Chapter 6
Regulatory T Cell–Based Immunotherapy:
Prospects of Antigen-Specific Tolerance Induction

Sonja Schallenberg
Center for Regenerative Therapies Dresden, Germany

Julia Riewaldt
Center for Regenerative Therapies Dresden, Germany

Cathleen Petzold
Center for Regenerative Therapies Dresden, Germany

Karsten Kretschmer
Center for Regenerative Therapies Dresden, Germany

ABSTRACT

$CD4^+CD25^+$ regulatory T (Treg) cells expressing the forkhead box transcription factor Foxp3 have a vital function in the maintenance of immune homeostasis and the prevention of fatal multi-organ autoimmunity throughout life. In the last decade, $Foxp3^+$ Treg cells have raised the hope for novel cell-based therapies to achieve tolerance in clinical settings of unwanted immune responses such as autoimmunity and graft rejection. Conceptually, the antigen-specific enhancement of Treg cell function is of particular importance because such strategies will minimize the requirements for pharmaceutical immunosuppression, sparing desired protective host immune responses to infectious and malignant insults. This chapter discusses current concepts of Treg cell-based immunotherapy with particular emphasis on antigen-specific Treg cell induction from conventional $CD4^+$ T cells to deal with organ-specific autoimmunity.

INTRODUCTION

Observations in mice and humans have demonstrated that $CD4^+CD25^+$ regulatory T (Treg) cells expressing the forkhead/winged helix transcription factor Foxp3 play an essential role in establishing dominant self-tolerance, controlling inflammatory responses and maintaining immune homeostasis (Sakaguchi, et al., 2008; Wing, et al., 2010). Foxp3 was initially identified as the X-linked gene mutated in the lymphoproliferative, autoimmune, inflammatory and allergic

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syndrome that develops in the *scurfy* mouse mutant (Brunkow, et al., 2001) and human IPEX (Immune dysregulation Polyendocrinopathy Enteropathy-X-linked syndrome) patients (Bennett, et al., 2001; Chatila, et al., 2000; Wildin, et al., 2001). Subsequent studies have established that the highly aggressive and fatal autoimmune disease caused by spontaneous mutations in the gene encoding Foxp3 can be recapitulated in mice by gene-targeted deletion of Foxp3 (Fontenot, et al., 2003; Gavin, et al., 2007; Lin, et al., 2007, 2005) and, to some extent, by Diphtheria Toxin (DT)-mediated ablation of Treg cells in adult mice with Foxp3-dependent expression of a human DT receptor as a transgene (Kim, et al., 2007; Lahl, et al., 2007). Overall, these experiments firmly established a lack of functional Treg cells as the primary cause of the severe autoimmune syndrome associated with Foxp3 deficiency.

A particularly striking example of the essential role of $Foxp3^+$ Treg cells in restraining destructive tissue-specific autoimmune responses is the observation that punctual ablation of Treg cells in adult Non-Obese Diabetic (NOD) mice carrying a pancreatic β cell-reactive T Cell Receptor (TCR) as a transgene unleashes overt autoimmune diabetes within three days (own unpublished observation; Feuerer, et al., 2009). Given their non-redundant function in maintaining immune homeostasis, it is not surprising that in recent years $Foxp3^+$ Treg cells have attracted considerable attention as particularly promising gain-of-function targets in clinical settings of unwanted immune responses, such as organ-specific autoimmunity and immune rejection of transplanted hematopoietic stem cells. Indeed, $Foxp3^+$ Treg cells have the potential to modulate innate and adaptive immune responses by suppression of activation, proliferation and function of various immune cell types, including macrophages, Dendritic Cells (DCs), $CD4^+$ T Helper (Th) cells, $CD8^+$ cytotoxic T cells, B cells and natural killer T cells (Vignali, et al., 2008). Mechanisms of Treg cell-mediated immune suppression include competition for growth factors, secretion of inhibitory cytokines, cell-contact-dependent inhibition through surface molecules, functional modification of Antigen-Presenting Cells (APCs) and induction of cytolysis (Miyara, et al., 2007; Shevach, 2009; Vignali, et al., 2008; von Boehmer, 2005). Although the relative importance of individual suppressor mechanisms has only recently begun to be explored, it appears likely that the contribution of the different mechanisms is context-dependent and modulated by the inflammatory milieu and magnitude of the immune response.

Both thymic and extrathymic $CD4^+CD25^+$ Treg cell developmental pathways have been proposed to feed into the overall pool of mature $Foxp3^+$ Treg cells in peripheral lymphoid tissues. A common hallmark of Treg cell lineage commitment is the induction of Foxp3 expression as a consequence of appropriate TCR engagement with Major Histocompatibility Complex class II (MHC-II): peptide ligands (Kretschmer, et al., 2006). Subsequently, expression of Foxp3 protein results in the stabilization and amplification of the Treg cell-specific transcriptional program (Gavin, et al., 2007; Lin, et al., 2007) through occupancy of key target gene promoters (Marson, et al., 2007; Zheng, et al., 2010). Experimental evidence suggesting an important function of the thymus in $Foxp3^+$ Treg cell generation includes the reduction of peripheral Treg cell numbers and concomitant development of autoimmune pathology upon thymectomy at day three after birth (Sakaguchi, et al., 1985), and the demonstration of the presence of $Foxp3^+$ T cells in the thymus by expression analysis in single cells (Fontenot, et al., 2005; Liston, et al., 2008; Wan, et al., 2005). Besides thymic Treg cell generation, early *in vitro* studies have provided first evidence that post-thymic $CD4^+Foxp3^+$ T cells can acquire suppressive capacity and some phenotypical characteristics of Treg cells, through either retrovirus-mediated ectopic expression of Foxp3 (Fontenot, et al., 2003; Hori, et al., 2003; Khattri, et al., 2003) or up-regulation of Foxp3 expression upon ligation of the TCR in the presence