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REVIEW

Cell-Based Therapeutic Strategies for Autoimmune Diseases

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Abstract: Currently, the management of autoimmune disorders still being a challenge in terms of safety, efficiency, and specificity. Cell-based therapeutic strategies have emerged as a novel approach for autoimmune disease treatment, employing different cell therapy platforms, including tolerogenic dendritic cells, regulatory T cells, conventional and regulatory chimeric antigen receptor-T cells, mesenchymal and hematopoietic stem cells, each with their biological features. Here, we discuss the different cell therapy platforms, their immunological mechanisms of action, their therapeutic potential and benefits in autoimmune diseases, and challenges related to their production, scaling up, risks, and patient safety.

Keywords: autoimmunity, cell therapy, CAR T cell, tolerogenic dendritic cell, regulatory T cell, stem cells

Introduction

Autoimmune diseases encompass various disorders characterized by the loss of self-immune tolerance, resulting in autoreactive T and B cell activation. This dysregulation can lead to specific damage to individual tissues or organs, which can be seen in conditions such as type 1 diabetes (T1D) and multiple sclerosis (MS), or provoke systemic chronic inflammation, evident in disorders like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). The etiology of autoimmune diseases is complex, influenced by multiple factors, including genetic predisposition,[1] and particularly related to human leucocyte antigen (HLA) genes,[1–3] epigenetic modifications,[4–6] environmental factors,[7,8] gestational conditions,[9,10] hormones,[11–13] gender,[14] and ethnicity.[15–17]

Current treatment strategies for autoimmune diseases predominantly involve using glucocorticoids, hydroxychloroquine, and a range of immunosuppressants.[18,19] While these medications can be effective in managing symptoms, they often lead to significant adverse events.[20,21] Common side effects include increased susceptibility to infections, gastrointestinal intolerance, leukopenia, and complications such as heart failure, hypertension, osteoporosis, and anorexia.[22,23] These adverse effects can limit treatments' long-term usability and negatively impact patients' life quality.[24] Furthermore, although biological therapies like monoclonal antibodies against the cluster of differentiation 20 (CD20),[25] tumor necrosis factor-alpha (TNF-α),[26] interleukin-1β (IL-1β),[27] or IL-6 receptor,[28,29] have shown improved efficacy and a reduced incidence of side effects compared to traditional immune suppressor drugs, their high costs restrict accessibility, particularly in low- and middle-income countries, and it is prioritized for non-responder patients.[30,31] Thus, substantial challenges involve the management of autoimmune diseases, including the need for more personalized treatments and safer alternatives to minimize side effects and improve the life quality of people with these affections.

Cell-based therapies have emerged as a promising therapeutic alternative in various fields,[32–36] including stem cell applications for regenerative medicine,[32] cancer treatment using chimeric antigen receptor (CAR) T cells[33,34] or dendritic cell-based vaccines.[35,36] These innovative therapeutic platforms offer new opportunities for treating autoimmune diseases by potentially restoring immune tolerance. Approaches like tolerogenic dendritic cells, regulatory T cells (Tregs), and CAR Treg therapies aim to modulate the immune response in an antigen-specific way.[37–39] On the other hand, currently

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approved CAR T cell therapies can be applied for autoimmunity, deleting autoreactive B cells.[40] Finally, stem cell-based therapies using mesenchymal stem cells focus on tissue repair and immune modulation.[41] However, in the case of hematopoietic stem cells, they can achieve an "immune reset" after a conditioning regimen, leading to recovery of self-tolerance.[42] Every therapy strategy mentioned above will be extensively addressed in this article, including findings in preclinical models and clinical trials in autoimmune diseases like T1D, MS, neuromyelitis optica (NMO), RA, idiopathic inflammatory myositis (IIM) and systemic sclerosis (SS).

This article discusses the novel cell therapy strategies developed for treating autoimmune diseases, focusing on their potential to restore immune balance and offer more targeted, long-lasting solutions. It addresses their mechanism of action and the challenges related to access, scalability, and safety for clinical applications. Highlighting the importance of this approach could represent a change in the management of autoimmune diseases that affect a large part of the population, offering safer and more effective treatments.

Emerging Cell Therapy Platforms

Tolerogenic Dendritic Cells

Dendritic cells (DCs) are the immune system's most potent antigen-presenting cells (APCs).[43] Through their ability to capture, process, and present antigens, they play a critical role in the onset of adaptive immune responses.[44] DCs express many pathogen-associated molecular patterns (PAMPs) receptors and cytokine receptors, which trigger DC maturation by their activation.[44–47] This maturation process is marked by a substantial increase in the expression of co-stimulatory molecules, such as CD40, CD80, CD83, and CD86, major histocompatibility complex (MHC) molecules and the chemokine receptor CCR7, which guide their migration to lymphoid tissues.[47–49] In these lymph nodes, mature DCs present antigens to T cells, activating and differentiating naïve T cells into effector T cells, ultimately shaping immune responses against pathogens or abnormal cells such as tumor cells.[45,49]

In contrast to these highly immunogenic DCs, immature DCs exhibit a distinct phenotype characterized by their low expression of co-stimulatory molecules, MHC, and chemokine receptors.[50,51] These cells, known as tolerogenic dendritic cells (tolDCs), are pivotal in maintaining immune homeostasis and promoting peripheral tolerance.[52–57] TolDCs prevent autoimmune reactions by presenting self-antigens to T cells in a manner that leads to their inactivation or the generation of regulatory T cells (Tregs) rather than triggering an inflammatory immune response.[50,51,58] The ability of tolDCs to suppress immune activation positions them as a key mechanism in avoiding autoimmune diseases and maintaining self-tolerance.[52,59]

The therapeutic potential of tolDCs has shown interest in recent years as a strategy for treating transplant rejection,[60] allergies,[61] and specialty for autoimmune diseases like SLE, MS, and RA.[37,51,62–65] These cells can be generated ex vivo from precursor cells, such as hematopoietic stem cells or monocytes, and their tolerogenic properties can be enhanced using specific agents that inhibit their maturation.[64,66,67] Agents such as dexamethasone, a potent glucocorticoid,[66,68–70] active form of vitamin D3,[69,71] interfering RNA (siRNA) to silencing B-cell activating factor (BAFF),[67] and the peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist rosiglitazone,[66,68] have been shown to induce the tolerogenic phenotype in DCs.[64,66–69,71] These DCs maturation inhibitors modulate the expression of stimulatory surface molecules, including CD40, CD80, CD83, CD86, and MHC-II,[64,66–68,71] and cytokines such as TNF-α, IL-6, IL-12, and IFN-γ that would otherwise promote a proinflammatory response (Figure 1A).[64,66–68]

Extensive preclinical research has been conducted in murine models of autoimmunity, demonstrating the therapeutic efficacy of tolDC in a wide range of conditions, including experimental autoimmune encephalomyelitis (EAE), SLE-prone mice, non-obese diabetic (NOD) mice, and proteoglycan induced arthritis model. For instance, tolDCs have been explored in models of MS, where their administration was evaluated in preventive and therapeutic schedules, observing a reduction of clinical score in both conditions, an increase in IL-10 expression, and a Treg cell expansion.[65] In NOD mice, murine type 1 diabetes model, tolDCs have delayed diabetes onset, leading to induction of splenic $CD62L^+$ Tregs and reduced proinflammatory cytokines like TNF-α and IFN-γ.[72] Similarly, tolDC in arthritis mice aims to enhance the proliferation of $CD62L^+$ and $FoxP3^+$ Treg subsets and reduce clinical arthritis manifestations.[73] Finally, in NZM2410

SLE-prone mice, tolDCs elicit reduced anti-histone and anti-dsDNA antibodies, improved clinical scores, and reduced cutaneous lesions.[66]

Addressing the clinical trials findings, tolDCs have been evaluated in autoimmune diseases, including T1D, MS, and RA. In T1D, two Phase 1 clinical trials were conducted (NCT00445913 and NCT03895996). In the first one, tolDCs were generated from peripheral blood monocytes and treated with antisense oligonucleotides targeting CD40, CD80, and CD86 gene primary transcripts to induce a tolerogenic profile, and they were injected subcutaneously.[74] The therapy was well tolerated, and no adverse events (AEs) reported could be related to the treatment.[74] Notably, there was an increase in the frequency of peripheral $B220^{+}$ $CD11c^{-}$ B cells and an increase of IL-4 and IL-10 compared with baseline.[74] The second clinical trial in T1D consisted of three autologous intravenous administrations of DCs differentiated from

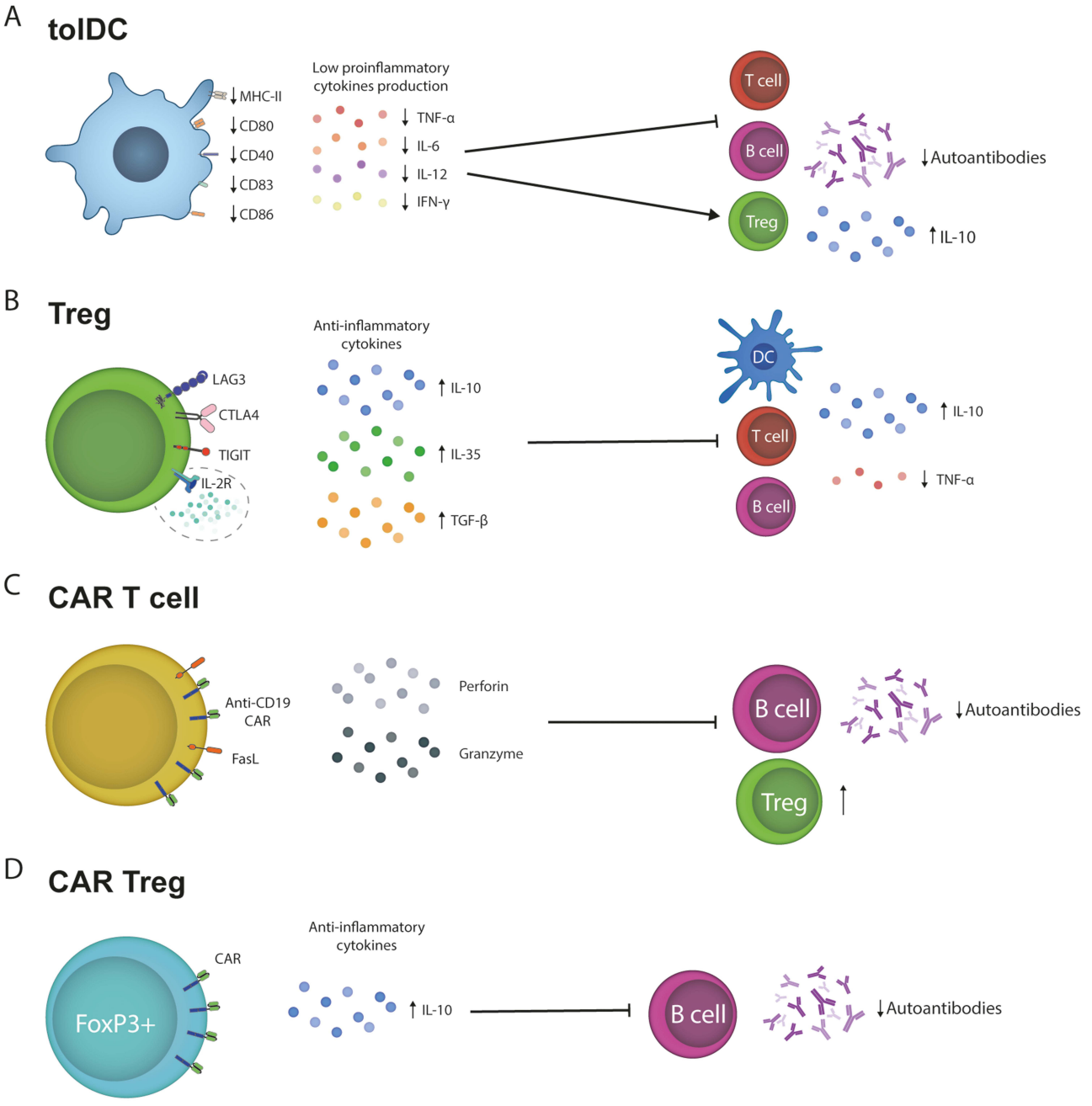

Figure 1 Continued.

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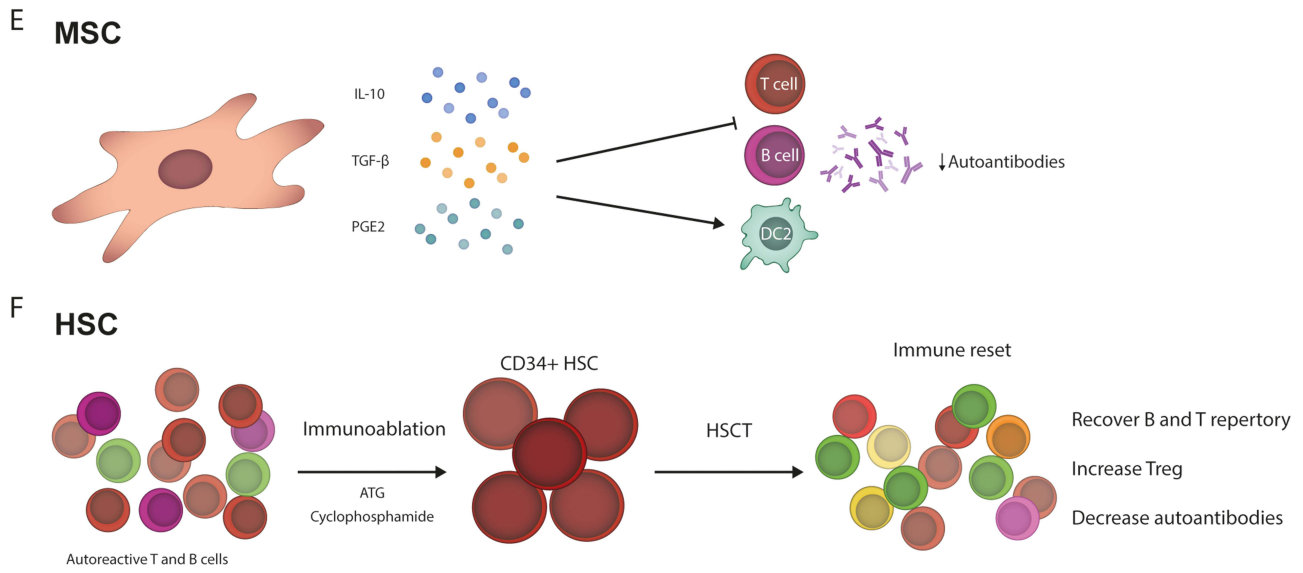

Figure 1 Main mechanisms of different cell-based therapy platforms. (**A**) Tolerogenic dendritic cells (tolDC) elicit an antinflammatory response by their low expression of MHC-II and low co-stimulatory molecules (CD80, CD40, CD83, and CD86). Additionally, tolDC produce low amounts of proinflammatory cytokines (TNF-α, IL-6, IL-12, and IFN-γ). tolDC have been reported to reduce T cell proliferation and autoantibodies production while increasing Treg cells. (**B**) Regulatory T cells (Treg) express regulatory surface molecules (LAG-3, CTLA-4, and TIGIT), leading to DC inhibition. Also, Tregs highly express anti-inflammatory cytokines (IL-10, IL-35, and TGF-β), which can inhibit both T and B cells, and systemic increase of IL-10 have been reported, while reduce TNF-α. (**C**) In this case, chimeric antigen receptor (CAR) T cells are engineered T cells to express a specific CAR for recognizing an antigen, CD19. After the recognition, the CAR T cell can kill the target cell by perforin/granzyme secretion or by inducing apoptosis by FasL signaling, diminishing B cells and then reducing autoantibodies production. (**D**) Regulatory CAR T cells are also engineered to overexpress FoxP3, which leads to a regulatory profile and anti-inflammatory function. When the CAR binds a $CD19^+$ B cell, this is inhibited by the IL-10 produced from CAR Treg cells, decreasing the autoantibodies secretion. (**E**) Mesenchymal stem cells (MSC) are characterized by their anti-inflammatory cytokines/compounds (IL-10, TGF-β, PGE2) secretion capacity. Those immune mediators inhibit both T and B cells, diminish autoantibodies, and induce an increase in anti-inflammatories DC2. (**F**) The application of hematopoietic stem cells (HSC) requires the previous use of anti-thymocyte globulin and cyclophosphamide as immunoablation conditioning, depleting autoreactive T and B cells. Subsequently, the HSC transplantation (HSCT) is performed, leading to an "immune reset", characterized by the recovery of TCR and BCR repertoire diversity, increasing of Treg and reduction of autoantibodies.

monocytes and loaded with a synthetic oligopeptide of a signal peptide derived from the leader sequence of heat shock protein 60 (Hsp60sp), therapy called AVT001. The treatment was generally well tolerated, but two grade 3 AE of neutrophil count decrease (both in AVT001 and placebo group) were reported.[75] Regarding the efficacy, the AVT001 treated group exhibited a lower decrease of C peptide compared to placebo. However, no apparent differences were found in hemoglobin A1c (HbA1c) or insulin-required dose.[75] Regarding MS and NMO, there is only one completed clinical trial with posted results (NCT02283671). In this clinical trial, tolDCs were generated from autologous monocytes, and after differentiation, the cells were treated with dexamethasone and loaded with myelin and aquaporin peptides.[76] Therapy with tolDCs was administrated in three intravenously doses every 2 weeks. It was well tolerated, without severe AE and without any therapy-related reactions. Patients remained stable clinically regarding relapses, disability, and magnetic resonance imaging and optical coherence tomography. In this case, it was reported an increase in IL-10 release from peripheral blood mononuclear cells (PBMCs) stimulated with the peptides and an increase in the frequency of a $CD4^+$ $CD10^+$ T cell, known as Tr1.[76]

Regarding RA, two clinical trials have been conducted (NCT03337165, NCT01352858). In the first one, tolDCs were generated from monocytes in the presence of dexamethasone, adding azoximer bromides as maturation stimuli.[77] The single intra-articular injection of tolDCs was safe and well tolerated, and no one participant reported any AE. Additionally, the therapy improved disease activity, pain, and function for up to 6 months.[77] Another trial in RA evaluated tolDCs produced from autologous $CD14^+$ monocytes, and the tolerogenic profile was induced with dexamethasone and the active form of vitamin D3. Then, they were loaded with synovial fluid autoantigens. The administration was intra-articular, and the injections were safe and well tolerated, with no major knee flares.[78] However, they did not show consistent clinical effects or sustained changes in the serum cytokines IL-8, IL-10, IL-16, IL-17, TNF-α, and IFN-γ. Despite this, two participants in the tolDC group showed symptom improvement and remained stable for 3 months, suggesting a potential beneficial effect.[78]

Regulatory T Cells Therapy

Regulatory T cells (Tregs) are a specialized subset of $CD4^+$ T cells defined by the transcription factor forkhead box P3 (FoxP3) expression, which is crucial for their development and suppressive function.[79] The pivotal role of this cell subset in immune homeostasis has been established by descriptions of Scurfy mice, which carry a FoxP3 mutation, conducing to the development of severe and lethal autoimmunity manifestations characterized by lymphoproliferation and multiorgan inflammation.[79,80] Phenotypically, Tregs are characterized by high surface expression of CD25 (IL-2 receptor), low or absent CD127 (IL-7 receptor),[38,81] and the presence of markers associated with their immunosuppressive capabilities such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), lymphocyte-activation gen 3 (LAG3) and T cell immunoreceptor with Ig and ITIM domains (TIGIT).[82–84]

Treg cells exert their immunosuppressive and inflammation control effects through various characterized mechanisms.[82] One of the most thoroughly studied involves the secretion of inhibitory cytokines, specifically IL-10, IL-35, and transforming growth factor beta (TGF-β),[85–89] which play crucial roles in suppressing effector T cells,[90] DCs,[91] and B cells.[88] However, their high expression of CD25 diminishes the availability of IL-2 cytokine, promoting a starvation environment for effector T cells (Figure 1B).[92]

In addition to cytokine-mediated suppression, Tregs engage in immunosuppression via direct cell-to-cell interactions. A key molecule in Treg-mediated suppression is CTLA-4, which interacts with CD80/CD86 on antigen-presenting cells, competing with the stimulatory coreceptor CD28 and ultimately reducing T cell activation.[84,93] Another cell-to-cell mechanism is caused by the lymphocyte-activation gene 3 (LAG3) expression on Treg cells, and this molecule interacts with MHC-II molecules from DCs and elicits a higher antigen presentation, decreasing their antigen uptake, collaborating to induce a tolerogenic profile.[94–96] TIGIT is another critical molecule highly expressed in Tregs that has emerged as part of cell-cell mechanisms controlling Treg function.[97,98] TIGIT binds to CD155 on DCs, promoting the development of a mature immunoregulatory profile characterized by the expression of CD80, CD83, and CD86 but a reduced IL-12 production and enhanced IL-10 secretion.[98] Moreover, $TIGIT^+$ Tregs exert direct suppressive effects on effector T cells, particularly Th1 and Th17 cells, by secretion of soluble fibrinogen-like protein 2 (Fgl2).[99]

The mechanisms attributed to this subset of T cells have highlighted their potential as a therapeutic tool for autoimmune disorders. Therefore, several researchers have investigated the effects of adoptive Treg transfer on the development of autoimmunity across various animal models, including EAE,[88] lupus-prone mice,[100] and collagen-induced arthritis (CIA) mice.[101] In EAE mice, adoptive transfer of Tregs resulted in reduced pain signs, delayed disease progression, and promoted IL-10 expression in T and B cells, attributing these effects to IL-35 production by Tregs.[88] Treg transfer has been evaluated in lupus-prone NZB/NZW mice, leading to decreased renal damage due to reduced immune complex accumulation, lower proteinuria levels, and increased survival. However, no reduction in anti-dsDNA antibodies was observed.[100] Finally, in the CIA model, a decrease in disease score and reduced TNF-α expression in T cells were noted.[101]

Moreover, the use of Tregs targeting a specific SLE antigen has been proposed, such as an overexpressing FoxP3 and a TCR specific for a peptide from Smith (Sm) antigen,[102] a relevant antigen targeted in SLE. In this case, in-vitro evaluation of Sm-TCR Treg cells in co-culture with PBMCs showed IL-10 to increase, while IFN-γ and IL-17A decreased. Additionally, in-vivo studies in a humanized mouse model showed that the transfer of Sm-TCR Treg cells significantly reduced proteinuria and improved renal injury histological markers.[102]

Chimeric Antigen Receptor T (CAR T) Cells and CAR Treg

Chimeric antigen receptor T cells are genetically engineered ex-vivo and then readministered to patients. This cell engineering strategy enables generating autologous cells with specificity for a target antigen and delivers highly targeted cytotoxic effects against cells bearing that antigen.[103] In the past few years, the therapeutic use of CAR T cells, specifically anti-CD19 or anti-B-cell maturation antigen (BCMA), has primarily targeted hematologic cancers such as non-Hodgkin lymphoma, acute leukemia, and multiple myeloma. Due to their effectiveness in these settings, CAR T cell therapies have gained recognition as the standard of care in some instances of refractory or relapsed hematologic cancers.[104] CAR T cells' primary mechanism of action is their cytotoxic activity,[105] primarily mediated through the secretion of perforin, granzyme B, and granzyme A, which induce target cell lysis. Additionally, CAR T cells express Fas ligand (FasL), triggering apoptosis in Fas-expressing target cells (Figure 1C).[105,106]

The ability of CAR T cells to target and deplete $CD19^+$ cells in the context of hematological cancers has increased interest in their applicability in autoimmune diseases, where dysregulated B cells and autoantibodies contribute significantly to disease pathogenesis.[107] Accordingly, anti-CD19 CAR T cells have been tested in autoimmune murine models,[108] such as SLE,[109,110] and EAE,[111] showing effectiveness in reducing clinical disease progression, diminishing proinflammatory cytokines, autoantibodies production, and elevating Treg cells.

In addition to conventional CAR T cell therapies, other CAR construct alternatives have been developed to generate therapeutic options, such as CAR Tregs.[39] This type of therapy has been investigated as a therapeutic approach in an induced SLE model, overexpressing FoxP3 CAR anti-CD19 cells were generated and showed to reduce inflammation by increasing IL-10 production, which led to serum anti-dsDNA antibodies reduction and reduced histological kidney damage (Figure 1D).[112]

More than 120 clinical trials are currently registered for evaluating CAR T cell therapy in different autoimmune diseases. Besides, recent clinical evidence of anti-CD19 CAR T cells has been published. For example, a case series of SLE, IIM, and SS patients, refractories to immunosuppressive therapies, were treated with anti-CD19 CAR T cells.[113] The therapy was considered safe, as no participants showed grade 3 or 4 cytokine release syndrome (CRS). One patient developed grade 4 neutropenia, which was resolved with clinical management. In the long term, another patient developed pneumonia, which resolved with antibiotic treatment.[113] A transient depletion of B cells after therapy infusion was observed, with their reappearance after a mean of 112 days.[113] Interestingly, in SLE patients, relevant autoantibodies against dsDNA, single-stranded DNA, secondary necrotic cells, nucleosomes, and Smith protein become negative and remain for at least one year of follow-up.[113] All the patients had remission or significant clinical improvement and stopped their immunosuppressive therapy at the last follow-up.[113] Similar results were reported in a phase 1 clinical trial (NCT04162353 and NCT05474885) where it was evaluated an anti-BCMA-CD19 compound CAR T cell for SLE patients with lupus nephritis.[114] In this study, patients did not present severe CRS, and a seroconversion of autoantibodies with a disease activity reduction was reported in 9 out of 13 patients, achieving a symptom medication-free remission with a significant improvement in renal function.[114]

While CAR T therapies hold promise as a potential tool for treating autoimmune diseases, numerous challenges remain to allow their scaling up and achieve their use as a standard of care. A significant challenge in autologous cell therapy is batch-to-batch variability, which arises from the reliance on patient-derived cells. Each cell product partially depends on the initial material's quality (apheresis product), including cell viability and T cell quantity.[115] A proposed solution uses allogeneic or "universal" CAR T cells, which utilize healthy donor cells as starting material.[116] This approach enables the production of larger cell quantities, allowing multiple doses to be obtained from a single batch. Additionally, it reduces costs associated with individual product processing and enhances manufacturing efficiency by providing ready-to-use products.[116] Moreover, allogeneic CAR T cells present the risk of immune rejection.[117] To mitigate this, gene engineering techniques have been applied to disrupt the expression of TCR and MHC, preventing these undesirable reactions.[117] Another key challenge is therapy safety, and current clinical trials have demonstrated good tolerance, as well as an absence of severe AEs related to therapy. However, further clinical studies, including different patient cohorts and larger sample sizes, are necessary to confirm both safety and efficacy robustly.

Stem Cells: Mesenchymal Stem Cells, Hematopoietic Stem Cells

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are multipotent stromal precursor cells originating from the embryonic mesoderm. These cells are well characterized, and their established hallmarks include self-renewal capacity, multipotency, transplantability, plasticity, maintenance of genome integrity, and dependence on niche signals.[118] They are harvested from various sources, including bone marrow, adipose tissue, menstrual blood, umbilical cord, placenta, and other tissues.[119] Their differentiation potential spans osteogenic, adipogenic, chondrogenic lineages, and other cell types under specific conditions.[120] Phenotypically, MSCs express markers like CD13, CD29, CD44, CD73, CD90, and CD105, while lacking markers such as CD14, CD19, CD20, CD34, CD45, CD79α and HLA-DR.[121] The criteria for MSC characterization include their adherence to plastic surfaces, expression of the specific surface markers CD73, CD90, and CD105, and

being negative for CD14, CD19, CD34, CD45, and HLA-DR, and capacity for tri-lineage differentiation into adipocytes, osteoblasts, and chondrocytes.[122,123]

In terms of mechanisms of action (Figure 1E), MSCs are known for their immunomodulatory properties through the secretion of various factors. They produce mainly TGF-β, IL-10, and prostaglandin E2 (PGE2), but also include IL-1 receptor antagonist (IL-1RA) hepatocyte growth factor (HGF), nitric oxide (NO), among others, which collectively limit immune responses. MSCs also influence immune cell populations by increasing regulatory T cells, anti-inflammatory Th2 cells, and type 2 DCs (DC2) while reducing pro-inflammatory Th1 cells, DC1 cells, and natural killer (NK) cells. Additionally, MSCs induce a shift in macrophage phenotype from the M1 (pro-inflammatory) to the M2 (anti-inflammatory), reducing IgG production in B cells.[120] On the other hand, MSCs can promote tissue regeneration, and is well known their capacity to secrete paracrine trophic factors, which enhance injury regeneration and aim cell migration to damaged tissues such as HGF, stromal-derived factor-1 (SDF-1), insulin-like growth factor (IGF-1), epithelial growth factor (EGF), nerve growth factor (NGF), transforming growth factor-alpha (TGF-α), and tissue angiogenesis vascular endothelial growth factor (VEGF).[124,125]

In preclinical studies of lupus using different murine disease models, MSCs have shown significant therapeutic potential. In a murine model of SLE, MSCs have been observed to induce apoptosis in $CD4^+$ T cells, thereby reducing kidney lesions associated with lupus.[126] Additionally, human embryonic MSCs have demonstrated efficacy in alleviating pathological changes in MRL/Fas^{lpr} mice, which is attributed to their regulation of Th17 cell differentiation. These effects include enhanced survival, reduced anti-dsDNA antibody levels, and decreased renal damage, indicating the capacity of MSCs to mitigate both immune dysregulation and end-organ damage in lupus.[127]

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are multipotent cells essential for maintaining the lifelong production of all blood cell lineages, including erythrocytes, leukocytes, and platelets, through hematopoiesis.[128] HSCs can be sourced from umbilical cord blood, collected from bone marrow, or mobilized to peripheral blood using recombinant G-CSF.[129–131] These cells exhibit similar hallmark properties as described before for MSCs, such as self-renewal, multipotency, plasticity, maintenance of genome integrity, and dependence on niche signal.[118] HSCs express key phenotypic markers, highlighting CD34 but also including CD33, CD133, CD90, and CD117, which allow their identification and characterization.[132] Their potential multipotency enables them to have regenerative capacity, making them indispensable in hematopoietic reconstitution for treating malignancies and non-malignant diseases like leukemia or aplastic anemia, respectively.[133,134]

Hematopoietic stem cell transplantation (HSCT) has represented a transformative approach for hematologic malignancies and resetting the immune system in autoimmune diseases.[42,131,135] Mechanistically, HSCT exerts its effects through profound immunological reprogramming, achieving a state of immune self-tolerance.[42,135] This is primarily mediated by two pivotal mechanisms: First, the elimination of autoreactive immune cells through immunoablation, and second, the regeneration of a naive immune repertoire, often referred to as an "immune reset".[42,135–137] Immunoablation using anti-thymocyte globulin and cyclophosphamide eradicates autoreactive memory cells, evidenced by the disappearance of pathogenic autoantibodies and clonal T-cell populations post-transplantation.[136] Simultaneously, HSCT stimulates functional renewal of Tregs, bolstering immune tolerance (Figure 1F).[136] Thymic reactivation following transplantation further replenishes the immune system, generating a repertoire of naive T and B cells akin to those observed in young individuals.[136–138]

mRNA-Based Therapies

Messenger RNA is a single-stranded RNA (ssRNA) that participates in protein synthesis.[139] Conventional mRNA-based vaccines code for a protein of interest, containing 5′ and 3′ untranslated regions (UTRs), flanking the coding region.[139,140]

mRNA vaccines are distributed in the body according to their formulation and route of administration, activating specific receptors that trigger a local inflammatory response.[141] This allows the recruitment of antigen-presenting cells and the generation of a robust adaptive immune response, with T cell activation and long-lasting antibody production.[140,141]

mRNA technology, known primarily for its use in vaccines to induce antibody production, could be applied innovatively to regulate antibody production in autoimmune diseases.[142] This strategy would take advantage of natural regulatory mechanisms of the immune system, such as feedback inhibition, where high-affinity antibodies can prevent B cell activation.[141,142] mRNA could encode molecules that enhance this regulation or induce selective apoptosis of B and plasma cells, reducing the production of harmful autoantibodies.[141] The mRNA could be engineered to produce molecules that interfere with key receptors such as BCRs and TLRs or immune checkpoints regulating B cell activation and function.[142] It could also be used to generate proteins that neutralize autoantibodies or modulate cytokine responses and intracellular signaling pathways, affecting B cell proliferation and activation.[142,143] Furthermore, it could enhance the function of regulatory T cells, which suppress autoimmune responses, or interfere with plasma cell survival, reducing antibody production under autoimmune conditions.[142]

Recently, a study revealed that vaccines based on mRNA modified with 1-methyl pseudouridine (m1Ψ) have the potential to induce antigen-specific immune tolerance in murine models of MS.[144] These vaccines, formulated in liposomes without adjuvant capacity (m1Ψ-LPX), achieved prolonged and non-inflammatory antigen expression by avoiding the activation of TLR7 receptors, thus reducing the release of inflammatory cytokines and the activation of immune cells.[144,145]

In an EAE model, vaccination with m1Ψ-LPX encoding the MOG35-55 antigen completely protected mice from developing the disease when administered preventively.[144] In cases of established disease, the vaccine stopped the progression and reversed the pathology in several cases. This effect was associated with the induction of regulatory T cells ($FoxP3^+$) and elevated expression of immune exhaustion markers such as programmed cell death protein 1 (PD-1) and CTLA-4 on antigen-specific $CD4^+$ T cells.[144] Furthermore, the vaccine specifically suppressed Th1, Th17, and Th1/Th17 inflammatory cells without eliminating them through immune checkpoint-mediated mechanisms since inhibition of PD-1 or CTLA-4 abrogated their protective effect.[144]

Notably, this strategy was also effective in EAE models with different antigenic epitopes (PLP139-151), demonstrating cross-tolerance but maintaining intact immune responses to unrelated antigens.[144] This approach's flexibility, rapidity, and low cost allow for the customization of vaccines and their adaptation to multiple autoantigens, positioning them as a promising and highly innovative tool for treating autoimmune diseases.[144,145]

Future Perspectives and Challenges

In recent years, advances in cell therapy have led the field of biomedical research, offering new alternatives in regenerative medicine and oncology. These therapeutic strategies have also introduced innovative options for treating autoimmune diseases. Due to the versatility and range of underlying biological mechanisms of various cell therapy platforms (Figure 1), it is possible to apply these cutting-edge strategies to different autoimmune pathologies.

To achieve the clinical implementation of these innovative therapies reviewed in this article, it is essential to advance clinical trials to evaluate their safety, feasibility, and efficacy in humans. Although several therapies have already completed clinical studies and published their results, it is not uncommon for some trials to be suspended or their outcomes to remain unpublished. Nonetheless, the large number of registered clinical trials currently in recruitment and active status suggests promising progress in this field in the coming years.

Another significant challenge to the broad adoption of novel cell therapy alternatives is their high production cost, representing an access barrier. This problem is exemplified by the CAR T cell therapies currently approved for patient use.[146,147]

Finally, further research into cell-based therapies may improve our understanding of the immunological mechanisms driving autoimmune diseases, dysregulated inflammatory response conditions, and loss of immune homeostasis. Lasting, providing insights could lead to developing safer, more effective, personalized therapies tailored to each patient's disease characteristics.

Conclusion

The emergence of novel and innovative cell-based therapeutic alternatives offers significant opportunities for patients suffering from autoimmune diseases. The various cell therapy platforms discussed above exhibit distinct mechanisms of action that enable treating, mitigating, and repairing the damage caused by autoimmunity. While these proposed approaches are highly promising, further clinical studies are needed, along with the completion of several ongoing trials

and thorough reporting of their results and findings. Additionally, enhancing academic collaboration with industry is crucial to improve scalability and offset the high costs associated with manufacturing biological products. These therapies require Good Manufacturing Practice (GMP) facilities, clinically compatible reagents, specialized equipment, and highly trained technical, scientific, and clinical personnel. Numerous challenges remain in developing cell therapies for autoimmune diseases, yet preliminary results are encouraging, and their continued progress could redefine the standard of care for these conditions.

This article highlights the importance of these innovations and their potential impact on treating autoimmune diseases, providing a comprehensive analysis of the challenges and opportunities that will define the future of cell therapy. With a deeper understanding of these approaches and increased investment in research and development, these strategies could revolutionize the standard of autoimmune treatments, offering more effective and personalized treatments for patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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