Elucidating the regulation of T cell subsets (Review)

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Abstract. CD4-positive T lymphocytes mainly direct immune as well as autoimmune responses against a variety of pathogens or allergens. This is achieved through the acquisition of specialized functions followed by differentiation into various T cell subsets. The differentiation process of naive T cells into effector subsets is regulated by dendritic cells and secreted cytokines. Signal transducer and activator of transcription proteins play critical roles in transmitting cytokine-mediated signals and specifying T cell differentiation. Epigenetic changes such as histone acetylation and methylation along with DNA methylation also regulate expression of differentiation-specific genes. Defining exactly how extrinsic signals control the specification of T cells will provide important insights and therapeutic opportunities.

Contents

1. Introduction

When naive T lymphocytes are primed by MHC class II-expressing dendritic cells, which are specialized antigen-presenting cells, CD4-positive T lymphocytes exhibit unusual effector function for host defense, and they play a major role in the regulation of adaptive immunity (1-3). Conversely, they are also fundamental regulators of autoimmunity when tolerance is lost. Several cytokines are then key mediators in the development of T lymphocytes playing crucial roles in controlling immunity (4,5). Naive T cells differentiate into different functional subsets. These include classical T helper cells, Th1 and Th2, which regulate immunity against intracellular and extracellular pathogens, respectively. Th1 and Th2 lineages also generate either cellular or humoral immune responses. Th1 cells produce interferon-γ (IFNγ), and Th2 cells express the cytokines IL-4, -5 and -13 (6,7). In addition, several effector T (Treg) cell subsets have been identified. They include regulatory T cells, IL-17-producing Th17 cells, IL-9-producing Th9 cells and a subset of IL-22-producing Th22 cells (8,9), which all determine the development of different types of T cell immunity (Fig. 1). Proper regulation of Th differentiation is critical for controlling immune responses and for maintaining immunological homeostasis.

T cell lineage maturation is governed by the expression of master regulator transcription factors that drive differentiation. Actually, Th cell differentiation is regulated by several distinct cytokines, which signal through ubiquitous transcription factors including the STAT family (10,11). These factors upregulate the expression of lineage-specific transcription factors, which function not only to promote its own lineage differentiation but also to inhibit alternative differentiation pathways. In addition, epigenetic mechanisms are also important for regulating appropriate gene expression in T cell differentiation (12-15). There are extensive cross-regulations of lineage-determining transcription factors. In addition, Th cell lineage commitment can be plastic in certain circumstances. The T cell plasticity and lineage fate may also be governed by cytokines and epigenetic regulations. There are many examples of plasticity in Th cell subsets (16,17). Autoimmune diseases can be driven by Th1, Th17 cells or their combinations. The inflammatory response is supported by innate immune mechanisms that are relevant to autoimmunity. Recent evidence on T cell subset reciprocal regulation (18) and counterbalance between Th1 and Th2 cells to Th17 and Treg has influenced the peripheral tolerance (19). Many autoimmune diseases are driven by cruel cycles of specialized T cells that are unable to be suppressed by regulatory T cells. Here we summarize and speculate on the current knowledge regarding the regulation and signaling for T cell subsets. The understanding of these insights into the mechanisms of autoimmune regulation may lead to novel therapeutic opportunities.

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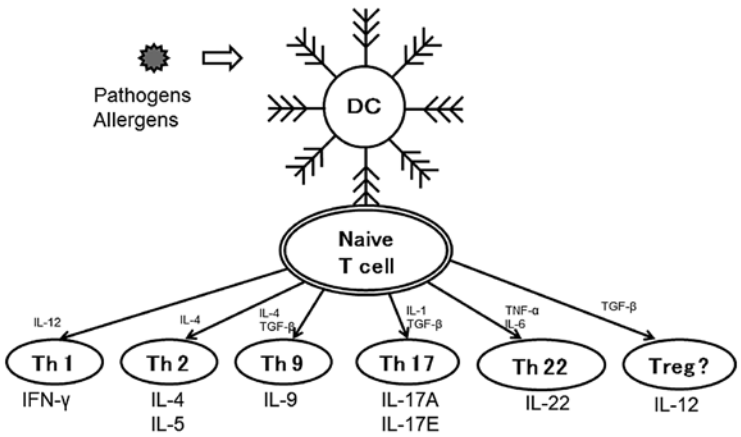

Figure 1. Schematic illustration of T cell subset differentiation. Following exposure to foreign antigens by dendritic cells, naive T cells are directed towards distinct developmental programs by various cytokines. The differentiation and production of cytokines of each subset are indicated above and below the cells, respectively. DC, dendritic cells; IL, interleukin; IFN, interferon; Th, T helper cell; Treg, regulatory T cells.

2. T cell subsets and antigen-presenting cells regulated by various factors

On antigen stimulation, naive CD4-positive T cells can differentiate into Th1 and Th2 effector cells, which rapidly produce IFN-γ and IL-4, respectively (1-4). The Th1 cell phenotype is dominated by IL-2, IFN-γ and tumor necrosis factor cytokine profiles. Th1 cells are involved in cell-mediated defense against intracellular microorganisms, and they also engage in the effector mechanisms of allergic disease. Th1 cells not only are themselves prone to activation and apoptosis, they also induce apoptosis of keratinocytes in atopic dermatitis and of epithelium and bronchial smooth muscle cells in asthma. Th1 cells differentiate after stimulation with IL-12 and IL-17 (20). IL-12, which is produced by macrophages, dendritic cells and B cells, is a regulatory cytokine that has an important function in initiation and regulation. Th1 cells thus respond to the release of IFN-γ by IL-12 and suppression of Th2 cytokines (21). Th1 cells in addition to natural killer cells and macrophages are the primary Th1 cytokine-producing cells. The Th1 cytokines are also involved in immunoglobulin class switching to the IgG2a isotype (22).

Th2 cells produce the highest amount of Th2 cytokines in addition to mast cells and basophils. The Th2 cytokines such as IL-4, IL-5, IL-10 and IL-13 are associated with humoral immunity and immunoglobulin class switching to IgG1 and IgE (23). The Th2 cytokines are also involved in controlling immune responses against extracellular parasites. In addition, IL-4 and IL-5 are implicated in atopic and allergic disease because of the role in regulating IgE-mediated immune responses via mast cells and eosinophils (24). Th2 cells predominantly mediate IgE responses. The differentiation of naive T cells into Th2 cells is induced in the presence of IL-4 (25). Cross-linking of IgE on effector mast cells results in the release of vasoactive amines such as histamine, leukotriene, chemokine and cytokines such as IL-4, IL-5 and IL-13, leading to the development of type 1 immediate hypersensitivity reaction (26). The cytokine expression patterns in Th1 and Th2 cells are controlled by transcriptional activation and repression via each subset differentiation.

Th9 is a distinct population of effector T cells involved in tissue inflammation. This subset is characterized by IL-9 and IL-10 secretion (27). The cells differentiate from naive cells after IL-4 and TGF-β stimulation. Th17 cells have been shown to induce host protection against extracellular pathogens. IL-9 together with TGF-β contribute to Th17 cell differentiation, and Th17 cells themselves produce IL-9. Th9 and Th17 cells control tissue inflammation through upregulation of inflammatory cytokines and chemokines (28). In addition, differentiation of Th17 cells is induced by IL-6, IL-21 and IL-23 (29). Th17 cells are also implicated in the pathogenesis of autoimmune diseases. Tregs suppress Th17 cells and autoimmunity. IL-1 also plays a crucial role in early Th17 cell differentiation. In immune responses against infection and autoimmune disease models, Th1 and Th17 cells often develop simultaneously (30). Perturbation of one pathway may result in augmentation of the other. They are involved in host defence against extracellular pathogens such as bacteria and fungi, but also in the pathogenesis of various autoimmune diseases. Another T cell subset (Th22) (31) has been demonstrated in T cells that independently express IL-22 with low expression levels of IL-17 and play a role in atopic dermatitis. IL-22 can be protective for colitis by induction of epithelial healing and mucus production.

Dendritic cells (DCs) are a heterogeneous group of antigen-presenting leukocytes (Fig. 2) that play an important role in the activation of both the innate and acquired immune system. They are essential for the differentiation of naive T cells via release of cytokines (32). Their role is to process antigens and to migrate to local lymph nodes, where they present to antigen-specific T cells. DCs loaded with allergen-derived peptides reach the lymph nodes within 24 h, where they interact with naive CD4-positive T cells to support the differentiation of Th1, regulatory T cells (33) and Th2 cells within five days. These cells subsequently migrate into the blood and back to mucosal tissues, resulting in allergen tolerance or activation. Two distinct subsets of DCs have been identified. Myeloid DCs express Toll-like receptor (TLR)2 and TLR6 and produce IL-12 in response to bacterial and viral stimuli (34). Plasmacytoid DCs express TLR7 and TLR9

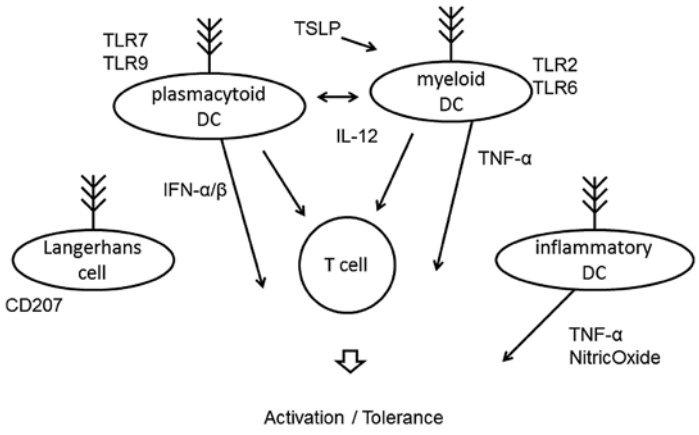

Figure 2. Schematic illustration of dendritic cell (DC) populations. Non-inflamed mucosal tissue contains Langerhans cells and plasmacytoid DCs. In addition, inflamed skin contains a large population of myeloid or inflammatory DCs. These dendritic cells are involved in T cell differentiation. TSLP, thymic stromal lymphopoietin; TNF, tumor necrosis factor; IFN, interferon; TLR, toll-like receptor.

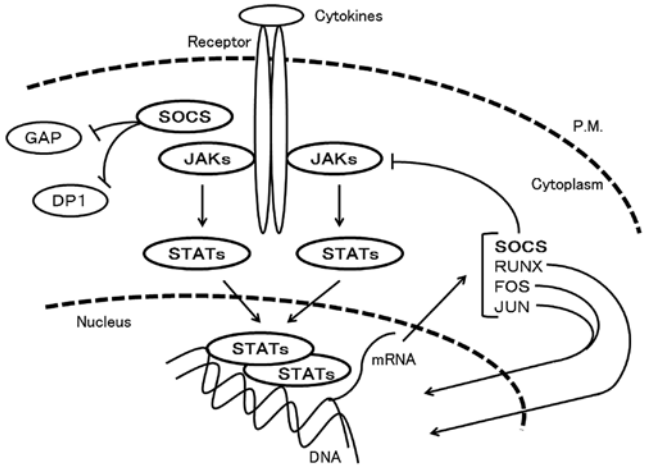

Figure 3. Schematic representation of intracellular signaling of T cells. Examples of the molecules known to act in the regulatory pathways are shown. Note that some critical pathways have been omitted for clarity. JAK, Janus kinase; STAT, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling.

(35), and release interferon during the outcome of responses. Plasmacytoid DCs directly suppress the ability of myeloid DCs to generate effector T cells, and they are capable of stimulating the development of regulatory T cells. The depletion of plasmacytoid DCs results in lack of tolerance to certain antigens. In addition, the other two DC populations that are present at inflammatory sites of the skin are the classical Langerhans cells and the inflammatory dendritic epidermal cells (36,37). The Langerhans cells are the predominant DC population in the epidermis and are the first line of defense against antigens. The inflammatory dendritic cells activate Th1 subsets, whereas classical Langerhans cells induce Th2 subsets. Thymic stromal lymphopoietin seems to play an essential role in allergic inflammation and activates myeloid DCs to induce inflammatory Th2 responses.

3. Signal transductions in T cell subsets

Cytokines play important roles in controlling adaptive immunity. Upon cytokine-induced activation, Janus kinases (JAKs) phosphorylate the cytoplasmic tail of the receptor, leading to the recruitment of signal transducer and activator of transcriptions (STATs), which also are phosphorylated by JAKs (38) (Fig. 3). The JAKs play a critical role in mediating immune responses, and their modulation represents a novel approach to the therapies of inflammatory immune-mediated diseases. Deficiency of JAK1 leads to nonresponsiveness to interferons (IFNs) and cytokines, whereas JAK2-deficient cells fail to respond to hormone-like cytokines such as erythropoietin, thrombopoietin and GM-CSF. TYK2, which is one of the JAK family kinases (39), transmits the signals derived from IFNs and the IL-12 receptor subunit, whereas JAK3 has a discrete function (40) and is associated only with the IL-2 receptor.

Activated STAT family proteins by JAKs dimerize and translocate to the nucleus. They regulate the expression of a multitude of genes including RUNX and SOCS. The STAT family proteins have pivotal roles in transmitting cytokine-mediated signals and specifying T cell differentiation. The STAT1 and STAT2 proteins have been discovered as a mediator of IFN action. STAT3 regulates the expression of Th17 cell-related cytokines and transcription factors. For example,

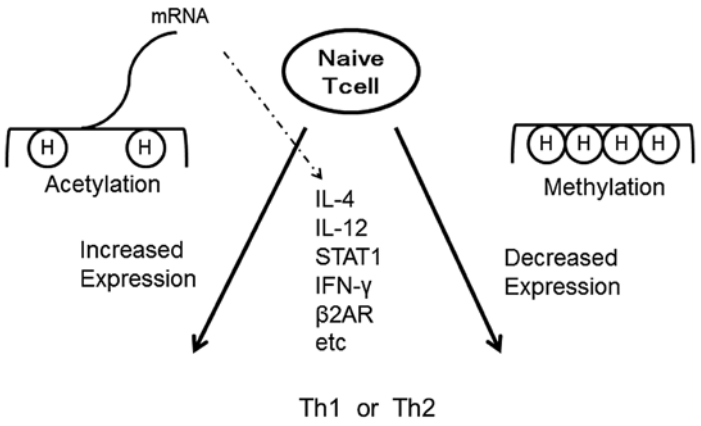

Figure 4. Epigenetic changes in T cell differentiation by key gene promoters. When naive CD4-positive T cells differentiate into Th1 or Th2 cells, histones (H) and DNA of several promoters undergo a multitude of changes. Left: as histones become acetylated, chromatin remains open, allowing access to transcription factors that can bind to the DNA to increase transcription and expression of the key genes for T cell differentiation. Right: as histones are methylated, chromatin will be closed, which decreases DNA access to transcription factors resulting in decreased gene expression. Note that some critical events have been omitted for clarity.

IL-21 is produced by Th17 cells in a STAT3-dependent manner (41). Identified STAT3 target genes in T cells include anti-apoptotic genes such as Bcl2, Fos and Jun. STAT3 is also activated throughout Th2 cell differentiation, and is required for Th2 cytokine production and transcription factor expression, and is required for Th2 cell-mediated allergic inflammation. STAT4 is activated mainly by IL-12, IL-23 and IFNs, and it predominantly functions in promoting Th1 cell differentiation (42). STAT4 is also the major regulator of IFN and IL-21 gene expression. STAT5 plays roles in Th2 cell differentiation by upregulating expression of the IL-4 receptor (43). STAT5 competes with STAT3 for binding to IL-17 and inhibits the function of STAT3 in activating IL-17 transcription, and consequently inhibits Th17 cell differentiation. STAT6 mediates the expression of the IL-4 regulated genes, and induces Th2 cell differentiation (44). Another key role of STAT family proteins includes shaping epigenetic patterns on target gene loci to maintain cell lineage specificity.

RUNX transcription factors have a central role in regulating Th cell differentiation. RUNX1, which is the direct target of STAT6, inhibits Th2 cell differentiation by downregulating GATA3 expression and binds to the IL4 silencer region (45). In addition, RUNX1 forms a complex with FOXP3 and RORC, which is necessary for Treg and Th17 cell function, respectively. Overexpression of RUNX1 is sufficient to accelerate the effects of IL-17A production in Th17 cells. The RUNX3 transcription factor augments Th1 and downmodulates Th2 phenotypes by interacting with GATA3. RUNX3 is upregulated in CD4-positive T cells during Th1 cell differentiation (46), and RUNX 3 functions with the T-box family transcription factor, T-bet, which is a master regulator of Th1 cell differentiation. BATF, which is also directly regulated by STAT6, regulates both Th17 and Th2 cell differentiation (47). STAT6 functions as a transcriptional activator, but it also functions as a functional repressor for certain genes.

The suppressor of cytokine signaling (SOCS) family of proteins is also a key regulator of cytokine responses, and downregulates specific cytokine signals and consequently modifies the immune response. SOCS1 and SOCS3 have been shown to affect the Th1 and Th2 balance (48). SOCS2 expression regulates IL-2 and IL-3 signals (49), and plays an important role in regulating Th2 cell expansion and development of type 2 allergic responses. SOCS3 expression correlates with the severity of asthma as well as serum IgE levels in patients with allergy (50). It is plausible that SOCS proteins play a significant role in Th cell polarization. Constitutive expression of SOCS3 facilitates Th2 expansion, whereas selective deletion of SOCS3 facilitates STAT3 activation and elevated IL-17 production in T cells. SOCS3 may also play a role in controlling Treg cell responses.

4. Genetic changes after T cell differentiation

Gene silencing mediated by epigenetic mechanisms is important for regulating proper gene expression in cell differentiation. Histone modifications of genes encoding Th cell subsets are of particular importance. In general, chromatin modifications control the accessibility of transcriptional activators and repressors (Fig. 4). Permissive marks on a particular cytokine gene are present in the relevant lineage that expresses that cytokine (51). Conversely, repressive marks are also present in other lineages that do not express the cytokine. The presence of the DNase I hypersensitive site clearly suggests functionally defined chromatin structures. For example, deficiency of DNase I hypersensitive sites in the IL-4 gene decreases IL-4 production, as IL-4 is expressed in Th1 cells. Similarly, several Th2-specific DNase I hypersensitive sites around IL-4 and IL-13 promoters in Th2 cells are found after differentiation. DNAs are predominantly methylated in naive T cells. After each T cell differentiation, CpG demethylation coincides at consensus GATA binding sites and DNase I hypersensitive sites appear (52). It seems that CpG methylation in certain genes could be a mechanism of suppression in permissive lineages.

The chromatin remodeling that is associated with both cytokine gene expression and repression in Th1 and Th2 cells is promoted by the activation of the transcription factor

GATA3 by IL-4, STAT-4 by IL-12 and T-bet by IFN-γ. Chromatin structures in the locus differ among naive, Th1 and Th2 cells. In these cells, several GATA-3 consensus binding sites are present at DNase I hypersensitive sites (53). The GATA family members are associated with CREB-binding protein, which is an acetyltransferase that acetylates not only histones but also GATA proteins. As mentioned above, epigenetic mechanisms are activated to promote the gene expression of cytokines resulting in Th1 and Th2 cells in naive T cell differentiation. Similar changes occur in the β2-adrenergic receptor (β2AR) promoter during differentiation (54). It has been shown that naive T cells and Th1 cell clones express theβ2AR (55), while Th2 cell clones do not. Increased β2AR gene expression in Th1 cells is mediated by an increase acetylation in histone 3 and histone 4. Genomic bisulfite sequencing shows that the level of methylated CpG dinucleotides within the promoter of the β2AR gene is increased in Th2 cells as compared to Th1 cells. In contrast, Th1 cells show an increase in pan acetylation and slight DNA methylation when compared to Th2 cells. β2AR gene expression is regulated in T cells as they differentiate which implies chromatin remodeling in the β2AR gene promoter. Catecholamine-mediated signal pathways may play a fundamental role in acute stress-mediated immune alterations (56).

5. Perspective

As T helper cells have emerged as an important mediator of human immune diseases, many factors have been identified as important in the Th cell differentiation process. How these factors function individually and collectively requires further elucidation. Another important issue involves the plasticity of Th cells. What factors regulate and maintain this plasticity require investigation. Furthermore, several other types of chromatin modifications such as ribosylation and ubiquitination may also occur as a mechanism controling expression of key genes. Precise understanding of the regulation of T cell subsets and development in this field will aid in the development of effective therapies for immune diseases. It is possible that transcription factors activated by cytokines may play roles in promoting chromatin modifications that occur within the promoter of certain T cell subsets. Understanding the epigenetic mechanisms may also lead to the development of novel treatments for immune disease. Many significant findings have emerged from this research field. It has become clear that an important part of gene regulation depends on epigenetic regulation. However, it is crucial to determine how STAT proteins affect epigenetic mark functioning. Further epigenetic analysis will provide evidence for both cytokine and regulator genes in T cells. The extent to which T cell subsets behave as flexible populations will be the focus of future research.

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