T regulatory Function and Modification for Future Application

Yikai Yang*
Chiway Repton School Xiamen, Xiamen, 361022, China

Abstract. T regulatory cell is a very particular type of T cell that plays an important role in maintaining homeostasis and peripheral tolerance. The Treg (T regulatory cell) is a CD4+ T cell that has many mechanisms to create immune tolerance by effecting B and T cells. They are important for the control of tumour immunity, microbiome, organ transplants, allergy and of course self-tolerance. There are also times where Tregs fail to create tolerance whether by the decrease in population, no recognition of certain antigens (Inheritance) and also many other reasons such as environmental (theory that our immune system exposed to less pathogens in the modern cities so our immune system starts to react against our own antigens, potential reason for the increase in allergy) but not enough scientific evidence is provided yet. The fail in immune tolerance can result in auto-immune diseases such as apoptotic dermatitis and DT1 (diabetes type 1). Research about cell and non-cell therapies are being researched and undergoing in clinical trials potentially cure or control autoimmune diseases as well as increase the success rates for organ transplant etc., by modifying Tregs.

1 Introduction

Tregs is a natural T-cell subpopulation, which can negatively regulate the immune response of the body and maintain the immune balance in the body by inducing and maintaining the tolerance to autoantigens [1-2]. In healthy people, Tregs can inhibit excessive immune response, thus preventing autoimmune diseases. Tregs cell therapy can restore patients' tolerance by stopping harmful inflammatory reactions in autoimmune diseases (such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis). Tregs cells have the natural ability to control harmful immune responses, making them an ideal choice for treating many diseases [3]. In addition, the ability of engineered Tregs cells to target specific pathogenic antigens also reduces the possibility of harmful systemic effects. Its role in tissue maintenance and repair provides a potential for lasting and effective restorative therapy [4-6].

This essay will cover the basic information on the function of Tregs and also possible modifications that can be applied for different problems. Most of the information would be simplified and only include a brief explanation enough to be understandable for readers that have basic knowledge of the immune system and on biology. The essay includes the potential methods of engineering Tregs such as CAR Tregs and TCR modification. Also, there will be brief explanations on autoimmune disease, transplantation and tumour/cancer to allow readers to understand better of how the modified Treg could help solve problems. Treg therapy right now shows the most potential in curing autoimmune diseases and research is critical for the future of organ transplants. The immune system is one of the few superbly complex systems in the area of biology where time and effort is required to progress. Overall this essay will have a brief insight into Tregs modifications as well as future applications allowing more people to gain interest or understand a bit of the amazing science of immunology.

2 Treg Function

T regulatory cells can create immune tolerance via many mechanisms (figure 1). Tregs could either act in an antigen-specific way where in contact with specific MHC molecules on APCs (antigen-presenting cells) could activate Tregs or as bystander suppression where a Treg specific to one antigen could react against many antigens that are similar (alleles) [7]. When a Treg recognizes an antigen it can react in a variety of ways to suppress the immune response. For example, in suppressing B cell function and antibody production could be through two paths, direct contact between cells through receptors or secretion of inhibitory cytokines can prevent the signal cascades programmed for the responses of B cells. These mechanisms are also used in suppressing T cells and inhibitory cytokines such as IL-10 and IL-35 to reduce inflammation [8]. Tregs can also act as a sink for IL-2 which is a pro-inflammatory cytokine where there are many surface receptors that can bind to IL-2, therefore, reducing the number of extracellular IL-2. Strong and direct responses involve the secretion of perforin and granzymes that command B cells to undergo apoptosis and in a result dampens or stops the immune response. Tolerization of Dendritic
cells to form immunosuppressive phenotypes are also essential in central and peripheral tolerance which also effects the production of Tregs. (further information on dendritic cells later on in the essay) [9].

3 Autoimmune Diseases

To understand how and why we use the techniques of Treg modification, we need to first understand what are autoimmune diseases. To simplify the function of T regulatory cell, it needs to create tolerance against specific antigens or molecules but at the same time maintain homeostasis for immune responses against pathogens and cancer cells. This balance fails in autoimmune diseases where the immune system starts to react against the self-antigens [10-12]. This leads to the destruction of tissues which are responsible to many diseases, such as multiple sclerosis and T1D. Autoimmune disease usually develops during a person’s lifetime due to environmental factors but the specific causes are unclear and hard to clarify. During the events, the immune system is triggered to lose self-tolerance against specific antigens leading to the stimulation of immune responses against the person’s own cells. Modification of TCR (T cell receptors) on Tregs in an antigen-specific manner can potentially cure or prevent autoimmune diseases and there are two types of approaches towards this problem; cell therapy and non-cell therapy.

4 Therapy

4.1 Non-cell Therapy

There are many approaches for non-cell therapy where physical modification of the Tregs are not involved and can be described as autoantigen. As the name suggests the T regulatory cells can automatically gain tolerance against a certain antigen without the engineering of the cell itself [13]. Many methods are being used in trials in mice and humans that can effect the tolerance of the antigen wanted but all follow the same principal of exposing the molecule to the immune system constantly and periodically to physically recreate tolerance. Our body as we know can adapt to different conditions especially in the modern world where we could travel and even modify the environment [14]. The same thing can happen with our immune system if we maintain the exposure of the antigen to the Tregs. Throughout the development of T cells the cells with TCR that bind to self-antigens too well are killed and with low affinity continue to mature into T cells. This process of maturation involves the exposure of APCs (antigen-presenting cells) to the T cells as they mature. T regulatory cells are the category that have medium affinity for self-antigens and gain tolerance to the antigens presented on MHC molecules of APCs [15]. Therefore we can take advantage of this process by somehow getting the APCs to present the antigen we want. There are a variety of ways to get APCs to present a specific antigen and one way is to expose the body to the molecule throughout a long period of time. Chronic exposure of antigen whether by oral treatments, intra-nasal (sprawls of the antigen in the nose) or even injection into the blood or skin would make more macrophages to be exposed to the molecule. Overtime more Tregs develop specific to the antigen and as numbers increase immune tolerance is created. Other methods are also available; DNA vaccination where the DNA plasmids...
are engulfed by the dendritic cells via phagocytosis and then converted to the protein it codes for inside the cell. The MHC molecules will start presenting the antigen to T cells and the same process is undergone. Another way of exposing the antigens to T cells is by using peptide/MHC coupled nanoparticles that are delivered to the thymus or other sites of T cell maturation.

### 4.2 Antigen-Specific TCR Therapy

One of the most effective cell therapy of Treg is the antigen-specific TCR therapy. Different from polyclonal Tregs (Tregs that are non-antigen specific developed through ex-vivo expansion) TCR therapy can target a specific antigen and be modified for the TCR to have high affinity towards the antigen [16]. The increased affinity of TCR means that it will have a higher potency of suppressive function compared to non-antigen-specific Tregs which can dramatically increase its effectiveness in curing autoimmune diseases. More importantly, antigen-specific Tregs only require one of the TCR connected to the MHC to be activated; therefore during therapy only small doses of Tregs needed compared to polyclonal. Research has shown that as few as 2000 antigen-specific Tregs were enough to completely reverse TD1 in mice. Despite its efficiency and usefulness there are also downsides in using TCR therapy. The immune system is extremely complex and Treg therapy is a relatively new field so there are many problems that scientist face. Tregs used in trails right now are isolated from the blood but as Tregs are mostly present in tissues it is hard for getting large numbers of Tregs to experiment with [17-18]. Aside from the isolation problem the modification process is much harder and complex. Each antigen-specific Treg has completely different TCR; therefore specific modification of each Treg cell is required; this increases the amount of work and time put into research and therapies increasing the difficulty. Especially when targeting at autoimmune diseases many different co-receptors are needed since diseases have multiple alleles and are different in every patient. The most time taking process though is identifying the specific types of antigens that cause each autoimmune disease. There are so many diseases out there known but only a few are deeply researched. Potential diseases that may have cures in the near future could be T1D, MS (multiple sclerosis) and acquired factor VIII deficiency. Overall antigen-specific TCR therapy has potential in restoring immune tolerance in many diseases but research in this area is much required.

### 4.3 CAR+Treg Therapy

CAR Treg therapy or Chimeric antigen receptor Treg therapy is also a popular method in approach to modifying Tregs. As the name suggests, the receptor on the Treg is more of a combination of many proteins just like a chimeric. Not just TCR specific to a MHC can be modified or applied to a Treg [19].

Theoretically, any protein or receptor could be transduced into a Treg meaning that receptors from T cells other than Tregs can be presented onto Tregs. CAR have molecules on the membranes which have the ability to bind to several similar types of antigens. This is advantageous in faster research since no specific antigen is needed and could potentially be used for different but similar antigens. This means that it is tissue/organ-specific without needing many co-receptors like TCR therapies do. CAR molecules also have higher affinity for the antigens but require higher amounts of antigen present in order for the CAR Treg to activate (TCR Tregs only need one). CAR therapy have focused on epitope-specific but may not be effective in autoimmune diseases as there are many epitopes of T and B cells involved in autoimmune diseases. CAR Treg therapy may not be effective in diseases that are throughout the whole body as it is tissue-specific so if the site of inflammation is elsewhere, it won’t be effective. CAR Treg therapy is definitely an important area of Treg modification since it can target multiple alleles of disease at the same time which can drastically reduce costs in production and research and may be the first in line to be available as cure.

### 4.4 Cancer Immunotherapy

Our immune system has many mechanisms to prevent cancer from developing from the DNA level in cell division to the protection of our genes from mutation [20]. Even if a cancer cell manages to develop our immune system is also there to kill the cells. When tumour develops, the slip past the immune system by secreting inhibitory cytokines which can almost shut down the B and T cells at the site from reacting towards the tumour cells. This is when also the balance is off and Tregs have too much tolerance towards cancer cell antigens. Modifying antigen-specific TCR could also help with this problem. When fully differentiated Tregs are engineered, the tumour-mediated TCR signals are unaffected against them. Inhibiting Foxp3 expression in Tregs can disable the Tregs function to suppress the immune system and other mechanisms can target in reducing or removing the immunity towards cancer cells.

### 5 Conclusion

T regulatory cell therapy is essential in curing and preventing autoimmune diseases and in many areas, such as organ transplant (modified Tregs specific to organ antigens or donor) and cancer. Also, it has potential but more trails, research and time is needed before the therapies are safe. The balance between tolerance is very important since too much and cancer cells can get away and too little will cause too much inflammation and other serious conditions. This is one of the main problems scientists face and in the future, once solutions are found it would contribute a lot to modern immunology and medicine. Other forms of therapies such as microbiome therapy and dendritic cell therapy are also in research. Few therapies such as the T1D are already in clinical trials and cures may soon be available.

### References


