Th17 and Treg cells, two new lymphocyte subpopulations with a key role in the immune response against infection

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In addition to the T helper 1 (Th1) and Th2 lymphocyte subsets, two new subpopulations Th17 and regulatory T (Treg) cells have recently been described. Th17 cells, which produce high levels of interleukin (IL)-17, are dependent on the transcription factor orphan nuclear receptor RORC2/RORγt and have been implicated in exacerbating the immune response to infections. Conversely, Treg cells, either thymus-derived or generated upon TCR activation of naïve T cells, express the transcription factor forkhead box P3 (Foxp3) and have regulatory functions mediated through either direct cell-cell contact or immuno-suppressive cytokines, being able to suppress the activation of T, B and NK cells. Based on the current knowledge of Th17 and Treg cell functions, new therapeutic strategies start to emerge, involving anti-cytokine treatments targeting Th17 functions or cell-based treatments in which Treg cells are generated from T cells either through Foxp3 gene transfer onto T cells with known specificities or transferring specific TCR genes onto Treg cells.

In spite of great advances in the biomedical sciences, infectious diseases keep increasing in the world population, both on terms of morbidity and mortality. Due to its non-debatable economic advantages, prevention strategies are the gold-standard on infection control. Together with the improvement in sanitary conditions, new therapeutic strategies and vaccines are the focus of current investigations. The new knowledge in the microbial-host interactions, infection pathogenesis and immune response are the clues and further basic research is essential to successfully achieve these goals. In this review, we provide a general overview of the response from different T lymphocyte subsets and their relation to infectious and non-infectious diseases, which might represent the key for future advances to successfully fight infection.

IMMUNE RESPONSE: Th1 Th2 AND MORE

The immune system evolved to protect higher organisms from infection by microorganisms and parasites. Its function is carried out by specialized cells and molecules, which are able to distinguish between self- and foreign-antigens, being tolerant to self-antigens to avoid autoimmunity and responding to foreign antigens to control and eliminate them. The activation of the innate arm of the immune response represents the first barrier against foreign antigens, which through antigen-unspecific mechanisms recruits immune cells to the infection site, starts inflammation, allows activation of the complement cascade and the removal of foreign substances present in organs, tissues or blood. It involves specialized white blood cells such as mast cells, phagocytes, neutrophils, basophils, eosinophils and natural killer cells. If the innate immune response is unable to effectively cope with the infection, the adaptive arm of the immune response is activated, which then deals with the infection on an antigen-specific manner, through the response against specific antigens present in the infectious agent. The lymphocytes of the adaptive immune response provide a highly versatile mean of defense and generate immunological memory, implying protection from subsequent re-infection by the same pathogen. The cells and the inflammatory cytokines and chemokines released during the innate immunity are essential for the initiation and determination of the type of the response developed during the adaptive response.

$CD4^+$ T cells represent one of the main components of the adaptive immune response. These cells control the functional activities of both innate and adaptive immunity and determine the outcome of the immune response against infections. After antigenic stimulation, naïve $CD4^+$ T cells proliferate and may differentiate into distinct effector subsets, which have been classically divided, on the basis of their cytokine production profiles, into T helper (Th) 1 and Th2 cells [1]. Th1 cells are characterized by the secretion of interferon (IFN) -γ, interleukin (IL) -2, IL-12, tumor necrosis factor (TNF) -α and TNF-β, and are involved in the eradication of intracellular pathogens. Conversely, Th2 cells are characterized by secretion of IL-4, IL-5, IL-6, IL-9 and IL-13, which are potent activators of B cells, are involved in the elimination of extracellular microorganisms and parasitic infections, and are also responsible for allergic disorders [2, 3]. In addition, a third type of Th cells, referred to as Th0 cells, with the capacity to secrete both Th1 and Th2 cytokines has been described [4]. More recently, two new subsets of $CD4^+$ T cells have been characterized, on the one hand, the Th17 subset, which follows different polarizing conditions and displays different functional activities than Th1 and Th2 cells [5, 6] and, on the other hand, the regulatory T (Treg) cell subset, which displays suppressor functions [7, 8] Fig. (**1**).

Th17 CELLS: A NEW T HELPER LYMPHOCYTE SUBSET

The first indication of a new Th subset came from data demonstrating that microbial stimuli induce, in both murine and human T cells, IL-17 and TNF-α production, in the absence of Th1 and Th2 cytokines [9], but the description of the Th17 phenotype came from analysis of mouse autoimmunity models historically associated with Th1 immune responses, namely experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA) [10, 11]. The discovery that the p40 subunit of IL-12 (p40/p35 heterodimer) is common to IL-23 (on p40/p19 heterodimer), allowed to demonstrate that both EAE and CIA were completely abrogated in IL-23 deficient mice but not in IL-12 deficient mice [12, 13]. These data demonstrated that IL23 was required for Th17-mediated immunopathology. IL-23 receptor is a heterodimer (IL-12Rβ1/IL-23R), not functional in resting T cells since IL-23R is up-regulated only upon T cell activation, thereby rendering activated cells responsive to IL-23 [14]. Thus, IL-23 cannot drive naïve T cell differentiation into Th17 cells, since only the latter express IL-23R [14, 15]. Subsequently it was demonstrated that the combination of IL-6 with transforming growth factor (TGF) -β triggered the secretion from naïve T cells of large amounts of IL-17 [16] and led to Th17 differentiation [17, 18] and up-regulated IL-23R expression [19], allowing IL-23

to stabilize and strengthen the Th17 phenotype and providing a survival signal for differentiated Th17 cells [18, 20]. Furthermore, IL-1 increases Th17 cell numbers generated *in vitro* [18] and in IL-1R$^{-/-}$ mice the Th17 response is weaker [21], suggesting a role of IL-1 in Th17 generation.

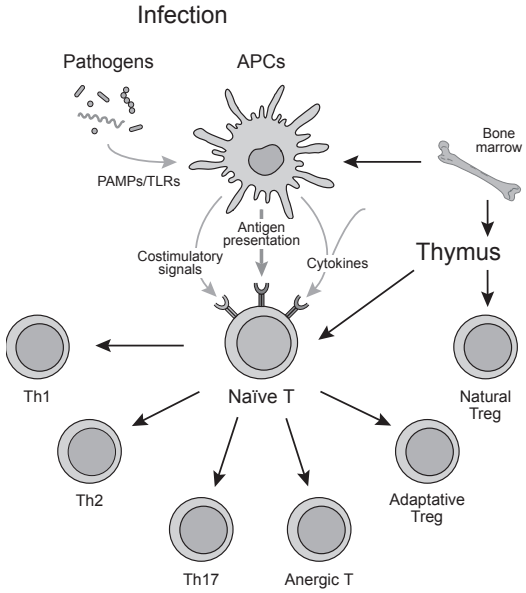

Fig. (1). ***Paradigms in Th and Treg cell differentiation.*** Dendritic cells recognize microbes by the molecular patterns that they expose (PAMPS), through an extensive array of surface receptors, including TLRs and C-type lectins. The microbe is then captured and the antigens are processed into small peptides, which subsequently associate with molecules from major histocompatibility complex (MHC) and then presented to T cells bearing on their surface specific receptors (TCR) specific for these antigen-MHC complexes. During TCR stimulation, naïve T precursors differentiate into distinct subsets, as a result of co-stimulatory signals and their cytokine environment. Th1 cells arise in the presence of IL-12 and drive cell-mediated immunity. Alternatively, in the presence of IL-4, naïve T cells differentiate into Th2 cells and mediate a humoral immune response. Th17 cells are a novel CD4$^+$ T cell subset that arise in the presence of IL6 and TGF-β, have a key role in inflammation and autoimmunity. Adaptive Treg cells arise in the presence of TGF-β and secrete immunosuppressive cytokines. The interaction between the different cell subsets is essential for immune response regulation. APCs = antigen presenting cells; PAMPS = pathogen-associated molecular patters; TCR = T cell receptor; Th = T helper lymphocytes; TLRs = Toll-like receptors.

RORC2/RORγt: master switch of Th17 cells

The different Th cell phenotypes develop from the same pool of naïve T cells [11]. Th1 differentiation is initiated by TCR signaling in the presence of IL-12, which lead to signal transducer and activator of transcription 1 (STAT1) activation [6, 22], which up-regulates the transcription factor T-bet (also known as Tbx-21), the master regulator for Th1 differentiation [23]. T-bet enables IL-12 signaling through STAT4, which in turn, further potentiates IFN-γ production and induces IL-18Rα expression [22, 23]. Thus, the later stage of Th1 differentiation induced by IL-12 enables mature Th1 cells to produce IFN-γ in an antigen-independent manner and allows suppression of Th2 and Th17 differentiation [5, 24]. Conversely, Th2 differentiation is initiated by TCR signaling in concert with IL-4 receptor signaling via STAT6, which cooperatively up-regulates the expression of the transcription factor GATA3, the master regulator of Th2 differentiation [25]. GATA3 auto-activates its own expression and blocks Th1 and Th17 differentiation through the suppression of STAT4, IL-12Rβ2 chain and IL-23R [5, 19].

The absence of Th17 cells in mice deficient for the transcription factor orphan nuclear receptor (RORγt, or RORC2 in humans) and its reversion upon transduction of RORγt-encoding retroviruses on naïve T cells [26] suggested a relevant role of this transcription factor on the generation of Th17 cells. Both RORγt and RORγ are encoded by the *Rorc* locus by the use of two different promoters, which are responsible for their differential expression [27]. Th17 differentiation is initiated by TCR signaling in the presence of IL-6 and TGF-β. These signals activate STAT3 and Smads which trigger, in turn, expression of the transcription factor RORγt. Latter stages of Th17 differentiation are induced by IL-23, which through the over-expression of TGF-β inhibits Th1 and Th2 development [17, 18, 28] Fig. (**2**).

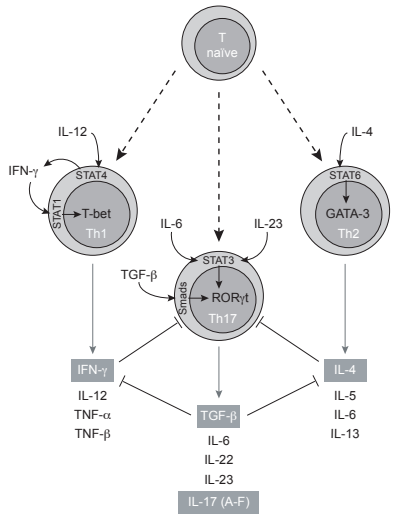

Fig. (2). ***Th1, Th2 and Th17 cell differentiation.*** Following TCR activation, naïve CD4 T cells may differentiate into either Th1 cells in presence of IL-12 or Th2 cells in presence of IL-4. IL-12 up-regulates IFN-γ synthesis via STAT4 signaling. This stimulates STAT1 activation and T-bet transcription factor expression, leading to a Th1 phenotype. Conversely, IL-4 activates STAT6 signaling, which induces GATA3 transcription factor expression and determines Th2 cell differentiation. The Th17 phenotype develops in response to IL-6, TGF-β and IL-23 via STAT3 and Smads signaling and the up-regulation of the transcription factor RORγt (RORC2 in humans) expression. In addition, Th1 and Th2 cytokines potently inhibit Th17 differentiation. Conversely, TGF-β inhibits the Th1 and Th2 differentiation both by inhibiting the IFN-γ and IL-4 synthesis by effector Th1 and Th2 cells and by blocking the IFN-γ and IL-4 activity on naïve T cells. IFN = interferon; IL = interleukin; Th = T helper lymphocytes; TGF = transforming growth factor; TNF = tumor necrosis factor.

Effector functions of Th17 cells

Activated human Th17 cells are phenotypically identified as CCR2$^+$CCR5$^-$ [29], whereas human memory CD4$^+$ T cells producing IL-17 and expressing RORC2 mRNA are CCR6$^+$CCR4$^+$ [30]. Th17 cells secrete several pro-inflammatory cytokines such as TNF-α, TGF-β, IL-6, IL-21, IL-22, IL-23, IL-26 and particularly IL-17, but neither IFN-γ nor IL-4 [31-33]. At the beginning of the 1990's, the first IL-17 was described, cloned and originally named cytotoxic T-lymphocyte antigen (CTLA) -8; it was subsequently renamed IL-17 and more recently IL-17A [34]. IL-17A is the prototypic IL-17 family member, a disulfide-linked homodimeric glycoprotein of 155 aminoacids, with a molecular weight of about 35 kDa [34, 35]. The IL-17 family consists of 6 family members (IL17-A to IL-17F), identified

TABLE 1

Human IL-17 cytokine and receptor families [36]

Ligand	Chromosome	Size [a]	Length [b]	Receptor	Chromosome
IL-17A	6p12	35	155	IL-17RA Also IL-17RC	22q11.1
IL-17B	5q32-34	41	180	IL-17RB/IL-17RH1	3p21.1
IL-17C	16q24	40	197	IL-17RC/IL-17RL	3p25.3
IL-17D	13q12.11	52	202	IL-17RD/hSED	3p21.2
IL-17E/IL-25	14q11.2	34	161	IL-17RE Also IL-17RB	3p25.3
IL-17F	6p12	44	153	IL-17RA Also IL-17RC	

[a]KDa
[b]amino-acid number

by homology-based cloning, evolutionarily conserved between rodents and humans, and all form homodimers [36]. These molecules signal through five distinct surface receptors (IL-17RA-E) [36] (Table 1).

The role of Th17 T cells in host defense against pathogens is just emerging, particularly on their destructive potential in autoimmune and chronic diseases. It has been proposed that Th17 cells are important in host defense against extracellular bacteria such as *Klebsiella pneumoniae* or *Bacteroides fragilis* as well as against fungal infections including *Candida albicans* [37-39]. Th17 lymphocytes constitute an early defense against severe trauma that could result in tissue necrosis or sepsis and represent a bridge between innate and adaptive immunity, synthesizing IL-17 and stimulating the generation and mobilization of neutrophils [40, 41]. Moreover, Th17 cells seem to antagonize Treg cell development, thereby amplifying the inflammatory responses and thus, playing a crucial role in the progression of inflammatory and autoimmune disorders [16, 42, 43].

IL-17A, IL-17C and IL-17F have direct effects on human blood neutrophil chemotaxis whereas IL-17E is involved in eosinophil migration [44, 45]. IL-17A enhances the expression of CXCL1, CXCL2 and CXCL8 (IL-8), strengthening the chemotactic activity of neutrophils in gastrointestinal and bronchoalveolar infections [44, 46], and induces increased expression of monocyte chemotactic protein-1 (MCP-1) in rat intestinal epithelial cells, promoting the accumulation of functional monocytes [47] In addition, IL-17A also activates neutrophils, increasing neutrophil elastase and myeloperoxidase activity and determining the pathological proteolysis in inflamed tissues [48]. IL-17A and IL-17D induce the production of granulocyte colony-stimulating factor (G-CSF) and granulocyte monocyte colony-stimulating factor (GM-CSF) in endothelial cells and bronchio-epithelial cells in humans, increasing the number of neutrophil progenitors and enhancing neutrophil survival [49, 50].

Th17 role in non-infectious and infectious diseases

The relevance of Th17 lymphocytes in autoimmunity has been unraveled in numerous studies. Treatment with anti-IL-17A antibodies on a rodent CIA model resulted in reduced joint inflammation, cartilage and bone destruction [51]. Consistently, IL-17A deficient mice displayed suppressed CIA development [52] and reduced EAE [53]. In humans, elevated IL-17 levels have been detected in the synovial fluid and serum samples from rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease (IBD) and multiple sclerosis (MS) patients [54-57]. In RA patients, IL-17A induced release of metalloproteinase (MMP) -1 and MMP-13 in the joint synovia, whereas in MS patients, up-regulated IL-17A expression was detected in central nervous lesions [58-60]. In a mouse model of allergic asthma, IL-17A regulates neutrophil recruitment in response to allergens in the bronchoalveolar space, determining the balance between neutrophil and eosinophil accumulation [61]. Consistently, asthma affected patients displayed an increase in local concentration of soluble IL-17A [62]. Moreover, healthy volunteers exposed to a swine confinement, which induces severe airway inflammation, showed a pronounced increase in soluble IL-17A in their bronchoalveolar tissues [63].

Although the role of the Th17 cells in cancer has been scarcely studied, some data pointed towards the participation of IL-17 cytokine family in cancer development. IL-17A promoted angiogenesis and tumor growth in a mice model of fibrosarcoma and triggered increased macrophage recruitment in human cervical cancer in nude mice [64, 65]. Conversely, in human prostate cancers, down-regulated levels of IL-17RC were detected, whereas an over-expression of IL-17RB was associated to the lack of recurrence of breast cancers [66, 67].

Skeletal homeostasis depends on a dynamic balance between the activities of the bone-forming osteoblasts (OBLs) and bone-resorbing osteoclasts (OCLs) [68]. This balance is tightly controlled by various regulatory systems, such as the endocrine system, and is influenced by the immune system, an osteoimmunological regulation depending on lymphocyte- and macrophage-derived cytokines [68-70]. An unbalance in favor of OCLs leads to pathological bone resorption as it has been observed in RA, periodontitis, osteoporosis, Paget's disease and bone tumors [68, 71].

During the 1970's the first observation pointing towards immune cells influencing OCLs activity was made. Indeed, a factor (OCL-activating factor or OAF) that stimulated bone resorption was detected in the supernatant from cultured human peripheral monocytes stimulated with phytohemagglutinin [72]. Purification of this activity led to the identification of IL-1β [73]. Nowadays, numerous cytokines have been demonstrated to stimulate bone resorption, including TNF-α, IL-1α, IL-1β, IL-6, IL-11, IL-15 and IL-17, whereas others such as IL-4, IL-10, IL-13, IL-18, GM-CSF and IFN-γ inhibited bone resorption [68, 69]. In this context, functional characterization of three novel members of the TNF-ligand and receptor superfamily, the receptor activator of nuclear factor-κB (RANK), its ligand (RANK-ligand or RANKL) and the soluble decoy receptor of RANKL named osteoprotegerin (OPG), have contributed significantly to the establishment of osteoimmunology, where these molecular mediators participate as key modulators of

physiological and pathological bone resorption [74-76]. RANKL exerts its biological effects directly through binding to RANK, inducing OCL differentiation, maturation and activation [77]. OPG inhibits the osteoclastogenesis and induces osteopetrosis when over-expressed in transgenic mice [78]. RANKL has been associated with diverse osteodestructive pathologies, including RA, bone tumors, osteoporosis, Paget's bone disease, osteolytic lesions of the facial skeleton, odontogenic lesions and periodontitis [79-86].

The identification of RANKL as the T cell cytokine TRANCE (TNF-related activation-induced cytokine) allowed to envisage the possibility that $CD4^+$ T cells may have the capacity to induce OCL differentiation and activation by directly acting on OCL precursors and on mature OCLs through synthesis of RANKL during osteo-destructive diseases [85, 87-89]. Furthermore, many well-known osteotropic factors, including TNF-α, IL-1β and IL-6, exert their osteoclastogenic activity by inducing RANKL expression on OBLs and $CD4^+$ T cells [90]. Th1 and Th2 cells inhibit osteoclastogenesis by acting on the precursor cells, mainly through IFN-γ and IL-18, which are released by Th1 cells, or IL-4 and IL-10, which are released by Th2 cells [91, 92]. In contrast, Th17 cells stimulated by IL-23 promote osteoclastogenesis mostly through production of IL-17 and RANKL [93]. Furthermore, IL-17 facilitates local inflammation by recruiting and activating immune cells, which leads to an abundance of inflammatory cytokines such as IL-1β and TNF-α that enhance the RANKL expression on OBLs and Th17 cells [94, 95] Fig. (**3**).

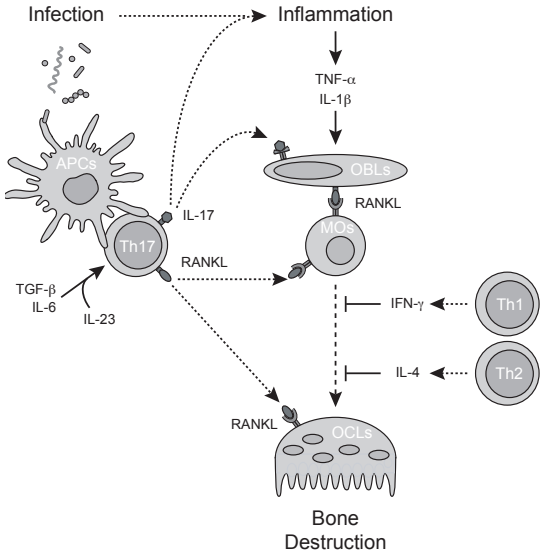

Fig. (3). ***Role of Th17 cells on bone destruction induced during infectious diseases through enhanced osteoclastogenesis.*** During early infection stages, an inflammatory response is established, characterized by synthesis of inflammatory cytokines, such as IL-1β and TNF-α. In the context of an unresolved infection, an adaptive immune response is established and, under determined conditions, Th17 cells may be activated, contributing to bone destruction by secreting IL-6, IL-17 and RANKL. IL-6 and IL-17 increase the inflammatory response and induce RANKL expression by osteoblastic stromal cells. Thus, Th17 cells may induce cell-to-cell interactions between osteoblasts and osteoclast precursors, inducing indirectly osteoclast differentiation. On the other hand, Th17 cells also may contribute directly to bone loss by synthesizing RANKL, thereby driving osteoclast differentiation and maturation by a cell-contact independent way. APCs = antigen presenting cells; Th = T helper lymphocytes; MOs = monocytes, osteoclast precursors; OBLs = osteoblasts; OCLs = osteoclasts.

Th17 cells represent a large proportion of the inflammatory cells invading the synovial tissues during RA [96]. High levels of IL-17A have been detected in the synovial fluid and IL-17-producing cells have been detected within the T cell-rich areas in patients with RA [57, 97]. Furthermore, IL-17A is able to promote cartilage destruction and bone erosion in experimental RA [57]. Increased levels of IL-17 were detected in gingival crevicular fluid and in biopsy samples from periodontal lesions, both at the mRNA and protein levels, in patients with chronic periodontitis, and these increased levels have been associated to $CD4^+$ T cells [98, 99]. Furthermore, RANKL and RANK were synthesized within periodontal lesions where IL-17 was produced by activated gingival T cells [43, 98]. These data are reinforced by the over-expression of RORC2 mRNA in active lesions from chronic periodontitis patients (R.V. unpublished data). Taken together, these data establish that Th17 cells represent the osteoclastogenic Th subset on $CD4^+$ T lymphocytes, inducing osteoclastogenesis and bone resorption through synthesizing IL-17 and RANKL.

FROM SUPPRESSOR CELLS TO REGULATORY T CELLS

The immune system has the potential to destroy invading microorganisms and control outgrowth of tumor cells, but must prevent the attack against self, a concept known as self-tolerance. Tolerance to self-antigens is attained initially by the elimination of self-reactive T and B lymphocytes during negative selection in the thymus and bone marrow, respectively. In addition, and as an additional safety mechanism, the immune system has peripheral mechanisms to deal with immune cells that escape to the central tolerance.

At the beginning of 1980's, the existence of a suppressor T cell population was proposed, suggesting that these suppressor T cells restrict the induction or expression of effector T cells and thereby prevent and control exaggerated immune response and autoimmune disease development [100]. The modern view of suppressor cells began with the observation that the transfer of T cells depleted of the IL-$2R\alpha^+$ ($CD25^+$) cell subpopulation induced multiorgan autoimmunity in recipient mice [101]. Nowadays, suppressor T cells have been renamed and are currently known as Treg cells. These cells have been isolated from mice and humans and their regulatory functions have been demonstrated not only *in vitro* but also *in vivo*.

It has also been established that several types of cells carry out regulatory activities. These include IL-10-secreting $CD4^+$ T regulatory-1 (Tr1) cells, TGF-β-secreting $CD4^+$ Th3 cells, NKT cells, $CD8^+CD28^-Foxp3^+$ cells, γ/δ TCR^+ cells, and $CD4^+CD25^{high}Foxp3^+$ T cells, the last one widely accepted as "professional Treg cells" or naturally occurring Treg cells [102, 103]. Some of these cells are induced in response to infectious challenge and develop from conventional naïve T cells exposed to specific stimulatory conditions, whereas others arise during the normal process of maturation in the thymus [7] Fig. (**1**).

Phenotype and classification of Treg cells

In spite of the experimental evidence for the existence of Treg cells, key aspects from this phenotype and mechanism of action still remain undefined. In fact, although many studies indicate that CD25 is a crucial cell-surface marker for the Treg cells, several other markers such as CD38, CD62L (L-selectin) or CD103 also identify this subset. Furthermore, the relative contribution of soluble cytokines compared with cell-cell contact to carry out their inhibitory activity also remains controversial [7, 103, 104]. It has been proposed that there are two main subsets of Treg cells, which differ in

terms of origin, generation and mechanisms of action. They have been named natural and adaptive Treg cells [7] Fig. (**4**).

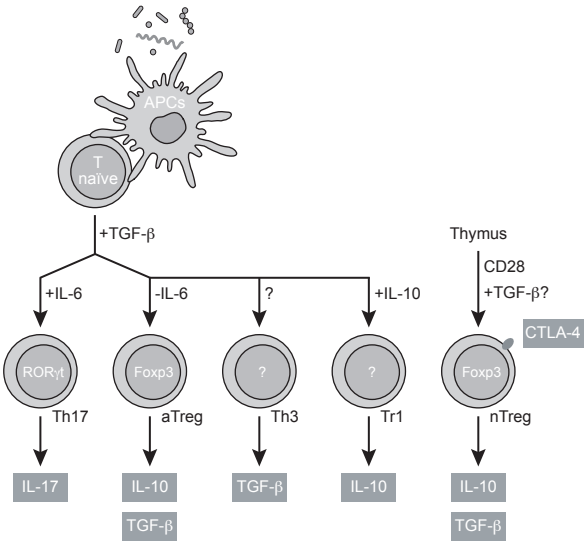

Fig. (4). ***Differentiation and function of Treg cells.*** In the periphery, chronic TCR stimulation is able to induce Foxp3 expression in naïve T cells. TGF-β is essential for acquisition of Foxp3 expression in peripheral induced Treg cells *in vivo*. Reciprocal developmental pathways have been described for Th17 and Treg cell generation, in which IL-6 is essential. In addition, it has been postulated that IL-10 signaling contributes to differentiation of Tr1 phenotype. The factors involved on Th3 differentiation, however, have not yet been described. On the other hand, the thymus represents the main site for natural Treg cell differentiation. Foxp3 expression in the thymus is dependent upon CD28 signaling and perhaps an additional unknown factor(s). *In vivo*, natural and adaptive Treg cells mediate their regulatory activities by producing immuno-suppressive cytokines such as IL-10 and TGF-β. In addition, natural Treg cells function by direct cell-to-cell interactions, at least *in vitro*, through surface molecules such as CTLA-4, mediator of natural Treg cell activities in APCs and effector T cells. APCs = antigen presenting cells; aTreg = adaptive Treg cells; IL = interleukin; nTreg = natural Treg cells; Th = T helper lymphocytes; TGF = transforming growth factor; CTLA-4 = cytotoxic T-lymphocyte antigen-4.

Natural Treg cells

Natural Treg cells are $CD4^+$ T cells that develop and mature in the thymus and carry out their regulatory function during normal surveillance of self-antigens [7]. On normal individuals, they represent 5-10% of the peripheral $CD4^+$ T cell population and are characterized by the constitutive expression of high levels of CD25 and low levels of CD45RB ($CD4^+CD25^{high}CD45RB^{low}$) [105]. Unlike conventional T cells, which transiently up-regulate CD25 expression after activation, these cells maintain the CD25 expression independent of their activation status [106]. Other surface molecules have been associated with natural Treg cells, including CD152 (CTLA-4), CD103 (α_E-integrin), and two members of the TNFR-superfamily receptor, namely CD134 (OX40; TNFRSF4) and GITR (glucocorticoid-induced TNF receptor family-related protein; TNFRSF18) [7, 107]. None of these markers is, however, exclusive for Treg cells and there are evidences of $CD4^+$ and $CD8^+$ T cells with regulatory functions devoid of CD25 and other Treg makers [104, 108].

The signals that are responsible for the generation of Treg cells in the thymus are incompletely defined. It has been proposed a key role of signaling through CD28 for both thymic development and peripheral homeostasis of natural Treg cells [109]. A combination of strong antigenic signals to TCR and maximal co-stimulation of CD80 (B7.1) and/or CD86 (B7.2) through CD28 are required for thymic Treg development [110-112]. A strong B7/CD28 co-stimulation is also required to their peripheral self-renewal and survival [111, 112]. In contrast to regular effector T cells, natural Treg cells show only marginal synthesis of mitogenic cytokines and cell proliferation *in vitro*, however, they proliferate extensively *in vivo* [7]. The absence of CD80/CD86 or CD28 results in decreased number of natural Treg cells in peripheral lymphoid tissues and their absence induce autoimmunity [111, 113].

Natural Treg cells appear to be mainly restricted by self antigens; however pathogen-specific Treg cell activity has also been proposed in infectious diseases [114]. The mechanisms involved in the suppressive activity of natural Treg cells are not fully understood. It has been postulated that direct cell-to-cell contact through surface molecules, for instance CTLA-4, is necessary for regulatory function *in vitro* [105, 115].

Adaptive or induced Treg cells

Adaptive Treg cells represent $CD4^+$ T cells that acquire their regulatory activity during activation [7]. Unlike natural Treg cells, which came out from the thymus as $CD4^+CD25^+$ cells, adaptive Treg cells originate from peripheral naïve T cells [7]. They are derived from $CD4^+CD25^-$ T cells and show variable expression of CD25 in mature state, depending on the disease and the site of regulatory activity [116]. Induced Treg cells require TCR stimulation for induction of regulatory functions and have demonstrated limited proliferation *in vitro* [104]. Critical determining factors for the induced Treg development are the type and the differentiation status of the antigen presenting cells (APCs) and the cytokine milieu during activation. Antigen presentation by immature dendritic cells (DCs) in presence of IL-10 and/or TGF-β during naïve T cell activation promotes differentiation into adaptive Treg cells *in vitro* [117]. In this context, it is worth to note that unlike natural Treg cells adaptive Treg cells do not require co-stimulation through CD28 for their development and function [118].

Inducible Treg cell populations include Tr1, Th3 and converted forkhead box P3 (Foxp3) cells [119]. The antigen specificity of the adaptive Treg cells remains unclear; however, it has been determined their regulatory activity is mediated by IL-10 and/or TGF-β expression [104].

FOXP3: T regulatory cells master switch

The transcription factor Foxp3, also known as scurfin, represents a lineage-specific marker for natural Treg cells and is a critical regulator of Treg cell development [120, 121]. Foxp3 is an acetylated and phosphorylated protein that forms oligomers associated as a large molecular complex [122, 123]. Its relevance on Treg cells development and function was demonstrated by natural mutations of *foxp3* gene both in mice and humans. Scurfy (*sf*) is a spontaneous X-linked recessive mutation of the *foxp3* gene in mice, characterized by lymphoproliferation, multiorgan infiltration, complete loss of natural Treg cells, autoimmunity and premature death of hemizygous (sf/Y) males [124]; the same phenotype was obtained in $foxp3^{-/-}$ genetically modified animals [125]. Similarly, mutations of *foxp3* gene in humans are responsible for the IPEX (immuno-dysfunction polyendocrinopathy enteropathy X-linked) syndrome, characterized by natural Treg cell function impairment and clinical manifestations of autoimmune disorders such as enteropathy and type 1 diabetes [126]. Furthermore, retroviral gene transfer of *foxp3* into $CD4^+CD25^-$ or $CD8^+$ T cells, but not into B cells, leads to the generation of cells with a regulatory phenotype [127].

Foxp3 is expressed both at mRNA and protein levels in peripheral $CD4^+CD25^+$ T cells [125]. In the thymus, Foxp3 mRNA has been detected in $CD4^+CD8^-CD25^+$ cells but not in immature thymocytes [128]. Low levels of Foxp3 expression have been detected in B and $CD8^+$ T cells and low but significant levels have been detected in $CD4^+CD25^-CD45RB^{low}$ T cells, a cell subset with regulatory activity [128]. In addition, Th1 and Th2 cells generated from $CD4^+CD25^-$ cells fail to express Foxp3 [121]. In humans, Foxp3 is also expressed in $CD4^+CD8^-CD25^+$ cells [129]. Unlike in mice, in humans a small subpopulation of $CD4^+CD25^-$ T cells up-regulate Foxp3 *in vitro* upon anti-CD3 and anti-CD28 stimulation, exhibiting suppressive activity and suggesting acquisition of regulatory functions [130].

In humans, Foxp3 expression is not exclusive to natural Treg cells. Recent work has demonstrated transient Foxp3 expression in activated $CD4^+CD25^-$ effector T cells. However, a transient wave of Foxp3 expression is not sufficient to confer regulatory activity [131], rather, a high and sustained Foxp3 expression induced by TCR-stimulation is required to generate functional adaptive Treg cells [132]. The Foxp3 up-regulation in human adaptive T cells is controlled by STAT5-dependent mechanisms [132] and maintenance of Foxp3 expression in natural Treg cells is also STAT5-dependent, suggesting a common molecular mechanism controlling Foxp3 expression in both natural and adaptive Treg cells [132].

IL-2 and TGF-β are essential for the expression of Foxp3, generation of Treg cells and maintenance of immunologic tolerance. Genetically deficient mice for either IL-2 ($IL\text{-}2^{-/-}$) or CD25 ($IL\text{-}2R\alpha^{-/-}$), harboring a $Foxp3^{gfp}$ knock-in allele, allowed to demonstrate that IL-2 signaling was required to induce Foxp3 expression in thymocytes. Thus, in addition to its known functions on the regulation of cell growth, IL-2 seems to be critical for maintaining *in vivo* Treg cell function [133]. $TGF\text{-}\beta^{-/-}$ or $CTLA\text{-}4^{-/-}$ mice show an uncontrolled T cell activation and develop generalized autoimmunity leading to a fatal lymphoproliferative disease, disclosing an important relation among TGF-β, CTLA-4 and the Treg phenotype [134]. Indeed, in TGF-β or CTLA-4 deficient mice, the number of natural Treg cells within the thymus is normal [135], but these factors seem to be required for a maintained $Foxp3^+$ expression [136]. Furthermore, TGF-β is also necessary to induce expression of Foxp3 on activated $CD4^+CD25^-$ T cells [137] Fig. (**4**).

Effector mechanisms of regulatory T cells

It has been postulated that natural Treg cells function, at least *in vitro*, through direct cell-cell interactions with APCs and responding effector T cells [105, 115]. Recently, it has been postulated, however, that IL-10 and TGF-β also appear to be important mediators of their regulatory activities *in vivo* [134, 138], a molecular mechanism that had already been suggested for the function of adaptive Treg cells [104]. Fig.(**4**). Indeed, whereas neutralizing antibodies to TGF-β did not affect $CD4^+CD25^+$ Treg function *in vitro*, abolished the therapeutic effects in inflammatory bowel disease and type 1 diabetes in mice *in vivo* [139, 140]. It has been reported that Treg cells in addition to secrete active TGF-β, also express membrane-bound TGF-β, having an important role in the functional properties of natural and induced Treg cells [134, 141]. On Treg cell-depleted $CD4^+$ T cells, it has been demonstrated that cell-cell contact-mediated suppression was independent from membrane-bound TGF-β [142]. When $CD25^+$ Treg cells where co-activated together with Treg cell-depleted $CD4^+$ T cells, anergized $CD4^+$ T cells were obtained and these, in turn, inhibited the activation of freshly isolated $CD4^+$ T cells, demonstrating that the suppressive activity transferred from $CD25^+$ Treg cells via cell contact was mediated by soluble TGF-β in a cell-contact independent way [142].

Both *in vitro* and *in vivo* studies suggest that Treg cells can suppress the proliferation and/or cytokine production of effector T cells [143]. Suppression of $CD4^+$ effector T cell proliferation by Treg cells has been observed *in vitro* on an APC-free model, and a block of $CD8^+$ T cell differentiation into cytolytic effector cells has been determined *in vivo* [143, 144]. Furthermore, it has been proposed that Treg cells can kill effector T cells directly in culture through the release of granzyme B and perforin [145, 146]. Treg cells may also modulate the immune response through DCs. Analyzing the effect of human natural Treg cells on maturation and function of monocyte-derived DCs, it has been demonstrated that Treg cells prevent immature DCs from becoming immunogenic, synthesizing increased levels of IL-10 and expressing reduced levels of CD80, CD83 and CD86 despite the CD40 pre-stimulation, an effect marginally reverted by neutralizing anti-TGF-β antibodies [147]. Furthermore, CTLA-4-expressing natural Treg cells induce the expression by APCs of the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan, and lack of this essential amino acid has been shown to inhibit T cell activation and promote T cell apoptosis [148].

Treg cells are also the principal producers of IL-10 and its expression is regulated by IL-6, IL-27 and TGF-β [149]. The mechanism by which IL-10 regulates T cell responses is fully understood by now. IL-10-systhesizing Treg cells inhibit the function of DCs through the repression of inflammatory cytokine production and the inhibition of MHC class II and costimulatory-molecule expression [150]. IL-10-deficient mice develop enhanced T cell activation and severe immunopathology upon infection [151]. Additionally, $CD4^+CD25^{high}CD45RB^{low}$ T cells from IL-10 deficient mice fail to protect from colitis and mice with the Treg cell-specific deletion of the *il10* gene develop colitis [149, 152].

TGF-β and IL-10 are regulatory cytokines with pivotal functions in the control of inflammation. TGF-β directly target T cells and DCs to ensure immune tolerance to self-antigens, whereas IL-10 regulates the interface of innate and adaptive immunity to limit the magnitude of immune responses to microbial antigens [149]. Because natural Treg cells constitutively express CD25, it has been suggested that IL-2 plays a role in regulatory Treg cell activity, although it remains controversial. Treg cells obtained from $IL\text{-}2^{-/-}$ and $IL\text{-}2R\alpha^{-/-}$ mice were fully able to suppress T cell proliferation *in vitro* [133]. More recently, adenosine, cyclic adenosine monophosphate (cAMP), histone/protein deacetylase (HPDA) -7, HPDA-9, heme oxygenase-1, galectins, IL-9 and IL-35 have also been shown to contribute to Treg cell suppressive activities, but their precise role has not yet been fully established [153-155].

Crosstalk between regulatory T cell populations

Interplay between natural and adaptive Treg cells has been described when their suppressor functions are exerted on APCs and effector T cells during disease pathogenesis. Thus, different Treg populations may have the capacity to influence the development and function of other Treg cells [156, 157]. During the first steps of an infection, inflammation is controlled by the expansion and local recruitment of natural Treg cells, which recognize self-antigens and limit the innate immune response through the expression of IL-10 and CTLA-4. CTLA-4 induces the synthesis of IDO by DCs

inhibiting effector T cell activation, inducing their death and leading, as a consequence to the activation and expansion of Tr1 and Th3 cells. Adaptive Treg cells are then generated, they synthesize IL-10 and TGF-β inhibitors of Th1 and Th2 cell activity, which are in turn responsible for disease outcome. Thus, the sequential role of various of Treg cell populations lets control the infection and limits collateral tissue damage on different stages of the disease, involving various regulation levels [156, 157].

Bystander suppression and infectious tolerance

Treg cell function is characterized by both bystander suppression and infectious tolerance. The bystander suppression involves that, following activation through their TCR, activated Treg cells can suppress unrelated immune responses in a non-antigen-specific manner either through cell contact or through synthesizing regulatory cytokines. Thus, infection specific-induced Treg cells may regulate and determine the outcome of secondary infections, as well as, autoimmune or allergic responses [158]. The infectious tolerance implies that Treg cells create a regulatory milieu that promotes regulation beyond their suppressor activity. That is, the state of tolerance induced by Treg cells may be maintained even after the original Treg population is inactivated or experimentally removed [159].

Regulatory T cells in human infectious diseases

During infections, a tightly controlled immune response must be developed, protecting the host through the development of mechanisms that recognizes and eliminates the invading microorganisms and parasites, but, at the same time, minimizing collateral damage to self tissues that would result from an exacerbated immune response. Both natural and adaptive Treg cells largely exert this control.

Whereas the antigen specificity of inducible Treg cells is associated with microbial antigens, the nature of the antigens recognized by natural Treg cells is less evident. During the onset of an acute disease, natural Treg cells recognize self antigens that are released by damaged tissues, however, evidences from chronic infections suggest that natural Treg cells can also recognize microbial antigens [119, 156].

In animal models, it has been evidenced the role of Treg cells in the suppression of innate and adaptive immune responses in experimental autoimmunity (arthritis, colitis, diabetes, autoimmune encephalomyelitis, lupus, gastritis, oophoritis, prostatitis and thyroiditis), transplantation, cancer development and growth, as well as in infectious diseases [104, 114, 156, 160-164]. Human Treg cells constitute a more heterogeneous population than their mice equivalents, greatly hampering the establishment of Treg cells role during human non-infectious and infectious diseases [156]. In humans, Treg cell induction and activity has been associated with cancer, cell and graft transplantation, diabetes, and various microbial diseases, including viral, parasitic, fungal and bacterial infections [119, 165-167].

Viral infections

Most studies that evaluate human Treg cell functions have been carried out analyzing peripheral blood, since it is the most accessible compartment for clinical examination. These measurements may not be, however, representative of all tissues, since in some chronic human infections Treg cells accumulate within the infected tissues and are rarely detectable in the blood. Decreased frequencies of natural Treg cells have been detected in peripheral blood from HIV infected patients, suggesting that Treg cells are progressively lost during chronic HIV infection [168]. Increased levels of the Treg cell-markers Foxp3, CD25 and CTLA-4 have been detected, however, in lymphoid tissues from these patients, strongly suggesting that the decreased frequencies of Treg cells in peripheral blood can be explained by their accumulation within the infected tissues [169].

In asymptomatic HIV-infected individuals, $CD4^+CD25^+$ T cells significantly suppressed *in vitro* cellular proliferation and cytokine production from $CD4^+$ or $CD8^+$ effector T cells in response to HIV antigens, independently of IL-10 and IFN-γ expression. These data point towards a role of Treg cells suppressing virus-specific immune responses and therefore contributing to the uncontrolled viral replication during early HIV stages [168].

Increased levels of $Foxp3^+$ Treg cells have been reported both in blood and liver of patients affected of chronic hepatitis B virus (HBV), which correlated with *in vitro* suppression of antigen-specific effector responses [170]. Similar findings were obtained from chronic hepatitis C virus (HCV) patients. In addition, HCV-specific IFN-γ secretion from PBMCs was enhanced following depletion of $CD4^+CD25^+$ Treg cells, and reversed by adding back the Treg cells [171]. Induced Tr1 cells with similar viral antigen specificity that protective Th1 cells have been isolated from patients chronically infected with HCV [172]. Taken together, these data strongly suggest that antigen-specific Treg cells have a role in controlling chronic inflammatory responses and contribute to liver pathologic events observed in HBV and HCV infections.

Infection with human T lymphotropic virus type 1 (HTLV-1) is associated with diminished expression levels of Foxp3 in peripheral T cells as compared to asymptomatic HTLV-1 carriers and healthy donors. This Foxp3 expression inversely correlated with HTLV-1 proviral DNA load, suggesting that impaired Foxp3 expression may contribute to inflammatory disease development during HTLV-1 infection [173].

In cytomegalovirus (CMV) infected patients, Treg cells depleted cultures show increased frequency of CMV-specific $IFN\text{-}\gamma^+CD8^+$ T cells, an increase reversed by the addition back of Treg cells [174]. On the other hand, the role of Treg cells in herpes simplex virus (HSV) has been analyzed in mice, but not in humans [114].

Parasitic infections

Human volunteers exposed to *Plasmodium falciparum* evidenced rapid increase on $CD4^+CD25^+Foxp3^+$Treg cells following the first days of blood-stage infection. This enhanced number of Treg cells positively correlated with TGF-ß secretion and with decreased proinflammatory cytokine production and antigen-specific immune response in effector T cells [175].

Analyzing the effect of *Leishmania viannia braziliensis*, the main etiologic agent of cutaneous leishmaniasis (CL) in Brazil, functional Treg cells, expressing CD25, CTLA-4, GITR, and Foxp3, were found in skin lesions of affected patients. These Treg cells produced large amounts of IL-10 and TGF-ß and suppressed PHA-induced proliferation of T cells obtained from healthy control subjects, suggesting that functional Treg cells accumulating within CL lesions contribute to the local control of effector T cells [176].

The role of Treg cells in other parasitic infection, such as *Leishmania mayor*, *Leishmania amazonensis*, *Plasmodium yoelii*, *Plasmodium berghei*, *Schistosoma mansoni*, *Schistosoma japonicum*, *Brugia pahangi*, *Litomosoides sigmodontis* and intestinal helminths have been demonstrated in mice, but, in humans, the exact role of either natural or adaptive Treg cells remains unraveled [114, 177, 178].

Fungal infections

Higher frequency of $CD4^+CD25^+$ Treg cells, expressing CTLA-4, GITR, membrane-bound TGF-β and Foxp3 were detected in peripheral blood of patients infected with paracoccidioidomycosis (PCM). Furthermore, these cells demonstrated stronger *in vitro* suppressive activity when compared with controls, evidencing a role of Treg cells controlling immune responses in patients with PCM-induced granulomatous diseases [179].

Bacterial infections

Tuberculosis (TB) infections in humans also lead to increased frequencies of $CD4^+CD25^+$ Treg cells both in blood and the active infection sites. In pleural fluid and peripheral blood, this increased frequency of Treg cells was inversely correlated with *Mycobacterium tuberculosis*-induced IL-10 and TGF-ß synthesis. These data suggest that Treg suppress the *M. tuberculosis* immune response, favoring persistence of the infectious agent in humans [180].

The stimulation of peripheral $CD4^+$ T cells with DCs pulsed with *Helicobacter pylori* induced proliferation and IFN-γ synthesis in both infected and uninfected individuals. Treg cells isolated from chronically infected patients were able to suppress *H. pylori*-specific $CD4^+$ T cell responses but not responses to unrelated antigens [181], clearly suggesting a role of Treg cells controlling *H. pylori* infections in humans.

Association of Treg cells with multi-infection diseases such as chronic periodontitis has been also established. Immunohistological analyses revealed higher numbers of $CD4^+CD25^+CTLA\text{-}4^+$ Treg cells in samples from periodontitis affected patients, as compared to gingivitis controls. Furthermore, increased Foxp3, TGF-β1 and IL-10 mRNA levels were also detected [182]. Foxp3 expression was associated with $CD4^+CD25^+$ T cells but not with $CD8^+$ T cells and $CD4^+CD25^+Foxp3^+$ cells isolated from periodontitis patients suppressed the proliferation of $CD4^+CD25^-$ cells [183].

INTERACTION BETWEEN Th17 AND REGULATORY T CELLS

Although induced Treg cells and effector Th17 cells play different roles, at least *in vitro*, during the pathogenesis of infections, it has been demonstrated reciprocal developmental pathways for their generation. Naïve T cells exposed to TGF-β up-regulate Foxp3 and become induced Treg cells; however, when cultured with TGF-β and IL-6, naïve T cells generate Th17 cells with pathogenic activities [16, 184]. Thus, when the immune response is not activated, TGF-β favours the generation of induced Treg cells, which suppress inflammation; however, when an infection is established, IL-6 is synthesized during the innate immune response, inhibiting the generation of Treg cells and inducing the differentiation of proinflammatory of Th17 cells in presence of TGF-β [19].

Induced Treg and Th17 cells may arise from the same precursor cell and selective differentiation would depend on the local cytokine milieu, which would determine the predominance of either Treg cells with suppressor activity or Th17 cells with pathologic activities, determining the outcome of the disease [19].

Th17 AND REGULATORY T CELLS: NEW THERAPEUTIC STRATEGIES

The therapeutic potential of Th17 and Treg cells has been approached from two points of view, involving cytokine- and cell-based immunotherapy strategies. Nowadays, most anti-inflammatory therapies that involve anti-cytokine strategies have targeted the IL-23/Th17 axis [185]. It has been proposed that therapeutic agents that antagonize signaling through the IL-17R complex might be suited candidates, since the IL-17R family members do not share significant homology with any other known cytokine receptor family [20, 66, 70]. Moreover, it has been proposed that neutralizing IL-23 alone would leave in place the collective regulatory and anti-tumor and anti-infective properties of Th1 pathways [185]. Even then, the research on the therapeutic potential of Th17 cells still represents, by now, the tip of an iceberg.

The therapeutic potential of Treg cells has created a lot of expectations and a large number of publications have assayed their potentiality either *in vitro* or in experimental models [186]. Treg cells suppress *in vitro* proliferation and cytokine production from co-cultured effector T cells [187]. In mice, both allospecific and polyclonal Treg cells, induced either *ex vivo* or *in vivo*, have therapeutic effects. In a TGF-β-dependent manner, $CD4^+CD25^{low}Foxp3^+$ Treg cells suppressed autoimmune diabetes and polyclonal $CD4^+CD25^+$ Treg cells altered the course of lupus [140]. Additionally, induced Treg cells have been successfully used to prevent organ graft rejection [134]. A model of combined therapy aimed to induce tolerance and restoration of β-cell function has shown promising results during treatment of type-1 diabetes in mice [187], but additional research is necessary for a better understanding of Treg cell physiology and to solve several yet unanswered aspects associated to their therapeutic potential in humans.

The number of cell populations harboring regulatory properties has grown dramatically and by now CD25 is no longer sufficient to characterize $CD4^+$ Treg cells. Separation on the basis of $CD25^{high}$ expression provides a highly purified Treg cell population, but allows the isolation of only a limited fraction (~25%) of the $Foxp3^+$ T cells [187]. Conversely, separation of either $CD4^+CD25^+CD127^{-/low}$ or $CD4^+CD25^{hight}CD45RA^+$ cells allows the isolation of $Foxp3^+$ T cells with a higher efficiency (>95%) [187-189]. Isolated $CD4^+CD25^+CD127^{-/low}$ Treg cells, when stimulated with microbeads coated with anti-CD3- and anti-CD28 mAbs, could be expanded 1,500-fold in the presence of IL-2, where the majority of the expanded population (75%) retains $Foxp3^+$ expression and the suppressive capacity *in vitro* [187]. In addition, it has been proposed that if the growth of enriched Treg cells takes place in the presence of the immunosuppressant drug rapamycin, the expanded cultures could be devoid of unwanted contaminating effector T cells [143].

Tr1 and Th3 are induced Treg cells, which are as effective as naturally occurring Treg cells *in vivo* preventing autoimmunity and graft rejection [119, 156]. Despite their weak and transient expression of Foxp3, they display an efficient regulatory phenotype since are induced under tolerogenic conditions. Thus, their potential in cellular therapy is highly limited [119, 156].

Antigen specificity of the suppressor response is necessary to ensure regulatory activities in the site of interest, even though the ultimate efficacy of the Treg depends on bystander suppression and infectious tolerance in the affected tissues. These characteristics may be attained by either conversion of conventional T cells into Treg cells, gene transfer, or isolating and expanding *in vitro* TCR-specific activated Treg cells to achieve therapeutically relevant levels. Thus, whether Treg cells can be isolated and expanded with sufficient purity and keeping their suppressor potential, whether Treg therapy is sufficient to control unwanted immunity and whether the

new therapeutic strategies are safe and effective are questions for future consideration.

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ABBREVIATIONS

APCs = Antigen presenting cells
BD = Bowel disease
cAMP = Cyclic adenosine monophosphate
CIA = Collagen-induced arthritis
CL = Cutaneous leishmaniasis
CMV = Cytomegalovirus
CTLA = Cytotoxic T-lymphocyte antigen
DCs = Dendritic cells
EAE = Experimental autoimmune encephalomyelitis
Foxp3 = Transcription factor forkhead box P3
G-CSF = Granulocyte colony-stimulating factor
GITR = Glucocorticoid-induced TNF receptor family-related protein
GM-CSF = Granulocyte monocyte colony-stimulating factor
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HPDA = Histone/protein deacetylase
HSV = Herpes simplex virus
HTLV-1 = Human T lymphotropic virus type 1
IDO = Indoleamine 2,3-dioxygenase
IFN = Interferon
IL = Interleukin
IPEX = Immuno-dysfunction polyendocrinopathy enteropathy X-linked
MCP = Monocyte chemotactic protein
MMP = Metalloproteinases
MS = Multiple sclerosis
OAF = OCLs-activating factor
OBLs = Osteoblasts
OCLs = Osteoclasts
OPG = Osteoprotegerin
PCM = Paracoccidioidomycosis
RA = Rheumatoid arthritis
RANK = Receptor activator of nuclear factor-κB
RANKL = RANK-ligand
ROR = Transcription factor orphan nuclear receptor
sf = Scurfy
STAT = Signal transducer and activator of transcription
TB = Tuberculosis
TGF = Transforming growth factor
Th = T helper lymphocytes

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