**HIGHLIGHTS**

**REVIEW**

**T cells at work: How post-transcriptional mechanisms control T cell homeostasis and activation**

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T cells are central players of the adaptive immune system by protecting us from recurring infections and by killing malignant cells. Protective T cell responses rely on the concerted production of effector molecules such as cytolytic mediators, granzymes, and perforins, as well as pro-inflammatory cytokines and chemokines. Once activated, T cells drastically change their gene expression and rapidly respond to insults by producing ample amounts of effector molecules. In the absence of antigen, T cells remain in a quiescent state and survey our body for possible pathogenic insults. Resting T cells are, however, not inert, but continuously regulate their protein production to survive and to be prepared for possible re-infections. Here, we review our current knowledge on the regulation of gene expression in activated and quiescent T cells. We specifically focus on post-transcriptional mechanisms that define the protein output and that allow dormant cells to undergo active signaling and selective translation, keeping them poised for activation. Finally, we discuss which signals drive T cell survival and their preparedness to respond to insults and which mechanisms are involved in these processes.

**Keywords:** post-transcriptional regulation · quiescence · proteome · RNA binding proteins · T cell activation

**Introduction**

T cells are critical in our defense against pathogens and malignancies. Whereas CD8⁺ T cells are poised to kill target cells by secreting effector molecules such as granzymes and perforins, chemokines and pro-inflammatory cytokines, CD4⁺ T cells produce ample amounts of cytokines and chemokines to support other cell types in their antipathogenic and antitumoral responses. To exert their effector function, T cells must swiftly respond to activation cues, and this rapid response requires a substantial rewiring of their gene expression profile. Upon activation, T cells need to alter their overall protein make-up, allowing them to exit their quiescent state and to become bona fide effector T cells. These alterations in gene expression allow for the production of proteins that mediate signal transduction, cell growth, division, and T cell differentiation [1–3].

Nevertheless, most T cells in our body are in a quiescent state. This includes naïve T cells that have not yet encountered their cognate antigen and memory T cells that are ready to respond to re-infections. In the past years, it has become evident that the quiescent state of T cells requires active gene regulation. In fact, T cells continuously receive low level of signals, which, although not essential for their survival, secures their homeostasis and active suppression of activation-associated genes [4–6]. At the same time, quiescent T cells are poised for the rapid proteome remodeling occurring upon activation.

The rewiring of activated T cells and the preservation of T cell quiescence requires extensive regulatory mechanisms, including...
epigenetic, transcriptional and metabolic switches [7]. Another critical layer that defines T cell rewiring and that maintains T cell quiescence is post-transcriptional regulation (PTR). PTR determines the protein output by regulating RNA splicing, RNA localization, mRNA stability and by regulating translation from mRNA into proteins [8–10]. Furthermore, effective translation of proteins is determined by the availability of tRNAs, energy, and the ribosomal machinery [11,12].

mRNA stability, mRNA localization and translation of the mRNA is determined by regulatory sequences and structures in the mRNA, both in the coding region and in the untranslated regions (UTRs), to which RNA-binding proteins (RBPs) or microRNAs can bind. In particular RBPs have recently regained interest in their capacity to drive gene expression in T cells [13]. RBPs encompass several thousand proteins, which modulate the fate of mRNA and regulate translation [14].

In this review, we will discuss how post-transcriptional mechanisms determine the protein make-up in activated and quiescent T cells and summarize our current knowledge on the signals that drive these post-transcriptional events.

Requirements for T cell priming and T cell activation

Priming of naïve T cells requires three signals, i.e., the engagement of the T cell receptor (TCR) with the cognate MHC-peptide complex, costimulatory signals such as CD28 and CD40, and cytokines released by antigen presenting cells (APCs) that drive T cell differentiation [15,16]. The reactivation of memory T cells—whether located in secondary lymphoid organs or in the periphery as tissue-resident T cells—also requires activation through the TCR, but is less dependent on co-stimulation or cytokines [17]. Both priming and activation allows T cells to exit the quiescent state. This change from quiescent to effector T cell is driven by a profound remodeling of the proteome, which is required for T cells to respond to IL-2 signaling, enter the cell cycle, increase nutrient uptake, remodel mitochondrial function, and to produce effector molecules [1,3,18,19]. To meet the high energy demand, activated T cells modify their metabolism, which includes an increased uptake of glucose, amino acids and fatty acids and a switch from oxidative phosphorylation to aerobic glycolysis [20–23].

Proteome remodeling upon T cell activation

A remarkable feature of T cell priming and activation is the substantial increase of proteins per cell [1–3,24–27]. Murine naïve CD8+ T cells that were activated for 24 h through the TCR tripled their protein amount [2,28]. This translated into an increase in copy numbers for over 6,000 proteins and an increase in cellular concentration for over 3,000 proteins [2]. Likewise, human effector and memory CD8+ T cells double their protein content per cell after 4 h of activation [1,25]. Thus, T cell activation substantially alters the proteome landscape of T cells.

Kinetics studies of the proteome provided insights how protein production is regulated to control T cell activation [2,24,29]. At 4 h after activation of both murine and human naïve CD4+ T cells, many regulatory molecules are produced. In murine T cells this includes transcription factors (JUNB, MYC), RNA binding proteins (ZFP36), and immediate early genes (BTG2/TOB) [24,29]. Also the “classical” early activation markers CD69, CD25, CD44, and the effector molecules TNF-α, IFN-γ, IL-2, Granulysin A, and Granzyme B were produced already at this time point in both murine and human T cells [1,24,29]. At 9 h of murine T cell activation, many metabolic proteins such as those involved in glycolysis, the pentose phosphate pathway, oxidative phosphorylation, and the TCA cycle were upregulated, suggesting that at this time point metabolic rewiring occurs [2,24]. Notably, not all proteins show an increase in abundance, as gene products involved in maintaining T cell quiescence are rapidly downregulated [2,3,29]. This includes CD62L, Kruppel-like family transcription factors 2 and 3 (KLF2 and KLF3), and sphingosine-1-phosphate receptor 1 (SIPR1) at 2 h of activation, and IL7RA, FOXO1, the TCRα, FAM65B, and TCF-1 at 6–9 h of activation of both murine and human T cells [1,2,29]. This dynamic rearrangement of the proteome is thus critical to tightly control the intricate regulatory networks that allow the exit of T cells from quiescence.

Increase in translation efficiency alters the protein content in activated T cells

T cell activation requires large amounts of energy, i.e., glucose, amino acids and fatty acids. To meet this high energy demand, the mitochondrial respiratory capacity increases by 10-fold [24]. The numbers of mitochondria increase in conjunction with an extensive proteome remodeling. This altered metabolic signature of mitochondria then supports T cell survival and proliferation [24,29,30]. Furthermore, upon TCR triggering, the two transcription factors MYC and GABPA promote the expression of mitochondrial ribosomal proteins, which in turn supports the translation of mitochondrial proteins such as electron transport components [29]. TCR stimulation also promotes the synthesis of nucleotides and the biosynthesis of the amino acids arginine and proline from glutamate [20,31].

To decipher the kinetics of translation rates in human T cells, Wolf et al. employed quantitative proteomics and transcriptomics combined with pulsed stable isotope labeling by amino acids in cell culture (SILAC) [1]. Increase in ribosomes correlated with a five-fold increase in protein content after 6 h of stimulation and a 13-fold after 24 h with αCD3/αCD28 antibodies [1]. Likewise, Howden et al. calculated a 10-fold increase of ribosomes in murine CD4+ T cells after 24 h of activation [2]. Intriguingly, the absolute mRNA copy numbers only increased by a 1.4-fold after 6 h of activation [1]. This finding thus indicates that translation rate is key in T cells in regulating the proteome dynamics. Indeed, estimates of absolute protein synthesis, obtained by the median
rate at which a single amino acid (aa) is translated, revealed an increase from ~0.8 aa/s in naïve CD4⁺ T cells to ~4.0 aa/s in 6 h activated T cells [1].

Not only the translational output increased, but also the transcript-specific translation efficiency altered upon activation. For instance, although CD69 mRNA increased by only 1.6-fold, the protein copies increased from 0 to 598 proteins per minute, indicating that each mRNA was translated 5.4 times per minute in activated CD4⁺ T cells compared to 0 in naïve T cells [1]. Similar results were found for CD40L and JUNB, both of which were translationally repressed in naïve T cells but rapidly translated once activated [1].

Another study used the murine Lymphochoriomenengitis virus infection model with polysomal analysis to estimate translational activity in T cells [3]. In this model, T cells showed high translation rates at 5 days post infection, as defined by high ribosomal occupancy of mRNAs [3]. At the peak of the response, i.e., at 8 days post infection, the translational activity of T cells was downregulated, which coincided with decreased T cell proliferation [3]. Nevertheless, at this time point, hundreds of mRNAs maintained their high ribosomal occupancy compared to naïve T cells—in some cases even compared to 5 days post infection [3]. This included Cd8a and Tbx21, a transcription factor (TF) T-bet that is critical in driving T cell effector function. The translation of T-bet did not substantially alter between day 5 and day 8 post infection compared to naïve T cells, coinciding with the ability of T cells to remain effector cells. Other TFs that were translationally upregulated at day 8 post infection compared to day 5 post infection associated with the cytotoxic function of CD8⁺ T cells (Foxo3, Nfat5, Stat1, and Stat5). This also was true for some integrins (Itgα1, Itgαl, and Itgαx) and kinase-related molecules (Pik3cap1, Pik3cd3, Pik3r1, and Rictor) [3]. In conclusion, activated T cells display a profound remodeling of their proteome, allowing them to retain effector functions, and alterations in translation efficiency play a substantial role herein.

**Signals that govern the remodeling of the proteome upon T cell activation**

Mammalian target of rapamycin (mTOR) and Myc, both well known for their wide-ranging effects in many organisms and cell types [32–35], have been identified as two major players in the rewiring of protein expression in T cells [28,29] (Fig. 1). mTOR is a serine-threonine kinase that senses environmental signals to regulate cell growth, (lipid) metabolism, and mRNA translation [2,20,36]. It encompasses two complexes, mTORC1 and mTORC2. mTORC2 phosphorylates AKT and appears to regulate T cell memory formation, whereas mTORC1 mediates T cell effector function [37]. In particular, mTORC1 is a key factor in driving activation-mediated translation [3,38–41]. mTOR-mediated phosphorylation of 4E-BP results in dissociation of this negative regulator of translation from the eukaryotic initiation factor 4E (eIF4E). eIF4E can then bind to the mRNA 5′ cap structure and associate with eIF4F and eIF4G [42]. The formed eIF4F complex facilitates the recruitment of ribosomes and tRNA to initiate translation [43].

Activated human T cells have increased levels of the methyl-capped mRNA translating eIF4F complexes, allowing for increased translation to occur [2,44]. Interestingly, the translation repressors 4E-BP1 and 4E-BP2 are also upregulated in activated T cells, but expression levels of the eIF4E complex outcompete those of 4E-BP. This balance may however, alter at later stages of T cell activation and then facilitate the termination of T cell responses. The RBP PDCD4, another translational repressor, is enriched in naïve T cells and is strongly downregulated upon activation [2]. Increased translation thus correlates with decreased expression of the translational repressor PDCD4 and excessive amounts of eIF4F in activated T cells.

Raptor-mTORC1 activity downstream of TCR and CD28 signaling results in metabolic reprogramming, which in turn
supports both murine and human T cells to exit quiescence [45]. mTORC1-mediated formation of the elf4F complex recruits the mRNA of the glucose transporter GLUT1 and the acetyl-CoA Carboxylase ACC1 to ribosomes and drives their translation [38]. GLUT1 and ACC1 play an important role in metabolic activation, and thus contribute to the reprogramming of human T cells to an effector phenotype [38]. mTOR was shown to drive translation of mRNAs that contain the 5’terminal oligopyrimidine (TOP) or TOP-like motifs [46]. 5’TOP mRNAs are present in many ribosomal protein (RP) mRNAs, which show increased translation upon murine T cell activation [3]. The importance of the 5’TOP motif was also shown upon inhibition of mTORC1/2 with Torin-1, which blocked the translation of nearly all 5’TOP containing mRNAs [1,46]. However, not all blocked mRNAs contained 5’TOP or TOP-like motifs. In fact, mTORC1 inhibition with rapamycin in murine T cells decreased the protein expression of ~800 genes, including metabolic and ribosomal proteins, glycolytic enzymes and proteins such as glucose and lactate transporters [2]. Furthermore, blocking mTORC1 with rapamycin did not result in complete inhibition of murine T cell differentiation, which may at least in part be due to the relatively normal expression of transcription factors T-Bet, MYC, BLIMP-1, IRF4, and BAFF [2].

The second major player in the rewiring of protein expression is the transcription factor Myc. Myc is, in part through mTOR signaling, rapidly induced upon CD3/CD28 stimulation and facilitates the biosynthesis of amino acids, lipids, and nucleotides through Myc-dependent catabolism [23,29]. Myc regulates mRNA translation by inducing the de novo transcription of ribosomes and genes encoding amino acid transport and protein synthesis. Moreover, it is involved in the formation of ribosomes and mitochondrial ribosomes [47,48]. This renders Myc essential in the remodeling of the proteome upon murine T cell activation [28,29]. Myc-deficient murine T cells completely failed to increase their protein production upon CD3/CD28 activation, which was at least in part due to an impaired expression of 40S and 60S ribosomal proteins, the elf4F complex and of amino acid transporters [28]. Interestingly, even though Myc regulates the expression of generic translation-associated genes, it does not universally regulate translation: the protein expression of CD69 and CD44, and the TFs cRel, JunB, T-bet and Irf4 were equally well induced in activated murine WT and MycKO T cells [28]. Myc and mTOR thus regulate translation in a selective manner.

Signals that orchestrate the maintenance of quiescent T cells

While T cells rapidly respond during pathogenic insults or other inflammatory conditions, the vast majority of T cells in the body, i.e., naïve T cells, memory T cells, and tissue resident T cells, are quiescent. T cell quiescence is, however, by no means a passive state. Rather, quiescent T cells require signals to undergo homeostatic proliferation [4–6]. Furthermore, in order to rapidly respond to T cell priming (naïve T cells) or to re-exposure to pathogens (memory and tissue-resident T cells), T cells are kept in a state of readiness. T cells receive these so-called “tonic” signals through the TCR, cytokine receptors, and through the S1PR1 [4,30,49–51]. TCR signaling occurs by engaging with self-peptide-MHC molecules [30,52], and by autocrine low-level TCR signaling [53]. This autocrine signaling is mediated through spontaneous conformational changes of the TCR, which results in low but constitutive phosphorylation through the kinase Lck [53]. Whether these TCR-mediated signals raise or lower the threshold of T cell activation is still debated [52,54]. Their necessity for homeostasis is however manifested [4–6].

Also tonic TCR-mediated signaling relies on mTOR [55]. The proximal TCR signaling molecules Zap70, LAT and SLP-76 engage the Ras exchange factor Rasgfp1, which then activates mTORC1 [55]. Ribo-sequencing data revealed that mTORC1 modulates the baseline translation of thousands of transcripts [30]. Tight regulation of mTORC1-mediated tonic signaling in resting T cells is however critical, because dysregulation thereof leads to aberrant T cell responses, loss of T cell quiescence, reduced proliferation, and potentially to autoimmune disease [30,36,56]. This is exemplified when the negative mTORC1 regulators tuberous sclerosis complex 1 and 2 (Tsc1/2) are ablated, which results in T cells exiting quiescence [37,57]. Of note, mTORC1 also promotes immune homeostasis and quiescence of effector T cells by coordinating the suppressive function of regulatory T cells [58,59].

IL-7 and IL-15 are the two main cytokines regulating T cell survival and homeostasis [60–62]. IL-15 receptor (IL-15R) is expressed in resting memory T cells, and mediates survival and homeostatic proliferation [63]. IL-7 receptor (IL-7R) signaling in quiescent naïve and memory T cells promotes survival by promoting the expression of anti-apoptotic BCL-2 family members through JAK-STAT and PI3K-AKT signaling [64,65]. Likewise, the PI3K-AKT pathway engages mTOR and GLUT1 [18]. Lastly, tonic signaling through S1PR1 is triggered by the chemokine S1P in the lymph, which provides energy to T cells through mitochondrial maintenance, making it crucial for survival of quiescent T cells [51]. S1PR1 is thought to interact with the activation marker CD69 and the chemokine receptor 7 (CCR7), hereby influencing T cell egress from the lymph node organs [66]. Although it is known that it signals through MAPK, PI3K/Akt, and phospholipase 3 in other cell types, its signaling nodes have yet to be uncovered for T cells [66].

Quiescent T cells are poised for activation yet actively kept inert

Continuous signaling through the TCR, cytokine receptors, and S1PR1 thus allows quiescent T cells to maintain their status quo to survive, to undergo homeostatic proliferation and to be prepared for T cell activation. For naïve T cells, this entails the preparedness for T cell priming. Memory T cells are poised to rapidly respond to insults because their translation machinery is set in place, and because they express ready-to-deploy mRNA for specific transcripts. Thus, de novo transcription and translation are continuously ongoing (Fig. 2). Maintaining the balance
of responding to tonic signals yet keeping T cells quiescent to prevent inappropriate activation is critical [7,67]. In this process of maintaining T cell quiescence, post-transcriptional mechanisms play a pre-eminent role.

One mechanism that blocks aberrant protein production in quiescent T cells is m^6^A modification of newly transcribed mRNA, which results in rapid degradation [68]. This is for instance observed when murine naive T cells sense IL-7. The mRNA expression levels and protein levels of the STAT signaling inhibitory proteins SOCS1, SOCS3, and CISH are actively restricted by the RBP Methyltransferase METTL3 [68]. This keeps the protein levels of these inhibitory molecules low, and allows quiescent T cells to respond to IL-7-mediated STAT5 tonic signaling and to undergo homeostatic proliferation [68].

Another means to maintain T cell quiescence is achieved by BTG1 and BTG2, two members of B cell translocation gene/Transducer of ERBB2 (BTG/TOB) family. BTG1 and BTG2 expression is enriched in quiescent naive and memory T cells compared to other T cell subsets [69]. Although direct binding of BTG1 and BTG2 to mRNA was not demonstrated, these two proteins interact with the poly(A)-binding protein (PABP) and CCR4-NOT deadenylase mRNA-degrading complex. Deletion of both BTG1 and BTG2 thus leads to a global stabilization of mRNA in murine naïve T cells [69]. As a consequence, because the expression of T cell activation- and proliferation-associated proteins increases, BTG1/2 KO T cells spontaneously exit quiescence and undergo clonal expansion and activation; a feature that is observed even with weak TCR stimulation, and in the presence of tonic cytokines (IL-7 and/or IL-2) [69]. BTG1 and BTG2 therefore actively suppress the activation of quiescent T cells, and possibly counteract tonic signaling to maintain T cell quiescence.

Also, the RBPs Regnase-1 and Roquin-1 dampen spontaneous activation of naïve CD4^+_T_ cells. They do so by destabilizing a specific set of target mRNAs, including mRNAs that encode for inflammatory functions, such as Icos, OX40, c-Rel, and Irf4 [70]. Although both RBPs bind to similar stem-loop structures in the 3'UTR of their target mRNAs, Regnase-1 acts as endonuclease, whereas Roquin-1 recruits mRNA degrading enzymes for destabilization [71–73]. Regnase-1 and Roquin-1 also play an important role in CD4^+_T_ helper cell differentiation into Th9, Th1, Th2, and Th17 [74–76]. For example, both Roquin-1 and Regnase-1 regulate the differentiation of murine Th1 cells, and do so in a non-redundant manner [77]. Another study showed that combined ablation of Roquin-1 and its paralogue Roquin-2 skewed murine CD4^+_T_ cells toward Th9 and Th17 cells [78]. Roquin-1, together with Regnase-1, targets mRNAs that play a role in Th17, but to a lesser extent also Th9 and Th1 differentiation such as IL-6, Icos, OX40, and Cta-4 [78]. In both studies, deletion of Roquin and Regnase-1 induces severe autoimmunity [76,78]. Regnase-1 was also shown to dampen the generation of cytotoxic CD8^+_T_ cells [79]. Interestingly, both Regnase-1 and Roquin are cleaved and inactivated upon T cell activation, pointing to a regulatory role of these RBPs in maintaining T cell quiescence [78].

Another layer of post-transcriptional regulation is the block of translation of ready-to-deploy mRNA. Murine naïve T cells contain pre-existing mRNA of glycolytic enzymes, which are only translated upon TCR activation [1,29]. Also human naïve and central memory T cells contain preformed mRNA of metabolic enzymes that are involved in glycolysis and fatty acid synthesis (FAS) [38]. Specifically, the translation of GLUT1 and ACC1 preformed mRNAs into corresponding proteins is almost fully repressed in resting naïve T cells in the absence of TCR stimulation [38]. This finding is in line with the notion that naïve and memory T cells primarily rely on fatty acid oxidation and not on glycolysis or FAS [80]. Interestingly, not all glycolytic enzymes are translationally repressed in naïve and memory T cells, as is the case for LDHA, GAPDH, ALDOA, and PGK [1]. The presence of
these proteins possibly helps the rapid switch to glycolysis upon T cell activation. Interestingly, it was shown in other cell types that many glycolytic proteins can act as RBPs [81,82]. It is therefore tempting to speculate that this moonlighting function could also play a role in T cells.

Similarly, ready-to-deploy mRNAs encoding for the early activation markers CD69 or CD40L and the T cell-activation mediating TFs, such as Myc, Irf4 and Fos, and JunB, are expressed but translationally silenced in naïve and memory T cells; a feature that is conserved between mouse and human [1,19]. Quiescent T cells thus exert selective inhibition of translation of specific proteins in order to maintain their resting state. The mechanisms that block these pre-formed mRNAs from translation are however not yet well defined. Notably, the above-mentioned activation markers and TFs contain one or more regulatory AU-rich elements (ARE) in their 3'UTR, which are hubs to mRNA-regulating RBPs. ARE-mediated translational block was in fact demonstrated in our lab in murine memory T cells for the key proinflammatory cytokines IFN-γ and TNF-α [40]. This translational block of pre-formed mRNA was achieved by the RBP ZFP36L2, by blocking the association of pre-formed mRNA with ribosomes [19]. Interestingly, murine naïve T cells also contain preformed Tnf mRNA and produce substantial amounts of TNF-α as early as 2 hours after stimulation [83,84]. The ability of naïve T cells to produce TNF-α protein is however acquired in the periphery [85]. Furthermore, Tnf mRNA in T cells is notoriously unstable [40], and its continuous expression must be linked to continuous *de novo* transcription of this mRNA, possibly driven by tonic signals T cells receive in peripheral secondary lymphoid organs.

Alternative polyadenylation is yet another post-transcriptional mechanism involved in regulation of gene expression through mRNA 3'UTR by creating alternative 3'UTR isoforms. Global analysis of alternative 3'UTR isoforms in both human and murine quiescent T cells showed higher expression of longer 3'UTR isoforms compared to activated T cells [86,87], because quiescent T cell preferentially use the distal polyadenylation sites. Extended 3'UTR isoforms contain more target sites for miRNAs and RBPs, which can lead to reduced protein expression in quiescent T cells, or even to functional diversity as was shown in human embryonic kidney HEK293 cells [86,88–91].

**Translational activity in quiescent T cells**

Translation is not generally repressed in quiescent T cells, but occurs only for about half of the transcripts in human naïve T cells [1]. For instance, human naïve and memory T cells contain mRNAs encoding for the ribosomal machinery, i.e., RNA polymerases, the small and large ribosomal subunits (RPS and RPL, respectively), and ribosomal trans-acting factors [38]. Although many transcripts that contain a STOP motif are translationally repressed in naïve T cells [1], ongoing translation of the RPs Rpl29, Rpl13, Rpl32, Rps5, Rps6, and Rps29 was demonstrated by association of mRNAs that encode RPs with polyosomes in naïve T cells [3]. Why some RPs are refractory to the block of translation through the STOP motif and others are not, remains enigmatic and points to a context- and tissue-dependent STOP regulation [92]. In addition, RBPs that interact with TOP motifs in RP mRNAs might define TOP mRNA translation downstream of mTORC1 in T cells. For example, in HEK293T cells, the RBP LARP1 binds to TOP motifs in both the 5'UTR and 3'UTR of RPL32 mRNA and regulates RPL32 translation depending on mTOR activity [93]. Intriguingly, LARP1 also binds to the TOP sequence of RPS6 mRNA, indicating that RBPs play an important role in regulating translation and ribosome biogenesis [94].

How does the translation and protein turnover look like in naïve T cells? Combined proteome and transcriptome analysis estimated that naïve T cells contain ~400,000 assembled ribosomes [1]. Another intriguing estimate is that naïve T cells synthesize as much as ~60,000 proteins every minute up to a total proteome of ~410 million proteins translated from ~77,000 mRNA molecules [1]. In line with previous examples, the mRNA to protein ratio of 1 to 5,400 suggested translational regulation in naïve T cells. Within 24 h, naïve T cells renew approximatively 20% of all proteins with fastest renewal rate in MHC-I proteins, followed by endocytic and autophagy receptors (SORL1 and SQSTM1, respectively) and transcriptional factors critical for T cell quiescence such as ETS1, TCF-1, FOXO1, FOXP1, etc. Proteins with the fastest synthesis rate are also degraded quickly through proteasome-dependent and independent mechanisms in naïve T cells [1]. Similarly, resting memory T cells show dynamic translation and turnover of ribosomal, proteasomal and glycolytic proteins. In comparison to naïve T cells, memory T cells have an even higher translational activity (~100,000 proteins per minute) and a faster ribosomal output upon activation, based on ribosomal protein and RNA counts [1]. Whether the higher translational activity also allows memory T cells to more rapidly respond to reactivation, and whether different T cell memory subsets such as effector memory, central memory and resident memory T cells have differential levels of translational activity is an attractive hypothesis yet requires experimental confirmation.

While these estimates shed light for the first-time in the dynamics of translation in T cells, the numbers should be taken with some caution. The numbers of fully assembled ribosomes are based on ribosomal protein and ribosomal RNA abundance. These estimates do however not take into account that ribosomes are by no means non-specialized, passively translating macromolecular machines. Rather, the composition of ribosomes is heterogeneous. Selected reaction monitoring (SRM) mass spectrometry revealed that of 6 out of 15 core RPs of mouse embryonic stem cell-derived polysomes were substoichiometric, and thus lacked at least one core RP [95]. This ribosome heterogeneity was also found for rRNAs, and for the interaction with different ribosome association proteins [96,97]. In addition, post-translational modification of RPs and ribosome association proteins, as well as rRNA modifications can determine the heterogeneity of ribosomes [98]. Heterogeneity consequently results in specialized function and selective translation, as exemplified by the preferential translation of mRNAs associated with cell growth and metabolic pathways by RPS25- or RPL10-containing ribosomes, respectively [95]. This
specialization of ribosomes to translate specific mRNAs was also shown for ribosomes containing RPL6, RPL28, or RPS28, which resulted in differential antigen presentation in HEK293 cells [99]. Therefore, it is tempting to speculate that ribosome diversity could also alter upon T cell activation and differentiation, and thus alter the preference of mRNA substrates that are translated.

Conclusions

We here provided an overview of how T cells maintain T cell quiescence and how they reboot and rewire their proteome upon T cell activation. We highlight that downstream of tonic signaling and T cell activation signals, post-transcriptional events are critical. However, we are only at the beginning of our understanding of how and which RBPs regulate these post-transcriptional events. Mouse models with RBP deletions provided first insights on RBP-mediated disease [10]. Translation into the human setting, in particular in T cell function, however, is still in its infancy. For instance, to date a comprehensive RBP map during T cell differentiation and activation is lacking. A recent overview on RBPs associated with human genetic diseases provides important insights and could form a basis to study RBPs also in immune-related disease settings [100]. Moreover, post-translational regulation and modifications further impacts proteomic modeling [29], leaving the post-transcriptional and post-translational mechanisms in a dynamic dance of regulation, which is time- and context-dependent.

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Abbreviations: eIF4E: eukaryotic initiation factor 4E · KLF2/3: Kruppel-like family transcription factor 2/3 · PTR: post-transcriptional regulation · RBP: RNA-binding protein · RP: ribosomal protein · S1PR1: sphingosine-1-phosphate receptor 1 · TCR: T cell receptor · UTR: untranslated region

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