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T Cell Help in the Autoreactive Germinal Center

Elliot H Akama-Garren[1,2], **Michael C Carroll**[1,*]

[1]Program in Cellular and Molecular Medicine, Boston Children's Hospital, Harvard Medical School, Boston MA 02115

[2]Harvard-MIT Health Sciences and Technology, Harvard Medical School, Boston, MA 02115

Abstract

The germinal center serves as a site of B cell selection and affinity maturation, critical processes for productive adaptive immunity. In autoimmune disease tolerance is broken in the germinal center reaction, leading to production of autoreactive B cells that may propagate disease. Follicular T cells are crucial regulators of this process, providing signals necessary for B cell survival in the germinal center. Here we review the emerging roles of follicular T cells in the autoreactive germinal center. Recent advances in immunological techniques have allowed study of the gene expression profiles and repertoire of follicular T cells at unprecedented resolution. These studies provide insight into the potential role follicular T cells play in preventing or facilitating germinal center loss of tolerance. Improved understanding of the mechanisms of T cell help in autoreactive germinal centers provides novel therapeutic targets for diseases of germinal center dysfunction.

Introduction

T cell dependent B cell activation is a key step in the formation of humoral immune responses. Following antigen priming, T and B cells meet at the T/B border in the spleen or interfollicular region in lymph nodes, forming extrafollicular foci (EF) or migrating to developing germinal centers (GC)[1]. Follicular helper T (TFH) cells differentiate from naïve CD4 T cells that have received antigen priming and co-stimulation from dendritic cells, leading to downregulation of CCR7 and PSGL-1 and upregulation of CXCR5 which enables follicular entry[2]. In the GC, B cells receive help from TFH cells via CD40L, IL-4, and IL-21, which leads to somatic hypermutation (SHM), class switch recombination (CSR), affinity maturation, and memory B cell formation[2,3]. This well-orchestrated yet intricate dance between T and B cells in the GC reaction underlies the remarkable ability of our immune system to produce robust, functional, and long-lasting responses to both infection and vaccination.

[*]**Correspondence:** Michael C Carroll, Ph.D., michael.carroll@childrens.harvard.edu, Telephone: 617-713-8700, Fax: 617-713-8702, 200 Longwood Ave; Warren Albert Building, Room 251; Boston, MA 02115.

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Conflict of Interest Statement

The authors declare no competing interests.

While GC responses help fight disease, they might also contribute to autoimmunity[4]. Pathogenic autoantibodies have been implicated in autoimmune disease[5] and are commonly used for diagnostic[6] and prognostic[7] clinical evaluation. These autoantibodies may be oligoclonal, class-switched, and hypermutated[8–11], suggesting a GC origin. However, both EF and GC-derived autoantibodies have been described in mouse models of autoimmunity[4]. As B cells can develop extrafollicularly without T cell help[12], these observations suggest that not all autoantibody responses are T cell dependent. Peripheral tolerance mechanisms prevent activation of autoreactive B cells, mediated by availability of T cell help, antigen abundance, intrinsic B cell signaling, and stromal regulation in the GC[13]. The breakdown of peripheral tolerance in autoreactive GCs suggests that TFH cells are dysfunctional in autoantibody disease.

Despite recognition of the importance of follicular T cells in autoreactive GC reactions, the molecular features of dysfunction in TFH and follicular regulatory T (TFR) cells have only recently been characterized. Developments in single cell sequencing and mass cytometry have facilitated interrogation of numerous cell types, including TFH and TFR cells, with unparalleled detail. These studies have both provided mechanistic insight and generated new hypotheses for the multifaceted roles follicular T cells may play in loss of B cell tolerance. Here we review the historical evidence that T cell help is a necessary and sufficient driver of autoantibody formation, describe emerging studies of follicular T cell dysfunction in autoimmune disease, and pose open questions to be addressed by future studies.

Main Text

T cell dependence of autoantibody responses

Autoantibodies have been identified in over 80 different autoimmune diseases[5]. These autoantibodies may have specificity for either tissue-specific antigens, such as thyroid peroxidase in autoimmune thyroid disease[14], or for ubiquitous antigens, such as dsDNA in systemic lupus erythematosus (SLE)[15]. Autoantibodies may also be pathogenic[16], such as anti-acetylcholine receptor in myasthenia gravis (MG)[17], or may be associated with disease, such as anti-cyclic citrullinated peptides in rheumatoid arthritis (RA)[18]. Autoantibody specificity may also evolve over time in a single patient, leading to reactivity against different autoantigens, termed epitope spreading[19]. The degree of epitope spreading correlates with disease severity, allowing autoantibody specificity to serve as a biomarker for both clinical diagnosis and prognosis[20–25]. Somatic mutations have also been identified in autoantibody sequences[11,26–32]. The evolving specificity, affinity maturation, oligoclonality, class switching, and chronic production of autoantibodies suggest that some may have T cell dependent GC origins[5].

GC-derived autoantibodies represent a breakdown of tolerance mechanisms normally in place to maintain GC homeostasis. Autoreactive B cells that escape central tolerance either die following failure to receive T cell help[33–36] or adopt an IgM low state with reduced antibody secretion in the periphery, termed clonal anergy[37,38]. Accumulating evidence has suggested that these anergic B cells are recruited into germinal centers where they undergo clonal redemption and lose autoreactivity[39,40], a process that if dysregulated could lead to autoantibody development and epitope spreading (Figure 1). Clonal redemption

in HEL3X bone marrow chimeras requires foreign antigen elicited T cell help[41] or in MRL/lpr mice requires CD40L but not B7-CD28 mediated TFH help[42]. Current models of clonal redemption state that only once B cells have mutated away from self and toward foreign antigen binding are they able to receive sufficient T cell help[39,40,43–45], suggesting that the failures of clonal redemption observed in autoantibody-mediated disease are due to provision of T cell help despite maintenance of B cell autoreactivity. Alternatively, autoreactive B cells may overcome T cell dependence due to TLR adjuvanticity, driven by large amounts of self-DNA and RNA from dying cells in the GC[46,47]. The stochastic nature of somatic hypermutation also leads to the generation of autoreactive BCRs in both healthy and autoimmune patients[11,48–50], but only results in high affinity pathogenic autoantibody production in disease[51], likely representing a fundamental breakdown of GC tolerance.

Given the importance of follicular T cells for maintaining GC tolerance, dysregulated TFH and TFR cells have long been thought to contribute to the development of autoreactive B cells. Increased TFH frequency has been observed in SLE, MG, Sjögren's syndrome (SS), multiple sclerosis (MS), autoimmune thyroid disease, and RA[52–62], and altered TFR frequency has been observed in SLE, RA, ankylosing spondylitis, SS, MG, and MS[63–67]. Mouse models of systemic autoimmunity such as OX40L overexpression, TLR7 overexpression, or *Roquin*$^{san/san}$ have increased TFH cells[43,68–70], which can also confer disease when adoptively transferred. Loss of GC TFH cells either through SAP deficiency[71] or Bcl6 haploinsufficiency[72,73] decreases GC cells, autoantibody development, and glomerulonephritis in *Roquin*$^{san/san}$ mice. Spontaneous GC formation and ensuing epitope spreading in a mixed 564Igi bone marrow chimera model of autoimmunity is CD40L dependent[74]. CTLA4Ig and anti-CD40L alone or in combination abrogates autoreactive GCs by inducing tolerance, prevents autoantibody development, and ameliorates disease[75–79]. These observations in human and murine autoantibody disease suggest that T cell help is both necessary and sufficient to propagate disease.

Mechanisms of T cell mediated peripheral tolerance in the GC likely involve crosstalk between autoreactive T and B cells. *CD40LG* and MHC class II are genetic risk loci for elevated levels of autoreactive B cells[80], suggesting that CD40 and TCR signals from follicular T cells to autoreactive B cells help maintain B cell tolerance. MRL/lpr mice with MHC class II-deficient B cells have decreased TFH frequency and autoantibody production[81]. IPEX patients bearing mutations in FOXP3 have defective peripheral B cell tolerance and increased B cell homeostatic proliferation[82], suggesting that regulatory T (T_{REG}) or TFR cells maintain peripheral B cell tolerance. These observations suggest that TCR and co-stimulation mediated help from follicular T cells likely serves as a checkpoint against autoreactive GC development. Despite recognition that some autoantibody responses are T cell dependent, more detailed characterization of the follicular T cell dysfunction underlying loss of tolerance have only recently been characterized through advances in immunological techniques.

Follicular T cell dysfunction

Comparisons of follicular T cell phenotypes between foreign and autoimmune responses have provided insight into the characteristics of follicular T cells that permit autoantibody

development. Flow cytometric profiling of follicular T cells in combination with more recent advances in single cell sequencing and mass cytometry have allowed for transcriptome and repertoire wide characterization of autoimmune follicular T cells. These approaches have led to appreciation for the heterogeneity amongst the follicular T cell population, identification of novel subsets of follicular T cells, gene expression to clonality correlational analyses, and developmental trajectory inference. Collectively, these studies have revealed changes in follicular T cell transcription factor expression, chemokine and cytokine profiles, co-stimulation, metabolism, exhaustion, trafficking, and differentiation in autoantibody disease (Figure 2).

Dysregulated transcription factors—Transcription factor expression not only governs TFH differentiation but can also influence TFH function[83]. TFH cells may express lineage-specific transcription factors in response to pathogen identity, ultimately influencing cytokine production and ensuing CSR[84–88]. TFH Bcl6 expression normally suppresses T-bet and RORγt expression, thereby reducing IL-17 production[89,90], and dysregulated IL-17 signaling contributes to SLE[91–95]. Gata3 and RORγt expressing circulating TFH cells are more prevalent and correlate with disease severity in juvenile dermatomyositis, SLE, SS, RA, and MS[96–98]. *ETS1* is an SLE risk locus and deletion of the transcription factor Ets1 in T cells leads to Gata-3 TFH2 cell-driven SLE-like autoimmunity in mice[99]. *Id3* expression was decreased on TFH and TFR cells in 564Igi bone marrow chimeras[100] and peripheral blood CD4 T cells from SLE patients[101]. ID3 is a transcription factor necessary for TFR maturation[102,103], suggesting that impaired TFR development might contribute to autoreactive GCs. *Tcf7* was negatively associated with clonal expansion in autoimmune TFH and TFR cells, but not foreign antigen elicited TFH and TFR cells[100]. TCF-1 (protein name for *Tcf7*) promotes TFH fate determination over TH1 cells by repressing Blimp1[104,105]. *Maf* and *Ikzf2* are upregulated in CD4 T cells from B6.Sle1yaa mice[106] and human SLE kidney biopsies[107]. c-Maf (protein name for *Maf*) is an AP-1 transcription factor necessary for TFH development and IL-21 production[108]. The transcription factor Helios (protein name for *Ikzf2*), although commonly used to identify thymic-derived T_{REG} cells[109], has also been observed on activated TFH cells[110]. TFH upregulation of FoxP3 facilitates GC contraction[111], failure of which could lead to chronic GCs observed in autoantibody disease. We hypothesize that these transcription factor changes represent instability in TFH identity following autoantigen-driven expansion.

Pathogenic cytokine secretion and improper co-stimulation—Follicular T cells canonically provide help to GC B cells through cytokine release and co-stimulation, which if dysregulated might permit autoreactivity. CD4 T cells from B6.Sle1yaa mice had dysregulated cytokine and chemokine profiles including increased expression of *Il12rb1 Il15ra, Il21, Il2rb, Ccl5, Ccl4, Il10ra, Il3ra, Il4,* and *Ifng*[70]. Human SLE risk loci include variants in *IL2, IL6, IL10, IL12A, TYK2, TNFSF4, STAT4, IRF5, IRF8, IL21,* and *IL21R*[112–125]. Administration of low dose IL-2 to SLE patients led to TFH contraction and reduced disease severity[126], supporting T_{REG} independent IL-2 mediated immunosuppression via Blimp-1 and T-bet suppression of Bcl6[127–129], suggesting that IL-2 deficiency might contribute to autoreactive GC development. In contrast, IL-6 deficiency in $Was^{-/-}$ murine lupus prevents TFH expansion and autoimmune pathology[130], suggesting

that excessive IL-6 signaling might promote loss of GC tolerance. *Il7r* expression was decreased on TFH cells from 564Igi bone marrow chimeras[100] and human SLE kidney biopsies[107], as well as peripheral blood CD4 T cells from SLE patients[101]. IL-7R is repressed by Bcl-6 and can negatively regulate TFH identity[131–133], possibly reflecting transcription factor influence on TFH fate in autoimmunity. TFH cell-derived IL-17 can increase RGS13 and RGS16 expression on B cells, contributing to autoantibody development in BXD2 and NZB/W F1 mice[91,92,134–137]. IL-17 in combination with TFH cell-derived BAFF can prevent BCR mediated B cell apoptosis, retain B cells in the GC, and traffic TFH to the light zone (LZ) of GCs[91,92,138], processes that if dysregulated in the setting of excess IL-17 might lead to autoreactive GC formation. Autoantibody production decreased in B6.Sle1yaa and NZB/W F1 mice following IL-21 blockade[139–142] and BXSB/Yaa mice have elevated serum IL-21[143], a TFH defining cytokine that promotes CSR and long-lived plasma cell (LLPC) formation but might also contribute to loss of GC tolerance by increasing the TFH to TFR ratio[144–146]. IL-23 correlates with disease severity in SLE[147] and IL-23 deficiency in B6/lpr or MRL/lpr mice leads to decreased TFH cells, autoantibodies, and glomerulonephritis[93,148,149], suggesting that IL-23 signaling could also promote loss of GC tolerance. A milieu of cytokines with disparate functions are dysregulated in autoimmune TFH cells, representing potential pathogenic drivers and therapeutic targets.

In addition to dysregulated cytokines, surface molecule expression on TFH cells is altered in autoimmune disease with potential functional consequences. Overexpression of ICOS in TFH cells is necessary and sufficient to induce autoreactive GC responses in the *Roquin*$^{san/san}$ mouse model of SLE[43,71,150,151] and is associated with autoantibodies and end organ damage in human disease[152–154]. CD95-deficient B cells can lead to fatal systemic immunity[155–159] whereas CD95L overexpression on T cells can suppress autoreactive B cells[160,161], suggesting that TFH cells can mediate negative selection of autoreactive B cells via CD95/CD95L. *Cd74* was more strongly associated with clonal expansion in TFR cells from 564Igi bone marrow chimeras[100] and *Fas*^{lpr}*Cd74*$^{-/-}$ mice have decreased autoantibodies and kidney pathology[162]. CD74 serves multiple functions in facilitating MHC class II peptide loading[163], regulating CD95/CD95L signaling[164], and in complex with CXCR4 serving as a receptor for the cytokine MIF[165–167]. Serum MIF levels correlate with SLE severity[168,169] and MIF deficiency reduces kidney pathology in MRL/lpr and NZB/W F1 mice[170,171], suggesting that MIF mediated CD74 signaling in follicular T cells might contribute to autoantibody production. CD153 was increased on TFH cells from 564Igi bone marrow chimeras[100] and on CD4 T cells from B6.Sle1yaa mice[106]. CD153^{+} follicular T cells are senescent yet pathogenic due to their ability to initiate spontaneous GCs and glomerulonephritis via osteopontin secretion[172]. Given the functional importance of these surface molecules, their dysregulated expression in autoimmune follicular T cells likely contributes to loss of GC tolerance.

Altered metabolic states—Autoimmune disease might also be influenced by altered metabolic states of lymphocyte populations, including follicular T cells. TFH differentiation and function require metabolic tuning, as HDL components can inhibit TFH formation[173,174] and 7α,25-dihydroxycholesterol can guide TFH positioning via EBI2

signaling[175]. ApoE-deficient bone marrow chimeras reconstituted with BXD2 bone marrow develop increased TFH cells, GCs, and autoantibodies[176], suggesting that dyslipidemia may contribute to TFH associated loss of GC tolerance. Bcl6[177] and PD-1[178] suppress glycolysis, but mTOR signaling is necessary for TFH activation[179–181]. CD4 T cells from SLE patients have increased mTORC1 signaling and glycolysis[182–190] and mTORC1 promotes Bcl6 expression in autoreactive TFH cells[191,192]. Inhibition of glycolysis in B6.Sle1.Sle2.Sle3, NZB/W F1, BXSB.yaa, or B6.lpr mice with 2-deoxyglucose and metformin reduced autoantibody and TFH levels but preserved the ability to mount humoral responses to foreign antigen[184,185,191,193]. Follicular T cells have increased glycolysis and hypoxia related gene signatures in 564Igi bone marrow chimeras[100] and computational metabolic modeling of CD4 T cells from B6.Sle1yaa mice revealed widespread increase in metabolic activity, including glycolysis[106]. These results suggest that glucose inhibition is an appealing therapeutic strategy to selectively target autoreactive TFH cells while preserving immunity against foreign pathogens.

Co-inhibitory module induction—Although best characterized in CD8 T cells, exhaustion and co-inhibitory receptor expression on follicular T cells might have functional consequences in autoimmunity. *Lag3* expression was increased on TFH cells in 564Igi bone marrow chimeras[100] and *Tigit, Lag3* and *Pdcd1* are upregulated in CD4 T cells from B6.Sle1yaa mice[106] and human SLE kidney biopsies[107]. Co-inhibitory module upregulation most commonly follows continuous TCR engagement and T cell activation to facilitate homeostatic contraction[194,195], and therefore their upregulation on TFH cells in autoimmune disease likely signals antigen experience in the GC. Alternatively, type I interferon signaling can also increase co-inhibitory module expression[196], and both 564Igi and B6.Sle1yaa have elevated interferon signaling[197–199]. As in CD8 T cells[200], PD-1 signaling can attenuate TFH expansion and activation[201]. PD-1 might also have GC specific functions, including promotion of IL-21 and IL-4 release and ensuing LLPC production[202,203]. PD-1 also influences TFH positioning within the follicle as PD-L1 expression on bystander B cells can limit follicular entry of ICOS negative CD4 T cells while facilitating GC entry of TFH cells[204]. Lag-3 inhibition in mice infected with *Plasmodium* resulted in increased TFH cells and malarial clearance[205,206]. Tim-3 expressing TFH cells identified in cancer patients were less responsive to stimulation and less capable to promote CSR[207–209]. We hypothesize that increased co-inhibitory receptor expression on autoimmune TFH cells is reflective of the chronic nature of autoreactive GCs and that targeting these pathways in autoantibody disease warrants caution given their multifaceted roles in TFH function.

Impaired GC trafficking—Follicular T cell differentiation and positioning within the GC are tightly regulated processes that may be dysregulated in the autoreactive GC. Following extrafollicular engagement with B cells, TFH fate determination and guidance towards the follicle is necessary for GC formation and is dictated by chemokine gradients and molecular cues such as downregulation of CCR7[210], miR-17–92[89], and PSGL-1[211] and expression of CXCR5[210], S1PR2[212], EPHB6[213], miR-155[214], EBI2[215], Sema4C[216], LFA-1[217,218], VLA-4[219], integrin α_V[220] and SAP[221]. TFH cell extrinsic signals also influence TFH migration towards and maintenance within the GC, such as B cell expression of PD-L1[204,222], SLAM receptors[221], PlxnB2[216], and EFNB1[213], and FDC expression of

CXCL13[223]. *Itgb1* and *Ahnak* are upregulated in CD4 T cells from B6.Sle1yaa mice[106] and human SLE kidney biopsies[107]. Integrin β1 is a component of VLA-4 (α4β1), whose expression on TFH cells may influence T-B conjugate formation[219] or interactions with FDCs via VCAM-1[224,225]. AHNAK is a scaffold protein necessary for Ca^{++} signaling in CD4 T cells[226,227] that also promotes pseudopod protrusion and migration on metastatic cancer cells[228]. *Itgb7* and *Selplg* are upregulated in TFH cells belonging to TCR specificity groups expanded in 564Igi bone marrow chimeras[100]. Integrin β7 is a component of α4β7, the receptor for the gut homing molecule MAdCAM-1[229], while PSGL-1 (protein name for *Selplg*) limits TFH entry to the GC[211] and may doubly serve as a checkpoint molecule[230], suggesting that TCR autoreactivity might influence T cell trafficking out of the GC. This hypothesis is supported by the observation that *Selplg* was negatively associated with clonal expansion in foreign antigen elicited TFH cells but not TFH cells from 564Igi bone marrow chimeras[100]. PSGL-1 mediated autoreactive TFH suppression or GC exit might have functional consequences, as a subset of central memory-like $CD44^{+}CD62L^{+}$ TFH cells are decreased in 564Igi bone marrow chimeras with a corresponding increase in $PSGL\text{-}1^{lo}CD62L^{lo}$ extrafollicular CD4 T cells[100]. CD4 T cells from B6.Sle1yaa mice also increased expression of *Cxcr3* and *Cxcr4*[106], chemokine receptors that regulate migration towards the interferon-inducible ligands CXCL9, CXCL10, and CXCL11[231] or between the LZ and dark zone (DZ)[232], respectively. TFH cells in autoreactive GCs modulate expression of key trafficking molecules, which we hypothesize represent a homeostatic response to autoantigen recognition that limits T cell help via GC exit.

TFR dysfunction—TFR cells are central regulators of the GC reaction that curtail autoreactive B cells[233]. TFR cells may suppress GC B cells directly by downregulating B cell expression of MHC class II and B7–1 and B7–2 via TFR expression of CTLA-4[234], suppressing GC B cell activation via release of neuritin, IL-10, and TGB-β[235–237], or killing GC B cells via granzyme mediated cytolysis[238]. TFR cells may also limit TFH cell help directly by granzyme mediated killing of TFH cells[239] or mechanically disrupting their interaction with GC B cells[240], a process potentially governed by TCR affinity[241,242]. $FoxP3^{Cre}Bcl6^{fl/fl}$ mice have increased autoantibodies after influenza infection, pristane injection, experimental SS, and spontaneously after 30 weeks[239,243–247]. Conditional deletion of TFR cells in $FoxP3^{Cre}Cxcr5^{LSL\text{-}DTR}$ mice after immunization led to the production of autoreactive IgG[248]. Single cell sequencing of TFR cells in 564Igi bone marrow chimeras revealed similar transcriptional changes as in TFH cells, including upregulation of *Ly6a* and *Gm42031* and downregulation of *Id3* and *Lag3*[100]. ID3 is necessary for maintenance of the regulatory T cell pool and ID3 depletion impairs TFR localization[103]. We propose that just as TFH cells aberrantly provide help to autoreactive B cells in autoantibody disease, dysfunctional TFR cells fail to suppress autoreactive B cells, representing an orthogonal breakdown of peripheral tolerance in the autoreactive GC.

Autoreactive follicular T cell repertoire

Maintenance of peripheral B cell tolerance is at least partially governed by limiting of T cell help dictated by cognate TCR interactions between TFH and GC B cells[5,249–251]. Inefficiency of central B cell tolerance[252] in combination with the stochastic nature of SHM therefore rely on the relatively greater efficiency of central T cell tolerance to

prevent autoantibody development[250,252]. Clonal redemption of autoreactive B cells is T cell dependent[42], with TCR specificity[42,242,253] and antigen availability[41,51] likely serving as selective pressures for BCR mutation away from self-reactivity. Despite long held models of the importance of follicular T cell specificity, only recently have advances in single cell sequencing allowed for unbiased study of the follicular T cell repertoire. These studies have provided insight into not only TFH and TFR clonality in normal immune responses, but also hypotheses for how these regulatory processes might fail in the autoreactive GC.

TFH and TFR cells have distinct repertoires[254], likely reflecting disparate ontogenies and functions. TCR transgenic experiments demonstrated that TFH recruitment into the GC is governed by specificity for the immunizing antigen, whereas TFR entry is not influenced by antigen identity[254]. Foreign immunization of TCR transgenic mice also results in oligoclonal expansion of TFH but not TFR cells, whose repertoire instead more closely resembles thymic-derived T_{REG} cells[254]. A low frequency of antigen-specific FoxP3$^-$ T cell-derived TFR cells emerged following immunization with either self or foreign antigen in IFA[255], suggesting that adjuvant identity may influence TFR development and clonality. TFR cells expressed greater Ki-67 than TFH cells in B6.Sle1yaa mice[106], possibly reflecting selective expansion in response to encounter with autoantigen-driven by differences in TFH and TFR specificities. These observations lead to the model that antigen-specific TFH cells focus B cell affinity maturation towards foreign antigens, while autoreactive TFR cells limit survival of B cells that gain autoreactivity.

TCR transgenic mice or reliance on tetramers likely fail to capture the true diversity of wild type TFH and TFR repertoires. Although less diverse than non-follicular T cell repertoires, TFH and TFR repertoires from non TCR transgenic mice were also polyclonal but non-overlapping[256]. Surprisingly, immunization of non TCR transgenic mice expands TFH and TFR pools but does not significantly alter their clonality[256,257], although greater clonotype overlap was observed amongst TFH cells following foreign immunization and amongst TFR cells following autoantigen immunization[256]. Instead, immunization resulted in non-specific TFH and TFR bystander activation[256] possibly due to TCR cross-reactivity[258–261]. Bystander activation may also be TCR independent and be driven by TLR signaling and cytokines rather than antigen[262–265]. TFH and TFR repertoires were also polyclonal and non-overlapping in 564Igi bone marrow chimera mice[100], suggesting that non-specific TFH and TFR bystander activation occurs in autoimmune disease as well. Notably, the polyclonal nature of follicular T cell responses may simply represent a generalizable T cell phenomenon that is only now being appreciated due to the unbiased nature of repertoire wide sequencing in a field that has previously relied on TCR transgenics and tetramer enrichment.

While repertoire wide analyses of TFH and TFR TCRs have provided insight into clonality, antigen specificity has remained elusive. Autoreactive CD4$^+$CD25$^-$ T cells regularly escape central tolerance and are found in the periphery of healthy mice and humans[261,266,267] but are curtailed by peripheral tolerance mechanisms including T_{REG} cells, anergy, and suppressive CD8 T cells[268–270]. Both conventional CD4 T (T_{CON}) and T_{REG} cells exhibit increased oligoclonality in B6.Sle1yaa mice compared to foreign antigen immunized mice[106]. Autoreactive CD4 T cells correlate with autoantibody mediated

disease severity[271–276]. In transgenic mouse models these autoreactive T cells can receive autoantigenic stimulation from autoreactive B cells, leading to TLR independent loss of tolerance and autoantibody production [46,47]. The representation of these autoreactive CD4 T cells in the homeostatic repertoire, their spatiotemporal location, and mechanism of driving loss of tolerance remain uknown[277–279]. Given the inherent differences between follicular and non-follicular T cell repertoires[256], conclusions regarding CD4 T cell specificity in autoimmune disease are difficult to extrapolate to TFH and TFR cells.

Although autoreactive T cells that escape central tolerance are incapable of SHM and clonal redemption like autoreactive B cells[39,40,43–45], they may still be subject to activation due to the highly cross-reactive nature of the TCR[258–261]. Just as TCR affinity influences thymic education[280], low TCR signal strength can promote TFH clonality[281] and polarization over TH1 commitment[241,282], possibly permitting lower affinity yet autoreactive TCRs[283–285] in the TFH repertoire. Computational prediction of antigen specificity revealed that follicular T cell repertoires from both foreign antigen immunized and 564Igi bone marrow chimeras had highly similar predicted specificities[100]. Similarly, TCR repertoires from foreign antigen immunized and B6.Sle1yaa mice shared the majority of predicted specificities[106]. This overlap likely represents bystander activation of non-antigen-specific follicular T cells with polyreactive TCRs[256,261]. A minority of predicted specificities were enriched in 564Igi bone marrow chimeras[100], possibly representing an autoantigen-specific response slightly detectable in a sea of non-specific proliferation, akin to the tetramer-specific responses observed after foreign antigen immunization[254,255]. Indeed, TCR database annotation could predict antigen specificities for follicular T cell clonotypes commonly expanded in both foreign antigen immunized mice and 564Igi bone marrow chimeras but not clonotypes enriched in 564Igi bone marrow chimeras[100], potentially reflecting the lack of annotated autoantigens in TCR databases. Further studies are needed to determine whether the follicular T cell clonotypes expanded in both foreign and autoimmune disease are specific for foreign antigens, autoantigens, or both.

Given the consistent bystander activation of TFH and TFR cells and convergence of follicular T cell predicted specificities in foreign antigen immunized and autoimmune mice, we hypothesize that autoreactive B cells co-opt cross-reactive TCRs present within the follicular T cell repertoire to license T cell help in developing autoreactive GCs. A follicular T cell repertoire that is cross-reactive with self might also explain how epitope spreading and molecular mimicry propagate. Given the importance of MHC class II expression to maintain peripheral B cell tolerance[46,47,80,81], we propose that autoreactive B cells overcome clonal anergy by internalizing and presenting self-antigens to cross-reactive follicular T cells which then provide help to B cells with specificities against unrelated antigens (Figure 3). Marginal zone (MZ) B cells have polyreactive BCRs and relatively decreased activation thresholds[286–288], and therefore might represent a B cell population capable of polarizing cross-reactive T cells against self. Notably, this model assumes both the presence of TCRs cross-reactive with autoantigens in the follicular T cell repertoire and the ability of autoreactive B cells to overcome mechanisms of peripheral tolerance.

Extrafollicular autoantibody development

In addition to TFH mediated help in autoreactive GCs, T cell help mediated by other cell types and in other immunologic niches have been identified in autoantibody disease (Figure 4). T cell help might be provided to autoreactive B cells not only by TFH and TFR cells, but also by peripheral helper T (TPH) cells, circulating TFH (cTFH) cells, and CD8 T cells. Autoreactive B cells might also develop in EF and tertiary lymphoid structures (TLS) or ectopic GCs. Indeed, mounting evidence suggests that extrafollicular origins might serve as the dominant source of autoantibodies in disease.

High resolution analyses of patient biopsies have led to the characterization of alternative T cell populations capable of providing T cell help[107,289]. Circulating, pre-follicular, and extrafollicular TFH cells all express CXCR5 and PD-1[290]. Indeed, the canonical markers of GC TFH cells are likely imprecise[290], as $CXCR5^{+}PD\text{-}1^{+}$ cells encompass both GC and non-GC TFH cells, two populations with distinct antigen requirements, gene expression, and repertoires[291]. TFH cells can inefficiently enter circulation[292], with varying levels of retained Bcl6, CXCR5, and PD-1 expression[293]. SLE patients have increased cTFH that correlate with disease severity, plasmablasts (PBs), and autoantibody levels[52,294–297]. These cTFH cells might simply be a marker of active GC reactions[292] or might represent a memory population capable of secondary lymphoid organ homing and GC re-entry[298,299].

TPH cells were identified in the synovium of seropositive RA patients and are distinct from cTFH cells due to their $PD\text{-}1^{hi}CXCR5^{-}Bcl6^{-}$ profile and ability to migrate to peripheral sites of inflammation[107,300–303]. TPH cells produce IL-21 and CXCL13[304], express TFH signature genes[289], exhibit hallmarks of exhaustion[289], can stimulate PB formation *in vitro*[289,304,305], and correlate with age-associated $CD11c^{+}CD21^{-}$ B cell (ABC) levels[304,306]. Antigen-specific TPH cells have been identified in celiac disease and autoimmune hepatitis[307,308], suggesting that TCR specificity influences TPH fate and possibly function. Other CD4 T cell populations such as resident helper T (TRH) cells[309,310], $CXCR3^{+}PD1^{hi}$ CD4 T cells[301], or TH17 cells[147,311] might also provide tissue-specific help to autoreactive B cells in autoimmune disease. Non-TFH sources of T cell help must be considered when designing therapy for autoantibody disease, as Bcl6-deficient mice are still capable of neutralizing antibody responses[312,313].

CD8 T cells exhibit dysfunctional phenotypes in autoantibody disease, including impaired cytotoxicity of circulating CD8 T cells[314–318], impaired suppressive ability of regulatory CD8 T cells[269,319–322], and effector memory phenotypes of tissue resident CD8 T cells[323]. Regulatory CD8 T cells represent a CD8 T cell subset that exert Qa-1 restricted suppression of TFH and GC B cells, preventing autoantibody development and glomerulonephritis[268]. KIR^{+} CD8 T cells can eliminate autoreactive CD4 T cells and are increased in the circulation of celiac disease, MS, SLE, and COVID-19 patients[324]. $CXCR5^{+}$ follicular CD8 T cells represent a distinct subset capable of GC entry where they facilitate autoreactive B cell CSR and autoantibody development[325–327]. $CD40L^{+}$ CD8 T cells are necessary for ectopic GC formation in RA[328,329]. These results suggest that CD8 T cells can provide B cell help, potentially in collaboration with TFH cells. Single cell sequencing of SLE kidneys revealed increased cytotoxicity of infiltrating CD8 T cells[107,317] whereas circulating CD8 T cells has decreased cytolytic capacity in SLE[316]. B6.Sle1yaa mice had decreased frequency

of splenic CD8 T cells, which also exhibited metabolic rewiring and clonal expansion of an effector subset[106]. Given the differences in circulating and tissue resident CD8 T cells, we hypothesize that tissue residence drives altered CD8 T cell metabolic profiles that facilitate cytotoxicity and contribute to autoantibody pathogenesis. Alternatively, these cytotoxic CD8 T cell phenotypes might be driven by TFH cell-derived IL-21, which can license CD8 T cell responses in both cancer[330] and chronic viral infection[331].

SHM, CSR, and memory B cell formation may occur outside GCs in EF in both T cell dependent and T cell independent manners[4,72,332–334]. Immunization results in early CD4 T and B cell proliferation in EF, ultimately leading to emergence of short-lived plasma cells in an ICOS and CD40L dependent manner[277,335–339]. Extrafollicular $Bcl6^{+}CXCR5^{lo}ICOS^{lo}$ CD4 T cells secrete IL-21 and IL-10 and can more efficiently convert naïve B cells into antibody secreting cells (ASC) than GC TFH cells[340]. Autoantibody levels decrease quickly following B cell depletion with anti-CD20[341–345], suggesting production by extrafollicular short lived plasma cells. SLE flares correlate with circulating PC frequency[346] and ASC development from activated naïve B cells followed by production of lowly mutated autoantibody[347], reminiscent of a non-GC origin. BAFF transgenic mice produce class switched autoantibody outside GCs in a T cell independent manner[348,349] and B6.56R mice loss B cell tolerance in a T cell and TLR9 independent manner[350]. TLR7 dependent extrafollicular ABCs expressing T-bet and CD11c, particularly $CXCR5^{-}CD21^{-}$ DN2 cells[351], are pathogenic in lupus[347,352]. T-$bet^{+}CD11c^{+}$ B cells arise outside the GC in the marginal zone, are TFH dependent, and can rapidly become ASC[353]. Indeed, RNA velocity analysis of B6.Sle1yaa splenic B cells suggested that autoreactive plasma cells (PCs) originate at least partially from MZ B cells[106], consistent with T cell independent activation of extrafollicular autoreactive MZ B cells observed in autoantibody disease[286–288,354–356]. These observations provide multiple distinct potential ontogenies of autoantibody secreting cells.

CD4 T cells with a TFH signature are also present in EF in lupus prone mice. B6.Sle1yaa and NZW/BXSB mice eventually lose splenic GC organization accompanied by extrafollicular localization of TFH cells[106,357]. 564Igi bone marrow chimeras have increased extrafollicular cells that also expressed increased PD-1 and *Selplg* expression on follicular T cells correlated with predicted autoreactivity[100], suggesting that TCR autoreactivity promotes EF responses. MRL/lpr mice develop autoantibodies from T cell dependent extrafollicular SHM and ASC production[72,358], likely due to increased extrafollicular $PSGL\text{-}1^{lo}$ T cells that express CXCR4 and facilitate IgG production via IL-21 and CD40L[277,335]. Although SHM and ASC production is T cell dependent in MRL/lpr mice, autoantibody production is T cell independent and instead requires TLR9 or TLR7 mediated MYD88 signaling[358,359]. In contrast, autoantibody production in *Dnase1l3*$^{-/-}$ mice by extrafollicular short lived ASCs is dependent on CD40L mediated T cell help, although is also promoted by TLR9 and TLR7 signaling[360]. Both GC TFH and extrafollicular T cells in BXSB/yaa mice express increased IL-21[143], suggesting simultaneous EF and GC responses. Autoantibody responses might originate in EF due to lack of tolerogenic pressures that normally facilitate negative selection or clonal redemption in the GC. We hypothesize that ultimately both EF and GC serve as sites of loss of tolerance with potential differences in threshold, kinetics, and T cell dependence in autoantibody disease.

Beyond EF in secondary lymphoid organs, TLS or ectopic GCs may also promote autoantibody development. TLS develop following chronic inflammation locally at sites of infection, autoimmune processes, or solid tumors[361]. Pathogenic TLS have been identified in the lungs of Wegner granulomatosis[362,363] patients, thyroid in Hashimoto thyroiditis[364,365], meninges in MS[366–370], thymus in myasthenia gravis[371], synovium in RA[372,373], salivary gland in Sjogren syndrome[374,375], and kidney in SLE[376,377]. Peripheral tolerance mechanisms are dysregulated in autoimmune TLS, as autoreactive B cells are capable of TLS entry and ensuing autoantibody production[372,378]. Gut associated lymphoid tissue is also capable of shaping the immature transitional B cell repertoire away from autoreactivity, a process that fails in SLE[379]. Autoimmune TLS harbor latent Epstein-Barr virus (EBV)[380,381] and EBV transformed B cells can produce autoantibodies[382,383]. Abnormal T cell help might also influence TLS autoreactivity, as CD8 and TH17 cells are necessary for TLS formation in RA synovium[329] and experimental autoimmune encephalomyelitis CNS[384–386], respectively. Although TFH like cells have also been identified in autoimmune TLS[385,387], their ontogeny and function remain unclear. We propose that TLS are established following secondary lymphoid organ loss of tolerance due to local antigen availability and their persistence allows for continual evolution of the autoantibody repertoire.

Other forms of germinal center dysfunction

In addition to contributing to autoantibody development, dysfunctional T cell help likely contributes to other abnormal GC responses. Insufficient, overactive, or dysfunctional GCs have been described in autoimmune disease, infection, and cancer. Molecular mechanisms of T cell help dysfunction in both autoreactive GCs and other diseases might reciprocally provide biological insight and therapeutic targets for each other. Recent discoveries have revolutionized our understanding of GC dysfunction in molecular mimicry, cancer, and COVID-19 (Figure 5).

Molecular mimicry is the process by which immune responses against foreign antigens lead to autoimmune responses against homologous antigens likely through epitope spreading or cross-reactivity[388,389]. Documented triggers include *Streptococcus pyogenes* infection leading to rheumatic heart disease[390], *Campylobacter jejuni* infection leading to Guillain-Barre syndrome[391], and EBV infection leading to MS[392]. BCR repertoire analysis from MS CSF revealed that SHM of an EBNA1 antibody led to cross-reactivity with the CNS restricted protein GlialCAM[26]. CSF oligoclonal PBs increased expression of HLA-DR[26] and latent EBV persists in meningeal TLS[380], suggesting that EBV reactive B cells may break T cell tolerance in meningeal TLS, allowing them to receive T cell help and mutate towards autoreactivity in MS. Molecular mimicry was exacerbated by phosphorylation of GlialCAM[26] and citrullinated peptides or phosphorylated Ro/La are targets in RA[393] and SLE[394], respectively, suggesting that tissue-specific post translational modification might explain escape from central tolerance mechanisms. Even after loss of tolerance, epitope spreading to an evolving set of autoantigens may occur with both diagnostic and prognostic utility in autoimmune disease[20–25,395,396]. We hypothesize that molecular mimicry and epitope spreading is facilitated by the cross-reactivity of the T cell repertoire[285], which

allows for non-specific bystander TFH activation and provision of T cell help leading to B cell SHM and autoreactivity, particularly in situations of chronic GCs.

Although cancer immunotherapies have historically focused on anti-tumor CD8 T cells, there is growing appreciation for the importance of CD4 T and B cells in anti-tumor immunity. Aberrant epitope spreading might also contribute to both beneficial anti-tumor immune responses[397–405] and adverse autoimmune events[406–410] following checkpoint blockade cancer immunotherapy. Paradoxically, epitope spreading and worse immune related adverse events (irAE) correlate with better anti-tumor immunity[411–415] and anti-tumor antibodies can evolve from pre-existing autoantibodies through SHM[416], suggesting that overcoming GC tolerance mechanisms might benefit cancer immunotherapy. TPH, TFH, and B cells have been identified in tumors and tumor associated TLS, and their presence correlates with improved survival[303,417–433]. Mice genetically engineered to express B cell neoantigens in lung cancer develop tumor-specific TFH and B cell responses with greater anti-tumor immunity[330]. IL-21 production by tumor-specific TFH cells is necessary for anti-tumor CD8 T cell cytotoxicity[330], suggesting cross talk from B cells to TFH cells to CD8 T cells. T cell help via IL-21 promotes formation of cytolytic CX3CR1^{+} CD8 T cells that are capable of controlling both chronic LCMV and tumor growth[434]. Similarly, TFH cell-derived IL-21 promotes antigen-specific CD8 T cell responses in chronic LCMV infection[331]. Given the increased CD8 T cell cytotoxicity observed in autoantibody disease[106,107,317], these studies highlight convergent mechanisms of T cell help in cancer, infection, and autoimmunity. While epitope spreading is pathogenic in autoantibody disease, it might provide therapeutic benefit in cancer.

GC dysfunction has also been described in COVID-19, as patients with severe disease lack TFH cells and GC structures[435]. Despite lack of GCs, severe COVID-19 patients still form extrafollicular T-B cell conjugates and class switched antibodies[435,436]. SARS-CoV-2 infection and vaccination results in generation of both TFH-dependent and TFH-independent antibodies[312,437,438]. Impaired TFH help in immunocompromised kidney transplant recipients likely accounts for decreased responsiveness to mRNA vaccination[439]. However, *Cd4*^{Cre}*Bclf6*$^{fl/fl}$ mice demonstrated that although TFH-independent antibodies were less somatically mutated, they were still neutralizing and broadly reactive against SARS-CoV-2 and heterologous viruses[312]. Although these antibodies appear protective, ongoing extrafollicular responses correlate with worse outcomes of COVID-19[436]. Autoantibodies targeting type I interferons correlate with COVID-19 severity[440], likely due to the protection conferred by type I interferons against SARS-CoV-2[441]. Pathologic autoantibodies against other immunomodulatory proteins such as cytokines, chemokines, and complement also emerge in COVID-19 and multisystem inflammatory syndrome in children (MIS-C), similarly affecting clinical outcomes[442–446]. Given the association between autoantibodies and atherogenesis and arrhythmias[447–450], aberrant autoantibody production might explain the cardiovascular complications of COVID-19. Autoantibody levels in COVID-19 patients also correlate with anti-SARS-CoV-2 antibody levels and is an independent risk factor for development of post-acute sequelae of COVID-19 (PASC) or long COVID-19[451]. Informed by the role of extrafollicular responses in autoantibody disease, we hypothesize that although capable of producing neutralizing antibodies against SARS-CoV-2, ongoing

extrafollicular TFH-independent B cell responses also lead to autoantibody development which directly exacerbates COVID-19 severity.

Conclusion

Technological advances have allowed for the study of the autoreactive GC at single cell resolution, transforming our understanding of the role of T cell help in loss of tolerance. These developments have led to new models of TFH and B cell crosstalk in not only autoantibody disease, but also other autoimmune diseases, cancer, and infection. Gene expression profiling has identified metabolism and adhesion molecule expression as therapeutic targets specific to autoreactive TFH cells. Repertoire analyses have revealed a surprising degree of bystander activation of follicular T cells, leading to the hypothesis that cross-reactive T cells might license B cell loss of tolerance and epitope spreading. Mass cytometry of patient biopsies identified novel T helper subsets such as TPH cells and highlighted the contribution of extrafollicular responses to autoantibody development. Lessons learned from the autoreactive GC can also provide mechanistic insight into the autoantibody development observed in MS and COVID-19. These hypotheses highlight the therapeutic potential of targeting alternative pathways such as TFH metabolism, bystander T cells, or extrafollicular B cells in autoantibody disease.

In addition to generating new hypotheses, recent discoveries have opened the door to many remaining questions of autoreactive GC biology. Although TFH cells share predicted specificities in foreign antigen immunized and autoimmune mice, the antigenic targets of these TCRs remains unknown. Indeed, reactivities against overlapping antigens between TFH cells and epitope spread B cells has not been established. Identification of target antigens might clarify whether bystander follicular T cell activation is a necessary component of autoreactive GC responses or is simply a consequence of GC development. The degree of T cell dependence of extrafollicular responses and the tolerance mechanisms that normally restrain MZ or DN2 B cell conversion to autoantibody secreting cells also remain unclear. The nature of T cell help provided by other populations such as TPH and CD8 T cells and in other locations such as TLS, as well as their ability to propagate autoantibody responses, is poorly characterized. Pressing questions such as why SARS-CoV-2 infection generates extrafollicular responses and whether these EF are the source of pathogenic autoantibody must be answered. Answers to these questions have the potential to not only improve our understanding of GC biology, but also lead to the development of more efficacious therapies for diseases ranging from autoimmunity to cancer.

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Abbreviations:

EF	extrafollicular foci
GC	germinal center

TFH	follicular helper T cell
SHM	somatic hypermutation
CSR	class switch recombination
TFR	follicular regulatory T cell
SLE	systemic lupus erythematosus
MG	myasthenia gravis
RA	rheumatoid arthritis
SS	Sjögren's syndrome
MS	multiple sclerosis
LZ	light zone
LLPC	long-lived plasma cell
DZ	dark zone
MZ	marginal zone
TPH	peripheral helper T cell
cTFH	circulating follicular helper T cell
TLS	tertiary lymphoid structures
PB	plasmablast
ABC	age-associated B cell
TRH	resident helper T cell
ASC	antibody secreting cell
PC	plasma cell
EBV	Epstein-Barr virus
irAE	immune-related adverse event
MIS-C	multisystem inflammatory syndrome in children
PASC	post-acute sequelae of COVID-19

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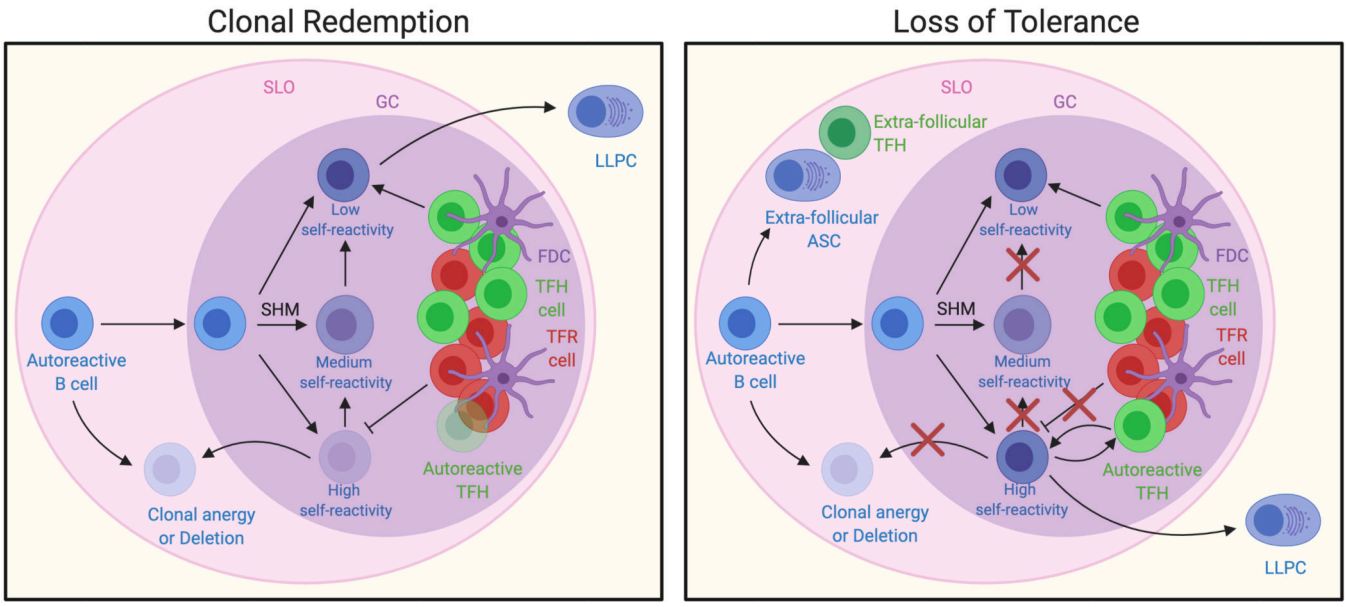

Figure 1. Failures in clonal redemption lead to loss of tolerance.

Autoreactive B cells normally undergo SHM to lose self-reactivity in a process termed clonal redemption. Anergic B cells that have escaped central tolerance are recruited into the GC of SLOs and mutate away from self to receive T cell help, which facilitates CSR and LLPC development. This process is regulated by checkpoints such as limited antigen-specific TFH cells, limited antigen availability on FDCs, co-stimulation provided by TFH cells, and TFR cells. We propose that in autoantibody disease an autoreactive B cell clone escapes clonal redemption due to failures of these checkpoints, triggering TFH dysfunction and epitope spreading towards autoantigens. SHM, somatic hypermutation; CSR, class switch recombination; GC, germinal center; TFH, follicular helper T cell; TFR, follicular regulatory T cell; FDC, follicular dendritic cell; LLPC, long lived plasma cell; SLO, secondary lymphoid organ; ASC, antibody secreting cell.

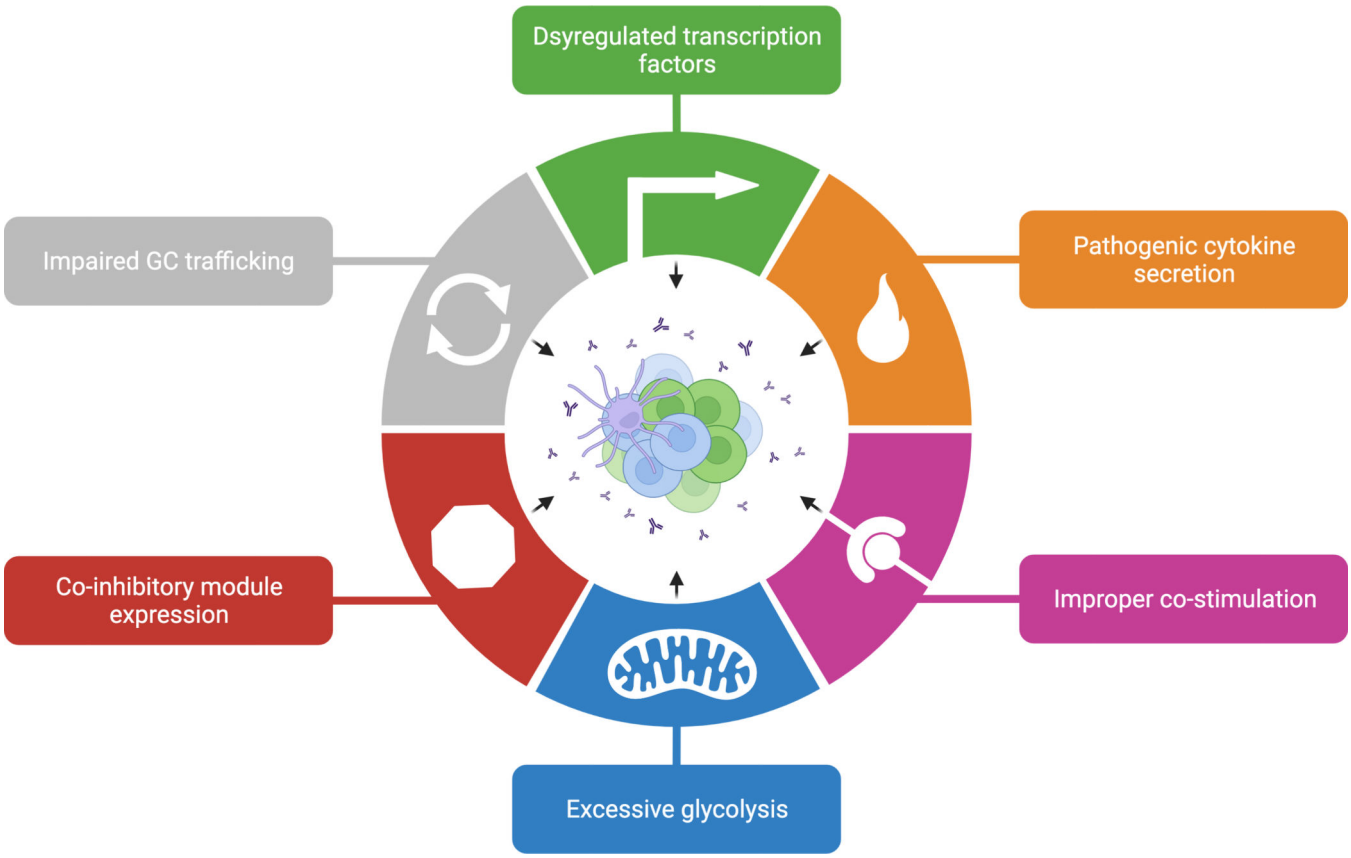

Figure 2. Hallmarks of TFH dysregulation in autoimmune disease.

TFH cells isolated from mice and humans with autoimmune disease exhibit transcriptional and functional changes. We propose that loss of GC tolerance is due to TFH dysregulation, albeit through various mechanisms of dysfunction. TFH cells might permit or promote autoreactive B cell development due to dysregulated transcription factor expression, cytokine and chemokine profiles, co-stimulation, metabolism, exhaustion, and trafficking. GC, germinal center; TFH, follicular helper T cell.

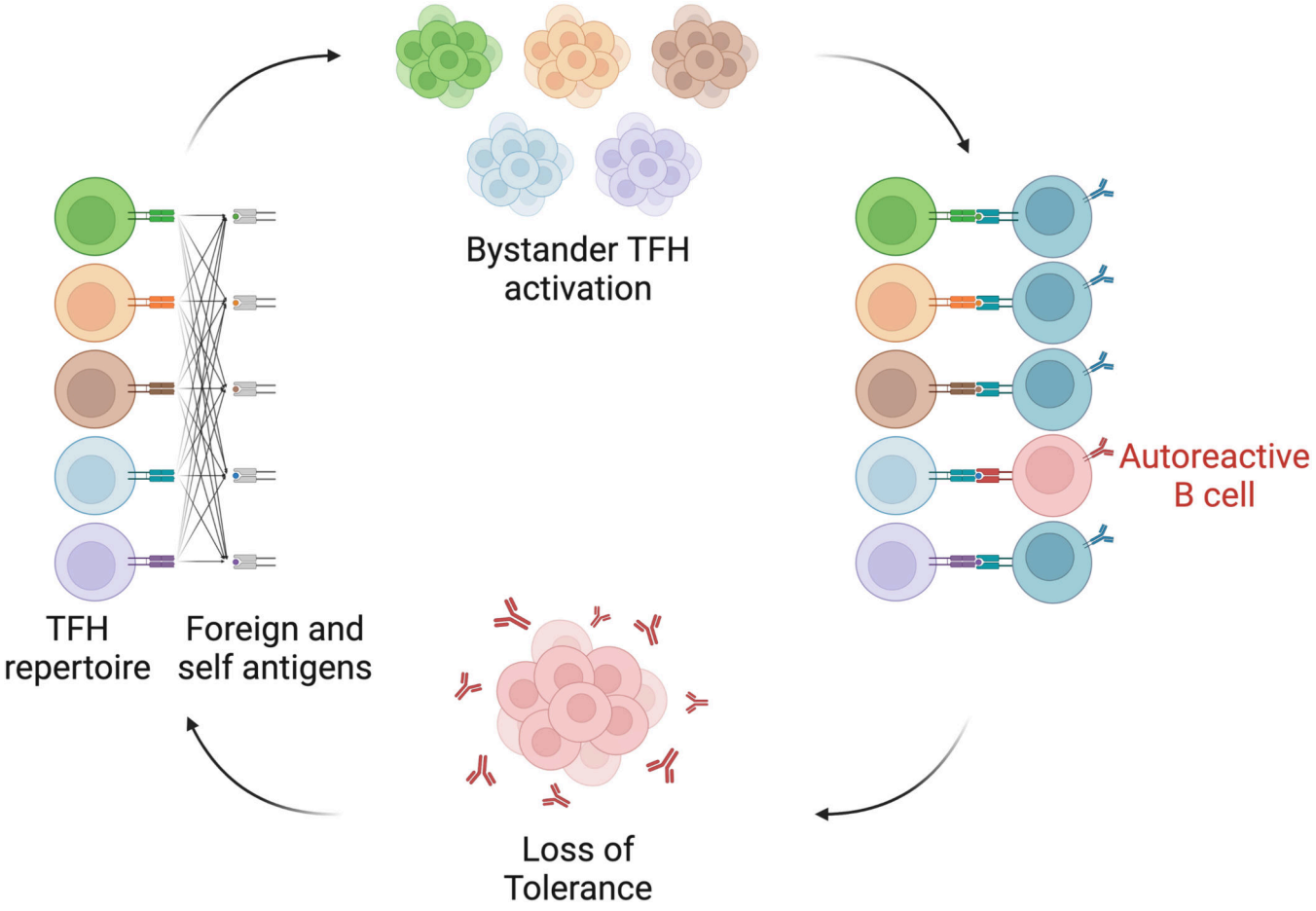

Figure 3. Bystander activation and cross-reactivity of the TFH repertoire.

Repertoire wide analyses have revealed that both immunization and autoimmune disease result in polyclonal responses of TFH and TFR cells. Computational prediction of antigen specificities also suggests overlap between autoimmune and foreign antigen elicited follicular T cell repertoire specificities. We propose that the cross reactivity of the TCR is responsible for non-specific bystander activation, which allows for provision of T cell help to autoreactive B cells, particularly in situations of chronic GC or extrafollicular B cell activation. GC, germinal center; TFH, follicular helper T cell; TFR, follicular regulatory T cell.

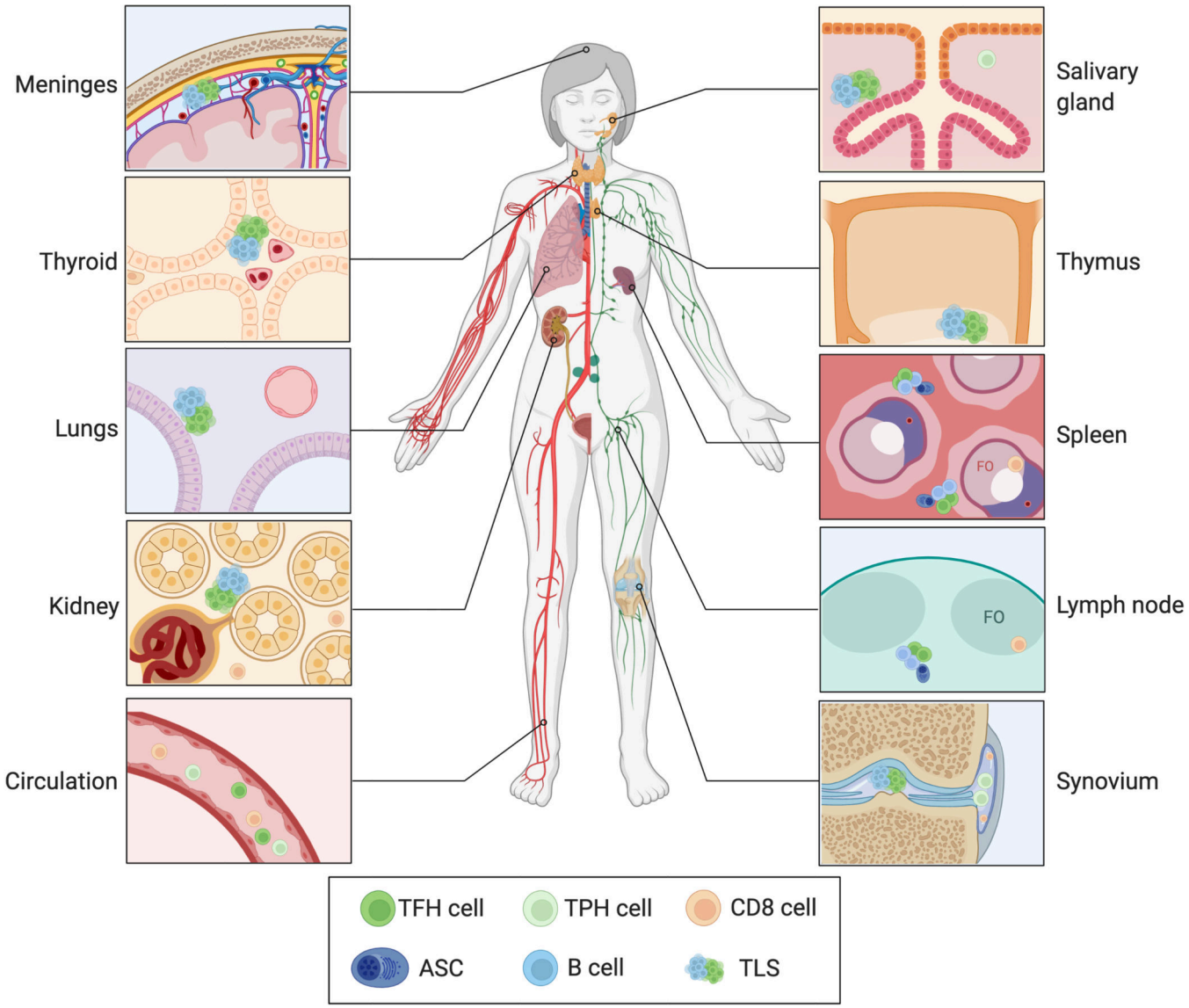

Figure 4. Extrafollicular sites of autoantibody production.

T cell help to autoreactive B cells may be provided by cells other than follicular T cells and at locations other than GCs. TPH, cTFH, TRH, TH17, and CD8 T cells exhibit dysregulation in autoantibody disease and might also contribute to loss of GC tolerance. Autoantibodies might also originate from SLO EF and TLS, which might serve as sites of loss of tolerance or epitope spreading, respectively. GC, germinal center; TPH, peripheral helper T cell; cTFH, circulating follicular helper T cell; TRH, resident helper T cell; EF, extrafollicular foci; TLS, tertiary lymphoid structure; FO, follicle; ASC, antibody secreting cell; SLO, secondary lymphoid organ.

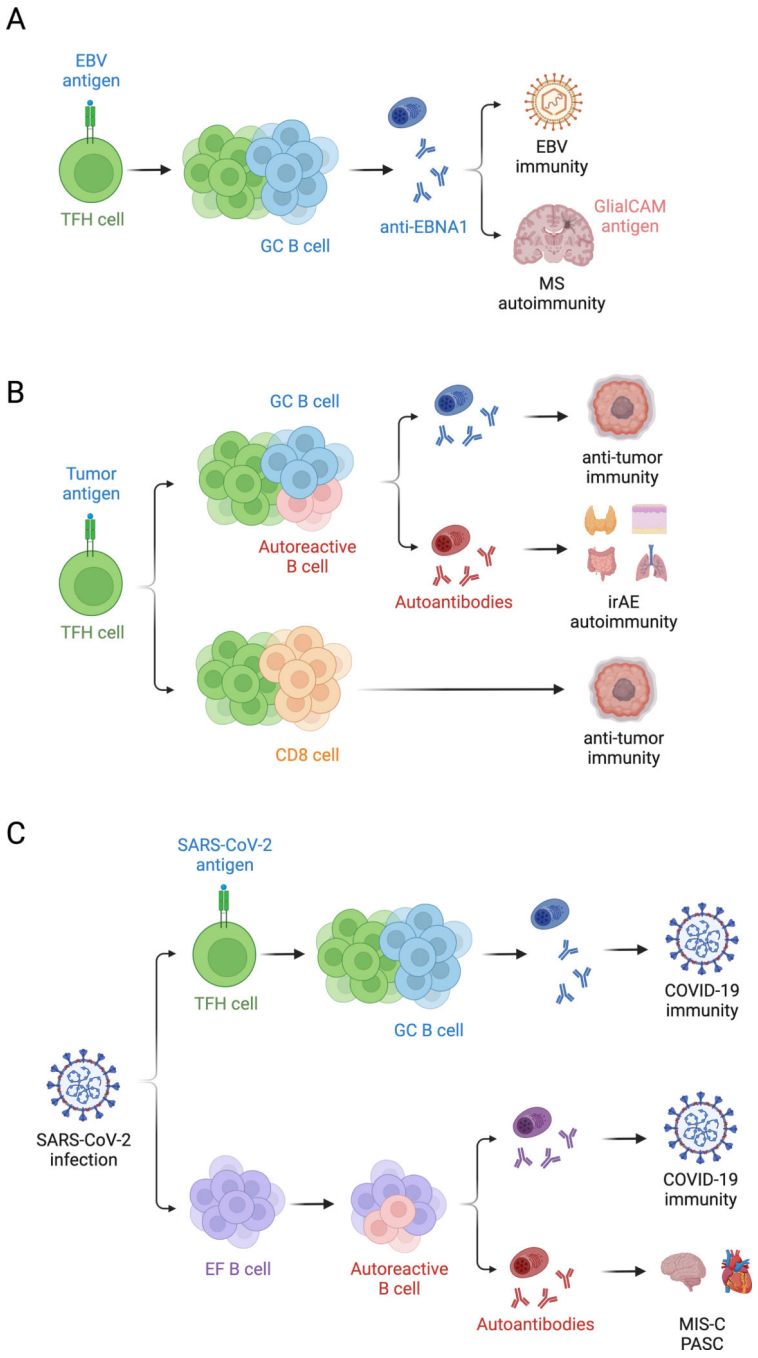

Figure 5. Dysregulated GCs in autoimmune disease, cancer, and COVID-19.

Mechanisms of dysfunctional T cell help in autoantibody disease are applicable to other forms of GC dysfunction. (A) Molecular mimicry is an etiology of MS and might be driven by the cross reactivity of the TFH repertoire. (B) In contrast, epitope spreading might enhance anti-tumor immune responses, although might also exacerbate irAE following immune checkpoint blockade in cancer. (C) T cell independent neutralizing antibodies against SARS-CoV-2 are made in COVID-19, although EF and pathogenic autoantibodies are also observed in severe COVID-19. GC, germinal center; TFH, follicular helper T

cell; EBV, Epstein-Barr virus; MS, multiple sclerosis; irAE, immune related adverse event; EF, extrafollicular foci; MIS-C, multisystem inflammatory syndrome in children; PASC, post-acute sequelae of COVID-19.