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Harnessing the plasticity of CD4$^+$ T cells to treat immune-mediated disease

Michel DuPage and Jeffrey A. Bluestone

Abstract | CD4$^+$ T cells differentiate and acquire distinct functions to combat specific pathogens but can also adapt their functions in response to changing circumstances. Although this phenotypic plasticity can be potentially deleterious, driving immune pathology, it also provides important benefits that have led to its evolutionary preservation. Here, we review CD4$^+$ T cell plasticity by examining the molecular mechanisms that regulate it — from the extracellular cues that initiate and drive cells towards varying phenotypes, to the cytosolic signalling cascades that decipher these cues and transmit them into the cell and to the nucleus, where these signals imprint specific gene expression programmes. By understanding how this functional flexibility is achieved, we may open doors to new therapeutic approaches that harness this property of T cells.

The hypothesis of T helper 1 (T_H1) and T_H2 cell subsets championed by Mosmann and Coffman in the 1980s, and others since, provided a framework to understand how CD4$^+$ T cells direct diverse immune responses[1,2]. By examining clonal populations of CD4$^+$ T cells, they found that different clones expressed selected patterns of cytokines — principally interleukin-4 (IL-4) in T_H2 cells or interferon-γ (IFNγ) in T_H1 cells — thus delineating CD4$^+$ T cells into specialized subsets on the basis of the cytokines they produced and providing a central paradigm for how CD4$^+$ T cells could be linked to different pathologies or associated with the control of different types of infection[3]. Since that time, the breadth of CD4$^+$ T cell subsets has broadened, from the long-studied T_H1 and T_H2 cell subsets, to a more expansive collection, including T_H17, T_H9 and T follicular helper (T_{FH}) cells, as well as thymically derived and peripherally induced regulatory T cells (tT_{Reg} cells and pT_{Reg} cells, respectively)[4–7]. Each T cell subset can be characterized by its ability to sense different inductive cytokines, programme the expression of distinct transcription factors and function by producing select cytokines and chemokine receptors to best control specific pathogens or prevent immune pathology (FIG. 1). However, new tools and techniques have revealed the capacity of polarized T cells, particularly of the T_H17 and pT_{Reg} cell subsets, to change their phenotype and repolarize towards mixed or alternative fates, fuelling the hypothesis that CD4$^+$ T cells are adaptable and can exhibit phenotypic plasticity in response to changing contexts[8–11]. Thus, there has been a re-emergence of T cell 'plasticity', as opposed to 'lineage stability', as the evolving paradigm[12] (BOX 1).

In this Review, we summarize a rapidly expanding literature surrounding CD4$^+$ T cell subsets and make the case for broad plasticity among these subsets. We present T cell plasticity as the culmination of the key underlying mechanisms that control it and emphasize how important differences between the inputs and circuitry of inflammatory and regulatory differentiation programmes may control their interconversion. Finally, we discuss how T cell plasticity is providing new avenues to treat immune-based disease.

Plasticity and reprogramming of CD4$^+$ T cells

Plasticity can be defined as the ability of a single CD4$^+$ T cell to take on characteristics of many T cell subsets simultaneously or at different times during the course of its life cycle. This can occur by transitions induced during a metastable T cell state or reprogramming between subsets. In the metastable state, individual human or mouse T cells, assessed directly *ex vivo*, can co-express many polarizing transcription factors, cytokines and chemokine receptors[13–15]. Reprogramming between distinct CD4$^+$ T cell subsets can be observed in human and mouse T cells under certain conditions *in vitro*[16–19] or in mice *in vivo* on transferring highly purified populations of cells[20–25]. By using lineage-tracing systems in mice, in which cells are engineered to express Cre recombinase under the control of transcriptional

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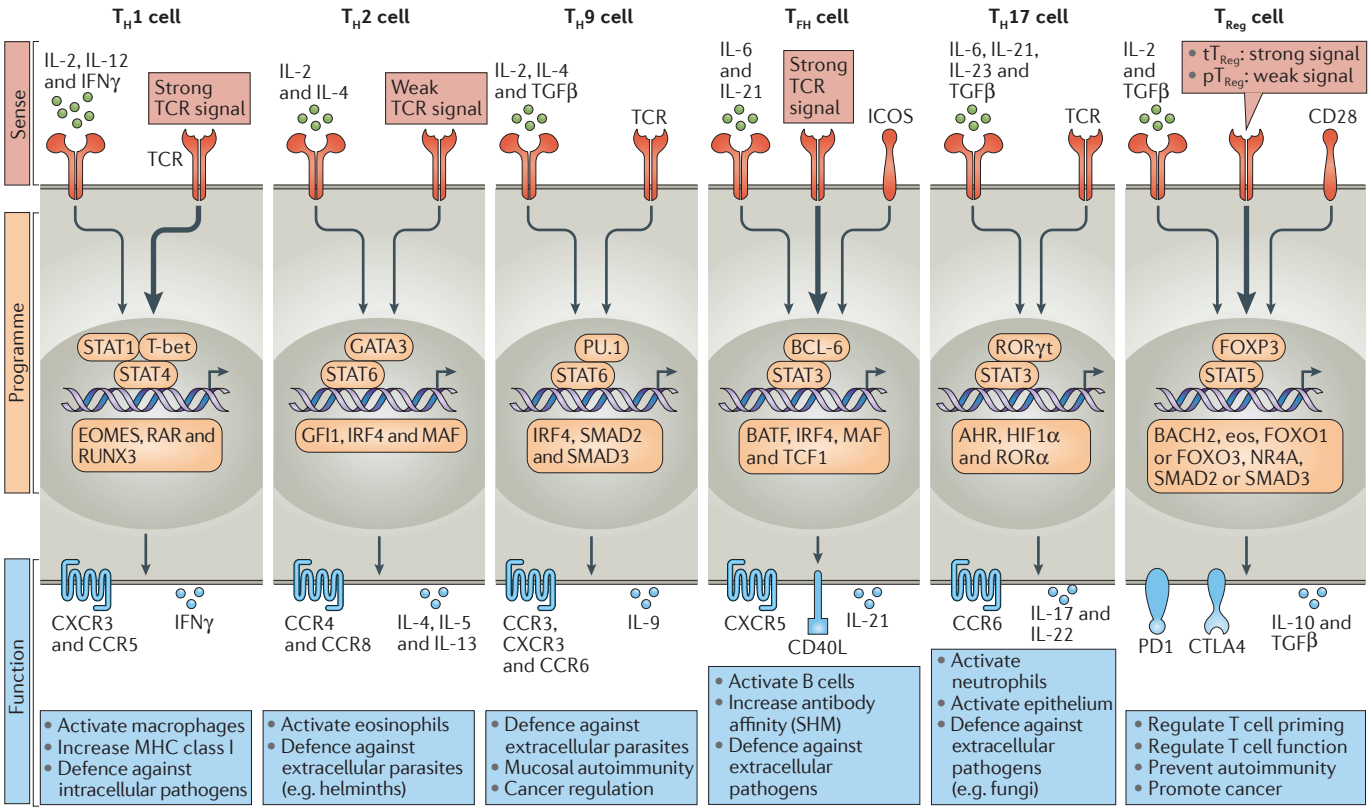


Figure 1 | **Polarized CD4⁺ T cell subsets.** Each CD4⁺ T cell subset can be defined by their distinct abilities to sense (red), programme (orange) and function (blue) in the control of specific pathogens or immune pathologies. The inductive cytokines, polarizing transcription factors and cytokines or chemokine receptors that are characteristic of each subset are shown, along with their association with specific forms of immune defence. AHR, aryl hydrocarbon receptor; BATF, B cell-activating transcription factor; BCL-6, B cell lymphoma 6; CCR, CC-chemokine receptor; CD40L, CD40 ligand; CTLA4, cytotoxic T lymphocyte antigen 4; CXCR, CXC-chemokine receptor; EOMES, eomesodermin; FOXO, forkhead box O; FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; GFI1, growth-factor independent 1; HIF1α, hypoxia-inducible factor 1α; ICOS, inducible T cell co-stimulator; IFNγ, interferon-γ; IL, interleukin; IRF4, interferon-regulatory factor 4; MAF, macrophage-activating factor; NR4A, nuclear receptor 4A; PD1, programmed cell death 1; pT_{Reg} cell, peripherally derived regulatory T cell; RAR, retinoic acid receptor; ROR, retinoic acid receptor-related orphan receptor; RUNX3, runt-related transcription factor 3; SHM, somatic hypermutation; STAT, signal transducer and activator of transcription; TCF1, T cell factor 1; TCR, T cell receptor; T_{FH}, T follicular helper; TGFβ, transforming growth factor-β; T_H, T helper; T_{Reg} cell, regulatory T cell; tT_{Reg} cell, thymus-derived regulatory T cell.

elements that regulate key polarization factors (such as cytokines or transcription factors) and a fluorescent protein reporter of Cre activity, endogenously polarized CD4⁺ T cells from many subsets have been found to change phenotype during their lifespan[26–29]. In humans, the combination of phenotypic analyses and sequencing of T cell receptors (TCRs), which act as unique barcodes for each T cell, has made it possible to investigate the phenotype of clonal descendants of single cells. This has uncovered a great degree of heterogeneity in the type of T cell response generated from single T cells, regardless of the initial stimulus[30,31], and may indicate that generating many functionalities associated with different T cell subsets from individual T cells is advantageous for host immunity. Taking this further, single-cell RNA sequencing has revealed that there is a great deal of heterogeneity among individual cells in populations of what are perceived to be homogeneous T helper cell subsets, as it was recently shown with single T_H17 cells that exhibited a range of phenotypes from pathogenic to regulatory in nature[32,33]. Finally, the prevalence of phenotypic plasticity in T cell immunity is perhaps best exemplified by tT_{Reg} cells, which, in response to different contexts, can polarize similar to other inflammatory T cell subsets (BOX 2). The phenotypic plasticity of T_{Reg} cells that mirrors each T helper cell subset supports a hypothesis of an inherent flexibility of T cells, both inflammatory and regulatory, to adapt their function to changing environments.

Putting order to the many phenotypic transitions that have been described between CD4⁺ T cell subsets in various settings in mice and humans is challenging. Therefore, we present T cell plasticity on the basis of its regulation at distinct levels within the cell. First, extracellular cues initiate the process of polarizing cells towards divergent functions; second, cytosolic signalling cascades decipher these extracellular cues and transmit them into the cell; and third, these signals are imprinted

Box 1 | **Lineage stability or plasticity?**

The T helper 1 (T_H1) versus T_H2 lineage hypothesis was ground-breaking because it established a paradigm for T cells to differentiate and acquire specific functions. However, it also diverted attention from the functional plasticity of T cells. Even at that time, demonstrations of the co-expression of interferon-γ (IFNγ) and interleukin-4 (IL-4) from human T cell clones was prevalent[199,200], and single cell analysis showed co-expression of T_H1- and T_H2-type cytokines, especially early after the initial stimulation of naive T cells[201]. Nevertheless, the capacity of $CD4^+$ T cells to exhibit stably polarized phenotypes both *in vitro* (under specific polarizing conditions) and *in vivo* (in individuals with immunopathologies) supported the hypothesis that distinct T cell lineages can develop that supersede plasticity[2,3,201]. However, as discussed in this Review, it is now apparent that T cells can exhibit both polarized T cell functions and phenotypic plasticity throughout their lifespan. Thus, terminology that encompasses both of these traits is important[6,10,116]. We favour the original descriptor — polarized T cell subset — because it implies an active process with degrees of divergence and leaves room for flexibility in phenotypes over time. This sets the stage for T cells transitioning between phenotypes, not as a consequence of failed maintenance of a 'specified' programme, as implied by loss of lineage stability, but owing to a programmed retention of plasticity or the capacity of T cells to dynamically control their function in response to changing contexts. Thus, T cell differentiation closely resembles the plasticity observed in the nervous system, wherein programmes are not hardwired but are flexible in response to changing environmental cues. The use of terms such as lineage, specification and master regulator are terms best aligned with developmental programmes, such as in *Caenorhabditis elegans*, in which the fate of each cell is predetermined and irreversible.

in the nucleus by generating new gene expression programmes (FIG. 2). It is the integration of these signalling nodes that enables T cells to either resist or remodel their functions dynamically in response to a diversity of environmental cues.

Regulation of plasticity by extracellular cues

Cytokines. More than any other extracellular cue that T cells encounter, specific cytokines have a clear and dominant role in driving the plasticity between $CD4^+$ T cell subsets. This is due in part to the capacity of key inductive cytokines to provide a simple and direct conduit between the environment and gene regulation[34]. The majority of these polarizing cytokines function by engaging their receptors and inducing a phosphorylation cascade of receptor-associated Janus kinase (JAK) and signal transducer and activator of transcription (STAT) proteins, leading to the nuclear localization of the STAT proteins where they act as transcription factors. The cytokines IL-4 and IL-12 were the first factors that were characterized to be sufficient to drive the polarization of T_H2 and T_H1 cell subsets, respectively[3]. However, reversing the conditions in recently polarized T_H1 cells by subsequent culture with IL-4 or by helminth infection *in vivo* repolarizes the cells to produce IL-4 and to extinguish the expression of IFNγ[16,24]. T_H2 cells are also coaxed to express T_H1-type cytokines by incubation with IL-12 in combination with IFNγ and, crucially, type I IFNs, which restores reduced IL-12 receptor β-chain (IL-12Rβ) expression in T_H2-polarized cells[11,35]. Thus, the same cytokines that have been identified to drive the polarization of each T helper cell subset during initial priming also drive the plasticity of established T helper cell subsets (FIG. 3). With the identification of the T_H9 cell subset came the discovery that these cells can be converted from T_H2-polarized cells by treatment with transforming growth factor-β (TGFβ)[36]. The capacity of the T_H17 cell subset to gain IFNγ expression or convert fully to T_H1 cells by losing the expression of IL-17 and retinoic acid receptor-related orphan receptor-γt (RORγt) requires the cytokines IL-12 or IL-23, both of which can activate STAT4, the quintessential STAT protein that is active in T_H1 cells[19,21,27]. Polarized T_{FH} cells from mice can be induced to make T_H1-, T_H2- or T_H17-type cytokines, in addition to IL-21, by culturing in the presence of IL-12, IL-4 or IL-6 and TGFβ, respectively, whereas T_H1, T_H2 and T_H17 cells can express IL-21, CXC-chemokine receptor 5 (CXCR5) and programmed cell death 1 (PD1) by culturing in T_{FH} cell conditions with IL-21 and IL-6 (REF. 37). Finally, these reprogramming effects can be mimicked by specific deficiencies in suppressor of cytokine signalling (SOCS) genes that oppose the activity of specific STATs through various mechanisms, highlighting the importance of cytokine signals in driving plasticity[38].

The cytokine environment can even influence plasticity between inflammatory and regulatory programmes. TGFβ is crucial for the conversion of T_H17 cells towards a regulatory phenotype through the promotion of forkhead box P3 (FOXP3) or IL-10 expression[39–41]. In addition, the pleiotropic cytokine IL-27 can induce IL-10 expression by various inflammatory subsets to promote regulatory functions, as well as induce the generation of type 1 regulatory T (T_R1) cells *de novo*[42–44]. Conversely, the treatment of tT_{Reg} cells from mice or humans with the T_H17 cell-inducing cytokines IL-6, IL-1β and IL-23 (especially in combination) can destabilize FOXP3 expression and induce IL-17 production *in vitro*[17,18], and STAT3 (which is activated in response to these cytokines) is required for reprogramming[45]. Expression of IFNγ and T-bet in $FOXP3^+$ T_{Reg} cells in response to IL-12 has been widely observed in mice and humans[14,46–48], and this may help T_{Reg} cells to control T_H1 cell-based immunopathology[49]. However, IFNγ-expressing T_{Reg} cells are also intermediates in the deviation towards an inflammatory T_H1 cell phenotype in which FOXP3 expression is lost[50,51]. Finally, IL-2 is essential for the maintenance of FOXP3 expression in T_{Reg} cells[52,53], whereas IL-2 is not required for most T helper cells to develop and can impede T_H17 or T_{FH} cell development[54].

TCR and co-stimulatory signal strength. The affinity of a TCR for its cognate antigen on MHC molecules, combined with co-stimulatory receptor–ligand interactions at the cell surface, generates variable intensities of cytosolic signals that flux through the cell, driving the activities of transcription factors such as activator protein 1 (AP-1), nuclear factor of activated T cells (NFAT) and nuclear factor-κB (NF-κB) (FIG. 2). Variations in signalling intensities can alter the differentiation of $CD4^+$ cell subsets by tuning the receptiveness of a cell to different cytokines, by inducing the expression of specific cytokine receptors or by impinging directly on the activation of specific STATs[55,56]. Stronger TCR signalling in naive T cells drives the polarization of T_H1 cell differentiation in preference to T_H2 or T_{FH} cell differentiation. However, with very high signal strength, such as with high antigen loads or high TCR affinities, polarization towards

T_H2 or T_{FH} cell differentiation can dominate[55–58]. By contrast, weak TCR signalling, by transient or low-affinity TCR interactions, favours the induction of FOXP3 expression[59,60]. Importantly, TCR signal strength drives the first divergence of inflammatory versus regulatory subsets during T cell development in the thymus. An increased strength of signal, which is imparted by TCRs that recognize self-antigen, imprints a distinct epigenetic state and induces FOXP3 expression to generate the T_{Reg} cell lineage[61,62].

TCR and co-stimulatory signals have key roles in the development of polarized T cell subsets, but less is known about the role of TCR stimulation in driving plasticity between subsets. Weaker TCR stimulation during priming *in vivo* allows for greater plasticity in secondary responses[63], but varying the strength of signal during recall responses also redirects T helper cell subsets, with stronger signals promoting T_H2 cell phenotypes in memory T_H1 cells[64]. Importantly, TCR stimulation is universally required for cytokines to reprogramme T cell subsets[35,65].

There are key differences in the requirements for TCR and CD28 signalling in inflammatory and regulatory T cells. Although dispensable for the persistence of memory T helper cells, T_{Reg} cells (perhaps as a consequence of self-antigen recognition) seem to be constitutively activated and require interactions through their TCR and CD28 to maintain effector populations[66–70]. However, strong TCR stimulation of T_{Reg} cells by an autoantigen that instigates autoimmune disease can transiently destabilize their FOXP3 expression[71], whereas the chronic stimulation of autoreactive effector T cells may induce FOXP3 expression in these cells and promote immune tolerance[72].

Notch signalling. Notch signalling has a pivotal role in the polarization of T cells, both by independent mechanisms and by impinging on other key regulatory nodes, such as cytokine, TCR and co-stimulation, cytosolic signalling, metabolic and transcriptional regulatory pathways[56,73]. Although Notch and other signalling pathways are not covered in this Review, they should not be overlooked when considering a system-wide control of T cell plasticity.

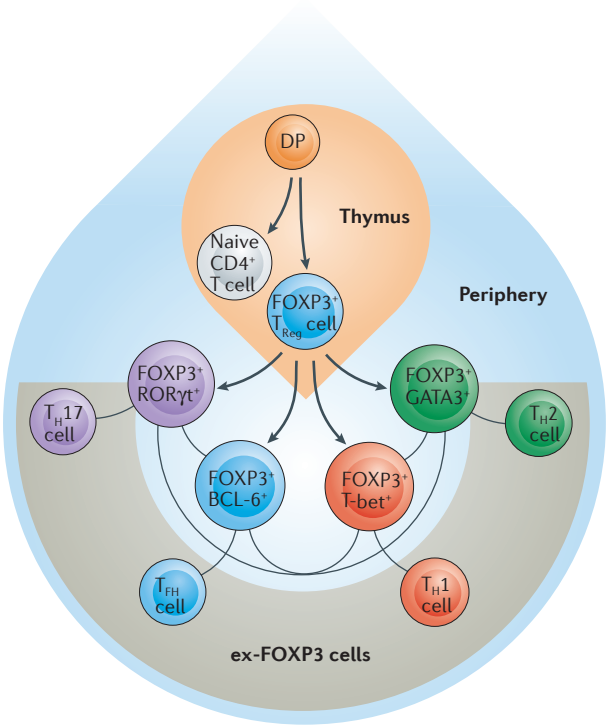
Regulation of plasticity by cytosolic signalling

PI3K–AKT–mTOR signalling. How extracellular cues that are engaged at the surface of the cell are communicated within the cell to control plasticity has only recently begun to take shape, and the phosphatidylinositol 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) pathway has a central role (FIG. 4). Activated by numerous

Box 2 | Phenotypic plasticity in inflammatory and regulatory T cell lineages

Regulatory T cells originating in the thymus (tT_{Reg} cells) provide the best example of a distinct lineage of $CD4^+$ T cells. They differ extensively from the naive precursors of T helper cells that also originate in the thymus and give rise to T helper 1 (T_H1), T_H2, T_H17 or T follicular helper (T_{FH}) cells on stimulation in the periphery. Similar to the separation of the $CD8^+$ and $CD4^+$ T cell lineages, tT_{Reg} cells diverge from naive $CD4^+$ T cells during T cell development in the thymus, recognize a distinct set of antigens[61], have different epigenetic landscapes[62] and uniquely express a defining transcription factor: forkhead box P3 (FOXP3). The finding that $FOXP3^+$ T_{Reg} cells can co-express each of the so-called master transcription factors of each T helper cell subset is important to our understanding of T cell plasticity[7]. Although the acquisition of properties defining each T helper cell subset is hypothesized to allow T_{Reg} cells to mirror, and thus better regulate, specific types of immune responses[7,49], co-expression of these transcription factors with FOXP3 supports the notion that the expression of these transcription factors is not lineage-defining but is responsive to environmental cues. Furthermore, although often a topic of controversy, the stability of FOXP3 expression in tT_{Reg} cells is pronounced, especially when compared to the plasticity with which the other master transcription factors can be induced or repressed. Nonetheless, the loss of FOXP3 expression and acquisition of inflammatory cytokine production does occur in several settings, most prominently during lymphopaenia or massive inflammation[26,46,202,203], and is augmented by disrupting specific genes and pathways in T_{Reg} cells[53,79,152]. It is these transitions, between inflammatory and regulatory programmes, that are likely to be of greatest importance in immunological disease as well as for therapeutic manipulation to treat disease.

BCL-6, B cell lymphoma 6; DP, double positive; GATA3, GATA-binding protein 3; RORγt, retinoic acid receptor-related orphan receptor-γt.



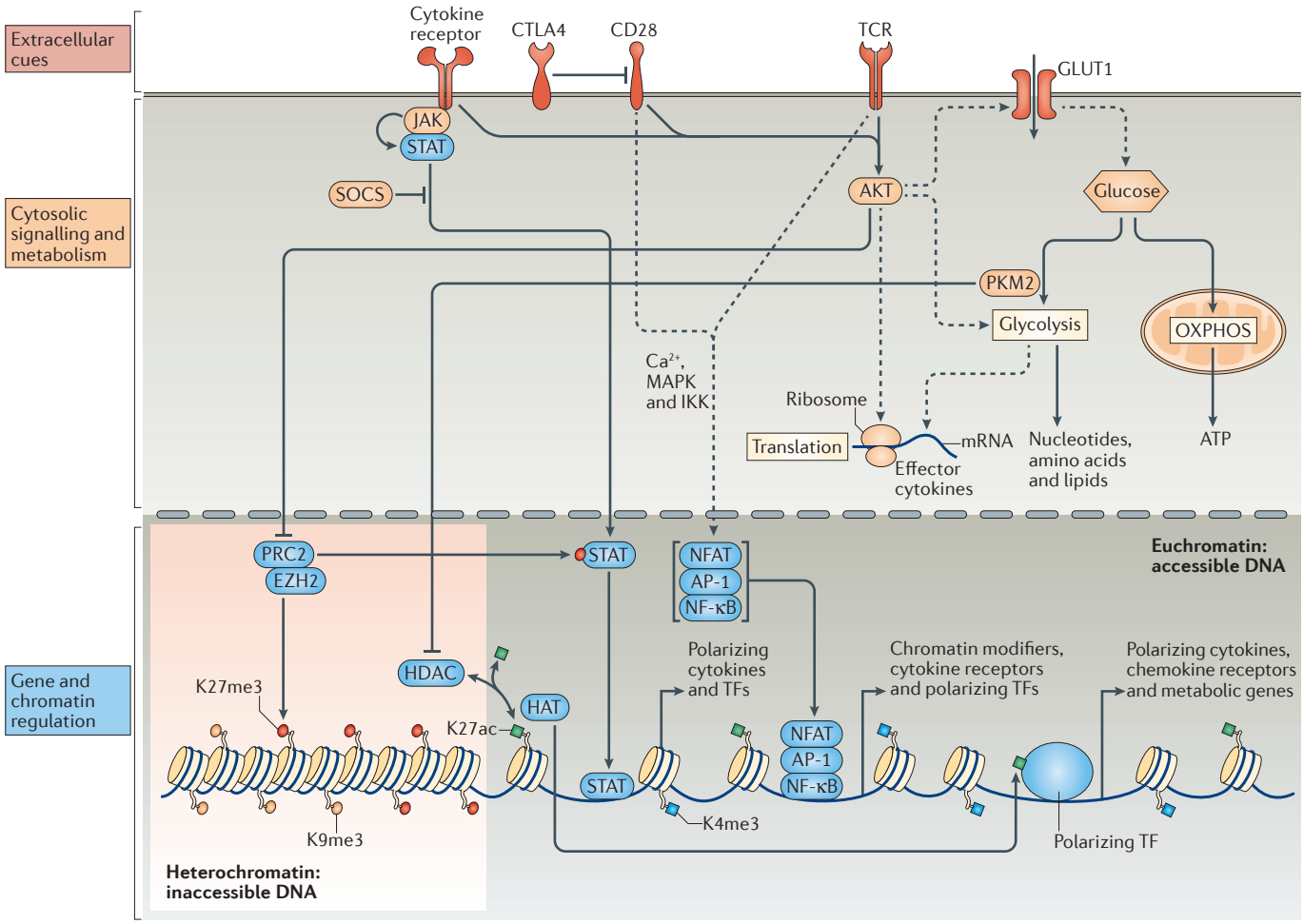


Figure 2 | **The integration of signals at many levels in T cells regulates plasticity.** The regulation of T cell plasticity is depicted at three levels in the cell: extracellular cues (red), cytosolic signalling and metabolic programmes (orange) and transcription factor (TF)- or chromatin-mediated gene regulation (blue). These pathways are integrated by mechanisms linking these levels of regulation. Direct protein–protein interactions are indicated by solid lines, whereas indirect links between proteins are denoted with dashed lines. AP-1, activator protein 1; CTLA4, cytotoxic T lymphocyte antigen 4; GLUT1, glucose transporter 1; HAT, histone acetyltransferase; HDAC, histone deacetylase; IKK, inhibitor of nuclear factor-κB kinase; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; OXPHOS, oxidative phosphorylation; PKM2, pyruvate kinase M2; SOCS, suppressor of cytokine signalling; STAT, signal transducer and activator of transcription; TCR, T cell receptor.

cues in T cells, including the TCR, CD28 and the IL-2 receptor, PI3K activates AKT by generating the phospholipid phosphatidylinositol-3,4,5-trisphosphate (PIP_3; also known as PtdIns(3,4,5)P_3), which acts as a docking and activation site for the kinase. AKT can then phosphorylate many substrates, including regulators of the canonical mTOR complex 1 (mTORC1) leading to its activation. Importantly, PI3K is opposed by the activity of phosphatase and tensin homologue (PTEN), which converts PIP_3 to phosphatidylinositol-4,5-bisphosphate (PIP_2; also known as PtdIns(4,5)P_2).

The PI3K–AKT–mTOR pathway is a crucial bifurcation point for inflammatory versus regulatory T cell programmes, as the activation of this pathway is required for the polarization and function of most T helper cells but is largely repressed in FOXP3$^+$ T_{Reg} cells[74,75]. AKT function is blunted in T_{Reg} cells by the activity of PTEN, as well as by PH domain leucine-rich repeat-containing protein phosphatases (PHLPPs) that directly inactivate AKT, effectively rewiring their response to IL-2 to selectively activate STAT5, but not AKT[76–78]. Removal of this regulation in T_{Reg} cells with PTEN deficiency results in severely compromised T_{Reg} cell stability and in their conversion into inflammatory T_H1 and T_H17 cells[79,80]. Dampened AKT activity in T_{Reg} cells supports the expression of IL-2 receptor α-chain (IL-2Rα; also known as CD25) and the nuclear localization of forkhead box O (FOXO) transcription factors, both of which are crucial for preventing T_{Reg} cell plasticity towards inflammatory programmes[79–81]. Additionally, neuropilin 1, a receptor that is highly expressed by mouse tT_{Reg} cells, recruits PTEN to the immunological synapse and blocks the activation of AKT during TCR stimulation, thus promoting T_{Reg} cell stability and function[82].

mTOR complex 1 (mTORC1). A complex consisting of: mammalian target of rapamycin (mTOR), which is a serine/threonine kinase; regulatory-associated protein of mTOR (RAPTOR); proline-rich AKT1 substrate of 40 kDa (PRAS40), which is an mTORC1 inhibitor; mLST8, which is of unknown function; and DEP domain-containing mTOR-interacting protein (DEPTOR), which is an mTOR inhibitor.

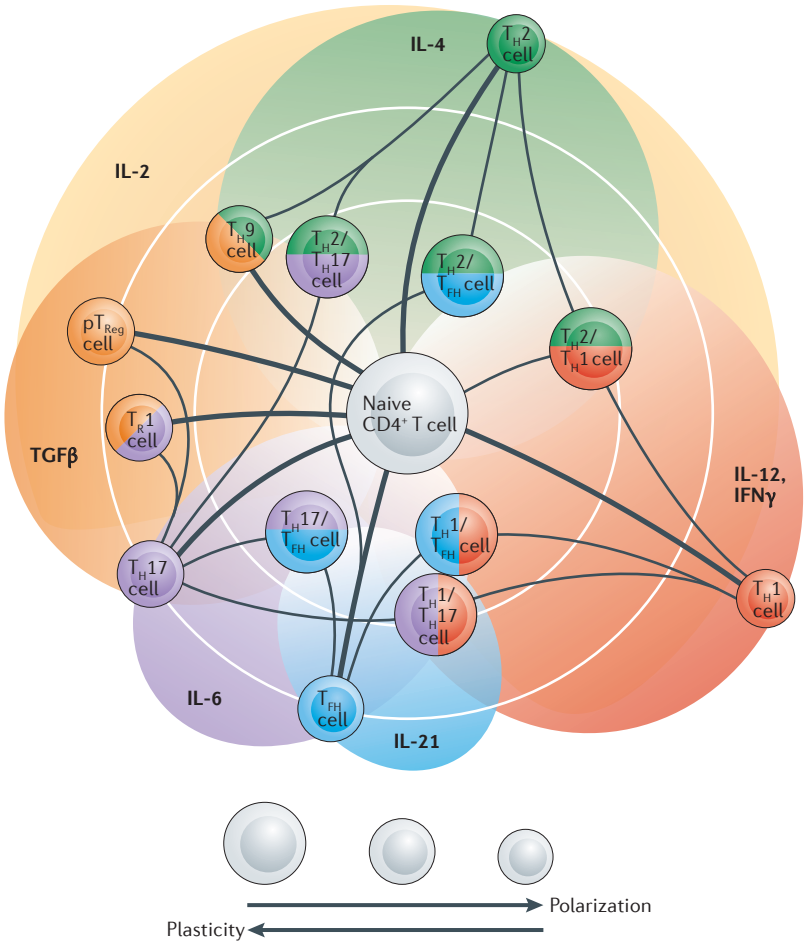


Figure 3 | **Cytokine-driven T cell plasticity.** The key inductive cytokines interleukin-4 (IL-4), interferon-γ (IFNγ), IL-12, IL-21, IL-6, transforming growth factor-β (TGFβ) and IL-2, alone or in concert, can polarize naive CD4+ T cells towards different functions. This pinwheel depiction is intended to reveal the interconnectedness of these different programmes based on the capacity of these inductive cytokines to promote polarization or plasticity between subsets. Polarization, and hence more restricted cellular function, is depicted both by the distance from the central naive T cell and by decreasing cell size. Grey lines linking the subsets depict known transitions. Evidence suggests that reprogramming between subsets may occur by transitioning through intermediate stages in which cells exhibit phenotypes of many subsets. pT_{Reg} cell, peripherally derived regulatory T cell; T_{FH}, T follicular helper; T_H, T helper.

In T helper cell polarization, PTEN deficiency favours the acquisition of T_H2 cell phenotypes[75], probably through increased activation of mTORC1 (REF. 83). However, although the selective blockade of either mTORC1 or mTORC2 has been described to promote or hinder distinct T helper cell subsets[84], the deletion of mTOR blocks T_H1, T_H2 and T_H17 cell polarization, indicating that both mTOR complexes have essential roles in the generation of inflammatory T helper cell subsets[83,85–87]. By contrast, mTOR deficiency favours the induction of FOXP3 expression *in vitro*, and mTORC2 seems to be largely dispensable for T_{Reg} cell stability and function *in vivo*[84,85,88]. In addition, although a requirement for some mTORC1 activity in tT_{Reg} cells has been demonstrated[88], rapamycin treatment (which preferentially inhibits mTORC1) actually promotes T_{Reg} cell stability[59,89], and hyperactivation of mTORC1 in T_{Reg} cells drives IL-17 production and loss of FOXP3 expression[90]. Furthermore, it seems that T_{Reg} cell instability associated with increased mTOR activity is driven most prominently by activated mTORC2, which, by acting upstream of mTORC1, has the potential to activate parallel pathways to further destabilize T_{Reg} cells[80,85]. Complicating the role of each mTOR complex is the finding that loss of mTORC1 may destabilize T_{Reg} cells by enhancing mTORC2 activation, as mTORC1 activity can negatively feedback on mTORC2 (REF. 88). Indeed, deciphering how numerous extracellular inputs are integrated within the cell to drive the plasticity of cells towards distinct functions is daunting, but mathematical modelling has successfully recapitulated the experimental observations described here and may provide an important platform to clarify this complexity[91].

Cellular energetics and metabolism. Following antigenic stimulation, T cells rapidly mould the acquisition and use of metabolites to meet their energetic and biosynthetic needs, and the metabolic programmes that are engaged can directly affect T cell function. A crucial decision for the T cell is how (and whether) to catabolize glucose. Oxidative phosphorylation breaks down glucose to yield the maximum amount of ATP, whereas glycolysis alone generates less ATP but creates precursors of amino acids, nucleotides and lipids from glucose (FIG. 4). Aerobic glycolysis, also known as the Warburg effect, allows rapidly proliferating cells to meet their biosynthetic needs by using glycolysis, rather than oxidative phosphorylation, when oxygen is replete[92]. CD28 signalling directly controls the metabolic switch to glycolysis during T cell activation by upregulating the expression of glucose transporter 1 (GLUT1; also known as SLC2A1) in a PI3K–AKT-dependent manner, thereby increasing the import of glucose into the cell[93,94]. Importantly, T_{Reg} cells do not use glycolysis after stimulation, largely owing to their selective blockade of PI3K–AKT activation, preventing GLUT1 upregulation. Instead, T_{Reg} cells heavily rely on fatty acid oxidation to feed the tricarboxylic acid cycle and generate energy through oxidative phosphorylation[95–97]. Thus, PTEN deficiency in T_{Reg} cells may drive loss of FOXP3 expression and effector cytokine production by enforcing glycolytic metabolism[79,80]. Short-chain fatty acids generated by commensal bacteria in the gut may induce FOXP3 expression and pT_{Reg} cell polarization by supporting the T_{Reg} cell metabolic programme[98,99]. In addition to glucose or fatty acids, glutamine is an important biosynthetic precursor that tips the balance between T_H1 and T_{Reg} cell polarization. Glutamine metabolism generates α-ketoglutarate, which is required for T_H1 cells but blocks T_{Reg} cell differentiation in an mTORC1-dependent manner[100]. Regulation of fatty acid metabolism and downstream cholesterol biosynthesis by CD5 antigen-like (CD5L) in T_H17 cells was recently shown to act as a crucial checkpoint promoting regulatory versus pathogenic activities within the T_H17 cell subset[32].

The transcription factor hypoxia-inducible factor 1α (HIF1α) is positively regulated by PI3K–AKT–mTOR signals[101,102]. HIF1α induces the expression of genes that are required for glycolysis when stabilized by low

mTORC2
A complex composed of mammalian target of rapamycin (mTOR), mLST8 and the adaptor proteins rapamycin-insensitive companion of mTOR (RICTOR) and stress-activated MAP kinase-interacting protein 1 (SIN1).

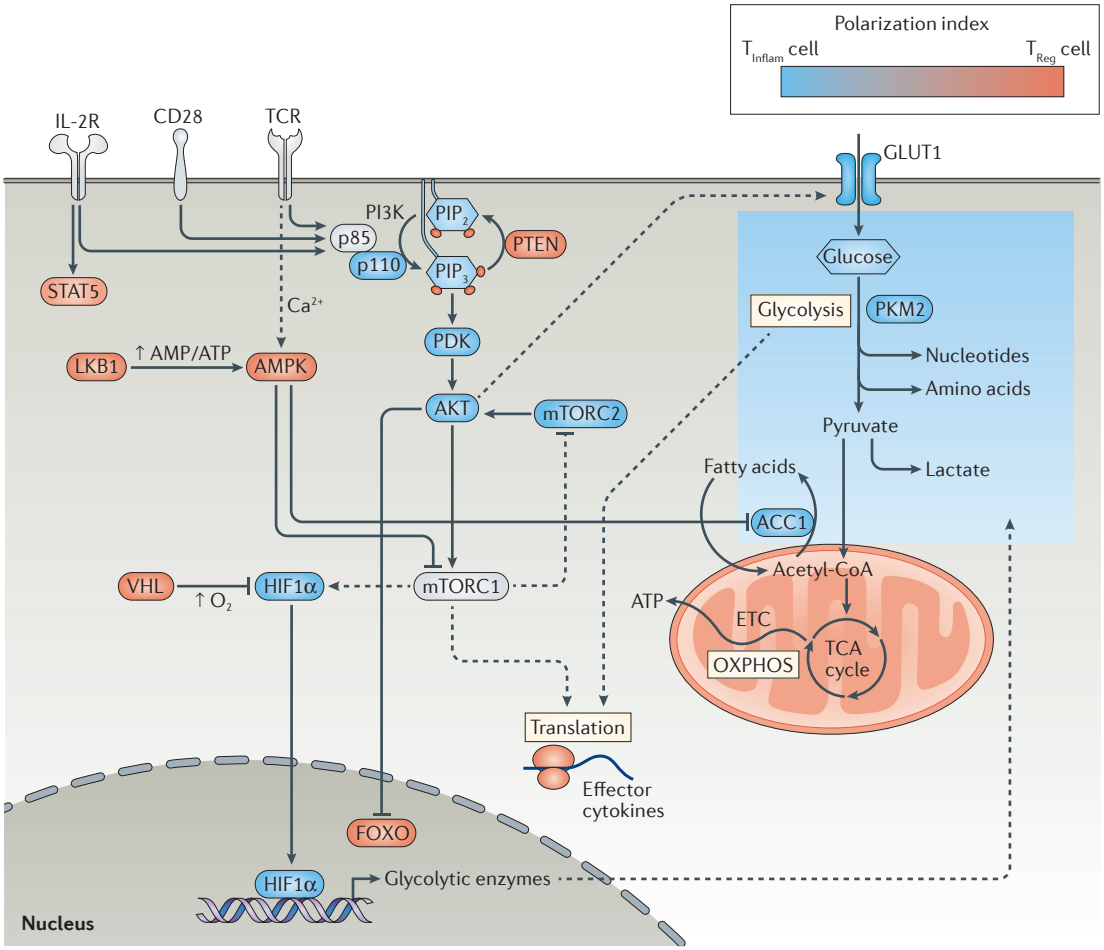


Figure 4 | **The PI3K–AKT–mTOR pathway and metabolic programmes converge to regulate the plasticity of inflammatory versus regulatory T cells.** Links between extracellular cues, the phosphatidylinositol 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) pathway, metabolic programmes and gene regulation are depicted. A polarization index indicates proteins or processes that favour the induction of inflammatory (blue) or regulatory (red) T cell programmes. Direct protein–protein interactions are indicated by solid lines, whereas indirect links between proteins are denoted with dashed lines. ACC1, acetyl-CoA carboxylase 1; AMPK, AMP-activated protein kinase; ETC, electron transport chain; FOXO, forkhead box O; GLUT1, glucose transporter 1; HIF1α, hypoxia-inducible factor 1α; IL-2R, IL-2 receptor; LKB1, liver kinase B1; mTORC, mTOR complex; OXPHOS, oxidative phosphorylation; PDK, phosphoinositide-dependent protein kinase; PIP_2, phosphatidylinositol-4,5-biphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PKM2, pyruvate kinase M2; PTEN, phosphatase and tensin homologue; STAT5, signal transducer and activator of transcription 5; TCA, tricarboxylic acid; TCR, T cell receptor; T_{Inflam} cell, inflammatory T cell; T_{Reg} cell, regulatory T cell; VHL, von Hippel-Lindau.

oxygen availability. T_{Reg} cells, by dampening the PI3K–AKT–mTOR pathway, also prevent the induction of HIF1α expression and glycolysis during TCR stimulation, reinforcing their unique bioenergetic programme. Indeed, deletion in T_{Reg} cells of von Hippel–Lindau (VHL), an E3 ubiquitin ligase that targets HIF1α, increases HIF1α activity, leading to ectopic IFNγ production and reduced FOXP3 expression[103]. HIF1α has a particularly important role in T_H17 cell polarization, for which, in addition to promoting glycolysis, it directly induces the expression of RORγt and supports its function[102,104]. The transcriptional activity of HIF1α is also opposed by the transcriptional repressor BCL-6 (B cell lymphoma 6), which competes for binding to many of the same genes, preventing the induction of glycolytic genes that may be detrimental to the T_{FH} cell programme[105].

The energy sensor AMP-activated protein kinase (AMPK) is activated by liver kinase B1 (LKB1; also known as STK11) when the ratio of AMP to ATP increases, but also by Ca^{2+} flux during TCR stimulation[92,106]. AMPK shuts down energy-consuming processes such as protein, cholesterol and fatty acid synthesis, while promoting energy-generating processes such as glucose import and fatty acid oxidation[92]. AMPK blocks protein translation by inhibiting mTORC1, and the deletion of LKB1 or AMPK in T cells promotes the translation of inflammatory cytokines, even under conditions of low energy availability[107,108]. AMPK deficiency also releases mTORC1 to activate HIF1α and promote the expression of genes that favour glycolysis[109], and aerobic glycolysis itself promotes the production of inflammatory cytokines[110]. Enforced activation of AMPK

Tricarboxylic acid cycle
(TCA cycle). This pathway (also known as the Krebs cycle or citric acid cycle) catalyses the oxidation of acetyl-CoA (from glucose or fatty acids or indirectly from amino acids) to generate NADH and FADH, which fuel the electron transport chain and thereby oxidative phosphorylation and ATP production. It also serves as a source of precursors for amino acid and lipid synthesis.

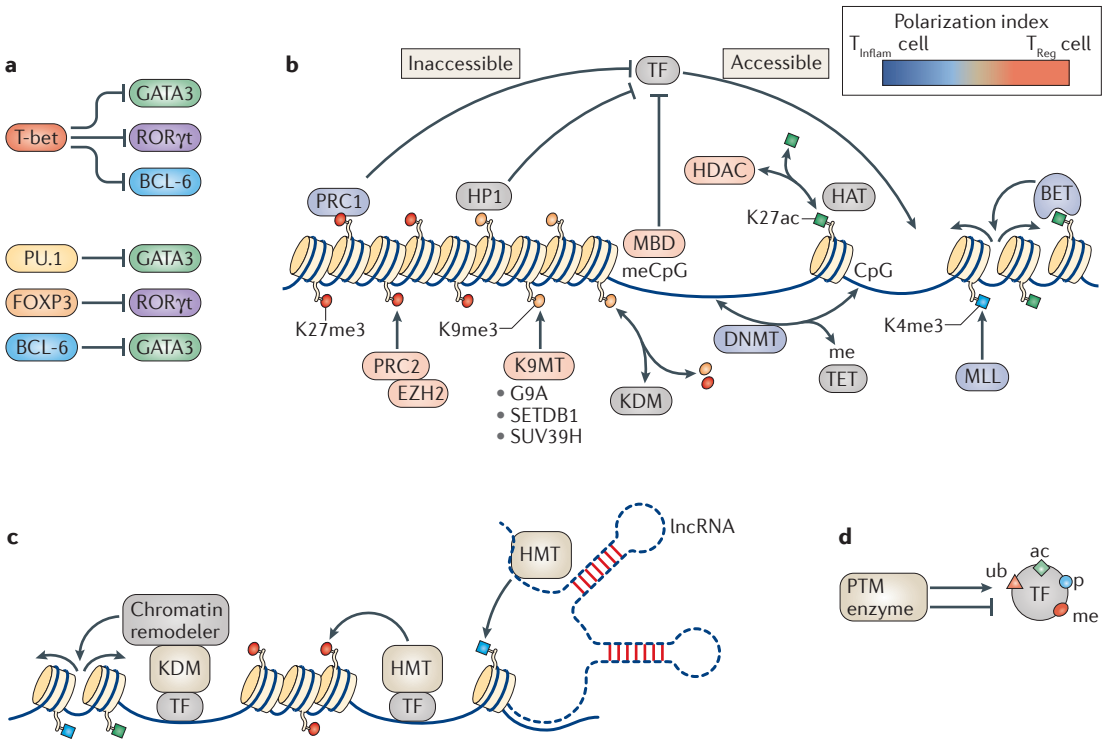


Figure 5 | **Mechanisms of gene regulation in T cell plasticity. a** | Direct interactions between transcription factors (TFs) can antagonize the function of opposing TFs. **b** | DNA accessibility controls gene expression. Histone modifications and DNA methylation can drive changes in chromatin structure, altering the accessibility of DNA to TFs. These epigenetic changes act to stabilize gene expression programmes during T cell responses in which driving or opposing TFs may be transiently lost or gained, respectively. A polarization index indicates proteins or processes that favour inflammatory (blue) or regulatory (red) T cell programmes. **c** | TFs and long non-coding RNAs (lncRNAs) link chromatin modifiers to specific genetic loci. **d** | Post-translational modifying (PTM) enzymes regulate the stability, activity and localization of TFs and may provide a therapeutic means to indirectly target TF activity. ac, acetyl; BCL-6, B cell lymphoma 6; BET, bromodomain and extraterminal protein; DNMT, DNA methyltransferase; FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; HAT, histone acetyltransferase; HDAC, histone deacetylase; HMT, histone methyltransferase; HP1, heterochromatin protein 1; KDM, histone lysine demethylase; K9MT, K9 methyltransferase; MBD, methyl-CpG-binding domain protein; me, methyl; MLL, mixed-lineage leukaemia; p, phosphate; PRC, polycomb repressive complex; RORγt,retinoic acid receptor-related orphan receptor-γt; TET, ten-eleven translocation; T_{Inflam} cell, inflammatory T cell; T_{Reg} cell, regulatory T cell; ub, ubiquitin.

with the agonist metformin broadly blocks effector T cell function but promotes T_{Reg} cell induction and function[96]. Activated AMPK blocks fatty acid biosynthesis by inhibiting acetyl-CoA carboxylase 1 (ACC1), and deletion of ACC1 in T cells favours T_{Reg} cell polarization at the expense of T_H17 cell polarization[96,111]. Thus, T cell plasticity can be controlled by the metabolic programmes of the cell that respond dynamically to fluctuations in the nutrients, oxygen levels and energy sources present in the environment. Such factors are likely to be important when T cells migrate between distinct microenvironments during immune responses, such as between lymphoid organs and tissue sites or tumour microenvironments[92].

Regulation of plasticity by gene regulation

Transcription factors. T helper cell subset functionality is rooted in the expression of transcription factors. However, given that transcription factors function during T cell plasticity as they do during the initial polarization of naive T cells[112], we only highlight a few important themes here. First, STATs drive T helper cell polarization or plasticity in direct response to the binding of cytokines to receptors. In general, selective cytokine receptor or SOCS protein expression serves as a major buffer to resist cytokine-driven repolarization of T cells, although DNA accessibility (discussed next) also has a crucial role. Second, the so-called 'master regulators' or 'lineage-defining' transcription factors T-bet, GATA-binding protein 3 (GATA3), RORγt, BCL-6 and FOXP3 have a substantial, but often incomplete, role in setting the transcriptional programmes of T_H1, T_H2, T_H17, T_{FH} and T_{Reg} cells, respectively[62,113–115]. The capacity for these transcription factors to directly antagonize each other's functions through direct protein–protein interactions may impart coherency in effector responses[11,116] (FIG. 5a). However, their induction or co-expression in opposing subsets, especially with FOXP3, indicates that counter-regulation of their expression is incomplete[37,117]. Thus, these so-called master transcription factors behave less like lineage-definers and more like executors, expressed in response to environmental

cues to carry out the induction of a defined set of gene effectors. Importantly, these transcription factors are also expressed by innate lymphoid cells to engender similar phenotypic traits[118]. Third, the expression of specific STATs and master transcription factors is not sufficient for polarization or plasticity of T helper cell subsets; rather, a collection of additional transcription factors are required[119,120] (FIG. 1). Additional transcription factors, such as the nuclear receptor 4A (NR4A) family, transcription regulator protein BACH2, RUNX proteins, retinoic acid receptors and aryl hydrocarbon receptor (AHR), clearly have essential roles in the maintenance of polarized states, as the disruption of these transcription factors leads to enhanced plasticity between subsets[43,121–125]. Nevertheless, even the expression of a suite of transcription factors is not sufficient to drive the transcriptional programmes of T helper cell subsets because access of the transcription factors to their DNA-binding sites in the genome is regulated.

DNA accessibility by modification of DNA and histones. In the nucleus, a delicate balance is struck between the logistics of packing DNA into this confined space (in heterochromatin) and providing access to DNA for transcription (in euchromatin). Post-transcriptional modifications of histone proteins, which make up nucleosomes, control how tightly nucleosomes are packed, and this has been adopted by the cell to regulate transcription in a semi-stable manner, along with the direct modification of DNA by methylation. These forms of gene regulation are termed 'epigenetic' because they promote the heritable transmission of distinct transcriptional programmes despite identical DNA sequences.

Generating accessible DNA. Regulation of T cell polarization by chromatin structure and DNA accessibility was first appreciated with the discovery that cytokine expression after TCR stimulation required a discrete number of cellular divisions[126–129]. This is largely due to the requirement for chromatin to be reorganized to create access to key differentiation loci. The opening of chromatin is aided by the recruitment of histone acetyltransferases (HATs), chromatin remodelling enzymes and histone methyltransferases (HMTs), as well as the recently discovered histone lysine demethylases (KDMs) and ten-eleven translocation (TET; also known as methylcytosine dioxygenase) proteins that initiate DNA demethylation[130–136] (FIG. 5b). Polarizing transcription factors, such as STATs, may participate in opening or stabilizing the local chromatin structure by recruiting these enzymes in a site-specific manner during T helper cell polarization[132,135–138]. At the *Foxp3* locus, DNA demethylation by the recruitment of TET proteins is necessary for the induction and maintenance of FOXP3 expression[135,139,140]. The recruitment of HATs, such as CBP (also known as CREBBP) and p300, is also crucial for maintaining T_{Reg} cell integrity by keeping the locus open; in their absence, T_{Reg} cells lose FOXP3 expression and gain IL-17 expression[141]. Activating HMTs, such as the trithorax family member mixed-lineage leukaemia (MLL; also known as KMT2A), which adds methyl groups to histone H3 lysine 4 (H3K4), is especially important for the retention of cytokine production specifically in memory T_H2 cells, but not T_H1 cells[142]. The recruitment of chromatin-modifying complexes to specific DNA loci is also promoted by long non-coding RNAs (lncRNAs), such as with *Tmevpg1* (also known as *NeSt*) recruitment of MLL to the *Ifng* locus[143,144], which bind through base pair complementarity and direct chromatin modifiers to specific sites in the genome[145] (FIG. 5c).

Inhibiting DNA accessibility by DNA methylation. Equally important to opening loci for transcription factors to bind is the ability to block accessibility to genes that would oppose the directed polarization of effector functions. Cytosine methylation directly blocks the binding of transcription factors to DNA and, through binding methyl-CpG-binding domain proteins (MBDs), recruits additional chromatin modifiers, such as histone deacetylases (HDACs) or repressive HMTs, to generate heterochromatin[8,131]. Ultimately, the effect on gene expression can vary depending on whether enhancer or repressor elements are methylated.

The dynamic nature of DNA methylation provides a paradigm for both the polarized function and plastic behaviour of T cells. Reduced DNA methylation early during activation assists the induction of polarizing factors, whereas selective DNA methylation during the highly proliferative expansion phase establishes the polarized functions of effector T cells and, finally, relaxed methylation allows for substantial plasticity following restimulation in the quiescent memory phase[112,146]. Thus, whereas DNA methyltransferase 3a (DNMT3a) deficiency does not affect the initial polarization of T_H1, T_H2, T_H17 or pT_{Reg} cell subsets, following restimulation with IL-12 (that is, T_H1 cell-polarizing conditions), all subsets produce IFNγ[147]. Disrupting the recruitment of DNMT3A to the *Foxp3* locus leads to the inappropriate induction of FOXP3 expression in T helper cells[148].

Inhibiting DNA accessibility with heterochromatin. Transcriptionally repressive heterochromatin is generated by several key complexes, including HDACs, the H3K27me3-associated polycomb repressive complex 1 (PRC1) and PRC2, and the H3K9me3-associated HMTs, and it seems to have a central role in preventing phenotypic plasticity between the polarized subsets[136,149]. In T_{Reg} cells, HDAC3 interacts with FOXP3 to repress the expression of IL-2 and IL-17 (REF. 150). Paradoxically, pan-inhibition of HDAC activity prevents loss of FOXP3 expression and IL-17 induction by human T_{Reg} cells cultured with T_H17 cell-inducing cytokines[17].

H3K27 HMT EZH2, acting within PRC2, interacts directly with FOXP3 and is required for the maintenance of the transcriptional programme and function of activated T_{Reg} cells[151,152]. During *in vitro* polarization, the activity of EZH2 also prevents plasticity between T_H1 and T_H2 cell subsets and supports pT_{Reg} cell generation by inhibiting IFNγ expression[153,154]. However, T_H17 cell polarization seems to be impaired by increased PRC2 activity[154,155]. Interestingly, in cells lacking H3K27 KDM

Innate lymphoid cells
Lymphoid cells that do not express unique antigen receptors derived from gene rearrangement or cell-surface markers that are characteristic of other immune cell lineages. However, in response to innate tissue-derived signals, they secrete cytokines that are associated with T helper cell subsets. They have important roles in innate immune responses to infectious microorganisms and in lymphoid tissue formation.

Long non-coding RNAs
(lncRNAs). A subset of non-coding RNAs that are greater than 200 nucleotides in length and distinct from other non-coding RNAs, such as tRNAs, rRNAs, snRNAs, small nucleolar RNAs (snoRNAs), and microRNAs. Although they are known to regulate gene expression, the mechanisms by which this is achieved is an active area of investigation.

JMJD3 (also known as KDM6B), T_H17 cell polarization is enhanced, and many polarized T cell subsets exhibit enhanced stability[156]. Finally, PRC1, which recognizes H3K27me3 marks and further condenses chromatin, is crucial for T_H2 cell function and for limiting their plasticity towards T_H1 cell phenotypes[136].

In contrast to H3K27 methylation, the regulation of H3K9 methylation is more complex, owing to its control by many distinct HMTs. This probably contributes to the diversity of consequences observed with the disruption of different H3K9 HMTs, as each enzyme may interact with different binding partners or target unique genomic loci. For example, deletion of H3K9 HMT SUV39H1 allows T_H2-polarized cells to express IFNγ when restimulated in T_H1 cell-polarizing conditions, whereas deficiency for HMT G9A (also known as EHMT2) drives T_{Reg} cell and T_H17 cell polarization by opening the *Foxp3* and *Rorc* loci[157,158]. In human T_{Reg} cells, H3K9 HMT SETDB1 is coupled to FOXP3 by a FOXP3-interacting KRAB domain-containing protein (FIK)–KRAB domain-associated protein (KAP; also known as TIF1β) complex to maintain repressive chromatin states at the *IL2* and *IFNG* loci[159].

Global analyses of histone modifications associated with transcriptionally accessible (H3K4me3) or repressed (H3K27me3) loci in different polarized T cell subsets provide further mechanistic insight into how T cells can both acquire specific functions yet retain plasticity. Whereas the cytokine loci of different T cell subsets exhibit either H3K4me3 or H3K27me3 marks, the chromatin structure at most polarizing transcription factor loci contains both marks, indicative of a permissive (or 'poised') chromatin state, allowing for the induction of transcription factors from opposing subsets to initiate cellular reprogramming[117]. However, as these studies must be performed on pooled cells, it is important to consider that mixed or bivalent marks at given loci may also represent heterogeneity in cell populations or even allelic variability within cells[11]. Importantly, the activities of chromatin-modifying enzymes are responsive to changes in the environment, exhibiting direct links to cytokine, metabolic and kinase signalling pathways[152,160–162] (FIG. 2). Overall, it is clear that most chromatin- and DNA-modifying enzymes have important roles in all $CD4^+$ T cell subsets, acting to stabilize transcriptional programmes and cell functions, often through cooperation with the polarizing transcription factors or lncRNAs in each subset. However, based on the current, albeit limited, state of investigations so far, it seems that inflammatory and regulatory programmes rely more heavily on different chromatin modifiers, which leaves open the possibility that fine-tuned inhibition of epigenetic enzymes might selectively drive different T cell functions.

microRNAs. Although not covered here, it is important to consider that T cell plasticity is regulated by microRNA-mediated post-transcriptional regulation of a wide variety of genes — such as those involved in cytokine signalling, TCR and co-stimulatory signalling, cytosolic signalling and transcriptional regulatory pathways[163].

Plasticity in disease

Plasticity is widely observed in immune-based diseases, such as autoimmunity and cancer. Patients with various forms of autoimmune disease, such as type 1 diabetes, multiple sclerosis or juvenile arthritis, exhibit reduced stability of FOXP3 expression in T_{Reg} cells and/or increased proportions of IFNγ-producing $FOXP3^+$ T_{Reg} cells[14,48,164–166]. In individuals with food allergies, T_{Reg} cells have characteristics of T_H2 cells, producing IL-4 (REF. 167). Plasticity towards T_H17 cell phenotypes is associated with several diseases, such as $IL\text{-}17^+FOXP3^+$ T_{Reg} cells in rheumatoid arthritis[168], $ROR\gamma t^+FOXP3^+$ T_{Reg} cells producing IL-17 in colorectal cancer[169] and IL-17-expressing T_H2 cells in atopic asthma[13]. Therefore, it stands to reason that unique microenvironments that are created in these diseases may instigate T cell reprogramming or that reprogrammed T cells may contribute to disease pathology. Indeed, in each of the examples described above, reprogrammed T cells could contribute to mouse models of the human diseases[13,26,71,167–169]. In addition, in mouse models of multiple sclerosis and inflammatory bowel disease, the transition of T_H17 cells to a T_H1 or mixed T_H17/T_H1 cell phenotype is necessary to drive the disease[19,25,122,170,171]. In patients with human T cell leukaemia virus type 1 (HTLV1)-associated myelopathy (also known as tropical spastic paraparesis), a neuroinflammatory disorder with multiple sclerosis-like symptoms resulting from infection with HTLV1, the virus is most likely to drive disease by selectively infecting T_{Reg} cells and converting them into IFNγ-producing T_H1-like cells by the direct induction of T-bet expression by virally encoded proteins[172]. Thus, T cell plasticity is an important factor in immunological diseases, and the capacity to control T cell programming could lead to new therapies that ameliorate disease by preventing deleterious, or promoting desirable, T cell functions.

Harnessing plasticity for immune therapy

Extracellular cues. Therapeutic targeting of the cues that drive the polarization or function of $CD4^+$ T cells is actively being pursued for the modulation of immunity. Targeting IL-6, which is a crucial bifurcating signal between T_H17 and T_{Reg} cell polarization, with tocilizumab, an antibody against the IL-6 receptor, dampens inflammation. Modulation of IL-2-induced signalling can tip the balance between inflammatory T cells and T_{Reg} cells, such as has been demonstrated in humans with low dose IL-2 (REFS 54,173). Alternatively, modulation of cytokine conformation, either by introduction of synthetic mutant cytokines or by antibodies that bind and alter cytokine conformation, may allow for selective cytokine signalling to specific T cell subsets, as recently demonstrated for IL-2 (REF. 173). TCR signal strength may also underlie the selective capacity of CD3-specific antibody treatment to deplete effector T cells while sparing T_{Reg} cells, delaying the progression of type 1 diabetes[174,175]. Modulating CD28 co-stimulation with antibodies blocking cytotoxic T lymphocyte antigen 4 (CTLA4) or with CTLA4–Ig fusion constructs can also drive immunity or tolerance, respectively[176].

Signalling cascades. The capacity to target key signalling cascades in T cells that control plasticity is aided by the development of many orally available kinase inhibitors. Downstream of the cytokine receptors, small molecule inhibitors of JAKs have proven to be successful as potent immunosuppressants, but their ability to target specific T helper cell activities is limited because several cytokine receptors use each kinase[34]. Blockade of mTOR activity with rapamycin in type 1 diabetes is already under investigation in combination with IL-2 to promote T_{Reg} cell function[177]. However, enhanced T_{Reg} cell frequencies with rapamycin and IL-2 is transient because, as discussed, it seems that inhibition further up the signalling cascade at AKT is most important for the promotion of T_{Reg} cell stability and function[79,80]. Importantly, inhibition of specific isoforms of PI3K may have differential effects on inflammatory versus regulatory cells, as inhibition of the PI3K subunit p110δ selectively disrupts T_{Reg} cell stability and promotes anticancer immunity[178]. In addition to direct administration to patients, inhibitors can be used during *in vitro* expansion of cells for adoptive cell transfer therapies to improve the functional stability of T cells after transfer into patients[179]. With the advent of chimeric antigen receptor (CAR) technologies to redirect cytotoxic T cells to specific antigenic targets comes the potential to engineer CARs that are linked to different intracellular signalling domains that promote distinct functions in $CD4^+$ T cells[180,181].

Enforcing specific metabolic programmes can redirect T cell responses to ameliorate autoimmune disease, such as blocking fatty acid synthesis by inhibiting ACC1 with soraphen A, which promotes T_{Reg} cell over T_H17 cell functions[111]. Blocking glycolysis with non-metabolizable glucose or with the AMPK agonist metformin promotes T follicular regulatory cell over T_{FH} cell polarization, reversing the severity of lupus[182].

Gene expression regulation. Although it is difficult to directly target transcription factor activity, the identification of several post-transcriptional modifications of key polarizing transcription factors does create the potential to indirectly target transcription factors by blocking the activity of the enzymes that modify them (FIG. 5d). Ubiquitylation of FOXP3, RORγt and T-bet controls transcription factor stability, and dysregulation of the ubiquitylating or de-ubiquitylating enzymes can induce phenotypic plasticity in these cells[183–185]. Blocking the activity of sirtuin 1 preserves FOXP3 acetylation, enhancing FOXP3 stability and T_{Reg} cell function[186,187], whereas inhibition of sirtuin 1 increases RORγt acetylation in T_H17 cells, which impedes RORγt activity[188], thus creating another therapeutically exploitable dichotomy between inflammatory and regulatory cells.

The pervasive dysregulation of chromatin regulation in cancer has led to the development of selective inhibitors of many regulatory enzymes, notably EZH2, that may be repurposed to provide novel means to control T cell plasticity[149,152,153]. In cancer, such targeting strategies could have dual effects by directly impeding the cancer cells and by modulating the antitumour immune response[189]. Inhibiting the activity of HATs globally has selective effects on T_{Reg} cell plasticity, driving T_{Reg} cells to lose FOXP3 expression and gain IL-17 production, and probably accounts for the improved antitumour immune responses observed with this approach[141,190]. Alternatively, blocking the interactions of bromodomain-containing proteins with acetylated histones through the use of BET inhibitors (bromodomain and extraterminal inhibitors) reduces the severity of autoimmune disease in mouse models of multiple sclerosis and type 1 diabetes by broadly skewing immunity towards regulatory phenotypes[191,192]. Finally, the fact that pathogens express proteins that mimic histone modification sites, which modulate chromatin functions and allow for immune escape, provides strong evolutionary evidence that targeting specific chromatin modifiers can affect T cell function[149].

Beneficial T cell plasticity

Although much emphasis is placed on the detrimental effects of plasticity, several examples have emerged recently to indicate that T cell plasticity can be beneficial, providing evolutionary support for why the process is tolerated. Intuitively, the retention of plasticity makes sense, as it allows T cells of a given specificity to have a great degree of flexibility to act differently in response to different pathogens, or even to the same pathogen but in different contexts[30]. For example, transitions from one effector response to another may allow for better eradication of pathogens that would escape detection by colonizing new niches, thus T cells that transition from producing IL-17 to IFNγ could combat pathogens migrating from extracellular to intracellular spaces[19]. Repurposing memory T cells that can respond differently in secondary infections may be important for maintaining robust immunity with age, when the reservoir of naive T cells is declining[10]. Somewhat surprisingly, an absolute requirement for T cell plasticity has been demonstrated in the setting of T cell help for germinal centre B cell production of IgA in the small intestine, in which $FOXP3^+$ T_{Reg} cells[193] or T_H17 cells can convert to T_{FH} cells to provide B cell help[171]. During vaccinations, a subset of $FOXP3^+$ T_{Reg} cells, marked by unstable expression of the transcription factor eos (also known as IKZF4), can transiently gain the capacity to produce effector cytokines (such as IL-2) and upregulate CD40 ligand (CD40L) expression, providing essential help to $CD8^+$ T cell responses against vaccines or tumours[194]. Thus, T cell plasticity can promote more effective immunity.

The plasticity of T cells may also be important for controlling detrimental immunity. The blended phenotype of 'T_H2/T_H1' cells that co-express IL-4 and IFNγ (as well as GATA3 and T-bet) or the induction of IL-10 expression by T_H1 cells can reduce the collateral damage associated with excessive T_H1 cell responses[20,35,42,195]. Extinction of pathogenic immune responses, such as those driven by T_H17 cells, is aided by the conversion of T_H17 cells into IL-10-producing T_R1 cells[41,44,196–198]. T helper cell transitions can also alter chemokine receptor expression and divert pathogenic cells to new tissues, reducing inflammation at the primary site[196,197]. These studies

Chimeric antigen receptor
(CAR). An artificial T cell receptor construct that consists of an extracellular single-chain antibody fragment that functions as the antigen-binding domain, together with transmembrane and intracellular signalling domains from the T cell receptor CD3 ζ-chain and/or from a co-stimulatory molecule such as CD28.

BET inhibitors
Inhibitors that bind the bromodomain and extraterminal (BET) motif of several bromodomain-containing proteins (BRDs), blocking their interaction with acetylated lysines on histones and preventing their promotion of transcription.

are revealing because they indicate that the retention of phenotypic flexibility in T cells is rooted in selective advantages to the host.

Concluding remarks

T cells polarize in response to different pathogens in the context of the unique microenvironments they create, establishing stably directed T cell responses, especially at sites of infection such as tissues. However, T cells also retain the capacity to mould their function anew upon re-activation in new polarizing environments. Cytokines and transcription factors can drive reprogramming, but they must do so within the confines of the cytosolic and epigenetic circuitry that is established in the cell to stabilize polarized T cell functions during effector responses. Several key regulatory nodes that broadly divert T cell functions towards inflammatory or regulatory capacities are now apparent, suggesting that modulating immunity by reprogramming T cell function may, in fact, be possible. However, for this approach to become a reality, it will be essential to determine whether targeting these nodes by systemic drug administration will have the desired effect on the intended cells, while not adversely affecting other important immune cells or tissues that are, or are not, related to the disease. Indeed, in some scenarios such as cancer, it might be possible to have beneficial effects both on the tumour and the immune response, but this is likely to be context dependent and require the identification and optimization of unique therapeutic windows for each drug. Finally, strategies to target the key nodes specifically in the desired cells could obviate the pitfalls of off-target effects. It is time to use our knowledge of T cell plasticity to develop new therapeutic approaches wherein we no longer selectively deplete restrictive populations to be replenished by beneficial T cells but, instead, harness T cell plasticity to drive immune functions that benefit patients.

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Competing interests statement
The authors declare no competing interests.