T regulatory cell (Treg)

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Regulatory T cells (Tregs) are a subset of CD4+ T lymphocytes that possesses the capacity to suppress immune responses to ensure that the immune system's response to foreign antigens and its response to self-antigens remains adequately balanced. This homeostatic balance ensures the immune system is inflammatory enough to respond sufficiently to foreign antigens, as well as neoantigens from cancer, and sufficiently counter-balanced or anti-inflammatory that inflammation does not get out of hand, leading to tissue damage or death. The immune-suppressive effects of Tregs regulate tumor immunity, antimicrobial resistance, allergy and transplantation. Tregs also play a central role in maintaining self-tolerance. Treg involvement in this mechanism is pivotal for protection from autoimmune diseases.

Treg nTreg T regulatory cell iTreg Treg phenotype Treg subsets Treg function T cell receptor TCR

1. Treg Phenotype

CD4+ T cells contain various pro-inflammatory and anti-inflammatory subsets, of which the Treg subset is the major anti-inflammatory subset. Tregs can be phenotypically distinguished from the other CD4+ T cell subsets by a high cell surface expression of the interleukin-2 receptor alpha chain (IL-2RA), CD25, as well as the transcription factor Forkhead box protein P3 (FOXP3), which has been shown to be critical for Treg development, function and stability [7][8]. Indeed, mutations in the *FOXP3* gene result in Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, characterized by Treg dysfunction and uncontrolled autoimmunity [9]. Treg phenotypic stability is best indicated by demethylation of the Treg-specific demethylated region (TSDR), a non-coding, evolutionarily conserved element within the gene locus of *FOXP3* [10]. In humans, but not in mice, Tregs are further distinguished from other CD4+ cells by a low expression of the IL-7 receptor CD127 [11]. These aforementioned markers have been critical in defining the Treg subpopulation, yet there are many other identifying markers which can assist in distinguishing Tregs beyond the scope of this review [12]. Such additional markers have a more variable expression, and for some, the mechanisms of their function are still being elucidated. The variation in Treg phenotype may depend upon the microenvironment or the target population to be controlled.

2. Treg Subsets

Tregs exist in two major subpopulations: natural Tregs (nTregs) and induced Tregs (iTregs). The iTregs can be further separated into subpopulations of IL-10-secreting CD4+ T regulatory 1 cells (TR1 cells), TGF-beta-secreting

Treg cells (Th3) and CD8+ Treg cells [13]. nTregs arise from CD4+ single positive thymocytes, leave the thymus as FOXP3+ nTregs, and are enriched for T cell receptors (TCRs) that have a high affinity for self-peptides, thus playing an important role in autoimmunity [14]. Some CD4+ FOXP3- T conventional cells leave the thymus and, due to their phenotypic plasticity, are induced and converted into iTregs in the periphery after encountering an antigen, particularly in the presence of TGF-beta and IL-2 [15]. The phenotypic plasticity of iTregs permits an immune-tolerant state in extreme inflammatory conditions and further assists nTregs in restoring immune tolerance when needed [16][17].

3. Treg Function

Tregs effect immune tolerance by direct and bystander suppression. In direct suppression, Tregs suppress the target cell in an antigen-specific manner [18][19]. In bystander suppression, Tregs specific for one antigen have the ability to suppress immune responses against other antigens due to their close proximity to the antigen-specific response. This anti-inflammatory response restores immune tolerance and maintains immune homeostasis [20]. Treg suppressive function occurs via cell-to-cell crosstalk mechanisms, which are contact-dependent, as well as the secretion of inhibitory cytokines such as IL-10, IL-35 and TGF-beta, which have anti-inflammatory signalling properties [14]. Tregs also suppress immunity by acting as an IL-2 sink; as they possess a high surface expression of IL-2 receptor (CD25), they can soak up extracellular IL-2, thereby dampening pro-inflammatory cytokine signalling. IL-2 is also critical for Treg functional activity and survival [21][22]. Antigen-specific direct suppression occurs when peptide-loaded MHC class II (MHCII) on antigen-presenting cells (APCs) engages with the TCR complex on the Treg. If the TCR is able to recognise this peptide-MHC, the TCR complex undergoes a signal transduction cascade, resulting in Treg activation and an increase in Treg suppressive function.

4. T Cell Receptor

The T cell receptor, present on all T cells, confers antigen-specificity to the T cell through interaction with its cognate peptide-MHC on APC, permitting it to activate in an antigen-specific manner. On Tregs, the TCR exists as an alpha-beta heterodimer that is restricted to antigens presented by MHCII [23]. There is a great diversity in the specificity of TCRs due to somatic V(D)J recombination in the thymus, which has the capacity to generate in humans up to 10^{61} different TCR sequences [24]. High affinity TCRs on Treg cells are known to elicit a strong response to self-peptides as a result of thymic T cell selection selecting for Tregs with high-affinity, self-peptide recognising TCRs. Conversely, CD4+ T conventional cells (Tconvs) possess TCRs that have a lower affinity for their cognate peptide-MHC, are more flexible in their cross-reactivity, and possess a higher specificity to foreign peptides, which aligns with their T effector functions [25][26][27]. After recessive immune tolerance deleting most self-reactive TCRs in the thymus, a subset of those that remain obtain FOXP3 expression and nTreg phenotype, which is promoted through the autoimmune regulator transcription factor AIRE [28][29][30][31]. Therefore, the TCR repertoire from thymically-derived nTregs differs from that of Tconvs. TCR signalling on Tregs is required for their activation and ability to suppress [18][19][32]. When TCR engages with peptide–MHCII in the periphery, it is able to activate the Treg by signal transduction through the TCR–CD3 complex. Compared to Tconvs, Tregs have impaired TCR signal

transduction, referred to as TCR hyposignalling [33]. The signalling components of the TCR signal transduction cascade between Tconvs and Tregs are significantly different in their phosphorylation status, but not in their abundance or composition, except for Themis which has been detected at lower levels in Tregs. [34] Compared to Tconvs, Tregs have altered mechanisms of co-receptor binding involving the TCR–CD3 complex. Lymphocyte Activation Gene 3 (LAG3) on Tregs is a homologue of CD4, and binds to MHCII at a higher affinity than CD4. This results in the further enhancement of Treg signalling and contributes to their suppressor activity [35]. Treg costimulation is different to that of Tconvs by constitutive surface expression of CTLA-4, a key inhibitory molecule dependent on FOXP3 that competes with the major costimulatory molecule, CD28. CTLA-4 is able to outcompete CD28, binding to B7 family members B7-1 (CD80) and B7-2 (CD86) on APCs [36]. CTLA-4 possesses additional suppressor functions by disrupting the location of CD28 at the immune synapse, resulting in a shortened dwell time between naïve T cells and APCs. CTLA-4 also inhibits TCR signalling through recruitment of phosphatases SHP-2 and PP2A [37][38]. Once the Treg is activated, it can broadly suppress by means of direct antigen-specific immune tolerance or bystander suppression, which enables the blocking of the responses of nearby cells. Not only does the TCR control the antigen-specificity of the response but, additionally, the affinity of a TCR for a given peptide–MHC complex determines the potency of the Treg response [39]. Therapies exploiting the TCR to elicit an enhanced, autoantigen-specific Treg activity and function are currently being explored as a cell-based therapy in autoimmune disease, and will be discussed in detail later.

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