Journal of Autoimmunity 148 (2024) 103303

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Antigen-specific T cells and autoimmunity

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ARTICLE INFO

Handling editor: C Selmi

Keywords:
Autoimmune diseases
Autoimmunity
T cells clone
Cross-reactivity
Antigen-specific T cells
Peptide-specific T cells

ABSTRACT

Autoimmune diseases (ADs) showcase the intricate balance between the immune system's protective functions and its potential for self-inflicted damage. These disorders arise from the immune system's erroneous targeting of the body's tissues, resulting in damage and disease. The ability of T cells to distinguish between self and non-self-antigens is pivotal to averting autoimmune reactions. Perturbations in this process contribute to AD development. Autoreactive T cells that elude thymic elimination are activated by mimics of self-antigens or are erroneously activated by self-antigens can trigger autoimmune responses. Various mechanisms, including molecular mimicry and bystander activation, contribute to AD initiation, with specific triggers and processes varying across the different ADs. In addition, the formation of neo-epitopes could also be implicated in the emergence of autoreactivity. The specificity of T cell responses centers on the antigen recognition sequences expressed by T cell receptors (TCRs), which recognize peptide fragments displayed by major histocompatibility complex (MHC) molecules. The assortment of TCR gene combinations yields a diverse array of T cell populations, each with distinct affinities for self and non-self antigens. However, new evidence challenges the traditional notion that clonal expansion solely steers the selection of higher-affinity T cells. Lower-affinity T cells also play a substantial role, prompting the "two-hit" hypothesis. High-affinity T cells incite initial responses, while their lower-affinity counterparts perpetuate autoimmunity. Precision treatments that target antigen-specific T cells hold promise for avoiding widespread immunosuppression. Nevertheless, detection of such antigen-specific T cells remains a challenge, and multiple technologies have been developed with different sensitivities while still harboring several drawbacks. In addition, elements such as human leukocyte antigen (HLA) haplotypes and validation through animal models are pivotal for advancing these strategies. In brief, this review delves into the intricate mechanisms contributing to ADs, accentuating the pivotal role(s) of antigen-specific T cells in steering immune responses and disease progression, as well as the novel strategies for the identification of antigen-specific cells and their possible future use in humans. Grasping the mechanisms behind ADs paves the way for targeted therapeutic interventions, potentially enhancing treatment choices while minimizing the risk of systemic immunosuppression.

1. Introduction

Autoimmune diseases (ADs) occur when the body's immune cells attack healthy tissues, causing damage and impairing function without a clear or immediate cause. In fact, these conditions are multifactorial. The immune system is tasked with the overwhelming responsibility of protecting us from a perpetual onslaught of pathogenic organisms including bacteria, viruses, fungi, and parasites. The most difficult challenge for the immune system is correctly identifying foreign

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https://doi.org/10.1016/j.jaut.2024.103303
Received 1 July 2024; Received in revised form 31 July 2024; Accepted 5 August 2024
Available online 13 August 2024

List of abbreviations

ADs	Autoimmune diseases
Agg	Aggrecan
AIH	Autoimmune hepatitis
APCs	Antigen-presenting cells
APL	Altered peptide ligand
BCR	B cell receptor
CAAR-T	Chimeric autoantibody receptor T cell
CAR	Chimeric antigen receptors
CAR-Treg	Tregs with chimeric antigen receptor
CFSE	Carboxy-fluorescein succinimidyl ester
ChgA	Chromogranin A
CIA	Collagen-induced arthritis
CII	Collagen type II
CMV	Cytomegalovirus
CNS	Central nervous system
D	Diversity
DAMPS	Damage-associated molecular patterns
DC	Dendritic cells
DN	Double negative
dsDNA	Double stranded DNA
Dsg	Desmoglein
Dsg3	Desmosomal glycoprotein desmoglein 3
EAE	Experimental autoimmune encephalomyelitis
EBNA-1	Epstein-Barr nuclear antigen 1
EBV	Epstein-Barr virus
ES	Epitope spreading
FITC	Fluorescein isothiocyanate
GAD	Glutamate decarboxylase
HCgp39	Human cartilage gp39
HIP	Hybrid insulin peptides
HIV	Human Immunodeficiency virus
I-A2	Insulinoma-associated antigen 2
IGRP	Islet-specific glucose-6-phosphatase catalytic subunit-related protein
J	Joining
MBP	Myelin basic protein
MHC	Major histocompatibility complex
MOG	Myelin oligodendrocyte glycoprotein
MS	Multiple sclerosis
NF-κB	Nuclear factor κB
NKT	Natural killer T cells
NOD	Non-obese diabetic
PADI	Peptidyl arginine deiminase
PAMPS	Pathogen-associated molecular patterns
PBC	Primary biliary cholangitis
PBMCs	Peripheral blood mononuclear cells
PF	Pemphigus foliaceus
pLNs	Peripheral lymph nodes
PLP	Proteolipid protein
pMHC	Peptide-MHC
PPI	Pre-proinsulin
PTMs	Post-translational modifications
PV	Pemphigus vulgaris
RA	Rheumatoid arthritis
RBC	Red blood cell
SLE	Systemic lupus erythematosus
T1D	Type 1 diabetes
TCRs	T-cells receptors
Tg	Transgenic
tolDCs	Tolerogenic DCs
Tregs	Regulatory T cells
V	Variable
ZnT8	Zinc-transporter 8
2D	Two-dimensional
TNC	Tenascin C
CRT	Calreticulin
DRiP	Defective ribosomal products
RNP	Ribonucleoprotein
TAL	Transaldolase

antigens expressed by these pathogens versus antigens expressed by self. All life has evolved using similar building blocks and thus proteins used by both humans and pathogens share considerable overlap in potential antigens. To identify threats the innate immune system (as a first line of defense) uses germ-line encoded receptors that recognize pathogen-associated molecular patterns (PAMPS) which initiate an inflammatory response to combat invading pathogens. However, these same innate immune cells can respond to damage-associated molecular patterns (DAMPS) resulting from trauma in the absence of infection (sterile inflammation) [1].

The innate immune system is comprised of several hematopoietic cell lineages. These include basophils, dendritic cells (DCs), eosinophils, Langerhans cells, mast cells, monocytes and macrophages, neutrophils, and NK cells. Of these, DCs are considered the primary antigen-presenting cells (APCs) and are responsible for initiating the adaptive immune responses. Through phagocytosis, these cells can internalize pathogens, digest them into small peptides, and then present these in the context of major histocompatibility complex (MHC) molecules expressed on the cell surface for recognition by cognate T cells using their individualized T/cell receptors (TCRs) that have specificity for the specific peptide:MHC molecules. The recognition of the foreign peptide induces activation of the T cells and depending on the co-receptors and cytokines expressed by the APCs, enables the T cells to co-ordinate the full complement of an anti-pathogen response including inflammation, antibody production, and cellular killing [2,3]. However, if the peptide is recognized as part of a self-protein, the T-cell will remain inactive, or if given the right circumstances, become activated to function as a regulatory T-cell to help shut down the inflammatory response and initiate the repair mechanism to restore tissue homeostasis [4].

Lastly, if the peptide is from a self-protein that is sufficiently distinct, it is recognized as non-self, leading to T-cell activation and an attack on self-tissue. Once initiated, this autoimmune reaction leads to cell death that in turn releases more self-antigen, which promotes more activated T-cells, perpetuating a vicious cycle that will eventually present as clinical symptoms of an autoimmune disorder. As central co-ordinators of the immune system, T cells have been a major focus in ADs research and a prime target for immune-therapeutic interventions in these conditions. While therapies targeting broad T-cell suppression have been in use, a major drawback is the increased risk of infection. The holy grail of autoimmune therapy is to target autoantigen-specific T-cells, leaving the rest of the immune system intact to fight infection. The current knowledge concerning the identification and manipulation of these antigen-specific T-cells in ADs is therefore the subject of this review.

The development of T-cell-mediated ADs is a complicated process that involves various stages. These stages include the failure of the immune system to eliminate autoreactive T-cells during thymic development, frequent exposure to antigens (that are either modified self antigens or mimics of self antigens), activation of autoreactive T cells, breakdown of immune regulation, migration of T cells to target organs, and subsequent tissue destruction [5]. Recent research has identified potential mechanisms that allow autoreactive T cells that have evaded the body's immune tolerance mechanism, to trigger the development of

ADs. These mechanisms include molecular mimicry, bystander activation, epitope spreading (ES), and superantigens, among others [2,3]. However, the timing, location, and means by which such autoreactive T cells are activated in most ADs are not yet fully understood (Fig. 1).

One of the main determinants of autoimmunity is thought to be associated with the molecular nature of the TCRs that recognize self-antigens. These receptors identify peptides (that serve as targets of self-antigens) that are expressed on the cell surface as an integral part of self-specific MHC molecules. This process is known as MHC limitation [6–8]. The TCR is remarkable though in that there is a near infinite number of possibilities for unique peptide/MHC binding. The synthesis of TCR assembly within precursor T cells in the thymus tissue requires recombination of the Variable (V), Diversity (D), and Joining (J) regions that play a crucial role in generating T-cell diversity [9]. Importantly, once a successful re-arrangement has occurred to produce a unique TCR, these newly minted T cells must undergo both positive and negative selection within the thymus. Those that recognize self-antigens with relatively high affinity, as well as those with no detectable affinity, are deleted and the remaining are considered positively selected for weak self-peptide-MHC recognition and enter the circulation. Therefore, all T cells that make it through thymic development have at least a minor affinity towards self-peptides. The VDJ genes encoding the TCRs can produce up to 10^{13} TCR clonotypes [10]. In addition, the TCR may only recognize a specific region of a presented peptide, not scanning all amino acids (known as discontinuous epitopes), leading to T cell recognition and activation [11,12]. Thus, in certain cases, the TCR can recognize multiple epitopes, both self and non-self. This phenomenon is known as "polyspecificity" [13,14].

The central dogma of immunity states that clonal expansion drives the selection of higher-affinity T-cell clones [15,16]. However, the emergence of novel methods, such as micropipette-based adhesion two-dimensional (2D) affinity tests, for detecting lower-affinity T cells has challenged the notion that MHC II tetramers accurately identify the entire population of autoreactive T cells [17,18]. This discovery has led to the understanding that there are both "low" and "high" affinity T cells, which have different implications for the initiation and perpetuation of autoimmunity in conditions like multiple sclerosis (MS) [19–22]. This has led to the development of the "two-hit" hypothesis in autoimmunity. High-affinity T cells trigger the initial response to autoantigens in the early stages of the disease. As the AD progresses, new epitopes may emerge, but antigen-specific T cells tend to exhibit lower affinity towards these new epitopes (Fig. 1). Nevertheless, it is reasoned that these T cells in concert perpetuate autoimmunity [19,23].

The identification of antigen-specific T cells is critical for the development of immune-based therapies in autoimmunity (Fig. 1). These therapies aim to selectively target and neutralize autoreactive T cells through various mechanisms, such as eliminating them *via* cytotoxic mechanisms or inducing tolerance through the activation of antigen-specific regulatory T cells (Tregs). This approach avoids the need for global immunosuppression [24]. To date, only a limited number of studies have successfully identified therapeutic targets for autoantigen-specific T cells. Notably, among the ADs investigated so far,

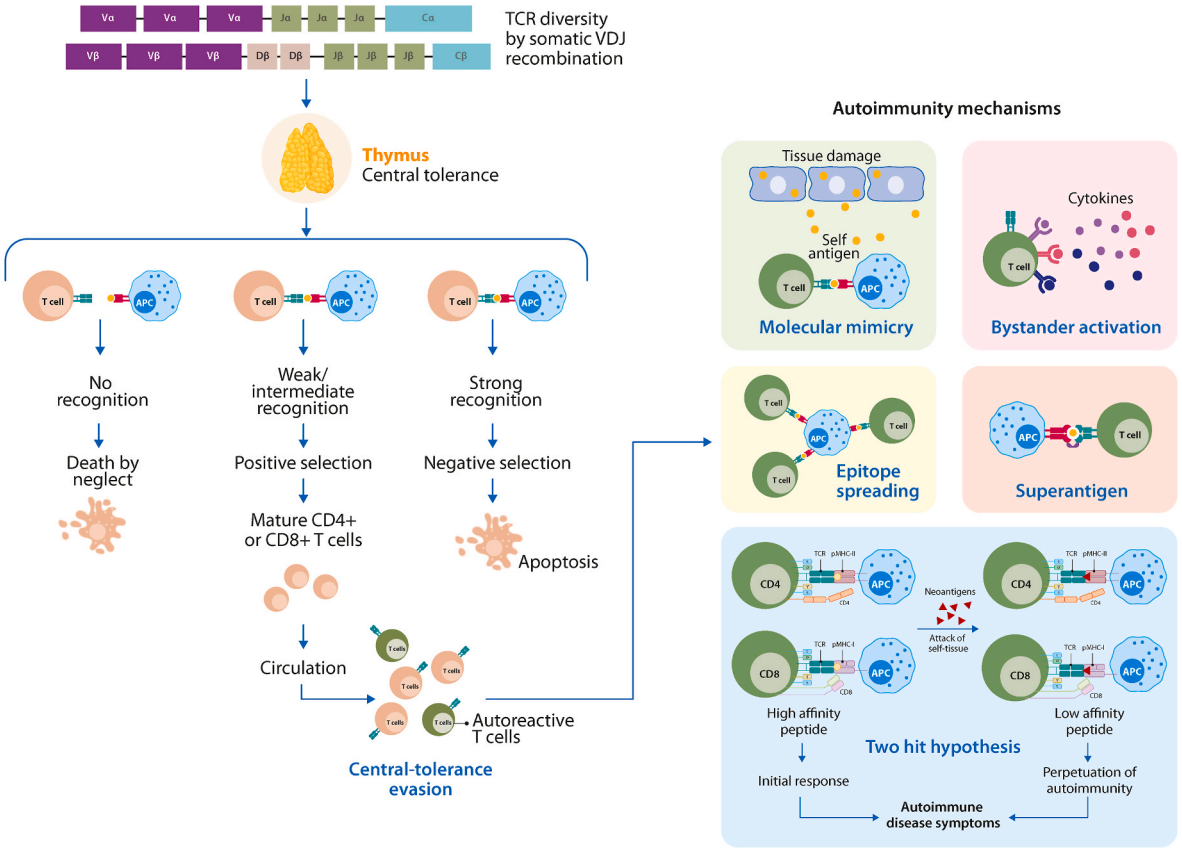

Fig. 1. Development of T-cell-mediated autoimmunity. The somatic recombination of TCR genes in immature thymocytes results in a mixture of cells, some with functional TCR specificities and many with either non-functional or potentially self-reactive specificities. The process of TCR synthesis and assembly within precursor T cells in the thymus involves VDJ recombination, which is essential for generating T cell diversity. In the central T-cell tolerance mechanism, thymocytes expressing TCRs that do not bind to self-peptide–MHC complexes die by neglect. Those with a low to intermediate affinity for self-peptide–MHC complexes survive and differentiate into $CD4^+$ or $CD8^+$ T cells through positive selection. Thymocytes with highly self-reactive TCRs are eliminated during negative selection. However, the failure of the immune system to eliminate autoreactive T cells during thymic development can contribute to the development of autoimmunity through several mechanisms, such as molecular mimicry, bystander activation, epitope spreading, and superantigens. Additionally, a novel hypothesis known as the "two-hit" model suggests that both high and low affinity T cells can contribute to the initiation and perpetuation of autoimmunity. TCR: T cell receptor.

MS, rheumatoid arthritis (RA), and type 1 diabetes (T1D) have shown the most promising results in this regard. However, besides isolating antigen-specific T cells, other factors such as HLA haplotypes and the utilization of animal models for validation would be necessary before these strategies can be further applied in humans [24].

2. Autoantigens and autoimmunity

One of the major challenges in identifying and isolating autoantigen-specific T-cell clones is understanding the precise nature of the epitope (s) of the autoantigens and their role in pathogenesis. Moreover, it is difficult to identify those that initiate the autoimmune response versus those that perpetuate it. Several antigens and peptide sequences have been identified that are associated with the activation of T cells and associated with immunopathology in organ-specific and systemic ADs (Table 1) [25–62]. Although a failure in central and peripheral tolerance is thought to be associated with ADs, molecular mimicry [2] and ES [63,64] are considered some of the main mechanisms driving autoimmunity exemplifying the polyspecificity of the immune response.

Some ADs are classified as organ-specific, meaning that the immune system specifically targets and attacks a particular organ or tissue in the body, while others are systemic and affect multiple organs. The exact cause of organ-specific ADs is not fully understood, but there are several possible explanations for this phenomenon. One key contributing element is the expression of tissue-specific antigens in the affected organ, as well as the presence of distinct immune cells and immune regulatory systems within each organ. For example, certain organs may have a higher concentration of the targeted cells, increasing autoantigen density in a single site, making them more susceptible to autoimmune attack. Additionally, the target cells from each organ may be endowed with biochemical and/or structural properties that may help to perpetuate autoimmunity (e.g., β cells in T1D) [1]. Environmental factors such as infections, chemical insults, and metabolic stress can also contribute to tissue damage and exposure to cryptic antigens. This, in turn, can lead to antigen presentation and the induction of an autoimmune response [77,78]. Identifying autoantigens that are potentially generated only within specific *in-vivo* organ niches therefore continues to remain a challenge.

Molecular mimicry is often regarded as a primary mechanism that leads to the development of autoimmunity [2]. Despite extensive research on the homology between several microbial peptides/proteins and native human tissue peptides/proteins, the intricacies of how microbial proteins are involved in the etiology of ADs remain unknown. Host factors such as defects in central or peripheral tolerance, *HLA,* and *non-HLA* polymorphisms [79–86], TCRs with diverse heterodimers or homodimers of α and β chains configuration [87], microbiome [88], and immune-senescence [89], all individually or collectively play a critical role in the susceptibility to ADs when molecular mimicry occurs in genetically susceptible individuals.

Several infectious agents are linked to ADs through molecular mimicry. For example, the Epstein–Barr nuclear antigen 1 (EBNA-1) from the Epstein-Barr virus (EBV) exhibits similarity with myelin basic protein (MBP), a key antigen in the development of MS. It has been demonstrated that EBV is associated with the progression and severity of MS [90]. SARS-CoV-2 is another example of infection that can trigger ADs through molecular mimicry [2,3].

These initial T-cell responses to molecular mimicry are followed by progressive AD, and in some conditions, autoimmunity only develops after chronic progression of the infectious disease. For instance, in the endemic form of pemphigus foliaceous (PF) known as Fogo Selvagem, it has been demonstrated that patients initially develop a response to desmoglein (Dsg), but this response does not correspond to pathogenic antibodies. However, as the disease progresses, patients develop reactivity to other determinants within the same protein that are considered pathogenic [91]. This illustrates the potential for the emergence of different reactivities at different stages of the disease, likely giving rise

Table 1
Antigens associated with antigen-specific T cell response in ADs.

Autoimmune disease	Antigen/peptide	Immune response	Reference
MS	MBP_{85-99}	HLA-DR2 molecules in MS lesions present this myelin-derived peptide.	[25]
	$MBP_{1–24,\ 30–54,\ 75–99,\ 90–114,\ 105–129,\ 120–144,\ 135–159\ y\ 150–170}$	The recognition profile and dynamics of T cells specific to these myelin antigens vary over time in patients with MS.	[26]
	MBP_{84-102}	Phase I dose-escalation clinical trial with MBP_{84-102} complexed with HLA-DR2 (AG284) in HLA-DR2+ secondary progressive MS patients demonstrated a favorable safety profile but no effect on clinical and radiological secondary outcome measures.	[56]
	PLP_{95-116}	Specific PLP-restricted T-cell lines from transgenic mice immunized with this portion of PLP, when adoptively transferred to RAG-2−/− mice expressing HLA-DR2 (DRB1*1502) molecules, generate neurological disorder manifested as ataxic movement without apparent paresis on days 3, 4, or 5 after cell transfer.	[37]
	$PLP_{95-116,\ 105-124}$	PLP specific T cells were more commonly found in patients with MS carrying the DR2 gene than in those without DR2. This suggests that the DR2-restricted T cells recognizing these epitopes play a role in the development of MS.	[48]
	$PLP_{95-116,\ 105-124,\ 139-155}$	PLP-specific T cells may play a role in the immunopathology of MS due to shared motifs along with surrounding amino acid identities.	[57]
	MAG	Multiple MAG peptides are recognized by circulating T and B lymphocytes of patients with polyneuropathy and MS.	[58]
	MOG_{35-55}	Induction of EAE one week after immunization	[59]
	MOG_{63-87}	MOG peptides are capable of inducing a significant number of IFN-specific secreting cells *in vitro* from peripheral blood of DR2 (15) + patients with MS, but not in healthy DR2(15) + individuals.	[60]
	S100-β	Specific T-cell lines derived from patients with MS demonstrated responses to HLA-restricted DR.	[61]
		The S100B inhibitor provides protection against EAE.	[62]
	Fatty acid–binding protein 7, prokineticin-2, reticulon-3, and	Immunization of mice induced antigen-specific responses and leukocyte infiltration in the CNS.	[27]

(*continued on next page*)

Table 1 (*continued*)

Autoimmune disease	Antigen/peptide	Immune response	Reference
	synaptosomal-associated protein 91		
	CNPase$_{343-373}$	Strong primary responses directed against CNP recognized in the context of HLA-DR2 molecules, were found in patients with highly active MS disease.	[28]
	Transaldolase	In sections of human brain and primary cultures of murine brain cells, it was demonstrated that TAL is selectively expressed in oligodendrocytes. Autoantibodies have been detected in the serum and cerebrospinal fluid of patients with MS.	[29]
RA	CII$_{263-270}$	T cells from patients with severe RA predominantly recognize the immunodominant CII peptide in its glycosylated form.	[30]
	CII$_{255-274}$	Increased antigen-specific T-cell responses in RA, especially in the early stages of the disease.	[31]
	CII$_{311–325}$	The exclusive binding of Cit-peptide to HLA-DRB1*10:01 suggests that the recognition of this citrullinated epitope varies among individuals carrying different HLA-DR molecules associated with RA.	[32]
	HCgp39	Induction of tolerance with intranasal administration of HCgp39 in DBA/1 mice.	[33]
	HCgp39$_{259-271}$	Antigen-specific cellular response associated with disease activity in patients with RA.	[34]
	Agg$_{84-103}$	Antigen-specific proinflammatory response in patients with RA.	[35]
	G1 globular domain of Agg	G1 autoreactive T cells in peripheral blood leukocytes and synovium of RA patients.	[36]
	Hsp60	Immunomodulatory role of antigen-specific T cells in the inflammatory processes of RA.	[38]
	hnRNP-A2$_{117/120–133}$	Immunodominant T-cell epitopes are associated with disease activity and bone erosion in RA.	[39]
	Fibrinogen-α$_{79–91}$	T-cell autoreactivity to citrullinated aggrecan peptides in patients with AR carrying shared epitope HLA-DRB1 alleles.	[40]
	CRT	Citrullinated CRT is overabundant in the synovial membrane of RA and enhances *in vitro* signaling activated by shared epitopes.	[41]
	TNC$_{22}$	T cells specific to Cyt-TNC from different HLA-DRB1*04:01 positive RA patients exhibit shared characteristics between peripheral blood and synovial fluid.	[42]
	α-enolase$_{26}$	The citrullinated peptide restricted by HLA-DRB1*04:01, Cit$_{26}$, elicited significant functional T-cell responses in primary cells from patients with RA. This antigen is recognized by T cells with high specificity for the citrulline residue.	[43]
JAI	Aggrecan, fibrillin, and MMP-3	Recognition of T cells in patients with JIA irrespective of MHC genotype. Antigen-specific T cells upon restimulation demonstrated IFN-γ/IL-17 production and inhibition of IL-10 production.	[44]
SLE	SmD1, RNP70, histones, Ro and La	CD4$^+$ T cells reactive to nuclear antigens expand in active SLE. These cells display a Th1 phenotype, producing IFN-γ, and infiltrate inflamed target organs, such as the kidney.	[45]
	70K$_{131–151}$	The 70K peptide is recognized by both T cells and autoantibodies produced by MRL/lpr mice.	[46]
	H2B$_{10-33}$, H4$_{16-39}$ and H4$_{71-94}$	The peptide autoepitopes activated pathogenic Th cells from lupus-prone (SWR x NZB)F1 mice *in vivo*, leading to the development of severe lupus nephritis.	[47]
	SmD$_{183-119}$	T cells from patients with SLE show strong reactivity to the SmD1 epitope. The presence of high-frequency and specific anti-SmD1 antibodies in SLE patients also indicates a possible involvement in the development of the disease.	[49]
	La$_{13-30}$	Immunization with the mouse peptide La$_{13-30}$ resulted in a T-cell proliferative response and the production of specific autoantibodies targeting both intrastructural (La) and intermolecular (Ro) components of the mouse La/Ro RNP.	[50]
MG	AChR	The frequency of proliferation of CCR6+ memory T cells and the production of IFN-γ and IL-17 in subjects with MG in response to AChR-derived peptides was significantly higher than that of healthy controls.	[51]
		The majority of patients with myasthenia gravis exhibited T-cell reactivities to different synthetic peptide sequences ($_{100-117}$, $_{113–130}$, $_{143–163}$, $_{161–179}$, $_{207–225}$, $_{221–240}$, and $_{235–255}$) derived from the α subunit of AChR.	[52]

(*continued on next page*)

Table 1 (*continued*)

Autoimmune disease	Antigen/peptide	Immune response	Reference
NMO	AQP-4	AQP4-specific T cells have the ability to cause a disease similar to NMO in mice, even in the absence of antibodies.	[53]
	AQP-$4_{268-285}$	AQP4-specific T cells can indeed cause NMO-like lesions in the presence of NMO-IgG, indicating their involvement in the pathogenesis of NMO.	[54]
	AQP-$4_{137–151,\ 222–236,\ 217–231\ y\ 69–283}$	The main immunodominant epitopes of the AQP4 protein were identified in patients with NMO. Specific T-cell lines from NMO patients mainly secrete IL-17 and IL-10	[55]

AChR: Acetylcholine receptor, Agg: Aggrecan, AQP-4: Aquaporin-4, CII: Collagen type II, CNPase: 2′,3′-cyclic nucleotide 3′-phosphodiesterase, CNS: Central nervous system, CRT: Calreticulin, EAE: Experimental autoimmune encephalomyelitis, HCgp39: Human cartilage gp39, hnRNP-A2: Heterogeneous nuclear ribonucleoprotein A2, Hsp60: Heat shock protein, IFN: Interferon, IL: Interleukin, JAI: Juvenile idiopathic arthritis, MAG: Myelin associated glycoprotein, MBP: Myelin basic protein, MG: Myasthenia gravis, MHC: Major histocompatibility complex, MMP: Matrix metalloproteinase, MOG: Myelin oligodendrocyte glycoprotein, MS: Multiple sclerosis, NMO: Neuromyelitis optica, PLP: Proteolipid protein, RA: Rheumatoid arthritis, RNP: Ribonucleoprotein, SLE: Systemic lupus erythematosus, T1D: Type 1 diabetes, TAL: Transaldolase, TNC: Tenascin C.

to both pathogenic and non-pathogenic antigen-specific T cells.

2.1. Neoepitopes

The role of post-translational modifications (PTM) on peptides and their preferred recognition by T cells in patients with select ADs has opened new possibilities in the search for potentially true autoantigenic epitopes. The discovery of these "neoepitopes" recognized by T cells represents a significant milestone in the field of autoimmunity research. In addition to conventional "native" peptides produced by the proteolytic processing of established antigenic proteins, alternative peptide species have been postulated to contribute to the expansion of the repertoire of disease-relevant T cells, particularly in organ-specific ADs like T1D [92,93]. Several mechanisms have been proposed as potential contributors to the emergence of neoepitopes, with one of the most notable being the generation of peptides resulting from PTMs of native peptides, such as citrullination or deamidation [92,93]. This plays a pivotal role in the pathogenesis of some ADs like RA, where the activation of peptidyl arginine deiminase (PADI) leads to the conversion of arginine to citrulline, creating potentially new antigens that become associated specifically to select RA-associated MHC haplotypes [94]. Environmental factors, such as smoking or *Porphyromonas gingivalis* infection are thought to be the major triggers of such PTMs [94–96]. This highlights the influence of the environment in the development of autoimmunity (i.e., autoimmune ecology), and its role in the emergence of neoepitopes [97,98].

Another perspective on the potential breakdown of self-tolerance emerges from the studies of Delong T et al. [99], who found that diabetes-inducing $CD4^+$ T-cell clones isolated from non-obese diabetic (NOD) mice recognize epitopes formed by covalent cross-linking of pro-insulin peptides to other peptides present in β cell secretory granules. These hybrid insulin peptides (HIPs) are antigenic for $CD4^+$ T cells and can be detected by mass spectrometry in the β cells of the pancreas. Furthermore, $CD4^+$ T cells isolated from the residual pancreatic islets of two organ donors who had T1D were also shown to recognize such HIPs. These findings suggest that autoreactive T cells that target such unique hybrid peptides may be the basis for the breakdown of self-tolerance [99–101].

Along similar lines of studies, a report showed that chromogranin A (ChgA) is an autoantigen for $CD4^+$ T cells in a similar NOD mouse model of T1D. The naturally processed chromogranin A peptide (WE14) acts as a weak agonist for the prototype T-cell clone named BDC-2.5, as well as other ChgA-specific T-cell clones. Of interest was the finding that mimotope peptides that share a C-terminal motif (WXRM(D/E)) showed a relatively higher degree of reactivity than the parent peptide. This motif is also present in WE14 (WSRMD) but at its N terminus. Therefore, to place the WE14 motif into the same position as seen in the mimotopes, the authors introduced the amino acid RLGL to its N terminus. Like the other mimotopes, RLGL-WE14 was found to be much more potent than WE14 in T-cell stimulation and was shown to activate a relatively more diverse population of $CD4^+$ T cells, which also respond to WE14 as well as islets from wild type, but not $CD4^+$ T cells from ChgA knock-out mice. The prediction that many different N-terminal amino acid extensions to the WXRM(D/E) motif are sufficient to greatly enhance T-cell activation led the authors to propose that such a post-translational modification may occur uniquely in the pancreas or pancreatic lymph nodes, perhaps *via* the mechanism of transpeptidation (*"the process of transferring an amino acid or group of amino acids from one compound to another"*). These modifications may underlie the mechanisms of escape of T cells in these mice from thymic negative selection [99–101].

Similar to HIP, certain peptides contain new junctions generated from alternatively spliced mRNA that appear solely in islets and not in the thymus or other lymphoid tissues in T1D [102–104]. Gonzalez-Duque et al. [105], found that β cells present conventional peptides (e.g., SCG5, PCSK2, UCN3) in association with HLA-A2. Alternate splicing of the mRNA (IAPP/IAPP) leads to the generation of spliced peptides (SCG5-009) and the fusion peptides. In addition, while these peptides are targeted by circulating naive $CD8^+$ T-cell repertoire in healthy donors, in patients with T1D the pancreas-infiltrating cells reactive to the HLA-A2-restricted $IAPP_{15–17/5–10}$ peptides were found to be significantly enriched, thus confirming the role of neo-epitopes *via* mRNA alternative splicing [105], although the precise mechanisms for such enriched infiltration into the pancreatic tissue remain undetermined.

Another concept to be considered is that peptides derived from defective ribosomal products (DRiP) could increase their expression levels *via* autoimmunity-associated gene polymorphisms [106]. This view is supported by the finding of the unchecked proliferation of cells in tumors that are associated with increased translation and buildup of anomalous translation products, i.e., DRiPs. These DRiPs arise from the translation of normally untranslated regions, ribosomal frame-shifting, or alternative initiation of translation, and give rise to a distinctive type of tumor-associated antigens that are expressed selectively by malignant cells [107–109]. The study by Kracht et al. [106], found that INS-DRiP induced the proliferation of T cells from patients with T1D, and INS-$DRiP_{1-9}$ specific $CD8^+$ T clones killed pancreatic β cells *in vitro*. In addition, data from transfected INS-DRiP expressing 293T cells showed that the induction of endoplasmic reticulum stress induced by thapsigargin induced the expression of the DRiP peptide [106]. This may suggest that under situations of stress (e.g., viral infections or metabolic imbalance), neo-epitopes that are generated could promote autoimmunity [110].

As different mechanisms for the emergence of neo-epitopes have been described, it represents a challenge in the study of autoimmunity and the subsequent development of antigen-specific T-cell therapies. As the disease progresses, new epitopes could emerge based on exposure to external (e.g., metabolic stress, viral or bacterial infections, tobacco consumption) or internal factors (genetic susceptibility). Future investigation of the discussed mechanisms of autoimmunity could allow the detection of multiple antigen-specific T cells in different stages of the disease (i.e., the two-hit hypothesis), which could have implications for

future strategies involving cell-based therapies that have the potential to advance into clinical trials.

3. Detection and isolation of antigen-specific T cells

The frequency of T cells specific for a single peptide-MHC (pMHC) ligand is extremely low, especially within the naive repertoire (range 0.2–60 cells/10^6 naive T cells), a consequence of the enormous diversity of the T-cell repertoire to a wide variety of diverse antigens to be encountered by a host [111–126]. Given such low frequencies, antigen-specific T-cell identification has traditionally relied on proliferation assays whereby T cells within the peripheral blood mononuclear cells (PBMCs) are incubated with DCs pulsed with the antigen of interest. The proliferation of T cells specific for epitopes within that antigen is then measured by either tritiated thymidine uptake, intercalating dye uptake, or dye dilution. However, the phenotype and frequency could be altered, and bystander proliferation cannot be excluded in such assays. Thus, multi-parametric strategies such as polychromatic flow cytometry that include the use of peptide-MHC bearing tetramers have emerged as novel strategies for the identification and isolation of T-cell clones as described below [127].

In general, there are two strategies to identify antigen-specific T cells. The first strategy involves using labeled recombinant peptide-bearing MHC multimers (such as tetramers or pentamers) that have specificity for being recognized by specific TCR. These multimers are capable of binding to specific clones of T cells (Fig. 2). By utilizing flow cytometry, the fluorescently labeled T cells can be easily analyzed/isolated and the frequencies of peptide-specific T cells within a heterogeneous population can be determined. The use of a cell sorter that allows for the collection of the unique population of tetramer-binding T cells provides a valuable resource for the isolation of the desired clonal population of T cells. This method provides unbiased access to the total pool of T cells with a distinct specificity and within a certain affinity range [127]. The second strategy involves assessing functional parameters to identify T cells that respond to specific antigenic challenge (Fig. 2). Upon antigen-specific activation, T cells have the potential to synthesize specific cytokines/chemokines, and express co-stimulatory molecules, induce cytotoxicity, and undergo proliferation. Fluorescently tagged antibodies against these functional molecules can be utilized, and the T cells synthesizing such molecules can be detected using flow cytometry and isolated using a cell sorter. Single-cell flow-cytometric assays can potentially access all relevant T-cell functions, and both intracellular and cell surface markers allow for the isolation of antigen-specific T cells [127].

In addition to the isolation of peptide-MHC binding T cells, the advent of single-cell sequencing methods, exemplified by the 10× Genomics platform, has revolutionized the study of intricate biological processes at the individual cell level [128–130]. Traditional bulk sequencing loses cellular diversity through averaging, masking essential variations. In contrast, 10× single-cell sequencing captures the transcriptome of each T cell, exposing nuanced gene expression patterns [129]. This facilitates the detection of uncommon, antigen-specific

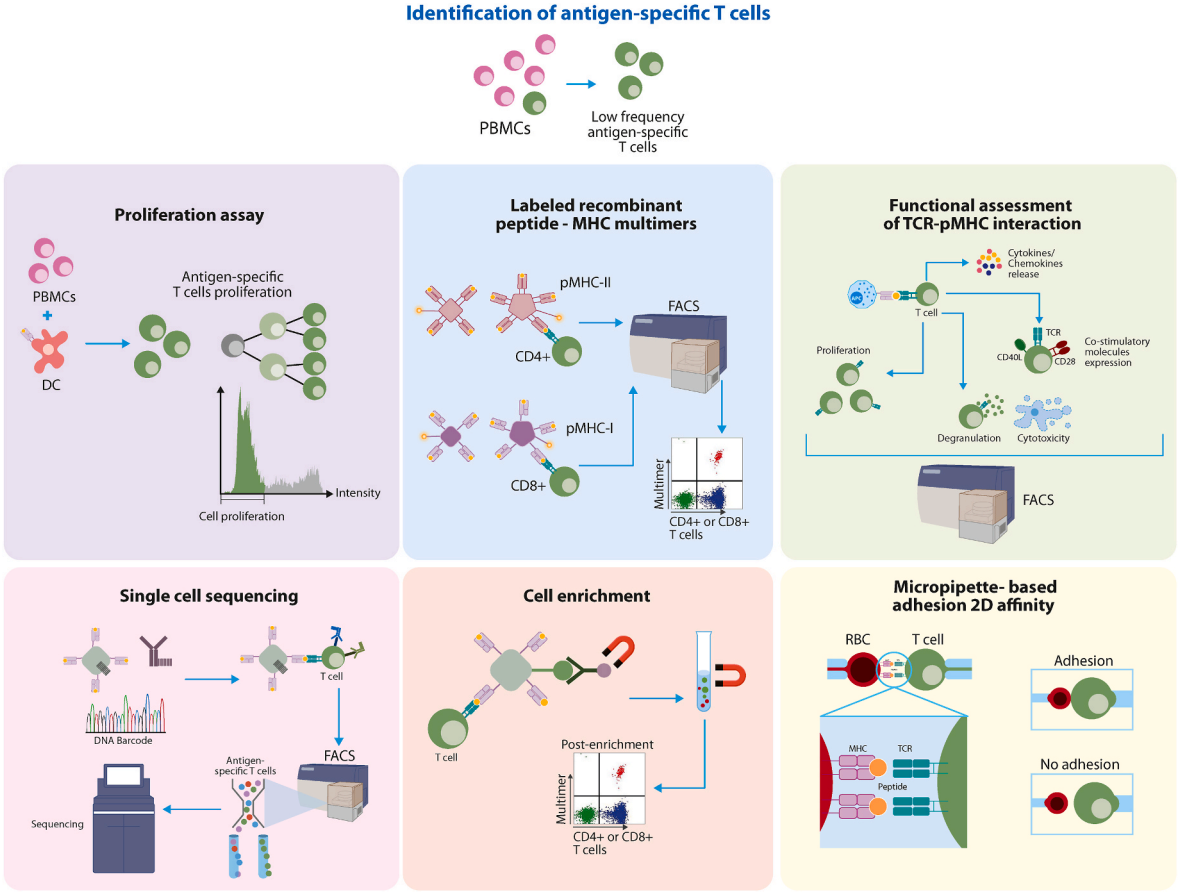

Fig. 2. Identification of antigen-specific T cells. Various approaches have been developed to characterize antigen-specific T cells, including, proliferation assays, flow cytometric identification of antigen-specific T cells *via*staining with labeled recombinant pMHC multimers, detection of TCR–pMHC interactions by assessing the functional response of T cells after exposure to specific antigens, identification of antigen-specific T cells *via*DNA-barcoded pMHC multimers followed by single-cell sequencing, magnetic bead enrichment of antigen-specific T cells using a pMHC multimer, and evaluation of cross-junctional receptor–ligand interactions through micropipette-based adhesion assays with two-dimensional tetramer. DCs: Dendritic cells, FACS: Fluorescence-activated Cell Sorting, MHC: Major histocompatibility complex, PBMCs: Peripheral blood mononuclear cells, RBC: Red blood cells, TCR: T cell receptor.

T-cell subsets often overlooked by bulk sequencing. This approach is particularly relevant in autoimmunity research, where immune reactions target self-antigens (Fig. 2). Using methods like tetramer staining or activation-induced marker assays, researchers can isolate these antigen-specific T cells. Subsequent profiling through 10× single-cell sequencing unravels gene expression signatures uniquely linked to autoimmune responses. It also aids in examining the diversity of T cell receptor sequences, allowing the tracking of clonally expanded T cell populations. By unraveling immune response diversity and the characterizarion of T cell populations with remarkable precision, this technique holds significant promise [128–130].

3.1. pMHC-multimers or pMHC-tetramers

Fluorescently labeled pMHC-multimers are used to isolate (flow cytometry), identify and characterize antigen-specific T cells. In recent years, the low binding affinity of pMHC-multimers has been enhanced through the multimerization of peptide-MHC complexes, resulting in increased relative binding avidity [131,132]. Class I multimers are widely used to isolate, quantify and characterize $CD8^+$ T-cell responses, while class II multimers present more challenges due to differences in MHC class II structure and TCR affinity.

Tetramer technology, however, has the limitation of requiring detailed characterization of the antigenic epitope, which is a specific peptide restricted to a particular MHC haplotype. Nevertheless, peptide-exchange technologies have facilitated the rapid engineering of multiple MHC-peptide reagents, enabling the development of quick epitope mapping techniques that have successfully identified numerous new T-cell epitopes [133–137]. Examples include antigen-specific cells for the hepatitis C virus [133], and *Chlamydia trachomatis* [135]. Combinatorial color-coded tetramers allow for the simultaneous detection of several clonal populations of T cells and a larger number of different antigen specificities [138,139]. However, tetramers still exhibit relatively low sensitivity in detecting low-affinity cells, which are unfortunately implicated mostly in chronic stages of autoimmunity [127].

Recently, MHC-dodecamers have emerged as the next-generation technology for isolating antigen-specific T cells. They offer significantly greater sensitivity and serve as a versatile alternative to pMHC-tetramers for the detection, isolation, and phenotypic analysis of antigen-specific T cells. Specifically, dodecamers can detect two-to fivefold more antigen-specific T cells in both human and murine $CD4^+$ and $CD8^+$ αβ TCR-expressing T cells compared to the corresponding tetramers [140]. The low-affinity, tetramer-negative, dodecamer-positive T cells showed comparable effector cytokine responses as those noted for the corresponding tetramer-positive T cells [140].

Another technique for identifying low-affinity T cells involves the utilization of pMHC dextramers. These dextramers are composed of pMHC-tetramers with an attached linear chain of dextran, which enhances the binding affinity. pMHC dextramers are more effective than pMHC tetramers in detecting low-affinity T cells and their study continues to evolve [141]. They have been used in the detection of antigen-specific T cells for cytomegalovirus (CMV), Human Immunodeficiency virus (HIV), and T1D-related antigens [141].

3.2. T cell antigen reactivity

The isolation of T cells using multimer reagents, however, does not provide information about the functionality of the isolated T cells. Functional parameters are crucial for assessing the quality of an immune response, particularly for T helper cells that exhibit different effector functions, which define their subtypes (i.e., Th1, Th2, Th17, Tregs, etc.) [127]. Identifying the functional phenotype of antigen-specific T cells requires *in vitro* stimulation using peptides, proteins, or lysates [127] (Fig. 2).

Flow cytometry can be used to directly quantify the frequencies of antigen-specific T cells by measuring the production of cytokines induced by the antigen *in vitro*, which is typically measured following incubation of the T cells with antigen-presenting cells pulsed with the antigen of interest for 4–12 h [142–144]. Cytokines can be detected either intracellularly or on the cell surface using a capture matrix. The latter method offers the advantage of detecting live cytokine-secreting cells and enabling enrichment *via* magnetic cell sorting [145,146]. However, cytokine production is limited to certain T cell subsets, so enumeration solely based on cytokine production may be incomplete. In addition, cells can synthesize multiple cytokines, and focusing on a single cytokine is associated with bias. Nevertheless, the enrichment of highly specialized subsets, such as purified virus-specific IFN-γ-secreting T cells, offers advantages for adoptive T-cell therapy of viral infections [147–150], and could be used for functional analysis of antigen-specific cells in autoimmune and/or allergic conditions [151].

In addition to the detection of cytokine production, flow cytometry can directly visualize antigen-specific T cells by detecting activation markers on the cell surface (after *in vitro* stimulation with APCs). These markers enable a comprehensive characterization of the entire pool of specific T cells against a given antigen, regardless of functional specialization, MHC allele, or without a precise definition of the antigenic epitope (discovering new immunodominant epitopes). Commonly, cells are stimulated *in vitro* and further assessed for the expression of activation markers and selection by cell sorter analysis [152].

Some markers that have been successfully utilized to identify this group of cells include CD69, CD154 (CD40L), and CD137 [153–162]. However, CD69 background expression is also found on non-stimulated T cells [158], and CD69 upregulation is not solely dependent on T-cell receptor activation [163,164], Therefore, additional markers such as CD154 and CD137 have been shown to increase the sensitivity and specificity for detecting T cell clones. CD154 is expressed by virtually all functionally activated $CD4^+$ T cells, regardless of their differentiation state [155–157], and it has extremely low background expression *ex vivo*, enabling highly specific detection of antigen-induced CD154-expressing T cells [151]. Another marker, CD137, is expressed on antigen-activated $CD4^+$, $CD8^+$, and γδ+ T cells. CD137 together with CD154 may represent the most accurate markers of cell activation following antigenic stimulation [161,165]. These activation markers could be used in the discovery and selection of clones in the context of pathogen infection, autoimmunity, and cancer [152].

3.3. Magnetic bead enrichment assays

Despite the above-discussed techniques, the isolation of low-frequency antigen-specific T cells remains a major challenge. An alternative approach to increase the number of rare antigen-specific T cells for accurate cytometric analysis is through quantitative pre-enrichment of target cells using magnetic cell separation This method enables the rapid processing of a large pool of cell samples [166,167]. The specificity of the sorting marker is a prerequisite for the magnetic enrichment of antigen-specific T cells, and additional exclusion criteria are necessary to improve sensitivity and specificity. This technology allows for the direct *ex vivo* detection and in-depth characterization of a small number of antigen-specific T cells from large sample sizes [166,167] (Fig. 2).

The enrichment of rare cytokine-producing T cells *via* the cytokine secretion assay has enabled the isolation of several other rare cytokine-producing T-cell sub-populations [142]. These include tetanus-specific $CD4^+$ T cells producing IFN-γ and IL-4, *Candida albicans*-specific $CD4^+$ T cells producing IL-17 [142,168], as well as autoreactive $CD4^+$ T cells producing IFN-γ and IL-4 in pemphigus vulgaris (PV) patients [169]. Additionally, rare allergen-specific producers of IL-4, IFN-γ, and IL-10 producers have been isolated from both allergic patients and healthy individuals [170]. However, it is important to note that cytokine secretion is heterogeneous and limited to specific subsets of T cells, which restricts the detection to only two or three cytokines at a time.

pMHC-tetramers have been used to detect and isolate rare antigen-experienced $CD4^+$ and $CD8^+$ memory T cells in humans and mice through magnetic enrichment [133,141,171–178], as well as to identify extremely rare antigen-specific $CD4^+$ and $CD8^+$ T cells within the naive T-cell repertoire [113–116,123–126]. Naive T cells specific for different antigens can exhibit significant variation in frequency, but they typically display limited variation between individuals. The size of the naive T-cell population associated with a particular antigen is linked to immune dominance and correlates with the magnitude of the memory T-cell response [115,117,118,120,126,179]. These strategies allow for the enrichment of rare antigen-specific T cells for subsequent functional and phenotypic characterization.

3.4. Micropipette-based adhesion 2D affinity assays

As emphasized above while enrichment assays allow for the detection of rare antigen-specific T cells, such assays do not allow for the identification and isolation of "low" or "ultra-low" affinity T cells. Therefore, other techniques such as the micropipette-based adhesion 2D affinity assays, have been developed. This technique uses a red blood cell coated with pMHC class II monomers that adhere to a single T cell. This process is repeated multiple times to determine the percentage of successful adhesions compared to the total number of contacts made. This measurement, representing the probability of adhesion, can then be used to calculate the effective 2D affinity of the TCR:pMHC interaction and are classified as either "lower" or "higher" affinity T cells [20–22] (Fig. 2). This technique has allowed for the identification of T cells associated with the initiation and progression of autoimmunity in MS [17,19].

4. Antigen-specific T cells in autoimmunity

The identification and characterization of antigen-specific T cells in autoimmunity are crucial for understanding the underlying mechanisms of the disease, developing diagnostic markers, and designing targeted therapies. Using the techniques outlined in section 3 above, investigators have identified disease-specific autoreactive T cells that have enabled better tools to track these cells in the course of human disease, as well as has led to the development of transgenic animal models to study autoimmune pathogenesis. In this section, we will cover four ADs and how self-reactive T-cell clone identification has been instrumental in potentially understanding their pathogenesis.

4.1. Multiple sclerosis

MS is a chronic and progressive autoimmune demyelinating disease that affects the central nervous system (CNS) and is characterized by relapsing and remitting episodes [180]. One method used in determining the pathogenicity of T-cell clones in autoimmunity involves the adoptive transfer of antigen-specific T cells (in animal models of the disease) capable of recognizing self-peptides and inducing the disease.

In the experimental autoimmune encephalomyelitis (EAE) model in SJL/J mice, which is considered the gold standard for studying MS, the autoimmune response is characterized by the reactivity of antibodies against myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP) [63,64]. In the PLP model, $CD4^+$ T-cell reactivity with specificity for $PLP_{139\text{-}151}$ is initiated within three days of immunization and remains present throughout the progression of the disease. Additionally, T-cell proliferation and delayed-type hypersensitivity assays have identified reactivity to $PLP_{178\text{-}191}$ that is associated with intramolecular ES just before and during the first relapse. Similarly, during the second relapse, inter-molecular ES is observed through the identification of $MBP_{84\text{-}104}$ responses [181]. In a humanized mouse model, the encephalitogenic epitope $PLP_{91\text{-}110}$ has been identified as capable of inducing clinical EAE in HLA-DR3 transgenic (Tg) mice (mice expressing a human MHC molecule). These Tg mice display inflammatory infiltrates that are specifically associated with EAE [182]. The utilization of this humanized mouse model of MS holds great value in elucidating the roles played by HLA molecules and autoantigens in the development and progression of MS.

Multiple TCR Tg mice have been generated for EAE-specific epitopes. Goverman et al. [183], and Lafaille et al. [184], independently created two strains of TCR Tg mice, V2.3/Vβ8.2 and V4/Vβ8.2, respectively. These mice were genetically modified to express TCRs that specifically recognize the NAc1-11 immunodominant epitope of MBP. Of interest was the finding that the oral administration of MBP protects against the development of EAE in both V2.3/Vβ8.2 and V4/Vβ8.2 mice. However, the induction of tolerance varies between the two strains and is influenced by the timing of oral antigen administration [185].

Muraro et al. [186], demonstrated that variations in the clonal frequencies of antigen-specific autoreactive T cells in the peripheral blood and cerebrospinal fluid of MS patients was associated with the clinical course of the disease. They identified a specific Th1 clone, P2-10, targeting $MBP_{83\text{-}99}$, which was involved in disease exacerbation in a patient treated with an altered peptide ligand (APL). The frequency of P2-10 markedly increased after the initiation of APL treatment, reaching a peak of 1 cell in ~1800 PBMCs just before the onset of a severe clinical exacerbation. The kinetics of the clonal frequency of clone P2-10 closely resembled the frequencies of encephalitogenic cells observed in animal models of MS.

Overall, the evidence supports the role of antigen-specific T cells in the development of autoimmunity in MS, but also highlights the role of the diversification of the immune response over time, which represents the main challenge in the development of new therapeutic approaches. Thus, different strategies would be required to control autoimmunity at the onset of the disease as compared with those required for the control during the chronic phase of the disease.

4.2. Systemic lupus erythematosus

Systemic Lupus Erythematosus (SLE) is a complex AD characterized by the production of autoantibodies and subsequent damage to vital organs, potentially leading to severe organ complications and even fatal outcomes [187]. Notably, the defining hallmark of SLE is the presence of autoantibodies targeting nuclear antigens, which are typically detected before the onset of clinical symptoms. However, autoreactive $CD4^+$ T cells play a crucial role in the pathogenesis of SLE by stimulating B lymphocytes to produce the pathogenic autoantibodies and actively participating in the damage within inflamed target organs [188].

Among the autoepitopes recognized by pathogenic T cells in lupus, several nuclear proteins have been implicated, including histones H4, H2B, H3, SmD1, SmB'/B, and 70-U1RNP [189]. These nuclear proteins are released from apoptotic cells during cellular damage and become available for presentation to T cells. The severity of the disease is indeed correlated with the frequencies of $CD4^+$ T lymphocytes specific to these nuclear antigens. These nuclear antigen-specific T cells secrete various cytokines, including IFN-γ, IL-17, and IL-10. Furthermore, the abundance of these $CD4^+$ T cells in the urine of patients with active lupus nephritis indicates their infiltration into the inflamed kidneys. This infiltration plays a role in contributing to the organ damage and inflammation associated with lupus nephritis [45].

Mice with a restricted TCR repertoire, such as MRL/lpr mice, exhibit enhanced survival and reduced production of autoantibodies. These observations indicate that an immune response involving antigen-specific T cells is crucial for the development of the disease. Moreover, the transfer of $CD4^+$ T cells from MRL/lpr mice to non-autoimmune mice with transgenic anti-snRNP B cell receptors (BCRs) is enough to trigger the production of autoantibodies, implying that the interactions between T and B cells with specific affinities play a significant role in the development of anti-U1-snRNP autoantibodies [190,191].

Kattah et al. [192], developed MHC class II tetramers that were

loaded with peptides from U1-70 spliceosomal protein that led to the identification of distinct $CD4^+$ T-cell populations in MRL/lpr mice. These $CD4^+$ T cells appear to recognize an epitope that varies with the presence/absence of phosphate at $serine_{140}$. The frequency of $CD4^+$ T cells specific for U1-70 (without phosphorylation) correlates with disease severity and the presence of anti-U1-70 autoantibodies. These $CD4^+$ T cells express RORγt and produce IL-17A. In SLE patients, IL-17A-producing $CD4^+$ T cells specific for U1-70 are increased, especially in mixed connective tissue disease.

Overall, despite the well-known role of autoantibodies in the development of SLE, antigen-specific $CD4^+$ T cells are critical for the development and progression of SLE. Treatments that focus on either elimination and/or regulating the antigen specific T cells would help to change the paradigm in the treatment of this disease, which would ultimately have a greater impact on the prognosis of the disease.

4.3. Rheumatoid arthritis

RA is an autoimmune condition characterized by persistent joint inflammation, where $CD4^+$ T cells play a critical role in driving disease progression. $CD4^+$ T cells recognize self-proteins such as collagen type II (CII) present in joint cartilage. Other proteins like human cartilage gp39 (HCgp39), aggrecan (Agg), p205, p68, IgG Fc region (i.e., rheumatoid factor), filaggrin, vimentin, fibrinogen, tenascin-C, glucose-6-phosphate isomerase, and heterogeneous nuclear ribonucleoprotein A2 have also been documented as autoantigens in RA [193]. Upon recognition, these $CD4^+$ T cells become activated and trigger an immune response, releasing pro-inflammatory cytokines [194]. This activation, in turn, stimulates other immune cells like macrophages and B cells, leading to the production of autoantibodies [195].

MHC haplotypes play a critical role in the susceptibility to RA. Thus, inheritance of the MHC class II HLA-DRB1*0401 allele has been identified as the host susceptibility gene in populations with European ancestry [196]. Likewise, in the mouse model of RA (collagen-induced arthritis, CIA), research has provided evidence that disease susceptibility is facilitated by the $H2\text{-}A^q$ MHC class II molecule. Of great interest is the finding that this molecule binds to the same region of CII peptide as the DR4 molecule (DRB1*0401) [197]. Interestingly, experiments in Tg mice that have been engineered to express human DR4 and human CD4, while lacking their own MHC class II molecules, have provided evidence that the post-translational modification of CII affects the extent of T-cell tolerance to this autoantigen. T cells from individuals with RA primarily recognize the immunodominant $CII_{263\text{-}270}$ peptide when it is glycosylated. This post-translational modification seems to play a significant role in TCR recognition by $CD4^+$ T cells with potential implications for tolerance induction in animal models and patients with RA [198]. Multiple other peptides derived from CII, Agg, and HCgp39 bind to HLA-DR molecules containing the shared epitope and are specifically recognized by T lymphocytes of RA patients [31] (Table 1). In addition, responses to carbamylated peptides have also been described in mice, which is thought to be analogous to humans. However, the isolation of antigen-specific T cells in this domain and their implication for antigen-specific T-cell therapies remains unknown [199].

The high frequencies of identical T-cell clonotypes in synovial tissues of RA patients suggest the generation of immune responses with specificity for common epitopes driven by antigens localized within the synovium [200]. In the early stages of RA, there is a similarity in CD4 TCR clonality between those present within inflamed peripheral lymph nodes (pLNs) and the joints. However, as the disease advances, the pLNs change TCR diversity, suggesting alterations in the T-cell repertoire [201]. These changes may eventually be reflected in the joint as the condition progresses over time. $CD4^+CD45RO^+$ T-cell clones obtained from the joints of RA patients specifically recognize antigens extracted from RA synovial cells only when those antigens are presented by APCs that match the HLA type of the patient. However, these T-cell clones do not respond to antigens extracted from synovial cells of individuals without RA, indicating the synovial tissue also plays an active role in disease pathogenesis possibly through different posttranslational modifications potentially secondary to stress [202].

The involvement of $CD8^+$ T cells in RA has been incompletely studied. $CD8^+$ T cells play a role in the establishment of germinal centers in RA patients, which strongly indicates that they might have a decisive role in the initiation and maintenance of the disease [203]. Citrullinated autoantigens of RA, when presented by MHC-I, specifically activate a clonal lineage of $CD8^+$ T cells that is associated with cytotoxicity. The GZMB + $CD8^+$ T cells, found in the blood of RA patients are an example [204]. This finding suggests that the antigens recognized by these T-cell clones are unique to RA synovial cells and contribute to the autoimmune response observed in patients with RA.

The T cells from TCR Tg mice carrying reorganized Vα11.1 and Vβ8.3 chains specific for bovine CII, exhibit a robust response when stimulated with bovine CII or its immunodominant determinant CII *in vitro*. However, these mice do not develop spontaneous arthritis on their own. Onset of arthritis in these Tg mice are only observed after immunization with CII [205,206]. Clones of Tregs derived from splenocytes of CII-specific TCR Tg mice have been demonstrated to effectively suppress the proliferation of CII-specific effector T cells *in vivo*. Moreover, when these clones of Tregs were adoptively transferred into models of collagen antibody-induced arthritis and CIA, they significantly reduced the occurrence and clinical symptoms of arthritis. This provides strong evidence that if autoreactive T cells can be skewed towards a Treg phenotype, the autoimmune response can be regulated and improve arthritis symptoms [207].

Besides specific T-cell reactivity, there is also evidence that human-specific B cells may play a role in the cross-reactivity of autoantibodies to post-translational modified antigens like citrulline, homocitrulline, and acetyllysine [208]. Using tetramers specific for those antigens, it was found that patients with RA exhibit B cells that could have multiple specificities, including the 3 studied peptides. Also, those B cells were characterized by high positivity for CD89 and low positivity for CD24 and CD21 [208]. Further studies evaluating the role of these cells in antigen-specific cell therapies are warranted.

4.4. Type 1 diabetes

T1D is an AD mediated by T cells, where both $CD4^+$ and $CD8^+$ T cells specifically target and attack insulin-producing pancreatic islet β cells. The pathogenesis of T1D appears to be initiated by the generation of β-cell derived neo-epitopes. Such neo-epitopes are thought to arise due to a myriad of factors that individually and/or collectively induce cellular stress [209]. In recent years, there has been increased recognition of the critical role played by β cells themselves in the etiology of T1D, as metabolic activity may drive β cell dysfunction (environmental stress leading to cell malfunction) and destruction that could lead to the development of T-cell autoreactivity [210,211]. It has been shown that β-Cells are more sensitive than α-cells to environmental stimuli, as illustrated by studies conducted on islets challenged by metabolic stress mimicking pathophysiological conditions in type 2 diabetes [212].

$CD4^+$ T-cells are not considered a major component in established T1D, as they have a more prominent role in disease initiation rather than in disease progression/amplification. $CD8^+$ T cells, on the other hand, are abundant in islets close to β-cells and are also found in the exocrine portion of the pancreas in individuals with T1D [213–215].

In humans, antigen-specific $CD8^+$ T cells against pre-proinsulin $(PPI)_{15\text{-}24}$ have been found in biopsies from patients with HLA-A*02:01 haplotype and during the early stages of the disease (3–5 weeks after diagnosis) [216]. Cloned PPI-specific $CD8^+$ T cells have been shown to be cytotoxic for human β cells *in vitro*, particularly when the β cells are exposed to high levels of glucose before the assay [217]. However, patients during the different stages of the disease further develop antigen-specific T cells against several other antigens such as insulin, insulinoma-associated antigen 2 (I-A2), glutamate

decarboxylase (GAD), zinc-transporter 8 (ZnT8), and islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP). In addition, antigen-specific $CD8^+$ T cells specific for islet amyloid polypeptide (IAPP), insulin gene enhancer protein (ISL1), urocortin-3 (UCN3), and SLC30A8 (also known as ZnT8) have also been detected in pancreatic tissues of TID patients [106,218]. This exemplifies the diversification of immune response *via* ES and points to the role of different antigen-specific T cells in different stages of the disease with critical implications in the development of antigen-specific therapies.

4.5. Primary biliary cholangitis

Primary biliary cholangitis (PBC) is an immune-mediated hepatic disorder delineated by cholestasis, biliary impairments, hepatic fibrosis, and chronic non-suppurative cholangitis. The etiology of PBC is complex, encompassing immune dysregulation, anomalous bile metabolism, and gradual fibrogenesis, culminating in the progression toward cirrhosis and hepatic insufficiency [219]. The disease is characterized by the presence of anti-mitochondrial antibodies (AMAs). The major mitochondrial antigen recognized by AMAs has been defined as the E2 component of the pyruvate dehydrogenase complex (PDC-E2) [220].

Pathology of the disease is characterized by the presence of both $CD4^+$ and $CD8^+$ T cell infiltrates within the portal tracts of the liver in PBC patients, and it is reasoned that they play a critical role in the initiation and perpetuation of the disease. MHC class II-restricted autoreactive $CD4^+$ T cells specific for PDC-E2 have been identified from both peripheral blood and liver and the immunodominant target epitope has been defined to be amino acids 163–176 of PDC-E2 [221]. Along these lines, Kita et al. [222], described the existence of $PDC\text{-}E2_{159\text{-}167}$–specific $CD8^+$ cytotoxic T cells in the liver of patients with the disease. After activation, $PDC\text{-}E2_{159\text{-}167}$ tetramer-positive cells exhibited increased production of IFN-γ, as well as increased cytotoxicity. Interestingly, this clonal population of T cells were restricted to $PDC\text{-}E2_{159\text{-}167}$ bearing HLA-A2, thus suggesting that antigen presentation is critical for the initiation and perpetuation of the disease. However, the functional validation of these T-cell clones through experimentation in transgenic mouse models remains pending. In addition, the identification of untapped reservoirs of antigen-specific cells awaits exploration with cutting-edge technologies that promise to elucidate previously unknown pathogenic pathways and reveal potential targets for therapeutic intervention.

4.6. Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a progressive and chronic inflammatory liver disease characterized by lymphocytic infiltration. In addition to histology abnormalities, higher liver function tests, elevated blood IgG, and the presence of specific and non-specific autoantibodies are distinctive [223–226]. The pathophysiology of this disease has been linked to T-cell-mediated damage, imbalance in regulatory and effector cells, and loss of immunological tolerance [227–230].

Longhi et al. [231] using HLA-A2 tetramers for detecting CYP2D6-specific $CD8^+$ T cells in the peripheral blood and liver biopsies of patients with AIH-2 found that patients with autoimmune hepatitis had increased frequencies of CYP2D6-specific $CD8^+$ T cells at diagnosis when compared to those at remission. Higher frequencies of CYP2D6-specific $CD8^+$ T cells were also associated with increased production of IFN-γ and enhanced cytotoxic activity. In a similar fashion, using the same tetramers but for CYP2D6-specific Tregs, it was found that these cells when cultured under antigen-specific conditions (i.e. with semi-mature DCs presenting the autoantigenic epitope of interest) displayed improved suppressive function and increased levels of *FOXP3*. The addition of retinoic acid to antigen-specific Treg cultures stabilized the function of these cells [232,233]. These results suggest the importance of antigen-specific T cells in AIH in humans and highlights possible targets for future therapies.

5. Antigen-specific cell therapies in autoimmune diseases

Over the past several decades, the treatment of ADs has undergone a significant transformation with the development of biological and small molecule therapies targeting key components of the immune system. These agents, which inhibit inflammatory cytokines (e.g., TNF, IL-6, IL-17, and IL-23), immune cells (e.g., cyclosporine, methotrexate, mycophenolate), and intracellular signaling pathways (i.e., JAK/STAT), have become foundational in managing conditions such as RA, psoriasis, and SLE. While these advancements have improved patient outcomes, there remains a need for more effective and safer treatments. Current research focuses on developing therapies that can restore immune balance without suppressing overall immune function, utilizing advanced technologies to achieve this goal [234].

Antigen-specific therapy is based on a strategy known as “reverse vaccination,” which aims to restore the loss of immunological tolerance [235]. The main challenge is to precisely target antigen-specific lymphocyte populations and develop strategies for the induction of durable protection against disease relapses. Strategies developed so far to achieve this goal include manipulating the immunomodulatory function of antigen-presenting cells, inhibiting or eliminating antigen-specific T or B cells, and inducing the generation of antigen-specific Tregs (Table 2)

5.1. Antigen-specific regulatory T-cell therapy

Treg cells play a crucial role in the maintenance of immune homeostasis by suppressing autoimmune responses to self-antigens and controlling inflammatory reactions [236]. Recent pre-clinical studies have shown promising results in the safety and effectiveness of adoptive therapies using polyclonal Treg cells [237]. Results from some of these studies suggest that antigen-specific Treg cells are more potent in regulating and enhancing immune tolerance in a targeted manner than other immune-modulating therapies. Currently, the generation and expansion of antigen-specific Treg cells *in vitro* and *in vivo* pose challenges, such as identifying precise peptide antigens, *in vivo* stability, and an understanding of the *in vivo* migratory behavior of transferred Treg cells. Genetic engineering allows for the *in vitro* modification of specificities of polyclonal Treg cells through the introduction of synthetic receptors and engineered TCRs [237].

In MS, numerous studies have been conducted both using animal models and a few limited clinical trials to restore tolerance with specificity for targeting of myelin-derived antigens. In a preclinical animal model, where MOG-specific Tregs are induced *in vivo* through hepatic gene therapy using an adeno-associated viral vector containing the complete DNA coding sequence for MOG, protection against EAE was observed. Interestingly, when administered to mice with pre-existing disease, the clinical symptoms of the disease and inflammation of the CNS were reversed [66]. Kim et al. [67], demonstrated that Treg cells derived from the peripheral blood of healthy donors can acquire reactivity to MBP when transduced to express MOG-specific TCR genes from an MS patient-derived Treg cell clone. These genetically modified Treg cells induced suppression of proliferation and cytokine production in MBP-specific effector T cells. Moreover, these Tregs demonstrated the ability to *in vivo* suppress neighboring cells *in vitro* and to regulate the development of MOG-induced EAE *in vivo*.

Tarbell et al. [68], successfully expanded $CD4^+CD25^+$ suppressor T cells specific to a single islet antigen from BDC2.5 mice using DCs from NOD mice. These expanded T cells demonstrated enhanced *in vitro* suppressive capacity, indicating that DCs can augment the number and function of antigen-specific $CD4^+CD25^+$ regulatory T cells. Remarkably, a relatively small number of these expanded $CD4^+CD25^+$ BDC2.5 T cells were effective in blocking autoimmunity caused by diabetogenic T cells in NOD mice, whereas a larger number of polyclonal $CD4^+CD25^+$ T cells from NOD mice remained inactive. The impairment in inducing Tregs during the early stages of islet autoimmunity in children highlights the

Table 2
Antigen-specific T cell therapies in autoimmunity.

Type of Therapy	Strategy	Challenges	Current evidence
Antigen-Specific Regulatory T-Cell Therapy	Tregs maintain immune homeostasis by suppressing autoimmune responses and controlling inflammation	Challenges include generating and expanding antigen-specific Tregs, peptide antigen identification, *in vivo* stability, and migration behavior [65].	**MS:** MOG-specific Tregs induced through hepatic gene therapy showed disease reversal in mice [66]. Tregs from healthy donors transduced with MOG-specific TCR genes suppressed MBP-specific T cells [67]. **T1D:** Expanded $CD4^{+}CD25^{+}$ T cells targeting a single islet autoantigen effectively blocked autoimmunity in NOD mice [68].
Chimeric Antigen Receptor-Based Therapy	Genetically modified T cells with CARs targeting autoreactive immune cells	Knowledge gaps on target autoantigens, stability, durability, trafficking, safety, efficacy, and persistence	**MS:** CAR-T cells targeting MOG_{35-55} prevented disease onset and reversed progression in EAE models [19]. CAR-Treg with specificity for MOG showed suppression of EAE and a sustained effect [69]. **PV:** T cells targeting Dsg3 eliminated Dsg3-specific B cells in PV models [70]. Pre-clinical study in humans showed lysis of anti-DSG3 reactive B cells from PV patients with clinical and histological resolution of disease [71]. **T1D:** CAR-Tregs directed against insulin showed reduced diabetes in NOD mice [72]. Monoclonal antibody in CAR-T cells delayed T1D onset in NOD mice [73].
Antigen-Presenting Cell-Based Therapies	TolDCs present antigens to induce antigen-specific Tregs by modulating T cell activation and promoting anti-inflammatory responses	Knowledge gaps on target autoantigens, stability, durability, trafficking, safety, efficacy, and persistence	**RA:** "Rheumavax" trial with autologous DCs in RA showed reduced effector T cells and disease activity, increased Tregs, and higher cytokine production [74]. **MS:** Phase 1b trial with tolDCs in MS and neuromyelitis optica demonstrated Th2 phenotype and functional tolerogenic efficacy [75]. **T1D:** Phase 1 trial in T1D with tolDC vaccines containing pro-insulin peptide showed lasting reduction in autoimmune responses and potential broad immune system modulation [76].

CAR-T cells: Chimeric antigen receptor T cells, DCs: Dendritic cells, EAE: Experimental autoimmune, encephalomyelitis, MBP: Myelin basic protein, MOG: Myelin oligodendrocyte glycoprotein, MS: Multiple sclerosis, NOD: Non-obese diabetic, PV: Pemphigus vulgaris, RA: Rheumatoid arthritis, T1D: Type 1 diabetes, TCR: T-cell receptor, tolDCs: Tolerogenic DCs.

importance of finding effective combination approaches to boost Tregs. One potential avenue for enhancing Tregs is through miRNA targeting, as it can improve Treg induction and stability by maintaining Treg identity and function. Also, certain miRNAs can promote the differentiation of naive T cells into Tregs which may improve the successful induction and maintenance of Tregs *in vivo* [238,239]. However, to achieve this, innovative strategies are needed to specifically modify miRNAs in particular cell types, ensuring targeted and effective interventions for T1D treatment [65].

Vaccination strategies that target specific autoantigens to induce Tregs and prevent islet autoimmunity are currently in preliminary stages. Serr et al. [240], demonstrated the successful induction of human autoantigen-specific Foxp3(+) Tregs *in vivo* using a humanized mouse model. Using powerful agonistic insulin mimotopes in the vaccination process, they successfully induced stable insulin-specific Tregs that exhibited higher expression of Treg signature genes and efficiently suppressed effector T cells.

Overall, Tregs are a promising treatment for ADs. While it is difficult to generate enough effective Tregs, researchers are engineering them to target specific disease antigens. Early animal studies with modified Tregs shows promise. Future directions include improving Treg stability and developing vaccines to induce these beneficial cells.

5.2. Chimeric antigen receptor based therapy

Genetically modified T cells armed with chimeric antigen receptors (CAR) T cells that specifically target and eliminate autoreactive immune cells represent a promising option for suppressing autoimmune manifestations. Preclinical studies of CAR-T cells have shown promising results. However, the limited extent in our knowledge of precise target autoantigens remains a fundamental challenge in the field of CAR-T cells. Other obstacles to clinical implementation include stability, durability, trafficking, safety, efficacy, manufacturing, and persistence of such CAR-T cells *in vivo* [241].

Yi et al. [19], designed CAR-T cells to recognize and eliminate autoreactive T cells by introducing a MOG specific peptide-MHCII (pMHCII) domain. In the EAE model, using pMHCII-CAR targeted to MOG_{35-55} (high-affinity TCR) prevented disease onset, while further modifications to improve pMHCII stability and *in vivo* survival led to the simultaneous selection of lower-affinity T cells, resulting in the reversal

of disease progression.

Thus, an opportunity exists to address the development of antigen specific Tregs with chimeric antigen receptor (CAR-Treg) technology [4]. Fransson et al. [69] genetically modified $CD4^+$ T cells using a lentiviral vector to express a CAR with specificity for MOG *in trans* with the murine *FoxP3* gene. The CAR-Treg cells demonstrated suppressive capacity *in vitro*. Furthermore, these Tregs efficiently infiltrated the brains of C57BL/6 mice and suppressed EAE. When symptom-free mice were challenged with a second EAE-inducing inoculum, they remained healthy, demonstrating the sustained effect of the engineered Tregs.

CAR-T cells have also been used to target and destroy antigen-specific B cells. In PV, a life-threatening autoimmune blistering disease caused by autoantibodies against the desmosomal glycoprotein desmoglein 3 (Dsg3), Ellebrecht et al. [70], created a CAR-T cells with specificity for the Dsg3 autoantigen. The construct in addition included the CD137-CD3ζ signaling domain. These CAR-T cells exhibited specific cytotoxicity against BCR-expressing cells with specificity for Dsg3 *in vitro* and following infusion *in vivo* effectively eliminated Dsg3-specific B cells in a murine model of PV. Recently, a pre-clinical study in humans with DSG3 specific CAR-T for mucosal PV demonstrated the lysis of anti-DSG3 reactive B cells from PV patients, leading to a reduction in autoantibody production and contributing to the clinical and histological resolution of blisters [71].

Currently, the primary focus of CAR-T cell therapy for T1D has been on the generation of CAR-Tregs. Fishman et al. [72], genetically re-directed pathogenic $CD8^+$ T cells. To achieve this, they constructed a specific MHC activation receptor that included the H-2Kd complex, the insulin B chain, and the b2m/CD3ζ receptors. NOD mice following infusion with such T cells showed a significant decrease in insulitis and diabetes, due to the inhibition of T cells that are sensitive to insulin or glucose-6-phosphatase. Zhang et al. [73], created a monoclonal antibody that targets the insulin beta chain residues 9–23 when bound to MHC class II molecules. This antibody was utilized as the extracellular domain in CAR-T cells, leading to cytotoxic effects on APCs and a delay in the onset of T1D in NOD mice.

5.3. Antigen-presenting cell-based therapies

DCs with regulatory properties are referred to as tolerogenic DCs (tolDCs). These cells present antigens to T cells that confer the down-regulation of the expression of co-stimulatory molecules, and increase in the expression of receptors for anti-inflammatory cytokines, leading to the induction of antigen-specific Tregs [242]. Autologous tolDCs generated from macrophages through *ex vivo* culture can restore antigen-specific tolerance *in vivo* through various mechanisms, including the elimination or inhibition of T cells, induction of T-cell anergy, or the generation and expansion of Tregs.

The therapeutic potential of tolDCs has been extensively explored in various experimental animal models of autoimmune disorders. Additionally, *in vitro* experiments utilizing *ex vivo* generated human tolDCs have shown promising results in the *in vitro* generation of antigen specific Tregs. Despite these positive outcomes, the main challenge lies in translating these findings from the laboratory to clinical applications in human patients.

Indeed, a phase 1 human clinical trial conducted by Benham et al. [74], known as "Rheumavax," demonstrated promising results in the context of RA. The trial utilized autologous DCs modified with a nuclear factor κB (NF-κB) inhibitor and exposed to four citrullinated peptide antigens. The trial's findings revealed a reduction in the number of effector T cells and a decrease in disease activity assessed by the DAS28 score (disease activity index). Additionally, the study showed an increase in the quantity of Tregs and a higher production of the cytokines IL-15, IL-29, and the chemokines CX3CL1 and CXCL11 when compared before the beginning of the therapy [74]. The increase in these cytokines may have relevance in the activation, proliferation, and stability of Tregs. These findings suggest a potential role for antigen-specific DC-based therapies in the treatment of RA by promoting immune regulation and dampening the autoimmune response. Moreover, a phase 1b clinical trial with tolDCs derived from monocytes, treated with dexamethasone, and loaded with specific peptides for MS and neuromyelitis optica demonstrated functional tolerogenic efficacy characterized by a Th2 phenotype [75].

Along similar lines of studies, a phase 1 clinical trial for long-standing T1D patients, tolDCs vaccines containing a pro-insulin peptide were administered. The trial demonstrated a noteworthy and lasting reduction in autoimmune responses to the pro-insulin peptide for up to three years after treatment. Moreover, the vaccine temporarily decreased T cell responses to other islet autoantigens, implying a potential broader modulation of the immune system [76]. These findings hold promise for the development of tolDC-based therapies for T1D.

6. Conclusions

Antigen-specific T cells play a critical role in the development and progression of ADs. In autoimmunity, the immune system identifies self-antigens as foreign or harmful, leading to the activation of autoreactive T cells. The identification and characterization of antigen-specific T cells in autoimmunity is crucial for our understanding of not only the underlying mechanisms of the diseases but also in the development of diagnostic markers and designing targeted therapies. Detecting and isolating these cells is challenging due to TCR diversity and their low frequency. Several techniques, such as pMHC-multimers, functional assays, and magnetic bead enrichment, have been developed to detect and isolate these cells.

The exploration of antigen-specific cell therapies in ADs presents a significant advancement in the field of immunotherapy. The future of antigen-specific cell therapies for ADs holds great promise, but it requires a dedicated and collaborative effort from the scientific community, clinicians, regulatory agencies, and industry partners.

CRediT authorship contribution statement

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Data availability

No data was used for the research described in the article.

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