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Helper T cell plasticity: Impact of Extrinsic and Intrinsic Signals On Transcriptomes and Epigenomes

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Abstract

$CD4^+$ helper T cells are crucial for autoimmune and infectious diseases; however, the recognition of the many, diverse fates available continues unabated. Precisely what controls specification of helper T cells and preserves phenotypic commitment is currently intensively investigated. In this review, we will discuss the major factors that impact helper T cell fate choice, ranging from cytokines and the microbiome to metabolic control and epigenetic regulation. We will also discuss the technological advances along with the attendant challenges presented by “big data”, which allow the understanding of these processes on comprehensive scales.

1. Introduction

The generation of diverse types of effector CD4 T cells and the balance with production of various types of regulatory T cells is crucial for the protection against infections, but is also critical for a variety of autoimmunity diseases (Reiner et al. 2007). In fact, understanding how CD4 T cells differentiate into these diverse fates has already provided insights not only into immunopathogenesis but also has facilitated the development of new therapies. CD4 T cell fate choice has been recognized since the late 1980's, but the remarkable complexity of options available to these cells continue to be elucidated. Aside from T helper 1 (Th1) cells and Th2 cells, subsets termed Th17, Th22, Th9 and follicular T helper (Tfh) cells (Zhou et al. 2009a) have been recognized. Equally relevant for the pathogenesis of autoimmune disease are the mechanisms that lead to different types of regulatory T cells, including those that express Foxp3 and those that do not (Rudensky 2011) (Ohkura et al. 2013) (Awasthi et al. 2007) (Gregori et al. 2012). But even among these defined subsets, we also appreciate considerable heterogeneity and plasticity (Cannons et al. 2013) (O'Shea and Paul 2010) (Coomes et al. 2013) (Yamane and Paul 2012) (Dong 2011) (Zhu and Paul 2010).

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Consequently, the previous 1:1:1 model of differentiation (one lineage/function, one signature cytokine and one master regulator transcription) has given way to a more nuanced view of specification (Crotty 2012), and the plasticity versus stability of these subsets, both effector and regulatory continues to be intensively investigated. Thus, more sophisticated understanding of helper T cell differentiation will surely continue to be useful for immunologists both in terms of understanding and treating disease.

In this review, we will discuss the current views of helper T cell diversity and evolving insights into the mechanisms that underlie their differentiation. The appreciation of the enormous range of T cells fates has occurred at a time when our basic understanding of the regulation of gene expression is changing and new techniques are being devised. The impact of the epigenome on cell fate determination is being re-examined as new technologies to measure these changes also emerge. Indeed, the more flexible view of cell fate has been a general lesson of cell biology, well beyond immune cells. It is premature at this time to propose a unifying framework of how networks of transcription factors and epigenomic changes converge to drive helper T cell fate choice while maintaining opportunities for plasticity. Nor can we hope to be comprehensive in covering all of these topics in a single review. Rather, we will try to provide a few illustrative examples of molecular mechanisms that can promote flexibility in the context of cellular differentiation. We will try to explain how new technologies have modified our views of the CD4 T cells biology and their capacity for plasticity in response to a constantly changing environment.

2. Old and new players in lineage specification of helper T cells

Based on their function and cytokine expression, activated $CD4^+$ T helper (Th) cells were initially classified into two subsets (Mosmann and Coffman 1989): Th1 cells that produce Interferon-γ (IFN-γ) and Th2 cells that produce interleukin (IL)-4, IL-5 and IL-13 as their respective signature effector cytokines. In this way, CD4 T cells orchestrate the type of immune response that ensues upon encounter of diverse microbial pathogens. Regulated cytokine production is required for the proper elimination of microbial pathogens: Th1 cells for intracellular microbes and Th2 cell for helminthes (Abbas et al. 1996). Extrinsic factors, especially cytokines, are also critical in that they activate transcription factors especially members of the signal transducer and activator of transcription (STAT) family, which in turn control helper cell differentiation. IFN-γ and IL-12 activate STAT1 and STAT4 whereas IL-4 activates STAT6. Th2 cells lose their sensitivity to the Th1 cell-inducing cytokine IL-12 via downregulation of IL-12 receptor ß2 (IL-12R ß2) and STAT4 expression (Szabo et al. 1997) (Usui et al. 2003). In addition to STAT4 and STAT6, STAT5 plays a critical role for both Th1 and Th2 cell differentiation, transmitting IL-2-dependent signals (Liao et al. 2011). Differentiation leads to high expression of transcription factors termed master regulators, which when over-expressed are sufficient to induce signature cytokines. For instance, T cell receptor (TCR) and STAT signals induce the T-box-containing protein, T-bet (encoded by *Tbx21*) (Szabo et al. 2000). Conversely, GATA-binding protein-3 (GATA-3) is critical for the development of the Th2 cell lineage (Zhang et al. 1997) and overexpression is sufficient to drive Th2 differentiation. Unlike T-bet though, GATA-3 also has other functions in thymic development.

While the appreciation of diverse CD4 helper cell fates was a breakthrough in elucidation of immunoregulatory mechanisms, it also became clear that a dichotomous view of Th1 and Th2 cells failed to explain many aspects of immune responses and especially autoimmunity. The discovery of another subset of cells, Th17 cells, subsequently provided a number of insights (Yang et al. 2008b) (Stockinger et al. 2007) (Korn et al. 2009) (Weaver et al. 2007) (Steinman 2007). Th17 cells are characterized by the production of IL-17A and IL-17F, but can also produce IL-21 and IL-22. Th17 cells are an important component of the adaptive immune response to certain microbes, particularly extracellular bacteria and fungi (McGeachy and Cua 2008). A number of transcription factors including retinoic acid-related orphan nuclear hormone receptor RORγτ, STAT3, Batf and IRF4 are involved in the differentiation of Th17 cells (Acosta-Rodriguez et al. 2007b) (Huber et al. 2008) (Yang et al. 2011) (Lohoff et al. 2002) (Brustle et al. 2007) (Biswas et al. 2010). A variety of cytokines also contribute to the differentiation of Th17 cells including transforming growth factor (TGF)-β, IL-1, IL-6, IL-23 (Mangan et al. 2006) and IL-21 (Korn et al. 2007) (Zhou et al. 2007) (Mangan et al. 2006). However, it is becoming increasingly clear that “Th17” cells represent a heterogeneous collection of cells, which may or may not be pathogenic (Ghoreschi et al.) (Zielinski et al. 2012) (Wu et al. 2013) (Yosef et al. 2013) (Lee et al. 2012). IL-17 and IL-22 production is also influenced by environmental factors such as aryl hydrocarbon receptor (AHR) ligands (Veldhoen et al. 2009) (Veldhoen et al. 2008a), which include environmental pollutants. Dietary components can also activate AHR and IL-17 is even influenced by dietary salt (Yosef et al. 2013) (Wu et al. 2013) (Lee et al. 2012) (Kleinewietfeld et al. 2013). In this context, it needs to be emphasized however, that $CD4^+$ Th17 cells are by no means the only source of IL-17 and IL-22 cytokines.

In addition to Th1, Th2 and Th17 cells, there are subsets of CD4 T cells that preferentially produce IL-9 and IL-22 (Veldhoen et al. 2008b) (Dardalhon et al. 2008) (Duhen et al. 2009) (Trifari et al. 2009). These are referred to as Th9 and Th22 cells; however, there are circumstances in which these cytokines are not produced exclusively, but are produced with other effector cytokines. IL-4 together with TGF-β induce a population of $IL\text{-}9^+IL\text{-}10^+$ T cells, which don't express Foxp3 but induced colitis and peripheral neuritis after transfer into RAG-1-deficient mice (Dardalhon et al. 2008). TGF-β can reprogram committed Th2 cells to switch to IL-9 secretion and therefore drives the differentiation of Th9 cells (b).

Adding to the complexity of $CD4^+$ T cells are follicular helper T cells, which provide help to B cells and are found within B-cell follicles or germinal centers. They express CXCR5, which contributes to their localization, PD-1 and IL-21; however, PD-1 and IL-21 are not exclusively expressed by Tfh. Moreover, in addition to IL-21 Tfh cells can produce IL-4, IL-17 and IL-10 (Crotty 2011) (Reinhardt et al. 2009). The “master regulator” for Tfh is the transcription factor Bcl-6 (Crotty 2011) (Johnston et al. 2009) (Yu et al. 2009) (Nurieva et al. 2009). The factors responsible for Tfh differentiation remain perplexing and the search for unique inducers has been frustrating; rather, it appears that multiple factors can contribute to Tfh differentiation. That is, STAT1, STAT3, and STAT4 all contribute to Tfh cell development whereas STAT5 supresses formation of this subset (Choi et al. 2014) (Johnston et al. 2012) (Yang et al. 2008a) (Nurieva et al. 2012) (Ma et al. 2012) (Nakayamada et al. 2011). Cytokines that activate these STATs, including IL-6, IL-21, IL-27 and IL-12, have all been implicated in driving Tfh cell differentiation, whereas IL-2

has a negative effect (Eto et al. 2011) (Schmitt et al. 2013) (Poholek et al. 2010) (Harker et al. 2011) (Batten et al. 2006) (Ballesteros-Tato et al. 2012). A summary of diverse T cell subsets can be found in Figure 1.

Traditionally, helper T cell differentiation has been viewed as a largely irreversible process akin to terminal differentiation of other specialized cells. In this way, naive CD4 T cells can be regarded as a pluripotent cell, specification of which is initiated by environmental triggers to generate distinctive “lineages” in which different master regulator transcription factors are induced that in turn supervise unique transcriptional programs. However, as the recognition of the number of different “lineages” and fate choices available for CD4 T cells continue to expand, the extent to which this view is apt has been re-examined. Moreover, considerable evidence continues to mount that argues for a view in which differentiated $CD4^+$ T cells retain the capacity to redirect their functional programs in response to changing milieus. The complexity of helper cell fate determination is made further complicated by the appreciation of overlap between “effector” and “regulatory” functions.

2.1 The Diversity of Regulatory T cells

In addition to orchestrating immune responses by production of key effector cytokines, diverse types of regulatory $CD4^+$ T (Treg) cells are essential for maintenance of immune self-tolerance and homeostasis by suppressing excessive immune responses (Sakaguchi et al. 2008). A subset of Treg cells is defined by their expression of the transcription factor forkhead boxp3 (FoxP3), which is necessary for the development and maintenance of these key cells (Zheng and Rudensky 2007). Mutations of *FOXP3* underlie the disorder termed immunodysregulation polyendocrinopathy eneropathy X-linked (IPEX) syndrome (Bennett et al. 2001). Likewise, mice that carry a mutation or deletion of *FoxP3* develop a fatal systemic autoimmune disease (Brunkow et al. 2001) (Fontenot et al. 2003). Overexpression of FoxP3 confers suppressive activity to conventional T cells, leading to the conclusion that FoxP3 serves as the master regulator and a lineage-specifying transcription factor for Treg cells (Hori et al. 2003). Equally though, it is also recognized that an array of other transcription factors contribute to the phenotype of Treg cells; indeed, FoxP3-dependent and FoxP3-independent factors are important for the phenotype of regulatory cells (Fu et al. 2012).

Treg cells that are derived from the neonatal thymus in response to self antigens have been termed thymic derived regulatory (tTreg) T cells (Shevach 2000). Their program of specification is critically dependent upon TCR signals that lead to induction of FoxP3 (Ohkura et al. 2012). Peripheral derived (p)Treg cells, by contrast, develop in the periphery in response to environmental self-antigens (Chen et al. 2003) (Horwitz et al. 2008) (Abbas et al. 2013). Induced Treg (iTreg) cells can be generated from naïve precursor cells in vitro through activation and cytokine receptor engagement (Figure 1). More specific markers, like the Ikaros family transcription factor Helios, or neuropilin-1, which are thought to distinguish tTreg and pTreg cells, have been described recently (Thornton et al. 2010) (Yadav et al. 2012) (Hansen et al. 2012) (Delgoffe et al. 2013). IL-2 signals through STAT5, which in turn binds directly to the *FoxP3* promoter. Continued stable expression of Foxp3 is influenced by IL-2 receptor expression, which presumably invokes STAT5 in maintenance

of FoxP3 expression (Miyao et al. 2012). Conversely STAT3-dependent signals can destabilize Foxp3 expression (Laurence et al. 2012). Stable Foxp3 expression depends on DNA methylation of a selected 5`intronic region, called Treg-specific determining regions (TSDR) of the Foxp3 gene (Huehn et al. 2009). All *trans* Retinoid acid (RA) has been shown to augment TGF-beta and TCR induced effects (Coombes et al. 2007) (Mucida et al. 2007). RA facilitates the binding of pSMAD3 to the enhancer of Foxp3 (Xu et al. 2010).

FoxP3-expressing Treg cells, however, are not the only regulatory T cells. On the contrary, multiple types of regulatory T cells exist and go by a variety of names such as Th3, Tr1 or Tr35 cells. These cells produce critical anti-inflammatory cytokines like TGFβ, IL-10 and IL-35 (Weiner et al. 2011) (Battaglia et al. 2006) (Collison et al. 2007) (Gagliani et al. 2013) (Awasthi et al. 2007). Absence of TGF-β or its receptors results in lethal autoimmunity. Many cells produce TGF-β but T cell expression of TGF-β and its receptors is critical (Li and Flavell 2008) (Oh and Li 2013) (Li et al. 2007a) (Li et al. 2006). Similarly, IL-10 is another key immunoregulatory cytokine. Mutations and polymorphisms of *IL-10* or its receptor are associated with inflammatory bowel disease (Glocker et al. 2009) (Engelhardt et al. 2013). IL-22 is yet another critical cytokine; in certain circumstances, it too has essential anti-inflammatory properties (Nakagome et al. 2011). Finally, IL-35 is a regulatory cytokine that is able to generate a population of cells with suppressive activity called Tr35 cells (Collison et al. 2007). Added to this is recognition that cytotoxic effector cells, including NK cells that express perforin, can have regulatory functions by limiting T and myeloid cell function (Magnani et al. 2011) (Crome et al. 2013).

Thus, it should be clear that what comprises the constellation of regulatory T cells and how they exert their immunosuppressive effects is anything but simple.

3. Blurring the lines of “lineages”

Despite views of different T cell subsets as stable terminally differentiated lineages, many lines of evidences argue for a more fluid view of regulation (Zhou et al. 2009a) (O'Shea and Paul). There are many examples at this point, so just a few illustrative examples will be provided: For instance, extended culture of Th17 cells leads to IFN-γ production (Mukasa et al.) and the IFN-γ^+ cells that arise also under Th17-inducing conditions can have properties distinct from conventional Th1 cells (Boniface et al.). IL17/IFN-γ double positive T cells are found under normal and inflammatory conditions in mouse and man (Annunziato et al. 2007) (McGeachy et al. 2007) (Acosta-Rodriguez et al. 2007a) (Chen et al. 2007) (Lee et al. 2009) (Bending et al. 2009). Recent data show that co-expression of T-bet and Runx1 or Runx3 is required for the generation of pathogenic IFN-γ producing Th17 cells. At this point, the notion that Th17 cells are heterogeneous collection of cells is no longer a subject of debate.

Many cells also produce IL-10, not just Tr1 cells. In fact, IL-10 was first noted in Th2 cells and Th17 cells also make IL-10. In *S. aureus*-primed cultures, Th17 cells produce IL17 and IL-10 (Zielinski et al. 2012). Again, it needs to be remembered that cells other than T cells clearly produce IL-10; this cytokine is widely produced by myeloid, B and NK cells in addition to T cells.

Th2 cells have a certain degree of plasticity too. Infection with lymphocytic choriomeningitis virus can reprogram Th2 cells into GATA-3^{+}T-bet^{+} cells, which gain the capability to produce IL-4 and IFN-γ (Hegazy et al.). This reprogramming is mediated by IFN-α and STAT1. Hybrid Th1/Th2 cells can develop in response to IFN-γ, IL-12 and IL-4 (Peine et al. 2013).

Tfh cells are one of the hardest cells to pigeonhole as a "lineage", as they do not have a unique pattern of signature cytokine secretion and have the ability to produce cytokines of other lineages. IL-21-producing Tfh-like cells generated *in vitro* can be re-differentiated upon re-culture with the appropriate cytokines to make IFN-γ, IL-4, or IL-17 (Lu et al. 2011). In addition, Tfh features are present early in Th1 differentiation but as differentiation proceeds, Tfh characteristics are repressed and Th1 features dominate (Nakayamada et al. 2011). This flexibility is not limited to *in vitro* differentiation. *In vivo*, Tfh cells express the cytokines that are signatures of a given infection. During helminth infection, for example, all the IL-4-producing cells in the lymph nodes are located in germinal centers, suggesting they are in fact Tfh cells (King and Mohrs 2009) (Glatman Zaretsky et al. 2009) (Reinhardt et al. 2009). Similarly, during a Th1-type bacterial infection, Tfh cells express IFN-γ (Reinhardt et al. 2009). Given this flexibility, it is hard to view Tfh cells as a classic lineage analogous to Th1 or Th2 cells. An alternative model that would incorporate inherent flexibility would be to differentiate between cells that are retained in the lymph nodes versus those that exit: only the former would be bonafide Tfh cells and those that migrate to the tissues would be viewed as Th1 or Th2 cells. In this way, the "lineage" would be defined by localization and not production of signature cytokines. T cells retained in the lymph node would likely receive additional signals from B cells, which would further enforce or stabilize the Tfh features of the T cell, while permitting acquisition of some features of Th1 or Th2 cell (Crotty 2011) (Deenick et al. 2010) (Goenka et al. 2011) (Cannons et al. 2013). Until the specific signals to drive Tfh cells are worked out, this will likely remain an area of active investigation.

While it is accepted that iTreg cells are prone to Foxp3 instability and can produce effector cytokines (Yang et al. 2008a), the debate to what extent tTreg cells are plastic or not is still ongoing (Bailey-Bucktrout and Bluestone 2011) (Hori 2011). Using Foxp3 lineage reporter mice, two groups reported that tTreg cells were stable (Rubtsov et al. 2010) (Miyao et al. 2012). Using a different model, it has been reported that Treg cells can lose Foxp3 expression, gain effector attributes and become drivers of inflammation (Zhou et al. 2009b) (Bailey-Bucktrout et al. 2013) (Komatsu et al. 2014).

3.1 Responding to more than one Master

The recognition of substantial plasticity of differentiated helper T cells begs the question as to what mechanisms drive stability and flexibility of phenotype. In the next sections, we will review these mechanisms. In broad, non-mutually exclusive terms can be influenced by flexible expression of "master regulators" and other transcription factors, which themselves are regulated by post-translational regulation of transcription factors and exert their effect in conjunction with metabolic, dietary and microbial factors. Along with well-known factors like cytokines, all these signals are integrated to modify diverse genomic switches in

developing CD4 T cells and techniques are rapidly being devised to measure the impact of transcription factors and epigenomic changes on global, comprehensive scales. We will start the discussion with insights into flexible and complex expression of master regulator transcription factors.

One important insight that has emerged in recent years is recognition of the limitations of viewing helper T cells from the perspective of a single “master regulator” effecting lineage commitment. Perhaps such a model is reasonably apt for some sessile tissues, like muscle, in which MyoD can appropriately be visualized as a true master regulator. Though the classical view of helper T cells as a homogenous population that expressed a signature cytokine in response to a single master regulator transcription factor was a useful construct, the limitations of this “fallacy” has also become increasingly apparent (Crotty 2012). A major limitation to a monolithic view of CD4 lineages is the proliferation of observations that helper cells can express multiple “master regulators”. T-bet, for example is now appreciated to be expressed in FoxP3$^+$-Treg, Bcl6$^+$-Tfh, Rorγt$^+$-Th17 and even GATA3$^+$-Th2 cells (Koch et al. 2009) (Oldenhove et al. 2009) (Ghoreschi et al.) (Cosmi et al. 2011) (Nistala et al. 2010) (Nistala et al. 2008).

In some cases, key transcription factors work in opposition, titering functionality. On the one hand, T-bet can recruit the transcriptional repressor Bcl-6 (Oestreich et al. 2011); at low cellular concentrations of Bcl-6 the formation of a T-bet-BCL6 complex can block Bcl6 from repressing its target genes (Oestreich et al. 2012). Analogously, FoxP3 represses ROR$\gamma\tau$ and both transcription factors can be co-expressed (Zhou et al. 2008) (Yang et al. 2008a) (Lochner et al. 2008) (Voo et al. 2009). In some circumstances, Treg cells can produce effector cytokines (Stock et al. 2004) (Sawitzki et al. 2005) (Wei et al. 2009) and in humans some IL17-producing cells arise from cells that expressed FoxP3 (Beriou et al. 2009). This is important to keep in mind insofar as FOXP3 is generally more fluid in its expression in human cells and is broadly induced in activated T cells and is not necessarily associated with suppressor cell functionality (Wang et al. 2007) (Roncador et al. 2005).

Another view is that expression of more than one “master regulator” can help provide specialized functions. Like other helper cell subsets, Treg cells are also heterogeneous. Co-expression of FoxP3 with T-bet, GATA3, Bcl6 or STAT3 has been argued to produce specialized subsets of Treg cells that control Th1, Th2, Tfh or Th17 responses (Oldenhove et al. 2009) (Koch et al. 2009) (Koch et al. 2012) (Wang et al. 2011d) (Chung et al. 2011) (Wohlfert et al. 2011) (Chaudhry et al. 2009). Similarly, Treg cell flexibility can also be controlled by transcription factors such as Eos (IKZF4), a known corepressor for FoxP3 (Sharma et al. 2013). The marked heterogeneity of Treg cells is further illustrated by the identification of populations of Treg cells in nonlymphoid tissues that can be characterized by differential chemokine receptor expression (Burzyn et al. 2013a) (Burzyn et al. 2013b). In adipose Treg cells, PPAR-γ collaborates with Foxp3 to impose on naïve T cells the distinctive transcriptional profile (Cipolletta et al. 2012).

Adding to this complexity is the increasing recognition that master regulators work in concert with an array of other transcription factors. Even though overexpression of a factor might be associated with a phenotype, the array of other factors present in the cell is

certainly not irrelevant. Indeed, in Treg cells much of the transcriptional signature is not ascribable to FoxP3 but rather to other factors and other signalling pathways (Fu et al. 2012). Another good example of a critical transcription factor that preserves immune tolerance is Bach2, which pervasively limits effector cell differentiation. Bach2 is important for homeostasis of both Treg and conventional T cells. In reality, a cadre of factors are important for helper T cells including Runx1, Runx3, Bcl6, c-Maf, Blimp1 (encoded by Prdm1), IRF4, Batf, NFκb, IKZF2, IKZF3 and many others. Exactly how these factors all work together is very poorly appreciated. What is clear is that along with GATA3 and Rorγt, which have functions at multiple points in development, networks of transcription factors may not neatly track with a single lineage. IRF4 is an obvious example – it is important for Th2, Th17, Th9, iTreg and TFH cells (Staudt et al. 2010) (Ahyi et al. 2009) (Brustle et al. 2007) (Kwon et al. 2009).

A technology that is revolutionizing how we think about transcription factor action is chromatin immunoprecipitation and massive parallel sequencing. This technique, developed in 2007, allows the enumeration of genome-wide binding sites for DNA binding proteins (Rivera and Ren 2013). This information is rapidly accumulating thanks to efforts like Encode and Roadmap (http://www.encode-roadmap.org); however, our understanding of the functional consequence of the binding of all these different transcription factors in distinct states of T cell activation is in its infancy. Even more challenging though is trying to make sense of this onslaught of data. As will be discussed below, we have some sense of what different transcription factors are doing with respect to organizing the epigenome and the results are surprising. Despite the daunting prospect of this task, it is now feasible to rigorously map binding of the major factors and try to impute their functions.

3.2. Transcription factors are regulated post-translationally

Another mechanism that needs to be borne in mind regarding transcription factors, including so-called master regulators is that they can be regulated post-transcriptionally. In other words, mere presence of transcription factor may not be sufficient for action of a transcription factor; covalent modifications of diverse types can positively and negatively regulate function. For instance, master regulators like T-bet are regulated by phosphorylation (Hwang et al. 2005a) (Hwang et al. 2005b) (Jang et al. 2013). Linking all the relevant pathways that might impinge upon this modification is important, but this area is surprisingly understudied and the number of potential modifications beyond phosphorylation is immense.

Also, like other proteins, transcription factors can be actively degraded and this offers another molecular mechanism for regulating phenotypic stability. This appears to be the case for FoxP3; the levels of this key protein can be controlled in a number of ways. HIF-1 attenuates Treg cell development by binding FoxP3 and targeting it for proteasomal degradation. Importantly, this regulation occurs under both normoxic and hypoxic conditions and HIF-1α-deficient T cells have reduced pathogenic potential (Dang et al. 2011). FoxP3 can be also regulated by polyubiquination of multiple lysine residues (van Loosdregt et al. 2013). Stress signals, like proinflammatory cytokines or lipopolysaccherids can also lead to the degradation of FoxP3 through the ligase Stub1 (Chen et al. 2013).

Degradation of key factors like FoxP3 and other “master regulators” obviously can have profound effects on helper cell function and stability of phenotype.

3.3. Control of helper cell fate by metabolic cues

We have discussed the importance of exposure to cytokines in the determination of how T helper cells differentiate after exposure to cognate peptide. In addition to cues from co-receptors and cytokines, the availability of nutrients, oxygen and even the balance of salts in their local environment influence T cell differentiation.

A resting naïve T cell required little energy and what little metabolism occurs does so aerobically. By contrast, an activated T lymphoblast switches on metabolic pathways, similar to cancer cells, catabolizing glucose anaerobically and using the metabolites to generate building blocks of protein, lipid and DNA synthesis (Fox et al. 2005). The serine kinase mTOR (mammalian Target of Rapamycin) acts as a nutrient sensor: it is inhibited by a deficiency in the availability of amino acids particularly leucine and glutamine (Christie et al. 2002) (Nicklin et al. 2009) or by a decrease in the ATP:AMP ratio (Gwinn et al. 2008). By contrast, mTOR is activated by T cell receptor, CD28 co-receptor stimulation and cytokines known to support T cell proliferation via their ability to activate Phospho-inositol phosphatidyl 3’ kinase (PI3K) (Brennan et al. 1997) (Lafont et al. 2000) (Kane et al. 2001). mTOR in the centerpiece of two signaling complexes: mTOR complex 1 (mTORC1) and complex 2 (mTORC2). mTORC1 is critical for the translation of many proteins including both metabolic enzymes and the transporters required for cells to take up local nutrients (Gordan et al. 2007) (Wang et al. 2011c). mTORC2 has a specialized role in activating members of the AGC serine kinase family including protein kinases B and C (PKB/Akt and PKC) and the serum and glucocorticoid inducible kinase-1 (SGK-1) (Guertin et al. 2006) (Garcia-Martinez and Alessi 2008). Complete inhibition of mTOR by the immunosuppressive rapamycin, blocks T effector cell differentiation and facilitates the development of $FoxP3^+$ Treg cells (Delgoffe et al. 2009) in part through its regulation of expression of HIF1a (Quinlan and Hall 2010).

Using genetic models it is possible to see the contributions of the individual mTOR complexes; loss of mTORC1 prevents Th1 and peripheral Th17 differentiation (Delgoffe et al. 2011) whereas loss of mTORC2 prevents Th2 differentiation and Th17 differentiation within the Thymus (Delgoffe et al. 2011) (Kim et al. 2013). Recent work has linked SGK-1 with IL-23 dependent Th17 differentiation, a process that is influenced by the sodium concentration of the environment (Kleinewietfeld et al. 2013) (Wu et al. 2013).

3.4. Control of helper cell differentiation by the microbiome

In thinking about factors that drive helper cell differentiation, it cannot be ignored that all barrier sites are inhabited by a community of commensal organisms, which greatly out-numbers the host in number of cells and genes (Grice et al. 2009) (Ley et al. 2006) (Beck et al. 2012). Our knowledge of composition of the microbiota has grown exponentially over the past decade as sequencing technology has allowed us to capture a better picture of the diversity amongst various commensal communities. What has also emerged it is not just pathogens that drive helper T cells specification – commensals are also critical factors. The

commensal microbiota of the GI tract in particular contributes to host health via the provision of key metabolites and nutrients derived from food that is otherwise indigestible by the host. However, since commensals are microbes, they have the potential to induce inflammatory immune responses. Therefore, the mammalian immune system has evolved complex mechanisms to prevent untoward activation at barrier sites (Hooper and Macpherson 2010). For instance, the immune system has evolved to receive homeostatic cues from the microbiota, as it has long been noted that the immune system does not properly develop in germ-free animal models (Smith et al. 2007) (Bauer et al. 1963). Multiple studies have revealed that some, but not all commensal strains can compliment certain immune defects associated with germ-free development, implying that the immune system interacts with specific commensals and their products (Mazmanian et al. 2005) (Umesaki et al. 1999) (Hall et al. 2008). Perhaps the best example of this phenomenon is the effect of segmented filamentous bacteria (SFB) on the development of Th17 T cells in the GI tract. The direct role for SFB in T cell differentiation came from studies of genetically identical animals from two different vendors that either lacked or possessed Th17 T cells in their GI tissue and the presence of SFB was shown to be sufficient for the differentiation of Th17 cells (Ivanov et al. 2008) (Ivanov et al. 2009) (Gaboriau-Routhiau et al. 2009). In contrast, bacteria of the *Clostridia* class have been shown to be associated with the differentiation of Treg cells in the colon (Atarashi et al. 2011) (Atarashi et al. 2013). Interestingly, these bacteria are particularly adept at the production of Short-Chain Fatty Acids (SCFA) and three recent studies have shown that the presence of SCFA powerfully supports the production and maintenance of Tregs in the GI tract (Smith et al. 2013) (Furusawa et al. 2013) (Arpaia et al. 2013) (Pryde et al. 2002). Since the production of SCFA from dietary fiber requires multiple bacterial strains, perhaps SCFA is a key metabolite via which the immune system can ascertain the health of the microbiota. It should be noted that while SFB and *Clostridia* are sufficient for the production of Th17 cells and Treg cells respectively, they are not strictly necessary as Treg cells are present in reduced numbers in the total absence of the microbiota (Atarashi et al. 2011). As well, some strains of *Bacteroides fragilis* are potent inducers of Treg cells in the GI tract (Round and Mazmanian 2010). Finally, Th17 T cells can be induced in some gnotobiotic mice that lack SFB entirely And Th17 cells at other barrier sites, such as the skin, rely on local bacterial populations and are independent of the GI microbiota (Geuking et al. 2011) (Naik et al. 2012).

One of the crucial unanswered questions in mucosal immunology is how any given T cell is directed to differentiate to a specific state, given the multitude of coincident signals associated with a diverse commensal microbiota. During infection, T cells specific to commensal antigens have been shown to differentiate according to the dominant inflammatory milieu, but at homeostasis where multiple signals may compete for prominence, how this works is less clear (Hand et al. 2012). Perhaps as a result of multiple signals, the barrier surfaces are home to many T cells that co-express transcriptional modules associated with different states. For example, Treg cells that co-express the transcription factor Rorγt, T-bet and GATA-3 are commonly found at barrier sites (Wohlfert et al. 2011) (Zhou et al. 2008) (Koch et al. 2009) (Wang et al. 2011d). As well, under inflammatory conditions ‘pathogenic’ Th17 cells that co-express IL-17A and IFN-γ are

commonly found in the GI tract (Ahern et al. 2010). While it is clear that commensal microbiota along with pathogenic microbes have a major impact on helper T cell differentiation and plasticity, where are really only just beginning to understand the rules. Suffice it to say that in considering all the environmental factors from cytokines to nutrients and pollutants that provide signals to helper T cells, the enormous diversity of microbial ecosystem is undoubtedly a major factor.

4. Gene Expression, Genomes and Chromatin Organization

It should be very evident at this point that the selective pattern of gene expression that occurs in differentiating helper T cells is the result of numerous extrinsic and intrinsic cues. Precisely how the cell interprets these cues to induce and maintain characteristic gene expression is obviously the critical question. However, the issues of selective gene expression that accompanies lineage commitment and terminal differentiation along with the capacity of differentiated cells to retain plasticity obviously go far beyond T cells. This is a fundamental issue in developmental biology. Accordingly, lessons learned from many systems have implications for understanding these processes in T cells. Reconsidering T cell plasticity is timely insofar as completion of the human and other genomes and advances in sequencing technologies are dramatically changing how fundamental biological problems are viewed (Rivera and Ren 2013).

A surprising finding resulting from the elucidation of human and other genomes was the paucity of “genes” within the genome. Of the roughly three billion of nucleotides in the genome, there are only on the order of 2×10^5 genes in mammals. Despite the paucity of classical genes, as defined by the central dogma of molecular biology (DNA transcribed to RNA translated to protein), it is now recognized that consideration of selective gene expression needs is controlled by a vast number of distal “switches” and that the majority of the genome is transcribed. How accessibility of genes is controlled both locally and by largescale changes in genomic architecture is currently the focus of intense investigation. In this context, it is worth reviewing some of the newer insights and how these might relate to helper T cell diversity. Like other specialized cells, for the most part (*TCR* locus excluded), changes in DNA sequence (genome) is not responsible for differential functions; rather it is the “epigenome” that changes dramatically. The epigenome refers to a variety of alterations in chromatin including histone tail modifications, DNA methylation, nucleosome compaction and long-range chromatin interactions. Production of long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) are additional mechanisms that to contribute to gene regulation, as do distal elements termed enhancers transcribed to produce eRNAs. Better understanding of the dynamic epigenomes of helper T cells have provided useful insights into our notions of plasticity, but this is certainly an area that will receive increasingly greater attention (Wilson et al. 2009) (Ansel et al. 2003) (Kanno et al. 2012) (Zhu et al. 2010). We will start by briefly summarizing the most important epigenetic modifications (Figure 2).

4.1 DNA methylation

The classic modification associated with silencing of gene expression is DNA methylation (Figure 2). DNA modification occurs at cytosine-guanine (CpG) dinucleotides, which are

often clustered within promoters and are associated with chromatin-remodelling factors such as methyl-DNA-binding proteins that promote the condensation and inaccessibility of chromatin. In contrast, demethylation of CpG motifs leads to a relaxation of chromatin and an increased accessibility of target sequences, thereby allowing the binding of specific transcription factors. Therefore CpG methylation at promoters is generally associated with transcriptional repression. CpG methylation is maintained by DNA methyltransferases (DNMTs), which use S-adenosylmethionine as the methyl group donor (Goll and Bestor 2005). Maintenance of a pre-existing methylation pattern is catalysed by Dnmt1; Dnmt1 recognizes a hemi-methylated DNA and introduces methyl-groups on the unmethylated strand (Bestor et al. 1988). In contrast, de novo DNA methylation is mediated by Dnmt3 methyltrasferases, (Okano et al. 1998) (Okano et al. 1999) (Bestor et al. 1988). Both processes are important for stabilizing helper cell phenotypes (Okano et al. 1999) (Young et al. 1994) (Winders et al. 2004) (Thomas et al. 2012) (Lee et al. 2001) (Makar et al. 2003).

As mentioned above *FoxP3* expression and stability of Treg cells is also regulated by the DNA methylation status at several key genomic loci called the Treg-specific demethylation region (TSDR) (Floess et al. 2007) (Baron et al. 2007) (Lal et al. 2009) (Janson et al. 2008) (Polansky et al. 2008) (Zheng et al. 2010) (Huehn et al. 2009).

Furthermore recent data show that methylation of tTreg cells is necessary for FoxP3 to acquire a genome-wide Treg cell-type gene expression pattern, lineage stability and suppressive activity. The Treg-cell specific hypomethylation pattern is dependent on T cell receptor stimulation and Foxp3 independent (Ohkura et al. 2012).

While DNA methylation is important for the maintenance of T cell lineage stability, it is also true that massive demethylation occurs during T cell activation and is selective with specification of subsets. For instance, the *Ifng* locus is demethylated during a Th1 differentiation, whereas differentiated Th2 or Th17 cells sustain their methylation status. Similarly, the *Il4*, *IL13* and *IL17a* loci are methylated in naïve T cells and are demethylated during Th2 and Th17 differentiation respectively (Santangelo et al. 2009) (Schoenborn et al. 2007) (Aune et al. 2013). The ability of Th17 to express IL-17 and IFN-γ concomitantly is associated with hypomethylation of the *IFN-γ, IL17a* and *Rorc* promoters (Cohen et al. 2011). DNA demethylation of *Rorc* under inflammatory conditions can lead to IL-17 production in Treg cells (Schmidl et al. 2011). Although this is a widely appreciated event, we have almost no understanding of the molecular basis of these changes. On one hand, the massive proliferation of T cells that occurs with activation is no doubt an important factor; what is less clear is how this process can be so selective.

Global dysregulation of DNA methylation has long been recognized as a potential contributor to autoimmune disease including RA and SLE (Richardson et al. 1990) (Corvetta et al. 1991) (Absher et al. 2013) (Altorok et al. 2013). To some degree it is hard to separate cause and effect since these diseases are associated with T cell activation; however, the fact that drugs known to affect DNA methylation are associated with lupus suggest at least some degree of causality. DNA methylation inhibitors like 5-azacytidine can induce T-cell autoreactivity and lupus symptoms in mice (Quddus et al. 1993) and drug induced lupus is associated with reduced DNA methylation (Cornacchia et al. 1988).

Over the past decade the global DNA methylation technologies have rapidly evolved; instead of measuring small, localized changes in DNA methylation, it is now possible to measure genomewide changes. At present though, the quality as compared to the average cost has to be taken into account and the high costs have limited acquisition of data for complete analysis of methylomes. Techniques like endonuclease digestion-based DNA methylation assays (MRE-seq) or affinity-based enrichment assays (MeDIP-seq) for example have moderate costs; although the resolution is comparatively low compared to MethylC-seq or reduced representation bisulfite sequencing (RRBS). Newer techniques like oxidative bisulfite sequencing (oxBS-seq) and TET-assisted bisulfite sequencing (TAB-sequ) yield single base resolution methods, but these remain costly (Rivera and Ren 2013). Array-based methylation assays (such as the Illumina HM450 array), however, can detect DNA methylation at single nucleotide resolution with low cost by only targeting known CpG islands using locus specific probes. As the costs of sequencing continue to decline, the expectation is that DNA methylation data sets will become far more commonplace. This is welcome as this epigenetic modification is thought to be one of the more stable marks.

4.2 Enumerating Global Histone Modifications

Another important factor that dictates accessibility of genes and therefore transcription is that DNA is wrapped into nucleosomes that consist of histone octamers. Histones can be modified by many different post-translational modifications including acetylation, methylation, phosphorylation, ubiquination, sumoylation, etc, which all contribute to define the overall structure of chromatin (Rivera and Ren 2013) (Kanno et al. 2012) (Figure 2); in fact, more than 130 different histone modifications have been described. In the interest of brevity, we will only discuss a few major modifications. Both active (euchromatin) and silenced (heterochromatin) configurations are associated with certain combination of histone modifications. For example, histone H3 lysine 4 tri-methylation (H3K4me3) is associated with active, accessible promoters whereas H3K36 tri-methylation is associated with actively transcribed coding regions. Enhancers are marked by histone H3 lysine 4 mono- and di-methylation (H3K4me1 and H3K4me2). H3 lysine 27 acetylation (H3K27Ac) in the context of H3K4me1 is a mark of an active enhancer; without this mark, H3K4me1 alone indicates a “poised” enhancer. In contrast, histone H3 lysine 27 tri-methylation (H3K27me3) and histone 3 lysine 9 tri-methylation (H3K9me3) are present in broad domains that encompass inactive genes. H3K4me3 and H3K27me3 modifications can both be present at some genomic regions, and these bivalent modifications have been suggested to poise genes ready for either activation or repression during differentiation.

H3K27 trimethylation is mediated by polycomb proteins, which comprise two major repressive complexes: polycomb repressive complex 1 (PRC1) and PRC2. The polycomb proteins Enhancer of Zeste Homolog 1 (Ezh1) and Ezh2 form two closely related PRC2 complexes that can trimethylate H3K27 and are required for maintenance of cellular identity at several stages of development. Ezh2 constrains differentiation and plasticity of Th1 and Th2 cells, by controlling the expression of *Tbx21* and *Gata3* in developing Th1 and Th2 cells and inhibiting spontaneous generation of IFNγ-producing cells via repression of *Eomes* (Tumes et al. 2013). Interestingly, in Th9 differentiation, TGF-β acting via Smad2 and Smad4 serve to displace Ezh2 from the *Il9* locus (Wang et al. 2013).

The global enumeration of histone marks for helper T cells has been accomplished and the findings help to explain some of their apparent plasticity (Wei et al. 2009). One striking finding is genes that encode key regulatory transcription factors including *Tbx21, Gata3, Rorc, Prdm1*, and others. The presence of bivalent poised domains suggests a potential for phenotypic plasticity even in terminally differentiated cells. This helps explain the previously unanticipated breadth of expression of "lineage-defining master regulators". Assessment of histone modifications reveal that Bcl6 is accessible in all subsets, thus explaining the flexibility of Tfh cells (Nakayamada et al. 2011). Thus, the epigenetic landscape of genes encoding master regulators may allow flexibility in expression and thereby permit the blurring lineages, allow fine tuning or provide subspecialization.

It is important to note that histone modifications can be targeted therapeutically. HDAC inhibitors are the best studied epigenetic therapeutic agents and have been proven to reduce the levels of proinflammatory cytokines (Leoni et al. 2005) (Leoni et al. 2002). Beneficial effects of HDAC inhibitors have been initially described in animal models of arthritis (Nishida et al. 2004) (Lin et al. 2007) (Nasu et al. 2008) (Saouaf et al. 2009) (Joosten et al. 2011). In humans 18 HDACs have been described and further characterized (Wang et al. 2009b). In line with this, it has been reported that blocking histone deacetylase is efficient in treatment of juvenile idiopathic arthritis (Vojinovic et al. 2011). However, the data on T cells are very limited. First of all, some HDAC inhibitors are not very specific and can target other transcription factors like NF-KB or STAT3, which are also important in inflammation. Second, most data come from other cell types like fibroblasts or macrophages. Studies from *in vivo* models, like CIA, point to a role of Treg cells, whose number and function was reported to be increased after treatment with valproic acid (Saouaf et al. 2009) (Wang et al. 2009a).

An additional level of gene regulation derives from proteins that "read" histone and DNA modifications, such as bromodomain-containing proteins that bind acetylated histones including BRD2, BRD3, and BRD4. The BET family member, BRD4 has a unique C-terminal domain that binds to the positive transcription elongation factor b (P-TEFb; composed of the cyclin-dependent kinase CDK9 and its partner, cyclin T1) complex. BRD4 recruits P-TEFb to acetylated histones, promoting phosphorylation of paused RNA polymerase II (Pol II) and the repressive complexes DSIF and NELF by CDK9, thereby allowing productive mRNA elongation. Of note, BET inhibitors appear to have efficacy in preclinical models of autoimmune disease (Bandukwala et al. 2012). In addition BRD2 and BRD4 associate with the *Il17* locus and control the Th17 differentiation (Mele et al. 2013).

4.3 Defining Enhancers

Many aspects of human biology depend on the tissue-specific control of gene expression (Noonan and McCallion 2010). Regulatory information creating such complex gene expression patterns is accommodated across the non-coding part of genome in the form of cis-regulatory elements. The key point is that only a subset of these cis-regulatory elements is brought into play in every cell type in a temporal and spatial-dependent manner.

Among many types of regulatory elements, enhancers play essential roles in cell-type-specific gene expression. Enhancers are non-coding DNA sequences that "enhance"

transcription of cognate target genes, regardless of their location or orientation. The *Ifng* and *Il4* loci are good examples of the complicated architecture of finely regulated lineage-specific genes (Wilson et al. 2009) (Ansel et al. 2006). For instance, a conserved noncoding sequence in the distal site of the *Il4* locus is critical for IL-4 expression in Tfh cells but not in Th2 cells (Harada et al. 2012). Likewise, a *FoxP3* enhancer (CNS1) is essential for peripheral Treg cells but dispensable for natural Treg cell generation; notably, this element is only active in placental mammals (Zheng et al. 2010) (Samstein et al. 2012).

A major breakthrough for enhancer biology was the discovery of the chromatin signatures of enhancers, facilitated by next-generation sequencing technology. It is now believed that presence of a unique combination of histone modifications map the enhancer elements of each cell type. Pioneering work identified H3K4me1-high, H3K4me3-low as a chromatin signature of enhancers in human cells (Heintzman et al. 2009). Not all H3K4me1-high, H3K4me3-low regions are functionally active and these regions are representatives of “poised” enhancers. Additional marks such as the binding of acetyltransferase p300 or H3K27Ac have been related to “active enhancers” in many studies.

It has been argued that the prominent action of master regulator factors supervise the creation of the enhancer landscape (Natoli 2010). Among key transcription factors in the immune system, early studies characterized the role of PU.1, encoded by *Sfpi1*, as an organizer of enhancer elements (Ghisletti et al. 2010) (Heinz et al. 2010). These studies suggested that master regulators of other cell types might have similar pervasive impacts on the enhancer cohorts. In the context of $CD4^+$ T cell subset differentiation, master regulators are defined as required and sufficient transcription factors for programming a T cell subset. Another aspect of this definition is that the master regulator has a restricted expression pattern, which means that it is only found in cells of a specific fate. As mentioned above FoxP3 has been argued to be necessary and sufficient for Treg cell development. However, FoxP3 has limited impacts on the enhancer landscape of Treg cells (Samstein et al. 2012). The major changes in the epigenetic landscape of tTregs are FoxP3-independent and are created by TCR-dependent signals. Likewise, the master regulators of Th1, Th2 and Th17 cells, have also limited impacts on key enhancer cohorts. Taken together, these studies provide compelling evidence that the master regulators involved in helper cell specification are not the factors that shape the enhancer landscape of $CD4^+$ T cell subsets. It remains a question then how the many T-cell expressed transcription factors work in concert to create the genomic enhancer landscape of T cells.

A key aspect in the acquisition of distinct T helper cell phenotypes is the cytokine milieu. Upon encounter of diverse microbial pathogens, dendritic cells and other cells of the innate and adaptive immune system produce cytokines, which serve to instruct distinct T cell fates. The major specifying cytokines exert their effect through STAT family transcription factors. Strikingly, the majority of differentially active enhancers in Th1 and Th2 cells and Th17 cells are STAT-dependent and many are direct STAT targets of STATs (Hirahara et al.). Importantly, reconstitution of STAT4- and STAT6-deficient cells with the master regulators T-bet and GATA3 failed to recover the active enhancer landscapes, again arguing for a primary role of environmental sensors in dictating global landscapes.

A new subset of enhancers termed “super” or “stretch” enhancers has recently been appreciated. Super-enhancers regions have been suggested to have crucial functions in defining cell identity. In embryonic stem cells for instance, super enhancer domains are associated with genes that play essential roles in ESC biology. Transcription at super-enhancer genes is also disproportionately sensitive to any perturbations. The superenhancer landscapes of helper T cells has not been catalogued, but this is obviously an area of considerable interest.

Transcription abounds—A recent surprise that even though only 2% of the genome represents standard, protein-coding genes, most of the genome is active and roughly 80% of the genome transcribed despite the fact that no protein is produced. RNA-seq technology and other technologies have permit this abundance of transcription, including the identification of the repertoire of non-coding RNAs that include microRNAs (miR), enhancer RNA (eRNA) and long noncoding RNA (lncRNA) (Birney et al. 2007) (Kapranov et al. 2007) (Kim et al. 2010). Work on eRNAs and lncRNAs is just beginning, although we already know that eRNAs are functionally important for promoting accessibility of canonical protein-coding genes (Mousavi et al. 2013) (Hu et al. 2013a).

4.4 microRNA and helper T cells

MiRNAs are transcribed by RNA polymerase II as long precursor transcripts termed pri-miRNAs, which are then processed into premiRNAs by the enzyme complex including the RNase III type endonuclease Drosha and its partner DiGeorge syndrome critical region gene 8 (DGCR8). In the cytoplasm, premiRNAs are further cleaved by the RNase III endonuclease Dicer to generate a miRNA-induced silencing complex (miRISC), which destabilizes target mRNA and reduces their translation into proteins (Bartel 2009) (Fabian et al. 2010). Loss of Drosha and Dicer can lead to instability of Th cells and cause autoimmunity (O'Connell et al. 2010b) (Bartel 2004) (Chong et al. 2008) (Liston et al. 2008) (Baumjohann and Ansel 2013). By targeting crucial T cell lineage commitment genes, miRNAs are involved in regulation of gene expression network that determines T cell identity, plasticity and function (Figure 2).

Individually, a variety of miRNAs have been shown to influence effector cell differentiation and stability. Once again, this is a fast moving field and our goal is not to be comprehensive, but rather to give a few relevant examples of factors that influence gene expression. For instance, MiRNA-155 is a multi-functional miRNA that regulates a number of aspects of B and T cell functions. Its effects include the development of Th1, Th17 cells and miR-155 deficient mice are also protected from EAE and CIA, (Murugaiyan et al. 2011) (Bluml et al. 2011) (O'Connell et al. 2010a). MiR-155 is also expressed in Tregs and miR155 deficient mice have lower numbers of Treg cells (Lu et al. 2009) and develop enteric and lung inflammation (Rodriguez et al. 2007). Mir-155 is regulated by several transcription factors, such as STAT3 (Escobar et al. 2013) and FoxP3 (Zheng et al. 2007) (Marson et al. 2007), which is compatible with miR-155 expression in Th1, Th17, and Treg cells.

One important target of MiR-155 is suppressor of cytokine signaling 1 (*Socs1*) (Lu et al. 2009), which negatively regulates IL-2 signalling, and is important for the maintenance of

Treg cells. MiR-155 also targets SMAD2 (Louafi et al. 2010), SMAD5 (Rai et al. 2010), and alters TGF-β signaling. In effector T cells, *Socs1* and SH2 domain-containing inositol polyphosphate 5′ phosphatase 1 (*Ship1*), which is negative regulator of cytokine signaling in addition to Socs1, are important targets of miR-155 as well as *Ifngr1* (Huffaker et al. 2012) (Banerjee et al. 2010). Recently, miR-155 directly targets Ets1, a negative regulator of Th17 differentiation, and subsequence down regulation of Th17-specific genes, such as IL-17F, IL-22, and IL-23R (Hu et al. 2013b).

Mir146a is another multi-functional MiRNA. Mir-146a-deficient T cells show increased IFN-γ production (Yang et al. 2012) (Huffaker et al. 2012) (Lu et al. 2010) because miR-146a regulates Th1 differentiation by targeting Stat1 (Lu et al. 2010). MiR-146a also targets IL-1 receptor-associated kinase 1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6), and derepression of IRAK1 and TRAF6 increase activation of NFκB. This leads to TCR hyper-responsiveness and subsequent upregulation of IFN-γ expression from effector T cells (Yang et al. 2012). In addition, miR-146a seems to have an effect on Treg cell function (Lu et al. 2010).

Mir-181 also augments TCR signalling. Mir-181a targets several phosphatases involved in proximal TCR signalling, such as tyrosine phosphatases H2 domain-containing protein tyrosine phosphatase 2 (*Shp2*) and protein tyrosine phosphatase non-receptor type 22 (PTPN22) and inactivator of MAP kinases dual-specificity protein phosphatase 5 (*Dusp5*) and *Dusp6* (Li et al. 2007b). Skewed TCR signalling by inhibition of miR-181a impairs sensitivity of double positive cells in thymus and obstruct positive and negative selection (Li et al. 2007b). Mir-181a is also important in the peripheral $CD4^+$ T cell response. Expression of miR-181a is high in human neonatal naïve $CD4^+$ T cells, and age-associated decrease of miR-181a increased DUSP6 expression, and diminished ERK phosphorylation via TCR stimulation (Palin et al. 2013). Reconstitution of miR-181a lowered DUSP6 expression, and restored $CD4^+$ T cell responses (Li et al. 2012).

The miR-17~92 cluster regulates several aspects of T cell activation but importantly, regulates Tfh differentiation, relevant targets being Rora (Baumjohann et al. 2013) and CXCR5 (Yu et al. 2009).

Mir-10a attenuates the conversion of iTregs into Tfh cells by targeting Bcl6; miR-10a can also limit Th17 differentiation (Takahashi et al. 2012).

MiRNAs regulate broad range of gene modification in various immune cells including Th cells. The role of miRNAs in different diseases has been studied extensively. Especially, the role of miR-155 and miR-146 has been best described as pro- and anti-inflammatory genes in both in infectious and autoimmune diseases in human and mouse. Silencing of miR-155 reduced the susceptibility of LPS treatment in murine model (Androulidaki et al. 2009). Contrary, lack of miR-146a exhibited exaggerated inflammatory response to LPS (Boldin et al. 2011). MiR-155 and miR-326 are overexpressed in active multiple sclerosis (MS) brain lesions, and mice lacking or silencing of these miRNAs leads to ameliorate the symptom of EAE, the mouse model of MS (Junker 2011). In another autoimmune disease, systemic lupus erythematosus (SLE), underexpression of miR-146a, a negative regulator of interferon

signalling, has a negative correlation with the disease activity (Tang et al. 2009). The involvement of MiR-155 and miR-146 is also reported in rheumatoid arthritis (Kurowska-Stolarska et al. 2011) (Nakasa et al. 2008) (Pauley et al. 2008), atopic dermatitis (Sonkoly et al. 2010), Sjoegren's syndrome, and IgA nephropathy (Wang et al. 2011b). Modulation of miRNAs might be an effective therapeutic approach. Recent reports have shown experimental evidences of the efficacy about blocking miRNA. Antagonizing miR-126 reduce the Th2 response in asthma model (Collison et al. 2011).

4.5 long non-coding RNAs

More recently long non-coding RNAs (lncRNAs) have taken the center stage within the non-coding world as critical regulators of cellular identity. Dramatically, germline knockouts of several lncRNAs have proven to be embryonic or postnatal lethal, emphasizing that lncRNA are not simply transcriptional noise (Sauvageau et al. 2013) (Marahrens et al. 1997). Work with ES and iPS cells have shown that lncRNAs are highly dynamic and play an integral role in both maintaining pluripotency and promoting differentiation, so it's attractive to envision that they would be essential players in the face of a dynamic $CD4^+$ immune response (Guttman et al. 2011) (Sheik Mohamed et al. 2010) (Loewer et al. 2010) (Figure 2).

lncRNAs are a remarkably diverse class of transcripts that together are defined as being larger than 200 nucleotides and lacking a functional open reading frame. Like mRNA, lncRNAs may be transcribed by RNA polymerase II, 5’ capped, spliced, 3’ polyadenylated, and bound by ribosomes (Ingolia et al. 2011). Several large scale studies have been conducted to identify lncRNAs resulting in an overwhelming number of transcripts: 9277 human lncRNA genes were identified through the ENCODE project (Derrien et al. 2012); using cDNA sequencing FANTOM found 34,030 lncRNA transcripts (Maeda et al. 2006) (Carninci et al. 2005); 1586 mouse and 1833 human novel lncRNAs were identified using adjacent H3K4me3 and H3K36me3 chromatin signature signifying activated genes (Guttman et al. 2009) (Khalil et al. 2009); and 4662 lncRNAs were established using RNA-seq across 24 human tissues and cell types (Cabili et al. 2011). Two studies have examined the lncRNA population with the adaptive immune compartment. The first used custom microarrays to identify ~1200 lncRNAs within human and mouse $CD8^+$ T cell with differential lncRNA expression between the naïve/memory and effector populations (Pang et al. 2009). Recently Keji Zhao's group through an impressive tour de force cataloged the both the poly-A and total lncRNA transcriptome from murine thymocytes and Th1, Th2, Th17, and iTreg differentiated $CD4^+$ T cells across a two-week time course (Hu et al. 2013a). 1524 lncRNA-expressing genomic regions were identified, the majority of which were polyadenylated, with 464 regions in the double-negative thymocytes, 515 in the double- and single- positive thymocytes, and 646 in the naïve / differentiated $CD4^+$ helper T cell subsets. The lncRNAs were dynamically regulated both temporally and across the various cell types; with the T helper cells subsets only 15.5% of the lncRNAs were shared, in contrast to 78% of the 13,934 mRNA transcripts.

lncRNAs have been shown to act through an assortment of differing mechanisms. A strong trend that has emerged is that lncRNAs play a prominent role forming ribonucleoprotein

complexes that mediate epigenetic regulation and transcriptional expression of highly specified target genes (Mattick et al. 2009) (Bernstein and Allis 2005) (Rodriguez-Campos and Azorin 2007). Not only is RNA is an integral component of chromatin but many histone methyltransferases lack DNA binding properties, instead possessing RNA binding motifs, indicating that lncRNAs may play a much more pervasive role that currently recognized (Rodriguez-Campos and Azorin 2007) (Khalil et al. 2009). One such example is TMEVPG1 (NeST; LincR-Ifng-3'AS), a lncRNA expressed in Th1 and $CD8^+$, but not NK cells (Vigneau et al. 2003) (Collier et al. 2012) (Gomez et al. 2013). This lncRNA protects against persistent Theiler's virus infection by regulating the epigenetics of Inf-γ through association with WDR5, a scaffolding protein for the SET1 family of methyltransferases.

In addition to acting as scaffolds for histone modifying proteins, lncRNAs have been reported to regulate multi-protein complexes responsible for transcription factor activity. NRON (ncRNA repressor of the nuclear factor of activated T cells), a lncRNA expressed in both mice and humans, acts to bring together NFAT, IQGAP1, and the NFAT kinases CK1, GSK3, and DYRK, thereby maintaining NFAT in a phosphorylated, inactive state (Willingham et al. 2005) (Sharma et al. 2011). Depletion of NRON resulted in enhanced NFAT dephosphorylation, nuclear transport, and increased IL-2 production. None of the proteins within the NRON-NFAT complex contained an identified RNA-binding domain, suggesting that lncRNAs may play a wider role in transcription factor regulation than previous appreciated.

lncRNAs can also serve as direct regulators of transcription, as is with the case of the lncRNA T early alpha (TEA). The act of transcribing TEA regulates transcription across the Jα segments of the TCRα by activating the Jα58, Jα57, and Jα59 promoters while also opening the chromatin associated with the promoter-less Jα61, Jα53, and Jα52 regions. Knocking out TEA, or inhibiting its transcription through the insertion of a transcription terminator cassette abrogates germline transcription across these segments (Abarrategui and Krangel 2006) (Abarrategui and Krangel 2007) (Corcoran 2010).

lncRNAs can also regulate T cell function by acting as decoy targets for protein and miRNAs. GAS5 represses the glucocorticoid pathway by acting to inhibit glucocorticoid receptor (GR) transcriptional regulation of glucocorticoid-responsive genes (Kino et al. 2010). Repression is mediated through a hairpin structure on GAS5 that resembles the glucocorticoid response element (GRE) found within DNA. The GAS5 GRE-decoy binds to the GR (Kd ~30 nM, compared to ~60 nM for DNA-GRE binding to GR), thereby preventing GR binding to the DNA. The lncRNA contains a 5' terminal oligopyrimidine tract (5' TOP) that results in active degradation by nonsense-mediated decay in proliferating cells but confers transcript stability under conditions that result in growth arrest such as serum starvation, loss of growth factors, or pharmacological inhibition of the mTOR pathway (Schneider et al. 1988) (Coccia et al. 1992). Depletion of GAS5 by siRNA in T cells prompted continued proliferation in otherwise exhausted cultures, while over-expression of GAS5 attenuated proliferation (Mourtada-Maarabouni et al. 2008). lncRNAs can also function as miRNA decoys (Poliseno et al. 2010) (Salmena et al. 2011). Termed competing endogenouse RNAs (ceRNAs), they can act as miRNA sponges to sequester miRNAs and protect protein-coding mRNAs from degradation. Recently a new class of

circularized miRNA sinks (cirRNAs) has been identified with increased stability and a higher capacity to sequester miRNAs than ceRNAs (Hansen et al. 2013) (Memczak et al. 2013).

An exciting new area of RNA biology is the discovery that active enhancers produce non-polyadenylated RNA transcripts, called eRNA (enhancer RNA) (Djebali et al. 2012). eRNAs are bi-directionally transcribed from the enhancer and function to promote chromatin looping and formation of the RNAPII transcription machinery (Mousavi et al. 2013) (Melo et al. 2013) (Li et al. 2013). Notably, the presence of eRNAs appear to have a strong association with active enhancers, and may prove to be a better indicator of enhancer activity than currently identified epigenetic markers (Wang et al. 2011a) (Figure 2).

Non-coding RNA is highly dynamic both in its expression and functionality. Given the central role that it plays in regulating epigenetic states and transcriptional networks, we predict that it will be increasingly found to play a pervasive role in the regulation of helper T cell plasticity.

4.6 Higher-order chromatin organization for cell identity

As mentioned previously, enhancers are the key to tune the cell-type specific gene expression profile. It is believed that enhancers act through physical contacts with target gene promoters. Therefore, higher-order chromatin conformation that forms loops to facilitate enhancer-promoter interactions and to exclude intervening genes has become a critical aspect for studying gene regulation. Indeed, the genome-wide mapping of promoter-enhancer interactomes reveals that global gene expression is fine-tuned by tissue-specific enhancers, even for those genes that are not cell-type specific (Kieffer-Kwon et al. 2013). For instance, within near five thousand promoter interactions shared by B cells and ES cells, up to 90% use at least one cell type-specific enhancer, indicating genome-wide dynamics of enhancer landscape during development and differentiation (Kieffer-Kwon et al. 2013).

In nucleus, the genome is folded complexly in a hierarchical manner (Gibcus and Dekker 2013). Instead of randomly tangling with each other, chromosomes tend to occupy their own territories that contain euchromatin and heterochromatin compartments for aggregation of active and inactive genes, respectively (Lieberman-Aiden et al. 2009). Using 3C-based assays, megabase-scaled topologically associated domains (TADs) are found in both euchromatin and heterochromatin compartments. The boundaries of TADs are invariant between different cell types and are conserved between distinct species (Dixon et al. 2012) (Nora et al. 2012). However, submegabase-sized interactions that reside within the TADs reveal cell-type specificity (Phillips-Cremins et al. 2013).

The DNA looping within sub-TADs can be partially explained by the interplay between three well-recognized chromatin organizers, CCCTC-binding factor (CTCF), Mediator and cohesin. It is appreciated that CTCF and cohesin colocalize to form long-range structural loops that may support short-range enhancer-promoter interactions bridged by Mediator and cohesin (Phillips-Cremins et al. 2013). Master transcription factors and Polycomb proteins also play essential roles for the formation of cell-type specific chromatin architecture. For instance, in mouse pluripotent stem cells, lineage-specific master transcription factors,

Nanog, Sox2, and Oct4, binding sites preferentially interact with each other and frequently colocalize with Polycomb proteins. Depletion of one master regulator or Polycomb subunit disrupts their associated DNA contacts, but not the overall chromosome topology (de Wit et al. 2013) (Denholtz et al. 2013).

Studies have identified cell type-specific and stimulus-inducible chromatin architecture on immune-related genes; most of them focus on uni-gene regulation. For instance, Ifng locus forms a chromatin hub specifically in Th1 cells but not in Th2 or naïve $CD4^+$ T cells. This Th1-specific chromatin hub is CTCF/cohesin/T-bet-dependent and is conserved between human and mouse (Sekimata et al. 2009) (Hadjur et al. 2009). Similarly, the contacts across Th2 cytokine (IL-4, Il-5 and Il-13) locus appear preferentially in T and NK cells but not in B cells or fibroblast (Spilianakis and Flavell 2004). Upon activation of Th2 cells, the Th2 cytokine locus transforms from a “poised” status to a more complicated “cage-like” configuration with multiple loops along with gene upregulation (Cai et al. 2006). Intriguingly, in primary human fibroblast cells, the enhancers of TNF-α responding genes already interact with their target promoters before stimulation (Jin et al. 2013), suggesting the cell-type specific chromosome topology can also set the stage for inducible genes to be rapidly activated.

Inter-chromosomal interactions also play a role in hierarchical gene regulation and co-regulation. During $CD4^+$T cells differentiation, Ifn-γ locus on chromosome 10 and Th2 cytokine on chromosome 11 interact with each other specifically in naïve $CD4^+$ T cells while they are inactive and then dissociates during differentiation, suggesting a co-regulation or “poised” nuclear organization for lineage-specific genes (Spilianakis et al. 2005). To sum up, the cell-type specific networking of chromatin architecture may determine cell identity by framing cis-regulatory element activity for gene expression.

5 Conclusions

What should be obvious at this point is that there is no shortage of mechanisms that can promote flexibility of responses in CD4 T cells. Indeed, recent advances have shaken fundamental views of terminal differentiation and lineage commitment – indeed, thanks to the pioneering work of Yamanaka and colleagues, it is commonplace to reprogram fully differentiated cells with four transcription factors and/or a cocktail of drugs (Yamanaka and Blau 2010) (Malik and Rao 2013) (Obokata et al. 2014) and most recently by incubating cells in acidic medium. If lymphocytes turn into stem cells by brief exposures to relatively innocuous stressors such as low pH or pipetting, it is increasingly difficult to argue that helper T cell subsets are immune from changing phenotypes. A few years ago, we would have said with certainty that CD4 and CD8 cells are unquestionably stable lineages; however, recent work points to the fact that even such cells can alter their transcriptional program (Mucida et al. 2013). In view of these developments along with much experimental data in CD4 T cells, it seems appropriate to recognize that terms like Th1, Th2 and Th17 cells, should really be thought of as a shorthand that approximates functionality. But we should not deceive ourselves: this convenient, but artificial shorthand should by no means be interpreted to suggest that populations of T cells are terminally differentiated and unable to acquire new functionalities.

In this review, we have tried to emphasize that helper T cells express a network of transcription factors that can work in concert, in opposition or to allow for specialized function. T cell master regulators, if they exist, work with a vast array of other factors. Transcription factors can be covalently modified to activate or inactivate their function and can be degraded. The epigenetic modifications of many of these key transcription factors permit flexible expression of master regulator transcription factors, even when modifications of effector cytokine genes appear “fixed”. Formation of the epigenetic landscape that modulates the accessibility of transcription factors and other key genes is profoundly affected by signals emanating from the T cell receptor and cytokine receptors. Moreover, we now recognize that cell signalling is intimately linked to cellular metabolism and microbiome. Epigenomic landscapes integrate all these environmental signals and thereby can be considered as an extension of signal transduction.

The good news is that we can now measure it all: genomes, epigenomes, metabolomes, microbiomes and transcriptomes. The bad news is that we can measure it all. How do we understand the complexity of multilayer networks built on top of each other? What tools do we need to develop to assist in providing models that explain the biology of CD4 T cells in health and disease? Moving ahead, all T cell biologists will need to adapt “systems biology” approach in some way. Although hypothesis-driven studies with a focus on a few select genes remain useful, one needs to bear in mind all the things that could, but are not being measured would influence the experimental outcome. As our annotation of the human genome becomes more complete and we develop more sophisticated understanding of the impact of human genetic variation, we are approaching a new era that can redefine T cell function in health and disease by employing “omic” views to comprehensively quantitate states of dynamic cellular activities.

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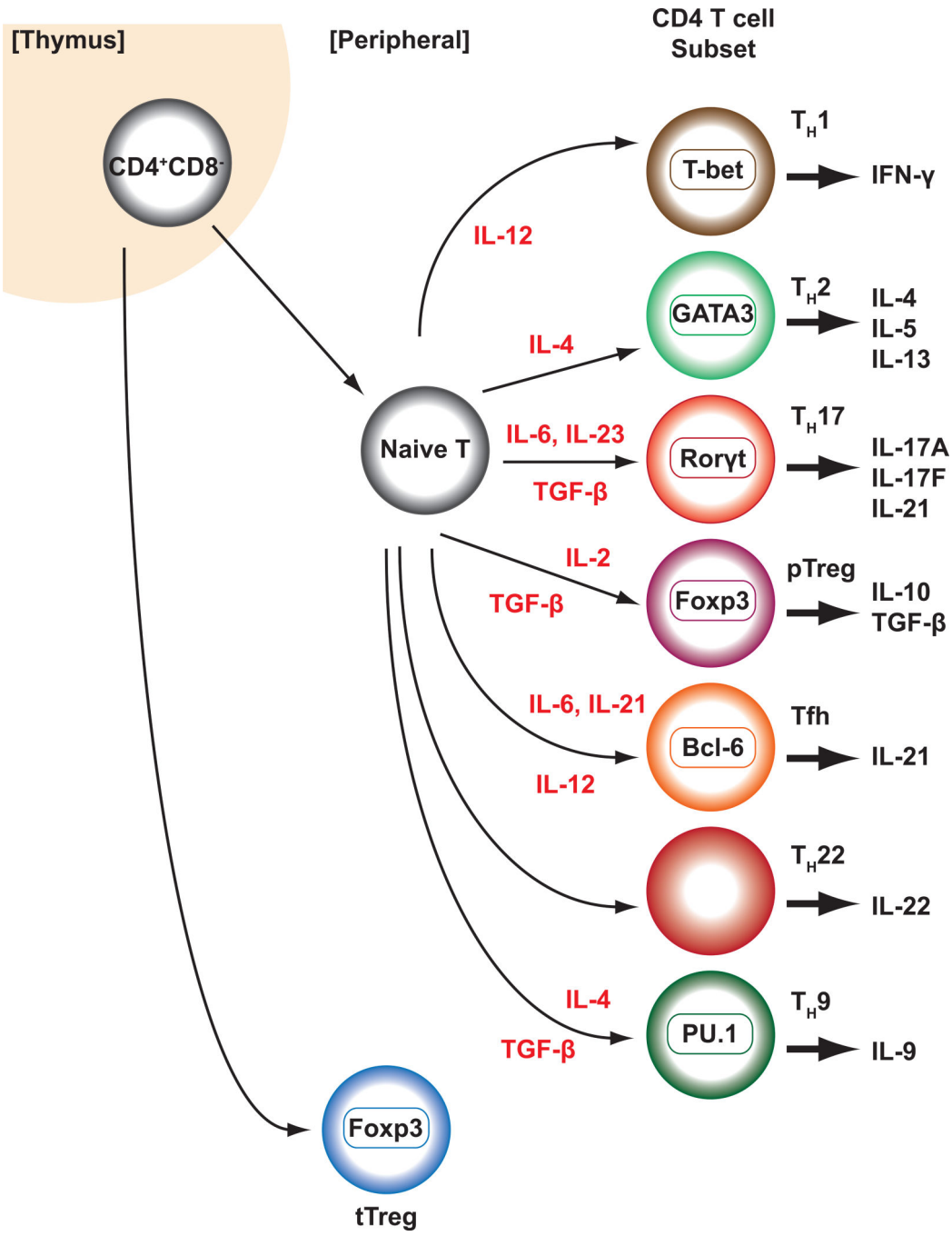

Figure 1. Classical view of helper T cell differentiation

Helper T cells can differentiate from naïve T cells into diverse helper T cells, including Th1, Th2, Th17, T follicular helper (Tfh) cells, Th9 and Th22 cells and peripheral derived regulatory T cells (pTreg) and in contrast to thymically derived regulatory T cells (tpTreg) cells that develop in the thymus.

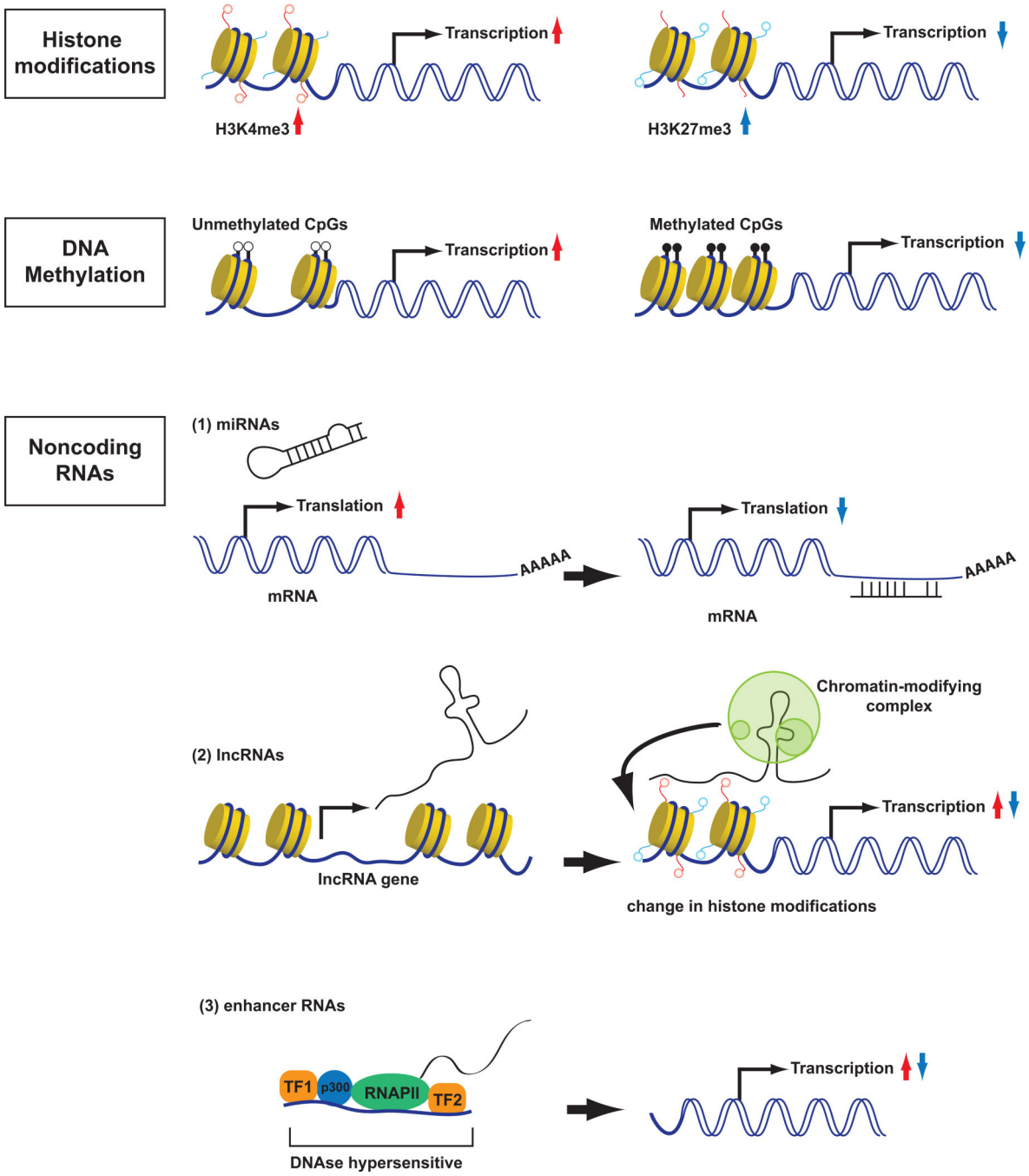

Fig 2. Epigenetic mechanisms that modify gene transcription

Specific alterations in chromatin including histone tail modifications, DNA methylation, production of long noncoding RNAs (lncRNAs), microRNAs (miRNAs) and enhancer RNAs (eRNAs) are mechanisms that to contribute to gene regulation.