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SMARTImmunology

The Immunology Newsletter from SMARTANALYST

B-cell Explosion in Autoimmune Disorders

Role of B cells in the humoral immune system

B cells act as effector cells as well as immunoregulatory cells to produce antibodies, cytokines such as TNF-α, IFN-γ, IL-2, IL-6, IL-10, TGF-β, and present antigens (Figure 1).[1,2] Regulatory B cells (Bregs) limit inflammation by secretion of IL-10 and TGF-β, which inhibit Th1 cytokines, B lymphocyte activation, and antigen presentation by B cells.[3] B-cell – T-cell cross-talk is essential for an effective immune response. Antigen presentation by B cells stimulates the B-cell to interact with follicular T helper cells (Tfh). This interaction is facilitated by the B-cell receptor (BCR), ligation of CD40/CD40L, IL-4, and IL-21. Tfh cells induce DNA editing enzymes to initiate somatic hypermutations (SHM) and class-switch recombinations (CSR). Mutations induced in the immunoglobulin genes during SHM allow a wide variety of immunoglobulin (Ig) proteins to be developed by the B cells. The CSR permits the transformation of IgM and IgD into IgG, IgA, and IgE to produce antigen-specific antibodies based on antigenic exposure during the B-cell development process.[4,5]

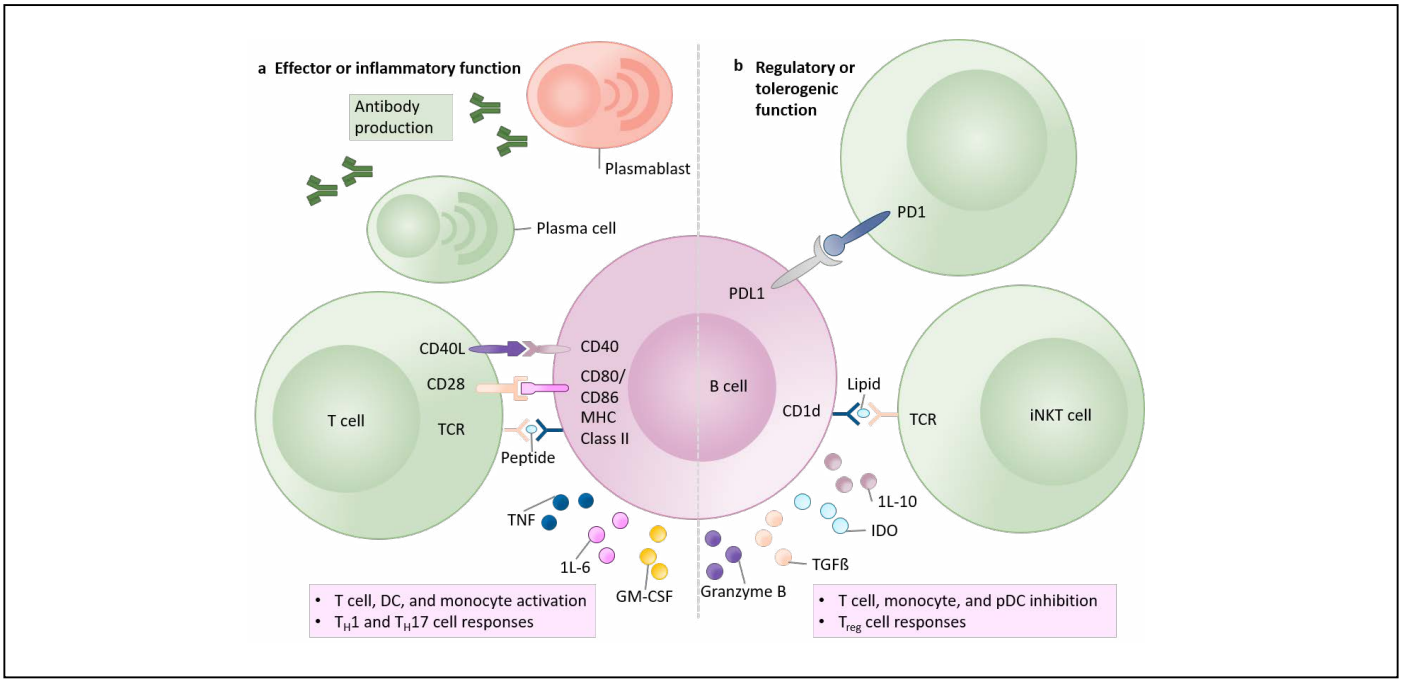

Figure 1. B cell – A key component of the immune cell orchestra[2]

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Role of B cells in autoimmunity

Although the exact mechanism is not well understood, the loss of tolerance to self-antigens in combination with inherited susceptibility, environmental factors, infections, or injuries may result in autoimmunity manifesting as an autoimmune disorder (Table 1). Activation of the humoral immune system involves close coordination of B-cell and T-cell functions where B cells have a key role to play.[2]

Table 1. B-cell mediated autoimmunity in key autoimmune disorders

Mechanism	Role of B Cells in Autoimmunity	Association with Autoimmune Disorders
Breakdown in tolerance	Disruption in the central and peripheral tolerance of the adaptive immune system to the self-antigens generates autoreactive B cells[6]	Break in tolerance to self-antigens has been reported in RA, T1D, MS, and SS
Genetic polymorphism	Defects in genes encoding B-cell functioning such as cytokine receptors, CD40, toll-like receptors (TLRs), and transcriptional regulators of the BCR have been implicated in autoimmunity[7,8]	Polymorphism in the *PTPN22* gene is associated with increased susceptibility for SLE, T1D, and RA BACH2 polymorphism is associated with risk of AS, T1D, MS, CD, and SLE
Dual stimulation of TLRs and BCRs	Endogenous nucleic acid from damaged cells can stimulate TLRs and BCRs, resulting in the generation of autoreactive B cells[9,10]	Autoantibody production by dual stimulation of TLRs and BCRs promotes pathogenesis of SLE, SS, and RA
Ectopic germinal centers	Autoreactive B cells promote new autoimmune germinal centers (GCs) which continuously produce autoantibodies[11,12]	Ectopic lymphoid structures have been demonstrated in the target organs of patients with SS, RA, SLE, MG, MS, LN, and Hashimoto's thyroiditis
Regulatory B-cell (Breg) defects	Bregs are critical for maintaining immune tolerance. Numerical and functional Breg defects are observed in autoimmune disorders[13,14]	Functional deficits of Bregs have been demonstrated in SLE, RA, MS, MG, SS, and PV
Defective BCR signaling	Defective BCR, CD40 ligand, TLR, CD80/86, MHC Class II, and BAFF signaling promotes the generation of autoreactive B cells by compromising central and peripheral tolerance checkpoints[15-20]	BAFF levels are increased in SLE, RA, SS, and SSc Altered MHC Class II signaling has been linked to RA, MS, PsO, AS, T1D, UC, and CD
Epigenetic modifications	DNA methylation/demethylation, non-coding RNAs (microRNA), and histone modifications modulate gene expression and allow SHM and CSR needed to generate antigen-specific antibodies by plasma cells. Defects in epigenetic modifications contribute to autoimmunity[21-24]	Epigenetic alterations have been implicated in the pathophysiology of SLE, PsO, and CAPS
Cytokines	Inflammatory cytokines play a central role in autoimmunity and the pathogenesis of autoimmune disorders. Unrestrained production of cytokines sets up a series of cascading events leading to tissue damage	IL-6 is elevated in JIA, SS, SLE, and RA IFN-α is elevated in SS, SLE, T1D, RA, and autoimmune thyroid disease TNF-α is elevated in RA, PsO, and PsA IL-2 and IL-4 are elevated in RA

AS: Ankylosing spondylitis; **CAPS**: Cryopyrin-associated periodic syndrome; **CD**: Crohn's disease; **LN**: Lupus nephritis; **MS**: Multiple sclerosis; **MG**: Myasthenia gravis; **PsA**: Psoriatic arthritis; **PsO**: Psoriasis; **PV**: Pemphigus vulgaris; **RA**: Rheumatoid arthritis; **SLE**: Systemic lupus erythematosus; **SS**: Sjogren's syndrome; **SSc**: Systemic sclerosis; **T1D**: Type 1 diabetes; **UC**: Ulcerative colitis

Therapeutic approaches targeting B cells

Rituximab, a B-cell modulator, was the first anti-CD20 monoclonal antibody to be approved in 2004 for NHL and since then it has found use in multiple autoimmune disorders and is now approved for RA, GPA, MPA, and PV. With the use of Rituximab, there has been an increasing focus on the role of B cells in autoimmune disorders. Abatacept, a B-cell–T-cell co-stimulation inhibitor (CD80/86-CD28), was approved in 2005 for RA followed by IL-6R inhibitor Tocilizumab for RA in 2010. In 2011, the first and only biological (Belimumab – BAFF inhibitor) targeting the B-cell survival factor was approved for SLE. In 2013, anti-CD52, Alemtuzumab was approved for B-cell depletion in MS. CD20 continues to be a valuable target and a second-generation anti-CD20, Ocrelizumab, with a better safety profile was approved in 2017 for MS and Ofatumumab is in pre-registration phase for MS. With the improved understanding of the role of B cells in autoimmune disorders, B-cell intracellular signaling is increasingly being targeted. Fostamatinib was the first Syk inhibitor to be approved for ITP in 2018.

Rituximab, a murine-human chimera, is associated with anti-drug antibodies and infusion reactions. CD20 mediated B-cell depletion is evolving and the second generation anti-CD20 agents, humanized (Ocrelizumab, Obinutuzumab) or fully human (Ofatumumab) are better tolerated and less immunogenic. Other B-cell signaling inhibitors, ABBV-105 (BTK inhibitor) is in Phase III for SLE, MS, and PV; Parsaclisib (Phosphatidylinositol-3-kinase (PI3K) inhibitor) is in Phase II for Sjogren's syndrome. However, targeted Bruton tyrosine kinase (BTK) inhibition has not worked in autoimmune disorders in the past since it leaves existing B cells intact to continue their damage. In a recent encouraging development, oral brain penetrating BTKi, SAR442168 led to an 85% relative reduction of new Gd-enhancing T1 hyperintense lesions in a Phase IIb study in MS patients.

Efficacy of B-cell depleting agents varies widely across patient segments and is short-lived. This may be attributed to the repopulation of B cells in the peripheral circulation from early pre-B cells as well as to the lack of CD20 receptors on plasma cells, which are the source of autoantibodies. Multiple plasma cell depletion assets in Phase II development are targeting proteasome inhibition (KZR-616 for SLE, LN), HDAC inhibition (CKD-506 for RA), and CD38 inhibition (TAK079 for MG).

Another novel B-cell targeting approach is simultaneous inhibition of B-cell proliferation and survival via BAFF and inhibition of B-cell–T-cell co-stimulation via inducible T-cell costimulation ligand (ICOSL/ICOS). Inducible T-cell co-stimulation ligand (ICOSL) on B cells ligates ICOS on T cells and induces Tfh differentiation, which is needed for B-cell antibody production and maintenance of GCs. A bi-specific molecule AMG570, a dual BAFF, and ICOSL inhibitor are in Phase II development for SLE.

B-cell targeting continues to get more refined with the increasing understanding of the role of B cells in autoimmune disorders and some promising and more specific treatment options could become available in the future. A few exciting B-cell modulation strategies that promote the B-cell regulatory functions are in development. FcγRIIb (CD32) receptor on B cells binds immune complexes and suppresses B-cell function in response to B-cell stimulators such as IL-4 and BAFF. It tightly regulates B-cell proliferation into plasma cells and suppresses autoimmunity. FcγRII agonist, PRM-151, is in Phase III development for IPF and is likely to be safer in comparison to B-cell depletion since it only silences the B cells. Another promising approach is to augment a Breg cell cytokine (IL-10). This is a tolerogenic cytokine that inhibits the autoreactive function of monocytes and plasmacytoid dendritic cells and limits inflammation associated with autoimmune disorders. The IL-10 agonist, Dekavil, is in Phase II development for UC and RA (Table 2).

Targeting homing receptors is another approach that may emerge as a treatment option in the future. B-cell migration to GCs and bone marrow niches occurs under the influence of multiple homing receptors and their ligands such as CXCR5/CXCL13, CXCR3/CXCL9, and CCR9/CCL25. Blockade of these homing receptors prevents the migration of immature B cells to the ectopic germinal centers to develop into mature B cells and plasma cells. CXCR3 inhibitor, E-6011, is in Phase II development for RA and CD and CCR9 antagonist, CCX-507, is in Phase II for UC.

Table 2. B-cell targeting approaches in approved indications[25-31]

B-cell Targeting Approaches	Mechanism of Action	Indication (Approved Asset)
B-cell differentiation	BAFF inhibition	• SLE (Belimumab)
B-cell depletion	CD20 inhibition (1st generation)	• RA, PV (Rituximab)
	CD20 inhibition (2nd generation)	• MS (Ocrelizumab)
BCR signaling	Syk inhibition	• ITP (Fostamatinib)
Cytokines	IL-6 receptor inhibition	• RA, JIA (Tocilizumab) • RA (Sarilumab)
B-cell–T-cell co-stimulation	CD80/86-CD28 inhibition	• RA, JIA, PsA (Abatacept)

GPA: Granulomatosis with polyangiitis; **ITP**: Immune thrombocytopenic purpura; **JIA**: Juvenile idiopathic arthritis; **MPA**: Microscopic polyangiitis; **MS**: Multiple sclerosis; **PsA**: Psoriatic arthritis; **PV**: Pemphigus vulgaris; **RA**: Rheumatoid arthritis; **SLE**: Systemic lupus erythematosus

Table 3. B-cell targeting approaches in development (≥Phase II)[32]

B-cell Targeting Approaches	Mechanism of Action	Indication (Asset Under Development, Phase)
B-cell differentiation	BAFF inhibition	• LN (Belimumab, Phase III) • SS, SSc (Belimumab, Phase II)
	BAFF receptor inhibition	• IPF, SLE, SS (Ianalumab, Phase II)
	APRIL inhibition	• IgAN (VIS-649, Phase II)
	Dual BAFF and APRIL inhibition	• RA (RC-18, Phase III) • SLE (RC-18, Phase III; Atacicept, Phase II) • IgAN (Atacicept, RC-18, Phase II)
	Dual BAFF and ICOSL inhibition	• SLE (AMG-570, Phase II)
B-cell depletion	CD20 inhibition (1st generation)	• MCD (Rituximab, Phase III) • SSc (Rituximab, Phase II)
	CD20 inhibition (2nd generation)	• LN (Obinutuzumab, Phase III) • MS (Ofatumumab, Phase pre-reg; Ublituximab,Phase III; BCD-132, Phase II)
	CD19 inhibition	• SLE (Obexelimab, Phase II)
BCR signaling	Syk inhibition	• SS (Lanraplenib, GS9876, Phase II) • RA (SKI-O-703, Phase II) • AD (Gusacitinib, Phase II) • LN (Lanraplenib, Phase II) • ITP (SKI-O-703, Phase II)
	PI3K inhibition	• SS (Parsaclisib, INCB-050465, Phase II)

B-cell Targeting Approaches	Mechanism of Action	Indication (Asset Under Development, Phase)
BCR signaling	BTK inhibition	• Pemphigus (PRN-1008, Phase III) • MS (Evobrutinib, SAR442168, Phase III) • SLE (Evobrutinib, Branebrutinib, ABBV-105, Phase III; Fenebrutinib, Orelabrutinib, Phase II) • SS (Tirabrutinib, GS-4059, Phase II) • RA (Fenebrutinib, Evobrutinib, ABBV-105, BMS-986142, TAS-5315, Phase II)
Cytokines	TNF-α inhibition	• RA (Ozarolizumab, Phase III; Atrosab, MBS-2320, SSS-07, Phase II) • JIA (Certolizumab, Phase III) • AD (Antroquinol, Phase II) • CD (V-565, Phase II)
	IL-6 receptor inhibition	• JIA (Sarilumab, Phase II)
	IL-2 agonism	• AS, RA, SSc, CD, SLE (Aldesleukin, Phase II)
	IL-4 inhibition	• AD (SB-414, Phase II)
	IL-6 inhibition	• RA (Olokizumab, Phase III; BCD-089, Phase II) • UC (Olamkicept, Phase II)
	IFN-α inhibition	• SLE (IFN-α Kinoid, Phase III) • SS (RSLV-132, Phase II)
	IFN-γ inhibition	• JIA (Emapalumab, Phase II)
	IFN-α receptor inhibition	• SLE (Anifrolumab, Phase III • LN (Anifrolumab, Phase II)
	IL-10 agonism	• RA, UC (Dekavil, Phase II)
	TGF-β agonism	• NASH (Nitazoxnide, Phase II)
B-cell membrane receptors	FcγRII agonism	• IPF (PRM-151, Phase III)
	TLR4 antagonism	• NASH (JKB-122, GBK-233, Phase III; JKB-121, Phase II) • RA (NI-0101, Phase II) • CD (JKB-122, Phase II) • MS (Ibudilast, Phase II)
	TLR9 agonist	• UC (Cobitolimod, Phase III) • EA (AZD-1419, Phase II)
B-cell–T-cell co-stimulation	CD80/86-CD28 inhibition	• SS (Abatacept, Phase III) • SLE, MCD (Abatacept, Phase II)
	CD40-CD40L inhibition	• AD (DS-107E, Phase III) • SS (Iscalimab, CFZ-533, Phase II)

B-cell Targeting Approaches	Mechanism of Action	Indication (Asset Under Development, Phase)
B-cell – T-cell co-stimulation	CD40-CD40L inhibition	• LN (Iscalimab, BI-655064, Phase II) • SLE (Iscalimab, Phase II) • UC (Ravagalimab, Phase II) • HS (Iscalimab, Phase II)
Plasma cells	Proteasome inhibition	• LN, SLE (KZR-616, Phase II)
	HDAC inhibition	• RA (CKD-506, Phase II)
	CD38 inhibition	• MG (TAK079, Phase II)
Homing receptors	CX3CR1 inhibition	• RA, CD (E6011, Phase II)
	CCR9 inhibition	• UC (CCX-507, Phase II)

AD: Atopic dermatitis; **AS**: Ankylosing spondylitis; **CD**: Crohn's disease; **EA**: Eosinophilic asthma; **GPA**: Granulomatosis with polyangiitis; **HS**: Hidradenitis suppurativa; **IgAN**: Immunoglobulin A nephropathy; **IPF**: Idiopathic pulmonary fibrosis; **ITP**: Immune thrombocytopenic purpura; **JIA**: Juvenile idiopathic arthritis; **LN**: Lupus nephritis; **MCD**: Minimal change disease; **MG**: Myasthenia gravis; **MPA**: Microscopic polyangiitis; **MS**: Multiple sclerosis; **NASH**: Nonalcoholic steatohepatitis; **PsA**: Psoriatic arthritis; **PV**: Pemphigus vulgaris; **RA**: Rheumatoid arthritis; **SLE**: Systemic lupus erythematosus; **SS**: Sjogren's syndrome; **SSc**: Systemic sclerosis; **UC**: Ulcerative colitis

Future considerations

Chimeric autoantigen receptor (CAAR) T cells that can neutralize B cells responsible for autoimmune disorders are under the development of MG (MuSK-CAAR-T) and pemphigus (DSG3-CAAR-T). The CAARs have the ability to instruct T cells to destroy autoantibody secreting B cells. Potential for severe off-target toxicities and logistical issues such as large-scale production for clinical use are the key challenges. IL-10 secreting plasma cells have demonstrated an anti-inflammatory role in animal models of autoimmune diseases. Upon identification of the phenotype of these plasma cells, therapies that induce such plasma cells may be developed.[33]

With increasing evidence of the role of B cells in the pathophysiology of autoimmune disorders, targeted therapies that eliminate pathogenic B cells or promote regulatory/immunosuppressive B cells are being explored. Pan-B-cell depletion is not desirable since it removes effector as well as regulatory B cells. Ideal B-cell targeting should preserve the protective actions of B cells. Disease heterogeneity in autoimmune disorders poses a considerable challenge for drug development. Development of targeted therapies and the selection of patients most likely to respond to a certain therapy on the basis of biomarker/molecular signatures is likely to be the way forward. For example, in SLE patients with skin manifestations, IFN signature is high. IFN-αR inhibitor, Anifrolumab, has demonstrated higher efficacy in patients with high baseline IFN signature in comparison to patients with a low baseline IFN signature. BAFF inhibitor (Belimumab) and BAFF and APRIL inhibitor (Atacicept) have demonstrated variable efficacy in autoimmune disorders in terms of reducing the levels of autoantibodies and clinical outcomes. These therapies could be more efficacious if the identification of patients likely to respond to these therapies is done on the basis of predictive markers. The success of B-cell targeting therapies in the last decade has firmly established the role of B cells in the pathogenesis of multiple autoimmune disorders. However, various B-cell targeting therapies approved thus far have demonstrated modest efficacy and are associated with the risk of infections. Significant heterogeneity in the pathogenesis of autoimmune disorders underscores the importance of personalized medicine. Based on these observations, future B-cell therapies that preserve regulatory and immune surveillance functions while limiting the effector functions are likely to be more effective. Identifying patient segments most likely to respond to such targeted therapies will usher in a new era in the management of autoimmune disorders.

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