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PATHOGENESIS AND TREATMENT OF AUTOIMMUNE RHEUMATIC DISEASES

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Abstract

Purpose of review.—Autoimmune diseases are of unknown origin, and they represent significant causes of morbidity and mortality. Here, we review new developments in understanding of their pathogenesis that have led to development of safe and effective treatments.

Recent findings.—In addition to the long-recognized genetic impact of the HLA locus, interferon regulatory factors, PTPN22, STAT4, and NOX have been implicated in pathogenesis of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Smoking, ultraviolet light, diet, and microbiota exert strong environmental influence on development of RA and SLE. Metabolism has been recognized as a critical integrator of genetic and environmental factors, and it controls immune cell differentiation both under physiological and pathological conditions.

Summary.—With the advent of high-throughput genetic, proteomic, and metabolomic technologies, the field of medicine has been shifting towards systems-based and personalized approaches to diagnose and treat common conditions, including rheumatic diseases. Regulatory checkpoints of metabolism and signal transduction, such as glucose utilization, mitochondrial electron transport, JAK, mTOR and AMPK pathway activation, and production of pro-inflammatory cytokines IL-1, IL-6, and IL-17 have presented new targets for therapeutic intervention. This review amalgamates recent discoveries in genetics and metabolomics with immunological pathways of pathogenesis in rheumatic diseases.

Keywords

Genes; epigenetics; miRNA; environment; metabolism; glutathione; oxidative stress; autoimmunity; metabolism; repurposing of established medications

Introduction

Autoimmunity occurs when an immune response is mounted against an antigen that is present in the body of the host. Autoimmune disease is when the specific autoimmunity

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Conflicts of interest

None

causes a pathologic condition. Typically, autoimmune disease involves the activation of the adaptive immune system, including both T and B cells that recognize self-antigens, as well as the innate immune system, comprised of macrophages and dendritic cells (DCs). Like all immune responses, autoimmunity is driven genetically by antigen recognition and cellular interactions. In addition, environmental agents may induce autoimmune responses [1]. Infections, such as Coxsackie virus, can provide the primary “natural” source antigen that mimics self-antigens and triggers myocarditis, an organ-specific autoimmune disease [2]. Alternatively, Epstein-Barr virus can act as an instigating agent as well as a polyclonal activator of B cells and contribute to organ-specific and systemic autoimmune diseases, such as multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [3]. Thus, autoimmune disease can be divided into two major categories: organ specific and systemic [4]. With the advent of personalized medicine with growing utilization of gene-based diagnostic technologies and biological drugs, it is imperative for the astute clinician to be informed of new developments in our understanding of the pathogenesis of autoimmune disorders.

Genetic predisposition

Further support for a genetic component of SLE can be found in twin studies. Concordance rate of lupus in monozygotic and dizygotic twins have been reported to be 24% and 2 %, respectively [5]. Close to 100 genes have been implicated in the pathogenesis of autoimmune rheumatic diseases [6]. Given an overwhelming genetic influence by the human leukocyte antigen (HLA) locus, which include major histocompatibility complex (MHC) and complement genes, individualized recognition and processing of antigens remain a leading pathway to pathogenesis of autoimmunity [7]. 90% of patients with C1q deficiency will develop lupus-like phenotypes [8;9], while deficiency of C4 causes SLE with >75% penetrance [10].

Genes that regulate signal transduction, such as the protein tyrosine phosphatase non-receptor type 22 (PTPN22) and the signal transducer and activator of transcription 4 (STAT4) confer fewer degrees of relative risk [11]. STAT4 polymorphisms have been associated with both RA and SLE, implying a common genetic pathway of pathogenesis [12]. Autoimmunity-associated polymorphisms in PTPN22 cause sustained signaling through the T-cell and B-cell receptors [13]. Activation of the innate immune system is controlled by interferon regulatory factors, IRF1 [14], IRF2 [14], and IRF7 [15], and IRF5 that are involved in cytokine signaling [16;17] Add IRF1 [14], IRF2 [14], and IRF7 [15]. Other polymorphisms linked to SLE include the integrin alpha M (ITGAM) and interleukin-1 receptor-associated kinase-1 (IRAK1) that mediate macrophage dysfunction in SLE [18]. Cytosolic DNA detection activates a cell intrinsic damage associated molecular pattern (DAMP), activating IFN response and systemic inflammation thus, the three prime repair exonuclease 1 (Trex1) gene was noted to play a factor of the IFN stimulatory response [18]. Trex1 metabolizes single stranded DNA that is reversed transcribed from endogenous retroelements. Single stranded DNA accumulates and stimulates Interferon-alpha (IFN α) production in Trex1 deficient cells hence preventing regulation of IFN α accumulation and precipitating autoimmunity [19].

Monogenic lupus typically presents at the early stage of life with severe disease manifestations [20]. Although these patients represent a small subset of lupus, their studies have provided useful insights into pathogenesis and potential treatment strategies of SLE. As an example, Aicardi-Goutieres Syndrome (AGS) is caused by mutations in the Trex1 gene [20]. AGS patients have thrombocytopenia, leukopenia, oral ulcers, arthritis, and IgG antibodies directed against nuclear antigens, ds-DNA, basement membranes, gliadins, endothelial cells and astrocytes as well as elevated type I IFN production [20–22].

The SAM domain and HD domain-containing protein 1 (SAMHD1) is responsible for synthesis of deoxynucleoside triphosphates (dNTPs), the building blocks of DNA [23]. In healthy individuals, it acts to promote cell stability and prevent reverse transcription of retroviruses. Mutations or deficiency of SAMHD1 causes loss of DNA replication and repair. The increase in damaged DNA leads to increased apoptosis and sustained IFN response by activation of the innate immune system [24]. SAMHD1 variants have been seen in familial chilblain lupus [25]. Ribonuclease H2 (RNaseH2) also acts as a nucleic acid repair enzyme that removes ribonucleotides from DNA hybrid complexes [20]. Mutations in the enzyme can lead to incorporation of ribonucleotides into genomic DNA which triggers the p53 pathway and type I IFN production. Fibroblasts in patients with SLE and AGS with RNaseH2 mutations accumulate both RNA and DNA in the cytoplasm which upregulates IFN production in response to UV light. These findings highlight another mechanism of interaction between genetic and environmental factors in the pathogenesis of SLE [20;26].

Epigenetics

In genetically susceptible individuals, epigenetic modifications such as DNA methylation and histone methylation and acetylation, are the driving forces for disease initiation in response to environmental factors. Typically, SLE patients with active disease have hypomethylated DNA [27]. In a recent study, 41 differentially methylated sites were identified between SLE and healthy controls, and about 85% of those sites were hypomethylated. Hypomethylation was highly prevalent among interferon-regulated genes [28]. Lymphocytes in patients with lupus have deficient glutathione [29], which reflects oxidative stress and favors DNA hypomethylation [27;30]. Histone acetylation influences gene transcription in disease and cell type-specific manners [31]. For example, in monocytes, H4 histones were noted to be hyperacetylated in SLE. Hyperacetylation of the H4 histones led to increased production of TNF α . In contrast to monocytes, lupus CD4 $^{+}$ T-cells exhibit hypoacetylation of histone H3, which inversely correlates with disease activity [27;32].

Similarly, hypomethylation has been reported in fibroblasts and T-cells of patients with Scleroderma, predominantly affecting interferon-regulated genes [33]. Hypomethylation of the promoter region of Integrin, alpha L antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide (ITGAL) which encodes CD11a, a cell-surface molecule involved in T-cell co-stimulation and adhesion, was detected in CD4 $^{+}$ T-cells of SSc patients and inversely correlated with disease activity. This association has been also noted in CD4 $^{+}$ T-cells of SLE patients [33;34].

MicroRNAs (miRNAs) also modulate gene expression after transcription [35]. In a recent study [36], miR-618 inhibited differentiation of plasmacytoid dendritic cells (pDCs), a primary source of IFN α in SLE. MiR-29a has anti-fibrotic properties by reducing expression of tumor growth factor β (TGF β) activated kinase 1 binding protein 1 which inhibits metalloproteinase 1 expression and collagen degradation and promotes cell death of fibroblasts [33]. Likewise, miR-21 increases apoptosis of fibroblasts as well, which may be used to treat patients with Scleroderma [33;37].

Molecular mimicry

Molecular mimicry is another pathway being widely analyzed. Structures of many microbial proteins/metabolites are identical or very similar to those expressed by their human host. Antibodies produced against said antigen can then bind to the host antigen causing amplification of the immune response [38]. Viruses stimulate dendritic cells activating innate immunity resulting in production of cytokines including type 1 Interferon (IFN-1) [39;40]. Viruses can persist in the body throughout life stimulating production of autoantibodies and inhibiting apoptosis. They often precede symptoms and signs of autoimmune disease [41]. The Epstein-Barr virus (EBV) has long been implicated in the development of autoimmune diseases such as SLE, Sjogren's syndrome and RA [41–43]. EBV is acquired and persists dormant in the host throughout life in memory B cells. Interaction between EBV and HRES-1/p28 epitopes can lead to epitope dispersion to include self-antigens and nucleosome components. It breaks tolerance in SLE via molecular mimicry [44]. There have been instances in which Parvovirus B19 (PVB19) has induced autoimmunity. During a reoccurrence of parvovirus infection, specific T-cells for the NS1 protein participated in the pathogenesis of several autoimmune diseases such as dermatomyositis, Sjogren syndrome, or granulomatous polyangiitis [45]. In a meta-analysis, the risk of developing anti-phospholipid antibody (aPL) syndrome (APS) was found to be enhanced in subjects infected with human immunodeficiency virus (HIV) and hepatitis C virus. Compared to healthy controls, HIV patients had elevated aPL production thereby increasing the risk of thromboembolic events [42;46]. Although less commonly studied compared to viruses, bacteria have been noted to participate in molecular mimicry as well. High titers of type II collagen antibodies have been reported in the synovial fluid of RA patients. Many bacterial species contain collagen that shows a high degree of homology with human type II collagen [42;47]. Thus, mycobacterium tuberculosis has been suspected in the development of SLE, RA, and sarcoidosis [48].

TNF inhibitor-induced autoimmune disease

While benefiting patients with RA, psoriasis, psoriatic arthritis, and spondyloarthropathy; tumor necrosis factor inhibitors have been linked to ANA and aPL production, SLE [49], and vasculitis [50;51]. While the pathogenesis is not completely clear, increased production of type I IFN [52;53] and inhibition of tumor necrosis factor α (TNF α) induced apoptosis have been suggested as unwanted consequences of TNF blockade.

Metabolic control of autoimmunity

Cellular metabolism plays an integral part in facilitating immune cell functions [54]. Following activation, T-cells engage in increased cell growth and proliferation. Essential biomolecules such as amino acids, nucleotides, or lipids are needed thus, the cells adapt their cellular metabolism in line with the targeted functional output [55]. Take Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) for example. GAPDH is an enzyme that catalyzes the sixth step of glycolysis. GAPDH is a component of the IFN- γ activated inhibitor of translation (GAIT) complex that binds to 3'-UTR elements in inflammatory mRNAs thus, suppressing their translation [56]. GAPDH functions in glycolysis and mRNA function are mutually exclusive. Hence, in glycolytic cells, GAPDH would be preferentially used in glycolysis leaving translation of IFN- γ and IL-2 mRNA unchecked [56;57]. This mechanism illustrates a link between rates of glycolysis and expression of immunological effector molecules.

Certain metabolic configurations will yield variable levels of metabolites that directly impact cellular function. Phosphoenolpyruvate, a glycolytic intermediate, is important in sustaining T-Cell receptor (TCR) signaling and T-cell effector functions by inhibiting Ca^{2+} re-uptake in the endoplasmic reticulum thus, sustaining nuclear factor of activated T-cells (NFAT) signaling [56;58]. T-cells that are unable to activate NFAT would be unable to engage in proliferation. Hypoxia inducible factor 1 α (HIF1 α) is a transcription factor involved in glycolytic reprogramming of T-cells. In M1 macrophages, Krebs cycle metabolites, such as succinate, stabilize HIF1 α resulting in prolonged production of IL-1 β . This mechanism involves the blockade of α -ketoglutarate-dependent prolyl-hydroxylases responsible for tagging HIF1 α for proteasomal degradation [56;59].

An oxidative environment generates reactive lipid species in SLE [60]. Peroxidation of lipids produces malondialdehyde (MDA) and 4-hydroxynoneal (4-HNE). MDA interferes with RNA polymerase II activity; disrupting transcription and resulting in aberrant gene expression [27;61;62]. 4-HNE represses histone deacetylase and promotes growth arrest and DNA damage gene (Gadd45) transcription. Gadd45 promotes demethylation and transcription of CD11a and CD70 in self-reactive cells. It is also triggered by UV light which induces lupus flares and oxidative stress. This evidence newly links Gadd45 to oxidative stress, lipid peroxidation, and epigenetic modifications underlying lupus flares [11;27;63].

Mechanistic target of rapamycin (mTOR) activation promotes inflammatory differentiation in the adaptive immune system

The mechanistic target of rapamycin (mTOR) was identified while investigating the mechanism of action of rapamycin, which has become a medication under the designation of sirolimus, developed to prevent organ transplant rejection [64]. mTOR forms three distinct protein kinase complexes, mTORC1, mTORC2, and mTORC3 [65;66]. The major function of mTORC1 is to sense nutrients, mitogenic signals, and oxidative stress. When favorable conditions are sensed, mTORC1 initiates biosynthetic pathways for cell growth and proliferation via phosphorylation of ribosomal S6K and eukaryotic initiation factor 4E

(eIF4E) [67;68]. It is also known to suppress autophagy which is needed to recycle cellular components and create nutrients under metabolic stress thus promoting cell survival [67;69]. mTORC2 primarily contributes to cell survival and cytoskeleton organization. Both have been tied to roles in regulation of immune responses [66]. Studies in animal models suggest that reduced activation of the mTOR can lead to immune deficiency while increased activation is associated with autoimmunity [62]. In mice, those with mTORC1/mTORC2 inhibition were known to be immunodeficient with impaired development, proliferation, and migration of lymphocytes [70]. In patients with SLE, activation of mTORC1 causes increased production of IL-4 [71], necrotic death of CD4-CD8- double-negative (DN) T cells as well as depletion of CD8 memory T-cells, CD4+, CD25+, FoxP3+, and Tregs [72–73]. Direct blockade of mTOR with rapamycin [72;74] and indirect blockade by N-acetylcysteine offers biomarker-driven clinical benefits in patients with SLE [75].

Uncontrolled Innate Immunity

At the cellular level, macrophages, neutrophils, natural killer cells, and DCs are critical components of the innate immune system. Traditionally, neutrophils are associated with acute inflammation while macrophages are associated with chronic inflammation [76;77]. New studies have challenged such theories indicating that neutrophils are key effector cells in adaptive immunity for resolution of chronic inflammation and monocytes/macrophages are important in acute inflammatory processes. Normally, monocytes are recruited after the release of cytokines by neutrophils and further differentiated into macrophages. New evidence has shown chemoattractants such as monocyte chemoattractant protein 1 (MCP-1) rapidly inducing monocyte/macrophage influx regardless of whether neutrophils are present or not [76]. Macrophages make up an important class of antigen-presenting cells (APC) that activate adaptive immunity: stimulation of B and T-cells, Th1 cell differentiation, repair of damaged tissue, homeostasis and phagocytosis [78;79]. Studies have also noted that macrophages cause cytokine release resulting in neuropathic pain [80]. Neutrophils can secrete IL-17 and regulate immunity inducing expression of pro-inflammatory factors from myeloid cells. They also interact with dendritic cells to activate NK cells [81]. Furthermore, neutrophils may express MHC II class and act as antigen presenting cells or MHC I class promoting differentiation of naïve CD8+ T-cells into cytotoxic T-cells [82]. Due to the ability of neutrophils and macrophages to initiate and control immune responses against exogenous pathogens and as well as self-proteins, they are likely to have an important role in the pathogenesis of autoimmune disorders. Just the nature of such role is not fully elucidated yet.

Infectious organisms and neutrophils secrete peptidyl arginine deaminase (PAD) that mediates protein citrullination leading to the formation of neo-antigens and the development of autoantibodies in RA patients [83]. These autoantibodies are then directed against fibrinogen, fibronectin, collagen type II, histones, and are often associated with joint radiographic damage and extra-articular manifestations [84;85]. In animal studies, neutrophil depletion with antibodies reversed joint swelling and inflammation [86]. Similarly to neutrophils, macrophages, specifically M1 macrophages, promote recruitment of pro-inflammatory cytokines, interleukins (TNF α , IL-1, IL-6, IL-12, IL-23) and enzymes responsible for the acute inflammatory response and joint destruction in RA. IL-1 and TNF-

α induce expression of other cytokines as well as antigenic factors, lipid mediators and inducible nitric oxide synthase. TNF α induces histone acetyltransferase activity (HAT) leading to acetylation of histones and modulation of transcriptional factors [87]. On the other hand, M2 macrophages have been shown to produce anti-inflammatory cytokines. IL-10 polarizes towards M2 macrophages and have been looked at in past studies as a target therapy [88–89]. Developmental switching from M1 to M2 macrophages would be a novel strategy of preventing inflammation and further bone erosion in RA.

Pathogenesis checkpoint-directed treatment targets

It is safe to say that the development of new treatments in the realm of autoimmunity is an active area of research. As discussed earlier, reduced glutathione (GSH) is profoundly depleted in lymphocytes of SLE patients [90]. Loss of GSH reflects oxidative stress. N-acetylcysteine (NAC) is a precursor of glutathione and stimulator of de-novo biosynthesis. In animal studies, NAC prevented the decline of GSH, reduced autoantibody production and the development of glomerulonephritis [90–91]. In a randomized placebo-controlled clinical trial [75], NAC had increased GSH levels, blocked mTORC1, expanded Tregs, and lowered disease activity [92]. In ancillary metabolome studies, kynurenine was identified to be the top predictor of NAC effect in SLE. Kynurenine also stimulated mTORC1. It has long been known that mTOR is a novel metabolic checkpoint in SLE pathogenesis [93], and as thus, clinical efficacy of NAC may involve this mechanism of action [75].

As shown for NAC and rapamycin, drug repurposing, identification of novel disease indications for already approved drugs, can offer shorter paths to approval for novel therapies. While many biologics have been approved for RA and psoriatic arthritis (Table 1), however, there is a relative paucity of clinical trials that succeeded in other autoimmune diseases such as SLE [94]. Important new aspects of clinical trial design include the definition of biomarkers that can optimize patient selection and define clinical responsiveness to therapeutic interventions [95;96].

The therapeutic use of miRNA has been facilitated by the development of delivery strategies that partially solve problems related to the biopharmaceutical properties of the molecules. Chemical nucleoside modifications and locked nucleic acid technology provide resistance against nucleases, and the introduction of lipid nanocarriers for miRNA-mimics or anti-miRNAs confers miRNA stability and limits immune rejection. Additionally, topical miRNA-directed therapies are showing promising results when applied to patient-derived skin samples, thereby encouraging further preclinical evaluation in Scleroderma [33;97]. Topical application of a miR-155 inhibitor suppressed collagen deposition in a mouse model of skin fibrosis. These findings suggest that delivery of miRNA modulators directly into the skin surface could be an alternative and more preferred form of therapy [33;98]. Other miRNAs such as miR-30 and miR-29 have been seen to control anti-fibrotic events.

Initial successes of RA treatment targeted TNF, IL-1, and IL-6. IL-17 has been noted to be elevated in synovial fluid and tissues in RA. In this context, researchers have hypothesized that the IL-23/IL17 pathway rather than IL-12/IFN pathway is more essential to promoting arthritis [99]. IL-17 amplifies or stimulates production of multiple cytokines and

keratinocytes, synoviocytes, inflammatory cells such as macrophages, fibroblasts and neutrophils [100]. Secukinumab, an IL-17 inhibitor, currently is approved for use for treatment of psoriasis and psoriatic arthritis. Studies have shown that IL-17 play a significant role in disease activity of RA. In particular, synovial fibroblasts play a role in erosive pannus formation [101;102]. Belimumab, an anti-Blys monoclonal antibody has shown considerable efficacy in SLE, and it has been approved for treatment of SLE since 2011 [117]. Most registered lupus clinical trials are focused on B cells [103]. Approaches include targeting B-cell specific proteins such as CD19, CD20, and CD22 or targeting co-stimulatory receptor/ligands (CD40/CD40 ligand) [104–105]. Most recently, Ustekinumab, an IL-12/IL-23 inhibitor has shown remarkable efficacy in SLE trials [106]. It is currently only approved for Crohn's Disease, psoriasis, and psoriatic arthritis. TLR inhibitors, Jak inhibitors, proteasome inhibitors, and histone deacetylase inhibitors have been also considered as potential therapies for SLE [107–108].

Figure 1 illustrates only a fraction of pathways involved in pathogenesis of autoimmunity and biologics currently used to target those pathways.

Conclusions

Autoimmune diseases have many layers of complexity in terms of scope, pathogenesis, severity, prognosis, and responsiveness to current treatment modalities. Autoimmunity develops from an interaction of genetic and environmental factors that shape the development of cells and elaboration of cytokines into directions that create organ-specific or systemic inflammation. Metabolic pathways include the generation of energy ranging from fatty acid oxidation in mitochondria to glycolysis in the cytosol, synthesis of nucleotides and production of antioxidant NADPH by the pentose phosphate pathway (PPP), support of cell growth through increased synthesis of proteins, lipids, and carbohydrates when fuels are abundant, and autophagy which ensures cell survival at times of metabolic stress and fuel shortages. In addition to blocking the effect of inflammatory cytokines and integrin that control tissue penetration, metabolic checkpoint of inflammatory lineage specification, such as: mitochondrial oxidative stress, GSH depletion, mTOR and JAK/STAT/Syk/TYK2 pathway activation, and sphingosine 1-phosphate receptor modulation have become targets of treatment. Since uncovering the impact of the epigenetic pathway, in addition to DNA methylation, histone modifications such as acetylation, methylation, phosphorylation, ubiquitination, or hydroxylation have been investigated in multiple autoimmune diseases. Many details of the mechanisms need further elucidation. The clinical heterogeneity within a single diagnostic entity, such as SLE, make our approach to select personalized therapy difficult but inherently necessary. A better understanding of the immunopathogenesis of autoimmunity can help clinicians select more effective interventions from a rapidly growing armamentarium of mechanistically-driven therapeutic approaches.

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Key Bullet Points

Autoimmunity occurs in the setting of genetic predisposition and environmental influence

Both genetic and environmental factors modulate the innate and adaptive arms of the immune system towards self-reactivity and inflammation

Metabolic pathways serve as key sensors and effectors of genetic, epigenetic, and environmental cues that shape the development and function of the immune system

Activation of the mechanistic target of rapamycin has emerged as a central regulator of metabolic stress that underlies pro-inflammatory lineage development in the adaptive immune system

Blockade of mTOR reverses the depletion of Tregs and CD8 memory T cells and moderates the expansion of inflammatory Th17 cells in autoimmune diseases with promising therapeutic efficacy

Figure 1.

Brief view of the immunologic network depicting common CD4+T cells, B-cells, pathways (regulatory genes, proteins and transcription factor), cytokines and functions of the immune system (blue). Targeted biologic therapies as well as the inhibitory effect of Treg cells is shown as well (red). IL: Interleukin; IFN: Interferon; TNF: Tumor necrosis factor; TGF: Tumor growth factor; Th: Helper T-cells; Treg: Regulatory T-cells, STAT: Signal Transducer and Activator of Transcription proteins; GATA3 gene; Foxp3: Forkhead box p3 protein; T-bet: T-Box transcription factor; ROR γ t: RAR-related orphan receptor gamma protein.

Table 1.

Current targeted therapies for autoimmune diseases. Many of the medications are undergoing repurposing for certain other autoimmune diseases. The ongoing clinical trials for many of the medications above and others not listed can be found at [ClinicalTrials.gov](https://clinicaltrials.gov). BAFF: B-cell Activating Factor of the TNF Family; mAb: monoclonal antibody; TNF: Tumor Necrosis Factor.

Drug	Target	Disease	References
Adalimumab	TNF- α inhibitor	Ankylosing Spondylitis Psoriasis/Psoriatic arthritis Rheumatoid arthritis Crohn's Disease	[97,108-111]
Belimumab	Anti-CD257 (BAFF) mAb Inhibits B-cell survival	SLE	[103,116-119]
Etanercept	TNF inhibitor	Ankylosing spondylitis Psoriasis/Psoriatic arthritis GVHD	[112-115]
Golimumab	TNF- α inhibitor	Ankylosing spondylitis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	[112-113]
Ixekizumab	IL-17A inhibitor	Psoriasis/Psoriatic arthritis	[100,113]
Rituximab	mAb directed against CD20 antigen on B-cells Depletes and inhibits B-cells	Granulomatosis polyangiitis Rheumatoid arthritis Pemphigus Vulgaris Microscopic polyangiitis	[103,116-120]
Secukinumab	IL-17 inhibitor	Ankylosing spondylitis Psoriasis/Psoriatic arthritis	[100,113]
Tocilizumab	IL-6 inhibitor	Giant cell arteritis Rheumatoid arthritis	[121-123]
Ustekinumab	IL-12/23 inhibitor	Psoriasis/Psoriatic arthritis Crohn's Disease	[124-125]