# 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**



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## 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).

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 downregulation 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 $C31F_1$ 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 $C31F_1$ 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 lymophoid 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 Vβ8.2 $CD4^+$ T cells and control the experimental autoimmune cerebrospinal meningitis (98,99). In addition, they express only $CD8\alpha\alpha^+$ dimers, which recognize the conserved region peptides of the TCR Vβ8.2 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 reprograming 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 $Qa\text{-}1^+$ follicular helper T cells can to 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).

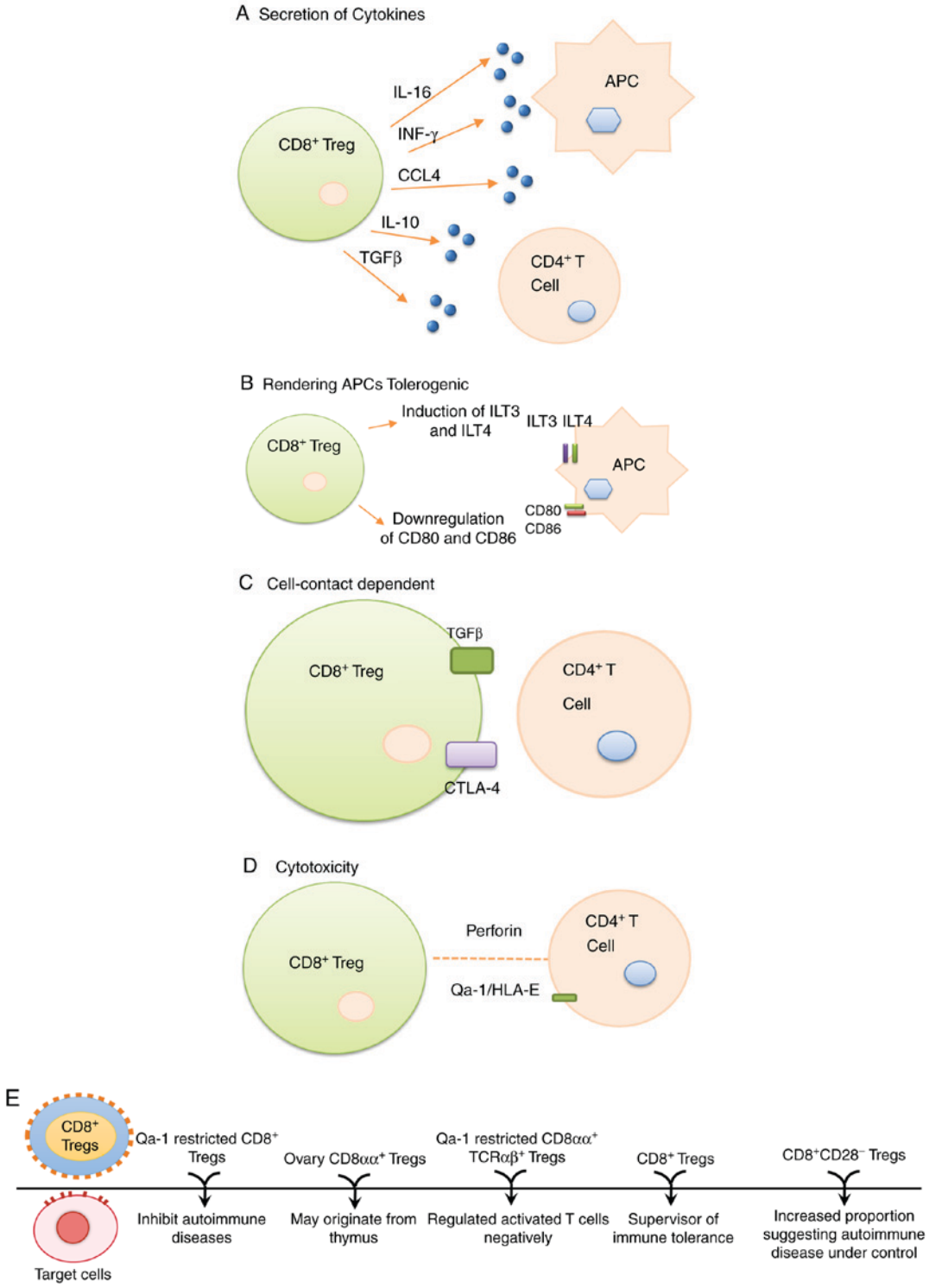


Figure 1. (A) CD8+ Tregs secret various inhibitory cytokines and chemokines, including IL-10, TGF-β, IL-16, IFN-γ and CCL4. (B) CD8+ Tregs render the antigen-presenting cells tolerogenic and anti-inflammatory by the induction ILT3 and ILT4, or through the downregulation of CD80 and CD86 on APCs. (C) 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; IFN, 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

Not applicable.

## 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 asssitance. 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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