Published in final edited form as:

Cell. 2009 August 7; 138(3): 606.e1–606.e2. doi:10.1016/j.cell.2009.07.020.

Snapshot: Effector and Memory T Cell Differentiation

Matthew E. Pipkin and Anjana Rao

Department of Pathology, Harvard Medical School, Boston, MA 02115, USA

The differentiation of T cells is an ideal system to study the molecular basis of lineage specification in mammalian cells. Upon stimulation with antigen during infection or inflammation, naive peripheral T cells differentiate into various types of effector T cells with specific immune functions. Naive CD4⁺ T cells differentiate into at least four subsets (lineages) of T helper (Th) cells: Th1, Th2, Th17, or “induced” regulatory T cells (iTregs). Each subset is distinguished by the cytokines that they produce (Ansel et al., 2006; Lee et al., 2006; Zhou et al., 2009). Naive CD8⁺ T cells differentiate into effector cytolytic T lymphocytes (CTL_{Eff}) that kill infected host cells using the poreforming protein perforin and serine esterases called granzymes (Cruz-Guilloty et al., 2009). Alternatively, naive CD8⁺ T cells can differentiate into memory CTLs (CTL_{Mem}) that survive long-term and protect the host from reinfection (Kaech and Wherry, 2007). T cell differentiation is in large part determined by signals from the environment and is shaped by numerous feedback and feed-forward loops (bold arrows) that modulate and reinforce the direction in which differentiation proceeds (Singh, 2007). Transcription factors (boxes) play a key role in this process by forming networks in which they reinforce or oppose each other’s actions. This Snapshot illustrates the differentiation pathways for several of the best characterized T cell subsets.

Naive

The transcription factor ThPok and transcription factors of the Runx family act in an antagonistic fashion to specify the development of naive CD4⁺ and CD8⁺ αβ T cells that emigrate from the thymus and colonize peripheral lymphoid organs (Taniuchi, 2009).

Antigen priming

Upon encountering antigen and with costimulation by antigen-presenting cells, naive T cells initiate a generic transcription program called priming (thin black lines) that depends on the activation of widely expressed, latent transcription factors including NFAT, NF-κB, and AP-1 (Fos-Jun). These, in turn, induce expression or activation of secondary transcription factors such as the early growth response (Egr) proteins (not depicted). They also induce expression of the cytokine interleukin-2 (IL-2) and the α and β chains of the IL-2 receptor (IL-2R). Binding of IL-2 to its receptor activates the Stat5 transcription factor. In certain settings, the transcription factors Blimp-1 and Bcl6 are induced and counteract each other’s expression (Martins and Calame, 2008; Johnston et al., 2009). During this phase, T cells also promiscuously activate low-level transcription of most “lineage-specific” genes (not depicted). Such genes include those encoding the T-bet and Gata3 transcription factors that impose Th1 and Th2 lineage specification, respectively. T-bet and Gata3 are both transcribed early in activated T cells, but in the presence of the cytokine IL-4 that drives Th2 differentiation, Gata3 expression is sustained whereas T-bet expression is silenced, thus reinforcing Th2 lineage commitment.

Cytokine programming and stabilization of the effector phenotype

Primed T cells quickly fall under the control of the cytokine environment. Cytokines program transcription factor networks that stabilize the phenotype and function of differentiating CD4⁺ T cells by driving chromatin modifications that activate lineage-specific and inactivate lineage-inappropriate genes (Ansel et al., 2006; Grogan et al., 2001; Lee et al., 2006). Key lineage-specific transcription factors—T-bet for Th1 cells, Gata3 for Th2 cells, ROR γ t for Th17 cells, and Foxp3 for regulatory T cells—are distinguished by the fact that their ectopic overexpression in differentiating T cells induces “reprogramming” of those cells to the lineage that they control, even in the presence of cytokines that ordinarily program a different lineage. These lineage-specifying factors cooperate with stimulation-induced transcription factors through direct physical interactions (black lines without arrows) to mediate their effects (Ansel et al., 2006; Zhou et al., 2009).

Less is known about the transcriptional networks that program CD8⁺ T cell differentiation into effector and memory CTLs, partly because most experiments have been performed in mice infected with model pathogens (Kaeche and Wherry, 2007). Many of these studies compared wild-type mice with mice carrying disrupted genes. Although genetic analyses can undoubtedly show that a missing gene product has a role in the development of effector or memory CTLs, such analyses cannot determine whether the role is direct or indirect—additional epistatic and biochemical analyses are needed, preferably using simplified cell-culture systems such as those used to examine CD4⁺ T cell differentiation. Such systems have helped to clarify that the transcription factor Runx3 is central to programming the function of CTLs, and that T-bet and Eomesodermin (Eomes) are induced in response to distinct signals and have distinct as well as redundant functions (Cruz-Guilloty et al., 2009).

Effector function after re-encounter with antigen

Early transcription factors act again, often cooperating with lineage-specific transcription factors at lineage-specific effector genes whose chromatin structure has been remodeled during differentiation for rapid, high-level transcriptional induction (Ansel et al., 2006).

Abbreviations

IL-2R, IL-4R, IL-6R, IL-12R, IL-21R, IL-23R	Cytokines and receptors: Interleukin (IL-2, IL-4) and receptors
IFN-γ	Interferon gamma
TGF-β	transforming growth factor β
T-bet	Transcription factors: T-box expressed in T cells
Stat	signal transducer and activator of transcription 1, 3, 4, 5, 6
Hlx	H2.0-like homeobox
Gfi-1	Growth factor independent 1
Gata3	GATA-binding protein 3
RORγt and α	retinoic acid receptor related orphan receptor gamma t and alpha
RBPJκ	recombination signal binding protein for immunoglobulin kappa J region
IRF-4	interferon regulatory factor 4

NF-κB	nuclear factor of kappa light polypeptide enhancer in B cells
NFAT	nuclear factor of activated T cells
Smads	similar to mothers against decapentaplegic are TGF- β activated transcription factors
Foxp3	forkhead box P3
Blimp-1	B lymphocyte induced maturation protein 1
Bcl6	B cell leukemia/lymphoma 6
Eomes	T-box factor Eomesodermin
Id2	inhibitor of DNA binding 2
Klf2	Kruppel like factor 2
c-maf	musculoaponeurotic fibrosarcoma proto-oncogene
ThPok	zinc finger and BTB domain containing 7B
Runx3	Runt related transcription factor 3

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