

Recent advances in CD8⁺ regulatory T cell research (Review)

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Abstract. Various subgroups of CD8⁺ T lymphocytes do not only demonstrate cytotoxic effects, but also serve important regulatory roles in the body's immune response. In particular, CD8⁺ regulatory T cells (CD8⁺ Tregs), which possess important immunosuppressive functions, are able to effectively block the overreacting immune response and maintain the body's immune homeostasis. In recent years, studies have identified a small set of special CD8⁺ Tregs that can recognize major histocompatibility complex class Ib molecules, more specifically Qa-1 in mice and HLA-E in humans, and target the self-reactive CD4⁺ T cells. These findings have generated broad implications in the scientific community and attracted general interest to CD8⁺ Tregs. The present study reviews the recent research progress on CD8⁺ Tregs, including their origin, functional classification, molecular markers and underlying mechanisms of action.

Contents

1. Introduction
2. Origin of CD8⁺ Tregs
3. Classification and functions of CD8⁺ Tregs
4. Common marker molecules
5. Mechanism of action of inhibitory CD8⁺ Tregs
6. Recent research progress on CD8⁺ Tregs
7. Summary and applications

1. Introduction

Immunization is critical for the maintenance of biological homeostasis. It refers to the physiological function by which a body's immune system fights against the invasion of foreign substances and distinguishes internal components from external ones. The immune system is responsible for the body's immune response and immune function. While it produces robust immune responses to attack various antigens, it also negatively regulates or inhibits abnormal immune responses, maintaining a relatively stable immune reactivity (1-3). The immune system consists of three major components, namely the immune organs, immune cells and immunologically active substances. In particular, immune cells are produced, mature and are concentrated in the immune organs. These cells can be divided into phagocytic cells and lymphocytes, which are composed of T and B cells that mature in the thymus and bone marrow, respectively. Immunologically active substances mainly refer to antibodies, lymphokines and lysozyme (4-6).

Physiologically, the tolerance of internal components and the response to 'non-self' antigens are under the strict control of the body's immune regulation mechanism. Immune regulation is crucial for the maintenance of the physical environment stability in the human body (7,8). Therefore, dysfunction of immune regulation will result in serious pathological consequences. For instance, if the immune system develops a strong immune attack on the body's own components, autoimmune diseases occur (9,10). The body may also be harmed if the immune system cannot respond adequately to an infection caused by external pathogenic microorganisms. In this case, a weak response can result in severe infection, whereas an excessively strong response can result in allergy (11-18). Therefore, immune regulation determines the occurrence and the strength of an immune response. This elegant and complicated regulation functions in multiple steps in an immune response process.

In 1970, Gershon and Kondo (19) identified CD8⁺ regulatory T cells (CD8⁺ Tregs). Later studies revealed the dual effects of these cells in immune responses. They have been reported to inhibit the immune response to pathogens and the host's inflammation following pathogen infection. However, by weakening the body's immune surveillance on malignant cells, the host can be relieved from autoimmune diseases (20-22). Although CD8⁺ Tregs were recognized >40 years ago, little is known regarding their function in negative regulation (23).

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Furthermore, recent studies on CD8⁺ Tregs revealed their crucial role in immunology (24-26), while CD8 $\alpha\alpha$ ⁺ T cell receptor (TCR) $\alpha\beta$ ⁺ Tregs, a novel subtype of CD8⁺ Tregs, was demonstrated to recognize the major histocompatibility complex class Ib (MHC-Ib) molecules Qa-1 in mice. Tregs only target activated T lymphocytes, and are considered to complement the inhibition function of CD4⁺ forkhead box P3 (FoxP3)⁺ Tregs (27,28). Therefore, further studies on CD8 $\alpha\alpha$ ⁺ Tregs may provide novel therapeutic strategies for human inflammatory diseases, tumor immunity, transplant tolerance and autoimmune diseases.

2. Origin of CD8⁺ Tregs

In the process of thymic negative selection, only T cell clones with high affinity to autologous antigens are removed (29,30). Therefore, certain T cells with low affinity to autologous antigens are leaked to the peripheral immune system. Under certain conditions, they may be activated and result in autoimmune diseases. Therefore, this process is monitored by a series of peripheral immune tolerance mechanisms, including Tregs with immunosuppressive effects, namely CD4⁺ and CD8⁺ Tregs (31-33).

3. Classification and functions of CD8⁺ Tregs

To date, there is no reliable surface marker that is able to distinguish CD8⁺ Tregs from ordinary CD8⁺ T cells. In different experimental systems, CD8⁺ Treg surface molecules have been demonstrated to differ. For instance, in an experimental autoimmune encephalomyelitis (EAE) model, CD8⁺CD28⁻ Tregs demonstrated an inhibitory effect on the secretion of interferon (IFN)- γ by myelin oligodendrocyte glycoprotein-specific CD4⁺ T cells through cell contact inhibition (34,35). Similarly, CD8⁺CD45R⁺ and CD8⁺CD122⁺ T cells also possess regulatory suppressor functions, including suppression of immune activity following autologous mixed lymphocyte reaction activation (36-38). In comparison, CD8⁺ Tregs induced by plasma-like dendritic cells (DCs) in the ascites of cancer patients are featured the interleukin (IL)-10⁺ C-C motif chemokine receptor 7 (CCR7)⁺ CD45RO⁺CD8⁺ phenotype. In particular, by secreting IL-10, CCR7⁺CD45RO⁺CD8⁺ Tregs inhibit the function of effective T cells that specifically attack tumor antigens (39-41). In addition, immature DCs induce the generation of CD8⁺ Tregs, while FoxP3⁺ antigen-specific CD8⁺CD28⁻ T cells can also be produced *in vitro* through rendering vascular endothelial cells tolerogenic (42-45). Notably, inhibitory CCR7⁺CD45RO⁺CD8⁺ T cells can originate from human tumor tissues, indicating their potential association with tumor-induced immune tolerance (46,47).

CD8⁺ Tregs in humans are predominantly CD8⁺CD28⁻ Tregs; however, two CD8⁺ Tregs subgroups can be produced by induction *in vitro*, namely CD8⁺CD28⁺ and CD8⁺CD28⁻ Tregs (48,49). Currently, the majority of studies conducted have investigated CD8⁺CD28⁻ Tregs, and three categories of these cells have been identified. Among them, type I cells have a direct contact with DCs to influence the expression of the costimulatory molecules CD80 and CD86, demonstrating a negative regulatory role. However, the inhibitory function of

type II cells is exerted through cytokine secretion, such as IFN- γ and IL-6, while direct contact with antigen-presenting cells (APCs) has not been observed. Finally, type III cells function by secreting IL-10 (50-52).

4. Common marker molecules

Common molecules that serve as markers for Tregs include FoxP3, CD25, CD127, CD39 and CD73. Among them, FoxP3 is a member of the fork-like transcription factor family and was first reported in 2001 by Brunkow *et al* (53). Studies have identified that FoxP3 expression and function are closely correlated with Tregs. FoxP3 is mainly expressed in lymphoid organs and tissues, including in the thymus, spleen and lymph nodes (54-56). In mice, FoxP3 has been reported to be preferentially expressed in CD4⁺CD25⁺ T cells, while its expression in CD8⁺ T cells was limited. By contrast, in humans, FoxP3 can be expressed in both CD4⁺CD25⁺ T cells and CD8⁺ T cells (57,58). However, its expression in CD4⁺ T cells is significantly higher in comparison with that in CD8⁺ T cells. Thus far, FoxP3 has been recognized as the most sensitive marker of Tregs (54-56).

Traditionally, the identification of Tregs mainly relied on CD25 labeling. However, it was later reported that identifying Tregs merely based on CD25 positivity was not accurate (59,60).

CD127, an IL-7 receptor, is downregulated in a subset of CD4⁺ T cells in the peripheral blood. These cells are FoxP3 positive, and CD25 weak positive or negative (61). The combination of CD4, CD25 and CD127 selection generates high purity Tregs, which exhibit a strong signal in functional inhibition tests. The population of Tregs that can be distinguished by CD4 and CD127 expression (including CD25⁺CD4⁺ and CD25⁻CD4⁺ cells) is three times as large as the T cell sub-population that can be selected by CD4⁺CD25^{hi} (62). As CD127 has been successfully applied to quantify the Tregs of patients, it has been proposed as a marker of human Tregs (63,64).

Studies have also reported that Foxp3⁺ Tregs express the cell surface CD39 and CD73 molecules simultaneously (65,66). When cell damage or apoptosis occurs, intracellular ATP is released, causing increased concentration of extracellular ATP. As the signaling molecules for cell damage, they activate a variety of immune responses. Furthermore, CD39 and CD73 are extracellular enzymes that are expressed by various immune cells, including DCs, B cells and T cells. Notably, they dephosphorylate ATP or AMP, as well as decompose AMP, thus achieving an immunosuppression function and inhibition of T cell inflammatory factors (67-69).

5. Mechanism of action of inhibitory CD8⁺ Tregs

Different types of CD8⁺ Treg subsets can function by secreting various inhibitory cytokines and chemokines, including IL-10, transforming growth factor (TGF)- β , IL-16, IFN- γ and chemokine (C-C motif) ligand 4 (33,70-77). CD8⁺CD28⁻ Tregs render the APCs tolerogenic by upregulating the expression levels of immunoglobulin-like transcript (ILT)3 and ILT4, which then function as cell surface inhibitory receptors. These tolerogenic APCs demonstrate an anti-inflammatory function. The down-regulation of costimulatory molecules CD80 and CD86 on

APCs by CD8⁺CD28⁻ Tregs also inhibits the immune response of CD4⁺ T cells. In addition, CD80 and CD86 are important for the inhibitory function of CD8⁺CD122⁺ T cells (78-80). Certain subsets of CD8⁺ Tregs exert an inhibitory function by cell contact-dependent mechanisms, in which TGF- β and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) expressed on the cell surface serve key roles (81,82). CD8⁺ Tregs exert a cytotoxic effect against antigen-activated CD4⁺ T cells, and this function depends on the expression of the MHC-Ib molecule Qa-1 in mice (HLA-E in humans) (28,83,84). The aforementioned mechanisms are presented in Fig. 1A-D.

6. Recent research progress on CD8⁺ Tregs

Recent advances. The recent research progress on CD8⁺ Tregs mainly includes the aspects presented in Fig. 1E. Briefly, CD8⁺ Tregs have been reported to inhibit autoimmune diseases, to potentially originate from the thymus, to negatively regulate activated T cells, to supervise the immune tolerance and to be associated with the management of autoimmune diseases.

Exploration of Qa-1-restricted CD8⁺ Tregs in autoimmune diseases. The mouse protein Qa-1 (homologous to HLA-E in humans) is essential for immune protection and immune regulation. In particular, Qa-1-restricted CD8⁺ Tregs recognize the MHC-Ib molecule Qa-1, and therefore inhibit the development and recurrence of autoimmune diseases (27,85). Notably, the immune response phenotype of Qa-1-deficient mice demonstrated two opposite effects: Enhanced CD4-dependent immune responses revealed the influence of Qa-1 target loss on CD8⁺ Treg activity, whereas a weakened CD4-dependent immune response demonstrated an unimpeded NKG2A-Qa-1/Qdm inhibition (86,87).

In order to illustrate the two Qa-1-dependent regulatory pathways, researchers performed experiments with Qa-1-deficient mice expressing different surface determinants (88,89). Notably, Qa-1 D227K is a mutant of Qa-1 that interferes with the binding of Qa-1 and CD8 co-receptors to prevent the expression of CD8⁺ cell effective molecules. As expected, Qa-1 D227K-deficient mice generated no active CD8⁺ Tregs, accompanied by worsened EAE symptoms. In addition, Qa-1/Qdm was demonstrated to bind to CD94/NKG2A on CD8⁺ Tregs, and may thus suppress the inhibitory activity of CD8⁺ Tregs through signaling factors (90,91). Therefore, the key for preventing CD8⁺ T cell autoimmune responses may be the regulation of Qa-1-restricted auto-activated cells through interaction between Qa-1-Qdm and CD94/NKG2A. It was also reported that the interaction of Qa-1-NKG2A with antibodies in EAE mice attenuated the pathogenic condition to complete remission (89,92). These findings demonstrated that Qa-1 serves a key role in the development and mediation of CD8⁺ Treg activity. Furthermore, a molecular level inhibitory mechanism emerged based on these results, suggesting that MHC-TCR interactions relied on the co-receptors of the CD8 molecule. Identification of Qa-1-restricted CD8⁺ Tregs enriched the occurrence and development mechanism of autoimmune disease, providing a theoretical basis for its treatment.

Potential role of CC chemokines expressed by specific CD8 $\alpha\alpha$ ⁺ Tregs and the thymus during ovulation. It is

widely considered that ovulation may be an inflammatory process (93,94); however, little is known regarding how immune cells participate in this process. Novel CD8 $\alpha\alpha$ ⁺ Tregs have been identified in the theca of the antral follicles (95). In addition, it has been observed that the ovaries of anovulatory C31F₁ mice under treatment with estradiol and of nude mice (thymus-free) with low fertility were lacking CD8 $\alpha\alpha$ ⁺ Tregs (26). Thymus-expressed chemokine (TECK) has previously been detected in the ovaries and was reported to attract CD8 $\alpha\alpha$ ⁺ Tregs to the ovaries. However, in anovulatory C31F₁ mice, ovarian TECK expression was normal, suggesting that the absence of CD8 $\alpha\alpha$ ⁺ Treg migration to the ovaries was responsible for the infertility of the mice. Finally, the origin of ovarian CD8 $\alpha\alpha$ ⁺ Treg was investigated, and it was observed that the migrated ovarian CD8 $\alpha\alpha$ ⁺ Tregs were able to return to the recipient's thymus (95,26). Therefore, it is reasonable to speculate that ovarian CD8 $\alpha\alpha$ ⁺ Tregs involved in ovulation-associated inflammation may originate from the thymus. Pathological alterations of the thymus may cause ovarian-associated inflammation, thus revealing a potential mechanism of ovaritis and providing a novel strategy for ovarian-associated inflammation.

Immune regulation of novel Qa-1-restricted CD8 $\alpha\alpha$ ⁺TCR $\alpha\beta$ ⁺ Tregs. CD8⁺ Tregs exhibit a gene expression spectrum similar to innate lymphoid cells, which is shared by mouse intraepithelial lymphocytes and thymus CD8 $\alpha\alpha$ ⁺ TCR $\alpha\beta$ ⁺ Tregs. However, the expression of several key regulatory molecules has been reported to be different among these cells (96,97). Specifically, CD8 $\alpha\alpha$ ⁺TCR $\alpha\beta$ ⁺ Tregs express a higher level of certain natural killer cell-associated receptors and tumor necrosis factor superfamily molecules. Their difference from the traditional MHC-Ia-like-restricted T cells lies in several lines of evidence. Firstly, they have been observed to activate V β 8.2 CD4⁺ T cells and control the experimental autoimmune cerebrosplinal meningitis (98,99). In addition, they express only CD8 $\alpha\alpha$ ⁺ dimers, which recognize the conserved region peptides of the TCR V β 8.2 chain in Qa-1a. Furthermore, they secrete only type I cell factor cytokines, but not IL-2 (84,100). In conclusion, CD8 $\alpha\alpha$ ⁺TCR $\alpha\beta$ ⁺ Tregs prevented autoimmunity caused by adoptive cell transfer or *in vivo* activation of CD4⁺ T cells. Notably, this negative feedback regulation is directed against activated T cells, which provides a novel strategy for the treatment of autoimmune diseases and transplant rejection.

CD8⁺ Tregs inhibit follicular helper T cells, and thereby serve a vital role in self-tolerance. The ability of excess tissue and organs to incite a strong immune response depends on the clearance of autoreactive T or B lymphocytes. However, immature and mature autoreactive T and B cells are not thoroughly cleared, and may require an effort from cell reprogramming to suppress the immune response. Notably, a sublineage of CD8⁺ Tregs is necessary for the maintenance of self-tolerance and the prevention of autoimmune diseases in mice (101-103). The interruption of gene functions associated with the interaction between these CD8⁺ T cells and Qa-1⁺ follicular helper T cells can lead to the development of systemic lupus erythematosus, indicating that these sublineage T cells serve an important role in the regulation of immune response, as well as in the surveillance of immune tolerance (104-106).

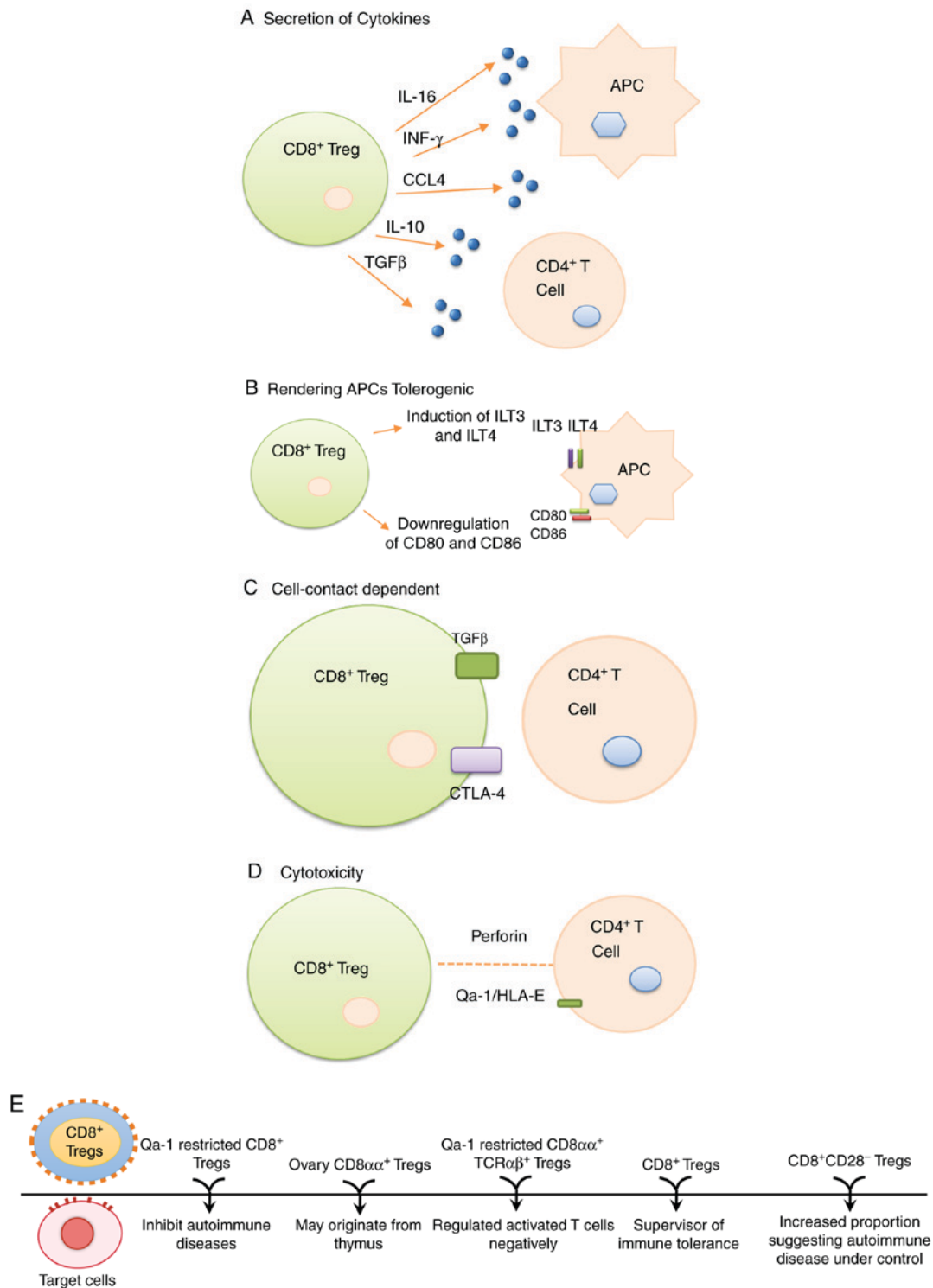


Figure 1. (A) CD8⁺ Tregs secrete various inhibitory cytokines and chemokines, including IL-10, TGF- β , IL-16, INF- γ and CCL4. (B) CD8⁺ Tregs render the antigen-presenting cells tolerogenic and anti-inflammatory by the induction of ILT3 and ILT4, or through the downregulation of CD80 and CD86 on APCs. (C) CD8⁺ Tregs serve an inhibitory function, in which TGF- β and CTLA-4 expressed on the cell surface are the key factors. (D) The cytotoxicity of CD8⁺ Tregs depends on the expression of the major histocompatibility complex class Ib molecule Qa-1 in mice and HLA-E in humans. (E) Recent advances in CD8⁺ Treg research. Treg, T regulatory cell; IL, interleukin; TGF, transforming growth factor; INF, interferon; CCL4, chemokine (C-C motif) ligand 4; ILT, immunoglobulin-like transcript; APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte associated protein 4; TCR, T cell receptor.

Association between CD8⁺ Tregs and autoimmune diseases. A decreased number or impaired function of CD8⁺ Tregs has been observed in patients with autoimmune diseases, including multiple sclerosis, localized ileitis and myasthenia gravis recurrence. The immunosuppressive effect

of CD8⁺CD28⁻ Tregs has also been confirmed by *in vitro* experiments (107-110). In addition, Rådinger *et al* has reported that CD8⁺ Tregs can also regulate the occurrence and development of allergic reactions by decreasing the number of chemokines and the recruitment of

eosinophils (111). These alterations occurred both prior to and following allergic reactions in order to reduce the body's immune reactivity (112,113). A preliminary study on a CD8⁺ T cell subpopulation in the peripheral blood has correlated the changes in cell distributions to the immune system disorder in patients with systemic lupus erythematosus. In particular, the proportion of CD8⁺CD28⁻ Tregs subset, as well as the CD8⁺CD28⁻/CD8⁺CD28⁺ T cell ratio, may reflect the disorder of cellular immune function. Furthermore, the increase of CD8⁺CD28⁻ Tregs has been demonstrated to be associated with the control of disease progress (114-118). Therefore, monitoring the proportion of CD8⁺CD28⁻ Tregs may help to judge the progression of the disease, while an increased proportion of CD8⁺CD28⁻ Tregs indicates that the autoimmune disease is under control.

CD8⁺ Tregs and other diseases. CD8⁺Foxp3⁺ Tregs existing in a prostate tumor have been reported to inhibit the immune responses (119), thus improving the possibility that the manipulation of CD8⁺Foxp3⁺ Tregs function may raise the efficiency of immunotherapy for prostate tumor patients. Furthermore, the tumor: Whole body ratio of CD8⁺ Tregs is associated with the prognosis of cancer patients, including in ovarian and cervical cancer among others (120,121). A high CD8⁺ Treg ratio in the tumor mass may indicate a favorable prognosis. Additionally, CD8⁺ Tregs can be recruited into the central nervous system during neuroinflammation. However, the recruitment of CD8⁺ Tregs into the inflammation organs depends on the level of B7-H1 on immunogenic DCs (73). This knowledge may be applied in the development of therapies based on DCs and CD8⁺ Tregs for neuroinflammation diseases.

7. Summary and applications

Currently, several issues remain unaddressed regarding the functions of Tregs and the corresponding research methodology (21,23). Firstly, phenotype identification and a functional/mechanistic study of CD8⁺ Tregs have to be further conducted in different experiment systems. In addition, it remains unclear whether different CD8⁺ cell subpopulations originate from common precursor cells. Finally, the application of CD8⁺ Tregs can be further explored in the scenarios of prevention, diagnosis and clinical treatment of diseases.

Thus far, relatively well-studied and well-recognized CD8⁺ Tregs include natural CD8⁺CD28⁻ T cells, as well as the induced CD8⁺CD28⁻, CD8⁺CD25⁺ and CD8⁺CD122⁺ T cells. A systematic analysis on the transcription profile of these CD8⁺ Tregs identified CD25⁺CD28⁻ to be the most common surface marker (5,122). Other surface markers include FoxP3, CD103, CD122 and CTLA-4 (49,123).

Studies on CD8⁺ Tregs are of great value for human disease treatment, and thereby attract increasing researchers into this field. Investigating this group of cells may provide novel ideas for immune regulation and immune intervention. Furthermore, this may elucidate the pathogenesis of associated disease and offer an objective index to their diagnosis, treatment and evaluation. We believe that studies on CD8⁺ Tregs will generate broad application prospects in the fields of inflammatory diseases, autoimmune diseases, tumor immunity and transplantation tolerance.

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Availability of data and materials

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Authors' contributions

YY was responsible for writing original draft, editing, analysis and designing of the work, and interpretation of data for the work. XM performed analysis, editing and validation. RG provided resources and performed review. JZ is mainly responsible for editing of references, reviewing and data analysis for the work. LW provided software assistance. JY made substantial contributions to the study design and acquisition and analysis of data. In addition JY was responsible for providing supervision and ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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