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REVIEW

Epigenetic priming as a driver of memory recall and dysfunction in T cells

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T cells are essential for protective immunity against pathogens and malignancies. While the initial activation of a naive T cell is slow, antigen-experienced or memory T cells mount near-immediate protective responses through their remarkable capacity to instantaneously reactivate inflammatory gene programs upon antigen rechallenge. Evidence is emerging that this immunological memory is underpinned by dynamic changes at the chromatin level or epigenome of T cells. Here, we review recent findings on how epigenetic mechanisms are a driving force guiding initial T cell activation and differentiation, and durably endow memory T cells with the ability to remember gene regulatory processes essential for high-magnitude protective immune responses. We discuss the molecular programs that may be involved in the establishment and maintenance of chromatin-based information in memory T cells during homeostasis, and how undesired epigenetic priming may program T cells for dysfunction in patients with chronic immune–related disease and cancer.

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Introduction

Our adaptive immune system can build durable immunity against harmful agents (Pulendran and Davis, 2020; Sallusto et al., 2010). A central pillar of this immunological memory comprises memory T cells: previously activated T lymphocytes that "remember" a prior interaction with their target antigen, such as proteins derived from tumors or pathogens, enabling them to mount vigorous and rapid recall responses upon antigen reexposure (Farber et al., 2014; Künzli and Masopust, 2023; Turner et al., 2021). Memory T cells provide the host with immunological protection against tumors and previously encountered pathogens that may last a lifetime (Derksen et al., 2023; Soerens et al., 2023). Current vaccination strategies—among the most effective medical interventions used today—are based on the concept of immunological memory formation (Pulendran and Davis, 2020; Sallusto et al., 2010). Nevertheless, generating memory T cells is not without risk. Aberrant memory T cells targeting harmless (self-)antigens can cause allergy or autoimmune disease (Collier et al., 2021; Hammad and Lambrecht, 2021). In addition, in the setting of cancer or persistent infection, chronically activated T cells often fail to adopt functional memory phenotypes and enter a state of dysfunction, in part explaining why long-term efficacy of current immunotherapies remains relatively modest (McLane et al., 2019; Thommen and Schumacher, 2018).

The importance of T cell memory to human health has raised the fundamental question of how memory T cells can so effectively and durably recall effector responses. Efforts to address this question have revealed that the remarkable functional qualities of memory T cells are strongly linked to their gene expression ("transcriptional") program. However, the mechanisms underpinning the unique transcriptional identity of memory T cells have long remained enigmatic. At the most basic level, gene expression is orchestrated by DNA-binding transcription factors (TFs) that interact with gene regulatory elements—such as promoters and enhancers—to activate or repress gene transcription (Grosveld et al., 2021; Voss and Hager, 2014). A prerequisite for TF-dependent gene regulation is the accessibility of their cognate binding sites within these gene regulatory elements, which is regulated at the chromatin level or "epigenome" of the cell. A first one-dimensional ("1D") level of epigenetic regulation is provided by the positioning of nucleosomes, which consist of histone proteins that package DNA into a chromatin fiber, along with covalent modifications of histones or DNA that may either facilitate or impede TF binding (Fig. 1) (Klemm et al., 2019; Luo et al., 2018; Wang et al., 2008). On top of this 1D composition, chromatin adopts a cell state–specific three-dimensional (3D) folding pattern (Pongubala and Murre, 2021; Zhao et al., 2022). Essential in shaping 3D genome organization are the architectural protein CCCTC-binding factor (CTCF) and the cohesin complex, which together extrude DNA into loops that form topologically associating domains (TADs) (Fig. 1) (Davidson and Peters, 2021). TADs are considered spatial neighborhoods in which genomic sequences can frequently

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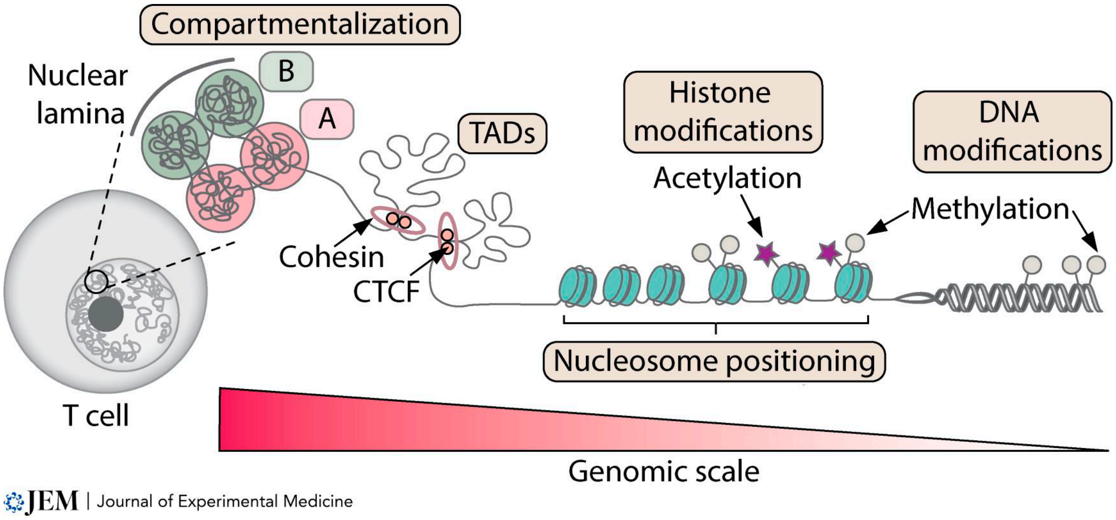

Figure 1. **Overview of the various epigenomic features involved in the regulation of gene expression.** At the largest genomic scales, chromosomes segregate within 3D nuclear space into a nuclear lamina-associated, transcriptionally repressed B compartment and a transcriptionally active A compartment that occupies the nuclear interior. Within these compartments, cohesin and CTCF together form TADs through a process called loop extrusion. TADs are spatially insulated genomic regions that facilitate interactions between genes and their regulatory elements (e.g., promoters, enhancers). At the level of the chromatin fiber, DNA is wrapped around nucleosomes consisting of histone octamers that can be posttranslationally modified (e.g., acetylation, methylation). DNA itself can also carry methylation modifications. Nucleosome positioning and histone/DNA modifications, together with 3D chromatin architecture, shape a local chromatin environment that either supports or inhibits the recruitment of TFs and RNA polymerases to control gene transcription.

interact, facilitating correct interactions between regulatory elements such as enhancers and their target gene promoters—which can be separated by large 1D genomic distances. At larger megabase scales, TADs and loops segregate into transcriptionally active ("A") and repressed ("B") nuclear compartments, which may further promote efficient transcriptional control of gene expression programs (Cuartero et al., 2023; Misteli, 2020; Stadhouders et al., 2019). Together, this multidimensional epigenome controls TF activity, gene regulation, and ultimately cellular identity and function (Fig. 1).

Excitingly, recent technological advancements have offered immunologists new tools to unravel the molecular basis of T cell memory. From these endeavors, it is becoming increasingly clear that epigenetic priming mechanisms control the transcriptional programs that underlie the rapid recall ability of memory T cells (Frias et al., 2021; Tough et al., 2020). Despite residing in a quiescent state under homeostatic conditions, resting memory T cells appear to utilize a dynamic interplay between dedicated TFs and a three-dimensionally organized chromatin landscape, which both foreshadows and facilitates adequate changes in gene expression upon antigen reencounter. These findings have begun to transform our understanding of the fundamental mechanisms of T cell–mediated immunity and how these may be exploited therapeutically. In this review, we will discuss recent insights into how memory T cells leverage an "epigenetic imprint" to stably store information and instructions received during their initial activation, granting them the capacity to "memorize" gene regulatory processes essential for high-magnitude effector responses. In addition, we will discuss how aberrant epigenetic imprints may drive (memory) T cells into a dysfunctional state in patients with chronic diseases.

Epigenetic regulation of T cell activation and differentiation

Equipped with highly specific αβ T cell antigen receptors, T cells continuously monitor their surroundings to detect pathogens and malignancies. T cells are classically subdivided into CD4$^+$ T cells, which recognize antigens presented by major histocompatibility complex (MHC) class II molecules and orchestrate immune responses by modulating the activity of other (immune) cells, and MHC I–restricted cytotoxic CD8$^+$ T cells, which can directly kill aberrant cells (Taniuchi, 2018). Activation of both CD4$^+$ and CD8$^+$ T cells follows the same general course, and requires the integration of three crucial signaling routes: antigen-dependent signaling through the T cell receptor (TCR; signal 1), costimulation provided by interaction between costimulatory receptors on the antigen-presenting cell (e.g., CD80/CD86) and their counter-receptors (e.g., CD28) on the T cell (signal 2), and the influence of cytokines (signal 3) (Hwang et al., 2020). The initial activation of a naive T cell—which has never seen its target antigen—licenses its clonal expansion and differentiation into a pool of numerically expanded effector cells that have acquired the ability to fight the threat. Following successful antigen elimination, the majority of the differentiated effector cells die, while a small fraction (~5–10%) of the activated, antigen-experienced population develops into long-lived memory T cells (Farber et al., 2014; Künzli and Masopust, 2023; Turner et al., 2021). These memory T cells return to quiescence, yet remain poised to mount near-immediate recall responses upon antigen rechallenge that are both faster and greater in magnitude compared with the primary response of naive T cells. The rapid recall ability of memory T cells resides, at least in part, in their ability to near-instantly reactivate the expression of genes essential for effector functions. These include the secretion of cytokines to stimulate other immune cells and/or inhibit pathogen

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replication ($CD4^+$ and $CD8^+$ T cells) and the production of cytotoxic molecules to directly kill infected or malignant cells (mostly $CD8^+$ T cells; Annunziato et al., 2015).

Distinct T cell states emerge through changes in gene expression programs imposed by TFs and multidimensional epigenetic mechanisms in response to environmental signals (Bediaga et al., 2021; Henning et al., 2018; Hosokawa and Rothenberg, 2021; Liu et al., 2024b; Tough et al., 2020; Yu et al., 2017). In fact, all three signaling routes required for T cell activation eventually lead to the engagement of signal-responsive TFs, including members of the STAT, AP-1, IRF, and NFAT families (Esensten et al., 2016; Hwang et al., 2020). Although the importance of these TFs for T cell activation and fate specification is broadly recognized, their individual roles and the mechanisms that regulate their activity and binding site accessibility are only beginning to unfold. Moreover, it is important to mention that current knowledge in the field is primarily based on the analysis of murine T cells, and translating these findings to human T cell biology remains pivotal.

Naive T cell activation

Prior to encountering an antigen, naive T cells exploit epigenetic mechanisms to actively maintain their naive phenotype and to remain quiescent. This includes large-scale chromatin compaction driven by the condensin II complex and H1 linker histone deposition (Rawlings et al., 2011; Willcockson et al., 2021), which prevent premature naive T cell activation, for example, by keeping binding sites for TFs implicated in T cell activation inaccessible. In addition, the 3D organization of chromatin into loops plays an important role in maintaining T cell naivety and homeostasis (Burren et al., 2017; Onrust-van Schoonhoven et al., 2023; Russ et al., 2023; Shan et al., 2022b). In $CD8^+$ T cells, key TFs such as TCF-1, LEF1, and BACH2 provide supervision of naive-specific chromatin accessibility and 3D genome organization—the latter through recruitment of CTCF (Roychoudhuri et al., 2016; Russ et al., 2023; Shan et al., 2021; Shan et al., 2022b). Importantly, the cooperation between TCF-1 and CTCF not only preserves the chromatin architectural landscape of naive T cells, but also enables changes in CTCF occupancy and chromatin interactions in response to IL-7 and IL-15 signaling, facilitating the transcriptional adaptations essential for homeostatic proliferation induced by these cytokines (Shan et al., 2022b). An inappropriate expression of genes encoding inflammatory cytokines is further precluded at the level of histone modifications and DNA methylation (Fields et al., 2002; Kersh et al., 2006; Wei et al., 2009; Zebley et al., 2021a). Moreover, gene silencing elements may contribute to preventing premature cytokine expression in naive T cells by diminishing enhancer–promoter interactions, as was recently shown for the *Ifng* gene (Cui et al., 2023).

Upon activation of a naive T cell, the mobilization of Ca^{2+} downstream of TCR signaling induces large-scale chromatin decompaction (Lee et al., 2015) (Fig. 2 A). Protein kinase C (PKC) plays a crucial role in initiating Ca^{2+}-dependent chromatin decondensation, through activation of p38 MAPK and NF-κB pathways (Funsten et al., 2020). NF-κB then induces the synthesis of IL-2 and its high-affinity receptor IL-2RA/CD25 (Pimentel-Muiños et al., 1994; Prasad et al., 2002). Additionally, PKC activates p44/42 MAPK (ERK1/2), which promotes phosphorylation of AP-1 family TFs and is required for T cell competence to respond to IL-2 (Funsten et al., 2020). Combined, these early signaling events ensure that only activated, antigen-specific T cells become receptive to IL-2–induced proliferation and chromatin remodeling orchestrated by the main target of IL-2 signaling, the STAT5 TF (Li et al., 2017). AP-1 family TFs, acting downstream of TCR and coreceptor signaling, also contribute to initial chromatin opening and the reorganization of chromatin loops in recently activated T cells (Ciofani et al., 2012; Pham et al., 2019; Tsao et al., 2022; Yukawa et al., 2020). In support of the pioneering role of AP-1 family TFs in this context, the ectopic expression of the AP-1 family member BATF, together with its partner IRF4, in fibroblasts was found to be sufficient to induce chromatin accessibility and transcription at several loci associated with T cell function (Tsao et al., 2022). AP-1 TFs may exert their chromatin remodeling activities either directly via binding to DNA or by recruiting the prototype mammalian chromatin remodeling complex, c-BAF (Pham et al., 2019; Tsao et al., 2022; Vierbuchen et al., 2017; Yukawa et al., 2020). For $CD8^+$ T cells, it was recently shown that c-BAF plays an essential role in facilitating de novo opening of enhancers shortly after activation (McDonald et al., 2023).

Effector T cell differentiation

T cell differentiation is accompanied by extensive rewiring of chromatin landscapes (Fields et al., 2002; Liu et al., 2023; Quon et al., 2023; Scott-Browne et al., 2016; Wei et al., 2009; Zhang et al., 2023). According to the current view, the pioneering activation-induced chromatin remodeling events mediated by STAT5, AP-1, and c-BAF render local chromatin environments permissive to subsequent binding by fate-determining TFs (Bevington et al., 2020; McDonald et al., 2023; Tsao et al., 2022). Within this framework, the cytokine milieu (signal 3) plays a decisive role in determining the functional properties that the activated T cell will acquire. For $CD4^+$ T cells, specific cytokines and their target STAT proteins induce differentiation into specialized T helper (Th) subsets through the induction of fate-determining TFs (Fig. 2 B). Specifically, IL-12/STAT4 signaling induces T-Bet expression and Th1 differentiation; IL-4/STAT6 signaling mediates GATA3 upregulation and Th2 differentiation; and IL-6/STAT3 evokes RORγt expression and Th17 differentiation (Annunziato et al., 2015; Zhu et al., 2010). These distinct TF combinations drive the expression of a unique repertoire of cytokines and functional qualities by the individual Th populations: Th1 cells secrete interferon-γ (IFN-γ) to fight intracellular microbes; Th2 cells produce interleukin (IL)-4, IL-5, IL-9, and IL-13 during anti-helminth responses; and Th17 cells use IL-17 to eradicate fungi and extracellular bacteria. Most activated $CD8^+$ T cells gain cytolytic activity and the capacity to produce IFN-γ through the expression of the EOMES and T-Bet TFs (Annunziato et al., 2015; Cruz-Guilloty et al., 2009). IL-12 and IFN-α/β—in addition to autocrine IFN-γ—are the main cytokines promoting this effector program (Curtsinger et al., 2012; Starbeck-Miller et al., 2014; Valbon et al., 2016) (Fig. 2

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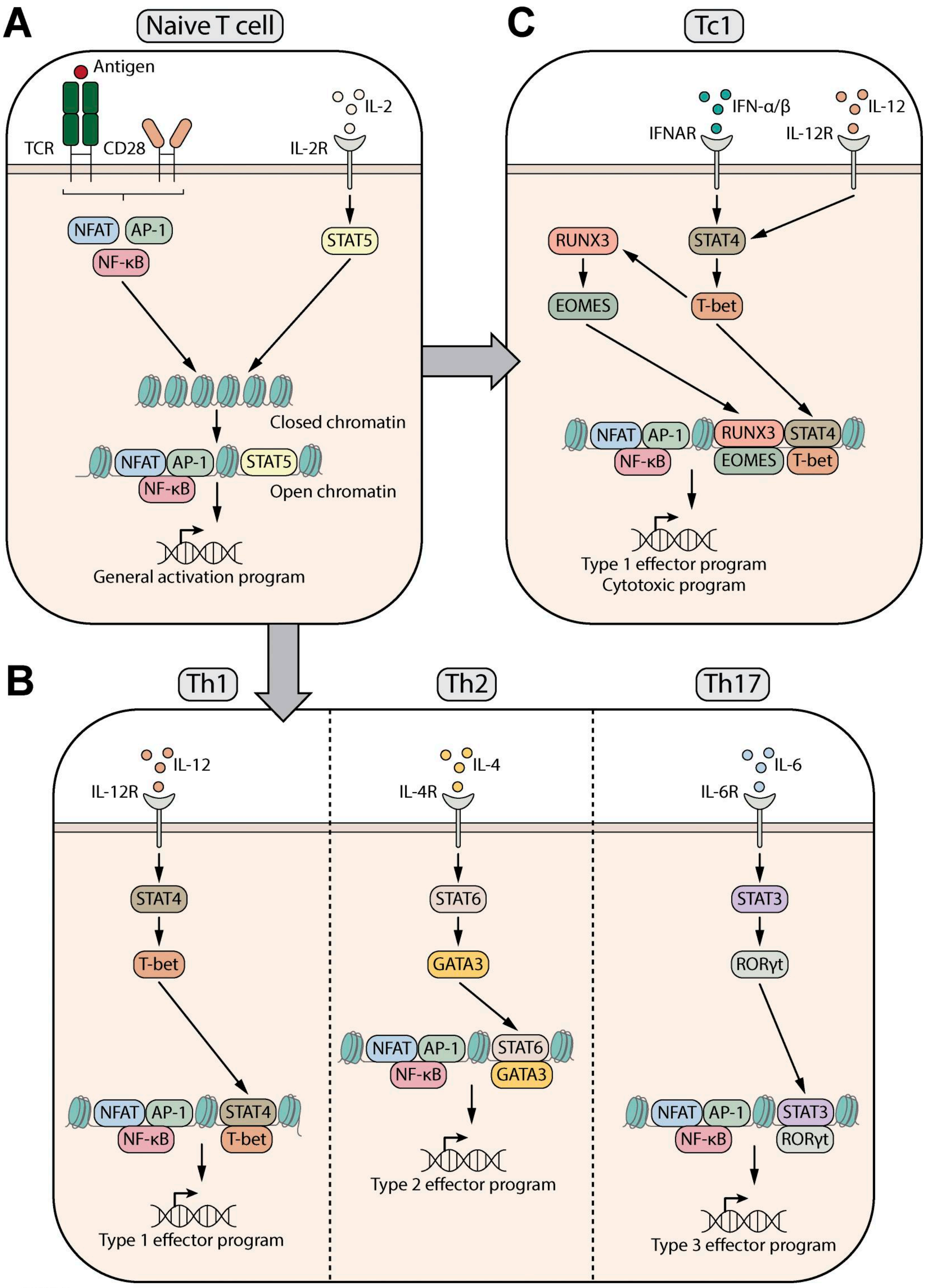

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Figure 2. **Molecular events driving naive T cell activation and subsequent effector differentiation. (A)** Antigen-dependent stimulation of the TCR (signal 1) on a naive T cell combined with CD28-mediated costimulation (signal 2) results in the activation of NFAT, AP-1, and NF-κB TFs that increase chromatin accessibility at regulatory elements controlling genes important for T cell activation. These include genes encoding IL-2 and its high-affinity receptor, which then establish an autocrine positive feedback loop that activates the STAT5 TF. In cooperation with the TCR-induced TFs, STAT5 is critical for chromatin remodeling and full activation of the general activation program. **(B and C)** After initial activation, exposure to specific cytokines (signal 3) induces effector cell differentiation toward specific Th (panel B) or cytotoxic T (Tc; panel C) cell subsets. These cytokines activate specific members of the STAT TF family that in turn activate lineage-defining TFs (i.e., T-bet, GATA3, RORγt, EOMES, and RUNX3), which team up with STAT proteins and TCR-induced TFs to activate the different effector programs.

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C). However, in addition to these classical type I cytotoxic effector CD8⁺ T (Tc1) cells, other subsets have been identified, including Tc2 and Tc17 cells that exhibit differentiation trajectories and functional characteristics that mirror Th2/Th17 populations (Annunziato et al., 2015). However, it remains poorly understood whether such Tc2/Tc17 properties are stably maintained over time within the pool of memory CD8⁺ T cells or solely reflect transient biological variability.

The distinct effector T cell populations are characterized by unique enhancer repertoires, suggesting an important role of dynamic changes in 3D chromatin organization during T cell differentiation. TFs belonging to the STAT family play a key role in establishing the chromatin landscapes that control the gene expression programs characteristic of functionally distinct effector T cell populations (Vahedi et al., 2012). The importance of STAT family TFs in this context is illustrated by the inability of the fate-specifying TFs T-Bet and GATA3 when overexpressed in STAT-deficient CD4⁺ T cells to reestablish the enhancer repertoires underpinning Th1 and Th2 effector fates, respectively (Vahedi et al., 2012). Further supporting a key role of 3D chromatin rewiring during T cell differentiation is the recently demonstrated critical involvement of the architectural protein CTCF in this process. Indeed, extensive redistribution of CTCF binding sites characterizes T cell activation and effector differentiation, and its absence results in failed terminal effector cell differentiation (Liu et al., 2023; Quon et al., 2023). In activated CD8⁺ T cells, CTCF acquires de novo binding sites and mediates effector T cell differentiation by inducing the formation of chromatin loops that favor the expression of genes associated with an effector phenotype, including inflammatory mediators such as *Ifng* and *Gzma* and TFs such as *Zeb2*, *Bhleh40*, and *Tbx21* (encoding T-Bet) (Liu et al., 2023). Importantly, T-Bet, in turn, contributes to CTCF recruitment in early effector CD8⁺ T cells, setting up a feed-forward loop that enforces the effector fate (Liu et al., 2023). In addition, chromatin regions that gain accessibility and CTCF occupancy in effector CD8⁺ T cells compared with naive CD8⁺ T cells are enriched for binding motifs of AP-1 family TFs (Liu et al., 2023). This finding suggests that inducible TFs downstream of TCR signaling—such as BATF and FOS-JUN—further facilitate CTCF recruitment and chromatin opening (Liu et al., 2023). Cooperation between BATF and CTCF has also been implicated in CD4⁺ T cell fate specification (Chandra et al., 2023; Liu et al., 2024a; Pham et al., 2019). Here, the BATF TF recruits CTCF to its binding sites, facilitating the restructuring of chromatin architecture to enable transcription of genes important for effector T cell differentiation. Moreover, cooperation between CTCF and the T-Bet and GATA3 TFs facilitates the expression of signature cytokine genes in Th1 and Th2 cells, respectively (Ribeiro de Almeida et al., 2009; Sekimata et al., 2009).

Memory T cell differentiation

Most of the differentiated effector T cells only provide protection against immediate threats and go into apoptosis following successful antigen elimination, leaving behind a relatively small population of cells that have developed into long-lived memory T cells. While effector T cells are strongly linked to the presence of antigen, memory T cells persist in a manner that does not depend on antigen exposure, but rather on cytokines belonging to the common γ-chain family, in particular the IL-2–related cytokines IL-7 and IL-15 (Raeber et al., 2018). It remains incompletely understood when and how the offspring of an activated naive T cell becomes committed to a short-lived effector versus memory T cell fate. The strength and duration of TCR signaling, clonal competition, and the cytokine milieu are likely to play an important role in these fate decisions, but the underlying mechanisms remain unclear (Muroyama and Wherry, 2021; Raeber et al., 2018; Ramos et al., 2009; Sarkar et al., 2007). Current knowledge on this topic is largely based on CD8⁺ T cells, as antigen-specific CD4⁺ memory T cell clones are usually of low abundance and technically more difficult to detect (Osum and Jenkins, 2023). There has been considerable debate over whether memory T cells develop through dedifferentiation of effector cells or arise at an earlier stage of activation, with published literature supporting both hypotheses (Akondy et al., 2017; Henning et al., 2018; Smith et al., 2018; Tough et al., 2020). Interestingly, it was recently shown that fate specification may occur as early as during the first division of the activated naive T cells, through asymmetrical distribution of c-BAF and the MYC TF among the two daughter cells (Guo et al., 2022). According to this model, cells with high levels of both c-BAF and MYC are destined to become short-lived effector cells, whereas those with low levels of both factors will become memory cells. Supporting this view is the observation that the c-BAF component ARID1A promotes the expression of key TFs associated with an effector phenotype and the accessibility of their cognate binding sites in recently activated T cells (McDonald et al., 2023).

In CD8⁺ T cells, a series of TFs, including—but not limited to—ID3, TCF-1, BCL6, STAT3, FOXO1, EOMES, and ZEB1, have been linked to memory formation (Banerjee et al., 2010; Cui et al., 2011; Delpoux et al., 2018; Ichii et al., 2002; Utzschneider et al., 2018; Yang et al., 2011; Zhou et al., 2010). Among these, TCF-1 levels appear particularly critical for promoting memory T cell differentiation. During differentiation, downregulation of TCF-1 by DNMT3a-mediated DNA methylation of its encoding gene, *Tcf7*, marks an important event in early fate decisions and is associated with the loss of self-renewal capacity, the silencing of memory-associated genes, and the acquisition of an effector cell phenotype (Abadie et al., 2024; Ladle et al., 2016; Lin et al., 2016; Silva et al., 2023). Meanwhile, cells that retain high TCF-1 levels are destined to seed the pool of memory T cells. Importantly, although loss of TCF-1 was originally considered to mark a point of no return in T cell differentiation, recent evidence suggests that epigenetic silencing of *Tcf7* is a stochastic and reversible process that allows effector-to-memory cell dedifferentiation (Abadie et al., 2024). This implies that transcriptional programming toward a memory phenotype can occur both early on and during later stages of naive T cell activation. In this context, it is important to note that chromatin-modifying enzymes—recruited to genomic loci by, for example, TFs (Gourisankar et al., 2024)—play critical roles in regulating (early) memory T cell formation (reviewed in Henning et al.

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[2018]). For example, the EZH2 histone methyltransferase controls the balance between effector and memory cell differentiation through regulating the expression of key genes such as *Id3*, *Prdm1*, and *Eomes* (He et al., 2017).

Memory T cell heterogeneity

T cells with memory potential can differentiate into various memory T cell subsets that differ in their multipotency, capacity for self-renewal, migratory properties, and functional qualities (Muroyama and Wherry, 2021). Originally, memory T cells were subdivided into lymph node–homing central memory cells (T_{CM}), and effector memory T cells (T_{EM}) that are capable of rapid infiltration into inflamed tissues (Sallusto et al., 1999). Relative to each other, T_{CM} have a higher proliferative potential and produce IL-2, while T_{EM} have a heightened ability for effector functions. Today, additional subsets of memory T cells have been identified, including a population of more differentiated T_{EM} that reexpresses CD45RA—a marker usually associated with naive T cells—designated T_{EMRA}, and a population of stem cell–like memory cells (T_{SCM}) that shares features with T_{CM} and naive T cells (Gattinoni et al., 2011; Larbi and Fulop, 2014). T_{EMRA} are mostly CD8$^+$ and arise in settings of repeated antigenic stimulation (e.g., in humans infected with cytomegalovirus [Henson et al., 2012]). Despite their high capacity for producing inflammatory molecules, their absolute role in providing immunological protection remains obscure. This can be explained, at least in part, by the absence of a known murine homolog for human T_{EMRA}. In addition to T_{SCM}, T_{CM}, T_{EM}, and T_{EMRA} that circulate through blood and (lymphoid) organs, a pool of sessile memory T cells exists that permanently resides in peripheral tissues (Christo et al., 2024; Kumar et al., 2017; Szabo et al., 2019). These tissue-resident memory T cells (T_{RM}) are believed to act as first responders, conferring local protection of the host tissue in which they reside.

The distinct memory T cell subsets exhibit specific gene expression programs, chromatin landscapes, and enhancer repertoires (Giles et al., 2022; He et al., 2016; Hombrink et al., 2016; Kumar et al., 2017; Muroyama and Wherry, 2021). In addition, for CD8$^+$ T cells, a unique combination of key TFs has been assigned to each memory T cell subpopulation, most likely enforcing its unique phenotypic and functional attributes: T_{SCM} are TCF-1^{hi}c-Myb^{hi}, T_{CM} are TCF-1^{hi}FOXO1^{hi}BLC6^{hi}STAT3^{hi}ID3^{hi}EOMES^{hi}T-Bet^{lo}, T_{EM} are Blimp1^{hi}Zeb2^{hi}STAT4^{hi}ID2^{hi}T-Bet^{hi}, and T_{RM} are Blimp1^{hi}RUNX3^{hi}Hobit^{hi}KLF2^{lo}EOMES^{lo}T-Bet^{lo}TCF-1^{lo} (reviewed in Christo et al. [2024], Martin and Badovinac [2018], Muroyama and Wherry [2021], Park and Mackay [2021]). In comparison, the CD4$^+$ T cell field is somewhat lagging behind, at least in part because the Th1/Th2/Th17 framework still awaits full integration with the concept of T_{CM}/T_{EM} subset specification (Osum and Jenkins, 2023). For both CD4$^+$ and CD8$^+$ T cells, a unifying framework for the development of the distinct circulating and tissue-resident memory T cell populations is lacking, and both the hierarchy between the individual subsets and the timing of fate commitment remain controversial. Based on DNA methylation states and chromatin accessibility landscapes, a linear differentiation model has been proposed, progressing from naive to T_{SCM}, T_{CM}, T_{EM}, and T_{EMRA} (Abdelsamed et al., 2017; Durek et al., 2016; Moskowitz et al., 2017). Notably, these analyses are solely based on the study of blood-derived T cells. As we are only beginning to understand the spatial control of T cell fate decisions, revisions of these models are likely needed in the future.

Mechanisms of transcriptional priming in memory T cells

Various mechanisms have been described that prepare memory T cells for future challenges. These mechanisms include changes in metabolism and altered TCR signal transduction, as well as the maintenance of a preformed pool of (translationally repressed) cytokine mRNAs (Farber, 2009; Geltink et al., 2018; Salerno et al., 2018). In addition, inducible effector gene programs can remain epigenetically primed for rapid reactivation during secondary responses. Indeed, although the majority of activation-induced chromatin changes revert back to baseline (i.e., naive) levels upon antigen clearance, part of the effector epigenomic landscape is maintained as an "epigenetic recording" of previous transcriptional activation in resting memory T cells (Bevington et al., 2016)—allowing for more rapid (re)activation during future challenges. In this section, we will discuss the various molecular mechanisms through which genes can be transcriptionally primed for recall.

DNA methylation

The chromatin at primed gene loci often carries specific epigenetic markings, remains accessible due to DNA-bound TFs, and/or adopts specific 3D configurations that facilitate rapid transcriptional reactivation (Fig. 3). While different in nature, all these molecular adaptations take away particular roadblocks that need to be resolved before robust gene activation can be achieved. The most evolutionary ancient epigenetic mark associated with transcriptional memory may well be DNA methylation at cytosines in CpG dinucleotides. Although the relationship between DNA methylation and transcription is complex, DNA methylation—particularly in promoters—is often linked to gene repression (Mattei et al., 2022). Mechanistically, DNA methylation of cytosine residues can inhibit binding of certain TFs (Yin et al., 2017; Zhu et al., 2016) and recruit repressive methyl-CpG–binding domain protein complexes (Mattei et al., 2022). Importantly, activation-induced DNA demethylation of effector loci is often maintained by memory T cells, even during sustained rounds of homeostatic proliferation (Abdelsamed et al., 2017; Youngblood et al., 2017). Interestingly, disruption of DNA methyltransferase (e.g., DNMT3A) or demethylase (e.g., TET2) activity can promote early memory CD8$^+$ T cell formation with more potent recall abilities during antiviral responses (Carty et al., 2018; Youngblood et al., 2017), although this may also disrupt stable commitment to specific memory T cell identities (e.g., Th1 [Baessler et al., 2023]).

Nucleosome remodeling and histone modifications

Altered local nucleosomal organization provides another opportunity for transcriptional priming. Several studies have

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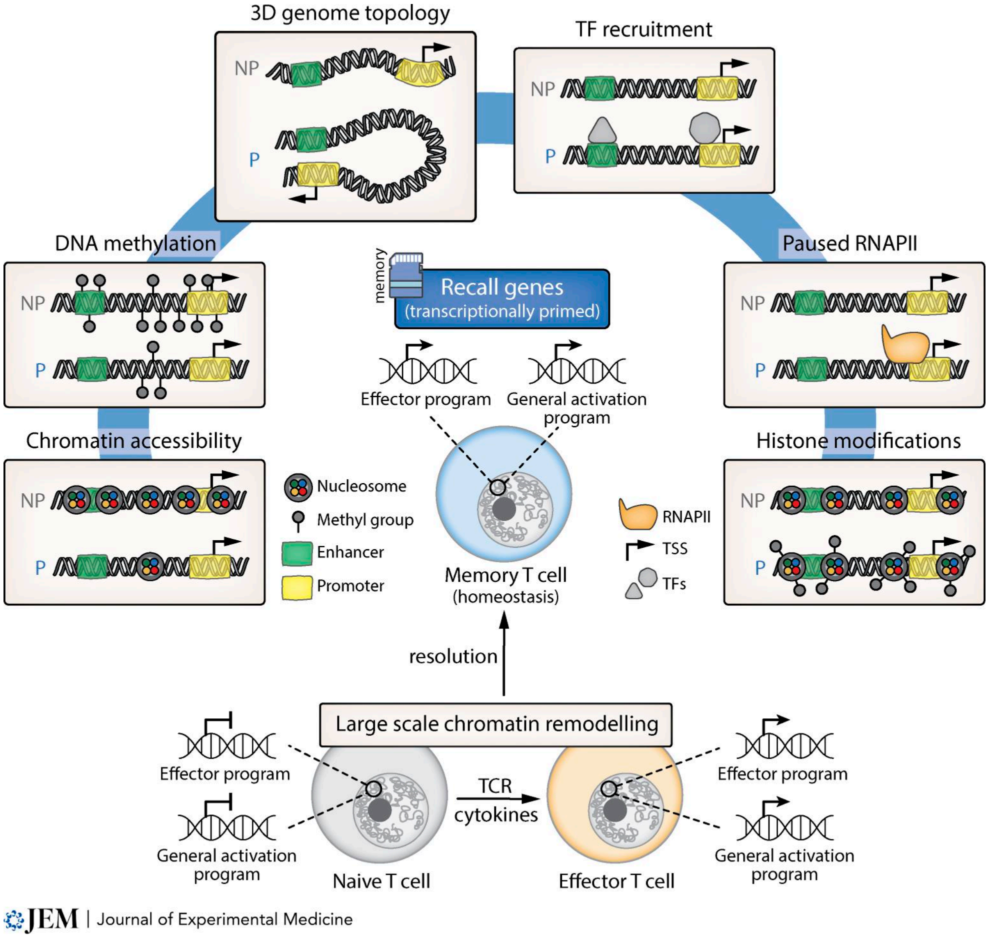

Figure 3. **Epigenomic features contributing to transcriptional priming in memory T cells.** TCR and cytokine signaling induce large-scale chromatin remodeling during naive-to-effector T cell differentiation, resulting in transcriptional induction of general activation and effector gene programs. Upon resolution of inflammation and under homeostatic conditions, memory T cells maintain a specific part of these activation-associated transcriptional programs in an epigenetically primed state. At the genomic loci harboring these so-called "recall genes," specific modifications to the local chromatin landscape at regulatory elements (i.e., promoters and enhancers) help prepare for rapid transcriptional activation upon secondary challenge of the memory T cell. Compared with the majority of NP genes, primed (P) genes can exhibit increased chromatin accessibility (i.e., through local loss of nucleosomes), reduced DNA methylation, altered histone modifications (e.g., increased histone methylation), paused RNAPII, recruitment of specific TFs, and changes in 3D genome topology (e.g., preformed promoter–enhancer contacts). All these molecular adaptations together prepare recall genes for near-instant transcriptional induction upon antigen re-encounter, and can be maintained and propagated as memory T cells undergo homeostatic proliferation. TSS, transcription start site; RNAPII, RNA polymerase II; NP, nonprimed.

shown that chromatin accessibility is maintained at inflammatory gene loci in resting memory T cells (Barski et al., 2017; Bevington et al., 2016; Mirabella et al., 2010; Tu et al., 2017; Zediak et al., 2011) and that these changes in accessibility coincide with enhanced transcriptional recall (Calderon et al., 2019; Onrust-van Schoonhoven et al., 2023; Rose et al., 2023; Santosa et al., 2023, *Preprint*; Scharer et al., 2017; Schauder et al., 2021). Also in other cell types exhibiting forms of transcriptional memory, keeping chromatin open at genomic loci of selected genes offers a direct explanation for their rapid activation by secondary stimuli (Naik and Fuchs, 2022; Natoli and Ostuni, 2019).

Apart from the presence or absence of histones, posttranslational modifications of histone tails, such as acetylation or methylation, have well-established associations with increased gene transcription (Bannister and Kouzarides, 2011; Talbert and Henikoff, 2021). While many dozens of histone modifications exist, only a handful have been investigated in the context of (T cell) transcriptional memory. Most studied are histone 3 lysine 4 methylation (H3K4me) and histone 3 lysine 27 acetylation (H3K27Ac). The presence of H3K4me at promoters (H3K4me2/3) or enhancers (H3K4me1/2) is a well-established marker of regulatory activity. Mono-, di-, and tri-methylated H3K4me can accumulate on primed genes in various contexts (reviewed in Naik and Fuchs [2022], Natoli and Ostuni [2019]), including short-term transcriptional memory in IFN-exposed HeLa cells (Siwek et al., 2020), cytokine-stimulated macrophages (Ostuni et al., 2013), and memory-like "trained" innate immune cells (Fanucchi et al., 2019; Saeed et al., 2014). Similar observations were made in memory T cells, for example, at the type II cytokine locus or in a more systematic fashion at primed genes in mouse and human $CD4^+$ memory T cells (Barski et al., 2017;

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Bevington et al., 2016; Onrust-van Schoonhoven et al., 2023). Whether H3K27Ac is also a reliable marker of transcriptional memory remains debated. Whereas primed genes in mouse skin and hematopoietic stem cells retain (moderate-to-weak) H3K27Ac signals after initial stimulation (Kaufmann et al., 2018; Larsen et al., 2021), our recent analysis of circulating human memory T cells revealed an absence of robust H3K27Ac on primed regulatory elements across the genome (Onrust-van Schoonhoven et al., 2023). Still, an earlier analysis of memory-like T cells generated in vitro did report H3K27Ac maintenance on primed genes (Bevington et al., 2016). However, "primed" T cells analyzed in this study were generated in vitro and still actively cycling in an IL-2–driven manner at the time of analysis (Bevington et al., 2016), which complicates comparisons with bona fide quiescent memory T cells generated in vivo. Loss of repressive histone marks, in particular H3K27me3, at effector genes in memory cells has also been proposed to contribute to transcriptional priming (Araki et al., 2009; Russ et al., 2014). Interesting to mention are the noncanonical histone variant proteins H2A.Z and H3.3, which can replace canonical H2A and H3 histones, respectively. These variants mark transcriptionally primed genes in model organisms such as budding yeast (Brickner et al., 2007) and fruit flies (Pascual-Garcia et al., 2017) or in cytokine-stimulated cultured cells (Kamadaa et al., 2018; Siwek et al., 2020). Interestingly, we noticed that H2A.Z also decorated the regulatory elements of primed recall genes in human memory CD4$^+$ T cells (Onrust-van Schoonhoven et al., 2023). Surprisingly, similar H2A.Z enrichment was already observed in naive T cells, suggesting that these elements may be premarked to be "memorized" at an even earlier stage of T cell development.

Collectively, these findings present a compelling case for the maintenance of chromatin accessibility, in combination with histone methylation and histone variants, as a hallmark of transcriptional priming in memory T cells. But are these epigenomic features causally involved in promoting rapid gene induction? For chromatin accessibility, this seems likely, since TF binding is strongly linked to local nucleosomal depletion (Klemm et al., 2019; Thurman et al., 2012). Disrupting chromatin remodelers in yeast was shown to deplete TFs from promoters and reduce gene expression (Brouwer et al., 2023; Nguyen et al., 2021). During T cell activation, loss of c-BAF–dependent chromatin remodeling activity impairs chromatin opening and induces a loss of TF binding that leads to dysregulated gene expression (McDonald et al., 2023). However, short-term transcriptional memory in cytokine-treated HeLa cells can occur in the absence of retained chromatin accessibility (Siwek et al., 2020). A causal role of H3K4 methylation in rapid recall seems unlikely at first glance, since it was shown to only play a minor role in transcriptional regulation—in contrast to H3K27me3 (Morgan and Shilatifard, 2020). Nevertheless, H3K4me2 is required for promoter priming in yeast (Light et al., 2013) and murine memory Th2 cells deficient in the H3K4 histone methyltransferase KMT2A exhibit impaired recall responses in vivo (Yamashita et al., 2006). Loss of the H3K27 histone methyltransferase EZH2 results in impaired memory CD8$^+$ T cell recall responses (Gray et al., 2017; He et al., 2017). Finally, histone variants are strong contenders, as H2A.Z was shown to poise genes for induction in yeast by destabilizing histone–DNA interactions (Brickner et al., 2007; Zhang et al., 2005) and H2A.Z—but not H3.3—promotes DNA accessibility (Li et al., 2023).

3D genome topology

Alongside the classical 1D DNA and chromatin modifications described above, alternative mechanisms for transcriptional priming have been proposed (Fig. 3). These include maintaining paused RNA polymerase II at primed gene promoters to facilitate rapid induction of transcription (Core and Adelman, 2019; D'Urso et al., 2016; Light et al., 2013), a phenomenon that may also occur in memory T cells (Getzler et al., 2023, *Preprint*; Onrust-van Schoonhoven et al., 2023). In addition, the 3D localization of genes and their regulatory elements in the cell nucleus has more recently been linked to transcriptional priming and memory (Cuartero et al., 2023; Ghavi-Helm et al., 2014; Stik et al., 2020; van Schoonhoven et al., 2020). For example, positioning genes away from the repressive chromatin environment of the nuclear periphery may facilitate rapid activation, as was observed for early responder genes during Jurkat T cell activation (Robson et al., 2017). Our recent analysis of human memory Th2 cells revealed a striking spatial compartmentalization of primed recall genes and their associated enhancers in 3D chromatin hubs and "memory TADs"(Onrust-van Schoonhoven et al., 2023). These structures localized to the more transcriptionally permissive nuclear interior, connecting primed genes with their regulatory elements during memory T cell homeostasis (Onrust-van Schoonhoven et al., 2023). Concentrating the primary actors and biochemical components (e.g., TFs, transcriptional cofactors) required for efficient transcriptional recall in 3D nuclear space offers an additional layer of priming that can act synergistically with local DNA and chromatin modifications. Similar to chromatin accessibility dynamics, we observed that these memory-specific 3D chromatin interactions closely resembled the architectural organization observed in recently activated cells, indicating that spatially organized nuclear neighborhoods are maintained in memory T cells after being established during their initial activation (Onrust-van Schoonhoven et al., 2023). Indeed, elegant studies of murine antiviral CD8$^+$ T cell responses support the concept that memory T cells retain effector-like 3D chromatin topology at genes primed for rapid transcriptional recall (Santosa et al., 2023, *Preprint*; Zhu et al., 2023), and CTCF is critical for efficient secondary responses in vivo (Zhu et al., 2023). Localization of selected genes near nuclear pore complexes has also emerged as a means for transcriptional priming (Light et al., 2010; Light et al., 2013; Pascual-Garcia et al., 2017), although the precise underlying mechanisms and the relevance for T cell memory remain to be determined.

In all of the abovementioned epigenomic strategies for transcriptional priming, TFs are likely to play critical roles as they interact with chromatin-modifying enzymes (Gourisankar et al., 2024), target them to genomic sites, and can organize 3D chromatin loops (Aboreden et al., 2025; Stadhouders et al., 2012). Although multiple TFs have been implicated in memory T cell

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formation (see above), their role in memory T cell homeostasis—including their contribution to the maintenance of transcriptional memory—is poorly understood.

Establishing and maintaining transcriptional memory

The epigenetic features associated with rapid transcriptional recall described above are intimately linked to T cell activation, and appear to be specifically retained at a small fraction of genomic sites as cells adopt a memory phenotype. But what mechanisms are responsible for establishing and maintaining the epigenomic memory signature after initial activation and during memory T cell homeostasis?

The role of TFs

As discussed earlier, TFs hold critical instructive power in shaping epigenomes. However, the role of TFs in establishing and maintaining the epigenomic signature of memory T cells remains surprisingly understudied, in particular since TFs can actively recruit chromatin-modifying complexes such as c-BAF and MLL to their target sites. In blood stem cells, long-lasting endotoxin-induced transcriptional memory—but not the transient primary response—requires the binding of the TF C/EBPβ to primed enhancers (de Laval et al., 2020). Elegant work in mouse epidermal stem cells by Fuchs and colleagues revealed a central role of STAT and AP-1 TFs in priming for enhanced secondary repair responses after an inflammatory stimulus (Larsen et al., 2021). The authors propose a two-step mechanism. First, a cell type–specific and stimulus-specific TF such as STAT3 cooperates with a universal stress response factor (e.g., AP-1 family member FOS) to establish primed chromatin at specific genes activated during the initial inflammatory response. Indeed, chromatin accessibility at such loci is abrogated by depletion of either STAT3 or FOS (Larsen et al., 2021). As the levels of these TFs are reduced in the resolution phase, TFs associated with the homeostatic phase (e.g., ATF3) start occupying the primed regions—likely maintaining local chromatin accessibility. Upon recall, recruitment of FOS for transcriptional reactivation no longer requires STAT3 (Larsen et al., 2021). Similarly, STAT1 was shown to be required specifically for induction of transcriptional priming but not for its maintenance in cytokine-treated HeLa cells (Tehrani et al., 2023). Hence, these studies demonstrate that the maintenance of transcriptional memory may rely on other factors than those responsible for its establishment. Important to take into consideration here is the role of so-called "pioneer" factors, a special class of TFs with the ability to initiate opening of closed chromatin (Balsalobre and Drouin, 2022; Zaret, 2020). Underlying this unique capacity is the ability of pioneer TFs to engage in transient interactions with nucleosomal DNA, allowing them to scan closed chromatin for their target motifs (Zaret, 2020). As such, pioneer TFs may prepare a locus for priming, enabling nonpioneer TFs and/or chromatin remodeling complexes to enter and aid in the establishment or maintenance of transcriptional memory.

This two-step model for transcriptional memory has clear parallels with the sequential waves of TF activity that guide the activation and effector differentiation of naive T cells (see Fig. 2). Although attractive, whether it also applies to memory T cell recall responses remains to be determined. A key issue is that the identity of the TFs that establish and maintain the primed chromatin landscape at recall-associated genes in memory T cells is only partially understood. We and others have consistently detected AP-1 family TF factor motifs strongly enriched within regions that (partially) retain chromatin accessibility in memory CD4$^+$ and CD8$^+$ T cells after their initial opening during primary activation of naive T cells (Bevington et al., 2016; Larsen et al., 2021; Lau et al., 2018; Onrust-van Schoonhoven et al., 2023; Sen et al., 2016). In the Fuchs et al. model, AP-1 TFs in T cells—acting immediately downstream of the TCR—perfectly fit the role of the broadly acting stress response factor. But which factors may be cooperating with AP-1 for memory establishment in T cells, and which TFs maintain the primed chromatin landscape during homeostasis? The same motif enrichment analyses also revealed potential cobinding of RUNX, ETS, and STAT TFs. Studies of in vitro generated memory-like mouse T cells indeed revealed binding of STAT5, RUNX1, and ETS1 to primed accessible regions in memory-like cells (Bevington et al., 2016; Bevington et al., 2020), although these did not include factor depletion experiments to validate their requirement for chromatin priming. However, removal of STAT5-inducing cytokines (i.e., IL-2/IL-7) or the IL-7 receptor resulted in reduced chromatin accessibility and diminished transcriptional reactivation (Bevington et al., 2020)—in line with a potential role of STAT5-inducing homeostatic signals (e.g., IL-7, IL-15) in maintaining epigenetic priming in memory T cells (Abdelsamed et al., 2017). In mouse CD8$^+$ T_{CM} cells, the TCF1 TF has recently been implicated in maintaining accessibility at a subset of primed regions, which were strongly enriched for AP-1 motifs (Shan et al., 2022a). Thus, a scenario in which an initial STAT/AP-1–driven establishment of memory is followed by the recruitment of additional homeostatic TFs for maintenance of memory may also occur in T cells, although this concept still awaits experimental validation. Interesting to consider in such studies is how TFs exploit or instruct 3D chromatin architecture. In murine CD8$^+$ T cells, it was shown that CTCF binding sites and 3D chromatin interactions acquired during the effector phase are partially conserved in T_{CM} cells (Zhu et al., 2023). These 3D hubs harbor genes that are strongly induced during memory recall, suggesting a critical role of CTCF and the stable rewiring of 3D chromatin organization in establishing transcriptional memory in T cells (Zhu et al., 2023).

The repeated observation that chromatin priming is established during an initial wave of transcriptional activation raises the possibility that TFs may promote memory formation via the induction of transcription. In HeLa cells, artificially activating genes with CRISPRa instead of IFN-γ exposure does not induce transcriptional priming (Tehrani et al., 2023). A history of transcription is therefore at least not always sufficient to induce memory. Experiments in yeast support a nonessential role of transcription itself, as repression of *INO1* transcription during the memory establishment phase did not prevent priming-associated nuclear relocalization of *INO1* (Brickner et al., 2007).

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Epigenetic marks during the cell cycle

One key aspect of stably maintaining an epigenomic imprint in a dividing population of cells—e.g., memory T cells undergoing homeostatic proliferation—is to faithfully reestablish DNA or chromatin modifications in daughter cells after completing the cell cycle (Dogra et al., 2016; Espinosa-Martínez et al., 2024; Flury and Groth, 2024). Particularly challenging for gene regulatory processes are (1) genome replication or S phase, which entails synthesizing two daughter strands using newly generated nucleotide and histone building blocks, and (2) mitosis or M phase, which involves drastic condensation and topological rearrangement of chromatin. In order to propagate a primed chromatin state across memory T cell generations, reliable mechanisms for copying or rapid reestablishment of epigenetic markings need to exist. For DNA methylation, the DNMT1 methyltransferase can recognize "hemi-methylated" DNA consisting of a methylated parental strand and the unmethylated newly synthesized strand. Upon recognition, DNMT1 restores CpG DNA methylation on the unmethylated strand, and global DNA methylation patterns are preserved in mitotic chromosomes (Espinosa-Martínez et al., 2024). How specific histone modifications are correctly and accurately transmitted during the cell cycle is a topic of active investigation (Espinosa-Martínez et al., 2024; Flury and Groth, 2024; Gonzalez et al., 2021). Recent studies support a model in which histone chaperone proteins, such as MCM2, ensure that parental histones—including their modifications—are symmetrically distributed on replicated chromosomes (Escobar et al., 2021; Espinosa-Martínez et al., 2024; Flury and Groth, 2024). Such recycling of modified parental histones occurs with high accuracy for many active and repressive marks, as well as histone variants, within ~250 bp of the original position (Flury and Groth, 2024). Modification- and locus-specific restoration mechanisms are thought to subsequently impose parental chromatin states onto naive histones through the action of protein complexes that can read and write histone modifications, in particular for repressive histone methylation marks such as H3K27me3 (Escobar et al., 2021; Espinosa-Martínez et al., 2024; Flury and Groth, 2024; Serra-Cardona et al., 2022).

After their restoration during the S phase, histone modifications—most prominently histone methylation marks—are retained on mitotic chromatin and transmitted to both daughter cells (Espinosa-Martínez et al., 2024; Wang and Higgins, 2013). In contrast, chromatin accessibility patterns are largely erased upon DNA replication but are then very rapidly reestablished as transcription restarts (Ostrowski et al., 2025; Ramachandran and Henikoff, 2016; Stewart-Morgan et al., 2019). During the S phase, TFs such as CTCF and the basal transcription machinery—first displaced by passage of the replication fork—are thought to compete with nucleosomes for binding the newly synthesized DNA strands (Ostrowski et al., 2025; Ramachandran and Henikoff, 2016). In the M phase, RNA polymerase II is displaced from the chromatin and most transcription ceases (Espinosa-Martínez et al., 2024; Zhang et al., 2019). However, chromatin accessibility is widely preserved during mitosis (Festuccia et al., 2019; Hsiung et al., 2015; Teves et al., 2016), and a set of TFs remains dynamically associated with mitotic chromatin—a process referred to as "mitotic bookmarking" (Gonzalez et al., 2021; Palozola et al., 2019; Teves et al., 2016). Interestingly, whereas 3D genome architecture is preserved during the S phase, all major topological features (i.e., chromosomal A/B compartments, TADs, and chromatin loops [Bonev and Cavalli, 2016; Oudelaar and Higgs, 2021; Stadhouders et al., 2019]) are erased during mitosis and rebuild immediately after mitotic exit when cohesin-mediated loop extrusion restarts (Nagano et al., 2017; Naumova et al., 2013; Zhang et al., 2019). In a complex and often cell type–specific (Espinosa-Martínez et al., 2024) interplay, these processes ensure that cells can transfer their epigenomic landscape—and their identity as a direct consequence—across cell divisions.

Maintenance of epigenetic priming in memory T cells

Few studies have directly addressed how transcriptional priming at the epigenome level is maintained in memory T cells under homeostatic conditions. Studies using transgenic mice often include Cre recombinase drivers that inactivate genes during thymic T cell development, making it difficult to separate effects on initial memory T cell differentiation from those that (also) act during homeostasis after memory T cells have been generated. Moreover, gene inactivation at later stages of development may still have unintended consequences for peripheral immune responses. Early work revealed that deletion of *Dnmt1* during mouse thymocyte differentiation resulted in reduced peripheral memory T cell numbers, which appeared to be caused by an impaired proliferative capacity of *Dnmt1*-deficient naive T cells (Lee et al., 2001). Carefully controlled de novo DNA methyltransferase activity by DNMT1 is likely also critical for maintaining a transcriptionally primed state in established memory T cells, but this remains to be experimentally shown. Loss of function of the c-BAF chromatin remodeling complex in mature mouse CD8^{+} T cells revealed only minor changes in the generation of circulating memory T cell subsets following a primary antiviral response (McDonald et al., 2023). However, these memory T cells showed severely impaired recall responses. Although the authors did not investigate this directly, it seems plausible to us that chromatin accessibility initiated and/or maintained by c-BAF at transcriptionally primed genes is critical for memory T cell recall. Compelling evidence for histone methylation being key for maintaining transcriptional priming comes from analyses of memory Th2 cells heterozygous for the H3K4 methyltransferase KMT2A (also called MLL1) (Yamashita et al., 2006). T cells from *MLL*$^{+/-}$ mice developed normally, showed equal responsiveness to TCR stimulation as wild-type cells, and were able to efficiently adopt Th1 or Th2 phenotypes in vitro. Strikingly however, resting memory *MLL*$^{+/-}$ Th2 cells lost their rapid recall ability, failed to maintain H3K4me2 levels at genomic loci of effector cytokine genes but also showed reduced levels of the key GATA3 TF (Yamashita et al., 2006). Interestingly, a recent preprint reported that during the initial TCR stimulation of naive T cells, MLL1 already deposits H3K4me3 at genes destined to be transcriptionally primed in memory T cells (Getzler et al., 2023, *Preprint*).

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Epigenetic basis of T cell dysfunction

T cell exhaustion

While epigenetic mechanisms durably endow memory T cells with the ability to rapidly recall inflammatory gene transcription, inappropriate chromatin priming may drive T cells into a state of relative dysfunction. Such undesired epigenetic remodeling is often observed in settings of chronic TCR signaling, such as in patients with diseases in which the source of antigen persists (Collier et al., 2021; Lan et al., 2023; McLane et al., 2019; Seo et al., 2021). In the context of chronic viral infections (e.g., HIV) and cancer, the resulting dysfunctional state that the chronically activated T cell enters is often referred to as "exhaustion." Exhausted T cells (T_{EX}) are characterized by sustained high-level expression of inhibitory receptors ("checkpoints," such as PD-1, TIM-3, CTLA4, and LAG3), metabolic alterations, and a hierarchical loss of their effector functionality and capacity for proliferation (Lan et al., 2023; McLane et al., 2019). T cell exhaustion has evolved as an a priori mechanism to manage potential chronic activation (Chu et al., 2025; McManus et al., 2025), but limits T cell–mediated immunity in chronic infection and cancer (Baessler and Vignali, 2024; Cornberg et al., 2013; Speiser et al., 2014). Revitalizing T_{EX} through immunotherapies that target exhaustion-associated inhibitory receptors has become a leading approach in the treatment of cancer and chronic infections, as recognized by the 2018 Nobel Prize in Medicine and Physiology (Kraehenbuehl et al., 2022; Wolchok, 2018).

Epigenetic anchoring of exhaustion

For CD8⁺ T cells, compelling scientific evidence has been obtained that their exhaustion is enforced by a discrete epigenetic signature that distinguishes T_{EX} from both effector and memory T cells (Belk et al., 2022; Ghoneim et al., 2017; Muroyama and Wherry, 2021; Sen et al., 2016). The epigenetic program of exhaustion becomes gradually imprinted during T_{EX} generation through stable rewiring of chromatin accessibility, histone modifications, and DNA methylation landscapes (Ford et al., 2022; Gennert et al., 2021; Ghoneim et al., 2017; Ma et al., 2025; Pauken et al., 2016; Philip et al., 2017). Herein, c-BAF–mediated chromatin remodeling appears to play a critical role by controlling the accessibility of TF binding sites (Battistello et al., 2023). These epigenetic changes contribute to the silencing of genes important for memory/effector T cell differentiation and functionality, such as *TCF7* (encoding TCF-1) and *IFNG*, while promoting the expression of T_{EX}-associated genes, including *PDCD1* and *HAVCR2*, encoding the PD-1 and TIM-3 checkpoints, respectively. For example, in T_{EX}, the *PDCD1* gene loses suppressive DNA methylation at the promoter region, acquires a bona fide accessible enhancer element that promotes its expression, and gains activating H3K4me1/2 and H3K27Ac histone modifications at several of its regulatory regions (Bally et al., 2020; Pauken et al., 2016; Philip et al., 2017; Sacristán et al., 2024). The precise role of 3D genome organization in T_{EX} development remains largely unknown. However, most of the exhaustion-associated changes in chromatin accessibility occur at distal enhancers, thus suggesting a potentially important role of chromatin architecture. Supporting this hypothesis, a study comparing exhausted and functional chimeric antigen receptor (CAR) T cells demonstrated changes in 3D chromatin architecture at exhaustion-associated genes, including *PDCD1*, *HAVCR2*, and *CTLA4* (Gennert et al., 2021).

The developmental path leading to exhaustion remains incompletely understood, and a full description is beyond the scope of this review. Most studies support a progressive model in which PD-1^{int}TIM-3^{-}TCF-1^{+}CXCR5^{+}SLAMF6^{+} progenitor T_{EX} transit through several intermediate T_{EX} stages and eventually give rise to terminally T_{EX} that are PD-1^{hi}TIM-3^{+}TCF-1^{-}SLAMF6^{-} (Beltra et al., 2020; Im et al., 2016; Miller et al., 2019; Utzschneider et al., 2016). Importantly, while progenitor T_{EX} are amenable to "rejuvenation" by immunotherapies, terminal T_{EX} are fate-locked in a hyporesponsive state (Im et al., 2016; Miller et al., 2019; Pauken et al., 2016; Sade-Feldman et al., 2019; Siddiqui et al., 2019). The exhaustion-specific epigenomic landscape cannot be reverted by immunotherapies and may persist even after cessation of antigenic stimulation, as demonstrated in patients with chronic viral infections (Hensel et al., 2021; Pauken et al., 2016; Yates et al., 2021). This suggests that T_{EX} eventually acquire "inappropriate memory" for a state of dysfunction, restricting the full potential of T cell–based immunotherapies, particularly immune checkpoint blockade and CAR T cell therapy (Pauken et al., 2016; Zebley et al., 2021b). Future endeavors aiming to unravel the initiating chromatin remodeling events and those that eventually lock terminal T_{EX} in a state of dysfunction are essential to accommodate the unmet need for improved efficacy of these therapeutic modalities. Excitingly, recent efforts exploring opportunities to target epigenetic regulators of T cell exhaustion are now beginning to pave the way for development of improved (combination) immunotherapies (Battistello et al., 2023; DeGolier et al., 2025; Isshiki et al., 2025; Kang et al., 2024; Prinzing et al., 2021; Urbanek-Quaing et al., 2024; Weiss et al., 2024). However, the exhaustion-associated epigenetic landscape is unlikely to be easily dismantled. For example, inhibiting c-BAF–mediated chromatin remodeling can prevent exhaustion, although it was not sufficient to revert exhaustion once it has been established (Battistello et al., 2023). Interestingly, terminal T_{EX} retain regions of active chromatin, including primed enhancers enriched for AP-1/bZIP family TF binding sites, which correlated poorly with gene expression (Ford et al., 2022). This decoupling between chromatin state and transcriptional output could be reversed through modulation of hypoxia and costimulatory signaling, indicating that therapeutic strategies for reinvigorating terminal T_{EX} can be identified (Ford et al., 2022).

TFs driving exhaustion

The dysregulation and altered usage of TFs that are normally crucial for effector functions are emerging as a driver of the exhaustion program at the chromatin level (Fig. 4). Upon acute antigenic stimulation, NFAT—induced by TCR-mediated Ca^{2+} signaling and calcineurin—physically interacts with the FOS-JUN heterodimer and binds to NFAT:AP-1 composite sites within gene regulatory elements (Chen et al., 1998). This NFAT:AP-1 partnership is essential for the activation of genes important to T cell activation and effector functions. Chronic activation

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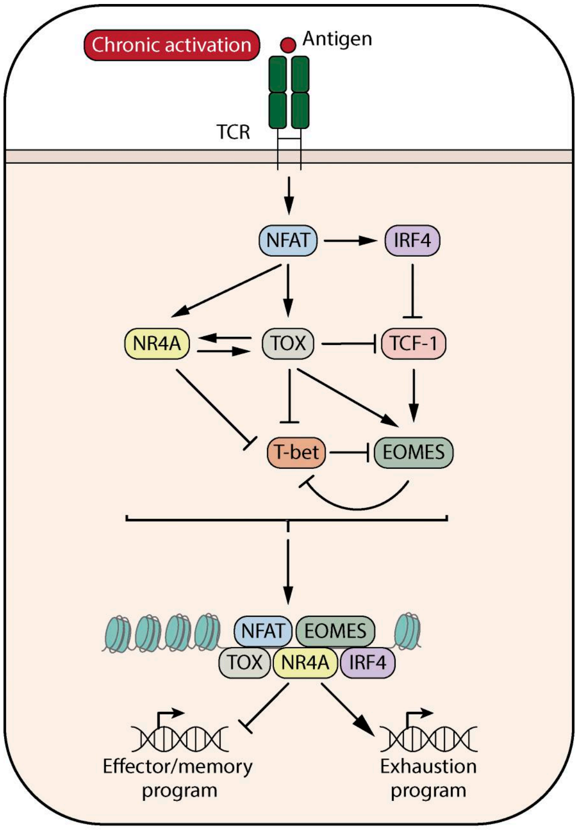

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Figure 4. **Molecular events driving CD8$^+$ T cell exhaustion.** Persistent antigen exposure leads to chronic TCR stimulation of effector (memory) CD8$^+$ T cells, which causes dominant NFAT TF activation at the expense of AP-1 TF activity. The NFAT:AP-1 imbalance triggers the expression of TOX, NR4A, and IRF4, which together repress T-bet and TCF-1 and (indirectly) promote elevated EOMES levels. As a result, NFAT, TOX, NR4A, EOMES, and IRF4 control the chromatin landscape of chronically activated CD8$^+$ T cells, promoting a transcriptional program that results in exhaustion while suppressing the effector/memory program.

imbalances NFAT:AP-1 complexes, resulting in "partnerless" NFAT and the acquisition of an exhausted phenotype (Martinez et al., 2015). Partner-less NFAT can directly bind to the regulatory elements of *Pdcd1* and *Havcr2* (encoding checkpoints PD-1 and TIM-3) to activate their expression (Martinez et al., 2015). In addition, NFAT induces the expression of TOX: a master TF of T_{EX} development (Alfei et al., 2019; Khan et al., 2019; Scott et al., 2019; Yao et al., 2019). TOX is a crucial initiator of the epigenetic remodeling that underpins exhaustion and is expressed by all T_{EX} subsets, with the highest levels being detected in terminal T_{EX} (Beltra et al., 2020). TOX expression is required for T_{EX} development, yet TOX activation alone is not sufficient to induce exhaustion (Sekine et al., 2020). TOX reduces chromatin accessibility at gene loci important for memory (e.g., *Tcf7*) and effector (e.g., *Klrg1*, *Zeb2*, and *Gzmb*) CD8$^+$ T cell differentiation and the opening of T_{EX}-associated genes (e.g., *Pdcd1*, *Entpd1*, and *Havcr2*), likely by recruiting epigenetic regulators such as KAT7, DNMT1, and SIN3A (Khan et al., 2019). Besides its role in the initiation of exhaustion, recent findings show that continuous TOX expression reinforces T_{EX}-specific chromatin accessibility landscapes in committed T_{EX} (Huang et al., 2025). This observation supports a model in which TOX actively contributes to limiting the potential of committed T_{EX} to enter a functional state, thus restricting immunotherapy efficacy. It was recently shown that IL-2/STAT5 signaling can antagonize TOX-driven epigenetic imprinting (Hashimoto et al., 2022). Interestingly, constitutive STAT5 activity induced partial rewiring of the T_{EX}-associated epigenetic program toward a memory/effector chromatin landscape, suggesting an opportunity to exploit STAT5 activity to reprogram T_{EX} toward more functional states (Beltra et al., 2023).

TOX appears to act in concert with NR4A family TFs for establishing the exhaustion program downstream of NFAT (Seo et al., 2019) (Fig. 4). TOX and NR4A1 show similar expression patterns during T_{EX} development, positively influence each other's expression, and both contribute to the downregulation of TCF-1 (Khan et al., 2019; Seo et al., 2019; Srirat et al., 2024). Mechanistically, NR4A1 inhibits recruitment of AP-1 factors to their target gene regulatory regions, thereby preventing AP-1–driven expression of effector molecules (Liu et al., 2019). In addition to TOX and NR4A, NFAT induces and cooperates with IRF4, which has been linked to multiple hallmarks of exhaustion, including metabolic changes, impaired cytokine production, and suppression of memory T cell formation (Hirsch et al., 2024; Man et al., 2017).

The severity of exhaustion is strongly linked to imbalanced expression of EOMES and T-Bet (Paley et al., 2012). These T-box family TFs are crucial for normal CD8$^+$ T cell differentiation and effector functionality but become dysregulated in chronically activated T cells (Beltra et al., 2020; Buggert et al., 2014; Intlekofer et al., 2005; Paley et al., 2012). While high levels of T-Bet are associated with progenitor T_{EX}, the sustained high-level expression of EOMES favors terminal exhaustion. It has been suggested that TCF-1 and TOX drive the altered T-Bet-to-EOMES ratio in favor of EOMES, thereby antagonizing effector T cell differentiation and endorsing terminal exhaustion (Alfei et al., 2019; Chen et al., 2019; Paley et al., 2012). EOMES promotes exhaustion, at least in part, through upregulation of inhibitory receptors (including PD-1 and LAG-3) and downregulation of memory-associated factors (such as TCF-1), while T-Bet represses PD-1 expression (Kao et al., 2011; Li et al., 2018; Yu et al., 2022). This imbalanced expression of T-box family TFs may even become irreversible: in HIV patients, high EOMES and inhibitory receptor levels were maintained even after 10 years of undetectable viral load and an absence of antigenic stimulation (Buggert et al., 2014).

Important to mention is that T cell exhaustion has been most extensively studied for CD8$^+$ T cells. Further research is required to better define CD4$^+$ T cell exhaustion, its molecular underpinnings, and potential for therapeutic applications (Miggelbrink et al., 2021). Nevertheless, aberrant chromatin priming most likely also plays an important role in CD4$^+$ T cell–driven diseases. Indeed, memory CD4$^+$ T cells are key drivers of chronic inflammation in various immune-mediated diseases, including allergies and asthma (Olsthoorn et al., 2025). We have recently shown that memory CD4$^+$ Th2 cells from asthma patients exhibit "hyperpriming" of their inflammatory transcriptional program during

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homeostasis (Onrust-van Schoonhoven et al., 2023). Recall-associated enhancers and gene promoters in these pathological memory T cells showed elevated H3K4me2 levels and transcriptional activity, despite an otherwise quiescent phenotype (Onrust-van Schoonhoven et al., 2023). These observations are indicative of a dysfunctional state in which memory T cells fail to maintain properly calibrated levels of transcriptional priming, which may render them vulnerable to premature activation and contribute to chronic tissue inflammation. However, future studies are needed to validate this concept.

Concluding remarks and future directions

Tremendous progress has recently been made in our understanding of how epigenetic priming underpins the remarkable capacity of memory T cells to mount superior secondary immune responses. Highly specific modifications of DNA and histones, positioning of nucleosomes, and 3D genome organization act in conjunction to establish a primed chromatin landscape that is stably maintained within the pool of long-lived quiescent memory T cells. Implemented and maintained by combinatorial TF action, this epigenetic imprint poises inflammatory genes for rapid transcriptional reactivation upon antigen rechallenge. The importance of epigenetic priming for T cell–mediated immunity is underscored by the growing body of scientific evidence demonstrating that its dysregulation underlies T cell dysfunction in patients with chronic disease. It is important to reiterate that most of the current knowledge in the field is based on murine T cells, and therefore, translating findings to a human context continues to be important. It is also worth noting that observations from studies aiming to assign functional roles to TFs, chromatin remodelers, and architectural proteins—proteins with a broad regulatory scope—through genetic deletion should be interpreted with some caution, as the resulting phenotypic outcomes often reflect both direct and indirect effects. Moreover, despite extensive efforts to profile the epigenome of (dys)functional T cell states, it often remains challenging to extract causal relationships—especially regarding 3D genome topology, which is difficult to experimentally manipulate. Excitingly, the rapidly expanding toolbox for CRISPR/Cas-based (epi)genome editing is now offering scientists opportunities to tackle this issue, and discriminate between cause and consequence.

Despite compelling evidence that transcriptional memory in T cells has an epigenetic basis, much remains unknown about the molecular mechanisms responsible for maintaining and propagating this chromatin-based information in mature memory T cells as they undergo homeostatic proliferation. We propose that TFs are prime candidates here, due to their sequence specificity, potential to recruit chromatin-modifying enzymes, and ability to retain close associations with chromatin during the cell cycle. Importantly, although many TFs have been associated with memory T cell generation, their roles in mature memory T cell function are often poorly understood. Most TFs linked to T cell memory have been identified based solely on differential gene expression analysis. However, alterations in the accessibility of their cognate binding sites or differential interactions with other regulatory (co)factors can have functional consequences (e.g., redistribution of TF occupancy) even if the TF-encoding gene is not differentially expressed (Liu et al., 2023; Zhao et al., 2024), suggesting that putative key regulatory (transcription) factors may be overlooked. Additional outstanding questions concern the heterogeneity of chromatin priming mechanisms in individual T cells, the molecular mechanisms underlying memory T cell heterogeneity, the timing of fate commitment toward specific (dys)-functional T cell states, and how the stability of epigenetic programs is influenced by the tissue microenvironment during health and disease.

We anticipate that addressing the main knowledge gaps mentioned above will be crucial for exploring possibilities to rationally target and reprogram epigenetic programs in T cells for the benefit of human health, paving the way for development of improved vaccination strategies and T cell–based immunotherapies. Finally, recent studies have challenged the traditional view that immunological memory is a distinguishing feature of adaptive immune cells. Indeed, innate immune cells and even nonimmune cells can enter a "trained" state that is characterized by transcriptional memory and altered secondary responses (Netea et al., 2020). Harnessing insights from T cell memory may help to unravel the molecular basis of trained immunity. Ultimately, we expect that dissecting the epigenetic underpinnings of transcriptional memory in both innate and adaptive immune cells offers tremendous potential for unlocking novel therapeutic strategies to treat or prevent immune-related diseases and cancer.

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