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Chapter 11

Post-Transcriptional and Translational Mechanisms of Regulation of Gene Expression in T Cell Subsets

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Abstract

The immune system is under strict regulatory control to ensure homeostasis of inflammatory responses, lying dormant when not needed but quick to act when called upon. Small changes in gene expression can lead to drastic changes in lineage commitment, cellular function, and immunity. Conventional assessment of these changes centered on the analysis of mRNA levels through a variety of methodologies, including microarrays. However, mRNA synthesis does not always correlate directly to protein synthesis and downstream functional activity. Work conducted in recent years has begun to shed light on the various post-transcriptional changes that occur in response to a dynamic external environment in which a given immune cell type encounters. In this chapter, we provide a critical review of key post-transcriptional and translational mechanisms of regulation of gene expression in the immune system, with an emphasis of these regulatory processes in various CD4+ T cell subsets and their related effector functions.

Keywords: inflammation, CD4+ T cells, transcriptional, translatome, immune regulation, immunity

1. Introduction

CD4+ T cells are key players in the adaptive immune response, capable of adapting their function depending on the immune challenge being faced. CD4+ T cells employ a wide variety of signaling pathways to integrate environmental cues and translate them into the requisite gene expression programs required to carry out their effector functions. These gene expression programs are enacted by a complex network of factors, involving the direct action of transcription factors to drive mRNA synthesis, epigenetic modification of DNA accessibility to modulate gene expression, as well as a variety of post-transcriptional mechanisms including RNA-binding proteins

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and microRNA that influence the stability and translation of synthesized mRNA. This complexity ensures that CD4+ T cells can mount an appropriate and adequate response to a wide variety of pathogens.

2. Transcriptional regulation of CD4+ T cell activation

Complex transcriptional changes are required for CD4+ T cell generation and egress from the thymus (reviewed in [1]). Recent thymic emigrant naïve CD4+ T cells are maintained in the periphery through the action of important cytokines, like IL-7, which support cell survival. Naïve CD4+ T cells maintain high levels of the IL-7 receptor (CD127), which is maintained in part through the action of the transcription factor, ETS-1 [2]. ETS-1 has been shown to directly bind the *il7ra* promoter to maintain expression on the cell surface, with levels of ETS-1 being shown to directly correlate with the levels of CD127 expression. Runx1 is another transcription factor that is required for CD127 expression in naïve CD4+ T cells, possessing a binding site in close proximity to ETS-1 in the *il7ra* promoter [3]. Signaling through CD127 is necessary to trigger phosphorylation of STAT5 and the expression of the antiapoptotic proteins BCL-2, BCL-xL, and MCL-1, all necessary for the survival of naïve CD4+ T cells during homeostatic expansion. This results in the maintenance of the pool of naïve cells prior to antigen engagement of the T cell receptor (TCR) [4]. The recognition of the cognate antigen by the TCR is responsible for the initial changes to the T cell transcriptional program through the activation of the Nuclear Factor of Activated T Cells (NFAT) transcription factor family. In naïve CD4+ T cells, NFAT is maintained in a phosphorylated and inactive state through the action of the kinases GSK3 and CK1 [5, 6]; however, the TCR signaling cascade and subsequent calcium influx result in the dephosphorylation of NFAT by calcineurin allowing for nuclear translocation of NFAT to enact its transcriptional program [7]. The nature of this transcriptional program is dependent on the presence of the NFAT binding partner, AP-1. The AP-1 complex consists of the FOS and JUN transcription factors and is assembled upon activation of the CD28 co-stimulatory pathway [8]. The cooperative action of NFAT and AP-1 drives the transcription of IL-2, which acts in an autocrine and paracrine fashion, and drives the proliferation of CD4+ T cells via phosphorylation of STAT5. STAT5 signaling is responsible for enhancing the transcription of genes necessary for the proliferation and survival of CD4+ T cells following activation, including promoting the expression of the high-affinity component of its own receptor CD25 (IL-2Rα chain), while reducing the transcription of CD127 [9, 10]. Co-engagement of the TCR and CD28 co-stimulatory molecule also promotes the activation of the NF-κB family of transcription factors, necessary to prevent activation-induced cell death and apoptosis [11]. While NFAT and NF-κB are necessary during the initial stages of T cell activation, they are also necessary for the differentiation o CD4+ T cells into distinct Th cell subset each endowed with its cytokine signature and specific effector functions [12, 13]. The CD4+ T cell lineage choice is determined largely by the extracellular milieu and presence of various cytokines that trigger the expression of a diverse network of transcription factors upon activation of the cytokine signaling pathways. This lineage choice is determined by a number of factors including the nature of the pathogen and genetic background of the host. Several Th

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cell subsets have been identified and include Th1 effector T (T_{EFF}) cells arise to enhance cytotoxic activity of immune cells against intracellular bacterial and viral infections, Th2 cells facilitating antibody generation, and Th17 cells protecting against extracellular pathogens including parasites and fungi, while regulatory T cells (T_{REG}) are necessary for the resolution of inflammation and to control aberrant T cell responses in the periphery to promote self-tolerance [14].

2.1. Transcription factor networks regulating CD4+ T cell differentiation

Th cell lineage commitment is dependent on the expression and function of lineage-specifying transcriptional factors. The transcription factor TBX21 (T-bet) is thought to be the main driver of the Th1 transcriptional program, which is initiated through the activation of STAT pathways by Interferon gamma (IFNγ) and IL-12 secreted by antigen-presenting cells (APCs) [15]. IFNγ-activated STAT1 binds the *Tbx21* promoter to drive the first round of T-bet expression [16]. This prompts the expression of the IL-12 receptor β2 subunit, allowing IL-12 present in the extracellular milieu to activate STAT4, which further drives T-bet expression [17]. T-bet also activates the transcription of the transcription factors H2.0-like homeobox (HLX) and runt-related transcription factor 3 (RUNX3) [18, 19]. T-bet can bind the IFNγ promoter facilitating chromatin looping, allowing for T-bet binding partners HLX and RUNX3 to drive IFNγ expression in Th1 cells [20]. IFNγ acts in a feed-forward loop to drive continued T-bet expression through STAT1. The production of IFNγ is also regulated by the NF-κB family member, RelA, with RelA deficiency being shown to reduce IFNγ expression. Additionally, the recruitment of RelA to the *ifng* locus is dependent on T-bet expression [21]. NFAT has also been shown to act synergistically with T-bet by binding the 5′ enhancer region of the *ifng* gene [22]. However, the NFAT enhancing activity is not limited to the Th1 cell differentiation, as it has been linked to the promotion of a variety of activation-induced genes in CD4+ T cells, with activation of these genes being blocked by calcineurin inhibitors [23]. T-bet is responsible for activating the majority of Th1-related genes including the chemokine receptors CXCR3 and CCR5 as well as the requisite ligand CCL3 and CCL4 for attracting other Th1 cells to the site of inflammation [24]. The T-bet-mediated Th1 transcriptional program also drives the expression of other Th1 cytokines including TNFα and lymphotoxin-α [25].

The Th2 transcriptional program is largely mediated through the action of GATA3. While GATA3 expression is already present in naive CD4+ T cells, it is insufficient to drive Th2 polarization [26]. Enhanced expression of GATA3 in Th2 cells can occur in response to two distinct pathways. IL-4 activates STAT6 to activate the transcription of GATA3 while signaling through the Notch pathway can activate GATA3 transcription independent of STAT6 [27, 28]. Activation of GATA3 induces its partner transcription factor c-MAF [29]. Together, they induce the expression of IL-4, which acts as an enhancer of Th2 differentiation in an autocrine loop through STAT6 leading to increased GATA3 expression [30]. GATA3 and STAT6 act in conjunction to activate transcription of Th2 cytokine genes *il5 and il13*, as well as further transcription of *il4* [26]. The transcription factor BCL3 has also been shown to transactivate the GATA3 promoter [31]. The NF-κB family member p50 is important for Th2 function, as mice lacking p50 are unable to transcribe *il4*, *il5*, and *il13* [32]. NFAT is also known to act as an enhancer for

GATA3 binding to *il4* locus to further cement Th2 lineage commitment due to an IL-4 feed-forward loop [33]. While GATA3 drives the Th2 transcriptional program, it can also restrict Th1 differentiation by repressing the transcription of IFNγ and STAT4 [34]. Conversely, T-bet in conjunction with RUNX3 can suppress *il4* transcription by competing with GATA3 for binding to the *il4* promoter [19].

Th17 cells arise in specific conditions where Th1 and Th2 differentiation can be inhibited as the presence of the Th1 or Th2 transcriptional program can repress Th17 differentiation. The transcription factor RORγT (encoded by the *rorc* gene) is responsible for driving Th17 differentiation and effector function [35]. RORγT induction is dependent on the Transforming Growth Factor β (TGF-β) signaling pathway, which inhibits both Th1 and Th2 differentiation [36, 37]. TGF-β signaling on its own favors the development of T_{REG} cells; however, the presence of exogenous IL-6 redirects cells toward a Th17 fate. IL-6 mediated activation of STAT3 is responsible for blocking expression of the master regulatory transcription factor of T_{REG} cells, Foxp3 [38, 39]. In the absence of Foxp3, TGF-β induces the transcription of RORγT that activates the transcription of Th17-related cytokines including IL-17A/F, IL-21, and IL-22 [35]. IL-21 amplifies STAT3 activity through an autocrine loop to further enhance Th17 differentiation [40]. RORγT is also responsible for inducing the expression of the IL-23R to allow for enhanced maintenance of RORγT expression [37]. Exogenous IL-23 and autocrine IL-21 act in concert with TGF-β to activate further transcription of RORγT, enhancing commitment to the Th17 lineage. The transcription factor DDx5 partner with RORγT to drive Th17 cytokine expression; however, it is dispensable for RORγT induction [41]. DDX5 and RORγT co-localize to the *il17a and il17f* loci to enhance Th17 effector function. The transcription factor BATF is another important early regulator of the Th17 transcriptional program. BATF-deficient mice possess normal Th1 and Th2 differentiation; however, Th17 induction in these mice was severely impaired as they failed to induce the expression of IL-21 and RORγT [42].

T_{REG} cells are central to the maintenance of peripheral tolerance and the resolution of inflammation. T_{REG} cells can differentiate in the thymus or under unique stimulatory conditions in the periphery. As such, The T_{REG} cell pool consists of thymic-derived T_{REG} cells (tT_{REG}) as well as peripherally induced T_{REG} cells (pT_{REG}) cells [43]. Foxp3 expression in tT_{REG} cells has been shown to be dependent on the binding of several transcription factors to both the *foxp3* promoter and conserved noncoding sequences (CNS), which function as enhancers of *foxp3* transcription [44]. The NFAT and AP-1 complexes bind to the *foxp3* promoter following TCR stimulation in the thymus to drive Foxp3 expression [44]. The NF-κB family member c-Rel is responsible for enhancing tT_{REG} generation through binding to CNS3, while the Foxo family member proteins, Foxo1 and Foxo3, enhance expression through binding to the *foxp3* promoter as well as to CNS2 [45, 46]. In the periphery, induction of Foxp3 in pT_{REG} cells is dependent on the action of key cytokines like TGF-β. TGF-β signaling activates Mothers Against Decapentaplegic Homologues 2 and 3 (SMAD2/3), which act in concert with NFAT to drive Foxp3 expression by binding to CNS1 [47]. Foxp3 has been shown to interact with ~361 binding partners that allow it to enable the T_{REG} transcriptional program. Foxp3 acts mostly as a transcriptional repressor preventing the expression of Th1 and Th2 characteristic cytokines including IFNγ, IL-2, and IL-4. This repressive activity is dependent on the interaction of Foxp3 and NFAT and Eos [48–50]. Repression of IL-2 expression and production means that T_{REG} cells, anergic by nature, are entirely dependent

on exogenous sources of IL-2 for proliferation and survival. However, this need is in part met by enhanced CD25 transcription by Foxp3. Moreover, upregulation of CD25 in T_{REG} cells allows them to receive the requisite STAT5 signals for the mediation of their suppressive effector function [43]. The transcriptional program enacted by Foxp3 is also responsible for upregulating the expression of genes that give T_{REG} cells their suppressive capacity. This includes the anti-inflammatory cytokine, IL-10, as well as surface proteins such as CTLA4 for contact-dependent inhibition of APCs, and CD39/CD73 to shift the extracellular milieu from an ATP-driven inflammatory state through conversion of ATP to adenosine [48, 51, 52]. T_{REG} cells have also been shown to depend on co-expression of T-bet, GATA3, and RORγT to mediate suppression of the CD4+ Th cell subsets, in turn enabling them to express distinct chemokine receptors to allow T_{REG} cells to traffic to inflammatory sites and suppress the corresponding T_{EFF} cell type [53]. T_{REG} cells are also known to downregulate Foxp3 expression resulting in their reprogramming into highly pro-inflammatory cells under certain inflammatory contexts [54]. However, the nature of environmental triggers, stability, and reversibility of this transformation remains a topic of intense investigation.

3. Epigenetic control of transcriptional programs in Th cell subsets

The transcriptional programs described thus far shed light on the mechanism leading to the differentiation of various CD4+ T cell subsets (**Figure 1**). However, the ability of transcription factors to drive their relative gene expression programs is dependent on several key factors including transcription factor abundance, their location, any posttranslational modifications, and importantly, whether the enhancer or promoter region they bind to is accessible in the DNA. The accessibility of DNA is dictated by chromatin accessibility dependent on nucleosome modifications as well as the methylation status of the DNA itself.

Methylation of cytosines in cytosine-phosphate-guanine (CpG) dinucleotides in promoter and enhancer regions of the DNA has been shown to directly impact the ability of transcription factors to drive mRNA expression by either directly inhibiting transcription factor binding or through recruitment of methyl-CpG-binding domain proteins [55]. DNA methylation markers are transferred to progeny DNA through the action of DNA methyl transferase 1 (DNMT1), while demethylating enzymes such as Tet2 can facilitate the removal of methyl groups from CpG islands [56, 57]. Unlike DNA methylation, the nucleosome modifications present in chromatin can be dynamic and varied. Nucleosomes can vary in their composition with variant form of histone H2, H3, and linker histones being incorporated or removed from the nucleosome to alter DNA accessibility. Histone modifications include the addition of acetyl or methyl groups as well as sumoyl, ubiquitin, and ADP-ribose to modify DNA-binding sites for regulatory elements that can either enhance or repress transcription [58]. Accessible DNA results in the creation of DNase1 hypersensitivity sites, which has allowed for identification of permissive sites in the DNA [59]. Recent studies have uncovered a wide array of possible histone modifications that take place within mammalian cells; however, a few main types of modifications stand out as being characteristic of silenced, readily accessible, and inactive but ready to be transcribed genes. Silenced genes are characterized by the presence of histone H3 with

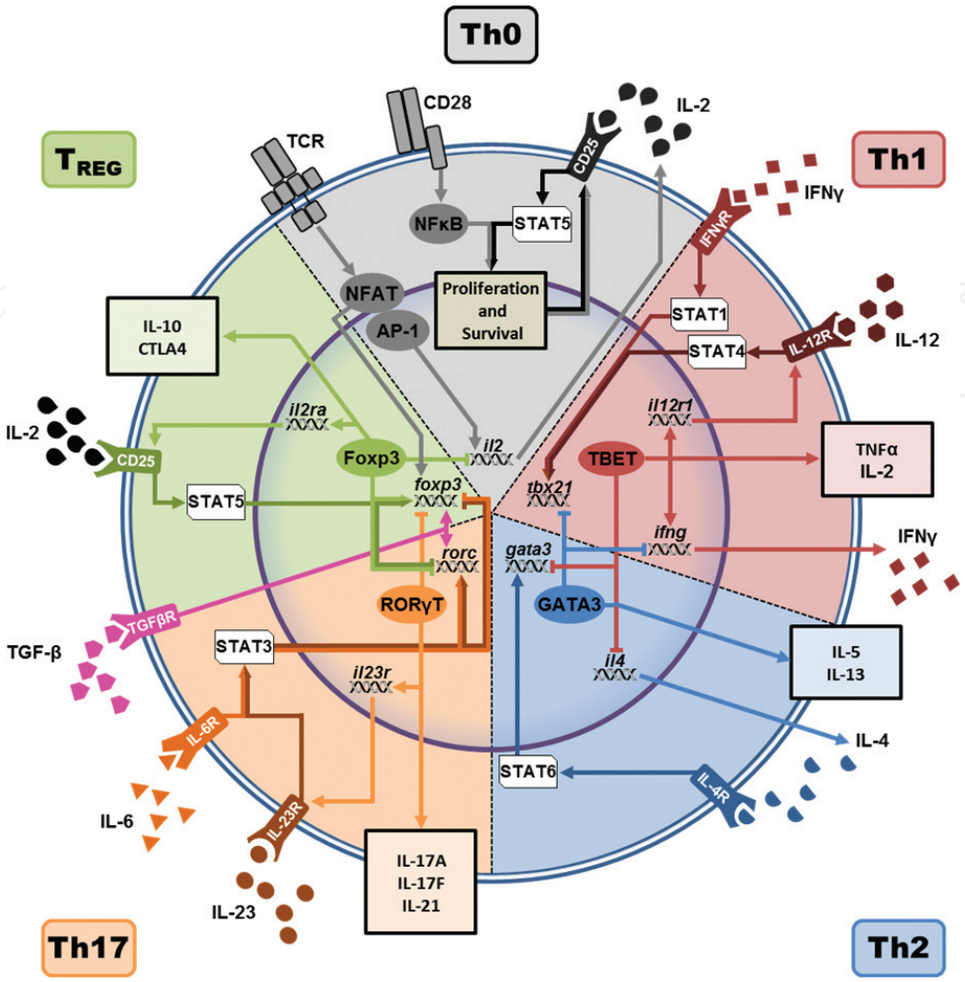


Figure 1. A generalized overview of CD4+ T cell activation and differentiation. Activation of the TCR and CD28 co-stimulation pathways is required for the induction of genes necessary for T cell proliferation and survival, allowing for further differentiation based on requisite signals. Activation of STAT1 and STAT4 pathways, triggered by IFNγ and IL-12 respectively, is required to induce the expression of T-bet resulting in the secretion of IFNγ and other Th1 cytokines. The Th2 lineage is driven by GATA3 upon activation of the STAT6 pathway by IL-4. TGF-β in conjunction with STAT3 activating signals is required to drive a Th17 response via expression of RORγT. Similarly, TGF-β and NFAT can facilitate the conversion of T_{EFF} cells to a T_{REG} phenotype through induction of Foxp3, resulting in the expression of proteins required for T_{REG} suppressive function but making them dependent on exogenous IL-2 for proliferation and survival.

either dimethylation or trimethylation of lysine 9 or 27 (H3K27 and K3 K9), whereas readily accessible and transcribed genes possess single, di-, or tri- methylation of lysine 4 on histone 3 (H3K4) [60]. In addition, the presence of acetyl groups on histones increases the mobility of nucleosomes, allowing enhanced transcription of genes in proximity to acetylated histones. Genes that are inactive but poised and ready to be transcribed possess bivalent modifications incorporating both permissive and silencing modifications. In recently activated naïve CD4+ T cells, the presence of these bivalent modifications at important cytokine loci allows Th subset-dependent factors to make the corresponding loci more accessible while silencing loci associated with alternate lineages. TCR stimulation results in the creation of DNAse-1 hypersensitivity sites in the *ifng* and *il4* loci dependent on the recruitment of NFAT to these loci, as inhibition of TCR activation with CsA ablated the creation of these sites [61].

During Th1 lineage commitment, the *ifng* locus is marked by the presence of both H3K4 and H3K27 modifications; however, progression through Th1 differentiation in response to the initial upregulation of T-bet leads to a significant increase in the presence of permissive H3K4 modifications, while H3K27 modifications are removed throughout the locus [62]. This results in a marked increase of DNase-1 hypersensitivity sites at regulatory elements of the IFNγ locus. STAT4 further contributes to the generation of a permissive environment at this locus through recruitment of chromatin-remodeling complexes to the promoter allowing for increased IFNγ expression [63]. However, while STAT4 signaling is required for enhancing Th1 differentiation, T-bet can drive lineage commitment in the absence of STAT4 signaling due to its ability to bind the *ifng* locus when it is repressively methylated and to recruit histone demethylases to remove repressive H3K27 modifications [64]. Additionally, T-bet is known to recruit methyl-transferases to create permissive H3K4 trimethylation [65]. Thus, T-bet expression can override the repressive modifications to the *ifng* locus during the process of Th2 differentiation.

The epigenetic modifications that arise during Th2 differentiation have been extensively studied in past decades. Unlike the loci for other subset-specific cytokines, the *il4* promoter possesses a reduced degree of CpG methylation allowing low-level transcription of *il4* mRNA following the TCR stimulation, allowing this locus to convert to a more permissive state as the level of Th2 cytokine signaling increases [66, 67]. The increased IL-4 signaling through STAT6 results in the recruitment of histone acetyl transferases to the GATA3 promoter [68]. As the expression of GATA3 increases in Th2 cells, it mediates a variety of epigenetic changes at Th2 cytokine loci. One action of GATA3 is to inhibit the binding of MBD proteins to CpG methyl groups and restrict the action of DNMT1, resulting in a loss of CpG methylation as cells continue to divide under Th2 polarizing conditions [69]. Even in committed Th1 cells, inhibition of DNMT1 results in the ability of Th1 cells to secrete IL-4, demonstrating the importance of GATA3-mediated demethylation of the Th2 cytokine locus in Th2 cell commitment [66]. GATA3 is also able to sustain its own expression through recruitment of methyltransferases to the *gata3* promoter to induce permissive H3K4 modifications, indicating that while STAT6 is necessary for the initiating the conversion of naïve CD4+ T cells to a Th2 phenotype, GATA3 transcriptional activity and epigenetic modifications are responsible for stabilizing commitment to the Th2 cell fate. In addition to maintain Th2 differentiation, GATA3 is known to bind the *ifng* promoter in conjunction with STAT6 to mediate recruitment of methyltransferases to increase the presence of repressive H3K27 modifications, as well as by recruiting histone deacetylase complexes to further repress transcription of the *ifng* locus and suppress Th1 cell commitment [70].

Unlike with Th1 and Th2 differentiation, there is no evidence that the master transcription factor of the Th17 lineage, RORγT, can induce the necessary epigenetic changes to facilitate the Th17 transcriptional program. However, STAT3 is known to recruit histone acetyltransferases to the *il17a* and *il17f* promoters to promote Th17 effector function [71]. Interestingly, analysis of histone modifications in freshly isolated Th17 cells has revealed that they possess bivalent modifications at both the *ifng* and *tbx21* loci, allowing for the generation of IFNγ+IL-17+ Th cells. These loci are thought to become permissive following TCR stimulation, and studies

with immunization of OT-II mice with ovalbumin reveal an increase in the amount of double positive cells compared to unimmunized controls with higher levels of *il12rb2* mRNA found within the Th17 cells of immunized mice [72].

The epigenetic landscape of T_{REG} cells is crucial for the induction and stable expression of Foxp3 and ensuing T_{REG} transcriptional program through alterations to the CNS regions of the *foxp3* locus. While the binding of c-REL to CNS3 is important for Foxp3 induction in tT_{REG} cells in the thymus, and the binding of SMAD/NFAT complexes to CNS1 is responsible for the induction of Foxp3 in pT_{REG} cells, CNS2 has been identified as being necessary for sustained Foxp3 expression in the maintenance of the T_{REG} phenotype [73]. This region, termed as the T_{REG}-specific demethylated region (TSDR), contains binding sites for various transcription factors involved in maintaining Foxp3 expression, including ETS-1, STAT5, CREB/ATF, as well as Foxp3 itself [74]. In tT_{REG} cells, this region is devoid of CpG methylation while being highly methylated in induced T_{REG} cells; however, pT_{REG} cells induced *in vivo* possess partially hypomethylated TSDRs resembling that of tT_{REG} cells [75]. Maintenance of the TSDR in T_{REG} cells is achieved in part through regulation of DNMT1 expression. DNMT1 has been shown to be able to disrupt the TSDR in tT_{REG} cells. DNMT1 expression is induced via activation of STAT3 in response to exogenous IL-6, resulting in methylation of the TSDR and downregulation of Foxp3 expression. In addition, the strength of TCR signaling during pT_{REG} induction has been shown to regulate the level of DNMT expression, with high levels of TCR signaling resulting in the impaired induction of Foxp3. Conversely, TGF-β signaling is known to antagonize DNMT1 activity in T_{REG} cells [76, 77]. Furthermore, the MBD protein MBD2 has been demonstrated to be essential for maintenance of the TSDR in tT_{REG} cells. tT_{REG} from MBD2−/− mice were shown to possess demethylated TSDR in the thymus but were unable to maintain the TSDR in the periphery. This is due to impaired recruitment of the demethylase Tet2 to the TSDR in the absence of MBD2, suggesting a role for MBD2 in the active demethylation of the TSDR [78].

4. Regulation of mRNA stability in CD4+ T cell subsets

Thus far, we have examined how transcriptional and epigenetic changes are able to influence various gene expression programs of CD4+ T cell subsets through the induction of mRNA synthesis to enact both lineage commitment and effector function. However, recent studies have demonstrated that the level of mRNA within a cell is dependent not only on the generation of new mRNA transcripts but also on the stability of mRNA in the cytosol allowing for continued protein expression. Several mechanisms have been described that are capable of regulating mRNA stability including RNA-binding proteins (RBP) as well as other RNA molecules.

RBPs are a specialized group of proteins that recognize conserved sequences present in the untranslated regions (UTR) of mRNA. One of the determinants of mRNA stability is the length of the polyadenylated tails with the removal of mRNA poly-a-tails being a precursor to the removal of 5′ CAP and subsequent degradation of mRNA [79]. The RBP CPEB1 has been

shown to recognize cytosolic polyacetylation motifs in the UTR of mRNA and can modulate the length of the poly-a-tail depending on its phosphorylation status. Other RBPs such as tristetraprolin (TTP) recognize AU-rich elements (ARE) and are responsible for degrading mRNA synthesized under homeostatic conditions, but can be inactivated in inflammatory contexts to facilitate mRNA translation. Conversely, RBPs-like HuR can stabilize mRNA within the cytosol, allowing for prolonged gene expression [80].

Recent years have seen an emergence in the study of how noncoding RNA molecules can regulate mRNA stability. This group consists of short RNA sequences called micro-RNA (miRNA) as well as longer noncoding sequences (LncRNA). miRNAs are synthesized as longer pre-miRNA; however, processing by various RNAse proteins, such as Drosha, Dicer, and DGCR8, cleaves the miRNA molecule to its mature ~22 nucleotide length consisting of a sequence that is antisense to its mRNA target, with binding sites being found primarily in the UTR regions of target mRNA transcripts. Mature miRNA recruits the RNA-induced silencing complex to target mRNA transcripts, inducing their degradation [81]. On the other hand, LncRNA has been shown to play a variety of roles, including miRNA sponges by providing decoy sites for miRNA binding as well as factors involved in facilitating transcription factor complex formation [82].

These mRNA stability mechanisms play an important role in the activation of naïve CD4+ T cells. The absence of miRNA in T cells through ablation of the processing enzyme DICER resulted in a decrease in the expansion of DICER-deficient CD4+ T cells following TCR stimulation [83]. Importantly, the miR 17~92 cluster has been found to have an important function in facilitating the CD28 co-stimulatory pathway through repression of the inhibitory protein PTEN, allowing for T cell proliferation [84]. miRNA has also been shown to modulate TCR sensitivity, with miR-181a targeting the inhibitory kinases PTPN22 and SHP-2, which act to terminate TCR signaling. Antagonizing miR-181a abolishes CD69 expression, a characteristic marker of recent TCR stimulation [85]. miR-21 also contributes to the epigenetic landscape in T cell by targeting DNMT1 mRNA, creating hypomethylated regions in CD4 + T cells, resulting in aberrant activation and cytokine secretion [86]. On the other hand, several miRNAs are known to restrict CD4+ T cell activation, and miR181c targets IL-2 mRNA to repress expression in naïve CD4+ T cells; however, its expression is downregulated following TCR stimulation allowing for IL-2 secretion [87]. mIR-125b has also been shown to be important in keeping CD4 + T cells in a naïve state by targeting key cytokines and cytokine receptors involved in CD4 + T cell differentiation [88]. However, another study has demonstrated that TCR activation causes lymphocytes to produce mRNA transcripts with shortened UTRs negating some of the inhibitory effect of miRNAs [89]. In addition, expression of the RBP HuR is increased in activated CD4+ T cells, resulting in increased mRNA stability [90].

mRNA stability has been shown to be a contributing factor in regulating Th1/Th2 differentiation. miR-155 facilitates Th1 differentiation by targeting the Th2 accessory transcription factor c-Maf to limit Th2 differentiation, while miR-17 has been shown to restrict expression of the TGF-β receptor subunit 2 to block Th17 and pT_{REG} conversion [91–93]. Other miRNAs have been shown to limit Th1 differentiation. miR-138 has been shown to alter the Th1/Th2 cell balance by targeting RUNX3 mRNA impeding the T-bet-mediated induction of IFNγ [94].

Signaling through STAT1 initiates the transcription of miR-29, which contributes to the restriction of Th1 lineage commitment by directly targeting both T-bet and IFNγ mRNA, preventing the IFNγ-mediated feed-forward loop from driving further T-bet expression [95]. The RNA-binding protein TTP is also known to degrade IFNγ mRNA in activated T cells resulting in a twofold reduction of the half-life of IFNγ-mRNA in CD4+ T cells [96]. TTP has also been shown to facilitate degradation of TNF*α* mRNA in other cell types, suggesting that a similar mechanism may be present in Th1 cells. The RBP HuR has shown to increase the half-life of *il4* and *il13* mRNA to promote Th2 differentiation. Furthermore, HuR protected GATA3 from TTP-mediated degradation by blocking the ARE element present in GATA3 mRNA [97–99]. miRNA has also been linked to increased Th2 responses. Studies employing the use of asthma models have revealed that miR-19 and mIR-146a are able to enhance Th2 responses with elevated levels being detected in Th2 cytokine-secreting cells [100]. Elevated cytokine secretion was seen in cells that express miR-19 compared to miR-19-deficient cells that express high levels of GATA3. Ablation of miR-146a resulted in a skewing toward Th1/Th17 differentiation [101]. Other miRNAs act to increase the DNA-binding activity of GATA3 with mIR-126 targeting a negative regulator of GATA3 transcriptional activity [102]. Conversely, some miRNAs act to reduce Th2 differentiation directly with miR-340 destabilizing IL-4 mRNA or indirectly with miR-128 resulting in increased ubiquitin-mediated degradation of GATA3 through targeting of BMI1 [103].

Many studies in recent years have also demonstrated the importance of miRNA in regulating Th17 and T_{REG} differentiation and function. miR-21 facilitates TGF-β signaling pathway by targeting the negative regulator SMAD 7, which can enhance the generation of both cell types [104]. The STAT signaling activity in these cells is also under regulation of miR-155. mIR-155 is thought to enhance T_{REG} survival through attenuation of SOCS1, and inhibitor of STAT signaling to enhance STAT5 activity in T_{REG} cells [105]. This miRNA, however, has also been shown to be important for the IFNγ and IL-17 secretion in response to *H. Pylori* infection indicating that miRNA can play a role in both suppressing and driving inflammation [106]. In Th17 cells, miR-155 has not been shown to directly target RORγT or BATF mRNA; however, there is a significant reduction in *il17f*, *il17a*, and *il22* mRNA transcripts in the absence of miR-155 [107]. miR-326 has an indirect effect in enhancing Th17 differentiation by targeting ETS-1, a known negative regulator of the Th17 lineage [108]. Other miRNAs have been shown to have subset specific functions. Elevated expression of miR-10a is detected in both tT_{REG} and pT_{REG} cells. While ablation of miR-10a results in a slight reduction of Foxp3 levels in tT_{REG} cells, its expression is important in maintaining lineage commitment in pT_{REG} cells through degradation of Bcl-6 mRNA to inhibit conversion of these cells to a follicular T helper (Tfh) phenotype [109]. Other miRNAs are involved in modulating T_{REG} effector function. miR-466 l has been shown to mask ARE elements in the 3′ UTR of IL-10 mRNA to prevent degradation via TTP in other cell types, while the miR-17~92 cluster has been demonstrated to be necessary for the expansion of IL-10 secreting T_{REG} cells [110, 111]. Conversely, miR-210 is involved in the downregulation of Foxp3 expression and miR142-3p and miR-31 are known to target the cAMP generation pathways, inhibiting T_{REG} metabolism [112–114].

The study of mRNA stability has revealed a convoluted network of miRNA and RBPs while adding another layer of complexity to the transcription factor and epigenetic modifications

dictating CD4 + T cell subset differentiation and function. Due to the permissive nature of miRNA base pairing, further investigation is necessary to uncover the mechanism by which miRNA targets specific mRNA for degradation depending on the context a cell finds itself in.

5. The emerging role of differential mRNA translation in modulating CD4+ T cell functions

The accessibility of DNA, the activity of necessary transcription factors, and the mechanisms governing how long mRNA lasts in the cytosol are all key factors in determining the total abundance of specific mRNA transcripts within cells. Historically, techniques measuring RNA abundance including RT-PCR and microarrays have been used to identify how specific factors mediate their effect in CD4+ T cells through examination of their RNA signature. These transcriptional signatures have been useful in inferring the genes involved in giving CD4+ T cell subsets their diverse and specific functions in regulating the adaptive immune response to achieve a balance between necessary inflammatory functions for host protection without undue detrimental effects from over activity. However, studies in recent years have revealed discrepancies between mRNA transcript and protein levels within cells, suggesting that mechanisms controlling gene transcription and mRNA stability are insufficient to explain the full scope of regulatory mechanisms governing immune cell function [115, 116]. From a functional standpoint, translational regulation of gene expression offers several advantages in controlling immune responses. Thus, translational regulation of gene expression enables rapid integration of environmental cues to control protein activity, allows rapid onset and reversibility of the response by utilizing the existing mRNA pool within a cell, and forgoes the need for de novo mRNA synthesis. The advent of techniques to measure ribosome loading on individual mRNA transcripts has led to the identification of multiple genes in both the innate and adaptive immune systems that are regulated at the level of mRNA translation.

Studies in CD4+ T cells have shown distinct translational regulation regulating several key components of cell function. IL-2 is translationally repressed in naïve CD4+ T cells through inhibition of ribosome loading to prevent aberrant expression prior to TCR stimulation [117]. The MAPK-signal integrating kinase, Mnk1, has been shown to promote the translation of TNFα via phosphorylation of the translational silencer hnRNP A1, preventing its binding to TNFα mRNA [118]. Additionally, the rate of GATA3 translation is increased following the activation of the CD28 co-stimulatory pathway in CD4+ T cells without direct increase in GATA3 mRNA abundance, while IL-4 signaling can facilitate IL-4 translation in a similar manner [97, 119]. Recently, a genome-wide study examined the role of mRNA translational regulation in CD4+ T cell subsets [120]. The isolation of polyribosome-bound transcripts, enriched with highly translated mRNA transcripts and comparison with total cytosolic mRNA, identified distinct translational signatures differentiating T_{REG} and T_{EFF} cells. While there was little discrepancy in the translational signature of naïve unstimulated cells, TCR stimulation causes these subsets to acquire divergent translational programs. The identified translationally regulated mRNAs were found to be co-regulated in groups corresponding to

specific biological processes. Among these, the genes involved in cell cycle progression were found to be translationally silenced in TCR-stimulated T_{REG} cells compared to T_{EFF} cells. Within this group of genes, there was a significant reduction in the translation of the eukaryotic translation initiation factor, eIF4E.

eIF4E is a key component of the eIF4F translation initiation complex responsible for binding the 5′CAP of mRNA to initiate ribosome assembly and mRNA translation. eIF4E is necessary for the translation of many genes encoding for proliferation, survival, and cell cycle progression [121]. During homeostatic conditions, the eIF4E-binding proteins, eIF4E-BP1 and 2, bind and sequester eIF4E. Growth factors, hormones, or cytokines signaling through the PI3K/AKT axis activate the mammalian target of rapamycin (mTOR). Activation of the mTOR pathway results in the phosphorylation of eiF4E-BP and the release of eIF4E into the cytosol, allowing for eIF4E-mediated translation. Consistent with the translational silencing of eIF4E in T_{REG} cells, mTOR gene deficiency or inhibition can abrogate the proliferation and differentiation of Th1, Th2, or Th17 cells, while promoting Foxp3 expression and adopting a T_{REG} phenotype [122]. In line with this, inhibition of eIF4E activity in CD4+ T cells abrogated their proliferation in response to TCR stimulation in the presence of IL-2 [120]. Surprisingly, inhibition of eIF4E activity in activated T_{EFF} cells also resulted in the induction of Foxp3 expression in a subset of cells, suggesting that modulation of eIF4E expression may impact CD4+ T cell lineage identity, with translational silencing of eIF4E being required for T_{REG} stability.

The study of mRNA translation regulation is an emerging concept in the study of CD4+ T cell function, offering a new perspective on the regulation of the complicated gene-expression programs found in CD4+ T cells. Further investigation is necessary to understand how CD4+ T cells can integrate environmental signals to fine tune a transcriptional landscape to modulate function without undoing the complex transcriptional and epigenetic changes necessary to acquire their specialized functions in the first place.

6. Conclusion

Several post-transcriptional mechanisms regulate gene expression for many key aspects of T cell activation, differentiation, and effector functions. During immune responses, the rapid induction and termination of various immune cell effector activities must be controlled in a timely and efficient manner to prevent the adverse consequences of pathologic inflammation. To achieve this fine control of biological responses, transcriptional mechanisms play an essential role for the regulation of gene expression. Moreover, many post-transcriptional mechanisms, including translational control of gene expression, are particularly advantageous to a cell as it integrates inflammatory signals with rapid and context-dependent protein synthesis and effector responses without the energy expenditures associated with time-consuming *de novo* mRNA synthesis. Recent single gene or genome-wide approaches highlight how post-transcriptional mechanisms control gene expression in various innate and adaptive cell types and potentiate a modular regulation of gene expression for a more efficient response to cellular activation and environmental cues.

The past decade has witnessed a rapid rise in research on post-transcriptional mechanisms directing gene expression programs in innate immune cells. However, the mechanisms underlying the regulation of adaptive immunity still remain poorly defined. For instance, uncovering the regulatory steps that control gene expression events during cell function in CD4+ T cell subsets, key orchestrators of adaptive immunity, may shed light into the identification of novel immune "checkpoints" and therapeutic applications. Unraveling the molecular definition of key pathways involved in T cell proliferation or differentiation, promotion of Foxp3+ T_{REG} activities in metastatic tumors, or those that induce pathogenic T cell lineages in autoimmune diseases, for example, could allow for the development of novel therapies to restore immune quiescence.

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References

[1] Shah DK, Zúñiga-Pflücker JC. An overview of the intrathymic intricacies of T Cell development. The Journal of Immunology. 2014;**192**:4017-4023

[2] Grenningloh R, Tai T-S, Frahm N, Hongo TC, Chicoine AT, Brander C, et al. Ets-1 maintains IL-7 receptor expression in peripheral T cells. The Journal of Immunology. 2011;**186**:969-976

[3] Lee H-C, Shibata H, Ogawa S, Maki K, Ikuta K. Transcriptional regulation of the mouse IL-7 receptor α promoter by glucocorticoid receptor. The Journal of Immunology. 2005; **174**:7800-7806

[4] Carrette F, Surh CD. IL-7 signaling and CD127 receptor regulation in the control of T cell homeostasis. Seminars in Immunology. 2012;**24**(3):209-217

[5] Neal JW, Clipstone NA. Glycogen synthase kinase-3 inhibits the DNA binding activity of NFATc. Journal of Biological Chemistry. 2001;**276**(5):3666-3673

[6] Okamura H, Garcia-Rodriguez C, Martinson H, Qin J, Virshup DM, Rao A. A conserved docking motif for CK1 binding controls the nuclear localization of NFAT1. Molecular and cellular biology. 2004;**24**(10):4184-4195

[7] Im S-H, Rao A. Activation and deactivation of gene expression by Ca 2+/calcineurin-NFAT-mediated signaling. Molecules & Cells (Springer Science & Business Media BV). 2004;**18**(1):1-9

[8] McGuire KL, Iacobelli M. Involvement of Rel, Fos, and Jun proteins in binding activity to the IL-2 promoter CD28 response element/AP-1 sequence in human T cells. The Journal of Immunology. 1997;**159**:1319-1327

[9] Nakajima H, Liu X-W, Wynshaw-Boris A, Rosenthal LA, Imada K, Finbloom DS, et al. An indirect effect of Stat5a in IL-2–induced proliferation: A critical role for STAT5A in IL-2–mediated IL-2 receptor α chain induction. Immunity. 1997;**7**(5):691-701

[10] Xue H-H, Kovanen PE, Pise-Masison CA, Berg M, Radovich MF, Brady JN, et al. IL-2 negatively regulates IL-7 receptor α chain expression in activated T lymphocytes. Proceedings of the National Academy of Sciences. 2002;**99**(21):13,759-13,764

[11] Jeremias I, Kupatt C, Baumann B, Herr I, Wirth T, Debatin KM. Inhibition of nuclear factor κB activation attenuates apoptosis resistance in lymphoid cells. Blood. 1998;**91**: 4624-4631

[12] Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations. Annual review of immunology. 2010;**28**:445-489

[13] Oh H, Ghosh S. NF-κB: Roles and regulation in different CD4(+) T cell subsets. Immunological Reviews. 2013;**252**(1):41-51

[14] Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine. 2015;**74**(1):5-17

[15] Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 2000;**100**(6):655-669

[16] Afkarian M, Sedy JR, Yang J, Jacobson NG, Cereb N, Yang SY, et al. T-bet is a STAT1-induced regulator of IL-12R expression in naive CD4+ T cells. Nature Immunology. 2002;**3**(6)

[17] Schulz EG, Mariani L, Radbruch A, Höfer T. Sequential polarization and imprinting of type 1 T helper lymphocytes by interferon-γ and interleukin-12. Immunity. 2009;**30**(5): 673-683

[18] Mullen AC, Hutchins AS, High FA, Lee HW, Sykes KJ, Chodosh LA, et al. Hlx is induced by and genetically interacts with T-bet to promote heritable TH1 gene induction. Nature Immunology. 2002;**3**(7):652-659

[19] Djuretic IM, Levanon D, Negreanu V, Groner Y, Rao A, Ansel KM. Transcription factors T-bet and Runx3 cooperate to activate Ifng and silence Il4 in T helper type 1 cells. Nature Immunology. 2007;**8**(2):1-11

[20] Sekimata M, Pérez-Melgosa M, Miller SA, Weinmann AS, Sabo PJ, Sandstrom R, et al. CCCTC-binding factor and the transcription factor T-bet orchestrate T helper 1 cell-specific structure and function at the interferon-γ locus. Immunity. 2009;**31**(4):551-564

[21] Balasubramani A, Shibata Y, Crawford GE, Baldwin AS, Hatton RD, Weaver CT. Modular utilization of distal cis-regulatory elements controls ifng gene expression in T cells activated by distinct stimuli. Immunity. 2010;**33**(1):35-47

[22] Lee DU, Avni O, Chen L, Rao A. A Distal Enhancer in the Interferon-γ (IFN-γ) Locus Revealed by Genome Sequence Comparison. Journal of Biological Chemistry. 2004; **279**(6):4802-4810

[23] Feske S, Giltnane J, Dolmetsch R, Staudt LM, Rao A. Gene regulation mediated by calcium signals in T lymphocytes. Nature Immunology. 2001;**2**(4):316-324

[24] Lord GM, Rao RM, Choe H, Sullivan BM, Lichtman AH, Luscinskas FW, et al. T-bet is required for optimal proinflammatory CD4(+) T-cell trafficking. Blood. 2005;**106**(10): 3432-3439

[25] O'Shea JJ, Ma A, Lipsky P. Cytokines and autoimmunity. Nature Reviews Immunology 2002;**2**(1):37-45

[26] Ho IC, Tai T-S, Pai S-Y. GATA3 and the T-cell lineage: essential functions before and after T-helper-2-cell differentiation. Nature Reviews Immunology. 2009;**9**(2):125-135

[27] Zheng W-P, Flavell RA. The transcription factor GATA-3 Is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. Cell. 1997;**89**(4):587-596

[28] Fang TC, Yashiro-Ohtani Y, Del Bianco C, Knoblock DM, Blacklow SC, Pear WS. Notch directly regulates Gata3 expression during T helper 2 cell differentiation. Immunity. 2007;**27**(1):100-110

[29] Ouyang W, Löhning M, Gao Z, Assenmacher M, Ranganath S, Radbruch A, et al. Stat6-independent GATA-3 autoactivation directs IL-4-independent Th2 development and commitment. Immunity. 2000;**12**(1):27-37

[30] Gilmour J, Lavender P. Control of IL-4 expression in T helper 1 and 2 cells. Immunology. 2008;**124**(4):437-444

[31] Corn RA, Hunter C, Liou H-C, Siebenlist U, Boothby MR. Opposing Roles for RelB and Bcl-3 in Regulation of T-Box Expressed in T Cells, GATA-3, and Th Effector Differentiation. The Journal of Immunology. 2005;**175**(4):2102

[32] Das J, Chen C-H, Yang L, Cohn L, Ray P, Ray A. A critical role for NF-[kappa]B in Gata3 expression and TH2 differentiation in allergic airway inflammation. Nature Immunology. 2001;**2**(1):45-50

[33] Rengarajan J, Mowen KA, McBride KD, Smith ED, Singh H, Glimcher LH. Interferon regulatory factor 4 (IRF4) interacts with NFATc2 to modulate interleukin 4 gene expression. The Journal of Experimental Medicine. 2002;**195**(8):1003-1012

[34] Usui T, Nishikomori R, Kitani A, Strober W. GATA-3 suppresses Th1 development by downregulation of STAT4 and not through effects on IL-12Rβ2 chain or T-bet. Immunity. 2003;**18**(3):415-428

[35] Manel N, Unutmaz D, Littman DR. The differentiation of human TH-17 cells requires transforming growth factor-[beta] and induction of the nuclear receptor ROR[gamma]t. Nature Immunology 2008;**9**(6):641-649

[36] Chen C-H, Seguin-Devaux C, Burke NA, Oriss TB, Watkins SC, Clipstone N, et al. Transforming growth factor β blocks Tec kinase phosphorylation, Ca2+ influx, and NFATc translocation causing inhibition of T cell differentiation. Journal of Experimental Medicine. 2003;**197**(12):1689-1699

[37] Ivanov II, Zhou L, Littman DR. Transcriptional regulation of Th17 cell differentiation. Seminars in immunology. 2007;**19**(6):409-417

[38] Zhou L, Lopes JE, Chong MMW, Ivanov II, Min R, Victora GD, et al. TGF-[bgr]-induced Foxp3 inhibits TH17 cell differentiation by antagonizing ROR[ggr]t function. Nature. 2008;**453**(7192):236-240

[39] Korn T, Mitsdoerffer M, Croxford AL, Awasthi A, Dardalhon VA, Galileos G, et al. IL-6 controls Th17 immunity in vivo by inhibiting the conversion of conventional T cells into Foxp3+ regulatory T cells. Proceedings of the National Academy of Sciences. 2008; **105**(47):18,460-18,465

[40] Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T, et al. IL-6 programs TH-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nature Immunology. 2007;**8**(9):967-974

[41] Huang W, Thomas B, Flynn RA, Gavzy SJ, Wu L, Kim SV, et al. DDX5 and its associated lncRNA Rmrp modulate Th17 cell effector functions. Nature. 2015;**528**(7583):517-522

[42] Schraml BU, Hildner K, Ise W, Lee W-L, Smith WAE, Solomon B, et al. The AP-1 transcription factor Batf controls T(H)17 differentiation. Nature. 2009;**460**(7253):405-409

[43] Bin Dhuban K, Kornete M, S Mason E, Piccirillo CA. Functional dynamics of Foxp3+ regulatory T cells in mice and humans. Immunological Reviews. 2014;**259**(1):140-158

[44] Maruyama T, Konkel JE, Zamarron BF, Chen W. The molecular mechanisms of Foxp3 gene regulation. Seminars in Immunology. 2011;**23**(6):418-423

[45] Isomura I, Palmer S, Grumont RJ, Bunting K, Hoyne G, Wilkinson N, et al. c-Rel is required for the development of thymic Foxp3⁺ CD4 regulatory T cells. The Journal of Experimental Medicine. 2009;**206**(13):3001

[46] Ouyang W, Beckett O, Ma Q, Paik J-h, DePinho RA, Li MO. Foxo proteins cooperatively control the differentiation of Foxp3+ regulatory T cells. Nature Immunology. 2010;**11**(7): 618-627

[47] Tone Y, Furuuchi K, Kojima Y, Tykocinski ML, Greene MI, Tone M. Smad3 and NFAT cooperate to induce Foxp3 expression through its enhancer. Nature immunology. 2008; **9**(2):194-202

[48] Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science. 2003;**299**:1057-1061

[49] Wu Y, Borde M, Heissmeyer V, Feuerer M, Lapan AD, Stroud JC, et al. FOXP3 controls regulatory T cell function through cooperation with NFAT. Cell. 2006;**126**(2):375-387

[50] Pan F, Yu H, Dang EV, Barbi J, Pan X, Grosso JF, et al. Eos mediates Foxp3-dependent gene silencing in regulatory T cells. Science (New York, NY). 2009;**325**(5944):1142-1146

[51] Borsellino G, Kleinewietfeld M, Di Mitri D, Sternjak A, Diamantini A, Giometto R, et al. Expression of ectonucleotidase CD39 by Foxp3+ Treg cells: hydrolysis of extracellular ATP and immune suppression. Blood. 2007;**110**(4):1225

[52] Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, et al. CTLA-4 Control over Foxp3⁺ regulatory T cell function. Science. 2008; **322**(5899):271

[53] Josefowicz SZ, Lu L-F, Rudensky AY. Regulatory T cells: Mechanisms of differentiation and function. Annual Review Of Immunology. 2012;**30**:531-564

[54] Zhou X, Bailey-Bucktrout SL, Jeker LT, Penaranda C, Martínez-Llordella M, Ashby M, et al. Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells in vivo. Nature Immunology. 2009;**10**(9):1000-1007

[55] Bird A. DNA methylation patterns and epigenetic memory. Genes & Development. 2002;**16**(1):6-21

[56] Fatemi M, Hermann A, Gowher H, Jeltsch A. Dnmt3a and Dnmt1 functionally cooperate during de novo methylation of DNA. The FEBS Journal. 2002;**269**(20):4981-4984

[57] Kohli RM, Zhang Y. TET enzymes, TDG and the dynamics of DNA demethylation. Nature. 2013;**502**(7472):472

[58] Patel DJ. A Structural Perspective on Readout of Epigenetic Histone and DNA Methylation Marks. Cold Spring Harbor Perspectives in Biology. 2016;**8**(3):a018754

[59] Crawford GE, Holt IE, Mullikin JC, Tai D, Center NIoHIS, Green ED, et al. Identifying gene regulatory elements by genome-wide recovery of DNase hypersensitive sites. Proceedings of the National Academy of Sciences of the United States of America. 2004; **101**(4):992-997

[60] Du J, Johnson LM, Jacobsen SE, Patel DJ. DNA methylation pathways and their crosstalk with histone methylation. Nature Reviews Molecular Cell Biology. 2015;**16**(9):519

[61] Agarwal S, Rao A. Modulation of chromatin structure regulates cytokine gene expression during T cell differentiation. Immunity. 1998;**9**(6):765-775

[62] Thomas RM, Gamper CJ, Ladle BH, Powell JD, Wells AD. De novo DNA methylation is required to restrict T helper lineage plasticity. Journal of Biological Chemistry. 2012; **287**(27):22,900-22,909

[63] Shi M, Lin TH, Appell KC, Berg LJ. Jak3-dependent signals induce chromatin remodeling at the Ifng locus during Th1 differentiation. Immunity. 2008;**28**(6):763-773

[64] Tong Y, Aune T, Boothby M. T-bet antagonizes mSin3a recruitment and transactivates a fully methylated IFN-γ promoter via a conserved T-box half-site. Proceedings of the National Academy of Sciences of the United States of America. 2005; **102**(6):2034-2039

[65] Miller SA, Huang AC, Miazgowicz MM, Brassil MM, Weinmann AS. Coordinated but physically separable interaction with H3K27-demethylase and H3K4-methyltransferase activities are required for T-box protein-mediated activation of developmental gene expression. Genes & Development. 2008;**22**(21):2980-2993

[66] Lee DU, Agarwal S, Rao A. Th2 lineage commitment and efficient IL-4 production involves extended demethylation of the IL-4 gene. Immunity. 2002;**16**(5):649-660

[67] Makar KW, Perez-Melgosa M, Shnyreva M, Weaver WM, Fitzpatrick DR, Wilson CB. Active recruitment of DNA methyltransferases regulates interleukin 4 in thymocytes and T cells. Nature Immunology. 2003;**4**(12):1183-1190

[68] Onodera A, Yamashita M, Endo Y, Kuwahara M, Tofukuji S, Hosokawa H, et al. STAT6-mediated displacement of polycomb by trithorax complex establishes long-term maintenance of GATA3 expression in T helper type 2 cells. The Journal of Experimental Medicine. 2010;**207**(11):2493-2506

[69] Tykocinski L-O, Hajkova P, Chang H-D, Stamm T, SÖzeri O, LÖhning M, et al. A critical control element for interleukin-4 memory expression in T helper lymphocytes. Journal of Biological Chemistry. 2005;**280**(31):28,177-28,185

[70] Hosokawa H, Tanaka T, Suzuki Y, Iwamura C, Ohkubo S, Endoh K, et al. Functionally distinct Gata3/Chd4 complexes coordinately establish T helper 2 (Th2) cell identity. Proceedings of the National Academy of Sciences. 2013;**110**(12):4691-4696

[71] Akimzhanov AM, Yang XO, Dong C. Chromatin remodeling of interleukin-17 (IL-17)-IL-17F cytokine gene locus during inflammatory helper T cell differentiation. Journal of Biological Chemistry. 2007;**282**(9):5969-5972

[72] Bending D, Newland S, Krejčí A, Phillips JM, Bray S, Cooke A. Epigenetic changes at Il12rb2 and Tbx21 in relation to plasticity behavior of Th17 Cells. The Journal of Immunology. 2011;**186**(6):3373-3382

[73] Polansky JK, Kretschmer K, Freyer J, Floess S, Garbe A, Baron U, et al. DNA methylation controls Foxp3 gene expression. European Journal of Immunology. 2008;**38**(6): 1654-1663

[74] Povoleri GAM, Scottà C, Nova-Lamperti EA, John S, Lombardi G, Afzali B. Thymic versus induced regulatory T cells–who regulates the regulators? Frontiers in Immunology. 2013;**4**:169

[75] Ohkura N, Hamaguchi M, Morikawa H, Sugimura K, Tanaka A, Ito Y, et al. T cell receptor stimulation-induced epigenetic changes and Foxp3 expression are independent and complementary events required for Treg cell development. Immunity. 2012;**37**(5): 785-799

[76] Zheng Q, Xu Y, Liu Y, Zhang B, Li X, Guo F, et al. Induction of Foxp3 demethylation increases regulatory CD4+ CD25+ T cells and prevents the occurrence of diabetes in mice. Journal of Molecular Medicine. 2009;**87**(12):1191

[77] HODGE DR, CHO E, COPELAND TD, GUSZCZYNSKI T, YANG E, SETH AK, et al. IL-6 enhances the nuclear translocation of DNA cytosine-5-methyltransferase 1 (DNMT1) via phosphorylation of the nuclear localization sequence by the AKT kinase. Cancer Genomics-Proteomics. 2007;**4**(6):387-398

[78] Wang L, Liu Y, Han R, Beier UH, Thomas RM, Wells AD, et al. Mbd2 promotes Foxp3 demethylation and T-regulatory-cell function. Molecular and Cellular Biology. 2013; **33**(20):4106-4115

[79] Piqué M, López JM, Foissac S, Guigó R, Méndez R. A combinatorial code for CPE-mediated translational control. Cell. 2008;**132**(3):434-448

[80] Anderson P. Post-transcriptional regulons coordinate the initiation and resolution of inflammation. Nature Reviews Immunology. 2010;**10**(1):24-35

[81] Cai Y, Yu X, Hu S, Yu J. A brief review on the mechanisms of miRNA regulation. Genomics, Proteomics & Bioinformatics. 2009;**7**(4):147-154

[82] Mathieu E-L, Belhocine M, Dao L, Puthier D, Spicuglia S. Functions of lncRNA in development and diseases. Medecine Sciences: M/S. 2014;**30**(8-9):790

[83] Muljo SA, Ansel KM, Kanellopoulou C, Livingston DM, Rao A, Rajewsky K. Aberrant T cell differentiation in the absence of Dicer. Journal of Experimental Medicine. 2005; **202**(2):261-269

[84] Xiao C, Srinivasan L, Calado DP, Patterson HC, Zhang B, Wang J, et al. Lymphoproliferative disease and autoimmunity in mice with elevated miR-17− 92 expression in lymphocytes. Nature immunology. 2008;**9**(4):405

[85] Li Q-J, Chau J, Ebert PJ, Sylvester G, Min H, Liu G, et al. miR-181a is an intrinsic modulator of T cell sensitivity and selection. Cell. 2007;**129**(1):147-161

[86] Pan W, Zhu S, Yuan M, Cui H, Wang L, Luo X, et al. MicroRNA-21 and microRNA-148a contribute to DNA hypomethylation in lupus CD4+ T cells by directly and indirectly targeting DNA methyltransferase 1. The Journal of Immunology. 2010;**184**(12):6773-6781

[87] Xue Q, Guo Z-Y, Li W, Wen W-H, Meng Y-L, Jia L-T, et al. Human activated CD4+ T lymphocytes increase IL-2 expression by downregulating microRNA-181c. Molecular Immunology. 2011;**48**(4):592-599

[88] Rossi RL, Rossetti G, Wenandy L, Curti S, Ripamonti A, Bonnal RJ, et al. Distinct microRNA signatures in human lymphocyte subsets and enforcement of the naive state in CD4+ T cells by the microRNA miR-125b. Nature Immunology. 2011;**12**(8):796-803

[89] Sandberg R, Neilson JR, Sarma A, Sharp PA, Burge CB. Proliferating cells express mRNAs with shortened 39 untranslated regions and fewer microRNA target sites. Science. 2008;**320**(5883):1643-1647

[90] Glascock J, Techasintana P, Magee J, Atasoy U. RNA-binding protein HuR controls IL-2 homeostasis in activated T cells by regulating CD25 expression (CCR3P.202). The Journal of Immunology. 2015;**194**(1 Supplement):49.3-.3

[91] Rodriguez A, Vigorito E, Clare S, Warren MV, Couttet P, Soond DR, et al. Requirement of bic/microRNA-155 for normal immune function. Science. 2007;**316**(5824):608-611

[92] Fedeli M, Riba M, Garcia Manteiga JM, Tian L, Viganò V, Rossetti G, et al. miR-17 ~ 92 family clusters control iNKT cell ontogenesis via modulation of TGF-β signaling. Proceedings of the National Academy of Sciences. 2016;**113**(51):E8286-E8E95

[93] Dews M, Fox JL, Hultine S, Sundaram P, Wang W, Liu YY, et al. Myc - miR-17~92 axis blunts TGFβ signaling and production of multiple TGFβ-dependent anti-angiogenic factors. Cancer Research. 2010;**70**(20):8233-8246

[94] Fu D, Yu W, Li M, Wang H, Liu D, Song X, et al. MicroRNA-138 regulates the balance of Th1/Th2 via targeting RUNX3 in psoriasis. Immunology Letters. 2015;**166**(1):55-62

[95] Steiner DF, Thomas MF, Hu JK, Yang Z, Babiarz JE, Allen CD, et al. MicroRNA-29 regulates T-box transcription factors and interferon-γ production in helper T cells. Immunity. 2011;**35**(2):169-181

[96] Ogilvie RL, SternJohn JR, Rattenbacher B, Vlasova IA, Williams DA, Hau HH, et al. Tristetraprolin mediates interferon-γ mRNA decay. Journal of Biological Chemistry. 2009;**284**(17):11,216-11,223

[97] Yarovinsky TO, Butler NS, Monick MM, Hunninghake GW. Early Exposure to IL-4 stabilizes IL-4 mRNA in CD4+ T cells via RNA-binding protein HuR. The Journal of Immunology. 2006;**177**(7):4426-4435

[98] Hosokawa H, Kimura MY, Shinnakasu R, Suzuki A, Miki T, Koseki H, et al. Regulation of Th2 cell development by polycomb group gene bmi-1 through the stabilization of GATA3. The Journal of Immunology. 2006;**177**(11):7656-7664

[99] Casolaro V, Fang X, Tancowny B, Fan J, Wu F, Srikantan S, et al. Posttranscriptional regulation of IL-13 in T cells: Role of the RNA-binding protein HuR. The Journal of Allergy And Clinical Immunology. 2008;**121**(4):853-859.e4

[100] Simpson LJ, Patel S, Bhakta NR, Choy DF, Brightbill HD, Ren X, et al. A microRNA upregulated in asthma airway T cells promotes TH2 cytokine production. Nature Immunology. 2014;**15**(12):1162-1170

[101] Okoye IS, Czieso S, Ktistaki E, Roderick K, Coomes SM, Pelly VS, et al. Transcriptomics identified a critical role for Th2 cell-intrinsic miR-155 in mediating allergy and antihelminth immunity. Proceedings of the National Academy of Sciences of the United States of America. 2014;**111**(30):E3081-E3090

[102] Mattes J, Collison A, Plank M, Phipps S, Foster PS. Antagonism of microRNA-126 suppresses the effector function of TH2 cells and the development of allergic airways disease. Proceedings of the National Academy of Sciences. 2009;**106**(44):18,704-118709

[103] Guerau-de-Arellano M, Smith KM, Godlewski J, Liu Y, Winger R, Lawler SE, et al. Micro-RNA dysregulation in multiple sclerosis favors pro-inflammatory T-cell-mediated autoimmunity. Brain. 2011;**134**(12):3575-3586

[104] Murugaiyan G, da Cunha AP, Ajay AK, Joller N, Garo LP, Kumaradevan S, et al. MicroRNA-21 promotes Th17 differentiation and mediates experimental autoimmune encephalomyelitis. The Journal of Clinical Investigation. 2015;**125**(3):1069

[105] Lu L-F, Thai T-H, Calado DP, Chaudhry A, Kubo M, Tanaka K, et al. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. Immunity. 2009;**30**(1):80-91

[106] Oertli M, Engler DB, Kohler E, Koch M, Meyer TF, Müller A. MicroRNA-155 is essential for the T cell-mediated control of Helicobacter pylori infection and for the induction of chronic gastritis and colitis. The Journal of Immunology. 2011;**187**(7):3578-3586

[107] Escobar Thelma M, Kanellopoulou C, Kugler David G, Kilaru G, Nguyen Cuong K, Nagarajan V, et al. miR-155 activates cytokine gene expression in Th17 cells by regulating the DNA-binding protein Jarid2 to relieve polycomb-mediated repression. Immunity. 2014;**40**(6):865-879

[108] Du C, Liu C, Kang J, Zhao G, Ye Z, Huang S, et al. MicroRNA miR-326 regulates TH-17 differentiation and is associated with the pathogenesis of multiple sclerosis. Nature Immunology. 2009;**10**(12):1252-1259

[109] Takahashi H, Kanno T, Nakayamada S, Hirahara K, Sciumè G, Muljo SA, et al. TGF-[beta] and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells. Nature Immunology. 2012;**13**(6):587-595

[110] Ma F, Liu X, Li D, Wang P, Li N, Lu L, et al. MicroRNA-466 l upregulates IL-10 expression in TLR-triggered macrophages by antagonizing RNA-binding protein tristetraprolin-mediated IL-10 mRNA degradation. The Journal of Immunology. 2010; **184**(11):6053-6059

[111] de Kouchkovsky D, Esensten JH, Rosenthal WL, Morar MM, Bluestone JA, Jeker LT. microRNA-17–92 regulates IL-10 production by regulatory T cells and control of experimental autoimmune encephalomyelitis. Journal of Immunology (Baltimore, Md: 1950). 2013;**191**(4):1594-1605

[112] Fayyad-Kazan H, Rouas R, Fayyad-Kazan M, Badran R, El Zein N, Lewalle P, et al. MicroRNA profile of circulating CD4-positive regulatory T cells in human adults and impact of differentially expressed microRNAs on expression of two genes essential to their function. Journal of Biological Chemistry. 2012;**287**(13):9910-9922

[113] Huang B, Zhao J, Lei Z, Shen S, Li D, Shen G-X, et al. miR-142-3p restricts cAMP production in CD4(+)CD25(−) T cells and CD4(+)CD25(+) T(REG) cells by targeting AC9 mRNA. EMBO Reports. 2009;**10**(2):180-185

[114] Rouas R, Fayyad-Kazan H, El Zein N, Lewalle P, Rothé F, Simion A, et al. Human natural Treg microRNA signature: Role of microRNA-31 and microRNA-21 in FOXP3 expression. European Journal of Immunology. 2009;**39**(6):1608-1618

[115] Kristensen AR, Gsponer J, Foster LJ. Protein synthesis rate is the predominant regulator of protein expression during differentiation. Molecular Systems Biology. 2013;**9**(1):689

[116] Schwanhäusser B, Busse D, Li N, Dittmar G, Schuchhardt J, Wolf J, et al. Global quantification of mammalian gene expression control. Nature. 2011;**473**(7347):337-342

[117] Garcia-Sanz JA, Lenig D. Translational control of interleukin 2 messenger RNA as a molecular mechanism of T cell anergy. The Journal of Experimental Medicine. 1996; **184**(1):159-164

[118] Buxadé M, Parra JL, Rousseau S, Shpiro N, Marquez R, Morrice N, et al. The Mnks are novel components in the control of TNFα biosynthesis and phosphorylate and regulate hnRNP A1. Immunity. 2005;**23**(2):177-189

[119] Cook KD, Miller J. TCR-dependent translational control of GATA-3 enhances Th2 differentiation. The Journal of Immunology. 2010;**185**(6):3209-3216

[120] Bjur E, Larsson O, Yurchenko E, Zheng L, Gandin V, Topisirovic I, et al. Distinct translational control in CD4+ T cell subsets. PLoS Genetics. 2013;**9**(5) e1003494

[121] Mamane Y, Petroulakis E, Rong L, Yoshida K, Lian Wee Ler K, Sonenberg N. eIF4E-from translation to transformation. Oncogene. 2004;**23**(18):3172-3179

[122] Delgoffe GM, Kole TP, Zheng Y, Zarek PE, Matthews KL, Xiao B, et al. The mTOR kinase differentially regulates effector and regulatory T cell lineage commitment. Immunity. 2009;**30**(6):832-844

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