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Review Article

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# Modulating the T Helper 17 Cell/Regulatory T Cell Balance: Roles of Natural Compounds and Cellular Therapies

**Sining Wang***

The High School Affiliated to Renmin University of China.

***Corresponding author:** Sining Wang

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***Abstract***

*T cells play important roles in the adaptive immune system. Among them, T helper 17 cells promote inflammation, while regulatory T cells maintain immune tolerance. Imbalance between these two subsets is commonly found in autoimmune and chronic inflammatory diseases. Recent studies have identified plant compounds Bergapten, Salidroside and Gegen Qinlian Decoction could act as potential regulators in several disease models, while cellular immunotherapies, including CAR-engineered Treg therapy and Breg cell expansion therapies, have already been used in preclinical and early clinical studies. This review will summarize and analyze emerging and current strategies.*

**Keywords:** Th17, Treg, autoimmune diseases, inflammation, immune balance.

## 1. Introduction

T cells are central components of the adaptive immune system, first identified by Jacques Miller in the early 1960s as thymus-derived lymphocytes with immune functions. In the late 1960s, T cells were shown to have the function of not producing antibodies themselves, but instead driving other bone marrow-derived cells to do so [1]. In subsequent decades, T cells were further classified into different types, including Cluster of Differentiation 4 positive (CD4+) T cells, which include regulatory T cells (Treg) and helper T cells, and Cluster of Differentiation 8 positive (CD8+) T cells, which are also called cytotoxic t cells. CD8+ T cells kill pathogens and neoplastic cells [2], while upon recognizing antigen fragments presented on MHC class II molecules by antigen-presenting cells, CD4+ T cells are activated, and thereby are able to stimulate B cells to produce antibodies [3]. Also, CD4+ T cells help maintain CD8+ responses and prevent their exhaustion [2].

In the early 2000s, the discovery of regulatory T cells (Tregs) and T helper 17 (Th17) expanded our understanding of T cell functions: Th17 promotes autoimmunity and induces the inflammatory process, while Treg orchestrates immune homeostasis [4]. An imbalance between Treg and Th17 has been consistently associated with autoimmune diseases, such as multiple sclerosis and psoriasis, as well as chronic inflammation [5,6]. Therefore, modulating the balance between Treg and Th17 may be critical for treating these diseases. Indeed, recent studies highlight natural compounds, particularly derived from traditional herbal medicine, like Bergapten, Salidroside, and Gegen Qinlian Decoction as potential regulators of the Treg/Th17 balance, showing promise as chemical therapeutics. Furthermore, efforts to develop cellular immunotherapies, like Car-T regulatory cells (CAR-Treg) therapy and adoptive B regulatory cells (Breg) transfer that modulates Th17/Treg have also been undergoing. This review aims to summarize these recent findings related to T-cell heterogeneity and efforts to develop new therapeutic methods to treat autoimmune diseases more effectively in the future.

## 2. Mechanisms of Signaling Pathways in Treg and Th17

### 2.1. T Cell Development

T cells originate from hematopoietic stem cells (HSCs) in the bone marrow, called T cell progenitors, but they migrate through blood vessels at the corticomedullary junction to the thymus for maturation and selection [7,8,9]. In the thymus, they first localize at the peripheral thymic cortex, and then undergo rearrangement of the T cell receptor (TCR) α and β loci; for thymocytes successfully pass TCRβ gene rearrangement and process preTCR signaling, they continue with rearrangement of the TCRα gene. After the completion of TCRβ rearrangement and initiation of TCRα rearrangement, they migrate to the thymic cortex, being in the CD4+CD8+ double-positive stage, and complete TCRα rearrangement [9,10]. For thymocytes recognize Major Histocompatibility Complex proteins (MHC) class II, they mature into CD4+ T cells [11]; for these recognize MHC Class I, they mature into CD8+ t cells [12]. This positive selection also causes the relocalization of thymocytes from the cortex to the medulla, and for thymocytes present CD4+CD8- or CD4-CD8+ phenotype, they mature and exit the medulla [9].

Naive CD4+ cells usually migrate to secondary lymphoid organs [13], where they can differentiate to various subsets: T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), and regulatory T cells (Treg), driven by different signaling pathways, transcription factors and cytokines. Among them, Tregs suppress excessive immune responses and maintain tolerance, whereas Th17 mediates pro-inflammatory responses [14].

### 2.2. Treg Cell Differentiation

Treg cells could be both generated inside and outside the thymus [15]. Both thymus-derived Treg(tTreg) cells and peripheral Treg (pTreg) cells depend on forkhead box P3 (Foxp3). tTreg differentiation is primarily directed by TCR signaling, the strength and duration of which are key determinants. The co-stimulatory receptor CD28 further promotes tTreg differentiation through activating transcriptional factors including NF-κB, the c-Rel subunit of which has been shown to bind to Conserved Non-coding Sequence 3 (CNS3), initiating chromatin remodeling at the Foxp3 locus, and promoter, facilitating Foxp3 transcription [16].

In addition to TCR-CD28 pathway, Interleukin-2 (IL-2) is essential for tTreg differentiation: it activates the Signal Transducer and Activator of Transcription 5 (STAT5) signaling pathway, and phosphorylated STAT5 binds to the Foxp3 promoter to promote induction, and Conserved Non-coding Sequence 2 (CNS2) to enhance and stabilize Foxp3 expression [17,18,19]; still, given that CNS2 is inactive prior to Foxp3 expression, there might be a cis-regulatory element to be targeted by IL-2-STAT5 signaling, whose identity and precise roles remain incompletely defined [19].

Different from tTreg cells, pTreg cell induction involves Transforming Growth Factor β (TGF-β). TGF-β mediates Mothers Against Decapentaplegic Homolog 2 and 3(SMAD2 and SMAD3): upon TGF-β binding to its receptor, SMAD2 and SMAD3 become phosphorylated, interacting with SMAD4, and then translocate to the nucleus to regulate gene expression [20]. Specifically, SMAD3 is the major factor binding to Conserved Non-coding Sequence 1 (CNS1) within the Foxp3 gene locus, which is dispensable for tTreg development but required for pTreg induction [16,21,22], thereby promoting Foxp3 transcription and further driving differentiation [23]. Similar to tTreg cells, pTreg cells also require initial TCR and CD28 co-stimulation, and share IL-2-STAT5 pathway.

### 2.3. Th17 Differentiation

Although TGF-β is involved in both Treg and Th17 differentiation, in the presence of Interleukin-6 (IL-6) and other pro-inflammatory cytokines, it supports Th17 lineage commitment instead of inducing Treg development [24,25,26]. IL-6 binds to the membrane-bound Interleukin-6 Receptor (IL-6R), which induces the formation of a complex consisting of IL-6, IL-6R and glycoprotein (gp130), further activating Janus kinase 2 (JAK2) [24]. JAK2 further promotes Signal Transducer and Activator of Transcription 3 (STAT3) phosphorylation [27]. Activation of STAT3 induces the expression of the transcription factor RAR-related orphan receptor (RORγt), which drives cells toward the Th17 subset [26].

Other cytokines, such as Interleukin-23 (IL-23), also bolster Th17 differentiation. IL-23 is produced by dendritic cells and activated macrophages and is required for Th17 maintenance and expansion [28]. It activates the JAK/STAT pathway [28], and IL-23R expression is upregulated by IL-6 and TGF-β, augmenting Th17 cells responses [29].

Additionally, Hypoxia-Inducible Factor 1 (HIF-1) promotes Th17 differentiation: it directly activates RORγt transcription and physically interacts with RORγt. The HIF-1/RORγt complex recruits the histone acetyltransferase p300, generating a permissive chromatin structure and enhancing transcription of Th17-associated genes [30].

### 2.4. Th17 and Treg Cells Regulation

Under normal conditions, Treg and Th17 are usually balanced by TCR signaling, in cooperation with costimulatory signals, cytokine signaling and metabolic pathways. However, in disease conditions, alterations in various factors like genetic predisposition, cellular metabolism, and the microenvironment can lead to increased Th17 cell differentiation and activation, contributing to the pathogenic conditions [31].

TCR signal regulates both tTreg and pTregs. The way that it regulates tTregs is specifically explained in previous part, while pTregs differentiation favors a weak signal from TCR. Attenuated TCR signaling in Interleukin-2(IL-2) inducible T cell kinase-deficient cells (Itk-/- cells) activates phosphatase and tensin homolog (PTEN) and inhibits Akt/mechanistic target of rapamycin (mTOR) pathway, thereby driving differentiation towards Treg cells rather than Th17 cells. PTEN levels also regulate Th17/Treg balance, as demonstrated [31]. The ways in which cytokines regulate Th17/Treg have been demonstrated in previous sections in Th17 and Treg cells differentiation.

The role of metabolic pathways in regulating Th17/Treg balance is evidenced by metabolic intermediates: Treg cells have more TCA-cycle intermediates, showing that they depend on pyruvate oxidation; Th17 cells have high levels of pyruvate, lactate and Pentose Phosphate Pathway intermediates, demonstrating that they rely on aerobic glycolysis and glutamine oxidation. Th17 cells are less like naive T cells, so they require a higher amount of ATP and depend on glycolysis to provide energy rapidly. Also, when PI3K signaling pathway is activated and the expression of Glucose Transporter (Glut) increases, it can promote Glut trafficking to the cell membrane. In addition, there are controversial hypotheses that glycolysis initiates other metabolic pathways and an enzyme engaged in glycolysis Glyceraldehyde-3-phosphate Dehydrogenase modulates T cell differentiation. NAD+ is also indispensable for regulation: NAD+ is required for synthesis of aspartate, which is significant for cell proliferation; extracellular NAD+ drives Th17 differentiation through the purinergic receptors P2RX4 and P2RX7; NAD+ modulates the function of sirtuins, and sirtuin 1 deacetylates RORγ, thereby enhancing Th17 cell generation [32]. Acetyl-CoA carboxylase 1, which mediates Fatty Acid Synthesis to produce phospholipids for cellular membranes, while also indirectly decreasing the level of glycolysis, influences Th17 differentiation and generation. Treg cells, by contrast, rely on fatty acids oxidation and can take up exogenous fatty acids [31,32,33].

## 3. Natural Compounds

### 3.1. Bergapten

Bergapten, also known as 5-methoxypsoralen, is a member of the furanocoumarin class of compounds. It is a major component of bergamot essential oil and could also be found in other citrus oils, such as grapefruit [34]. It has been shown to have significant immunomodulatory properties: it exhibits antibacterial functions, as well as induces apoptosis in various cancer types, including liver, breast, colorectal cancer [34,35,36,37].

Its anti-inflammatory activity has also been studied. In vitro experiments using human peripheral blood mononuclear cells (PBMCs) stimulated with lipopolysaccharide (LPS) show that bergapten significantly reduces the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [38, 39]. As discussed above, IL-6 is known to activate the JAK/STAT signaling pathway, leading to STAT3 phosphorylation. Consistently, bergapten inhibits the phosphorylation of JAK2 and reduces STAT3 activation. Decreased p-STAT3 levels subsequently lower the expression of RORγt, the key transcription factor driving Th17 differentiation. TNF-α has also been shown to promote Th17 differentiation indirectly in autoimmune diseases and inflammatory diseases, such as Rheumatoid Arthritis, primarily by enhancing the production of IL-6 and other pro-inflammatory cytokines [40,41]. Therefore, these findings suggest that bergapten suppresses Th17 cell development.

In an in vivo study using a Combined allergic rhinitis and asthma syndrome (CARAS)/PM2.5-induced airway inflammation model in BALB/c mice, bergapten treatment led to decreased levels of IL-6 and IL-1β. IL6, together with IL-1β, is known to enhance and sustain STAT3 phosphorylation, which promotes the expression of RORγt and Th17 cell differentiation. Bergapten treatment reduced STAT3 activity and RORγt expression, resulting in lower Th17 cell levels. In contrast, levels of IL-10 and Foxp3 were increased in nasal and bronchoalveolar lavage fluids (NALF and BALF), supporting a shift toward Treg cell differentiation [42].

This change in the Th17/Treg balance is associated with reduced inflammatory symptoms. These findings suggest that bergapten may control the balance of Th17/Treg, thereby holding therapeutic potential for autoimmune and inflammatory diseases.

Bergapten has also been shown to balance between T helper 1 and T helper 2 in the same in vivo study [42], which means it may help maintain the homeostasis of all kinds of T cells related to certain inflammatory conditions and autoimmune diseases.

Although Bergapten is present in foods like citrus fruits, dietary exposure is generally limited. Nevertheless, due to its photosensitizing properties, its safety and optimal dosage require careful evaluation, and people may experience mild side effects such as dizziness, muscle cramps and heartburn following intake.

### 3.2. Salidroside

Salidroside is a naturally occurring bioactive compound, specifically a glucoside of tyrosol, found in the plant *Rhodiola rosea*. It has unique values in anti-hypoxia, antioxidation, antiaging, as well as anti-inflammation [43]. Some studies suggest that salidroside may play crucial roles in modulating T cell responses under autoimmune diseases and inflammatory conditions.

Under high-altitude hypoxia, which induces oxidative stress and inflammation, a report has shown that salidroside inhibits the JAK2/STAT3 signaling pathway, thereby suppressing the expression of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, and MCP-1, both in serum and hepatic tissues. These cytokines are known to contribute to a Th17-skewing inflammatory milieu. Therefore, the downregulation of JAK2/STAT3 may indirectly contribute to limiting Th17 cell responses, which helps reestablish immune homeostasis [44]. However, Salidroside also activates Nuclear factor erythroid 2-related factor 2 (Nrf2), which further reduces Reactive Oxygen Species (ROS) level under conditions like oxidative stress [45]. Studies have shown that both excessive and insufficient ROS levels impair Treg function and differentiation, which might be a consideration for the interpretation of this result [46].

In aplastic anemia (AA), which is an immune-mediated disorder characterized by decreased Treg frequencies and increased Th17 responses, another study also shows that salidroside exerts regulatory effects. It has been shown to downregulate the expression of hypoxia-inducible factor 1-alpha (HIF-1α) at both mRNA and protein levels. HIF-1α is a crucial transcription factor that promotes Th17 differentiation by upregulating RORγt and concurrently inhibits Treg lineage commitment by targeting the Foxp3 protein for proteasomal degradation. Thus, by downregulating HIF-1α, salidroside not only suppresses Th17 development but also enhances Treg differentiation, ultimately promoting the Treg/Th17 balance. Moreover, HIF-1α upregulation may depend on STAT3 under Th17-skewing conditions, which could be another possible explanation [47].

Based on these observations, this drug may assist in reducing autoimmune disease symptoms through immunoregulatory mechanisms. Nonetheless, Salidroside could not be used for a long time: it is possibly safe when taken for 6-12 weeks, and it may cause dizziness, dry mouth, or excessive saliva.

### 3.3. Gegen Qinlian Decoction (GQD)

Gengen Qinlian is a classic Traditional Chinese Medicine, also known as Gegen Qinlian Decoction, composed of four herbs: Pueraria (Gegen), Scutellaria baicalensis(Huangqin), Coptos chinensis(Huanglian), and Glycyrrihiza uralensis(Zhi Gancao). GQD has been shown to fight inflammatory intestinal diseases and metabolic diseases [48].

Under dextran sulfate sodium induced ulcerative colitis, a report has shown that Th17 cells infiltrate the intestinal ulcer sites, contributing to mucosal damage. GQD alleviates inflammation by modulating the Treg/Th17 cell ratio. It downregulates IL-6 expression, thereby inhibiting Th17 cell differentiation. Reduced IL-6 levels lead to decreased activation of JAK2 and subsequent phosphorylation and nuclear translocation of STAT3, resulting in downregulation of downstream targets such as RORγt and IL-17. Ultimately, differentiation towards Th17 cell is suppressed, contributing to the restoration of immune balance [49].

One of the key bioactive components of GQD, berberine, has also been reported to exert similar effects through both direct and indirect pathways in the context of Vogt-Koyanagi-Harada disease. Berberine directly suppresses IL-17 production in CD4+ T cells and indirectly attenuates Th17 cell differentiation by impairing dendritic cell (DC) function. It downregulates the expression of costimulatory molecules (CD40, CD80, CD86) on Dcs and significantly reduces the secretion of IL-6, IL-1β, and IL-23, which are essential for Th17 commitment. Through these mechanisms, it acts as a potent negative regulator of the Th17-mediated immune response, thereby contributing to the overall immunosuppressive and anti-inflammatory properties of GQD [50].

## 4. Immunotherapy

### 4.1. Breg cells expansion

Regulatory B cells (Bregs) are a subset of B lymphocytes, playing a crucial role in suppressing immune responses and maintaining immune tolerance by balancing Th17 and Treg cells. Usually, in autoimmune diseases such as experimental multiple sclerosis and sepsis, Breg cells are reduced [51]. Therefore, various studies suggest that stimulating Breg cell production could be used as a treatment, which restore Th17/Treg cells balance. However, most of them were conducted in mice, which could be a limitation.

In mice with Experimental Autoimmune Encephalomyelitis, which is a widely used animal model of multiple sclerosis, research has shown that injecting IL-35 induces Breg cells in-vivo: through IL-12Rβ2 and IL-27Rα receptors, STAT1 and STAT3 are activated, leading to the secretion of IL-10 and IL-35. Transferring these cells promote Treg differentiation, as well as inhibit Th17 [52].

In a sepsis model induced in mice pretreated with anti-CD22 antibody, the expression of T-bet and RORγt increased, whereas Foxp3 expression remained unchanged. Through adoptive transfer of ex vivo–expanded regulatory B cells (Bregs)—that is, isolating Bregs from mice, expanding them in culture, and injecting them back—Foxp3 expression was upregulated, promoting Treg differentiation. Meanwhile, RORγt expression decreased, resulting in a lower Th17 proportion. These effects were accompanied by elevated IL-10 levels and reduced IL-22 and IL-17 production [53].

However, Breg cell expansion and transplantation still face challenge:exposure to incorrect concentrations or chronic stimulation with proinflammatory cytokines may impair Breg function and even lead to a reduction in the number of functional Bregs[54].

### 4.2. CAR-Engineered Treg cells

CAR-T therapy is a type of immunotherapy where a patient's own immune cells are genetically modified in a lab to destroy target cells. It was first used in the treatment of pediatric and young adult patients with relapsed or refractory acute lymphocytic leukemia [55], but now it has been investigated for autoimmune diseases.

There have been at least four approaches to CAR-T therapy so far: CD19-targeted therapy, Dual Targeting for optimal treatment, Chimeric autoantibody receptor engineering, and Engineered Treg (CAR-Tregs). In most autoimmune diseases and inflammation, Treg cells are highly deficient, as demonstrated in previous parts. By engineering Treg cells to target pathological features of diseases, their symptoms have been reduced. For instance, in lupus erythematosus patients, IL-2 gene is epigenetically silent, leading to the decreased production of IL-2. By engineering Tregs and injecting the resultant CAR-Tregs cells, the levels are restored by improving immune suppressive capabilities. Another example, vitiligo, restoration of normal pTreg cells is able to protect against skin depigmentation, and increase the secretion of IL-10, restraining cytotoxicity of melanocytes [56]. While for EAE mice, Treg cells are engineered with Foxp3 and a CAR targeting myelin oligodendrocyte glycoprotein (MOG), which could drive Treg cell differentiation, maintain the Treg cell phenotype, and specifically target MOG-expressing cells, ultimately reducing disease symptoms [57].

Still, CAR-T therapy has side effects, most commonly Cytokine Release Syndrome, which presents with fever, low blood pressure, and shortness of breath. Another is Immune Effector Cell-Associated Neurotoxicity Syndrome, which can cause confusion, difficulty, and seizures.

## 5. Conclusions, Limitations and Future Directions

Both plant-derived compounds and cellular therapies show potential in the treatment of autoimmune diseases. Compared to CAR-T therapy, plant compounds generally display milder side effects, making them more acceptable from a safety perspective. However, their therapeutic mechanisms remain insufficiently examined, as studies have focused on a limited range of autoimmune and inflammatory conditions, and even some of them are inconsistent or contradictory. They require more rigorous and standardized investigations, as well as optimal levels of drugs. Moreover, these compounds are often applied as immune modulators rather than direct cures. Future research should aim to clarify their immunomodulatory mechanisms, establish standardized levels, and evaluate their efficacy across a wider range of autoimmune conditions.

In contrast, CAR-T therapy and adoptive transfer of regulatory B cells have been more extensively studied and are under preclinical and early clinical investigations. However, their clinical application is often hindered by severe side effects, which are less likely to gain trust from the public. Future research should focus on improving the safety of these therapies by reducing toxicity and enhancing the precision of cellular engineering.

In addition, plant-derived compounds may hold potential as adjunct therapies, serving as immune modulators to enhance the efficacy or reduce the toxicity of CAR-T cell treatments. Exploring this combinatorial approach or choosing between natural compounds and cellular treatments according to the severity could help develop safer and more effective therapies.

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