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Running Title: Bystander activation of T cells in autoimmune diseases

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ABSTRACT

Autoimmune disease is known to be caused by unregulated self-antigen-specific T cells, causing tissue damage. Although antigen specificity is an important mechanism of the adaptive immune system, antigen non-related T cells have been found in the inflamed tissues in various conditions. Bystander T cell activation refers to the activation of T cells without antigen recognition. During an immune response to a pathogen, bystander activation of self-reactive T cells via inflammatory mediators such as cytokines can trigger autoimmune diseases. Other antigen-specific T cells can also be bystander-activated to induce innate immune response resulting in autoimmune disease pathogenesis along with self-antigen-specific T cells. In this review, we summarize previous studies investigating bystander activation of various T cell types (NKT, γδ T cells, MAIT cells, conventional $CD4^+$, and $CD8^+$ T cells) and discuss the role of innate-like T cell response in autoimmune diseases. In addition, we also review previous findings of bystander T cell function in infection and cancer. A better understanding of bystander-activated T cells versus antigen-stimulated T cells provides a novel insight to control autoimmune disease pathogenesis.

INTRODUCTION

Autoimmune disease is known to be caused by the dysregulated immune response mediated via self-antigen-specific T cells. Genetic and environmental factors such as infection have been proposed to explain the significant and sensitive immune response to self-antigens. However, it is not still clear how a few clones of self-reactive T cells can trigger significant tissue damage in autoimmune diseases. Recently, antigen non-related T cells have been shown to play a potential role in the pathogenesis of autoimmune diseases, as well as infection and cancer (1-3).

The antigen specificity of T cells is derived from T cell receptors (TCRs), which interact with antigen-derived peptide presented by the components of major histocompatibility complex (MHC) expressed on the surface of the antigen-presenting cells (APCs). Activated T cells express antigen-specific immunity via clonal expansion and differentiate into memory cells resulting in long-term immunity. However, antigen non-specific T cells are also involved in immune response because they can be activated independent of antigen (4-6). Such T cell activation is called “bystander activation”. During pathogen infection and inflammatory response, cytokines, toll-like receptors (TLRs), ligands and other immune mediators activate self-reactive T cells, which activate the autoimmune response (Fig 1A). Besides, initial self-antigen-mediated inflammatory response including activation of self-antigen-specific T cells can also lead to bystander activation of other antigen-specific memory T cells, which secrete pathogenic inflammatory cytokines contributing to autoimmune diseases (Fig 1B). Therefore, in this review, we summarize previous studies investigating bystander activation of T cells in various conditions and emphasize their potential role in autoimmune disease as well as infection and cancer.

History of bystander T cell studies

The phenomenon of T cell activation without TCR signaling has been reported since the 1980s. In 1989, Yang et al. reported the proliferation and activation of LCMV-specific cytotoxic T lymphocytes (CTLs) following infection of lymphocytic choriomeningitis virus (LCMV)-hyperimmunized mice with various viruses such as mouse cytomegalovirus (MCMV) and vaccinia virus (VV) (7). They reported that LCMV-specific CTLs, which are not specific to the challenged virus, are bystander-activated by cytokines produced by virus infection. In 1994, when resting $CD4^+$ T cells were stimulated with IL-2, IL-6, and TNF-α in vitro, the expression of CD69 on both $CD45RO^+$ and $CD45RA^+$ CD4 T cells was upregulated and $CD45RO^+$ cells secreted IFN-γ and IL-4 (8). In 1996, David F. Tough et al. established bystander T cell activation of $CD8^+$ $CD44^{high}$ T cells in vivo suggesting that bystander activation is mediated by type 1 interferon rather than TCR signaling (4). Another group showed that memory T cells proliferate upon NKT cell activation via IL-12 and IFN-γ-dependent pathway in addition to type 1 interferon. In the late 1990s, although substantial evidence suggested that T cells can be activated via TCR-independent pathway, the role of bystander-activated T cells in immune response was disputed. Zarozinski et al. disputed that polyclonal expansion of CTL response to LCMV infection is virus-specific and bystander activation of non-virus-specific CTL did not play a significant role (9). Additionally, Kaja et al. used virus-peptide tetramer staining to show that when adult mice were infected with LCMV, 50%-70% of activated $CD8^+$ T cells were LCMV-specific in both primary and secondary immune response (10). However, it is clear that bystander T cell activation occurs during pathogen invasion and contributes to disease pathogenesis. In 2005, it was shown that

parasitic infection may have a significant impact on the dynamics of $CD4^+$ T cell populations regardless of antigen specificity (11). OVA-specific (DO11) T cells were transferred to naive recipient mice and the recipient was immunized to generate memory DO11 cells. After 6 weeks, the mouse was exposed to *Leishmania donovani* inducing expansion of both naïve and memory DO11 cells. Guo et al. suggested that rested Th1, Th2, and Th17 cells can be bystander-activated by the IL-1 family and STAT-activating cytokines to secrete effector cytokines (12). In addition, *Nippostrongylus brasiliensi*-induced Th2 cells responded to a challenge with papain or house dust mite extract (HDM) by releasing IL-13 without TCR signaling (13). In 2018, it was reported that during acute hepatitis A (AHA), non-HAV-specific memory $CD8^+$ T cells were bystander-activated via IL-15 to aggravate liver injury independent of TCR (1). We previously reported that memory Th17 cells can be stimulated by IL-1β and IL-23 without antigen recognition and may exacerbate experimental autoimmune encephalomyelitis (2). Likewise, intensive studies reported that bystander T cell activation and effector function can affect tissue damage.

Bystander activation of various T cell types

T cells are composed of different populations, each of which expresses unique surface markers and transcription factors. In the thymus, conventional T cells develop into $CD4^+$ or $CD8^+$ T cells with TCRs consisting of α and β chains responsible for antigen specificity. However, unconventional T cells such as γδ T cells carry TCRs with γ and δ chains instead of and, β chains. Natural killer T (NKT) cells and mucosal-associated invariant T (MAIT) cells are unconventional T cells with a limited diversity or specificity to the restricted group of antigens. They are usually localized in tissues such as liver and mucosa for tissue immunity

but also present in the circulation.

Natural killer T (NKT) cells

Invariant NKT (iNKT) cells recognize lipid antigens such as α-galactosylceramide (α-GalCer) presented by MHC class I-like molecule CD1d (14). NKT cells can be divided into type 1 and type 2 NKT cells. Type 1 NKT cells carry CD1d-restricted semi-variant αβ TCR with limited β chain (Vβ8, Vβ7 or Vβ 2 in mice, and Vβ11 in humans), while type 2 NKT cells are known to contain a broader TCR repertoire. Leite-de-Moraes reported that splenic $CD4^+$ NKT cells in MHC class II-deficient mice secreted IFN-γ without further stimulation after a single injection of IL-12 plus IL-18 (15). In 2008, it was reported that IL-$17RB^+$ $CD4^+$ NKT cells secrete IL-13 and Th2 chemokines upon stimulation with IL-25 in vitro, and depletion of these cells by IL-17RB-specific monoclonal antibodies or NKT cell-deficient mice failed to trigger IL-25-dependent airway hypersensitive reaction (AHR) in an animal model of asthma (16). According to Jean-Marc Doisne, $NK1.1^-$ iNKT cells in peripheral lymph nodes stimulated by IL-1 and IL-23 secrete IL-17 and IL-22 to control early infections (17). In brief, various NKT subsets can exert effector functions in the TCR-independent pathway.

Gamma delta (γδ) T cells

Gamma delta (γδ) T cells are unique T cells carrying TCRs, each composed of γ and δ chains instead of α and β chains (14). They constitute about 4% of all T cells in the lymphoid tissue and are abundant in the skin and gut. Murine γδ T cells can be roughly divided into two types: IFN-γ^+ and IL-17^+ cells, depending on the type of cytokines they secrete (18). Haas et

al. divided γδ T cells into two subsets based on NK1.1 and CCR6 expression suggesting that stimulation with IL-12 and IL-18 induced IFN-γ production by NK1.1^{+} γδ T cells, while IL-23 induced IL-17A synthesis by CCR6^{+} γδ T cells (19). Bystander activation of human γδ T cells remains to be studied more.

Mucosal-associated invariant T (MAIT) cells

Mucosal-associated invariant T cells (MAIT cells) express semi-invariant αβ TCR and similar to other unconventional T cells have limited TCR diversity (Vα19–Jα33 and Vβ8 or Vβ6 in mice, Vα7.2–Jα33 and Vβ2 or Vβ13 in humans) (14). MAIT cells recognize microbial-derived vitamin B metabolites presented to β2M-associated MHC-related 1 (MR1) (20). MAIT cells are CD161^{+} Vα7.2^{+} CD8^{+} CD4^{-} CD3^{+} T cells secreting effector cytokines independent of TCR. Compared with other T cell subsets, CD161^{high} CD8^{+} T cells in human PBMC express IFN-γ more sensitively in response to IL-12 and IL-18 (21). In addition, IFN-γ synthesis was TCR-independent and not inhibited by cyclosporin A, which inhibits calcineurin in TCR signaling. In 2016, Wilgenburg et al. found that MAIT cells are abundant and activated during human viral infections in vivo (22). They reported that this activation was TCR-independent but dependent on IL-18 with IL-12, IL-15, and/or IFN-α/β. Thus, MAIT cells might be activated in a TCR-independent manner and have effector functions in diseases.

CD4^{+} T cells

CD4 T cells, also known as T helper cells, can be divided into several types, such as Th1, Th2, Th17, and Treg. When they are activated, each effector CD4^{+} T cell type secretes specific

cytokines following immune response. Interestingly, several studies show that $CD4^+$ T cells can be activated even without TCR stimulation (23). In 1999, Gangappa et al. suggested that herpes simplex virus (HSV)-induced lesions may occur via bystander activation of $CD4^+$ T cells because TCR-transgenic mice backcrossed to SCID mice recognizing on OVA peptide but not HSV proteins still develop ocular lesions upon HSV infection and $CD4^+$ T cells are found in the lesions. Thus bystander activation of antigen-independent $CD4^+$ T cells was detected in the virus-induced milieu. Therefore, cytokines are one of the factors inducing bystander activation of $CD4^+$ T cells (24). According to the study by Unutmaz et al., human naive ($CD45RA^+$) $CD4^+$ T cells and memory ($CD45RO^+$) cells are activated upon stimulation with IL-2, TNF-α, and IL-6 to express activation markers, and initiate cell cycle and proliferation (2). Chakir et al. showed that activation of naive T cells by high doses of IL-2 respond to IL-12 and IL-18 even in the absence of TCR ligation and express signs of Th1 phenotype (25). L. Guo et al. suggested that Th2 secretes IL-13 and IL-5 by IL-33 and STAT5 activator in an antigen-independent manner (7). In addition, Th17 secretes IL-17 by IL-1β and STAT3 activator (26, 27), and Th1 produces IFN-γ following stimulation by IL-18 and STAT4 inducer (27, 28). W. Jiang et al. revealed that memory $CD4^+$ T cell cycling during HIV infection is related to the levels of lipopolysaccharide (LPS), plasma HIV RNA, and memory $CD8^+$ T cell cycling (29). Therefore, exposure to microbial products, plasma viremia, or proinflammatory cytokines resulting from HIV infection rather than peptide stimulation increases memory $CD4^+$ T cells in HIV disease. According to S. van Aalst et al. in 2017, injection of complete Freund's Adjuvant (CFA) leads to $CD4^+$ T cell proliferation, activation, and intravenous transfer (30). In addition, this local bystander activation occurred when incomplete Freund's Adjuvant (IFA) was used as a booster after priming with CFA. Our previous study confirmed that $CD4^+$ T cells primed with IL-1β and IL-23 differentiated similar to pathogenic Th17 cells that express RORγt or GM-CSF (10). Using EAE, it was

confirmed that memory-like Th17 cells which are not specific to antigen can infiltrate into the spinal cord, and secrete IL-17A, IFN-γ, and GM-CSF, suggesting that the actual antigen-nonspecific cells are bystander-activated and exhibit pathogenic effects.

$CD8^+$ T cells

Zhang et al. first reported that memory-phenotype ($CD44^{high}$) $CD8^+$ T cells can be activated by IL-15, which mimics the effects of type I IFN (31). They also suggest that IL-12, IL-18, and IFN-γ induce selective proliferation of $CD44^{high}$ $CD8^+$ T cells in vivo. In 2002, it was reported that IL-15 induced not only activation of effector $CD8^+$ CTLs in an antigen-independent manner and maintained for up to 60 days but also proliferation and survival of memory-phenotype $CD8^+$ T cells (32). In addition, cytokine immunotherapy in cancer can promote anti-tumor immunity mediated via bystander-activated memory $CD8^+$ T cells activated by IL-2 or IL-12 and expressing NKG2D and granzyme B, while depletion of NKG2D in mice decreased antitumor effects after immunotherapy (33). Chu et al. confirmed that bystander-activated CTLs (BA-CTL) directly eliminate target cells in NKG2D induced with IL-12, IL-18, and IL-15 suggesting the role of memory $CD8^+$ T cells in the early innate immune response (34). In 2014, Crosby et al. found that LCMV and *Listeria* immune mice exhibited a significant increase in the size of leishmanial lesions compared with mice infected with *Leishmania major* alone (35). The bystander-activated LCMV specific memory $CD8^+$ T cells play a role in an unrelated immune response and increase immunopathology via NKG2D-dependent mechanism because treatment with NKG2D-blocking antibodies diminished the increase number of lesions in LCMV immune mice. Besides, during HIV infection, IL-15 may induce substantial bystander expansion and cycling as well as granzyme B^+ $CD45RO^+$ $CD8^+$ T cells related to high morbidity and mortality in untreated patients (36).

Recently, during HAV infection, the role of bystander $CD8^+$ T cells was established in acute hepatitis A (AHA). Kim et al. reported that HAV-unrelated $CD8^+$ T cells were activated by IL-15 and developed intrinsic cytotoxicity via NKG2D and NKp30 leading to liver injury (1). They also suggest that the migration of bystander-activated memory $CD8^+$ T cells from the circulation to the liver is mediated by CCR5 (37).

Bystander-activated T cell and Autoimmunity

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disease mainly induced by uncontrolled infiltration of T and B cells into the central nervous system (CNS) resulting in inflammation and demyelination in the CNS. In experimental autoimmune encephalomyelitis (EAE), one of the murine models of MS, the activation or adoptive transfer of myelin-recognizing T cells such as myelin oligodendrocyte glycoprotein (MOG)-specific T cells is known to play a key role in demyelination. Although, MOG-specific T cells are required for tissue damage in CNS during EAE progression, surprisingly, most CNS-infiltrated T cells are unrelated to MOG antigen specificity (38-40). Non-myelin-specific T cells such as ovalbumin (OVA)-specific T cells increased the susceptibility to EAE by enhancing the number and function of APC in the CNS following injection of a synthetic peptide of myelin basic protein (MBP) (41). Toll-like receptors (TLRs) play an important role in innate immune activation; however, the loss of TLR2 and TLR4 in $CD4^+$ T cells reduced disease symptoms in the EAE model, which regulates the production of IL-17, IL-21, RORγt, and IFN-γ (42, 43). In addition, TLR2, TLR4, and TLR9 are highly expressed on $CD4^+$ and $CD8^+$ T cells of patients with MS

compared with healthy controls, and the proportion of cytokine-secreting TLR^+ T cells are correlated with the degree of brain lesion (44). In addition, injection of LPS induces bystander activation of MBP-specific T cells contributing to EAE in MBP TCR-transgenic mice, which requires physical contact with antigen-presenting cells via CD86 co-stimulation (45). Recently, our studies revealed that IL-1β and IL-23 contributed to bystander activation of OVA-specific Th17 cells, which turn pathogenic by producing IL-17A, IFN-γ, and GM-CSF. As a result, the augmented antigen-specific T cell response led to severe EAE symptoms (2). Collectively, multiple reports demonstrated the presence of nonmyelin-specific T cells in the CNS with significant effector functions contributing to autoimmune encephalomyelitis.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease caused by the destruction of joint cartilage and bone. Autoreactive $CD4^+$ T cells secrete cytokines resulting in the activation of osteoclasts and destruction of joint elements. Several studies investigating the factors triggering RA proposed bystander activation of T cells as one of the causes. In 2000, L. C. Tan et al. found many Epstein-Barr virus (EBV) -specific $CD8^+$ T cells in synovial fluid (46). These virus-specific T cells in joints express activation markers such as CD69 and CD38 and secrete pro-inflammatory cytokines, suggesting bystander activation of $CD8^+$ T cells during arthritic inflammation. In 2004, M. Kobayashi et al. revealed the proliferation of autoantigen-reactive T cells induced by bystander activation via different antigenic epitopes, leading to severe lesions in aged mice with Sjogren's syndrome (47). Also, V. Sobek et al. demonstrated T cells can be activated by TLR2 signaling initiating RA by IFN- γ secretion in the absence of cognate antigen recognition (48). F. Brennan et al. found that cytokine-activated T cells (Tck cells) partially resemble the phenotypes of T cells in RA synovial tissue such as $CD25^{high}$,

CD69^{high}, HLA-DR^{high}, CD49d^{high}, and the effector function suggested the role of cytokine-activated effector memory T cells in the synovium (49).

Type 1 Diabetes

Type 1 diabetes (T1D) is an autoimmune disease caused by the selective destruction of insulin-producing β cells in the pancreas of islets of Langerhans. In 1998, Marc S. Horwitz et al. revealed that resting autoreactive T cells were re-stimulated by coxsackie virus infection and induced T1D (50). Infection with rotavirus, enterovirus, and influenza A virus can also induce T1D (51, 52). Therefore, pathogen infection triggers bystander activation of self-reactive T cells resulting in induction of autoimmune diseases such as T1D. During the development of T1D in non-obese diabetic (NOD) mice, innate-like T cells such as iNKT17 cells infiltrate the pancreas and secrete IL-17, which exacerbates T1D (53). Likewise, in NOD mice, γδ T cells infiltrate the islets of pancreas resulting in severe T1D when γδ T cells are adoptively transferred to NOD mice (54). In 2017, Rouxel et al. proposed that MAIT cells play a role in direct killing of β cells in human T1D and NOD mice (55). Therefore, innate-like T cells can contribute to T1D pathogenesis via independent TCR activation.

Role of bystander T cells in other diseases

Infection

Bystander T cell activation has been observed in studies of infection. Tough et al. first reported CD8^{+} CD44^{high} T cell proliferation in response to type I interferon induced by

polyinosinic-polycytidylic acid (poly(I:C)) and LPS injection (4, 5). During *Burkholderia pseudomallei* infection, $CD8^+$ $CD44^{high}$ T cells are a major source of rapid synthesis of IFN-γ suggesting bystander activation of CD8 T cells by IL-12 and IL-18 induced by the infection (56). In the early 2000s, the possibility of bystander T cell activation in HIV infection was proposed following the discovery of activated $CD8^+$ T cells specific to EBV, cytomegalovirus, and influenza virus during primary HIV Infection (57). In 2014, Bastidas et al. showed that this activation of $CD8^+$ T cells is triggered mainly by IL-15 independent of antigen specificity (58). In addition to $CD8^+$ T cells, cycling memory $CD4^+$ T cells were proportionally more frequent in HIV infection and activated the expression of CD38 and PD-1 (29). During influenza A virus (IAV) infection causing acute severe pneumonia, IL-15 plays a critical role in the pathogenesis of acute lung injury implying bystander activation of $CD8^+$ T cells in IAV infection (59). In addition, hepatitis A (HAV) infection causes acute hepatitis A (AHA) and induce IL-15 production, which can stimulate memory $CD8^+$ T cells to acquire innate-like cytotoxicity via TCR-independent pathways (1). Recently, in the middle of the COVID-19 pandemic, Gregorova et al. reported increased frequencies of T-cells specific for unrelated antigens in a COVID-19 patient who developed recurring ventilator-associated pneumonia (VAP) caused by *Pseudomonas aeruginosa* strain, suggesting significant bystander activation (60).

Cancer

In 2006, Joncker et al. reported antigen-independent activation of T cells in human and murine tumors implying tumor infiltration of effector or memory T cells independent of tumor antigens (61). However, recent studies investigated the immunological role of tumor-antigen non-related T cells (3, 33, 62, 63). Simoni et al. reported that bystander $CD8^+$ T cells,

which recognize a wide range of epitopes unrelated to cancer, are abundant in human lung and colorectal cancer and can be distinguished from tumor antigen-specific $CD8^+$ T cells, suggesting that bystander $CD8^+$ T cells express low level of CD39 compared with tumor-related $CD8^+$ T cells (3). Further, according to Ponzetta et al., unconventional T cells can participate in antitumor response mediated by IL-12 generated from neutrophils and macrophages and secreting IFN-γ (64). Interestingly, injecting viral peptides into tumors to reactivate antiviral memory $CD8^+$ T cells can arrest the growth of checkpoint blockade-resistant and poorly immunogenic tumors in mice (65). Danahy et al showed that compared with tumor-specific $CD8^+$ T cells, pathogen-induced memory $CD8^+$ T cells inside tumor increased the sensitivity to tumor-derived inflammation resulting in activation and better control of tumor growth in antitumor immunity in the absence of cognate antigen recognition (66). Interestingly, the tumor microenvironment can be reprogrammed by intratumoral treatment with seasonal influenza vaccine, which could convert “cold” tumors to "hot" types resulting in systemic $CD8^+$ T cell-mediated antitumor immunity (67). Likewise, ongoing studies are investigating the role of bystander-activated T cells in tumors to repurpose as cancer immunotherapy.

CONCLUSION

Various types of T cell populations such as NKT cells, γδ T cells, MAIT cells, and conventional $CD4^+$ and $CD8^+$ T cells can be induced to exhibit innate-like effector function via bystander activation. Although antigen-specific T cell response is a hallmark of the adaptive immune system, antigen non-related T cells proliferate significantly and synthesize effector cytokines in inflammatory tissues. During pathogen infection, antigen-specific T

cells are activated by cytokines to reject tumors or to ensure protective immunity. In addition, in the absence of cognate antigen recognition, bystander activation of various types of T cells to secrete inflammatory cytokines can also facilitate the clearance of pathogen or tumor cells. Otherwise, bystander T cell function is of limited interest in understanding the mechanism of autoimmune disease pathogenesis. Few studies in RA and EAE suggest infiltration of antigen-nonrelated T cells into inflammatory tissues and synergistically contribute to autoimmune diseases. The detailed mechanisms of inflammatory infiltration of antigen non-specific T cells and regulation of their effector functions have yet to be elucidated. Based on the summary of previous studies, we propose the mechanism of autoimmune disease pathogenesis via bystander activation of either self-antigen-specific T cells or non-related T cells (Fig. 2). Further studies are needed to distinguish antigen-specific T cells from bystander-activated T cells to better understand disease pathogenesis. Collectively, the elucidation of bystander-activated T cell function along with antigen-stimulated T cells is required to understand the pathologic mechanism of autoimmune disease and to develop novel drug candidates targeting autoimmune disease.

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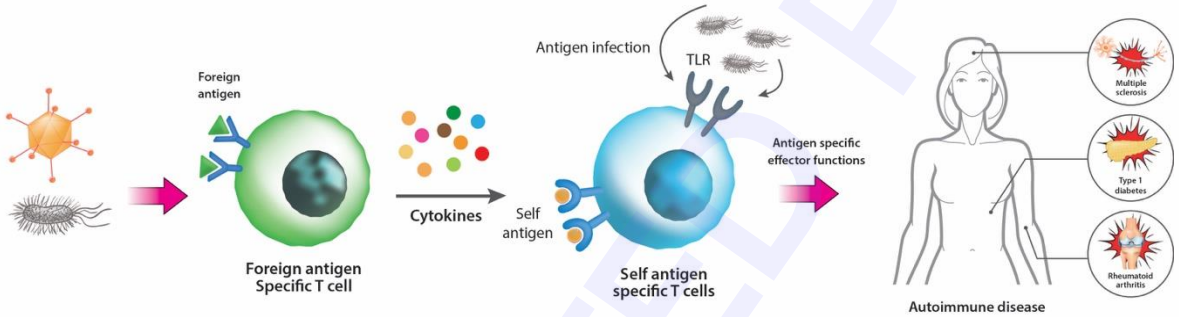
CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FIGURE LEGENDS

A.



B.

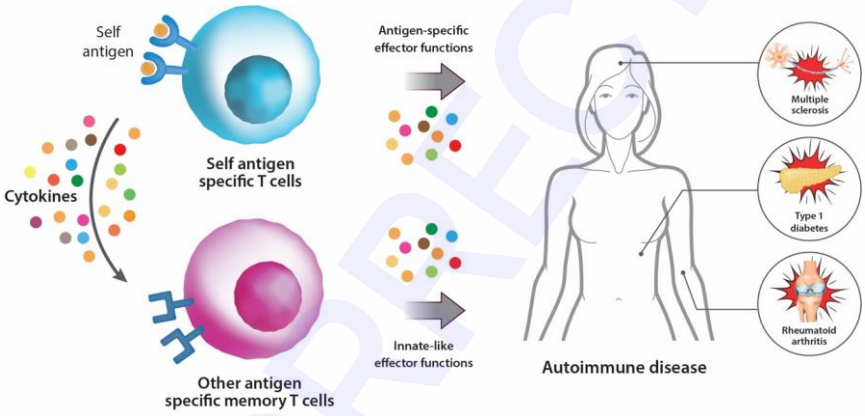


Figure 1. Model of bystander activation of T cells

(A) Pathogen infection triggers inflammation which in turn bystander-activates self-antigen specific T cells. (B) During self-reactive T cell mediated inflammation, other antigen-specific T cells are bystander activated to produce inflammatory cytokines.

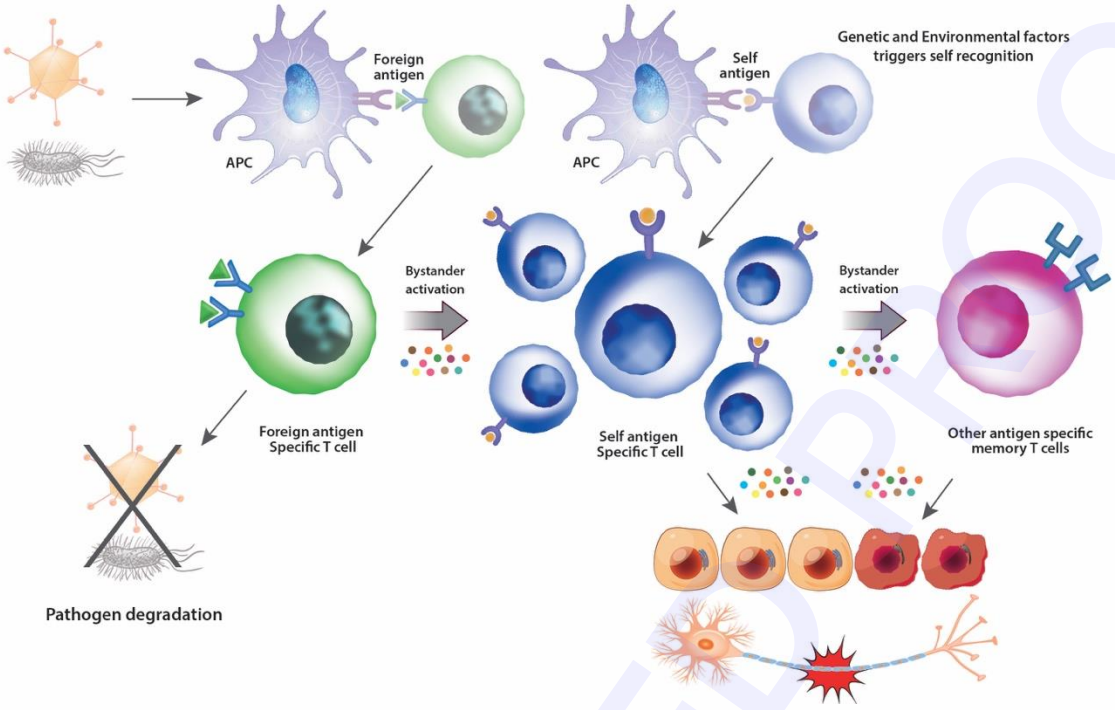


Figure 2. Hypothesis of bystander T cell functions in autoimmune diseases

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