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T cell-Intrinsic Peripheral Tolerance: A Checkpoint Target to Treat Autoimmunity

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Abstract

Recent advances highlight the importance of intrinsic peripheral tolerance in the maintenance of a steady state. Peripheral tolerance is tightly regulated and any alteration in its biological process contributes to the breakdown of immune tolerance and induction of autoimmunity. Recent evidence related to T cell tolerance mechanisms inspired researchers to treat autoimmunity via modulation of tolerant checkpoints that are involved in intrinsic T-cell tolerance such as ignorance, anergy, exhaustion, and senescence. So, understanding the underlying mechanisms might present an opportunity for therapeutic intervention. Here, we primarily highlight the importance of T cell-intrinsic peripheral tolerance mechanisms and their contribution to the development of autoimmune disorders, and then briefly discuss potential strategies to normalize T cell hemostasis in autoimmunity.

Keywords: Autoimmunity, Autoimmune-related disorders, Intrinsic peripheral tolerance, Immune checkpoint, Immunotherapy

Introduction

T cells are effector immune cells that coordinate the immune responses to cognate antigens in the presence of appropriate co-stimulatory molecules and cytokines. T-cell stimulation results in extended proliferation and differentiation of immune cells to eliminate pathogens/antigens (expansion phase). Clearance of antigens is associated with the contraction phase, during this phase, most of the immune cells undergo apoptotic cell death, while a small fraction is differentiated into central or effector memory cells, which accelerates pathogen clearance following the next exposure [1]. Given the nature of the immune system, its functional mechanisms should be under precise control, on one hand avoiding unwanted immune responses (over-activation or autoimmunity) and on the other initiating robust immune responses against infectious agents or tumors [2-4]. Several regulatory mechanisms have been suggested to control T cell hemostasis during differentiation, which mainly refers to T cell tolerance. T-cell tolerance can be divided into central and peripheral tolerance. Central tolerance is composed of several processes that finally induce clonal deletion of high-affinity autoreactive T cells in the thymus [5]. However, it seems to be almost imperfect, partly due to the lack of proper presentation of all peripheral auto-antigens in the thymus and incomplete clonal deletion (60-70% efficacy) [6], so there is an urgent need for peripheral tolerance mechanisms to avoid autoimmunity [7]. Peripheral tolerance involves several arms to eliminate/inactive autoreactive T cells that escape from central tolerance, including clonal deletion or suppression by regulatory T cells (Treg) and intrinsic peripheral tolerance mechanisms that force autoreactive T cells to remain unresponsiveness in a steady state [8,9]. In fact, T cell tolerance is tightly regulated and any alteration in its biological process contributes to the breakdown of immune tolerance and induction of autoimmunity. Recent evidence related to T cell tolerance mechanisms inspired researchers to treat autoimmunity via modulation of tolerance checkpoints that are involved in intrinsic T cell tolerance such as ignorance, anergy, exhaustion, and senescence. These tolerance checkpoints control immune tolerance through different mechanisms (**Figure 1**). At the naive stage, ignorance and anergy maintain tolerance, while

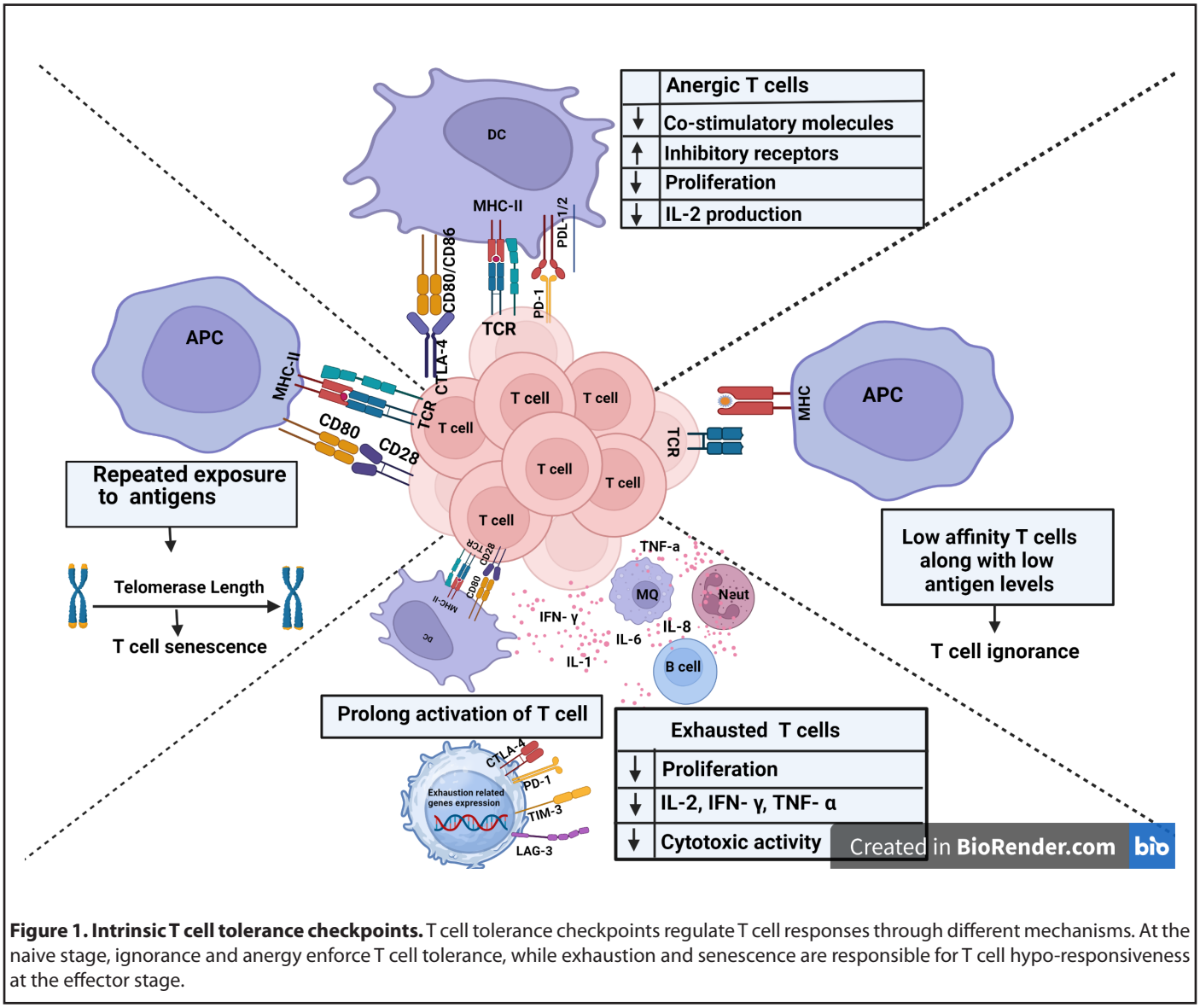

Figure 1. Intrinsic T cell tolerance checkpoints. T cell tolerance checkpoints regulate T cell responses through different mechanisms. At the naive stage, ignorance and anergy enforce T cell tolerance, while exhaustion and senescence are responsible for T cell hypo-responsiveness at the effector stage.

at the effector stage, exhaustion and senescence are the main tolerance checkpoints that prevent the over-activation of the immune system and limit its responses (More details are shown in **Table 1**). So, understanding the specific role of each tolerance checkpoint in T cells might represent an opportunity for therapeutic intervention. Here, we primarily highlight the importance of T cell-intrinsic peripheral tolerance mechanisms and their contribution to autoimmunity. Then discuss potential strategies to normalize T cell hemostasis in autoimmunity. On this basis, the authors wish to build up a framework to develop more refined therapies for autoimmune-related disorders.

Tolerance Checkpoints

Ignorance

T-cell ignorance is the maintenance of low affinity autoreactive naïve T cell phenotype in a steady state [7,10]. Simply, autoreactive T cells fail to induce autoimmunity despite the presence of auto-antigens and remain ignorant or unaware. The precise mechanisms that control immune ignorance are not fully understood. However, one probable mechanism that maintains T cells in a naïve state is their lower affinity for auto-antigens [11]. In fact, self-reactive T cells that escape from central tolerance have different affinities for auto-antigens. It's believed that autoreactive T cells with high affinity can rarely pass the clonal deletion process in the thymus, but if so, they probably become anergic T cells in the absence of appropriate co-stimulatory signals [12]. Thus, primarily low-affinity autoreactive T cells constitute an immunologically ignorant state. Besides, ignorance could be related to low expression of auto-antigens and/or their anatomical location such as immune-privileged tissues (eye, testis, blood-brain barrier) that sequestered antigens from the immune system [13]. Indeed, the concept of ignorance came from observations that indicate physical damage to a specific organ

Table 1. Main features of intrinsic peripheral tolerance checkpoints.

Intrinsic peripheral tolerance checkpoints	Main features	T cell status	Predictive markers	Reversible/ Irreversible
Ignorance	• Ignorance is the maintenance of low affinity autoreactive T cells in a steady state due to low expression of auto-antigens or their anatomical location such as immune-privileged tissues (eye, testis, blood-brain barrier) in the absence of appropriate co-stimulatory signals.	• Naïve	• Un known	• Reversible
Anergy	• T cell anergy is a long-term hypo-responsive state of T cells which is characterized by a lack of growth factors production and proliferation following strong engagement of TCR in the absence of co-stimulatory signals.	• Naïve	• $CD44^{high}$ • $CD73^{high}$ • $FR4^{high}$ • $Foxp3^{neg}$ • $LAG3^{pos}$ • $NRP1^{pos}$	• Reversible
Exhaustion	• T-cell exhaustion is a hypo-responsive state of T cells in the presence of persistent antigen exposure alongside appropriate co-stimulatory signals.	• Effector/ memory-precursor stage	• T-bet • Tox • TCF-1 • XBP1 • Eomes • NFAT • $PD1^{pos}$ • $TIGIT^{pos}$ • $LAG3^{pos}$ • $TIM3^{pos}$	• Reversible
Senescence	• Senescence is permanent cell cycle arrest after extensive proliferation due to telomere shortening.	• Effector/ memory stage	• $CD28^{neg}$ • $CD27^{neg}$ • $CD57^{pos}$ • $TIM\text{-}3^{pos}$ • $KLRG\text{-}1^{pos}$ • $CD45RA^{pos}$ • $NKG2D^{pos}$ • $IFN\alpha/IFNAR^{pos}$	• Irreversible

leads to altered antigen expression and the development of autoimmune disease as seen in the case of sympathetic ophthalmia [14]. Besides, transgenic mice have brought substantial information due to the ignorance phenomenon. Various foreign antigens could be determined as auto-antigen when inserted into the genome of mice. Antigens-specific autoreactive T cells probably proceed to be ignorant, anergic, or regulatory. In fact, immunological ignorance was originally described by Ohashi and colleagues using transgenic mice. They observed LCMV-specific T cells of RIP-LCMV mice which crossed with LCMV-specific TCR transgenic P14 mice ignored LCMV antigens [15]. However, further studies demonstrated that immune ignorance could be broken down following LCMV infection (appropriate viral load) which leads to autoimmune diabetes and mainly indicates immune ignorance is reversible [16]. Generally, it has been accepted that inflammation caused by infectious agents is one of the most important mechanisms for activating autoreactive T cells [17]. Of note, ignorant T cells are not unresponsive/dysfunctional and have the capacity to activate in the presence of exogenous stimuli such as infection, inflammatory context, or cytokines [15,18,19]. Therefore, there is a possibility that immunological ignorance overcomes and potentially induces auto-inflammatory disorders. However, the underlying mechanisms or key initiating mediators which contribute to the breakdown of immunological ignorance are less clear and further investigation is essential to determine its role in autoimmunity.

Anergy

T cell anergy is a long-term hyporesponsive state of T cells which is characterized by a defect in growth factors secretion and proliferation following strong engagement of TCR in the absence of co-stimulatory molecules [20,21]. Interestingly, the engagement of co-inhibitory receptors alongside cognate antigens induces/ or maintains an anergy state [22]. Recent studies indicate the upregulation of multiple negative checkpoints such as cytotoxic T lymphocyte associated antigen 4 (CTLA-4), programmed cell death protein-1 (PD-1), lymphocyte activation gene-3 (LAG-3), and E3 ubiquitin ligases by anergic T contribute to the maintenance of anergy state [23,24]. Of note, there are no specific markers to distinguish anergic T cells from other T cell subsets. However, several predictive markers have been suggested to characterize anergic T cells, including expression of high levels of CD44, CD73, FR4, and lack of Foxp3 expression [25]. Correlation of these factors with impairment in cell cycle and cytokines production (main hallmarks of anergy) has been reported [20]. Besides, anergic T cells tend to be hypo-responsive even after exposure to the same antigen stimuli in the presence of optimal co-stimulation [20]. However, *in vivo* studies showed that the anergy state is reversible and anergic T cells could slowly recover their functional properties in the absence of cognate antigens or Treg cells, which indicates maintenance of a long-lasting anergy state requires persistence of antigen exposure and/or the presence of Treg cells [25-27].

Anergic T cells are commonly classified as clonal anergy (*in vitro*) and adaptive tolerance (*in vivo*) [20]. Indeed, clonal anergy could be induced in the presence of a strong first signal (TCR-peptide interaction) without supporting secondary signals (infection/adjuvant) or in the existence of low doses of agonist in optimal co-stimulation [28, 29], whereas *in vivo* anergic T cells primarily induced in the thymus and in the periphery following exposure to auto-antigens in suboptimal stimulation or inhibitory microenvironment which seen in cancer [28,30]. It is worth noting that, despite several overlapping properties such as an impairment in IL-2 production and T cell proliferation, deep investigation demonstrated substantial differences in the molecular pattern, phenotype, and functional properties of the *in vitro* and *in vivo* anergic state which indicates the requirement for different approaches to restore or maintain their properties [30]. For example, different signaling pathways have been found in clonal anergy and adoptive tolerance. Clonal anergy mainly showed deficiency in RAS/MAPK activity and NF-κB mobilization to the nucleus whereas defects in Zap70, calcium mobilization and NF-κB activity have been reported in *in vivo* anergy [28,30]. In addition, only *in vitro* anergy showed reversible capacity in the presence of external IL-2 or diacylglycerol kinase-α inhibitor [31,32].

It is believed that anergy has the capacity to limit the responsiveness of potentially autoreactive T cells and induce the progenitors of Treg cells [25,33]. Of note, it has been found that anergy-derived Treg cells could suppress the development of inflammatory bowel disease and arthritis in animal models [33]. Besides, anergy-derived Treg cells could induce anergy in other autoreactive T cells [33]. In turn, Treg cells are substantial for anergy state induction/maintenance [34]. Moreover, inhibition of mTORC1 activity induced anergy state [35]. Similarly, impairment in mTORC1 signaling leads to Foxp3 expression and differentiation of Treg cells [36]. Thus, anergic T cells along with Treg cells dampen the autoimmunity, so any alteration in the anergy state might lead to autoimmune-related disorders. Of note, the association of anergic phenotypes with several autoimmune disorders has been reported [37,38]. It has been reported that most insulin-specific $CD4^+$ T cells in diabetes-susceptible NOD mice had an anergic phenotype in diabetes-susceptible NOD mice which decreased with age. These data suggest that NOD mice maintain tolerance via anergy which is lost by age [39]. In addition, the correlation of the anergy state with a better prognosis of rheumatoid arthritis (RA) has been reported [34]. Besides, Moulton *et al.* reported distinctive properties of T cells that were isolated from systemic lupus erythematosus (SLE) patients. Somewhat they showed activated/effector function and, on the other hand, anergic state properties which probably indicate impairment in anergy induction is associated with SLE progression [40]. It seems that many molecular mechanisms, especially defects in anergy state, are involved in autoimmunity pathogenesis, thus identification of these mechanisms might eventually lead to a better understanding of the nature of autoimmune disorders and the development of novel approaches to normalized T cell function.

Exhaustion

T-cell exhaustion is a hyporesponsive state of T cells at the effector stage which contributes to immune system dysfunction [41]. It was originally described in CD8 T cells during chronic viral infection in the presence of constant antigen exposure with the support of co-stimulatory signals from the local microenvironments [42,43]. Of interest, a strong T cell exhaustion state is associated with antigen exposure for longtime, poor CD4 T cell help, and over co-expression of inhibitory receptors [44,45]. The exact mechanisms that initiate the transition of effector T-cells into an exhausted state are not fully determined. However, various transcription factors have been reported to be involved in the induction of T cell exhaustion state, such as T-bet, Tox, TCF-1, XBP1, Eomes, and NFAT [46-48]. Exhausted T cells are mainly characterized by substantial changes in gene expression, transcription molecules, epigenetic profile, and cellular metabolic, which leads to over co-expression of inhibitory receptors (PD-1, LAG-3, T-cell immunoglobulin domain and mucin domain-3 (TIM-3), B and T lymphocyte attenuator (BTLA), T-cell immune

receptor with Ig and ITIM domains (TIGIT), CTLA-4, and 2B4/CD244) and finally failure of effector functions [48,49].

It has been thought that T cell exhaustion is a compensatory mechanism in the presence of persistent antigen (in the case of chronic infection or cancer) to avoid over-activation of the immune system that may cause tissue injury, immunopathology, or even host death [50-53]. Since exhaustion could act in favor of dampening autoimmunity, it has been proposed that T cell exhaustion might be considered as another regulatory mechanism that suppresses the immune system against self-antigens that escape from central tolerance [54]. There are some studies that indicate an association of T cell exhaustion with better prognosis in several autoimmune-related disorders such as anti-neutrophil cytoplasmic antibody-associated vasculitis (ANCA), idiopathic pulmonary fibrosis, type 1 diabetes (T1D), SLE, and RA [55-57]. Interestingly, the extent of T cell exhaustion is inversely related to the severity of the disorders [57]. There was a positive link between $CD8^+$ T-cell exhaustion accompanied by poor $CD4^+$ help with a better prognosis in SLE, ANCA, and T1D [55,58]. Of interest, the proportion of the polyclonal exhausted population was relatively higher in systemic autoimmune diseases compared to T1D [56-58]. This difference might be related to the disease nature, as SLE and ANCA are systemic autoimmune diseases whereas T1D is organ-specific (autoimmune responses mainly localize in the pancreas) [59]. Besides, unique expression of inhibitory receptors on enriched exhausted $CD8^+$ T-cells in different disorders has been reported [60]. It seems that T cell exhaustion is specifically context-dependent and its contribution to each disease is complex and needs further research to elucidate the precise mechanisms.

It is generally accepted that T cell exhaustion is a reversible process, so blocking the inhibitory receptors might have a beneficial effect against chronic viral infection or cancer, as documented in several studies [61,62]. There are various inhibitory pathways that are deeply studied in T cell exhaustion, especially PD-1/PD-L1-2 and CTLA-4 inhibitory receptor signaling [63-65]. It is widely known that the PD-1 and CTLA-4 receptors have a negative effect on the immune system and the U.S. Food and Drug Administration has approved their inhibitory function. Other immune checkpoints implicated in T cell exhaustion are TIM-3, BTLA, CD160, 2B4, CD39, TIGIT, and LAG-3 [66,67]. It is also worth noting that the clinical use of immune checkpoints has a significant effect on the treatment of chronic infectious diseases and cancers [50,68,69]. Interestingly, the 2018 Nobel Prize in Physiology or Medicine was awarded for cancer immunotherapy using an immune checkpoint to Allison and Honjo. Regarding the promising results obtained from cancer therapy using checkpoint blockers, it is tempting to propose that the induction of checkpoint molecules in the case of autoimmune disease might have a beneficial effect and targeted research in this field might be an important step to developing novel therapeutic approaches.

Senescence

Immunosenescence is a dysregulated function of immune cells which is primarily characterized by a reduction in telomerase activity and/or increment of telomere frailty, cessation in proliferative capacity, reduction in chemotactic and phagocytic activity, and changes in inflammatory mediators profile [70,71]. Indeed, immunosenescence proceeds during the normal aging process, but inflammation due to several circumstances such as chronic infection, cancer, and chronic autoimmune disorders could imitate the aging process and accelerate immunosenescence regardless of physiological age [72-75]. It's believed that repeated exposure to antigens and stress during the lifespan leads to constant activation of the immune system and induction of low-grade inflammation which is collectively called inflammaging. Inflammaging is an important hallmark of immunosenescence and mainly contributes to the development of several chronic age-related disorders and accelerated immunosenescence in young healthy individuals [76]. Reciprocally, immunosenescence could potentially induce chronic autoimmune disorders, indicating its substantial role in immune system homeostasis [76]. Generally, aging alters all aspects of the immune system, in particular T cell bioactivity [77]. Aging affects the proportion of circulatory naïve T cell decrease which is accompanied by alteration in T cell subtype composition [78]. In fact, the frequency of T helper type 2 cells (Th2), Treg cells, and memory T cells increases. This alteration might contribute to insufficient adaptive immune responses and/or alteration in memory cell responses, which finally leads to T cell dysfunction [79-81].

Interestingly, the association of T cell senescence phenotype with the progressive down-regulation of co-stimulatory molecules (CD28 and CD27), reduction in TCR signaling activity, and up-regulation of other surface receptors such as killer cell lectin-like receptor subfamily G member 1 (KLRG-1), CD57, T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) and CD45RA have been reported [72,82-85]. Besides, senescent T cells produce a myriad of bio-active molecules known as senescence-associated secretory phenotypes (SASP) including cytokines, chemokines, proteases, and other pro-inflammatory mediators which probably are involved in the dysregulated properties of the immune system [83,86-88].

Immunosenescence also plays a substantial role in the development of autoimmune-related disorders [89,90]. Broux and colleagues reported the infiltration of $CD4^+$ $CD28^-$ T cells in the CNS of MS patients [91]. Along this line, van nierop et al. observed the presence of chronically activated cytotoxic $CD8^+$ T cells in MS patients [92]. Further studies in the auto-inflammatory setting demonstrated significant telomere frailty in $CD4^+$ T cells obtained from inflamed synovium of RA patients [93,94]. Notably, senescent T cell phenotype ($CD28^-$ $CD57^+$ $KLRG\text{-}1^+$ $CD8^+$ T cells) was associated with SLE pathogenesis [95,96]. Similarly, a higher frequency of cytotoxic $CD28^-$ $CD8^+$ T cells has been observed in patients

with Ankylosing Spondylitis (AS), Graves' disease (GD), and Behçet's disease (BD) [97-99]. Taken together, these results strongly suggest the involvement of T cell senescence in autoimmunity pathogenesis. However, relatively little is known about the underlying mechanisms. It appears that understanding the precise mechanisms might be a means to prevent chronic inflammation right before its contribution to developing autoimmunity.

Therapeutic Potential of Immune Checkpoints

In recent years, autoimmune diseases have increased uncontrollably and despite great endeavor and vast expense, current treatments are not specific and efficient enough to treat autoimmune-related disorders. In addition, long-term use of these non-specific immunomodulatory agents increases the risk of infectious diseases or malignancies [100]. Thus, there is still an urgent necessity to develop novel treatments that specifically focus on mechanisms driving autoimmunity. The breakdown of intrinsic peripheral tolerance is one of the most important mechanisms that contributes to autoimmunity pathogenesis [101-103]. So, restoring function or modulating pathways involved in autoimmunity might be an important step in developing new immunotherapeutic strategies. Recent studies in the understanding of intrinsic peripheral tolerance mechanisms inspired researchers to treat autoimmunity via modulation of tolerance checkpoints that are involved in intrinsic T cell tolerance. These include the use of soluble peptides, nanoparticles, small molecules, or agonists/antagonists that block co-stimulatory molecules or trigger inhibitory receptor expression. The first example is immunotherapy with soluble peptides designed as antigen-processing independent T-cell epitopes (apitopes). Sundstedt *et al.* reported Ac1–9 (N-terminal peptide of MBP) as an apitope and administration of its analog (4Y) induces an anergy state in the Tg4 mouse model [104]. Further studies by Burton *et al.* showed that repeated exposure to soluble apitopes (4Y) in Tg4 mice induces upregulation of inhibitory receptors including CTLA-4, PD-1, LAG-3, and TIM-3 and anergy state, leading to lifelong protection of disease [105]. Nanoparticles containing disease-specific antigens might induce anergy, as Jamison *et al.* demonstrated the efficacy of nanoparticles containing insulin–ChgA hybrid peptide in the induction of anergy state in NOD mice [106]. Besides, antagonists such as teplizumab, an anti-CD3 blocking antibody, could modulate inhibitory receptor expression indirectly and induce an anergic or exhausted state in T cells of T1D patients [55,107]. Of interest, there are several clinical trials that investigated the efficacy of immune checkpoints in autoimmune-related disorders. Among them, abatacept (CTLA-4-Ig), which blocks co-stimulatory signals, showed significant clinical benefits for RA patients and has now been approved by the US Food and Drug Administration (FDA) [108-111]. Abatacept was also studied in clinical trials for lupus nephritis and juvenile RA, the results were encouraging [112-115]. Rosnilimab and Peresolimab are PD-1 agonist antibodies that have been used for RA therapy and showed significant clinical benefits for RA in phases I and II clinical studies [116,117]. In addition, Rosnilimab demonstrated a significant reduction in ulcerative colitis (UC) clinical manifestation and is now in Phase II clinical studies [118]. These clinical trial studies indicate the promising effects of immune checkpoints for the treatment of autoimmune-related disorders.

Taken together, it seems that this therapeutic intervention has a great advantage over current treatment. Most importantly, it is antigen-specific, so it avoids systemic suppression of the immune system and maintains the benefit of the immune response. Despite such valuable benefits and promising results, tolerance checkpoints are still far from being an effective treatment for autoimmune disorders. To begin with, the timing of therapeutic intervention is critical. Given the epitope spread and complex inflammatory milieu after the development of autoimmune disorders, it is reasonable to suggest that such therapeutic strategies may be more effective early in the course of autoimmune disease and be defined as a prophylactic treatment in genetically susceptible individuals. Furthermore, it is often highly challenging to identify appropriate agonists or antagonists to treat autoimmune disorders based on the nature or stage of the disease to achieve therapeutic purposes. Accordingly, there is a lack of appropriate biomarkers to evaluate its clinical benefits. Finally, it should not be forgotten that the concept of the therapeutic potential of immune checkpoints is very abstract, and the current data is limited, so further studies are still needed to evaluate the potential of these approaches and probable side effects.

Conclusions and Final Remarks

The evidence that emerges from recent studies highlights the potential clinical benefits of tolerance checkpoints to treat autoimmunity. However, the precise mechanisms that maintain a tolerant state remain to be elucidated. One major challenge is identifying master genes, transcription/epigenetic factors, or other regulators that are involved in the maintenance or disruption of intrinsic peripheral tolerance. In addition, there is little or no data about the outcome of therapeutic intervention. It is not clear whether targeted tolerance checkpoint therapy has enough efficacy and safety or can even modulate the immune responses without deleterious side effects. This data and a comprehensive conception of the tolerant state will be essential for designing new effective therapeutic strategies to treat autoimmune-related disorders.

Statements and Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

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Authors' contributions

Naser GHolijani: performed the literature search, Manuscript writing, final approval of the manuscript; Golamreza Daryabor: performed the literature search, Manuscript writing, final approval of the manuscript; Fatemeh Rezaei Kahmini: Conceptualized the study, performed the literature search, manuscript writing, final approval of the manuscript, revising the manuscript and overall supervision.

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