Journal of Translational Autoimmunity 4 (2021) 100130

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

# Regulatory T cell function in autoimmune disease

Anandi Rajendeeran, Klaus Tenbrock *

*RWTH Aachen University, Department of Pediatrics, Pediatric Rheumatology, Pauwelsstr 30, 52074, Aachen, Germany*

ARTICLE INFO

*Keywords:*
Foxp3
IL-2
Regulatory T cells
Juvenile idiopathic arthritis
SLE

ABSTRACT

Autoimmune diseases are characterized by a failure of tolerance to own body components resulting in tissue damage. Regulatory T cells are gatekeepers of tolerance. This review focusses on the function and pathophysiology of regulatory T cells in the context of autoimmune diseases including rheumatoid and juvenile idiopathic arthritis as well as systemic lupus erythematosus with an overview over current and future therapeutic options to boost Treg function.

## 1. Regulatory T cells

Regulatory T cells are important gatekeepers of the immune system. They maintain tolerance, prevent autoimmune diseases and are characterized by expression of CD4, CD25 and Foxp3. $CD4^+CD25^+Foxp3^+$ Regulatory T cells (Treg) inhibit activation and expansion of $CD4^+$ helper T (Th) cells, of cytotoxic $CD8^+$ T cells and prevent B cell activation. This is best exemplified by the fact that a loss of Foxp3 protein and a subsequent lack of regulatory T cells have fatal effects. Foxp3-deficient *scurfy* mice develop signs of autoimmune inflammation with exaggerated Th1, Th2, and Th17 responses and eventually die by 3–4 weeks of age [1,2]. Mutations in the *Foxp3* gene in humans result in a wide clinical disease spectrum with severely impaired immune regulation, polyendocrinopathy and enteropathy. Since Foxp3 is coded on the X-chromosome, this syndrome is X-linked and called IPEX [2]. Except from Foxp3 there are some key molecules within Tregs that mediate their function including IL2RA (CD25) or CTLA4. Fatal autoimmune disease also occurs in individuals with mutations of the IL2RA [3], while autoimmune diseases of different spectrum can develop in individuals with heterologous mutations of CTLA-4 including CTLA-4 haploinsufficiency, which result in suboptimal Treg expression of CTLA-4 in resting as well as activated states [4,5].

## 2. Regulation of Tregs in homeostasis

The functional analysis of Tregs is hampered by the fact, that the lineage defining transcription factor in Tregs is the intracellular protein Foxp3. This precludes this protein as a marker for cell sorting in the human system. CD25, which is the receptor for IL-2 as another Treg surface marker allows isolation and therefore functional analyses of these isolated cells, however since CD25 is upregulated in all activated T cells, it has some limitations. In the murine system inducible CRE lines have been generated, which upon activation of the Foxp3 promoter express a fluorescent protein (GFP or YFP) that makes these cells sortable and thus useable for functional in vitro as well as in vivo studies after transfer. In addition, after activation, the CRE recombinase excises genomic sequences which have been flanked by so called flox alleles and thus a targeted deletion of specific genes is possible in Tregs. This approach has taught us a lot about the transcriptional regulation of Tregs.

Tregs are categorized as thymus-derived (tTreg) or induced Tregs (iTreg). As the name implies, tTregs develop in the thymus, whereas iTregs differentiate from naïve T cell precursors in the periphery [6–9]. The generation in the thymus depends on the presentation of a thymic self-peptide/MHC activation, which forces the precursors to differentiate into functionally competent antigen-specific suppressive regulatory T cells. This development requires the coordinated activation of a number of Treg-specific enhancers Cd25, Ctla4, Eos and Helios, which become gradually activated at the precursor stage before FoxP3 expression [8].

While the differentiation of tTregs requires interactions with self-peptide-MHC complexes, the differentiation of peripheral iTregs most likely occurs in response to non-self antigens, e.g. commensal microbiota, food and allergens and depends on the signaling strength as well as abundance of the antigen. Moreover these Tregs need TGF-β for induction [10]. Induced Tregs display a methylated or only partially de-methylated TSDR. However, in vitro studies showed that they lose Foxp3 expression as well as their suppressive capacities after

* Corresponding author.
*E-mail addresses:* arajendeeran@ukaachen.de (A. Rajendeeran), ktenbrock@ukaachen.de (K. Tenbrock).

https://doi.org/10.1016/j.jtauto.2021.100130
Received 31 August 2021; Accepted 26 October 2021
Available online 30 October 2021

re-stimulation when TGF-β is withdrawn [11–13].

Both tTregs and iTregs express Foxp3 as the most important and lineage-specific transcription factor in this T cell subpopulation [6,8,9,14–16]. The *Foxp3* locus is regulated on different levels but contains a highly conserved CpG-rich region in the first intron (+4201 to +4500), which seems to be critical for *Foxp3* gene regulation [17–19]. As CpG residues in this region are completely methylated in non-Treg T cells ($CD4^+CD25^-$) and fully de-methylated in tTreg T cells ($CD4^+CD25^+$) in mice and humans, this region was termed the Treg-specific demethylated region (TSDR) [18–20]. Demethylation of the TSDR is associated with high and stable expression of *FoxP3* and is therefore used to identify Tregs. Treg generation is largely dependent on the presence of IL-2 which is not only required for homeostatic maintenance but also for their thymic development [21]. IL-2 cannot be produced by regulatory T cells and therefore has to come from other sources, mainly $CD4^+$ T cells. IL-2 has also been shown to be crucial for the development and maintenance of Treg cells. IL-2 also directly affects suppressive function of Tregs [15,22,23]. IL-2 directly activates and phosphorylates the transcription factor STAT5, which binds to both promoter and intronic elements of the FOXP3 gene and induces Foxp3 gene transcription [23]. Mice with IL-2 or IL-2 receptor deficiency display an enlargement of peripheral lymphoid organs including lymph nodes and spleen, impaired activation-induced cell death, and autoimmune disorders which have been attributed to a decreased generation of Tregs [3].

In addition, certain data point to the fact that Tregs lose Foxp3 expression and become autoimmune effector cells under certain conditions [13,24]. Therefore, additional molecular events might complement Foxp3 function in the generation of Tregs and the maintenance of their function and phenotype. It was shown that the signature transcription factor for Th17 cells, RORγT, is also induced by TGF-beta, which suggests a link between the differentiation of Treg and Th17 lineages. In the absence of a second signal from a proinflammatory cytokine during T cell differentiation, FOXP3 can inhibit RORγT function and drive Treg differentiation. However, when the cell also receives a signal from an inflammatory cytokine (e.g., IL-6), FOXP3 function is inhibited and the Th17 differentiation pathway is induced. Therefore, the balance between FOXP3 and RORγT expression is crucial for CD4 T cell fate and the type of immune response that will be consecutively generated [13].

Moreover, Treg subpopulations with a complete ($Helios^+Foxp3^+$) or partial ($CD161^+Foxp3^+$) demethylation of the TSDR are able to expand in certain settings of inflammation like SLE [25] or juvenile idiopathic arthritis [26]. These Treg subpopulations are considered to be functionally suppressive as either shown by completely demethylated TSDR or by in vitro suppression assays, however produce inflammatory cytokines under certain conditions.

## 3. Regulatory T cells in different human autoimmune and inflammatory diseases

Autoimmune diseases are characterized by a failure of tolerance to own body components. This results in local tissue inflammation. Failure of tolerance occurs when mechanisms of immune-suppression are hampered by either functional deficits in regulatory cells or when cellular damage with presentation of multiple autoantibodies overwhelm anti-inflammatory mechanisms. This can therefore be the case in certain settings of inflammation and infections, in which tissue damage result in activation of the adaptive immune system with subsequent failure of tolerance. Tregs are critical mediators to prevent damage within this setting. Once failure has occurred, consecutive tissue damage might result in disease manifestation. We will now exemplify this in different immune mediated diseases.

## 4. Regulatory T cells in human SLE

Systemic lupus erythematosus is the classical autoimmune disease, in which, as the final stage, binding of autoreactive antibodies results in complement activation and subsequent organ damage. Organ damage can affect multiple organs like the skin, the kidneys, the central nervous system, the heart, the liver, the lung and the immune system. Environmental, immune-regulatory, hormonal, genetic and epigenetic factors contribute sequentially or simultaneously to SLE pathogenesis [27]. These factors can be affected within the adaptive as well as innate immune system. We have learned that e.g. certain complement deficiencies can result in the development of SLE as well as defects in macrophage activation or defects of T cell and B cell activation. The production of autoantibodies by B cells is only the final step in the failure of tolerance in which regulatory T cells might play a decisive role and their numbers and function therefore vary depending on disease onset, therapeutic interventions and disease flares. Tregs have been extensively studied over the past years with quite contradictory results in particularly in humans. Some studies report reduced numbers or impaired function of circulating Tregs, while other groups observed no abnormalities [25,28–31]. Some studies even report increased levels of Tregs in SLE compared to healthy controls or a resistance of lupus effector T cells to Treg suppression instead of functional defects of SLE Tregs [32]. These discrepancies arise from differences in the techniques to study Tregs. This includes flow-cytometric and Treg isolation protocols, use of different in vitro stimuli as well as presence or absence of antigen-presenting cells in ex vivo functional assays [33]. They also partly arise from a lack of a unique marker as mentioned above to identify and isolate Tregs. Some groups used CD25 or Foxp3 alone or in combination for quantitative analysis of Tregs and CD25 or combinations of CD25 and CD127 to isolate Tregs for *ex vivo*-performed qualitative analysis. CD25 is the receptor of IL-2 and can be expressed by activated T cells as well as Foxp3 [34], which suggest that these populations might also contain effector T cells due to persistent T cell activation in SLE. In addition, IL-2 production is compromised in SLE and CD25 levels from SLE patients are lower compared to those of healthy individuals [35,36]. Thus, $CD25^{low/-}$ cells may also contain $Foxp3^+$ Tregs. This points to the fact that different subsets within Treg populations exist, which might differ in function and could therefore affect disease outcome in SLE to variable extents.

As mentioned above, IL-2 is a crucial factor in the production and maintenance of Tregs. Patients with SLE display reduced IL-2 levels, which might be responsible for their enhanced susceptibility towards infectious diseases [27,35–38]. Moreover this resulted in therapeutic efforts to supplement IL-2. Starting with trials in severe cases of SLE, which failed in conventional therapies, exogenous IL-2 supplementation resulted in remarkable clinical success [39]. Low-dose interleukin-2 treatment selectively modulates $CD4^+$ T cell subsets in patients with systemic lupus erythematosus [40,41] including upregulation of Tregs. Moreover, a recently published study showed that IL-2 enhances the conversion of T follicular helper cells (Tfh), which are necessary to provide help to B cells in order to produce Immunoglobulins and to advance the switch from IgM producing to IgG producing plasma cells, into T follicular regulatory cells, which are a special subtype of Tregs particularly located in lymph node germinal centers [42]. This subtype is characterized by increased expression of BCL6 and CXCR5 within Foxp3 positive cells. CXCR5 is a homing surface receptor on T cells for lymph follicles. Moreover, IL-2 stimulation suppressed the generation of $CD38^+CD27$high, IgG producing plasmablasts. These data point to the fact that indeed subpopulation of Tregs can play a particular role in different diseases depending on the pathophysiological context and local surrounding. It is know that Tregs are highly abundant in the skin and do not migrate. Interestingly, Foxp3 Tregs seem to be reduced in the skin lesions of patients with cutaneous SLE [43] and alopecia areata, which can be a clinical sign of SLE. Alopecia areata is also a defined common autoimmune disease in which T cells attack hair follicles, is associated with a FOXP3 promoter polymorphism and low-dose IL-2 treatment is an effective treatment [44]. This suggest that Tregs located in regional tissues like the skin are affected and dependent on the local availability

of IL-2. This might thus also be the case for the skin manifestations in lupus.

## 5. Regulatory T cells in arthritis

Tregs expand at local sites of inflammation. This holds true in rheumatoid arthritis (RA) and in juvenile idiopathic arthritis (JIA), where Tregs are expanded within the affected joints, while the numbers are not different from healthy controls in the peripheral blood. In JIA, Tregs are characterized by a restricted T cell receptor repertoire, by decreased FOXP3 stability and CD25 expression [45], altered cytokine and chemokine production [46] and decreased responsiveness to IL-2 [45] suggesting impaired Treg function in JIA. However, a number of reports found that JIA synovial fluid and peripheral blood Tregs are fully demethylated [45] and clearly suppressive outside the joint in vitro [26,46–48]. Thus the inflammatory microenvironment is most probably responsible for the inappropriate function of JIA Tregs, a term which is called resistance to suppression and is related to functionality of effector T cells [48]. This resistance to suppression is dependent on activation of protein kinase B (PKB)/c-akt and can be reversed by treatment with TNFα antagonists [47]. Moreover, adding synovial fluid to in vitro cultures can increase Treg FOXP3 expression [49] and induces mechanisms in effector T cells which makes them resistant to Treg-mediated suppression ex vivo as well [47,48,50].

Except from being immunosuppressive, depending on the inflammatory milieu, Tregs can also start producing proinflammatory cytokines including IL-17. In a groundbreaking paper, using fate mapping mice, the group of Jeffery Bluestone showed 2014 that Tregs can lose their Foxp3 expression (thus becoming Ex-Foxp3) and start to produce IL-17 [51]. These IL-17 producing cells are particularly arthritogenic and osteoclastogenic and induce severe damage within the joints. IL-17 producing Tregs have also been identified within the inflamed joints of patients with RA.

Mmoreover, those findings were confirmed in patients with JIA. The natural Killer cell receptor CD161 is a marker of human IL-17-producing T cells [52]. $CD4^+CD161^+$ cells accumulate in the synovial fluid of children with Juvenile idiopathic arthritis (JIA) [26]. Interestingly, $CD161^+$ $CD4^+$ cells also contain a fraction of $Foxp3^+$ cells [26,53]. Treg cells are not typically pro-inflammatory, but recent reports have shown that a small proportion of Treg cells are capable of producing inflammatory cytokines and these subsets are enhanced the context of autoimmunity or chronic inflammation. The $CD161^+Foxp3^+$ subset contains a high frequency of cells producing pro-inflammatory cytokines such as IL-2, IFN-γ and IL-1 [26]. Since CD161 is a surface marker, $CD161^+$ and $CD161^-$ Tregs could be isolated by FACS sorting and revealed a comparable suppressive capacity in suppression assays. $CD161^+$ Treg cells are highly enriched within the inflammatory environment of rheumatoid arthritis as well as JIA.

The inflammatory environment within the arthritic joint also contains TNFα. In patients with RA, the Ser418 site of the Foxp3 protein is specifically dephosphorylated by protein phosphatase 1 (PP1) in Tregs. PP1 expression and enzymatic activity are induced in the inflamed synovium by tumor necrosis factor α (TNF-α) resulting in impaired Treg cell function. In addition, TNFα-induced Treg cell dysfunction correlates with increased numbers of interleukin-17 (IL-17)(+) and interferon-γ (IFN-γ)(+)CD4(+) T cells within the inflamed synovium in rheumatoid arthritis [54]. Adding to this, a recent paper described the importance of TNF receptor 2 in Tregs of patients with RA, in which the involvement of Tumor Necrosis Factor Receptor Type II in FoxP3 atability and as a aarker of Tregs specifically expanded by anti-Tumor Necrosis Factor treatment in RA was published [55].

As another mechanism of Foxp3 regulation in RA, micro RNAs have been described to regulate Foxp3 expression. In detail, miR-34a attenuated human and murine Foxp3 gene expression via targeting their 3′ untranslated regions (3′ UTR) [56]. The human miR-34a was found increased in peripheral blood mononuclear cells (PBMCs) and $CD4^+$ T cells from rheumatoid arthritis (RA) as well as systemic lupus erythematosus (SLE) patients, displayed a positive correlation with some serum markers of inflammation including rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as the Th17 signature gene RORγt, but inversely correlated with the mRNA expression levels of Foxp3 [56]. In addition to this, another microRNA, mir155, directly regulates Foxp3 expression and is vice versa a target of Foxp3. Mir155 targets the suppressor of cytokine signaling 1 (SOCS1), which blocks the signal downstream of CD25 and thereby enhances the response of Tregs towards IL-2 [57]. Thus high expression of mir155 enhances the functional fitness of TRegs. Mir155 is indeed found upregulated in patients with RA and our group now showed that mir155 is one of the most highly expressed miRNA in synovial fluid cells of JIA patients (more than 20-fold, Rajendeeran et al. manuscript accepted in Rheumatology).

In addition to DNA methylation at the TSDR and expression of miRNAs other epigenetic mechanisms like histone modifications regulate the expression of Foxp3 as well. The chromatin modifier enhancer of zeste homolog 2 (EZH2) methylates lysine 27 of histone H3 (H3K27) and regulates T cell differentiation. EZH2 inhibition suppressed FOXP3 transcription and Treg differentiation. It upregulated SMAD7 expression in $CD4^+$ T cells, which is an inhibitor of TGFβ. RA synovial fluid and fibroblast-like synoviocytes suppressed EZH2 expression in $CD4^+$ T cells, which was neutralized by an anti-IL17 antibody [58].

## 6. Regulatory T cells in ankylosing spondylitis and inflammatory bowel disease

Ankylosing spondylitis (AS) and inflammatory bowel disease (IBD) are closely linked and belong to diseases that are characterized more by inflammation than autoimmunity. There is also a substantial overlap of AS with familial Mediterranean fever (FMF), a classical autoinflammatory disease, in which a number of patients develop enthesitis as well as arthritis. While Tregs have not been well studied in FMF, in AS, a number of studies have been performed and recently a meta-analysis of 47studies involving 4373 participants has been published [59]. Interestingly, and comparable to SLE, the diversity of Tregs surface markers used in each study made it difficult to draw conclusions. The levels of Tregs varied based on the cellular identification markers used. The proportions of $CD4^+CD25^+FOXP3^+$Tregs, $CD4^+CD25^{high}CD127^{low/-}$, or $CD4^+CD25^+CD127^{low}$ in blood of AS patients were significantly decreased as compared with those in healthy blood donors. Interestingly, in an animal model of AS, a low dose of IL-2 administered before disease onset was moderately effective for boosting Treg numbers but failed to prevent SpA development in B27-rat. Studies in humans have not been performed with regard to IL-2 [60].

AS is often characterized by (low to moderate grade) inflammation of the colon and in particular the terminal ileum. Using mucosal biopsies, a significant up-regulation of IL-2, TGFβ, FoxP3, STAT-5, and IL-10 transcripts in the terminal ileum of AS patients with chronic ileal inflammation was reported [61]. Flow cytometric analysis of Treg cells showed significant peripheral expansion in both patients with AS and chronic inflammation and patients with CD. This was the first evidence that an active Treg cell response, mainly dominated by IL-10 production, occurs in the gut of AS patients and is probably responsible for the absence of a clear Th17 polarization in the ileum of AS patients [61].

As like in inflamed joints, and demonstrated by the study of Ciccia, Tregs are expanded in the colonic mucosa of patients with inflammatory bowel disease. This might be related to the inflammation itself but also to gut metabolites which are produced by bacterial commensals and pathogens within the gut. These include short and medium chain fatty acids as well as components of bile acids, which have been shown to promote peripheral Treg expansion [62,63]. Comparable to the situation in the joint, colitogenic T cells can develop resistance to suppression. This is dependent on Smad7, which was already described above as an antagonist of TGFβ signaling. As well as IL-2, TGFβ is absolutely

necessary for the induction of iTregs [64]. Tregs control immune activation by acting directly or indirectly on effector CD4 and CD8 T cells and antigen-presenting cells. Cyclic AMP (cAMP) is long known as a potent suppressor of T cell activation and function. Tregs generate and accumulate high levels of cAMP, which can be transferred into target cells as one mechanism of suppression [22,65,66]. Indirect mechanisms include the secretion of cytokines, such as IL-10, IL-35 and Tgf-β. IL-10 plays an important role in suppressing $CD4^+$ effector T-cell function. Additionally, IL-10 prevents activation of antigen-presenting cells (APCs) such as dendritic cells and macrophages by downregulating their expression of costimulatory molecules and production of inflammatory cytokines [67]. Selective ablation of IL-10 in $Foxp3^+$ Tregs revealed that IL-10 production by Tregs is essential for keeping the immune response in check at environmental interfaces such as colon and lungs [68]. IL-10 also acts in an autocrine manner by maintaining FoxP3 expression and the suppressive capacity of Tregs [69,70]. With that respect it is interesting that patients with IL-10 and IL10R deficiencies develop early onset inflammatory bowel diseases in childhood as a cardinal symptom pointing to the relevance of this pathway at mucosal surfaces [68,70]. Another molecule that is critical for the homing and function of regulatory T cells in the gut is IL-33, which belongs to the IL-1 cytokine family. The IL-33 receptor ST2 is preferentially expressed on colonic Treg cells, where it promotes Treg function and adaptation to the inflammatory environment and limits inflammation in mouse models of colitis [71].

## 7. Therapies affecting Tregs in autoimmune diseases

Expansion of Tregs as well as modulation of their immunosuppressive properties might be a promising treatment option of autoimmune diseases. A very recently published paper by the group of Sascha Rudensky shows that in genetically modified scurfy mice using a tamoxifen inducible knockin of Foxp3 a fullblown autoimmune phenotype can be reversed. Thus, even during ongoing inflammation Treg expansion can restore control over pathogenic T cell functions and resolve inflammation and pathology in mice [72]. Expansion of Tregs can be performed outside the body in vitro, which needs huge efforts in manufacturing and will most probably be related to severe refractory cases. This includes nonautoimmune diseases like Graft versus host disease after stem cell transplantation [73].

In vivo, expansion of Tregs can be achieved by supplementation of IL-2 and we have already discussed above that IL-2 treatment can be used as experimental treatment option in SLE and alopecia areata, where it augments Foxp3 expression and fitness of Tregs. This is the case in human patients as well as in mouse models of SLE [39,74]. However, with regard to IBD, enhanced IL-2 signaling may predispose to disease manifestation as shown by a very early onset refractory colitis, in which a duplication of CD25 was found, which causes excessive STAT5 signaling [75]. Thus, IL-2 might be a double edged sword in the context of inflammation since it also boosts effector T cell proliferation. The combination of an IL2-sIL2 compound which is primarily sensed by high affinity IL-2 receptors on Tregs overcomes the limitations of IL-2 and has paved the ground for the clinical success of IL-2 in SLE. Nevertheless, this is not yet approved for therapy in humans but might be a promising option in the future.

Glucocorticoids (GC) are the backbone of anti-inflammatory therapy in autoimmune diseases. One possible mechanism could be the induction of regulatory T cells, however publications on this topic are inconclusive, In Multiple Sclerosis (MS), MS patients at relapse compared to controls showed higher percentages of $CD4^+$CD25high + TRegs. After 5 days of intravenous methyl prednisolone, activated T-lymphocytes decreased, while $CD4^+CD25^+$ and $CD4^+$CD25high + Tregs increased. However, Foxp3 was not used as a marker and thus the results are questionable [76]. In adult patients with idiopathic thrombocytopenic purpura, dexamethasone increased the numbers of Foxp3 positive Tregs [77], while in a cohort of patients with acute hearing loss and tinnitus but without an underlying inflammatory disease who received high-dose intravenous prednisolone followed by stepwise dose reduction to low oral prednisolone, circulating Treg numbers and frequencies did not change [78]. Thus, from these studies it seems questionable that the clinical efficacy of GCs is achieved by modulating Treg cell numbers and it might also depend on the type of glucocorticoid used. Local corticosteroid therapy however reduces CD4+Foxp3+ cells in synovial biopsy specimens 7–14 days after local GC injection [79]. In SLE, therapeutic effects on Treg expression have been described also by glucocorticoids [29], however have been attributed to remission rather than to treatment regimen [28].

Besides GC-treatment, the therapeutic regime in autoimmune diseases often requires the usage of disease modifying drugs (DMARDs). Regarding approved medications, methotrexate is the most widely used DMARD in RA and JIA and published data point to the fact that treatment with MTX indeed affects Treg biology. In patients with psoriasis, MTX might restore the immunosuppressive function of Tregs through upregulating CD73, activating AMPK and inactivating the mTOR pathway. Treg cells from MTX-treated RA patients had restored suppressive function. This restored suppression was associated with increased expression of FoxP3 and CTLA-4 in Tregs. Bisulfite sequencing PCR of Tregs cultured in MTX revealed a significant reduction in methylation of the FOXP3 upstream enhancer. Moreover, it was shown, that low expression of CD39 on regulatory T cells was a biomarker for resistance to methotrexate therapy in rheumatoid arthritis and that this was related to a decreased suppressive activity of these cells through reduced adenosine production, which is dependent on CD39 [80]. Interestingly, CD39 is also of relevance for the treatment response in IBD. Increased expression of CD39 by peripheral blood Tregs was observed in the setting of clinical and endoscopic remission in inflammatory bowel disease. Deficiency of CD39 expression by Tregs was linked to inability to suppress experimental colitis [81].

TNF inhibition is also commonly used in RA but the effects on Tregs seem to be dependent on the type of the TNF inhibitor. It was shown that Th1 and Th17 responses are controlled through distinct mechanisms by Treg cells from patients responding to anti-TNF antibody therapy. Adalimumab, but not etanercept therapy, induces a potent and stable Treg cell population with the potential to restrain the progression of IL-17-associated inflammation in RA via regulation of monocyte-derived IL-6 [82]. Mechanistically, it was shown in another paper that adalimumab, but not etanercept, promoted the interaction between monocytes and Tregs isolated from RA patients. Adalimumab bound to monocyte-membrane-TNF from RA patients and unexpectedly enhanced its expression and its binding to TNF-RII expressed on Tregs. As a consequence, adalimumab expanded functional Foxp3(+) T regs equipped to suppress Th17 cells through an IL-2/STAT5-dependent mechanism [83].

## 8. Conclusions

Regulatory T cells play a major role in autoimmune and inflammatory diseases. Dysfunction of Tregs as well as unresponsiveness of effector T cells can cause and aggravate the clinical outcome. Tools to boost Treg function represent a valuable therapeutic option and could hold a promise for the treatment of autoimmune diseases in the future.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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