SATB1: Key Regulator of T Cell Development and Differentiation

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1. Introduction

Vertebrates have evolved a lymphocyte based adaptive immune system which specifically recognises antigens (Pancer and Cooper, 2006). The lymphoid progenitor cells migrate to the thymus a primary lymphoid organ for the development of T cells (Yang et al., 2010; Zlotoff and Bhandoola, 2011). Progenitor cells undergo a stringent selection process which leads to the development of T cells which have a T cell receptor that specifically reacts with the foreign antigens and not with the self antigens. The pre-T cells further differentiate into many subpopulations in the thymus or the peripheral organs, which perform different functions and are responsible for the adaptive immune responses. The maturation and development of T cells is typically defined by the expression of specific cell surface receptors. The early immature thymocytes that do not express either CD4 or CD8 are called double negative (DN) thymocytes. At these stage the cells undergo the rearrangement of T cell receptor (TCR) β chain. Subsequently, these cells express both $CD4^+$ $CD8^+$ and are referred to as the double positive (DP) cells. During this stage, the rearrangement of the α chain of TCR happens and the cells express the complete T cell receptor (Kreslavsky et al., 2010). The DP thymocytes undergo proliferation and depending on the strength of TCR signaling further develop into either $CD4^+$ or $CD8^+$ single positive (SP) T cells via repression of the gene encoding the other receptor.

The mature T cells migrate to the periphery wherein they encounter the antigens and develop into effector cells. The differentiation of naïve cells into the effector cells depends on the signaling pathways, the pathogen or the cytokines secreted by the antigen presenting cells (APCs). Naïve CD4 T cells mature into various subpopulations which secrete characterisic effector cytokines that define the functions of T cells. Based on the cytokines produced the CD4 T cells are distinguished into multiple subtypes such as T_H1, T_H2, T_H17, induced regulatory T cells (iTregs), Tfh and T_H9 (Zhu et al., 2010). Table 1 provides general overview of various lineages of $CD4^+$ T cells with their key factors and cytokines secreted. The first functionally distinct subpopulations of $CD4^+$ T cells were identified and described as the T_H1/T_H2 paradigm by Mosmann and Coffman, (Mosmann et al., 1986; Mosmann & Coffman, 1987) followed by delineation of the roles of T_H1 and T_H2 cells in cell-mediated and humoral immunity respectively. IL-12 signaling via STAT-4 results in the development of T_H1 cells. IL-4 signaling in conjunction with STAT-6 skews the cells towards T_H2

phenotype. Another major subtype of CD4+ T cells that has gained considerable importance in recent years is T_H17 which produce IL-6 and IL-17. The transcription factors STAT-3 and RORγt act as master regulators for T_H17 differentiation (Park et al., 2005; Dong et al., 2008). Major function of T_H cells is to help B cells to develop antigen-specific antibody response. A subset of T_H cells enter into germinal center and interact with developing B cells and assist them for class-switching. This subset of cells is known as Follicular Helper T cells (Tfh). The Tfh cells secrete IL-4 or IFNγ depending upon their priming (King et al., 2008). Naïve peripheral CD4+ T cells can be induced to give rise to iTreg cells which require FOXP3 transcription factor. These cells are shown to be involved in suppressor function of immune system and for maintainance of tolerance to self-antigens (DiPaolo et al., 2007). T_H9 is another recently discovered type of CD4+ T cells which produce IL-9 and whose function is not clearly understood. However it is proposed that these cells might be involved in confering immunity against helminth infection (Staudt et al., 2010).

Subset of CD4+ T cells	**Important Transcription factors**	**Hallmark cytokines secreted by cells**	**Function (Described in)**
T_H1	STAT-4, T-bet	IFN-γ	Cell mediated Immunity (Mosmann & Coffman, 1987)
T_H2	STAT-6, SATB1, GATA-3	IL-5, IL-4, IL-13	Humoral Immunity (Mosmann & Coffman, 1987)
Treg	FOXP3		Maintainance of tolerance (Sakaguchi et al., 2008)
T_H17	STAT-3, ROR γt	IL-17A, IL-17F	Inflammation, autoimmunity (Hirota et al., 2011)
Tfh	Bcl-6	IL-21	Mediate help and class switching in B cells in germinal centers (Kitano et al., 2011)
T_H9	IRF-4	IL-9	Immunity against helminth infection, most important cell type responsible for the pathogenesis of Asthma (Staudt et al., 2010)

Table 1. **Functional subtypes of CD4+ T lineage.** Various characterized subtypes of CD4+ T cells are listed with their reported essential factors required for lineage determination, key cytokine secreted and function of these cells. For details see text.

2. SATB1 and its role in transcriptional regulation of multiple genes

The cell signaling pathways which initiate the differentiation process ultimately lead to expression of a specific transcription factor. The key transcription factors are important for the expression of specific cytokine gene and maintenance of the phenotype. SATB1 is a T cell enriched transcription factor that regulates large number of genes involved in T cell development and is also required for the maintainance of higher-order chromatin architecture (Alvarez et al., 2000; Kumar et al., 2006; Cai et al., 2003; Cai et al., 2006, Kumar et al., 2007). Ablation of SATB1 causes dysregulation of genes required for the development of T cells and the development is stalled at the DP stage (Alvarez et al., 2000). Thymocytes from SATB1 knockout mice revealed ectopic expression of genes such as *IL-2R* and *IL-7R*. SATB1 is known to regulate genes by selectively tethering their regulatory regions and via formation of a characteristic cage-like structure around the heterochromatic regions in Thymocytes (Cai et al., 2004), presumably demarcating the active and inactive domains (Galande et al., 2007). SATB1 also acts as a docking site for chromatin remodeling/modifying factors such as ISWI, ASF1 and NURD complex containing HDAC1, leading to the repression of genes (Yasui et al., 2000). Post-translational modifications of SATB1 such as acetylation and phosphorylation act as molecular switches regulating its ability to govern gene expression. The PDZ-like domain of SATB1 undergoes phosphorylation by PKC and acetylation by PCAF acetyltransferase in signal-dependent manner (Kumar et al., 2006). Acetylation of SATB1 negatively influences the DNA binding activity of SATB1 whereas phosphorylated form of SATB1 is shown to bind tightly to the *Il-2* promoter and repress *Il-2*. Interaction of SATB1 with the CtBP1 corepressor via its N-terminal PDZ-like domain represses transcription. Upon inhibition of Wnt signaling by LiCl treatment SATB1 is acetylated, loses its interaction with CtBP1 and thus leads to activation of *Il-2* (Purbey et al., 2009). Further, SATB1 is also known to regulate chromatin loop domain organization ('loopscape') in a cell type-specific manner. In Jurkat T cells, SATB1 organizes the MHC class I locus into a 'loopscape' comprising six loops. However, CHO cells which express comparatively less SATB1 exhibit a different 'loopscape' of the MHC locus. Intersstingly, overexpression of SATB1 in CHO cells rendered the 'loopscape' similar to that in Jurkat cells underscoring the importantance of SATB1 in cell-type specific higher-order chromatin organization (Kumar et al., 2007; Galande et al., 2007). In T_H2 cells, SATB1 organizes the loop domain architecture of the T_H2 cytokine locus and governs the coordinated expression of *IL-4, IL-5* and *IL-13* and thus regulate T_H2 differentiation (Cai et al., 2006). Thus, SATB1 has emerged as an important factor orchestrating gene expression by modulating the higher-order chromatin architecture in a cell-type specific and signal-dependent manner.

Number of studies in the past few years have demonstrated the role of SATB1 in cancer. It has been shown that siRNA-mediated knockdown of SATB1 in higly aggressive breast cancer cells reversed the tumorogenic capability of cells and also inhibited the tumor growth (Han et al., 2008). Downregulation of SATB1 in cancerous cells resulted in alteration in the expression of about thousand genes. Furthermore, overexpression of SATB1 in a non-aggressive tumor cell line resulted in augmenting the tumorigenic and metastatic capacity of these cells indicating its direct role in coordinated regulation of multiple genes. SATB1 presumably reprogrammes gene expression by inducing specific epigenetic modifications at target gene loci, leading to upregulation of metastasis-associated genes and simultaneously causing downregulation of tumor suppressor genes (Han et al., 2008). These studies point to a coordinated mechanism of tumor progression.

3. SATB1 in T cell development and differentiation

3.1 Overview of T cell development

T cells arise from the hematopoietic stem cell precursors that migrate to the thymus. Early stage T cell precursors (ETPs) that migrate to the thymus lose the capability to give rise to B cells, however they have the propensity to develop into lineages other than T cells such as macrophages, dendritic cells and NKT cells (Yui et al., 2010). The ETPs also called DN1 phenotypically are $CD4^-$, $CD8^-$, $CD3^-$, $CD25^-$, $CD44^+$ cells. These cells undergo extensive proliferation and are not yet completely committed to T lineage (Rothenberg et al., 2010). The next stage of development is characterized by upregulation of CD25 and is called DN2 stage at which cells are $CD4^-$, $CD8^-$, $CD3^-$, $CD25^+$, $CD44^+$. Further, CD44 is downregulated and such cells are referred to as DN3 stage ($CD4^-$, $CD8^-$, $CD3^-$, $CD25^+$, $CD44^-$) and at this stage they are committed to the T cell lineage. The DN3 cells stop dividing and undergo rearrangement of TCRβ chain. Successful assembly of the β chain facilitates the movement of cells and this process is known as β-selection (Michie & Zuniga-Pflucker, 2002). Subsequently, these cells downregulate both CD25 (IL-2Rα) and CD44, the stage is called DN4 and these are fully committed towards T lineage and start proliferation. Following the successful rearrangement of αβ TCR, thymocytes start expressing CD4 and CD8 coreceptors on the cell surface. The DP thymocytes undergo a stringent selection process, where the TCRs that cannot bind to self antigens undergo death by neglect, whereas those which bind to self MHC with intermediate affinity undergo positive selection (Marrack & Kappler, 1997). Further, these thymocytes either develop into $CD4^+$ or $CD8^+$ SP thymocytes dependent on the TCR signals and the expression of specific transcription factor(s) (Singer et al., 2008). In the periphery, the mature T cells differentiate into effector T cells depending on the antigen encountered and cytokine signals.

3.2 Role of SATB1 in thymocyte development

SATB1 knockout mice exhibit a severe defect in T cell development. SATB1-null mice have disproportionately small thymi and spleens as compared to the wild-type mice. At the cellular level, these mice exhibit multiple defects in T-cell development. The population of immature $CD3^-$,$CD4^-$,$CD8^-$ triple negative (TN) thymocytes is greatly reduced. Most strikingly, the thymocyte development is blocked at the double positive stage and the $CD4^+$ or $CD8^+$ SP thymocytes fail to develop (Alvarez et al., 2000). Ablation of SATB1 also results in dysregulation of multiple genes such as *Il-2R* and *Il-7R* involved in T cell development and differentiation (Alvarez et al., 2000). Within the thymus majority of the DP thymocytes are eliminated via apoptosis during positive and negative selection process (Surh & Sprent, 1994). Dexamethasone-induced apoptosis of thymocytes resulted in rapid dissociation of SATB1 from chromatin. Furthermore, SATB1 is specifically cleaved by caspase-6 after the aspartate residue at position 254 which led to the identification of the PDZ-like domain in the N-terminal region of SATB1. In vitro analysis revealed that caspase-6 cleavage also abolished the DNA-binding ability of SATB1 (Galande et al., 2001). The cleavage of SATB1 during T cell apoptosis might be required for the initiation of DNA fragmentation. In SATB1- null mice peripheral $CD4^+$ T cells fail to respond to activation stimulus and undergo apoptosis demonstrating indispensible role of SATB1 during proper T cell development (Alvarez et al., 2000). Comparison of the wild-type mice with the $SATB1^{-/-}$ mice indicated that repression of *Il-2R* gene was caused specifically by recruitment of histone deacetylases by SATB1 (Yasui et al., 2002). Immunostaining of SATB1 in mouse thymocytes revealed that it forms a unique cage-like structure differentiating euchromatin from heterochromatin (Cai et al., 2003; Notani et al., 2010). In thymocytes, SATB1 is also known to cooperate with other regulatory factors such as β-catenin and CtBP-1 in signal-dependent manner and regulate gene expression (Purbey et al., 2009; Notani et al., 2010). SATB1-binding site-driven reporter assays revealed that SATB1:β-catenin interaction regulates the expression of Wnt target genes in TCF-independent manner (Notani et al., 2010). The recruitment of β-catenin to SATB1 target genes is preceded by deacetylation of SATB1 upon Wnt/β-catenin signaling in thymocytes and $CD4^+$ T cells. SATB1 directly binds to cis regulatory elements at the CD8 enhancer and required for the CD8 SP thymocyte development from the DP thymocytes (Yao et al., 2010). Thus, SATB1 which is highly expressed in thymocytes acts as a global regulator in their development.

3.3 Role of SATB1 in T_H2 differentiation

$CD4^+$ SP thymocytes from the thymus migrate to peripheral lymphoid organs, where they encounter antigen presented by the antigens presenting cells (APCs) and further differentiate into T helper (T_H) effector phenotypes. T_H1 population is involved in cellular immunity wherein they assist macrophages and cytotoxic T cells (Tc) for clearance of infected cells while T_H2 cells help B cells in generating humoral response by increasing production of neutralising antibodies against the pathogen (Zhu and Paul, 2008). T_H2 population is characterized by the effector cytokines it secretes viz., IL-5, IL-13 and IL-4. Strikingly, SATB1 which is known to have a important role during thymocyte development is upregulated during T_H2 differentiation (Lund et al., 2005; Notani et al., 2010). SATB1 was shown to regulate the expression of T_H2 cytokines by remodeling the chromatin in an actively transcribed loop form (Cai et al., 2006). T cell activation along with IL-4 cytokine stimulus showed that SATB1 forms higher-order chromatin structure of the 200 Kb T_H2 cytokine locus and regulates *Il-5, Il-13* and *Il-4.* SATB1 induces expression of these cytokines by recruiting chromatin modifying enzyme Brg1 and RNA Pol II converting the locus into transcriptionally active region (Cai et al., 2006). Furthermore, induction of SATB1 expression in $CD4^+$ cells during T_H2 differentiation is STAT-6 dependent (Lund et al., 2005 and Ahlfors et al., 2010). Transcriptome profiling of differentiating $CD4^+$ cells into T_H1/ T_H2 subtypes revealed that SATB1 is involved in regulation of over 300 genes indicating its crucial role during T_H cell differentiation (Ahlfors et al., 2010).

An important insight into the role of SATB1 in T_H differentiation was obtained when the gene expression profiles of various subsets of T_H cells were compared with the TCR-activated $CD4^+$ T cells, a condition referred to as T_H0. To ascertain whether SATB1 regulated genes are involved in T_H cell differentiation, Ahlfors et al., (2010) silenced expression of SATB1 using siRNAs in T_H cells. Their studies revealed that expression of multiple genes was altered upon SATB1 knockdown in T_H1, T_H2 and T_H0 population. The RNA expression profile revealed that in differentiating $CD4^+$ T cells, expression of 319 genes was altered. Out of these, 70 genes were selectively affected in T_H2 population while 43 genes had altered expression in T_H1 population. Thus total of 40% (43+14+43=127) genes showed altered expression upon cytokine treatment suggesting SATB1 targets were partly specific to T_H subsets. Notably, 48% of SATB1 target genes were regulated by IL-4. Furthermore, TCR stimulation alone regulated one third of SATB1 targets and only 18% of SATB1 target genes were not regulated by TCR or combination of T_H1/T_H2 polarizing cytokines. The gene expression profiling clearly indicated that SATB1 is likely to play an essential role in the development or function of various T_H subtypes (Ahlfors et al., 2010). Another important contribution of this study was the finding that IL-5 which is predominantly secreted by T_H2 cells is repressed by SATB1 during early stages of polarization. The repression of *Il-5* promoter by SATB1 was during brought about by recruiting HDAC1 corepressor to the *Il-5* locus (Figure 1). Later the course of differentiation, the competition between binding of SATB1 and GATA-3 results in binding of GATA-3 to the *Il-5* promoter which derepresses *Il-5* locus and IL-5 is produced (Ahlfors et al., 2010). IL-5 plays important role in differentiation and activation of eosinophils and dysregulation of *Il-5* results into eosinophila (Mosmann & Coffman 1987; Campbell et al., 1988; Sanderson, 1988). Hence regulation of IL-5 is not only important in proper T_H differentiation but also in understanding its role in diseases such as eosinophila.

T_H2 differentiation is also regulated by the downstream transcription factors like GATA-3 and STAT-6. GATA-3 is a transcription factor predominantly expressed in T cells and brain (Oosterwegel et al., 1992). GATA-3 has been shown to play an important role in thymocyte development and also during T_H2 differentiation (Ho et al., 2010). The essential role of GATA-3 was demonstrated by creating mice lacking GATA-3 expression. GATA-3-deficient $CD4^+$ T cells cannot differentiate into T_H2 phenotype and they produce IFNγ under T_H2 polarizing conditions (Zhu J et. al., 2004). IL-4-STAT6 signaling pathway is known to cause the upregulation of GATA-3 in T_H2 differentiating cells. However, a recent report provided an alternative view by demonstrating that $CD4^+$ T cells can differentiate to T_H2 phenotype in absence of STAT6 via notch signaling although with a reduced efficiency (Amsen et al., 2004). In this review we have focused on the newly dicovered mechanism for regulation of GATA-3 expression by SATB1 in Wnt-dependent manner.

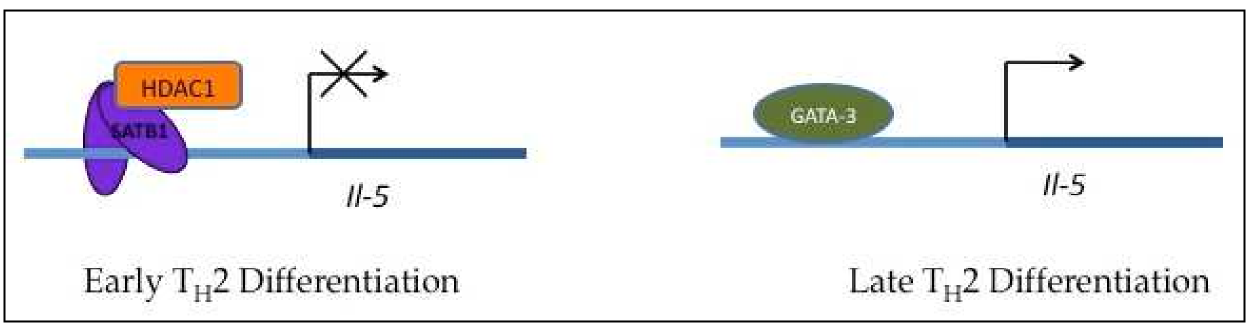


Fig. 1. **SATB1 mediated regulation of *Il-5* during T_H2 differentiation.** IL-5 is a late T_H2 cytokine**.** SATB1 directly binds to *Il-5* promoter and inhibits its expression by recruiting HDAC repressor complex. During allergic conditions GATA-3 displaces SATB1 bound to the *Il-5* promoter and upregulates IL-5 cytokine expression (Ahlfors et al., 2010).

3.4 SATB1 as a mediator of Wnt signaling

Recently, a new role for SATB1 has been discovered as a mediator of Wnt-signaling pathway during T_H differentiation (Notani et al., 2010). Wnt signaling is one of the well studied and highly conserved pathways responsible for various developmental processes and cell fate decisions (Logan and Nusse, 2004). β-catenin is the key transducer of canonical Wnt signaling cascade which upon Wnt signaling is stabilized in the cytoplasm, then translocates to the nucleus and interacts with T cell factor (TCF) family transcriptional factors. Asociation of β-catenin with the TCF family proteins alters the expression of Wnt-responsive genes (Logan and Nusse, 2004). SATB1 brings about T_H2 cell differentiation via Wnt signaling by recruiting β-catenin to its genomic targets (Notani et al., 2010). This study demonstrated that SATB1 represses target genes in undifferentiated cells. Upon Wnt signalling in the polarized cells, SATB1 interacts with β-catenin, recruits it to *Gata-3* promoter and derepresses it leading to T_H2 commitment (Figure 2). Several SATB1 regulated genes are activated by SATB1:β-catenin complex in Wnt-dependent manner. Post-translational modifications of SATB1 act as molecular switches regulating its DNA-binding activity and ability to interact with multiple partner proteins (Kumar et al., 2006). Upon Wnt signaling SATB1 is deacetylated and directly interacts with β-catenin through its PDZ-like domain. The physical interaction between SATB1 and β-catenin is required for T_H2 differentiation. The two prominent factors TCF and SATB1 compete for β-catenin interaction. SATB1 competitively recruits β-catenin and hence also affects the transcription of TCF regulated genes. However, TCF and SATB1 do not interact with each other suggesting that they have non-overlapping effects (Notani et al., 2010). Thus, these two mediators of Wnt signaling presumably bind to their genomic targets independent of each other. LEF/TCF family proteins were the only known β-catenin partners for number of years. Another β-catenin partner known to be involved in pituitary gland development and lineage determination is the homeodomain protein Prop-1 (Olson et al., 2006). The report by Notani et al. (2010), demonstrated that homeodomain-containing transciption regulator SATB1 is also a β-catenin-binding factor and is involved in T_H2 differentiation.

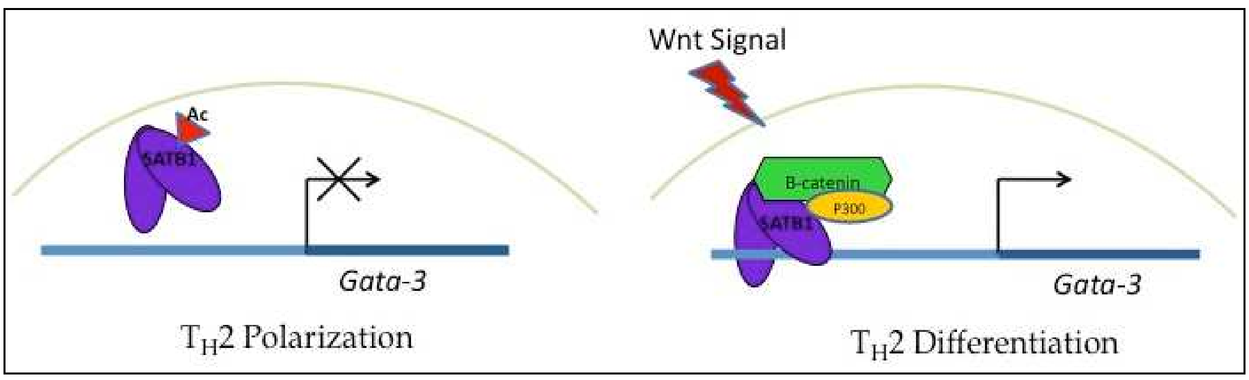
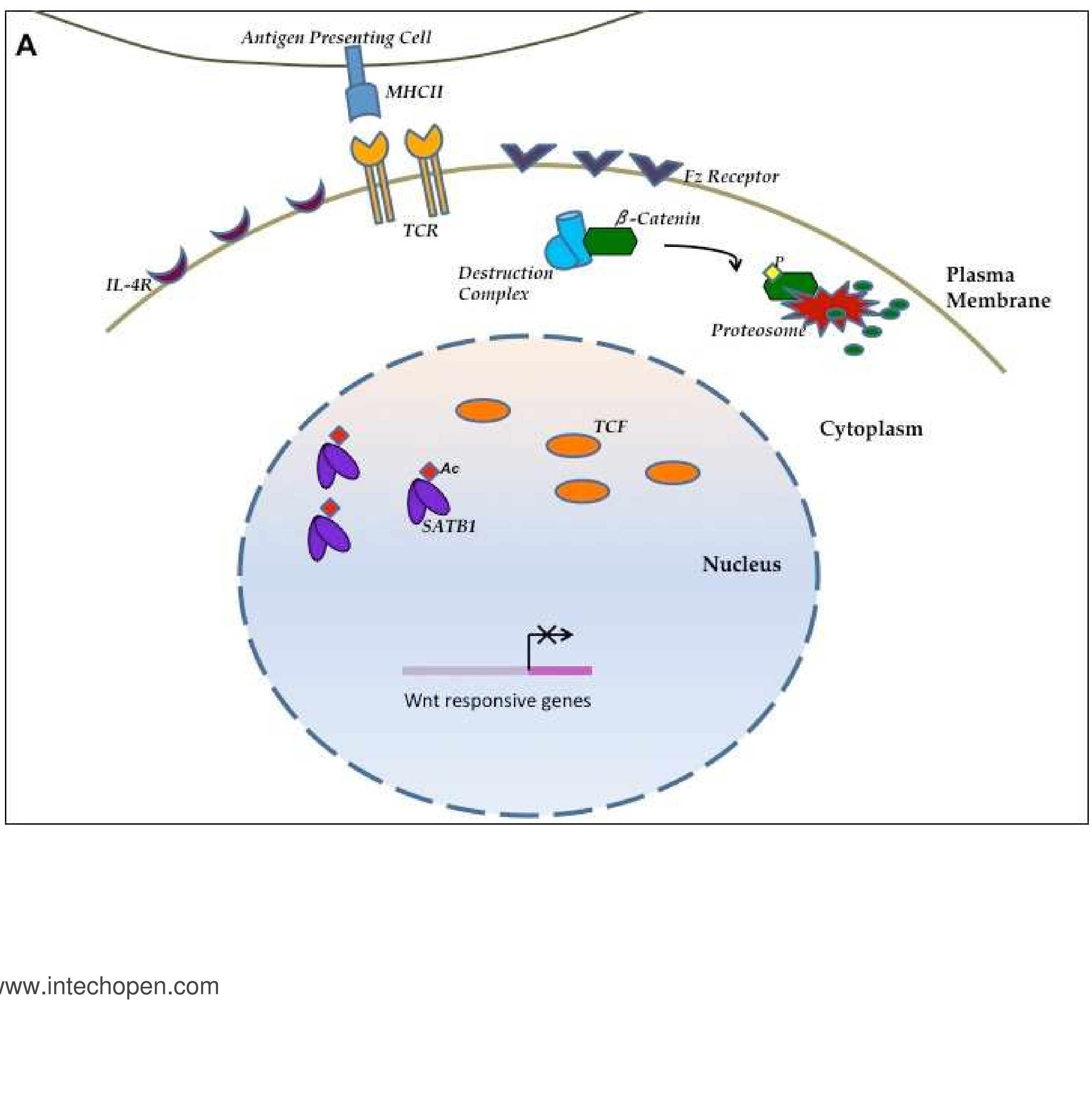


Fig. 2. **SATB1: β-catenin complex regulates *Gata-3* expression during T_H2 differentiation.** Upon Wnt signaling β-catenin translocates into the nucleus. SATB1 interacts with β-catenin and regulates multiple genes. GATA-3 is known to be a master regulator of T_H2 differentiation. In differentiating T_H2 cells, SATB1: β-catenin complex binds to the *Gata-3* promoter and upregulates Gata-3 expression by recruiting the p300 activator complex. SATB1: β-catenin complex regulates *Gata-3* expression in Wnt-dependent manner and thus regulates T_H2 differentiation (Notani et al., 2010).

Role of transcription factor GATA-3 in T_H2 polarization by upregulating IL-4 secretion and inhibiting IFN-γ expression is very well established (Avni et al., 2002; Spilianakis et al., 2004). SATB1 positively regulates GATA-3 expression in T_H2 cells by recruiting p300 acetyltransferase and β-catenin to *Gata-3* promoter upon Wnt signal (Figure 2). The role of Wnt signaling in T_H2 cell differentiation was further demonstrated by using DKK1, an inhibitor of Wnt signaling. Upon DKK1 treatment in T_H cells, GATA-3 expression was suppressed and also T_H2 cytokines were downregulated. Quantitative transcript profiling revealed that expression of GATA-3 was suppressed upon Dkk1 treatment in T_H2 subset, suggesting that Wnt signaling is necessary for the upregulation of GATA-3 during differentiation of T_H2 cells. Overexpression and siRNA mediated silencing of SATB1 and β-catenin provided the conclusive evidence for their direct roles in the differentiation of CD4+ cells. Upon siRNA-mediated silencing of SATB1 the expression of GATA-3 was downregulated in T_H2 cells. Overexpression of SATB1 led to a significant increase in the expression of GATA-3 in T_H2, suggesting that SATB1 positively regulates GATA-3 expression (Notani et al., 2010). In summary, Wnt signaling is essential for T_H2 differentiation whereby SATB1 upregulates GATA-3 expression which further enhances IL-4 secretion. $CD4^+$ T cells are receptive to Wnt signals because they produce different Wnts themselves (Notani et al., 2010). The differential sensitivity of T_H cell subtypes to Wnt signaling could be due to the fact that the downstream processes such as stabilization of β-catenin occur prominently in the T_H2 subtype and not T_H1 (Notani et al., 2010). Thus, these evidences clearly argue in favor of requirement of SATB1 and Wnt/β-catenin signaling during T_H cell differentiation.

GATA3 facilitates chromatin remodeling of T_H2 cytokine locus leading to conversion of the *Il4–Il5–Il13* locus to an open conformation, allowing transcription of this locus by transcription factors involved in T_H2-cell differentiation (Avni et al., 2002). The associated specific epigenetic changes include histone modifications upon binding of GATA-3 to its DNA targets were found to be mainly H3K4 and H3K27 methylation (Wei et al., 2011). Another chromatin protein CTCF binds to T_H2 cytokine locus and assists GATA-3 and SATB1 mediated T_H2 commitment (Almeida et al., 2009). Thus, collectively the three regulators namely SATB1, GATA-3 and CTCF could be responsible for orchestrating the coordinated regulation of T_H cell differentiation.

A model for regulation of T_H2 differentiation by SATB1 is illustrated in Figure 3. T_H0 cell is activated and polarized by TCR docking and IL-4 cytokine respectively. In the absence of



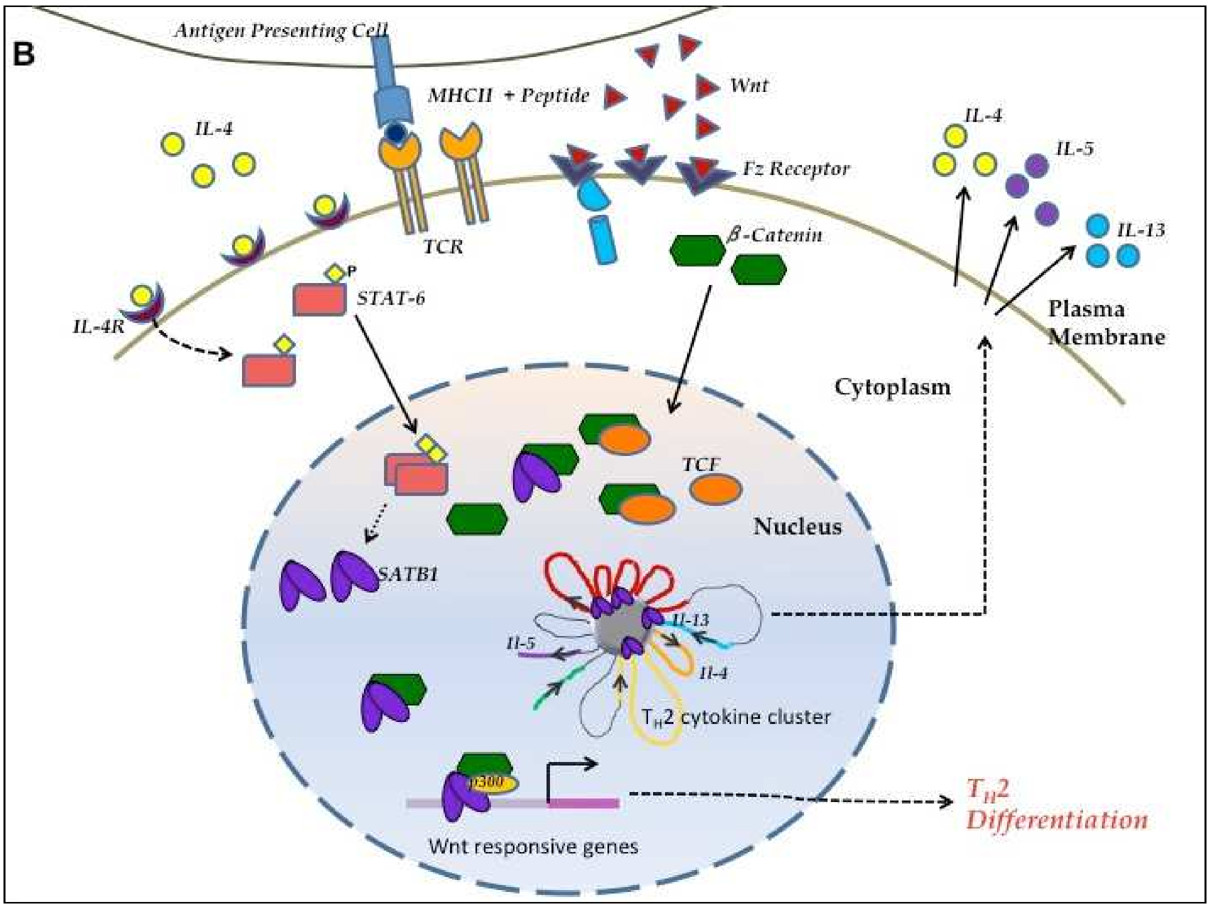


Fig. 3. Model depicting the early events occurring upon Wnt signaling in polarized T_H2 cell and role of SATB1 in this process. In the complex paradigm of T_H2 polarization model there have been several studies suggesting role(s) of different mechanisms and it is now evident that SATB1 plays a major role during this process of T_H2 commitment. **A**, In naïve cells when IL-4 signalling is absent, expression of SATB1 is low and GATA-3 is not upregulated. **B,** Under T_H2 conditions, when a peptide antigen is presented by an antigen presenting cell (APC) to the TCR on T cell surface and IL-4 secreted by the APCs causes the activation of Jak Kinases which phosphorylate STAT-6, which in turn upregulates SATB1 and GATA-3. SATB1 interacts with β-catenin which is translocated to the nucleus in Wnt-dependent manner and this complex regulates *Gata-3* expression. STAT-6, SATB1 and GATA-3 coordinatively regulate *Il-4* expression which is a characteristic cytokine of T_H2 differentiation. However, the role of STAT-6 in regulation of SATB1 as depicted here is speculative.

Wnt signaling, β-catenin is phosporylated by destruction complex and targeted for degradation to proteosomal complex. SATB1 is acetylated and has low DNA-binding affinity in the absence of Wnt signal. Also, in the absence of nuclear β-catenin TCF does not regulate Wnt responsive genes and hence their transcription is suppressed (Figure 3A). Upon Wnt signaling, the destruction complex that sequesters β-catenin does not form and β-catenin is stabilized, which then translocates to nucleus. SATB1 is deacetylated upon Wnt signaling and it then competes with TCF for interaction with β-catenin. Deacetylated SATB1 recruits β-catenin to genomic targets and regulates Wnt-responsive genes resulting into T_H2 differentiation (Notani et al., 2010). SATB1 also binds to T_H2 cytokine locus and upregulates transcription of *Il-4*, *Il-5* and *Il-13* resulting into T_H2 commitment (Figure 3B).

4. Regulation of SATB1 via STAT-6

Signal transducer and activator of transcription (STATs) are important in various biological processes such as development, programed cell death, organogenesis, cell growth regulation and adaptive immunity (Horvath, 2000). Upon appropriate cytokine signaling STAT molecules are phosphorylated by Janus kinases and they form homodimers. The phosphorylated STATs translocate to the nucleus and affect the transcription of their target genes (Schindler and Darnell, 1995). Cytokine signaling mediates the activation of specific STAT molecules and plays an important role during T helper cell differentiation. During the T_H differentiation STAT-4 and STAT-6 play seminal roles during T_H1 and T_H2 differentiation process respectively. IL-12 signaling initiates from binding of IL-12 to the IL-12 receptor, which further associates with protein tyrosine kinases and Jak2. The Jak2 kinase specifically causes the phosphorylation of STAT-4 (Waltford et al., 2004). STAT-4 causes the expression of Interferon γ and transcription factor Tbet during T_H1 differentiation (Thieu et al., 2008, Robertson et al., 2005). IL-4 secreted by the APCs engages to the IL-4 receptor on $CD4^+$ T cells which then recruits Jak 3 kinases and causes the activation of STAT-6 (Witthuhn et al., 1994). STAT-6 regulates the expression of IL-4 and GATA-3 during the T_H2 differentiation (Zhu and Paul, 2008). The knockout models of STAT-4 and STAT-6 have revealed that T cells cannot differentiate into their respective effector phenotypes (Wuster et al., 2000). Genome-wide analysis of occupancy of STAT factors have shown that they preferentially bind to the promoters and intergenic regions in the genome. STAT proteins have a palindromic GAA consensus binding site. STAT molecules generally colocalize with the active histone marks, and it is shown that both proteins SAT4 and SAT6 colocalize with H3K4 trimethylation marks in the genome (Wei et al., 2010). Gene expression studies along with elucidation of the epigenetic marks at key loci using STAT knockout mice have revealed that STAT are important for the maintenance of epigenetic marks on such genes and thus regulation of gene expression.

STAT-6 knockdown caused the downregulation of CRTH2 expression in cells polarised to T_H2 phenotype (Elo et al., 2010). Another study also demonstrated that STAT-6 knockdown resulted in downregulation of SATB1 expression at both RNA and protein level (Ahlfors et al., 2010). Microarray-based gene expression profiling data from different groups using mouse and human models depicted similar results showing downregulation of SATB1 (Wei et al., 2010; Elo et al., 2010). Bsed on these finding, we hypothesize that STAT-6 may directly bind to the SATB1 promoter and mediate activating epigenetic histone modifications leading to the upregulation of SATB1 during T_H2 differentiation. SATB1 in turn causes positive regulation of *Il-4* expression.

Interestingly, two recent studies have implicated Foxp3 in the regulation of SATB1 (Beyer et al. 2011; McInnes et al., 2011). Foxp3 tumor suppressor regulates SATB1 expression in breast epithelial cells and downregulates its expression in miRNA-dependent manner (McInnes et al., 2011). Repression of SATB1 has been also identified as a crucial mechanism for the phenotype and function of T(reg) cells. Foxp3 acts as a transcriptional repressor for the SATB1 locus and indirectly suppresses it through the induction of microRNAs that bound the SATB1 3' untranslated region (Beyer et al., 2011). Thus, elucidation of such regulatory loops will be important steps towards understanding the regulation and in vivo functions of SATB1.

5. Loss of SATB1 function: Sézary syndrome

Adaptive immune response raised against pathogen includes clonal expansion of antigen-specific T cells which are then cleared from the system mainly by activation-induced cell death (AICD), a type of apoptosis (Krammer et al., 2007). Sézary syndrome which is a variant of cutaneous T cell lymphoma results by clonal accumulation of mature T cells originating from skin (Willemze et al., 2005). This accumulation of cells occurs as a result of resistance of cells to AICD (Klemke et al., 2006). The pathogenesis of Sézary Syndrome (SS) is still not very clear. A recent study by Wang et al. (2011) revealed that the deficiency of SATB1 leads to SS. Sézary cells obtained from patients are $CD4^{+}$ $CD7^{-}$ mature memory T cells and show a T_H2 cytokine profile with loss of expression of CD7. Transcription profiling of the Sézary cells from patients and Hut78 (Sézary-derived cell line) revealed that SATB1 was drastically downregulated in these cells as compared to non-Sézary control cells such as Jurkat T cells. Additionally, immunofluorescence staining showed a lowered nuclear localization of SATB1 in of primary Sézary cells as well as in Hut98 cells (Wang et al., 2011). Retroviral transduction mediated restoration of SATB1 in Hut98 cells increased apoptosis in these cells within 4 days without changing their proliferation rate. Subsequently, it was demonstrated that the SATB1 restored cells were sensitized to AICD. The transcriptome analysis of these SATB1 restored cells showed remarkable up-regulation of FASL/CD95L which is a death receptor ligand. Further, 32 out of total 153 (12%) dysregulated genes in Sézary cells were normalized upon SATB1 restoration in these cells (Wang et al., 2011). The increased AICD in SATB1 restored Sézary cells was shown to be induced by FASL via caspase 8-dependent pathway. These studies strongly suggested that SATB1 plays a very important role in pathogenesis of Sézary syndrome and it plays a vital role in regulation of homeostasis of T cells. Sézary cells are known not to respond to radiation therapy as these cells do not have increased proliferation but rather possess resistance to apoptosis. Currently the therapies for SS include upregulation of FASL to sensitize these cells for apoptosis. Restoration of SATB1 in Sézary cells could be a promising new strategy for the treatment of Sézary syndrome. The SS cells would also serve as a knockout model for studying role of SATB1 in human T cell functions.

6. Conclusions

In the field of T cell biology, T_H differentiation is itself a complex phenomenon, one reason being that T_H cell fate is not pre-decided during development in thymus, it is primarily executed upon the encounter of undifferentiated T cell with the antigen in the peripheral immune system. Hence T_H cell polarization leading to final differentiation is a multi-cascade process with several epigenetic changes invoked in response to various signals. In this Chapter we focused on role of SATB1 which is an important global regulator involved in T cell development, maturation and differentiation. We elaborated on the role of SATB1 during T_H cell differentiation which is an important pool of cells for humoral as well as cell mediated immunity. To summarize the findings of various studies, it can be concluded that SATB1 plays an important role at the very early stages of T_H cell differentiation. The studies discussed here suggest that SATB1 represses the chromatin in undifferentiated cells by recruiting repressors to the gene loci. Upon early events of cell polarization such as TCR signal and cytokine secretion by cells, SATB1 immediately responds to even lower level of cytokine signal such as IL-4 by changing the chromatin 'loopscape' of specific loci in T_H2

cells which culminates into synthesis of downstream transcription factors required for further differentiation such as GATA-3. Wnt signaling acts as a booster for the differentiation signal in these cells which brings about changes in chromatin organization via SATB1 as a mediator of Wnt signaling and promotes GATA-3 transcription. In the later stages of differentiation, T_H subtype specific factors such as GATA-3 take over and competitively overcome the SATB1 mediated repression of T_H2 cytokines and in turn upregulate the T_H2 signature cytokines such as IL-5. Thus, SATB1 presumably acts as a regulatory switch at the very early stages of cell polarization and differentiation by repressing various cell type specific genes, however it specifically responds to polarization signal by changing its acetylation status. The indispensible role of SATB1 in T_H cell differentiation is exemplified by diseases such as Eosinophila and Sézary syndrome, the later manifests as a result of SATB1 deficiency.

7. Future perspectives

The role of SATB1 in differentiation of $CD4^+$ T cells has come into the limelight as described in this review. However, the role of SATB1 during earlier events such as thymocyte maturation are not studied in detail and requires further investigation. Since SATB1 is known to regulate genes such as *Thpok* which are important for the lineage commitment process, it is essential to evaluate whether SATB1 plays a direct role during the thymocyte lineage commitment. Findings from recent studies have highlighted the requirement for delineation of molecular mechanisms governing the expression of SATB1 during the process of thymocyte maturation. In the $CD4^+$ T cells, it would be important to study the regulation of SATB1 which might be regulated by an IL-4:STAT6-dependent mechanism as seen during the differentiation of T_H2 cells. It would be also interesting to investigate whether SATB1 plays any role(s) in the differentiation of the other subtypes of $CD4^+$ T cells. Studies elucidating role of miRNAs in the regulation of SATB1 in these various subtypes of T cells would also shed light on the signaling pathways and associated mechanisms regulating the development and differentiation of various subtypes of T cells.

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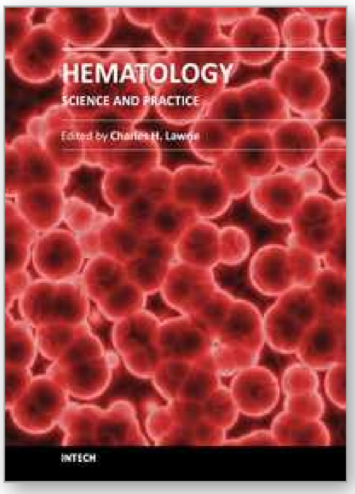

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