recruits Th1 cells into thyroid.	No data.	[137,138]
AITD	Tg-specific cells induce bystander lymphocytes infiltration within the thyroid gland in naïve mice.	Lymphocytes infiltration in mouse model.	[139]

AIH: autoimmune hepatitis; AITD: autoimmune thyroid disease; DMARDs: disease-modifying anti-rheumatic drugs; EAE: experimental autoimmune encephalomyelitis; IFN: interferon; IL: interleukin; JIA: juvenile idiopathic arthritis; LPS: lipopolysaccharide; MICA/B: MHC class I chain-related protein A and B; MS: multiple sclerosis; NKG2D: natural Killer group 2D; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; T1D: type 1 diabetes; Tg: thyroglobulin; TGF: transforming growth factor; TLR: toll-like receptor; TNF: tumor necrosis factor; TRIM-21: tripartite motif 21.

Carvalho et al. [49] infected DCs with *L. braziliensis*, although not all DCs were infected in the culture, uninfected DCs increased the expression of activation markers and production of IL-12. These bystander DCs had greater antigen-presenting capacity and increased TNF-α secretion as compared to the infected ones. In addition, macrophages infected with *Leishmania amazonensis* release extracellular vesicles that induce IL-12 and TNF production in uninfected macrophages to control parasite infection [50].

2.4. Bystander activation and vaccination

Vaccines will first stimulate innate immunity by non-specific proinflammatory antigens such as lipid fraction A of LPS [51]. During this process, T cells can non-specifically activate independently of TCR ligation in the context of an adjuvant-containing vaccine or adjuvant alone.

$CD4^+$ T helper memory (Thmem) cells are essential in the longevity of protective immunity induced by vaccination. Di Genova et al. [52] demonstrated that in subjects vaccinated with tetanus toxoid, bystander $CD4^+$ Thmem cell specific for tuberculin protein or *Candida albicans* were activated. Interestingly, the bystander activation was limited to pre-existing Thmem cells but did not occur in naïve $CD4^+$ T cells. Comparable effects were detected in a mouse model, where T cells activated *in vitro* presented receptors for IL-2 and IL-7, suggesting that these cytokines are intermediaries in bystander activation [29]. On the other hand, van Aalst et al. [53] established a TCR-transgenic, T-cell transfer mouse model to assess bystander activation of $CD4^+$ T cells. A donor transgenic mouse with TCR specific to human proteoglycan (hPG) antigen was immunized with hPG. Splenectomy was performed in order to sort hPG-specific $CD4^+$ T cells. These cells were passively transferred to a recipient mouse treated with complete Freund's adjuvant (CFA) or incomplete Freund's adjuvant (IFA). They showed that antigen-specific responses were enough for local bystander activation and that neither CFA nor IFA enhanced this mechanism. These studies demonstrated that bystander activation could occur in an adjuvant-independent manner. Nevertheless, more studies are needed to understand the role of vaccine-mediated bystander activation in the development of ADs. Fortunately, such events are rare and should never deter the use of public vaccination.

3. Bystander activation in autoimmune diseases

Bystander activation has been associated with onset or relapse of different ADs such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), multiple sclerosis (MS), autoimmune hepatitis (AIH), and autoimmune thyroid disease (AITD), among others. This activation can be mediated by bystander activation of auto-reactive cells. The migration of these cells to the site of inflammation, followed by their unspecific activation and cytokine secretion, is enough to induce autoimmune pathology (Table 1). In this section, we will focus on ADs in which evidence of bystander activation has been shown.

3.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease in which the immune system attacks and damages the diarthrodial joints [54,55]. The genetic background [56], gender [57], autoantibody production [58], the environment, epigenetics [59], and the severity of inflammation are variables that influence the course of the disease [60,61]. Stimulation of self-reactive T cells is possible through secondary signals such as costimulatory receptors or molecules independent of TCR signaling (Fig. 2).

Various clinical and animal model studies have suggested that microbial infections play a pivotal role in the onset and perpetuation of RA. For example, microbes such as *Porphyromonas gingivalis* (*P. gingivalis*), *Proteus mirabilis*, EBV, and *Mycoplasma* can trigger and/or aggravate the pathogenesis of RA. These microbes have different arthritogenic mechanisms such as bystander activation [62,63]. In the latter, *P. gingivalis* and *Escherichia coli* LPS activate monocytes and induce the production of cytokines such as IL-1 and IL-33 mediated by TLR pathways [25,64,65]. On the other hand, $CD8^+$ T cells can identify infected cells and secrete inflammatory cytokines and exocytose cytotoxic granules in order to kill the target cells. In these conditions, infection can trigger a cytokine storm produced by monocytes, macrophages, $CD8^+$ T cells, and dying cells, which contribute to maintain an inflammatory microenvironment. The cytokines produced in this inflammatory microenvironment, in turn, can activate bystander T cells and perpetuate the inflammatory milieu in a vicious cycle [63]. This

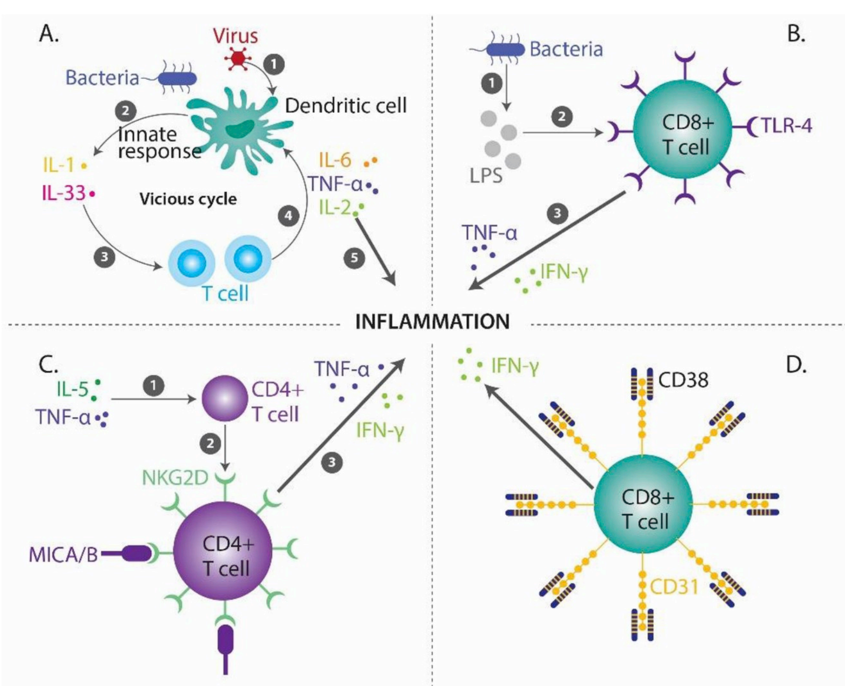

Fig. 2. Mechanisms for the perpetuation of inflammation in RA patients by bystander activation of T cells. **A.** Infection induces a strong innate immune response by monocytes and/or DCs (1), inducing the secretion of IL-1 and IL-33 (2) which active the T cells adaptive response (3) and subsequent secretion of proinflammatory cytokines (4) perpetuating a cycle of inflammation (5). **B.** Bacterial infection leads to LPS (1) which can stimulate a subset of TLR-4^+ $CD8^+$ T cells (2), triggering INF-γ and TNF-α secretion perpetuating the inflammation (3). **C.** IL-5 and TNF-α (1) lead to upregulation of NKG2D on $CD4^+$ T cells which will be activated by its own ligands (2) inducing IFN-γ and TNF-α secretion perpetuating the inflammation (3). **D.** $CD8^+$ T cell in RA express CD31 and can be activated by CD38 ligand inducing IFN-γ secretion. IFN: interferon; IL: interleukin; LPS: lipopolysaccharide; MICA/B: MHC class I chain-related protein A and B; NKG2D: natural Killer group 2D; TLR: toll-like receptor; TNF: tumor necrosis factor.

information is further supported by Brennan et al. [66], who reported that cytokine-driven activation of bystander T cells secrete IL-2, IL-6 and TNF-α, which activate monocytes in a similar manner to the activation induced by RA synovial T cell. With these results, they postulated that cytokine-activated bystander T cells are pivotal in perpetuating the inflammatory cycle in the synovium of RA patients.

In patients with RA, CD28-negative $CD4^+$ T cells within peripheral blood and synovial tissue express NKG2D, a membrane receptor that is normally absent on $CD4^+$ T cells. This receptor is a ligand of MICA/B and it can be up-regulated by IL-5 and TNF-α, which are proinflammatory cytokines abundant in the synovium and sera of RA patients. Moreover, abnormal expression of MICA/B in synoviocytes from RA patients can increase auto-reactive T-cell stimulation, releasing more cytokines, increasing proliferative responses, and contributing to joint disease perpetuation [67].

In contrast, Kobayashi et al. [68] studied the development of RA in a murine model of Sjögren syndrome (SS). They found that older mice developed severe autoimmune arthritis; this age-related immune dysregulation elicited rheumatoid factor, antibodies against single stranded DNA, type II collagen, and α-fodrin. Additionally, they observed a strong bystander proliferation of type II collagen-specific T cells in the spleen when mice were immunized with two α-fodrin antigens, demonstrating the role of the bystander stimulation. However, the authors do not explain the mechanism inducing such activation in this model.

The role of $CD4^+$ T cells in RA has been largely studied; however, $CD8^+$ T-cell involvement in this disease is controversial. Cytotoxic $CD8^+$ T-cell numbers and phenotype have been correlated with the outcome and severity of the disease [69]. Although some studies state the contrary, $CD8^+$ T cells have mainly been described as regulatory cells in inflammatory joints [70,71]. However, Tripathy et al. [72] demonstrated an increased expression of TLR-4 in $CD8^+$ T cells, which changes their phenotype towards an activated and proinflammatory one. This TLR-4 overexpression was associated with the severity of the RA. Additionally, this was correlated with $CD8^+$ T cell secretion of perforin, granzyme B, and inflammatory cytokines such as IFN-γ and TNF-α.

Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and tofacitinib have been used in the treatment of ADs, particularly RA [73]. These drugs are associated with bystander activation of lymphocytes. Piscianz et al. [74] developed an *in vitro* model of inflammation, in which phytohemagglutinin-stimulated cells in the presence of methotrexate and/or tofacitinib activate unstimulated cells in a bystander manner. Bystander activation was time frame-sensitive, as the unstimulated cells only responded to the first administration of DMARDs but were not sensitive to a second drug administration. Control of these bystander cells are of great interest especially in long-term and sequential therapeutic strategies. The authors also point out the importance of understanding the effects of DMARDs on lymphocyte activation, since non-responding patients could be more sensitive to a DMARD-mediated bystander activation than responding ones.

In juvenile idiopathic arthritis (JIA), the most frequent chronic AD in childhood, no apparent etiology has been described [75]. In synovial fluid from JIA patients, Dvergsten et al. [76] described a rare subset of cytotoxic $CD8^+$ T cells with a high level of expression of CD31 and lacking CD28. CD31 works as a TCR-independent immune receptor, it promotes production of IL-2, IL-17, IL-10, and IFN-γ, and induces the expression of granzymes [76,77]. Ferguson et al. [78] demonstrated that ligation of CD31-CD38 induced the expression of RORγT, and subsequent activation of *IL-17A* promoter favoring the perpetuation of inflammation in the synovium.

3.2. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex chronic AD characterized by an autoimmune response with activation of self-reactive B and T cells leading to the presence of autoantibodies, deposition of immune complexes, and tissue damage [79–82]. Besides the clinical picture of SLE, the disease is characterized by anti-double strand DNA antibodies and anti-Smith antibodies, among others [83]. In SLE patients, bystander activation has been described as protective. Indeed, Dai et al. [84] demonstrated that bystander activated $NKG2D^+$ $CD4^+$ T cells secrete immunosuppressive cytokines such as IL-10 and TGF-β. The authors established a regulatory role of $NKG2D^+$ $CD4^+$ T cells through inhibition of T-cell proliferation. Furthermore, SLE activity and age-of-onset was inversely correlated with $NKG2D^+$ $CD4^+$ T-cell frequency.

Remarkably, there are various studies demonstrating a high

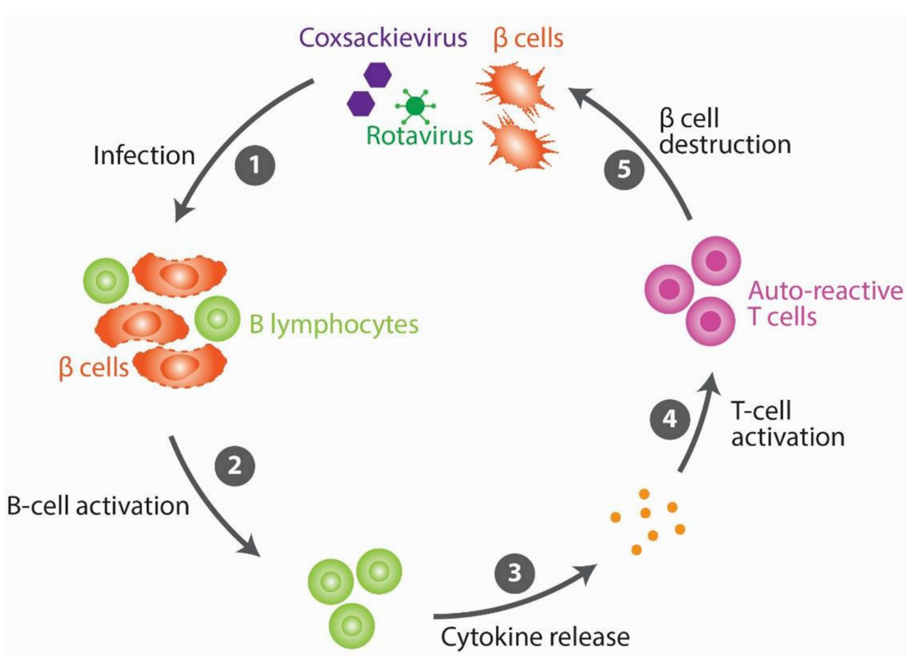

Fig. 3. Mechanisms of induction of T1D by bystander activation. Coxsackievirus or rotavirus infection of pancreatic β-cells (1) results in an immune response by B lymphocytes(2), with subsequently secretion of cytokines (3) inducing bystander activation of auto-reactive T cells (4) leading to pancreatic β-cells destruction (5).

occurrence of allergy in SLE [85]. A recombinant protein of *Dermatophagoides pteronyssinus* group 2 (Der p 2) is the main allergen of house dust mites, accounting for around 90% of IgE and IgG antibody responses in allergic patients. Yu et al. [86] demonstrated that IL-1β, IL-6, IL-8 and CXCL5 could be upregulated by Der p 2 in peripheral blood mononuclear cells (PBMCs) from allergic SLE patients. Moreover, TRIM-21 expression appears to be increased in B cells from these patients. Such stimulation also induced autoantibody production, which was attributed to bystander activation of B cells.

3.3. Type 1 diabetes

Type 1 diabetes (T1D) is characterized by an autoimmune damage of pancreas insulin-secreting β cells, resulting in a decrease and absence of insulin secretion responsible of metabolic and clinical manifestations of disease [87]. T1D incidence varies largely depending on geographic location and ethnicity, which is explained by genetic [88] and environmental factors [89]. How the environment plays a key role in T1D has not completely been elucidated, but factors such as diet, vitamin D, and infectious exposures have also been associated with the disease [90–92].

In this context, the role of infection in T1D development in genetically susceptible subjects has been largely evaluated [93]. Multiple studies have demonstrated that infection by enterovirus, specifically coxsackievirus are more frequent in T1D patients than in healthy controls [94–98]. Either molecular mimicry or bystander activation mechanisms may explain this association. However, Horwitiz et al. [99], in 1998, demonstrated that induction of T1D by coxsackievirus was more likely triggered by bystander activation than by molecular mimicry (Fig. 3). Indeed, mice with a susceptible MHC-I able to recognize either autoantigens or coxsackievirus epitope did not develop disease after viral infection. This is in contrast to mice having resting auto-reactive T cells (recognizing pancreatic islet antigens but not cross-reacting with the virus), which developed T1D after viral challenge. These observations led to the conclusion that T1D induction by virus was the result of auto-reactive T-cell re-stimulation by the proinflammatory milieu induced by infection.

More recently, a polymorphism within *IFIH1* gene, associated with T1D susceptibility, was associated with regulation of antiviral immune response in coxsackievirus infected human pancreatic islets. Indeed the risk polymorphism was associated with a stronger innate immune response after viral infection, thus suggesting a bystander activation induced by this strong inflammatory anti-viral response [100]. Besides the enterovirus infection, rotavirus infection has also been linked to T1D development by epidemiological studies [101] and confirmed in mouse models [102]. Pane et al. [103] demonstrated that rotavirus infection in NOD mice upregulated MHC-II in B cells in pancreatic and mesenteric lymph nodes, which induced, B-cell secretion of cytokines triggering an unspecific T-cell proliferation and INF-γ secretion by $CD8^+$ T cells. Furthermore, when mice where immunized with a viral peptide with sequence similarity to thus from the islet autoantigen, no T cell proliferation nor IFN-γ secretion was observed, thus questioning molecular mimicry in this model. Other viruses, such as influenza and adenovirus, have been suggested to be associated with T1D [104].

3.4. Multiple sclerosis

Multiple sclerosis (MS), a chronic autoimmune inflammatory disease from the central nervous system (CNS), is characterized by demyelinating plaque lesions with T-cell infiltrates in the white matter of the brain and spinal cord [105,106]. MS has been largely studied in mouse models, in which a similar disease, called experimental autoimmune encephalomyelitis (EAE), can be prompted either by injection of myelin-derivate antigen or by adoptive transfer of auto-reactive myelin-specific T cells [107,108].

How auto-reactive T cells are activated and migrate to the CNS is not known but it is thought that in genetically susceptible individuals an inflammatory environment may trigger this aberrant activation. In

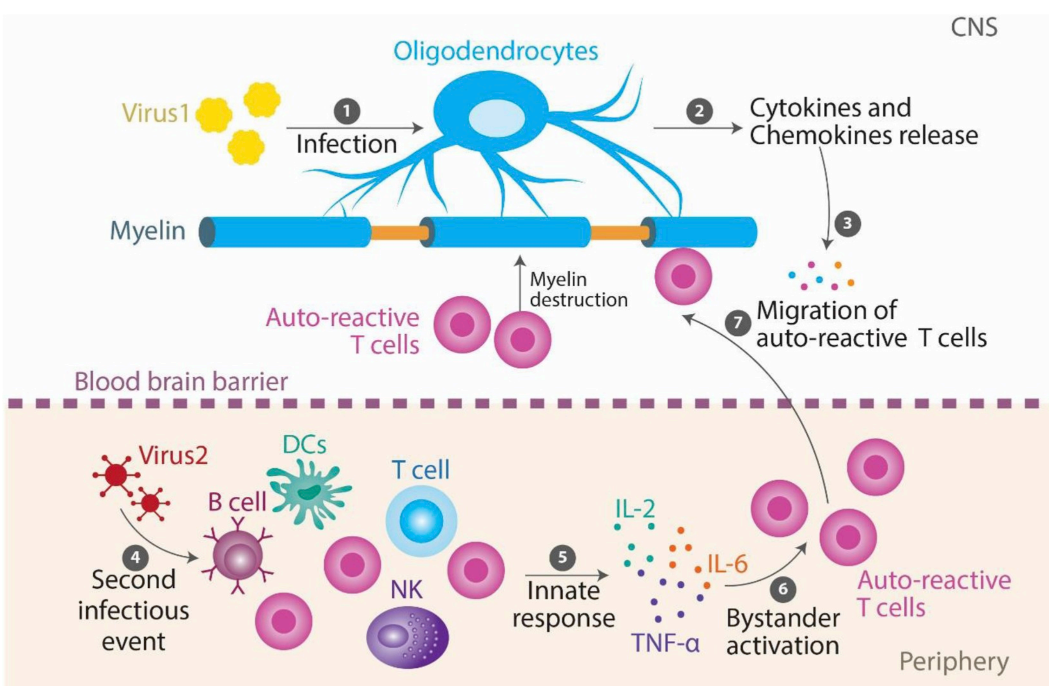

Fig. 4. Mechanism of onset of MS by bystander activation. A first infectious event can occur within the CNS (1) originating a confined immune response (2) with cytokines and chemokines release at the CNS (3). A second infectious event at the periphery (4) induces an innate response with release of cytokines (5), able to activate auto-reactive cells in the periphery (6). Chemokines and cytokines in the CNS support auto-reactive T cell migration to the CNS (7). Presence of auto-reactive T cells at the CNS will induce myelin destruction. CNS: central nervous system; DCs: dendritic cells; IFN: interferon; IL: interleukin; NK: natural Killer; TNF: tumor necrosis factor.

this regard, infection preceding MS onset has been described, and association between MS exacerbation and infectious diseases has also been established [109–111]. How a peripheral infection can contribute to the development of MS is not well established. Mechanisms such as molecular mimicry (reviewed elsewhere [3]) or bystander activation of auto-reactive T cells could explain this phenomenon (Fig. 4).

Martino et al. [112,113] demonstrated *in vitro* that inflammatory cytokines such as TNF-α, IL-6, IL-2, and IFN-γ were able to activate auto-reactive T cells by stimulating calcium influx via two different signaling pathway in a TCR-independent fashion. In this context, it is tempting to hypothesize that pathogens induce an inflammation which trigger the increase of proinflammatory cytokines leading to the activation of auto-reactive T cells. Further, how auto-reactive T cells cross the blood-CNS barrier is not fully understood. Martino et al. [114] proposed a "dual signal hypothesis" in which the triggering of MS would be driven by two majors events; a first inflammation confined to CNS, probably due to a pathogen infection directed specifically towards CNS cells (i.e., oligodendrocytes) inducing the accumulation of fluid and immune cells, followed by cytokines and chemokines secretion. The second event would be a concomitant peripheral inflammatory process due to another pathogen challenge inducing a non-specific, cytokine-mediated, auto-reactive T-cell activation, prompting their migration into the CNS. Indeed, T cells can home and be retained in the CNS if their own cognate antigens is present [115,116].

McCoy et al. [117] reviewed the possible association between viral infection and MS development and proposed a two-mechanisms model: a priming of auto-reactive T cells mediated by a pathogen induced activation based on molecular mimicry followed by a second unspecific viral challenge which would induce bystander re-activation of auto-reactive T cells. In order to prove this hypothesis, they tested whether mice infected with a VV encoding for a peptide derived from myelin proteolipid protein called PLP developed EAE symptoms after a second unrelated virus infection such as murine CMV (MCMV), lymphocytic choriomeningitis virus (LCMV) or wild type VV. They found that 5 out of 9 mice infected with MCMV following a first VV-PLP prime developed CNS lesions but no lesions were observed for mice infected first with VV-PLP followed by LCMV or VV challenge. Thus, they concluded that priming induced a T-cell activation mediated by molecular mimicry. However, this activation was not efficient to trigger the CNS lesions unless an unrelated virus such as MCMV was present after the first challenge. No LCMV nor VV were able to induce any lesion formation, which was explained by the fact that unlike MCMV that triggers high levels of IL-12 response (that is able to activate auto-reactive T cells in a bystander fashion), LCMV and VV induce only high levels of IFN-α/β, which are associated with a better control of the inflammatory response. Thus, they concluded that nerve lesions in this MS mouse model was induced by a two non-exclusive mechanism: first molecular mimicry activation followed by bystander activation induced by a viral infection.

Bacteria may also trigger bystander activation in EAE, Nogai et al. [118] demonstrated that exacerbation of the EAE could be induced by LPS injection which activate the auto-reactive CD4$^+$ T cells in a bystander manner.

3.5. Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a liver disease characterized by a loss of self-tolerance towards the liver parenchyma leading to tissue destruction and development of chronic fibrosis [119–122]. Diagnostic hallmarks of AIH include high levels of γ-globulin and the presence of autoantibodies (i.e., anti-histone, anti-ribonucleoproteins, anti-nucleic acids, anti-smooth muscle antibodies, anti-liver kidney microsomal type 1 (anti-LKM1), anti-liver cytosol type 1 and/or anti-LKM3) [123,124]. Virus such as hepatitis A virus, hepatitis B virus, hepatitis C virus (HCV), hepatitis E Virus, influenza virus, EBV and other herpesviruses have been linked to the development of AIH but causal relationships have not been proven [125,126].

Molecular mimicry is the most probable mechanism by which these associations exist; a peptide within the human protein CYP2D6 discloses molecular mimicry with proteins encoded by HCV and members of the herpesvirus family. Furthermore, anti-LKM1 antibodies can cross react with both viruses and human protein [127]. Nevertheless, other authors have demonstrated that T cell bystander activation may play a pivotal role in hepatic tissue damage after a viral infection (Fig. 5). For instance, Polakos et al. [128] supported this hypothesis using a respiratory infection mouse model followed by hepatic damage. The authors demonstrated that when mice were infected twice with influenza virus, during the secondary infection, mice developed a strong CD8$^+$ T cell response specific for Influenza. They found that influenza-specific CD8$^+$ T cells were then trapped into the liver and the number of CD8$^+$ T cells infiltrated in the liver correlated with hepatocyte apoptosis and tissue injury. The pathway that leads to CD8$^+$ T cells accumulating in the liver is not fully understood. Nevertheless, evidence has demonstrated that CD8$^+$ T cells may promote hepatocytes bystander killing

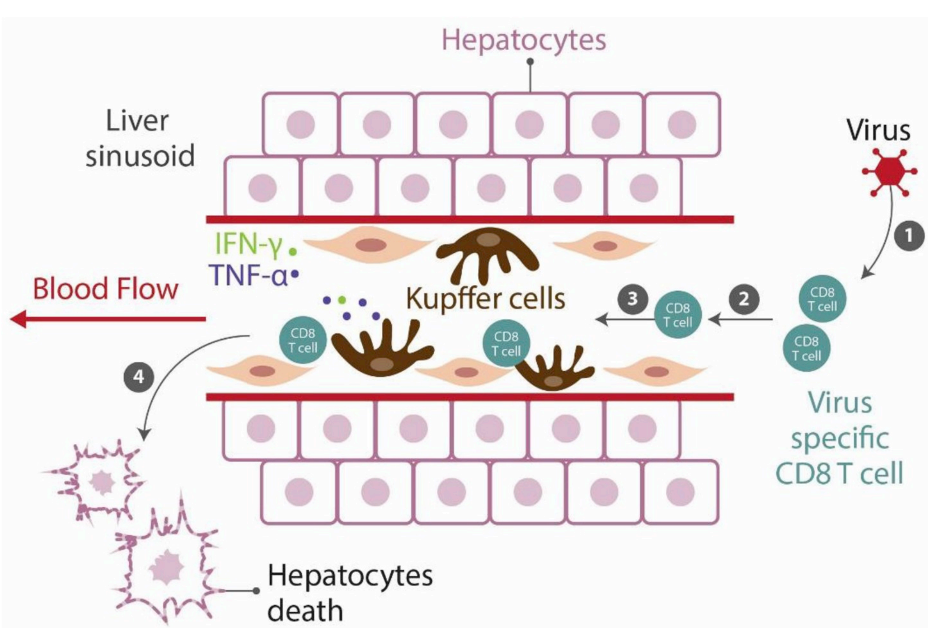

Fig. 5. Mechanism of bystander activation in AIH. Viral infection (1) generates a specific immune response and clonal expansion of virus-specific CD8$^+$ T cells (2), thus virus-specific CD8$^+$ T cells are trapped by Kupffer cells on the liver sinusoid (3), secretion of IFN-γ and TNF-α by such CD8$^+$ T cells will injure hepatocytes and induce an AIH (4). IFN: interferon; TNF: tumor necrosis factor.

via Fas-mediated apoptosis and not by cytolytic effects [129].

Bowen et al. [130] used another model of transgenic mouse, in which T cells expressing a transgenic specific TCR were adoptively transferred into mice which ubiquitously expressed the cognate antigen, or into mice in which hepatocytes did not express the cognate antigen. They found that in both models, $CD8^+$ T cells accumulated into the liver and induce hepatocyte death, in the absence of the cognate antigen. When anti-IFN-γ and anti-TNF-α blocking antibodies were injected into the mice, tissue injury was abrogated. These observations demonstrated that after a non-liver related viral infection, $CD8^+$ T cells are trapped into the liver and can lead to hepatocytes death and liver injury in an antigen-independent manner. It is then probable, that bystander activation may play a role in the development of AIH.

3.6. Autoimmune thyroid disease

Autoimmune thyroid diseases (AITDs) includes Hashimoto's thyroiditis (HT) and Graves' disease (GD). Both diseases have similar immunopathogenic mechanisms and the presence of autoantibodies against thyroid antigens [131,132]. In GD, the production of autoantibodies leads to organ damage and abnormal increase of the thyroid hormone, thus generating hyperthyroidism. HT is characterized by intrathyroidal cell infiltration and production of autoantibodies (anti-Tg and anti-thyroid peroxidase), accompanied by hypothyroidism with damage of thyroid follicles [133,134].

CD40 has a key role in the activation of T lymphocytes and therefore in the production of autoantibodies. Although these conditions are highly polygenic, studies have described that *CD40* acts as an immune-modulating susceptibility gene in GD [135]. Polymorphisms in this gene increases the translation of CD40 in the thyroid, resulting in the production of cytokines and consequent bystander activation of neighboring T cells [136].

Some findings have postulated that viral infections induce HT through bystander activation of auto-reactive T cells. HCV-infected patients present viral RNA in thyroid tissue, this virus induces the production of IL-8 that recruits immune cells to the thyroid [137]. In addition, the presence of chemokines in serum from HCV-infected HT patients promotes the infiltration of Th1 cells into the thyroid [138].

An experimental autoimmune thyroiditis mouse model has been used to study AITD by immunization with Tg. Arata et al. [139] transferred GFP-Tg-specific cells to naïve mice and observed thyroiditis with lymphocytes infiltration within thyroid glands. When the infiltrated cells were analyzed they found GFP and non-GFP lymphocytes (normal host cell), demonstrating the infiltration of both Tg-specific cells and bystander T cells.

4. Conclusions

Bystander activation of T cells and B cells contributes to the understanding of the link between environmental agents and autoimmunity. Some animal models and *in-vitro* assays reflect the existence of this phenomenon and its role in autoimmune responses. For instance, in RA, expression of CD31, NKG2D, and TLR-4 receptors on T cells induces proinflammatory cytokine release which exacerbates inflammation and disease activity. In T1D, MS, EAE and AITD, viral and bacterial infections can induce a strong innate response which in turn will cause non-specific activation of $CD8^+$ T, $CD4^+$ T, and B cells, leading to onset and/or exacerbations of these diseases.

In SLE, bystander activation has been linked with immunosuppressive responses that attenuate the disease. However, data has been limited by the wide variation in the human immune response and the long latency period between loss of tolerance and appearance of clinical manifestations. Animal models that focus on the earliest events that lead to loss of tolerance are necessary and may provide insight into the physiopathology of ADs in humans. Furthermore, new therapeutic approaches that modulate bystander activation of T and B cells could be useful to avoid the development of ADs after an external insult. These treatments should be directed against bystander actors such as proinflammatory cytokines, membrane co-receptors, and signaling molecules, among others. Also, they should aim to attenuate the chronic inflammatory milieu in AD patients to avoid the perpetuation of disease, often with a relapsing-remitting nature, in a bystander fashion.

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