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Generation of regulatory T cells by T cell receptor gene transfer

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Summary

Our lab and others have demonstrated T cell receptor (TCR) gene transfer as an efficient way of redirecting the specificity of a bulk T cell population to that of a known antigen. Thus far there has been considerable effort put into the use of TCR gene transfer into conventional CD8+ and CD4+ T cells in order to initiate or augment immune responses. There has, as yet, been little investigation into the potential use of TCR gene therapy at the other end of the spectrum: control of immune pathology using regulatory T cells. Here we will briefly discuss the evidence indicating that the generation of Ag-specific Tregs, potentially via TCR gene transfer, may be an efficacious treatment for various forms of immune-pathology and briefly outline the challenges towards realizing the full potential of this type of therapy.

Keywords: regulatory T cell, immunotherapy, T cell receptor (TCR) gene transfer

Introduction

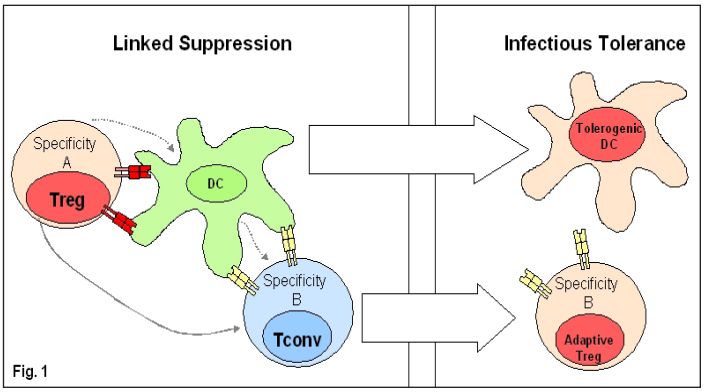
Tregs play a crucial role in maintaining immune tolerance during normal homeostasis as well as controlling and resolving active immune responses [1]. Several different groups of regulatory T cells have been identified, which play varying roles in the maintenance of physiological immune tolerance [2]. The most intensely studied of these are the FoxP3+ Tregs, which will be the focus of the remainder of this review. Until recently it was thought that FoxP3+ Tregs were generated exclusively in the thymus, hence their common description as natural Tregs. However, it has now been demonstrated that a proportion of FoxP3+ Tregs are generated in the periphery from conventional CD4+ T cells, termed adaptive Tregs [3]. FoxP3+ Tregs exert regulation via a number of different mechanisms, which at present remain poorly defined. The known mediators of these mechanisms can broadly be split into the contact-dependent mechanisms, including membrane-bound TGF β [4], CTLA-4 [5,6] and intra-cellular/peri-cellular adenosine compound generation [7,8]; and the contact-independent cytokine mediated mechanisms, which include the effects of IL-10 [9] and TGF β [10].

TCR gene transfer into Tregs

Like conventional T cells, Tregs require stimulation via TCR interaction with a cognate peptide: MHC complex in order to exert suppression [11]; therefore they would be malleable to specificity re-direction by TCR gene transfer. Tregs are capable of potently suppressing T cell responses at naïve, effector and memory stages. In addition they have also been demonstrated to act on various other immune cells, including B cells [12], DCs [5], and monocytes [13]. Many aspects of Treg-mediated suppression make them ideal candidates for Ag targeted therapy of immuno-pathology. Firstly, although Tregs require Ag specific stimulation via the TCR, they suppress in an Ag non-specific manner [11]. This phenomenon, termed linked suppression, means that a Treg of one specificity can suppress a conventional T cell of an unrelated specificity provided the cognate Ag for both is expressed on the same antigen-presenting cell (APC). Utilizing this phenomenon of linked suppression along with an intelligent Ag targeting, it would be possible to direct suppression toward the organ or tissue which is affected regardless of whether the causative epitope, or indeed any of the epitopes additionally involved by antigenic spreading, have been identified. Secondly, Treg-mediated tolerance against one peptide specificity can be transferred to other related specificities [14]. This process, referred to as infectious tolerance, is mediated by modulation of dendritic cells (DC) and de novo induction of adaptive Tregs, and would allow for the generation of long lasting multi-epitope mediated tolerance regardless of the limits of the Ag specificity and persistence of the transferred Tregs. Thirdly, Tregs are an endogenous immune control mechanism, present in all healthy individuals. It is clear that all normal inflammatory protective immune responses are elicited in the presence of Tregs, indicating that re-establishing tolerance via Treg adoptive transfer would not preclude future protective immune responses. This is supported by skin graft models, in which Treg-induced

tolerance to allo-grafted skin on the flank was not affected by the rejection of a distinct skin allograft on the contra-lateral flank [15]. If these properties of Tregs could be effectively harnessed they could provide the therapeutic panacea for clinical immune pathology, namely a long lasting Ag-specific control without the complications of a general immune suppression.

Figure 1. Linked suppression and infectious tolerance. Two important concepts of Treg function are linked suppression and infectious tolerance. Linked suppression allows that a Treg of specificity A can suppress a conventional T cell of specificity B provided the cognate antigen for both is expressed on the same antigen presenting cell. This suppression can occur either via the intermediary of the antigen-presenting cell or directly by soluble mediators or Treg to T cell interaction. Infectious tolerance is the process whereby the tolerogenic state of the Treg is transferred to a previously non-tolerogenic T cell. Again, this phenomenon can occur indirectly, via the generation of a tolerogenic DC or directly via interactions between the Treg and conventional T cell.



Tregs in autoimmunity

There are numerous examples of the use of Tregs to prevent murine models of autoimmunity. However, to the best of our knowledge there are only three examples of reversion of ongoing autoimmunity using Tregs. Intriguingly, two of those studies were carried out using Ag specific Tregs [16,17]. The third was carried out in a model where the Treg niche was empty before adoptive transfer of the Tregs [18]. It is postulated that the reconstitution of this niche may have created a situation whereby Ag-specific expansion of the Tregs was favored-hence providing the level of Ag specificity required to reverse the ongoing disease. It is compelling that in the former study non-obese diabetic mice were reverted from ongoing autoimmunity using a Treg population specific for a single pancreatic Ag [17]. In this elegant study the authors demonstrated that a transgenic monoclonal Treg population was capable of reverting disease by controlling a multiple epitope T cell responses against peptides derived from an entire organ. This work is a clear indication that Ag specificity is required to revert ongoing autoimmunity, and that Tregs specific to a single disease-related Ag may be sufficient to control a complex and advanced immune response. The importance of Ag specificity in autoimmunity, therefore, is of clear importance: autoimmunity is rarely a predictable disease and typically presents after the establishment of a strong immune response and considerable damage.

Tregs in transplantation

Hematopoietic stem cell transplantation is an effective treatment for a number of hematological diseases, but is accompanied by the potential for development of graft versus host disease (GvHD). Several murine studies have demonstrated the efficacy of adoptive Treg transfer in curing GvHD. In addition to this, whilst the adoptive transfer of Tregs in murine models could prevent GvHD, they did not impact on the advantageous graft versus leukemia (GvL) response. The need for Ag-specific targeting in the prevention of GvHD is less clear than is seen in an autoimmune setting. This is probably due to two factors. Firstly, the Tregs are being adoptively transferred into irradiated and hence lymphopenic hosts, and the subsequent expansion of the Tregs to fill their niche may allow for the preferential expansion of allo-Ag specific Tregs. Secondly, and directly related to the first point, there is likely to be a larger proportion of allo-Ag specific Tregs than auto-Ag specific Tregs in the autoimmune situation. Interestingly in GvHD, Ag-specific Tregs offer only marginal improvement in protection upon adoptive transfer when compared with polyclonal Tregs [19,20]. These promising pre-clinical studies using polyclonal Tregs have encouraged two separate groups to begin early clinical trials in adoptive Treg transfer in the treatment of human GvHD. However, the potential efficacy of polyclonal Tregs in the treatment of GvHD does not negate the need to examine the potential of Ag-targeted Tregs to treat this disease. Indeed, it should be noted that in all three of the murine studies quoted here, very high number of Tregs were transferred to induce tolerance (around 1:1 Treg:conventional T cell). It is likely that if these Tregs were Ag-specific the number could be reduced substantially. In addition, work is ongoing to identify the distinguishing factors between the development of GvHD and GvL; any advancement in our understanding of this difference will likely allow for targeted Treg therapy to prevent GvHD without impacting on GvL.

There is a clear correlation in the clinical setting between solid organ transplant tolerance and Treg levels. In contrast to autoimmune and GvHD settings, prevention of solid organ rejection by polyclonal Treg transfer in murine models has not been demonstrated. However, numerous studies have demonstrated that the transfer of Tregs from previously tolerized mice is sufficient to prevent rejection of solid organs [21]. More recently, it has been additionally demonstrated that Tregs expanded in vitro against allo-antigen are capable of mediating prevention of rejection [15,22]. These latter studies also highlighted the importance of Tregs directed against indirect allo-Ag in preventing chronic rejection. Both strategies demonstrate the need for Ag specificity targeted against the most appropriate Ag to induce Treg-mediated tolerance.

FoxP3$^+$ Tregs: Potential for antigen specific therapy

It is clear that Ag specificity will be an important factor in successfully translating the promising pre-clinical data into a clinical setting. There are many obstacles to generating Ag-specific Tregs, mainly related to the physiological nature of Tregs as a small population of poorly responsive (in vitro) T cells. Whilst in vitro protocols to expand Ag specific Tregs have advanced in recent years [23] they still represent at present a labor intensive, expensive, and flawed process. Identification of a functional

Treg population is at present an imperfect process. Whilst the transcription FoxP3 is generally considered as the only reliable Treg marker, as an intracellular protein it is of no use in identifying functional Tregs. For this reason Tregs are generally identified by a constellation of surface markers, mainly CD4 and CD25. However, CD4+CD25+ population also includes a contaminating fraction of activated conventional T cells. Expansion of this bulk population—whether Ag-specific or polyclonal—leads to an outgrowth of this contaminating conventional T cells population [24]. The more expansion required, the more outgrowth of these cells is seen. The numerous rounds of stimulation required to achieve a sufficient numbers of Ag-specific Tregs for effective treatment in a human setting, if at all possible, would undoubtedly lead to substantial outgrowth of this contaminating population. This contamination population of conventional T cells could potentially be a risk in exacerbating disease. Numerous surface markers have been added to CD4+CD25+ in identifying Tregs (GITR, CD127, CD39, FR4, HLA-DR CD45RA) [25-29] and although many of them allow for higher purity Treg sorting, each additional parameter leads to a decrease in the proportion of Tregs obtained. This is a practical problem when dealing with a population of cells already limited by their paucity.

We are currently examining TCR gene transfer into bead-sorted CD4+CD25+ Tregs. We have been consistently able to express a TCR of known specificity in 60-90% of polyclonally activated Tregs after a single round of activation and transduction. These Tregs demonstrate in vitro Ag-dependent linked suppression of a naïve TCR transgenic CD8+ T cells up-to 30 fold greater than that seen in absence of Ag. With appropriate modifications, including exploration of alternative Treg sorting strategies and optimizing (i.e., reducing) proliferation and transduction protocols, this approach could be used to generate large populations of Ag-specific highly pure Tregs. Other advantages of this approach include the ability to select TCR from outside the normal Treg TCR repertoire. It may be possible to use higher affinity TCR generated in the conventional T cell repertoire or indeed generate high affinity TCR using the allo-restricted strategy [30]. However, it is also important to acknowledge that safety issues must be addressed before the routine use of TCR gene transfer into Tregs. Briefly, those risks primarily involve the danger of development of malignancy caused by insertional mutagenesis and the potential for the creation of unknown specificity TCR from mis-pairing of the endogenous and introduced TCR. The risk of insertional mutagenesis is greatly decreased in mature T cells compared to hematopoietic stem cells, but it remains an important consideration before proceeding with any form of stable gene insertion. The second issue is the generation of novel specificity TCR through mis-pairing of the introduced TCR alpha or beta chains with the corresponding alpha and beta chains endogenously expressed in each T cell. These novel TCR have not been thymically educated and may potentially be strongly self-reactive. It is unclear what the effect of any self-reactive TCR generated through mis-pairing might have in Tregs. It is possible that TCR mis-pairing may be less of an issue in Tregs which are proposed to have a bias in TCR selection towards self specific Ag:MHC complexes. However, it cannot be ruled out that Tregs with a TCR affinity greater than that normally selected during Treg TCR selection may mediate inappropriate suppression. There is considerable effort being employed in addressing these issues in conventional T cells and any advance in TCR gene therapy in that setting will almost certainly be applicable Tregs (see King et al. in this issue for more in-depth review of these issues).

Genetically induced Treg-like T cells

As well as the use of naturally occurring Tregs to treat immune-pathology, there have also been a number of studies using genetically modified "Treg-like" cells. It is well documented that ectopic expression of the regulatory transcription factor FoxP3 induces Treg-like function in conventional murine T cells [31]. Similar to the study described earlier in NOD mice, two studies demonstrated the transduction of FoxP3 into pancreatic islet specific transgenic CD4+ and CD8+ T cells was capable of ameliorating diabetes in NOD mice [32,33]. FoxP3 expression in polyclonal T cells had no affect in these models. Similar findings have been demonstrated in GvHD settings [34] and solid organ transplantation [35]. Transfer of this concept into a human setting is hindered by subtle differences in the expression and function of FoxP3 in human T cells. Human conventional T cells have been shown to transiently up-regulate FoxP3 subsequent to activation, without the acquisition of any regulatory function. In addition, the ectopic expression of FoxP3 does not consistently instill the same level of regulatory function in human T cells [36]. However, a recent study has demonstrated that lenti-viral mediated expression of FoxP3 in human T cells under a constitutive (i.e., activation state independent) promoter produces consistently efficient regulatory like phenotype [37].

We are currently examining the potential of co-transfer of TCR genes along with the FoxP3 transcription factor using a single tri-cistronic vector to generate functionally suppressive T cells. Subsequent to transduction these cells show limited proliferation and little or no IFN γ and IL-2 secretion. Whilst in our hands the level of Ag-dependent suppression elicited by these T cells is less marked than TCR expressing CD4+CD25+ Tregs, it has proven a reliable method of generating large numbers of homogenous TCR expressing Treg-like T cells. It should also be noted that

Figure 2. Generating antigen specific Tregs using TCR gene transfer; two approaches. Using lenti or retro viral gene transfer it is possible to generate antigen-specific suppressive T cells. Two strategies have been utilized to achieve this: (A) Gene transfer of TCR alpha and beta chains of a TCR of known specificity into a poly-clonally activated population of sorted Tregs, and (B) Co-transfer of the genes encoding TCR alpha/beta chains and the regulatory transcription factor FoxP3 into a poly-clonally activated population of conventional CD4+ T cells.

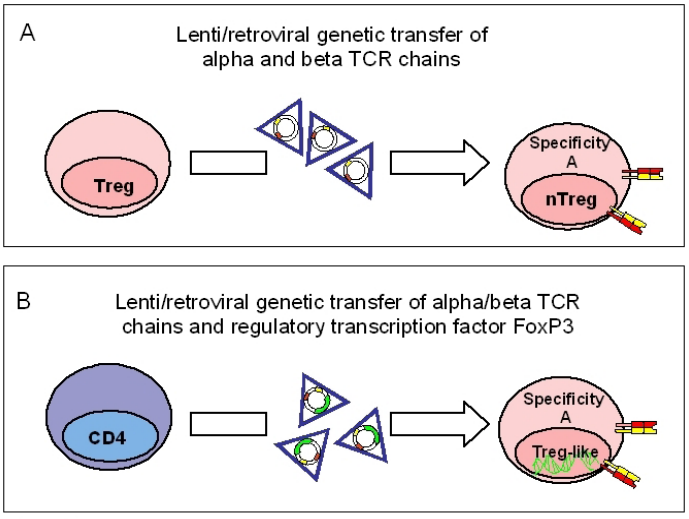


Fig. 2

although the in vitro linked suppression assay is a useful indicator of suppressive ability it is not always completely predictive of the level of suppression in vivo. It will be interesting to compare these two types of regulatory T cells in vivo.

Conclusion

There is now a substantial body of evidence in pre-clinical models for the efficacy of Tregs in the treatment of immuno-pathology. However, as yet there are only two ongoing human clinical trials, both in a GvHD setting. Many unanswered questions and obstacles stand in the way of utilizing Tregs to their maximal effect. Not least amongst these is the question of how to generate sufficiently large populations of Ag-specific regulatory T cells. Here we have highlighted the importance of Ag specificity and proposed that TCR gene transfer into polyclonally expanded Tregs as well as artificially generating FoxP3+ TCR expressing T cells may provide an efficient way of generating large populations of Ag specific Tregs. Studies are ongoing as to the efficacy of each of these approaches in models of auto-immunity and GvHD, and from initial indications we expect these methods to show considerable efficacy in the treatment of immune mediated pathology.

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Генерация регуляторных Т-клеток посредством переноса Т-клеточных рецепторов

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Резюме

Регуляторные Т-клетки (Treg) способны сильно подавлять Т-клеточные реакции на стадии «наивных» клеток, эффекторной фазе и в клетках памяти. Кроме того, они также действуют на различные другие имунные клетки, включая В-клетки, дендритные клетки и моноциты. Многие аспекты Treg-опосредованной супрессии делают их идеальными кандидатами для антиген-направленного лечения иммунопатологических состояний. Наша и другие лаборатории показали, что перенос гена Т-клеточного рецептора (TCR) является эффективным способом переориентации специфичности основной популяции Т-клеток на определенный антиген. До сих пор существенные усилия вкладывались в применение переноса гена TCR в обычные CD8+ и CD4+ клетки, для того, чтобы запускать или усиливать иммунные реакции. Но до сих пор было немного исследований по потенциальному использованию генной терапииTCR на другом крае этого спектра – для контроля иммунопатологических процессов с применением Т-регуляторных клеток. Здесь мы кратко обсуждаем сведения, указывающие на то, что генерация антиген-специфических Treg, в потенциале - через перенос гена TCR, может быть эффективным лечением различных форм иммунопатологии и кратко упоминаются трудности на пути понимания полного потенциала этого типа терапии. Проводилась адоптивная пересадка этих Т-регуляторных клеток облученным мышам, и дальнейшее размножение Treg с заполнением ниши может дать возможность для преимущественной экспансии клеток, специфичных к аллоантигенам. Имеется четкая корреляция в клинических условиях между толерантностью при трансплантации органов и уровням Treg. Здесь мы подчеркнули важность специфичности антигенов и предположили, что перенос гена TCR в размножающиеся поликлональные Т-клетки, продуцирующие FoxP3+ TCR, может обеспечить эффективный путь генерирования больших количеств антигенспецифических Treg-клеток.

Ключевые слова: Т-клетки, регуляторные, FoxP3, иммунотерапия, Т-клеточный рецептор (TCR), перенос гена TCR, трансплантация