Review

Targeting Inflammatory Cytokines in Autoimmune Diseases: Mechanisms and Therapeutic Advances with Antibody-Based Therapies

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Abstract: Autoimmune diseases occur due to dysregulated immune responses against self-antigens, marked by chronic inflammation caused by pathogenic cytokine networks. Key inflammatory mediators, such as TNF-α, IL-6, IL-17, IL-23, and type I/II interferons, promote disease progression by activating autoreactive lymphocytes, recruiting immune cells, and causing ongoing tissue damage. The development of therapeutic antibodies targeting these cytokines has transformed treatment approaches, providing targeted immunomodulation while reducing systemic immunosuppression. Clinically approved biologics, including TNF inhibitors (Adalimumab, Infliximab), IL-6R blockers (Tocilizumab), and IL-17/IL-23 pathway antagonists (Secukinumab, Ustekinumab), show strong efficacy in various autoimmune conditions like rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. Emerging strategies, such as bispecific antibodies and AI-optimized designs, further enhance therapeutic precision by targeting multiple inflammatory pathways or refining antibody functions simultaneously. This review highlights the pivotal role of inflammatory cytokines in autoimmune pathogenesis and assesses the clinical impact of cytokine-targeted biologics, emphasizing their potential for achieving disease modification and long-term remission. Future advancements in personalized immunomodulation are expected to improve therapeutic outcomes for refractory autoimmune diseases.

Keywords: autoimmune disease; therapeutic antibody; immune complexes; Fc gamma receptors; cytokines

1. Introduction

Under physiological conditions, the immune system maintains homeostasis through precise discrimination between "self" and "non-self": T cells undergo negative selection in the thymus to eliminate autoreactive clones, while B cells achieve central tolerance through receptor editing and clonal deletion [1]. The human immune system establishes a multi-layered defense network through the coordinated action of innate and adaptive immunity. The innate immune system (neutrophils, macrophages, etc.) rapidly recognizes pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs), triggering nonspecific inflammatory responses [2,3]; adaptive immunity (T/B lymphocytes) achieves precise recognition through antigen-specific receptors (TCR/BCR) and forms an immune memory. After differentiating into plasma cells, B cells secrete antibodies (immunoglobulins, Ig), which eliminate antigens by neutralizing pathogens, activating the complement system, and facilitating phagocytosis through opsonization [1]. Immune homeostasis is maintained through central tolerance (thymic/bone marrow negative selection) and peripheral tolerance (regulatory T cells/Tregs, PD-1/CTLA-4 inhibitory signals), ensuring immune quiescence against self-antigens [4–6]. However, when the immune system becomes abnormally activated, this control over self-antigens is lost, disrupting immune homeostasis and leading to chronic inflammatory diseases characterized by attacks on self-tissues.

Genetic predisposition [7], environmental triggers [8], and microbiome dysbiosis [9] can break immune tolerance, allowing autoreactive lymphocytes to escape to the periphery. Upon exposure to autoantigens, these aberrantly activated B cells differentiate into plasma cells that produce autoantibodies targeting nuclear components, cell-surface receptors, or intracellular enzymes. Subsequent tissue injury occurs through complement activation, immune complex deposition, and Fc receptor-mediated inflammatory responses [10,11]. Concurrently, autoreactive T cells recognizing either modified self-antigens or molecular mimics of self in peripheral tissues

become activated, enabling them to directly kill target cells or provide help to B cells for autoantibody production, thereby driving autoimmune disease pathogenesis.

Notably, cytokines play a vital role in maintaining autoantibodies production by B cells. Cytokines facilitate B cells in producing autoantibodies through a complex network of interactions primarily involving T follicular helper (Tfh) cell–derived cytokines such as IL-21 and IL-4, and innate cytokines like IL-6 and BAFF (B-cell activating factor). IL-21, secreted by Tfh cells, promotes germinal center B cell proliferation, class-switch recombination to pathogenic autoantibody isotypes, and plasma cell differentiation by activating key transcription factors. IL-4, produced by Tfh and Th2 cells, supports class switching to IgG1 and IgE and enhances the survival and activation of autoreactive B cells. IL-6 plays a pivotal role indirectly by inducing IL-21 production from CD4+ T cells, which further sustains germinal center formation and autoantibody generation. BAFF, produced by myeloid and dendritic cells, binds B cell receptors to promote survival and maturation of autoreactive B cells and plasma cells, sustaining long-lived autoantibody production. This cytokine network creates amplification loops that skew immune balance toward pathogenic autoantibody production, with dysregulation at any point potentially leading to the chronic inflammation characteristic of autoimmune diseases. In addition to receiving these cytokine signals, B cells themselves can produce cytokines that modulate immune responses, further influencing autoimmunity dynamics. Targeting these cytokines represents a strategic approach to interrupting pathological autoantibody generation in autoimmune conditions.

2. From Immune Complexes to Inflammatory Cascades

Autoimmune tissue damage arises from a self-amplifying loop of immune complex deposition, complement activation, and Fc gamma receptors (FcγR) signaling, ultimately leading to dysregulated cytokine production. The inflammatory cascade begins when immune complexes (ICs), formed by autoantibodies binding self-antigens, deposit in tissues, activating complement and engaging FcγR on myeloid cells. C5a enhances FcγR-mediated inflammation by recruiting neutrophils and upregulating FcγR III expression [12,13], while defective complement regulation exacerbates IC deposition (Figure 1).

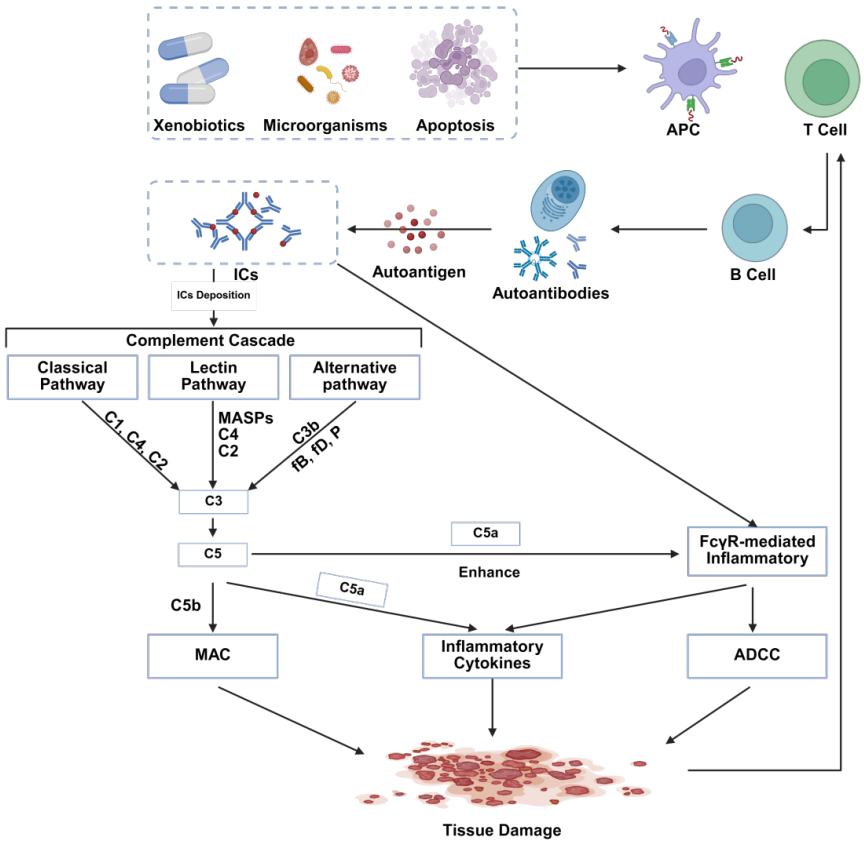

Figure 1. Mechanism of Autoimmune Disease. The immune system's intolerance to its molecules, cells, or tissues, cross-reactions caused by foreign antigens, and changes caused by drugs or environmental factors will lead to the production of self-antigens, which are then presented to T cells by Antigen-presenting cells (APC). Plasma cells

secrete IgG antibodies, which bind to self-antigens to form ICs. After ICs are deposited, they can activate the complement cascade reaction, forming a membrane attack complex (MAC), leading to cell lysis. At the same time, ICs bind to FcγR, enhance FcγR-mediated inflammatory response, release inflammatory cytokines, and further aggravate tissue damage. Some inflammatory factors promote T cell differentiation, further enhancing the release of inflammatory cytokines.

2.1. Immune Complex Deposition

Autoantibodies (predominantly IgG/IgM) produced by B cells form ICs upon binding to self-antigens. These ICs deposit in tissues where they simultaneously activate both the complement cascade and Fc receptor-mediated inflammatory pathways [14]. The deposition process is further facilitated by hemodynamic factors (such as glomerular hypertension and vascular branch turbulence) and local receptor expression (including C3b receptors on renal endothelial cells), which promote preferential ICs accumulation in target organs like kidneys and joints [15].

The pathogenic mechanisms involve the Fc regions of IgG/IgM-antigen complexes activating the classical complement pathway while simultaneously engaging FcγR on myeloid cells. This dual activation triggers phagocytosis and inflammatory cell activation [16]. Importantly, autoantibody-mediated tissue damage typically requires the cooperative action of both Fc receptor and complement pathways, with their synergistic interaction resulting in amplified inflammatory responses and more severe tissue injury.

2.2. Complement Activation and Membrane Attack Complex (MAC) Formation

2.2.1. Classical Pathway Activation

Immune complex deposition is influenced by multiple factors, including antigen-antibody ratio, hemodynamic conditions, and local tissue characteristics [14]. When these complexes deposit along basement membranes or vascular walls, they initiate the classical complement pathway through sequential activation steps: C1q binds to the Fc regions of IgG/IgM, triggering cleavage of C4 and C2 to form the C3 convertase (C4b2b). This enzyme then activates C3 and C5, generating the anaphylatoxins C3a and C5a, and ultimately leading to the formation of the membrane attack complex (MAC, C5b-9) [17,18]. C5a acts as a potent chemoattractant for inflammatory cells while simultaneously upregulating FcγR expression on monocytes, enhancing their phagocytic capacity for ICs, and promoting the release of pro-inflammatory cytokines like IFN-α. This creates a positive feedback loop that stimulates plasma cells to produce additional autoantibodies [19]. C3b facilitates immune complex clearance through binding to CR1 receptors on erythrocytes. However, in autoimmune diseases, dysfunction of complement regulatory proteins (CD55, CD59) impairs this clearance mechanism, exacerbating tissue deposition [20]. The MAC forms transmembrane pores that disrupt osmotic balance, leading to target cell lysis. While crucial for host defense against pathogens, excessive MAC activation causes significant tissue damage [21].

2.2.2. Alternative Pathway Activation

In addition to the classical pathway, the alternative pathway contributes significantly to complement activation in autoimmune diseases. This pathway is continuously active at a low level via spontaneous hydrolysis of C3 ("tick-over"), resulting in the formation of an alternative C3 convertase (C3bBb) that amplifies complement activation independently of antibodies [22]. In C3 glomerulopathy (C3G), autoantibodies called C3 nephritic factors (C3NeFs) stabilize the C3 convertase, preventing its normal degradation. This stabilization leads to persistent complement activation on glomerular surfaces, causing inflammation and structural damage [23]. Clinically, this results in proteinuria and progressive kidney dysfunction, characteristic of C3G.

2.2.3. Lectin Pathway Activation

The lectin pathway is initiated by pattern recognition molecules such as mannose-binding lectin (MBL), which bind pathogen-associated or altered self-structures. MBL-associated serine proteases (MASPs), primarily MASP-2, become activated upon MBL binding, cleaving C4 and C2 similarly to the classical pathway to form C3 convertase [22]. In IgA nephropathy (IgAN), aberrant glycosylation of IgA1 leads to deposition in the mesangium, triggering lectin pathway activation through MBL recognition. This promotes local complement activation, inflammation, and subsequent glomerular injury [24]. Clinically, lectin pathway activity correlates with disease severity and progression in IgAN.

2.3. Fc Receptor-Mediated Inflammatory Amplification and Regulatory Imbalance

FcγR plays a dual regulatory role in inflammatory responses by recognizing the Fc portion of ICs [25]. The maintenance of immune homeostasis critically depends on the dynamic equilibrium between activating receptors and inhibitory receptors (FcγRIIB). Under pathological conditions, cross-linking of platelet-expressed FcγRIIA by ICs triggers platelet degranulation via αIIbβ3 integrin signaling, leading to the release of inflammatory mediators such as serotonin (5-HT) and platelet factor 4 (PF4). This cascade can induce systemic inflammatory responses that are clinically significant in conditions ranging from anaphylactic shock to rheumatoid arthritis-associated vasculitis [26,27]. Importantly, genetic polymorphisms in FcγRIIB are frequently observed in systemic lupus erythematosus (SLE) patients and result in impaired inhibitory function, causing B-cell hyperactivation and subsequent overproduction of autoantibodies, establishing a self-perpetuating pathological feedback loop [28].

Complement-derived inflammatory mediators, particularly C3a and C5a, serve to amplify FcγR-mediated inflammatory responses [29]. C5a exhibits multifaceted effects, as it not only recruits neutrophils and monocytes to inflammatory sites but also modulates FcγR expression patterns on immune cells, thereby enhancing their responsiveness to immune complexes (ICs) [30,31]. Emerging evidence indicates that the interaction between C5a and its receptor C5aR (CD88) plays a pivotal role in fine-tuning the balance between FcγR activation and inhibition, creating an intricate bidirectional regulatory network that coordinates inflammatory responses [32].

2.4. T Cell-Driven Autoimmunity

2.4.1. Dysregulation of T Cell Tolerance and Autoimmune Activation

T cells are central regulators of immune tolerance, responsible for distinguishing self from non-self while preventing autoimmune responses. Following hematopoiesis, T cell progenitors migrate from the bone marrow to the thymus, where they undergo a tightly regulated developmental program. Initially, double-negative ($CD4^-CD8^-$) thymocytes differentiate into double-positive ($CD4^+CD8^+$) cells. Through the processes of positive and negative selection mediated by thymic epithelial cells, T cells bearing T cell receptors (TCRs) with low affinity for self-peptide–MHC complexes survive and mature into single-positive $CD4^+$ or $CD8^+$ T cells. These mature T cells then enter the peripheral circulation as part of the naïve T cell pool. However, central tolerance is imperfect, and some autoreactive T cells escape thymic deletion and populate peripheral tissues [33].

In the periphery, such autoreactive T cells can encounter autoantigens, which may be native self-proteins, modified self-antigens, or molecular mimics of self-derived from pathogens. Upon activation, these T cells contribute to the breakdown of immune regulation, migrate to target organs, and mediate tissue destruction. Several mechanisms facilitate activation of autoreactive T cells, including molecular mimicry (pathogen-derived peptides resembling self-antigens), bystander activation (non-specific activation during inflammation), epitope spreading (broadening of antigen specificity during chronic inflammation), and superantigen-mediated polyclonal activation (bacterial or viral superantigens triggering extensive T cell activation). The failure of both central and peripheral tolerance checkpoints underlies the pathogenesis of many autoimmune diseases [34].

2.4.2. Effector T Cell Subsets and Inflammatory Cytokine Production

T cell-mediated autoimmunity can be categorized into distinct immunophenotypic profiles based on T helper cell polarization and their signature cytokines, providing important insights into disease mechanisms and therapeutic targets. The type 1 immune polarization is characterized by Th1 and cytotoxic $CD8^+$ T cells producing IFN-γ and TNF-α, which drive tissue inflammation in diseases such as alopecia areata, where IFN-γ–producing $CD8^+NKG2D^+$ T cells are both necessary and sufficient for disease in animal models [35–37]. In vitiligo, melanocyte-specific $CD8^+$ T cells target autoantigens like TRP-1 and TRP-2 [38], with keratinocyte-derived CXCL9/10 chemokines fostering their recruitment [39].

The type 2 immune polarization involves Th17 and Th22 cells secreting IL-17, IL-21, and IL-22. Psoriasis (PsO) exemplifies this profile, with HLA-C*06:02-restricted $CD8^+$ T cells recognizing the melanocyte autoantigen ADAMTSL5 [40]. Additionally, complexes of the antimicrobial peptide LL37 and self-DNA activate plasmacytoid dendritic cells via TLR9, forming a self-perpetuating inflammatory loop [41]. Oligoclonal expansion of intraepidermal T cells and the persistence of tissue-resident memory T cells maintain disease chronicity [42].

In type 3 polarization, Th2 cells producing IL-4, IL-5, and IL-13 contribute to atopic dermatitis pathogenesis through both allergic and autoimmune mechanisms. Autoimmunity in this context is linked to responses against autologous sweat gland antigens and molecular mimicry involving microbial proteins such as *Malassezia* MGL_1304 and human keratinocyte antigens [43], which trigger autoreactive T cell and IgE responses [44].

Finally, defects in regulatory T cell (Treg) function and impaired TGF-β/IL-10 signaling underlie fibrotic autoimmune conditions like systemic sclerosis, where aberrant immune activation results in excessive collagen deposition and tissue remodeling [44]. This immunophenotypic framework not only enhances understanding of autoimmune pathogenesis but also informs targeted therapeutic strategies aimed at modulating specific T cell subsets and their cytokines.

2.4. Inflammatory Cytokines

Inflammatory cytokines play a critical role as downstream amplifiers in these pathological processes. In SLE, ICs containing nuclear antigens are captured by FcγRIIa on myeloid dendritic cells (mDC) and internalized into endosomes, where they activate TLR7/9 signaling to induce massive type I interferon-α (IFN-α) production [45]. This creates the characteristic "IFN signature" that disrupts immune tolerance [46]. Concurrently, FcγRIIIb-mediated signaling in neutrophils activates Syk and TAK1 kinases, triggering the MEK/ERK pathway and leading to reactive oxygen species (ROS) generation and neutrophil extracellular trap (NET) formation [47]. NETs not only release abundant inflammatory mediators but also expose autoantigens, further promoting autoantibody production and immune complex formation in a self-perpetuating vicious cycle [48]. SLE patients exhibit elevated levels of multiple cytokines, including IL-6, IL-1, TNF-α, IL-17, and IL-21, which collectively enhance B cell survival and T cell helper activity [46]. Similarly, in RA, ICs and cytokine networks (particularly TNF-α and IL-6) work synergistically to maintain synovial inflammation and osteoclast activation, driving progressive joint destruction [49,50].

These inflammatory cytokines function not merely as amplifiers of immune dysregulation in autoimmune diseases, but also represent crucial therapeutic targets. The clinical success of various biologics targeting IL-6, TNF-α, and IL-1β, which effectively alleviate inflammatory symptoms and delay the progression of organ damage, provides definitive evidence for their central role in disease pathogenesis. This therapeutic validation underscores the importance of cytokine networks as pivotal mediators in autoimmune disorders.

3. Targeting Inflammatory Cytokines

Inflammatory signaling is predominantly mediated by pro-inflammatory cytokines and chemokines, which activate immune cells such as Th17 cells and macrophages, while recruiting inflammatory mediators to establish a chronic inflammatory microenvironment [51]. In autoimmune diseases, dysregulated inflammatory signaling disrupts immune equilibrium and precipitates tissue injury. Therapeutic antibodies counteract these pathogenic processes by selectively targeting pro-inflammatory cytokines or their receptors, thereby suppressing aberrant immune activation and attenuating tissue injury (Figure 2).

In SLE patients (Figure 2a), B cells and T cells are abnormally activated, producing a large number of autoantibodies that bind to autoantigens released by apoptotic cells to form immune complexes. These complexes are deposited in tissues such as the kidneys and skin, inducing complement activation and local inflammation. In addition, plasmacytoid dendritic cells (pDCs) secrete large amounts of IFN-α after being stimulated by immune complexes, which in turn activates downstream interferon regulatory genes, leading to abnormal expression of multiple inflammatory factors (TNF-α, IL-6, IL-10, BAFF, etc.), further aggravating the immune activation state and forming a persistent immune inflammatory response [52]. Therapeutic antibodies targeting IFN-α inhibit the IFN-I-mediated JAK-STAT signaling pathway by blocking the binding of IFN-I to its receptor, thereby reducing the expression of inflammatory factors, immune cell activation, and tissue damage.

In PsO patients (Figure 2b), the skin's innate immune system is abnormally activated, inducing keratinocytes (KCs) and pDCs to release IFN-α/β, which in turn activates mDC to release pro-inflammatory factors such as IL-12 and IL-23. Among them, IL-12 induces Th1 cell differentiation and the production of IFN-γ and TNF-α, while IL-23 drives Th17 cells to produce inflammatory factors such as IL-17A, IL-17F, and IL-22. These cytokines can significantly promote keratinocyte proliferation and inflammation amplification [53]. Anti-TNF-α antibodies reduce inflammatory responses by blocking the activity of TNF-α. IL-12/23 dual-target antibodies block the Th1 and Th17 pathways by recognizing the common p40 subunit of IL-12 and IL-23, while antibodies targeting the IL-23 p19 subunit and the IL-17 pathway have higher specificity and sustained efficacy in inhibiting downstream inflammatory amplification links.

In patients with inflammatory bowel disease (IBD) (Figure 2c), the intestinal mucosal immune system mounts an abnormal immune response to the intestinal flora and its products, leading to persistent inflammation and tissue damage. Immune cells such as dendritic cells, macrophages, and T cells are activated, secreting large amounts of proinflammatory cytokines, including TNF-α, interleukins 12/23 (IL-12/23), and IL-17. These factors drive inflammation and intestinal wall damage [54]. Antibodies to TNF-α significantly reduce the inflammatory

response by neutralizing TNF-α. Targeting the common p40 subunit of IL-12/23, which blocks key Th1 and Th17 immune pathways, is highly effective in refractory Crohn's disease.

In ankylosing spondylitis (AS) patients (Figure 2d), mechanical stress triggers micro-injury of the attachment points, and intestinal flora imbalance and B27 misfolding jointly activate dendritic cells to secrete IL-23, driving Th17/γδT cells to release pro-inflammatory factors such as IL-17 and TNF-α, triggering attachment inflammation and synovitis; early on, RANKL upregulation leads to osteoporosis, and later, Wnt-TGF-β-Hedgehog signaling is overactivated and Sclerostin/Dkk-1 is downregulated, inducing ligament osteophyte formation and spinal ankylosis [55,56]. The inflammatory response can be significantly reduced by neutralizing TNF-α. In addition, antibodies targeting IL-17A can directly block the Th17-mediated inflammatory pathway, which can effectively relieve inflammation, improve symptoms, and delay disease progression.

In myasthenia gravis (MG) patients (Figure 2e), AChR (Acetylcholine receptor) antibodies activate the complement system, leading to the formation of the MAC. MAC inserts into the muscle cell membrane, causing damage and disruption to the postsynaptic membrane at the neuromuscular junction and reducing the number of functional AChR [57]. Complement-inhibiting antibodies specifically bind to the complement protein C5, blocking its cleavage into C5a and C5b, thereby inhibiting the formation of the MAC and reducing complement-mediated neuromuscular junction damage.

In rheumatoid arthritis (RA) patients (Figure 2f), activated $CD4^+$ T cells and synovial macrophages release a large number of inflammatory factors. TNF-α is a key initiator and amplifier of the RA inflammatory cascade. It can induce the expression of other proinflammatory cytokines (IL-1, IL-6), chemokines, adhesion molecules, and others, promoting synovial cell proliferation, angiogenesis, and bone erosion. IL-6 promotes B cell differentiation, antibody production, and Th17 cell differentiation. Ultimately, this leads to joint deformity and loss of function [58]. Anti-TNF antibodies can significantly inhibit the release of inflammatory factors and synovial cell activation, while anti-IL-6R antibodies can inhibit IL-6-mediated acute phase reactions and B cell activation.

The continuous breakthroughs in understanding inflammatory cytokines and their roles in autoimmune diseases have spurred the development and optimization of biologics that precisely target these key inflammatory pathways. This progression toward increasingly specific inhibitors reflects a deepening understanding of the exact mechanisms driving these conditions, paving the way for more personalized and effective therapeutic interventions. To better understand current treatment strategies and future research directions, we have compiled and organized therapeutic antibodies for autoimmune diseases that are either approved or in various stages of clinical research (Table 1).

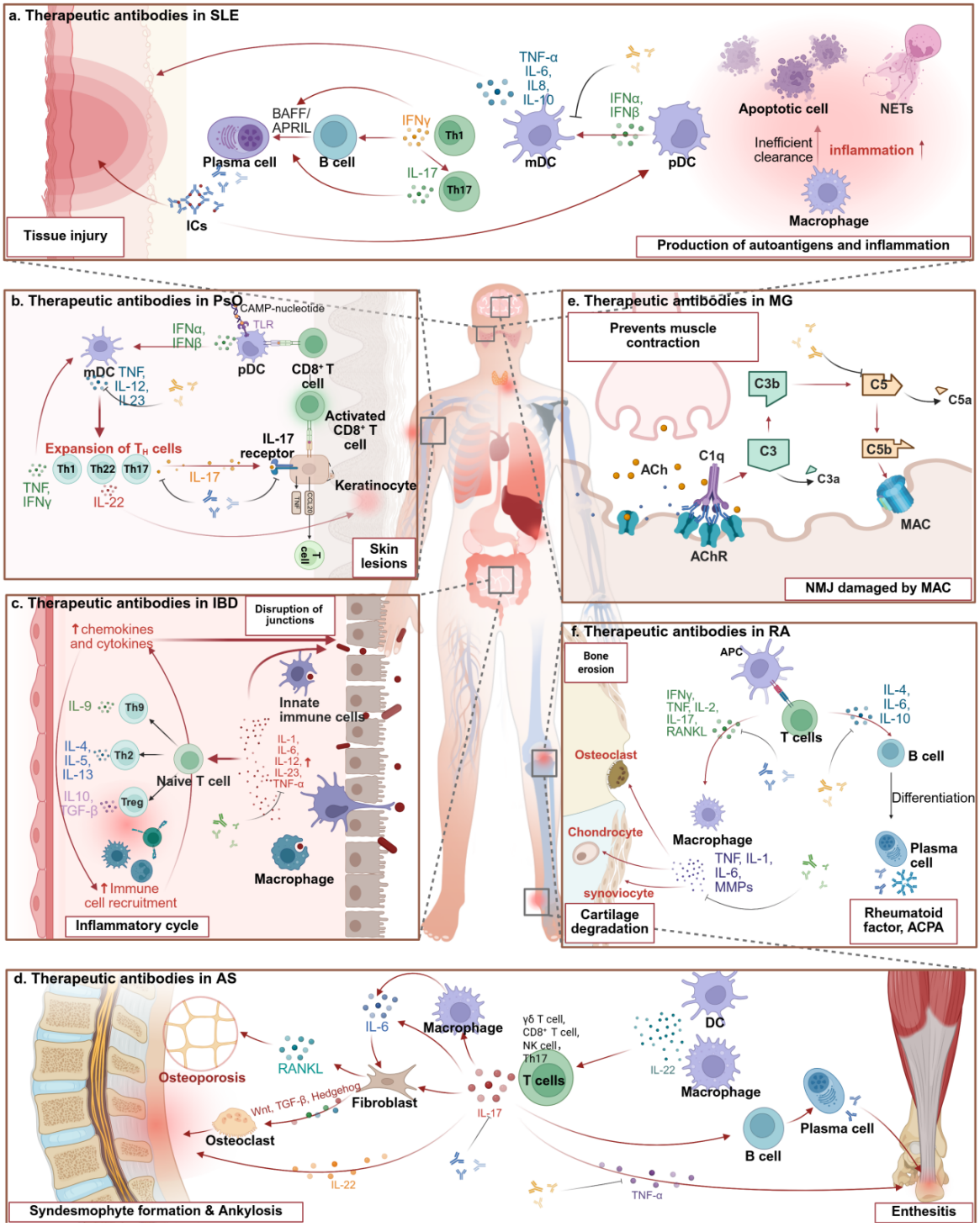

Figure 2. Targeting Inflammatory Cytokines. (**a**). In SLE, autoantibodies form immune complexes that trigger inflammation and the production of pro-inflammatory factors, which therapeutic antibodies targeting IFN-α can inhibit by blocking the JAK-STAT pathway; (**b**). In PsO, an overactive innate immune system leads to a cascade of pro-inflammatory factors (like IL-12/23 and IL-17) that promote skin cell proliferation and inflammation, which can be blocked by antibodies targeting TNF-α, IL-12/23, or IL-17; (**c**). IBD is characterized by an abnormal immune response to gut flora, leading to chronic intestinal inflammation driven by pro-inflammatory cytokines such as TNF-α and IL-12/23, which therapeutic antibodies can neutralize; (**d**). In AS, micro-injuries and immune imbalances cause inflammation at attachment points, driven by IL-23, IL-17, and TNF-α, leading to tissue damage and bone formation, which anti-TNF-α and anti-IL-17A antibodies can mitigate; (**e**). MG involves autoantibodies to acetylcholine receptors that activate the complement system, forming the MAC and damaging neuromuscular junctions, a process that can be inhibited by antibodies that block complement protein C5; (**f**). In RA, activated immune cells release inflammatory factors like TNF-α and IL-6, which are key drivers of joint inflammation, damage, and bone erosion, and can be treated with anti-TNF and anti-IL-6R antibodies.

Table 1. Therapeutic antibodies (antibody analogs) for the treatment of autoimmune diseases.

Drug Name	Target	Format	Mechanism of Action	Indications	Phase	Clinical Trial Identifier	Reference
Mepolizumab (Nucala®)	IL-5	Humanized IgG1 antibody	Targeting IL-5, blocking its binding to the IL-5 receptor on the surface of eosinophils, inhibiting the growth, differentiation, and survival of eosinophils	EGPA; CSS (Registered)	2015 (approved by the FDA)	NA	[59,60]
Tocilizumab (ACTEMRA®)	IL-6R	Humanized IgG1 antibody	Blocks IL-6-mediated inflammatory signaling pathways, reduces inflammation	RA; sJIA; pJIA; GCA	2010 (approved by the FDA)	NA	[61–63]
Sarilumab (KEVZARA®)	IL-6R	Fully human IgG1 mAb	Reduces inflammatory responses by inhibiting IL-6-mediated signaling through high-affinity binding to membrane-bound and soluble IL-6R	RA	2015 (approved by the FDA)	NA	[64]
Satralizumab (ENSPRYNG®)	IL-6R	Humanized IgG2 antibody	Inhibit the IL-6 signaling pathway and reduce the inflammatory response	NMOSD	2020 (approved by the FDA)	NA	[65,66]
Olokizumab	IL-6	Humanized IgG4κ mAb	Directly targeting IL-6 ligands rather than IL-6 receptors, inhibiting inflammatory signaling by blocking the binding of IL-6 to the receptor	RA	Registered	NCT02760368 NCT02760407 NCT02760433 NCT03120949	[67,68]
Sirukumab	IL-6R	Fully human IgG1κ mAb	Selectively blocks circulating IL-6 and inhibits downstream JAK/STAT and MAPK pathways	RA; GCA	Phase 3 (discontinued)	NCT00718718 NCT02019472	[69,70]
Secukinumab (COSENTYX®)	IL-17A	Fully human IgG1κ mAb	Specific binding to and neutralizing interleukin-17A (IL-17A), inhibiting its interaction with IL-17 receptors, thereby reducing inflammatory responses	AS; nr-axSpA; PsO; PsA	2015 (approved by the FDA)	NA	[71,72]
Ixekizumab (TALTZ®)	IL-17A	Humanized IgG4 mAb	High affinity binding to IL-17A, effectively neutralizing its inflammatory activity	AS; nr-axSpA; PsO; PsA	2016 (approved by the FDA)	NA	[73]
Brodalumab (SILIQ®)	IL-17RA	Humanized IgG2 mAb	Binds to and blocks IL-17RA, inhibiting multiple IL-17 family pathways, including IL-17A, IL-17F, IL-17E, etc.	PsO	2016 (approved by the FDA)	NA	[74]
Tibulizumab	BAFF & IL-17A	Tetravalent bispecific antibody	Dual inhibition of BAFF and IL-17A, blocking abnormal B cell activation and inflammatory factor release	SSc; RA; SjS; HS	Phase II	NCT06843239 NCT04563195	[75]
Tildrakizumab (ILUMYA®)	P19(IL-23)	Humanized IgG1κ mAb	Blocking the binding of IL-23p19 to IL-23R inhibits Th17-mediated inflammation	PsO	2018 (approved by the FDA)	NA	[76,77]
Risankizumab (SKYRIZI®)	P19(IL-23)	Humanized IgG1 mAb	Neutralizes IL-23p19 with high affinity and potently inhibits activation of the IL-23/IL-17 axis	PsO; PsA; CD	2019 (approved by the FDA)	NA	[78]
Guselkumab (TREMFYA®)	P19(IL-23)	Humanized IgG1κ mAb	Specific neutralization of IL-23p19, blocking its activation of Th17 and IL-17+ cells	PsO; PsA	2017 (approved by the FDA)	NA	[79]
Ustekinumab (STELARA®)	P40(IL-12/IL-23)	Humanized IgG1κ mAb	Blocks the common p40 subunit of IL-12 and IL-23, inhibiting the Th1/Th17 pathway	PsO; PsA; UC; CD	2009 (approved by the FDA)	NA	[80]
Anifrolumab (SAPHNELO®)	IFNAR1	Fully human IgG1κ mAb	Block the signal transduction of type I interferons (such as IFN-α, IFN-β) and inhibit the immune-inflammatory response mediated by them	SLE	2021 (approved by the FDA)	NA	[81,82]

Table 1. *Cont.*

Drug Name	Target	Format	Mechanism of Action	Indications	Phase	Clinical Trial Identifier	Reference
Emapalumab (GAMIFANT®)	IFN-γ	Humanized IgG1 mAb	Neutralizes free IFN-γ, inhibiting its-induced macrophage activation, IL-12/IL-18 signaling, and excessive inflammation	HLH	2018 (approved by the FDA)	NA	[83]
Dazukibart	IFN-β	Fully human IgG1 mAb	It specifically binds to and neutralizes IFN-β, blocks the JAK-STAT pathway initiated by IFNAR1/2, and inhibits interferon-induced inflammatory gene expression.	DM	Phase II	NCT03181893	[84]
Canakinumab (ILARIS®)	IL-1β	Fully human IgG1κ mAb	Blocking the binding of IL-1β to its receptors, inhibiting downstream inflammatory signaling pathways (such as NF-κB), reducing the release of pro-inflammatory factors, and thus controlling the inflammatory response	AOSD; CAPS; FMF; JRA	2009 (approved by the FDA)	NA	[85]
AMG 108	IL-1R1	Fully humanized IgG2κ mAb	Binds to IL-1R1, blocks IL-1α and IL-1β signaling, and reduces inflammatory responses	RA	Phase II (discontinued)	NCT00110942	[86]
Infliximab (REMICADE®)	TNF-α	Chimeric murine/human mAb	Binds to TNF-α with high affinity, neutralizes soluble and membrane-bound TNF-α, blocks its receptor binding, and induces apoptosis of TNF-α-producing cells.	AS; BS; CD; PsO; PsA; RA; UC	1998 (approved by the FDA)	NA	[87–89]
Adalimumab (HUMIRA®)	TNF-α	Fully human IgG1 mAb	Binds to TNF-α and blocks its binding to the receptor, acting on both soluble and membrane-bound forms of TNF-α.	RA; AS; PsA; CD; UC; PsO; JIA; HS; UV	2002 (approved by the FDA)	NA	[90,91]
Golimumab (SIMPONI®)	TNF-α	Fully human IgG1κ mAb	Binds to soluble and transmembrane TNF-α, blocking its interaction with receptors, thereby inhibiting TNF-α-mediated inflammation.	RA; AS; PsA; UC	2009 (approved by the FDA)	NA	[92,93]
Certolizumab pegol (CIMZIA®)	TNF-α	PEGylated humanized Fab' antibody fragment	Binds to soluble and membrane-bound TNF-α, neutralizes TNF-α activity (no Fc region, does not induce ADCC or CDC effects).	RA; AS; PsO; CD; nr-axSpA	2008 (approved by the FDA)	NA	[94]
Eculizumab (SOLIRIS®)	C5	Humanized IgG2/κ mAb	Specifically binds to complement protein C5, inhibiting its cleavage into C5a and C5b-9, thereby blocking complement-mediated inflammatory response and cell damage	MG; NMP/NMOSD	2007 (approved by the FDA)	NA	[95,96]
Ravulizumab (ULTOMIRIS®)	C5	Humanized IgG2/4 mAb	Specifically binds to complement protein C5, inhibiting its cleavage into C5a and C5b-9, thereby blocking complement-mediated inflammatory response and cell damage	gMG; NMOSD	2018 (approved by the FDA)	NA	[97–99]
Gefurulimab	C5	Bispecific mini antibody	Combines complement protein C5 and human serum albumin (HSA), inhibits activation of the terminal complement pathway by blocking C5 cleavage, and reduces inflammatory damage	MG	Phase III	NCT05556096 NCT06607627	[100]

Table 1. *Cont.*

Drug Name	Target	Format	Mechanism of Action	Indications	Phase	Clinical Trial Identifier	Reference
Avdoralimab	C5aR1/CD88	Fully humanized IgG1 mAb	Inhibiting the C5a-mediated inflammatory signaling pathway by blocking the binding of C5a to C5aR1	BP	Phase II	NCT04563923	[101]
Ordesekimab	IL-15	Fully humanized IgG1κ mAb	Specific binding to IL-15, inhibiting its interaction with IL-2Rβ and γ chain (common γ chain), thereby blocking IL-15-mediated pro-inflammatory signaling and reducing inflammatory responses	Celiac Disease	Phase II (discontinued)	NCT04338581 NCT03439475	[102]
Otilimab	GM-CSF	Fully human IgG1 mAb	Block the binding of GM-CSF to its receptor, inhibiting inflammatory signal transduction	RA	Phase III (discontinued)	NCT04333147	[103]
Namilumab	GM-CSF	Humanized IgG1κ mAb	Prevents GM-CSF from binding to the cell surface receptor GM-CSFR. Inhibits GM-CSF-mediated signaling to prevent inflammation	RA	Phase II	NCT02129777 NCT02379091	[104]
ASK8007	Osteopontin	Humanized IgG1 mAb	Specifically binds to osteopontin and inhibits its interaction with cell surface receptors (such as CD44, integrin αvβ3), thereby blocking the activation of downstream NF-κB and MAPK signaling pathways, reducing the release of pro-inflammatory factors (such as IL-6, TNF-α), and osteoclast differentiation	RA	Phase II (discontinued)	NCT00411424	[105,106]
Sibeprenlimab	APRIL/TNFSF13	Fully humanized IgG2 mAb	Neutralizes the activity of APRIL and blocks its binding to B cell surface receptors (BCMA/TACI), thereby inhibiting the production of pathogenic galactose-deficient IgA1 (Gd-IgA1) and the deposition of ICs in the kidneys	IgAN	Phase III	NCT04287985 NCT05248659 NCT05248646	[107]

3.1. Targeting Cytokines and Their Receptors

Inflammatory cytokines and their receptors are central regulators of immune signaling pathways that orchestrate autoimmune pathology. Therapeutic antibodies designed to selectively neutralize these molecules aim to disrupt pathological inflammatory cascades, thereby mitigating tissue damage and clinical symptoms. This section provides a focused overview of key cytokine targets—such as IL-6, IL-17, IL-12/23, interferons, TNF-α, and IL-1—highlighting their biological functions, mechanisms of involvement in autoimmunity, and the therapeutic advances achieved through antibody-based interventions.

3.1.1. Interleukin-6

IL-6 represents a pleiotropic pro-inflammatory cytokine with critical functions in immune regulation, secreted by diverse cell types including T cells, macrophages, and fibroblasts [108]. This multifunctional molecule plays pivotal roles in B cell maturation, acute phase response modulation, and T cell differentiation pathways [109]. In pathological conditions, dysregulated IL-6 overexpression activates the JAK/STAT3 signaling cascade, driving sustained inflammatory responses that contribute significantly to the pathogenesis of various autoimmune disorders, including RA, SLE, and Still's disease (SD) (Figure 2) [110,111].

Clinical validation of IL-6 pathway inhibition has been firmly established through therapeutic antibodies targeting either IL-6 or its receptor. The anti-IL-6 receptor monoclonal antibody Tocilizumab (Table 1) has demonstrated remarkable clinical efficacy across multiple indications, including RA, juvenile idiopathic arthritis (JIA), SD, and giant cell arteritis (GCA) [112]. Tocilizumab demonstrates rapid efficacy in RA patients, normalizing C-reactive protein (CRP) levels within two weeks of treatment initiation and significantly alleviating synovitis and systemic inflammation [62]. Other notable therapeutic agents in this class include Sarilumab and Satralizumab (Table 1). Clinical experimental evidence shows that Salirumab treatment significantly improves the ACR20/50/70 response rate of RA patients, and the therapeutic effect can be maintained in long-term follow-up [113]. These biological agents exert their therapeutic effects through precise blockade of IL-6-mediated signaling, effectively interrupting the downstream inflammatory cascade, reducing production of inflammatory mediators, and consequently improving clinical symptoms and disease outcomes.

3.1.2. Interleukin-17

The IL-17 cytokine family, particularly IL-17A, is primarily secreted by Th17 cells, γδ T cells, and group 3 innate lymphoid cells (ILC3s) [114], playing a pivotal role in neutrophil recruitment and induction of downstream pro-inflammatory mediators including IL-6, IL-8, and G-CSF [115,116]. Substantial clinical evidence has established that aberrant IL-17 production is critically involved in the pathogenesis of multiple autoimmune disorders such as multiple sclerosis (MS), Hashimoto's thyroiditis (HT), SLE, RA, and PsO (Figure 2). This mechanistic understanding has positioned the IL-17 signaling axis as an important therapeutic target in autoimmunity [117].

Clinically approved biologic agents targeting this pathway include the IL-17A-specific monoclonal antibodies Secukinumab and Ixekizumab, along with Brodalumab (Table 1), which targets the IL-17 receptor A. Clinical trials have demonstrated these agents' remarkable efficacy in ameliorating cutaneous manifestations and joint inflammation in PsO, Psoriatic Arthritis (PsA), and AS, while maintaining favorable safety profiles. For example, Secukinumab directly neutralizes IL-17A, achieving a ≥75% improvement in PsO Area and Severity Index (PASI75) scores in over 60% of PsO patients after 12 weeks of therapy [118]. Ongoing investigations are exploring the therapeutic potential of IL-17 inhibition in other autoimmune conditions, including Sjögren's syndrome (SjS) and SLE. Treatment with these biologics typically results in a significant reduction of inflammatory markers and stabilization of disease activity, highlighting their value as targeted therapeutic options in immune-mediated inflammatory diseases.

3.1.3. IL-12/23

The interleukin-23 (IL-23) cytokine is a pivotal regulator of immune-mediated inflammatory disorders, primarily secreted by activated macrophages and dendritic cells in inflamed tissues and is a heterodimer composed of a unique p19 subunit and a shared p40 subunit [119]. As a key member of the IL-12 cytokine family, IL-23 exerts its biological effects by signaling through a receptor complex that includes IL-23R and the shared IL-12Rβ1 chain, primarily on IL-23R-expressing immune cells such as T helper 17 (Th17) cells, IL-17-

producing CD8+ T cells, and certain natural killer (NK) cell subsets. This signaling activates the JAK-STAT pathway, notably involving STAT3 and STAT4, which promotes the proliferation and survival of these cells and induces the robust secretion of pro-inflammatory cytokines, most notably IL-17A, IL-17F, IL-22, IL-6, and TNF-α [120–122]. These mechanisms establish IL-23 as a master regulator in the initiation and perpetuation of various immune-mediated inflammatory disorders, including PsO, PsA, and IBD (Figure 2) [119].

IL-12, a heterodimer of the p35 and p40 subunits, is crucial for the differentiation of naive T cells into Th1 cells. While IL-12 plays a distinct role, its shared p40 subunit links it directly to IL-23 [123]. The involvement of both IL-12 and IL-23 in different yet sometimes overlapping inflammatory processes highlights their complex interplay in autoimmune pathology. For instance, in PsO, while the IL-23/IL-17 axis is considered the central driver, the Th1 axis can also contribute to the inflammatory milieu [124]. The nuanced understanding of these distinct yet interconnected pathways has been crucial for developing targeted therapeutic strategies.

Therapeutic targeting of IL-23 has been realized through distinct antibody strategies: Ustekinumab, which neutralizes the shared p40 subunit of both IL-12 and IL-23, and newer generation p19-specific inhibitors, including Guselkumab, Risankizumab, and Tildrakizumab **(**Table 1) [125]. Clinical validation of this approach is evidenced by Ustekinumab's approval for moderate-to-severe PsO and Crohn's disease (CD), while emerging p19-specific biologics have demonstrated superior efficacy compared to anti-TNF and anti-IL-17 therapies in both PsO and PsA [126]. The IL-23/IL-17 axis inhibitors collectively represent a transformative therapeutic strategy [121], offering significant alleviation of target organ inflammation and addressing the clinical heterogeneity characteristic of autoimmune disorders through precise immunomodulation.

The pivotal roles of IL-12 and IL-23 in chronic inflammation have led to the development of targeted therapeutic antibodies. Early strategies, such as Ustekinumab **(**Table 1), block the shared p40 subunit of both IL-12 and IL-23. By doing so, Ustekinumab simultaneously modulates both the Th1 and Th17 pathways, which have proven effective in conditions like moderate-to-severe PsO and Crohn's disease (CD) [127]. This dual inhibition addresses the involvement of both axes in the disease pathology.

Highly selective inhibitors like Guselkumab, Risankizumab, and Tildrakizumab **(**Table 1) specifically target the p19 subunit unique to IL-23. These agents offer a more precise immunomodulation by exclusively inhibiting the IL-23/IL-17 axis without affecting the IL-12/Th1 pathway [125]. This selectivity has shown significant clinical advantages; these p19-specific biologics have demonstrated superior efficacy in achieving and maintaining high levels of skin clearance in PsO and favorable outcomes in PsA compared to broader anti-TNF and even anti-IL-17 therapies [126]. Furthermore, by avoiding inhibition of the beneficial IL-12/Th1 pathway, these p19 inhibitors may offer a more favorable safety profile, particularly regarding the risk of certain infections.

Therapeutic antibodies have been developed targeting either the shared p40 subunit of both IL-12 and IL-23 (Ustekinumab) or the IL-23–specific p19 subunit (Guselkumab, Risankizumab, Tildrakizumab). While Ustekinumab has been clinically validated and approved for moderate-to-severe PsO and CD, the next-generation p19-specific antibodies demonstrate superior efficacy and better safety profiles by selectively inhibiting IL-23 without affecting IL-12 pathways. Collectively, inhibitors of the IL-23/IL-17 axis represent a transformative therapeutic advance, providing precise immunomodulation that significantly alleviates target organ inflammation and addresses the clinical heterogeneity seen in autoimmune disorders.

3.1.4. Interferon

The interferon family, comprising type I (IFN-α/β), type II (IFN-γ), and type III (IFN-λ1/2/3) interferons, plays a dual role in autoimmune disease pathogenesis. IFN-γ, primarily secreted by Th1 cells, NK cells, and CD8+ T cells, promotes macrophage activation and major histocompatibility complex (MHC) expression while modulating autoreactive lymphocyte and accessory cell function in certain autoimmune conditions [128,129]. However, excessive IFN-γ production in hyperinflammatory states like hemophagocytic lymphohistiocytosis (HLH) exacerbates disease severity, leading to the 2018 FDA approval of Emapalumab (Table 1), an anti-IFN-γ monoclonal antibody for refractory primary HLH [130]. Conversely, in SLE, type I interferon signaling drives disease activity, a mechanism targeted by the 2021-approved anti-IFNAR1 monoclonal antibody Anifrolumab (Table 1) for moderate-to-severe cases [82]. Current research is exploring additional antibodies targeting the type I interferon pathway, such as IFN-β-neutralizing or IFNAR-blocking antibodies, for potential applications in DM and macrophage activation syndrome (MAS), representing a promising therapeutic approach for refractory autoimmune disorders through selective blockade of distinct pro-inflammatory pathways. For example, a Phase 2 trial demonstrated that Dazukibart, a monoclonal antibody targeting IFN-β, significantly reduced disease activity in adults with DM, particularly those with skin-predominant disease, and was generally

well tolerated [84]. Type III interferons exhibit context-dependent roles in autoimmunity, driving pathogenesis in diseases, such as SLE and RA, through Th1 polarization [131], chemokine-mediated leukocyte recruitment [132], and amplification of inflammation [133].However, they exert protective effects in IBD by maintaining epithelial integrity [134]. Although pegylated interferon lambda (PEG-IFN-λ) has been extensively studied in antiviral clinical trials, such as NCT01204762 for chronic hepatitis B and NCT04724924 for COVID-19, selective targeting of IFN-λ isoforms or its receptor IFNLR1 in autoimmune diseases remains in early development. To date, no antibodies directly inhibiting IFN-λ or IFNLR1 have received regulatory approval or advanced to early or late-stage clinical trials for autoimmune disorders. Current strategies rely on indirect approaches like JAK inhibitors, such as baricitinib (approved for RA and under investigation for SLE), that broadly suppress cytokine signaling but lack specificity. This underscores the critical need to develop isoform-selective anti-IFN-λ antibodies, enabling precise intervention in IFN-λ-driven pathologies, such as SLE, RA, while preserving its barrier-protective functions and minimizing systemic immunosuppression. Overcoming challenges in tissue-specific delivery (limited IFNLR1 expression) and functional duality (pro-inflammatory vs. protective) will be essential for translating targeted IFN-λ blockade into safe, effective therapies. These developments highlight the growing precision in immunomodulatory strategies, where targeted interferon inhibition can address specific pathological mechanisms while minimizing broad immunosuppression.

3.1.5. Tumor Necrosis Factor-α

TNF-α, a classical pro-inflammatory cytokine primarily secreted by activated macrophages and T cells, mediates tissue damage through TNFR1/2-dependent activation of NF-κB and MAPK signaling pathways [135]. This process triggers the release of secondary inflammatory mediators (IL-1, IL-6, IL-8) that promote leukocyte infiltration and tissue destruction, positioning TNF-α as a central driver in RA, IBD, PsO, and other autoimmune disorders (Figure 2) [136,137]. The clinical translation of TNF-α inhibition has been systematically realized through five approved biologics: the monoclonal antibodies Infliximab, Adalimumab, Golimumab, and Certolizumab pegol (Table 1), alongside the TNF receptor-Fc fusion protein Etanercept. These agents demonstrate broad therapeutic efficacy across multiple immune-mediated conditions, including AS, PsA, CD, ulcerative colitis (UC), non-infectious uveitis, and JIA [138].

Miserocchi et al. documented effective disease control within one year in 23 Golimumab-treated uveitis patients, predominantly with Behçet's disease or RA complications [139]. Notably, Certolizumab pegol exhibits unique advantages in pregnancy, two cases of Cogan's syndrome (autoimmune ocular/aural inflammation), showed sustained disease remission with 400 mg monthly (tapered to 200 mg biweekly) without fetal malformations or postpartum relapse, while maintaining compatibility with breastfeeding [140]. The SONIC (Study of Biologic and Immunomodulator-Naive Patients in Crohn's Disease) trial further demonstrated superior outcomes with Infliximab-azathioprine combination therapy in moderate-to-severe CD, achieving higher clinical response rates, steroid-free remission, and enhanced mucosal healing compared to monotherapy [115,141,142]. These findings underscore the precision of cytokine/receptor-targeted strategies in disrupting inflammatory cascades. These findings collectively validate TNF-α blockade as a versatile strategy in autoimmune management, with differential agent properties enabling context-specific applications, particularly Certolizumab's pregnancy safety profile, while combination regimens may optimize therapeutic depth in refractory cases.

3.1.6. IL-1

The IL-1 cytokine family, particularly IL-1α and IL-1β released primarily by mononuclear phagocytes, represents a potent class of proinflammatory mediators capable of inducing fever and stimulating production of downstream inflammatory factors, including IL-6 [143,144]. These cytokines play a central pathological role across various autoimmune and autoinflammatory disorders such as rheumatic diseases, adult-onset Still's disease (AOSD), and familial Mediterranean fever (FMF) [145]. Therapeutic targeting of IL-1 signaling has been successfully achieved through several biologic agents: the recombinant IL-1 receptor antagonist Anakinra, the human anti-IL-1β monoclonal antibody Canakinumab (Table 1), and the fusion protein Rilonacept [146]. Extensive clinical trials and observational studies have established the efficacy of these IL-1 inhibitors in various periodic fever syndromes, AOSD, and RA. For example, in a study involving 21 AOSD patients, Canakinumab significantly reduced inflammatory indicators such as fever, joint pain, and CRP, with a complete remission rate of 67% and no serious adverse reactions observed [147]. The IL-1 blockade strategy demonstrates a favorable safety profile, with injection site reactions and mild infections being the most reported adverse effects, while providing substantial clinical benefits through effective inflammation control in affected patients [148].

3.2. Inhibition of Chemokines and Their Receptors

Chemokine receptors, members of the G protein-coupled receptor (GPCR) superfamily, play pivotal roles in orchestrating immune cell migration to inflammatory sites under both physiological and pathological conditions [149].

In PsO, IL-17A stimulates epidermal KCs to secrete CCL20, recruiting CCR6+ Th17 cells to lesional skin and amplifying inflammation [150]. Although antibody-based therapies targeting chemokines remain investigational, the CCL20/CCR6 axis emerges as a promising therapeutic target. Anti-TNF-α antibody Infliximab significantly suppresses regional CCL20 induction, demonstrating therapeutic potential in PsO [151]. Furthermore, anti-CCL20 antibody treatment in IL-23-induced psoriatic dermatitis models reduces CCR6+ T cell infiltration and attenuates dermal thickening [152].

CX3CL1 (fractalkine), expressed on endothelial cells, facilitates macrophage and $CX3CR1^{+}$ T cell migration to target tissues. Luong et al. demonstrated that anti-CX3CL1 monoclonal antibodies inhibit pro-inflammatory protein expression in human dermal fibroblasts and ameliorate skin inflammation and fibrosis in systemic sclerosis (SSc) murine models [153]. Subsequent studies revealed that anti-CX3CL1 therapy suppresses cutaneous and pulmonary fibrosis in sclerodermatous chronic graft-versus-host disease (Scl-cGVHD) models without significant adverse events, accompanied by downregulation of cGVHD-associated gene clusters and reduced macrophage/T cell infiltration [154], suggesting its applicability in human fibrotic disorders like SSc.

Additionally, the CXCL12/CXCR4 axis, critical for adaptive/innate immunity and bone marrow homeostasis [155], is upregulated in autoimmune diseases. Preclinical evidence indicates that CXCL12 antagonists delay inflammatory disease onset and progression [149], positioning anti-CXCL12 antibodies as potential therapeutic candidates.

3.3. Modulation of Complement System Activity

Dysregulated complement activation is a hallmark of numerous autoimmune diseases. All activation routes converge at C5 cleavage, producing C5a (a potent chemotactic and pro-inflammatory factor) and C5b (the MAC initiator). C5a binds specific receptors on phagocytes and other cells, driving inflammatory activation [156,157], while C5b complexes with C6-C9 to form pore-like MAC structures that disrupt cell membranes, exacerbating tissue damage [158,159]. Therapeutic antibodies targeting C5 block its proteolytic processing, effectively suppressing both C5a-driven inflammation and MAC-mediated cytotoxicity (Table 1). Eculizumab, a C5 inhibitor that binds the α-subunit, prevents C5 cleavage and terminal complement activation. Clinical data from 21 refractory MG patients showed rapid improvement in MG-ADL and QMG scores within one month of Eculizumab treatment, with 57.1% achieving “minimal symptom status” and a >90% reduction in acute exacerbations over 12 months [160,161]. Ravulizumab, a C5-targeted antibody engineered with Fc modifications to extend its half-life to ~49.7 days, enables dosing every eight weeks instead of biweekly, enhancing patient compliance [97]. Two Phase III trials demonstrated Ravulizumab’s non-inferiority to Eculizumab in endpoints such as transfusion avoidance and lactate dehydrogenase (LDH) normalization, alongside a lower risk of breakthrough hemolysis [161–163]. These advances underscore the therapeutic potential of complement modulation in autoimmune disorders.

The complexity of autoimmune diseases lies not only in the abnormalities of individual mediators, but also in the intricate interactions and feedback loops between these key cytokines, chemokines, and complement components that collectively drive and maintain chronic inflammation and tissue damage (Figure 3).

IL-6 acts on immune cells through classical, trans-signaling, and trans-presentation/cluster signaling pathways, and activates JAK/STAT3 through gp130, causing T cells to differentiate into Th17 and produce IL-17 [164]. It also promotes the differentiation of B cells into plasma cells and the production of acute-phase proteins [165]. IL-17A is secreted by Th17 and some innate immune cells, which can induce target cells to produce inflammatory factors such as IL-6, TNF-α, IL-1β, and various chemotactic molecules, thereby amplifying the inflammatory response [166]. IL-6 enhances Th17 differentiation to produce IL-17, and IL-17 amplifies IL-6 production, forming a positive feedback loop [167]. Similarly, TNF-α activates NF-κB, which in turn upregulates the expression of genes such as IL-1β, IL-6, and IL-8. IL-1β also activates MyD88/IKK through its receptor, further enhancing NF-κB activity and forming a loop [168]. Therefore, classic inflammatory factors such as TNF-α and IL-1β often promote each other, driving macrophages and endothelial cells to continuously secrete inflammatory mediators, leading to tissue destruction. IL-12/23 shares the p40 subunit. IL-12 mainly promotes Th1 cell differentiation and IFN-γ production through STAT4, while IL-23

mainly promotes Th17 cell maintenance and IL-17 release through STAT3, and can partially activate STAT4 to enhance inflammation [166,169].

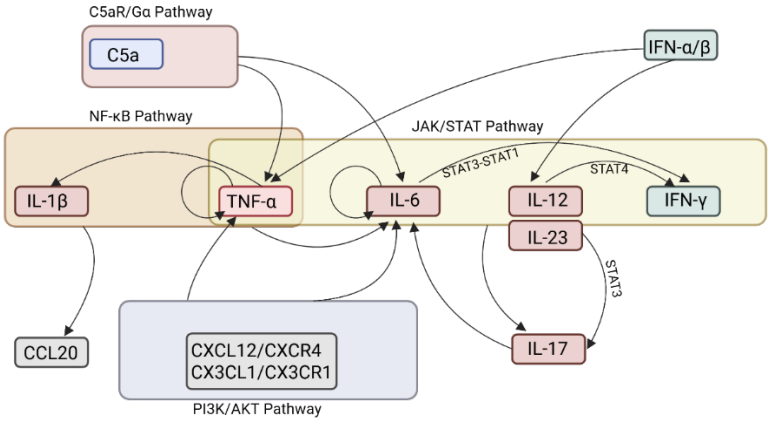

Figure 3. Cross-regulation between Inflammatory Cytokines. In autoimmune inflammation, various cytokines and chemokines interact to form a complex positive feedback network, maintaining chronic inflammation.

In addition, IFN-α/β is secreted by plasmacytoid dendritic cells and primarily enhances humoral immunity and inflammatory responses by inducing BAFF, promoting Th1 differentiation, and synergizing with IL-6/TNF-α [170]. IFN-γ is secreted by Th1/NK cells, activates macrophages, and enhances MHC-II expression. On the other hand, it amplifies cell-mediated immune responses and tissue infiltration by forming a positive feedback loop with IL-12/IL-18 and TNF-α and inducing chemokines. Also, it is regulated by some cytokines in autoimmune diseases, such as IL-6, which mediates STAT3 activation, can increase expression of STAT1, thereby enhancing IFN-γ response [171]. It often participates with IFN-α/β in autoimmune inflammatory diseases such as SLE and RA.

The complement split product C5a is a potent chemoattractant. In macrophages, C5a activates the C5aR/Gα pathway, releasing cytokines such as IL-1β and TNF, further enhancing NF-κB/MAPK signaling [172]. In γδ T cells, C5a activates the PI3K/Akt pathway and directly enhances IL-17 secretion [166]. In addition, C5a can promote the secretion of IL-1β and IL-6 by monocytes, indirectly enhancing the expression of IL-17[173].

In inflammatory sites (such as RA synovium), TNF-α, IL-1β, or IL-17 can induce synovial cells to produce CCL20, attracting CCR6^+ Th17 migration and exacerbating inflammation [174]. The CXCL12/CXCR4 and CX3CL1/CX3CR1 signal axis can amplify inflammatory responses by activating the PI3K/AKT signaling pathway. When these chemokines bind to their receptors, they initiate a PI3K-mediated signaling cascade, activating AKT [175,176]. This in turn promotes the survival, activation, and chemotaxis of immune cells and induces the release of inflammatory cytokines such as TNF-α and IL-6. Furthermore, this pathway enhances vascular permeability and the expression of adhesion molecules, promoting tissue infiltration of inflammatory cells.

4. Challenges and Future Perspectives

Therapeutic antibodies for autoimmune diseases represent a major advancement in medicine, shifting from broad-spectrum immunosuppression to more precisely targeted interventions. Currently, multiple antibodies are approved for specific autoimmune diseases, all with promising results. Despite these clinical advances, this progress is not without challenges. The human immune system is an independent, orderly ecosystem. Would simply inhibiting a single target cause further imbalance? Antibodies targeting different key targets for the same disease also have varying effects. How should we choose the right therapeutic target for a given disease? Furthermore, many patients may not fully respond to treatment (Table 2). These issues highlight the vast unmet need for more precise, targeted, and safer therapeutic interventions. Many drug candidates have shown promise in early proof-of-concept studies, but maintaining efficacy across a broad patient population while minimizing off-target immunosuppression remains a significant challenge in late-stage development. This suggests that while monoclonal antibodies represent a significant step forward in precision, their limitations in disease eradication and the potential for adverse effects with long-term use are driving the search for more durable solutions with greater potential for cure.

Table 2. Therapeutic antibodies in the treatment of autoimmune diseases.

Disease	Target	Antibody	Efficacy	Half-Life (Administration)	ADA Incidence
AS	TNF-α	Infliximab (REMICADE®)	At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 44%, and 28%, respectively, of patients receiving REMICADE, compared to 18%, 9%, and 4% respectively, of patients receiving placebo	7.7–9.5 days (IV)	NA
		Adalimumab (HUMIRA®)	At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving HUMIRA, compared to 21%, 10%, and 5% respectively, of patients receiving placebo	10–20 days (IV)	9% (16/185)
		Golimumab (SIMPONI®)	At 24 weeks, the ASAS 20/40 responses were achieved by 56% and 44%, respectively, of patients receiving SIMPONI ± DMARDs, compared to 23% and 15% respectively, of patients receiving placebo ± DMARDs	9–15 days (IV)	24% (16/338)
		Certolizumab pegol (CIMZIA)	At 12 weeks, the ASAS 20/40 responses were achieved by 42–47% and 30–37%, respectively, of patients receiving CIMZIA, compared to 20% and 11% respectively, of patients receiving placebo	Approximately 14 days (IV)	97% (248/255) in nr-axSpA patients
	IL-17A	Secukinumab (COSENTYX®)	At 16 weeks, the ASAS 20/40 responses were achieved by 61% and 36%, respectively, of patients receiving COSENTYX, compared to 28% and 11% respectively, of patients receiving placebo	22–31 days (IV/SC)	＜1%
		Ixekizumab (TALTZ®)	At 16 weeks, the ASAS 20/40 responses were achieved by 48% and 25%, respectively, of patients receiving TALTZ, compared to 30% and 13% respectively, of patients receiving placebo	Approximately 13 days (SC)	5.2%
RA	TNF-α	Infliximab (REMICADE®)	At 54 weeks, the ACR 20/50/70 responses were achieved by 62–66%, 46–50%, and 33–37%, respectively, of patients receiving REMICADE + Methotrexate (MTX), compared to 54%, 32%, and 21% respectively, of patients receiving placebo + MTX	7.7–9.5 days (IV)	10%
		Adalimumab (HUMIRA®)	At 12 months, the ACR 20/50/70 responses were achieved by 59%, 42%, and 23%, respectively, of patients receiving HUMIRA + MTX, compared to 24%, 10%, and 5% respectively, of patients receiving placebo + MTX	10–20 days (IV)	5% (58/1062)
		Golimumab (SIMPONI®)	At 24 weeks, the ACR 20/50/70 responses were achieved by 63%, 35%, and 18%, respectively, of patients receiving SIMPONI + MTX, compared to 32%, 13%, and 4% respectively, of patients receiving placebo + MTX	10–18 days (IV)	16% (59/369)
		Certolizumab pegol (CIMZIA)	At 24 weeks, the ACR 20/50/70 responses were achieved by 59%, 37%, and 21%, respectively, of patients receiving CIMZIA + MTX, compared to 14%, 8%, and 3% respectively, of patients receiving placebo + MTX	approximately 14 days (IV)	7% (105/1509)
	IL-6R	Tocilizumab (ACTEMRA®)	At 24 weeks, the ACR 20/50/70 responses were achieved by 30–50%, 17–29%, and 5–12%, respectively, of patients receiving ACTEMRA + MTX, compared to 10%, 4%, and 1% respectively, of patients receiving placebo + MTX	approximately 21.5 days (IV)	2% (57/2876)
		Sarilumab (KEVZARA®)	At 24 weeks, the ACR 20/50/70 responses were achieved by 58–66.4%, 37–45.6%, and 19.8–24.8%, respectively, of patients receiving KEVZARA + MTX, compared to 33.4%, 16.6%, and 7.3% respectively, of patients receiving placebo + MTX	8–10 days (IV)	9.2%

Table 2. *Cont.*

Disease	Target	Antibody	Efficacy	Half-Life (Administration)	ADA Incidence
PsO	TNF-α	Infliximab (REMICADE®)	At 16 weeks, 71% of patients on REMICADE achieved a PASI 75 compared with 7% on placebo.	7.7–9.5 days (IV)	NA
		Adalimumab (HUMIRA®)	At 10 weeks, 72–77% of patients on HUMIRA achieved a PASI 75 compared with 1% on placebo.	10–20 days (IV)	8% (77/920)
	IL-17RA	Brodalumab (SILIQ®)	At 12 weeks, 86% and 44% of patients on SILIQ achieved a PASI 75 and PASI 100, respectively compared with 8% and 2% on placebo.	NA	No neutralizing antibodies were detected
	IL-17A	Secukinumab (COSENTYX®)	At 12 weeks, 67–76% of patients on COSENTYX achieved a PASI 75 compared with 5% on placebo.	22–31 days (IV/SC)	＜1%
		Ixekizumab (TALTZ®)	At 12 weeks, 87%, 68% and 38% of patients on TALTZ achieved a PASI 75/90/100, respectively compared with 7%, 3% and 0% on placebo.	Approximately 13 days (SC)	9–22%
	IL-23	Guselkumab (TREMFYA®)	At 16 weeks, 73% of patients on TREMFYA achieved a PASI 90 compared with 3% on placebo.	15–18 days	6%
		Risankizumab (SKYRIZI®)	At 16 weeks, 75% and 51% of patients on SKYRIZI achieved a PASI 90 and PASI 100, respectively compared with 5% and 0% on placebo.	Approximately 28 days	24% (263/1079)
		Tildrakizumab (ILUMYA ®)	At 12 weeks, 64%, 35% and 14% of patients on ILUMYA achieved a PASI 75/90/100, respectively compared with 6%, 3% and 1% on placebo.	Approximately 23 days	6.5%
	IL-12/IL-23	Ustekinumab (STELARA®)	At 16 weeks, 67–76% of patients on STELARA achieved a PASI 90 compared with 4% on placebo.	14.9 ± 4.6–45.6 ± 80.2 days (SC)	6–12.4%
MG	C5	Eculizumab (SOLIRIS®)	A statistically significant difference favoring SOLIRIS was observed in the mean change from baseline to Week 26 in MG-ADL total scores (−4.2 points in the SOLIRIS-treated group compared with −2.3 points in the placebo-treated group)	5.875–36.75 days	No neutralizing antibodies were detected
		Ravulizumab (ULTOMIRIS®)	A statistically significant difference favoring ULTOMIRIS was observed in the mean change from baseline to Week 26 in MG-ADL total scores (−3.1 points in the SOLIRIS-treated group compared with −1.4 points in the placebo-treated group)	Approximately 56.6 days	No neutralizing antibodies were detected
CD	TNF-α	Infliximab (REMICADE®)	At Week 30, 39–46% of patients on REMICADE achieved clinical remission compared with 25% on placebo	7.7–9.5 days (IV)	10%
		Adalimumab (HUMIRA®)	At Week 26, 40% of patients on HUMIRA achieved clinical remission compared with 17% on placebo	10–20 days (IV)	3% (7/269)
		Certolizumab pegol (CIMZIA)	At Week 26, 29% of patients on HUMIRA achieved clinical remission compared with 18% on placebo	Approximately 14 days (IV)	8%
	IL-12/IL-23	Ustekinumab (STELARA®)	At Week 8, 21% of patients on HUMIRA achieved clinical remission compared with 7% on placebo	14.9 ± 4.6–45.6 ± 80.2 days (SC)	2.9%
	IL-23	Risankizumab (SKYRIZI®)	At Week 12, 42% of patients on HUMIRA achieved clinical remission compared with 20% on placebo	Approximately 21 days	3.4% (2/58)

All information comes from the FDA online label library.

4.1. Limitations of Specificity, Tissue Penetration, Immunogenicity, and Resistance Mechanisms

The development of therapeutic antibodies for autoimmune diseases confronts multiple interconnected challenges that span molecular, cellular, and clinical dimensions. At the mechanistic level, the heterogeneous nature of pathogenic immune cell populations, particularly evasive memory B cells and long-lived plasma cells, complicates target specificity, while cross-reactivity with healthy tissues risks off-target effects and unintended immunosuppression [177,178]. These limitations are compounded by physical barriers to drug delivery, as the macromolecular nature of antibodies restricts penetration into fibrotic tissues and privileged sites like the CNS, with abnormal vascular permeability further impairing target accumulation [179]. While strategies such as ADC-naked antibody combinations show promise in enhancing tissue specificity [180], they must be balanced against emerging concerns about immunogenicity, exemplified by >80% anti-drug antibody (ADA) incidence in anti-CD25 therapy for multiple sclerosis [181], and long-term safety issues including opportunistic infections and paradoxical inflammatory rebounds from over-suppression [182].

The clinical landscape reveals additional complexity, with TNF inhibitors demonstrating 10–40% primary non-response rates and 30–50% secondary resistance within one year [183,184], driven by diverse escape mechanisms from neutralizing antibodies to pathway redundancy. This therapeutic heterogeneity is being addressed through several innovative approaches: bispecific antibodies for multi-pathway targeting, conditionally-activated pro-antibodies responsive to disease microenvironments, advanced nanocarrier systems for tissue-specific delivery, and rationally-designed combination therapies [185–187].

4.2. Antibody Engineering

4.2.1. Bispecific Antibodies

Bispecific antibodies are revolutionizing autoimmune disease treatment through their ability to simultaneously modulate multiple immune pathways, offering superior therapeutic effects with reduced systemic toxicity compared to conventional monoclonal antibodies [188,189].

A prime example is the TNF/IL-6 bispecific nanobody developed by Biesemann et al., which demonstrated sustained remission of synovitis in RA models by concurrently inhibiting both cytokines while downregulating Th17 cell activity and altering pathogenic gene expression patterns [190]. Recent developments have expanded the therapeutic scope of bispecific antibodies to include targeted depletion of autoantigen-specific B cells in membranous nephropathy [191], Similarly, Lamendour et al. designed dendritic cell-targeting bispecific antibodies that convert pro-inflammatory dendritic cells into tolerogenic phenotypes through surface pattern recognition receptor crosslinking, achieving significantly higher IL-10 secretion than conventional therapies [192] and phenotypic conversion of pro-inflammatory dendritic cells to tolerogenic states through enhanced IL-10 production [193]. In addition, by simultaneously inhibiting IL-17A and BAFF, Tibulizumab may produce a synergistic therapeutic effect of "1 + 1 > 2", surpassing single-target drugs. For example, in systemic sclerosis, IL-17A is associated with fibrosis [194], while BAFF plays a critical role in the activation, survival, and maturation of B cells [195]. Inhibiting both simultaneously may more effectively improve multiple aspects of the disease. In the Phase I clinical trial, Tibulizumab was well tolerated and successfully interfered with two key pathways in the pathogenesis of the disease by simultaneously neutralizing IL-17A and BAFF [196]. Two key Phase II clinical trials are currently underway, including evaluating its efficacy and safety in patients with SSc and Hidradenitis Suppurativa (HS).

4.2.2. Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs) combine the precision of antibody targeting with potent cytotoxic payload delivery, enabling localized treatment of pathogenic immune cells while minimizing systemic toxicity [197,198]. The modular design of ADCs, comprising monoclonal antibodies, specialized linkers, and potent therapeutic payloads [199], allows for customized approaches to autoimmune disease management.

Recent developments highlight the versatility of this platform, including a BDCA2-targeting ADC that effectively suppresses plasmacytoid dendritic cell-mediated IFN-α production through glucocorticoid receptor agonist delivery [200], and CD6-directed ADCs that selectively eliminate activated T cells while sparing resting populations in autoimmune uveitis models [201]. Technological advancements are further enhancing ADC specificity, exemplified by light-activatable systems enabling precise, spatiotemporal control of regulatory T cell depletion for organ-specific applications like lupus nephritis [202]. Additional refinements focus on optimizing target selection and linker chemistry to maximize therapeutic effects while minimizing off-target interactions, as demonstrated in CTLA-4-targeted ADCs that modulate pathogenic T-cell/B-cell crosstalk [203].

In RA, AbbVie has developed two TNF-α ADCs, ABBV-3373 (adalimumab coupled to a glucocorticoid receptor modulator) and ABBV-154 (a second-generation, more stable linker design). Both ADCs have completed Phase II clinical trials in RA patients. The experimental results showed that their ACR50 response rate was significantly better than that of the placebo or control group [204–206]. Domestic and foreign research is also exploring other RA target ADC solutions, such as anti-IL-7R ADC (A7R-ADC), anti-CD74 hormone-loaded ADC, etc., which have shown anti-inflammatory effects in animal models. In SLE, Duality Biosciences' BDCA2 antibody ADC DB-2304 is the first immunomodulatory ADC targeting BDCA2 and the world's first ADC for SLE [200]. Preclinical data demonstrate that DB-2304 significantly inhibits pDC type I IFN signaling and pro-inflammatory cytokine expression in vitro and in animal models, with a favorable safety profile. Phase 1 trials were initiated in 2024, and the drug has received clinical approval in China for the SLE indication, marking a significant milestone in the development of ADCs for SLE [207].

The potential of ADCs continues to expand with innovative payload strategies, including the incorporation of conventional DMARDs like methotrexate for enhanced anti-inflammatory effects with reduced toxicity in RA [197]. These advances position ADC technology as a transformative approach for autoimmune diseases, enabling dual-dimensional targeting of both cell type and activation status.

4.2.3. Fc Engineering for Functional Optimization

The Fc domain represents a critical functional module that bridges humoral and cellular immunity through its interactions with Fc receptors and complement proteins [208]. Recent advances in Fc engineering, including strategic amino acid substitutions and glycoengineering approaches (Table 3), have enabled precise tuning of antibody effector functions to optimize therapeutic outcomes [209,210]. This molecular "control switch" demonstrates remarkable sensitivity to structural modifications, as exemplified by Obexelimab's S267E/L328F mutations that enhance inhibitory FcγRIIb signaling while maintaining B cell homeostasis [211], offering a safer alternative to conventional depletion strategies. The recycling of IgG antibodies depends on the pH-dependent interaction with FcRn in particular. FcRn in the acidified endosomes binds with IgG antibodies that have been transported into the endosome by the pinocytosis mechanism, thereby preventing degradation of the antibodies via the lysosomal pathway. Ravulizumab, through the M428L/N434S (LS) mutation, enhances the pH-sensitive binding between Fc and human FcRn, prolonging the antibody's retention time and extending its serum half-life to 49.7 days. [97], and TAVO101's L234A/L235A mutations that reduce cytokine storm risk while preserving pharmacokinetic properties [212,213]. The engineering toolkit extends to complement system modulation, with K322A mutations selectively abolishing complement-dependent cytotoxicity (CDC) activity [214] and N297A deglycosylation eliminating both antibody-dependent cellular cytotoxicity (ADCC) and CDC effector functions [210,215], while other modifications like S267E/H268F/S324T can dramatically enhance C1q binding for targeted immune complex clearance [216]. These examples illustrate how Fc engineering has evolved into a sophisticated platform for customizing antibody therapeutics, enabling researchers to fine-tune immune activation, prolong circulation time, and minimize adverse effects through precise structural modifications.

Table 3. Application of Fc engineering in the treatment of autoimmune diseases.

Targets	Strategies	Mechanism	Representative Studies
Enhances FcγRIIb inhibitory signaling	S267E/L328F double mutation	Enhances FcγRIIb binding, inhibits B cell activation and autoantibody secretion, and blocks Ca^{2+} flux [208]	Obexelimab (XmAb5871): In a Phase II clinical trial for the treatment of SLE, 42.0% of patients in the Obexelimab group-maintained improvement at day 225, compared with 28.6% in the placebo group [217,218]
Blocking pro-inflammatory FcγR signaling	IgG4 subtype or L234A/L235A mutation	Eliminate FcγRI/FcγRIIIa binding, reduce ADCC/ADCP effects, and release of inflammatory factors [219]	Odronextamab (IgG4-type dual antibody): Reduce T cell loss [220]
Inhibition of CDC	K322A mutation	Blocks C1q binding, reduces the complement cascade reaction, and tissue damage [221]	In animal models, the K322A mutant has a greatly reduced ability to mediate CDC, but retains significant ADCC activity [222]
Prolonging antibody half-life	M428L/N434S (LS) mutation	Enhances pH-sensitive binding between Fc and FcRn, prolonging antibody retention time [223]	Ravulizumab (Ultomiris®): half-life extended to 31.1 days [97], a maintenance dosing schedule of every 4–8 weeks is more conveniently achieved compared to the maintenance dosing schedule of Eculizumab every 2–3 weeks [99]
Accelerate the clearance of pathogenic antibodies	M252Y/S254T/T256 (YTE) mutation	High affinity binding to FcRn, promoting degradation of autoantibodies [224]	In the Phase III ADAPT study, 40% of patients in the efgartigimod treatment group achieved minimal symptom expression (MG-ADL of 0 or 1), compared with 11% in the placebo group [225,226]
Blocking FcγR-mediated inflammatory responses	Fc trimer	Competitive binding to FcγR, inhibiting inflammatory signals activated by [227]	In preclinical studies, CSL730 has demonstrated efficacy in multiple animal models of autoimmune diseases induced by exogenous antibodies, including ITP, collagen antibody-induced arthritis (CAIA), and epidermolysis bullosa acquired (EBA) [227,228]
Elimination of Fc effector function	N297A deglycosylation mutation	Removal of N-glycan modifications, eliminating ADCC/CDC effects [210,215]	Atezolizumab (anti-PD-L1): Reducing inflammatory toxicity via the N297A mutation [215].

4.3. AI-Assisted Antibody Design

The traditional antibody discovery process has been described as "costly, time-consuming, with low success rates," "ridiculous with uncertainty," and reliant on "specific biological sample types." AI significantly reduces these risks through rapid in silico screening, developability predictive modeling, and de novo design, by identifying issues early and reducing reliance on physical samples and iterative experimental cycles [229].

In the areas of precision targeting and immune modulation, AI plays a key role in designing antibodies that can distinguish between pathogenic and healthy self-antigens. While traditional therapies often involve broad immunosuppression, AI can, through precise epitope mapping and multi-target optimization, design antibodies with high specificity and precise targeting of pathogenic antigens while avoiding the risk of ADA. For example, the YabXnization platform combines traditional computational design with AI-assisted approaches. It uses machine learning models (specifically, a deep forest-based humanization assessment model) to analyze antibody sequences and predict their potential immunogenicity. This AI model can identify subtle sequence changes, known as "back mutations," that can make antibodies more human-like while retaining their original binding affinity and functionality. This approach minimizes the risk of immunogenicity while achieving a success rate of up to 90% [230].

In clinical development, AI is significantly accelerating drug development timelines. For example, AU-007, jointly developed by Biolojic Design and Aulos Bioscience, is the world's first fully AI-designed antibody for human use. It targets the IL-2 pathway and aims to enhance anti-tumor immunity while minimizing side effects. It blocks IL-2 binding to CD25 without affecting its binding to CD122/CD132, thereby restoring the cytotoxic activity of T cells. This drug initiated Phase 1 clinical trials in Australia in 2022 and has now entered Phase 2 clinical trials, marking a significant milestone in the advancement of AI-designed antibodies into human therapeutics [231,232]. Another representative example is ABS-101, developed by Absci, which targets the TL1A pathway for the treatment of autoimmune diseases such as inflammatory bowel disease. This project took only approximately 24 months from sequence design to clinical advancement, with lower R&D costs than traditional approaches. In clinical practice, the drug is administered subcutaneously, making it more convenient for patients [233]. These advances demonstrate the significant advantages of AI in accelerating antibody screening, affinity optimization, and immunogenicity prediction. Furthermore, while some products have already entered the clinical stage, many biopharmaceutical companies are actively expanding AI platforms to a wider range of antibody design applications. For example, BigHat Biosciences has developed an iterative optimization system that combines deep learning models with a high-throughput experimental platform. In collaboration with Amgen, through several rounds of design, they achieved a more than tenfold increase in antibody binding affinity while also improving thermal stability and expression levels. This platform enables multi-objective optimization of multiple antibody properties in a short period of time, significantly shortening the R&D cycle [234,235].

While the application of AI in autoimmune antibody development holds great promise, it also faces significant technical and data challenges. First, the accuracy of AI models is highly dependent on high-quality, large-scale, and representative training data. Due to the complexity and diversity of autoimmune diseases, integrating and standardizing data from various sources (such as genomic, proteomic, and clinical data) is a daunting task. Furthermore, the "black box" nature of modern AI models, especially deep learning models, makes their decision-making processes difficult to interpret. This not only hinders trust in clinical validation but also poses challenges for regulatory approval. On the regulatory and ethical front, evolving regulatory frameworks require transparency and traceability of AI models, while also addressing issues such as data privacy, ownership, and algorithmic bias to ensure equitable access to healthcare.

Nevertheless, the future of AI remains promising. Recent advances have highlighted AI's role in creating "functionally active antibodies capable of modulating biological pathways in novel ways" or "programming antibodies as dynamic functional switches." Ability Biotherapeutics is developing "logic-gated biotherapeutics" that are "conditionally activated to target specific cells and disease sites [236]." This goes beyond simply improving binding; it involves designing antibodies that intelligently respond to their microenvironment. This development demonstrates that AI is not only making antibody design faster and more precise, but is also spawning a new generation of "smart" antibodies capable of highly controlled, context-dependent therapeutic effects. This is particularly transformative for autoimmune diseases, as the goal is to modulate specific pathological pathways without causing widespread immunosuppression, thereby enabling true "precision" immunotherapy.

4.4. Combination Therapies

The complex pathogenesis of autoimmune diseases necessitates multidimensional therapeutic strategies. Emerging approaches combine cell-based therapies (including regulatory T cells, CAR-T cells, and mesenchymal

stem cells) that restore immune homeostasis through pathogenic cell clearance or immune reset, with antibody therapies that precisely target disease-specific antigens or inflammatory pathways. This synergistic combination enables comprehensive immune rebalancing across multiple dimensions. Clinical trials using CD19-targeted CAR-T cells have achieved complete drug-free remission in severe SLE and other conditions, with sustained B-cell depletion (112 ± 47 days) and favorable safety profiles (only 10% grade 1 cytokine release syndrome) [237].

Recent advances include the development of universal allogeneic CAR-T products, such as the CRISPR-engineered TyU19, which achieved complete B-cell clearance in refractory patients without preconditioning chemotherapy [238]. In B-cell mediated autoimmunity, CAR-T therapy reduced pathological lesions by 82% compared to conventional treatments [239]. Innovative designs incorporating regulatory functions, such as Fox19CAR-Tregs that combine B-cell depletion with immunomodulatory cytokine secretion, have shown synergistic effects in expanding regulatory T cell populations while mitigating end-organ damage [240].

Current limitations include antigen escape (18% incidence) and treatment-related hypogammaglobulinemia (23% incidence), prompting the development of dual-targeting approaches and supportive therapies [241]. Future refinements may incorporate precision control elements through CRISPR engineering to optimize safety and efficacy. These developments position CAR-T therapy as a transformative option for treatment-refractory autoimmune diseases, transitioning from experimental applications toward standardized clinical protocols.

4.5. Clinical Challenges Limiting the Efficacy of Current Cytokine-Targeting Biologics

Despite significant advances, cytokine-targeting biologics face clinical hurdles including primary non-response, secondary loss of efficacy, and considerable adverse effects [242,243]. This limited therapeutic success arises from the immune system's complex redundancy, where blocking one cytokine activates compensatory inflammatory pathways, and cellular heterogeneity alongside phenotypic plasticity among pathogenic immune cells complicate precise targeting [242,244]. Additionally, immunogenicity frequently leads to anti-drug antibody (ADA) formation that neutralizes biologics or accelerates clearance, diminishing drug concentrations and promoting treatment resistance [245]. Pharmacokinetic limitations, such as inadequate tissue penetration, further restrict drug access to key inflammatory sites like fibrotic tissues or the CNS. These multifactorial obstacles collectively curtail the long-term effectiveness of current single-target biologics.

4.6. Systems Immunology Perspective: Reconceiving Autoimmune Pathogenesis and Therapy

To transcend the pitfalls of conventional cytokine blockade, a systems immunology framework is essential. This perspective conceptualizes autoimmunity as a dynamic, interconnected cytokine and immune cell network rather than isolated molecular targets. High-dimensional immune profiling (e.g., single-cell RNA-seq, mass cytometry) combined with computational network modeling identifies critical "hub" cytokines and signaling nodes that orchestrate pathogenic inflammation [246,247]. Such insights enable patient stratification based on immune signatures predictive of therapeutic response, facilitating personalized medicine. Moreover, systems analysis supports the design of adaptive therapies that dynamically adjust treatment regimens guided by immune monitoring to preempt compensatory escape pathways and resistance, providing a rational basis for multi-target interventions [248].

4.7. Innovative Therapeutic Strategies Informed by Network-Centric Approaches

Building on systems immunology principles, emerging therapeutic modalities—such as bispecific and multispecific antibodies, antibody-drug conjugates (ADCs), and Fc engineering—enhance selective targeting, reduce systemic immunosuppression, and improve tissue penetration [249,250]. Integration of systems pharmacology and computational modeling further guides rational selection of therapeutic combinations and dosing schedules to circumvent resistance. Additionally, cutting-edge cellular therapies—such as engineered CAR-T or CAAR-T cells designed to selectively deplete or regulate cytokine-producing pathogenic immune subsets—offer promising personalized approaches for durable disease control [251,252]. Collectively, these innovative modalities embody a network-centric paradigm, empowering more effective and safer interventions aligned with the immune system's complexity.

5. Conclusions

Autoimmune diseases, characterized by chronic inflammatory responses resulting from aberrant immune attacks on self-tissues, represent a growing global health challenge with steadily increasing incidence rates. Antibodies play dual and paradoxical roles in autoimmune diseases pathogenesis and treatment: as pathogenic drivers that mediate tissue

damage through complement activation, ADCC, and immune complex deposition; and as therapeutic agents that precisely target immune cells or inflammatory factors to significantly improve clinical outcomes.

The dysregulation of inflammatory cytokines constitutes a central pathogenic mechanism in autoimmune diseases, orchestrating a self-amplifying cascade of immune activation and tissue damage. These molecular mediators, including TNF-α, IL-6, IL-17, IL-23, and type I/II interferons, establish complex inflammatory networks that disrupt immune homeostasis through multiple mechanisms: promoting autoreactive lymphocyte activation, enhancing leukocyte recruitment, and sustaining chronic inflammatory microenvironments. The clinical significance of these pathways is evidenced by the characteristic cytokine signatures observed in various autoimmune disorders, such as the IFN signature in SLE and the Th17 cytokine predominance in PsO and RA.

Therapeutic antibodies targeting these inflammatory cytokines have transformed autoimmune disease management through precise immunomodulation. TNF-α inhibitors demonstrate broad efficacy across multiple conditions by disrupting the core inflammatory cascade, while IL-6 pathway blockade (Tocilizumab, Sarilumab) effectively controls systemic inflammation and prevents end-organ damage. The success of IL-17/IL-23 axis inhibitors (Secukinumab, Ustekinumab) in psoriatic diseases validates the pathogenic role of Th17-mediated inflammation, with newer agents achieving unprecedented clinical response rates. Notably, interferon-targeting therapies (Anifrolumab, Emapalumab) exemplify the growing sophistication of cytokine modulation, addressing specific disease mechanisms while minimizing broad immunosuppression.

These biologic agents achieve therapeutic effects through multiple mechanisms: neutralizing soluble cytokines, blocking receptor interactions, and modulating downstream signaling pathways. Clinical outcomes demonstrate not only symptom control but also disease modification, with preserved treatment responses and delayed disease progression observed across multiple studies. The ongoing development of bispecific antibodies and engineered Fc variants further enhances therapeutic precision, enabling simultaneous targeting of multiple inflammatory pathways or selective modulation of immune effector functions. As our understanding of cytokine networks deepens, these targeted therapies continue to redefine treatment paradigms, offering improved outcomes for patients with refractory autoimmune conditions.

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Abbreviations

ACh	Acetylcholine
AChR	Acetylcholine receptors
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AI	Artificial intelligence
AOSD	Adult-onset Still's disease
APC	Antigen-presenting cell
AS	Ankylosing spondylitis
BAFF	B-cell activating factor
BCR	B-cell receptor
BP	Bullous pemphigoid
CD	Crohn's disease
CDC	Complement dependent cytotoxicity
CRP	C-reactive protein
CSS	Churg-strauss syndrome
DM	Dermatomyositis
DMARDs	Disease-modifying antirheumatic drugs
EGPA	Eosinophilic granulomatosis with polyangiitis
FcγR	Fc gamma receptors
FMF	Familial mediterranean fever
GCA	Giant cell arteritis
GPCR	G protein-coupled receptor
HLH	Hemophagocytic lymphohistiocytosis
HS	Hidradenitis suppurativa

HT	Hashimoto's thyroiditis
IBD	Inflammatory bowel diseases
ICs	Immune complexes
IgAN	IgA Nephropathy
ILC3s	Group 3 innate lymphoid cells
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
KCs	Keratinocytes
LDH	Lactate dehydrogenase
MAC	Membrane attack complex
MAS	Macrophage activation syndrome
mDC	Myeloid dendritic cells
MG	Myasthenia gravis
MHC	Major histocompatibility complex
MS	Multiple sclerosis
MTX	Methotrexate
NET	Neutrophil extracellular trap
NMJ	Neuromuscular junction
NMOSD	Neuromyelitis optica spectrum disorder
NMP	Neuromyelitis optica
nr-axSpA	Non-radiographic axial spondyloarthritis
PAMPs	Pathogen-associated molecular patterns
pDC	Plasmacytoid dendritic cell
PM	Polymyositis
PRRs	Pattern recognition receptors
PsA	Psoriatic Arthritis
PsO	Psoriasis
RA	Rheumatoid arthritis
ROS	Reactive oxygen species
SD	Still's disease
SjS	Sjögren's syndrome
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
TCR	T-cell receptor
TGF-β	Transforming growth factor-β
Th1/2/17/22	T helper 1/2/17/22 cells
TNF-α	Tumor necrosis factor-α
UC	Ulcerative colitis
UV	Uveitis

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