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Review

The multifaceted role of Notch signal in regulating T cell fate

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ABSTRACT

Notch signaling pathway facilitates important cellular functions of the host. Notch signal is essential for the development of T cells, and the role of Notch in fine tuning of αβ versus γδ T cell lineage commitment is fundamentally different in mice and human. The Notch family of cell surface receptor likewise plays a critical role in regulating T cell activation, and influences T cell response both intrinsically and through the local environment. In this review, we take an overview of Notch signaling pathway and also emphasize the role of Notch signal in T cell lineage differentiation and activating effector function of peripheral T cells.

1. Introduction

The Notch signal is an evolutionary conserved pathway that plays an essential role in both invertebrates and vertebrates. This signal controls cellular fate, cell growth and differentiation. The action of Notch signal is pleiotropic, influencing embryogenesis, differentiation and homeostasis in adult tissue. Notch signal contributes to the diversity of different cell types and enables the cell to execute its functions. Perturbations in the Notch signaling pathway has been associated with various genetic disorders and cancers [1]. An accumulating number of studies suggest that the Notch pathway plays a crucial role in development and effector functions of T cells. Notch signal is essential for different stages of T cell development and diversification in the thymus [2]. The activation of peripheral T cell and differentiation of effector cells to act against invading pathogens and cancer is also regulated by Notch signal [3–5]. Here, we review the mechanism underlying the transduction of Notch signal and the current understanding of the role of Notch signal in determining the T cell fate.

2. The Notch signaling pathway: mechanism of action

An important feature of Notch is that it acts both as a transmembrane receptor and a transcription factor [6]. In mammals, there are four Notch genes (Notch1–4) along with five different genes for the ligands (Delta-like (Dll) 1, 3, and 4; Jagged (Jag) 1 and 2) [6]. At the cell surface, both the Notch receptor and its ligands are present as transmembrane proteins with large extracellular domains. The initiation of Notch signal requires binding of its ligand to the EGF repeats of the Notch extracellular domain (NECD) (Fig. 1). The other part of the Notch, i.e., Notch intracellular domain (NICD) is basically a membrane-tethered transcription factor whose release is regulated by ligand binding [7]. The interaction between NECD and any of its ligands result in the exposure of an extracellular metalloprotease site which becomes susceptible to cleavage by transmembrane proteases family of the ADAM/TACE (a disintegrin and metallopeptidase/tumor necrosis factor-α converting enzyme). This cleavage generates a membrane-tethered Notch extracellular truncation (NEXT) that serves as a substrate for γ-secretase enzyme, a multicomponent intramembrane cleaving proteases (I-CLiPs) [8–10]. The cleavage of NEXT at the transmembrane site by γ-secretase results in the release of NICD followed by its transmigration to the nucleus. In the nucleus, NICD act as a transcription factor by binding to RBPJ or CSL (CBF1, Suppressor of Hairless, Lag-1), and this complex in the presence of coactivators such as Mastermind-like (MAML) and p300 turn on the expression of target genes [9,11–13]. The coactivator MAML directly interacts with NICD-RBPJ and then recruits the histone acetyltransferase p300 to create a transcriptional activation complex. The NICD-containing activation complex goes on to promote transcription of downstream target genes such *as hairy enhancer of split (HES)*, *Hes-related repressor protein (Herp)*, the cell cycle regulator *Cdkn1a*, the gene for *Notch-regulated ankyrin repeat protein (NRARP)* and *Deltex (DTX)* [14–18]. Notch signaling can be turned off by modulators such as Numb, SEL-10 and F-box protein that interacts with nuclear NICD and promote ubiquitin mediated proteosomal degradation [19,20]. The Notch target gene-*NRARP* could also act as a negative feedback regulator of Notch signal by binding to NICD activated complex and mediating loss of NICD [21].

Overall, the transmission of Notch signal essentially involves physical contact between cells. Furthermore, the T-cell receptor mediated

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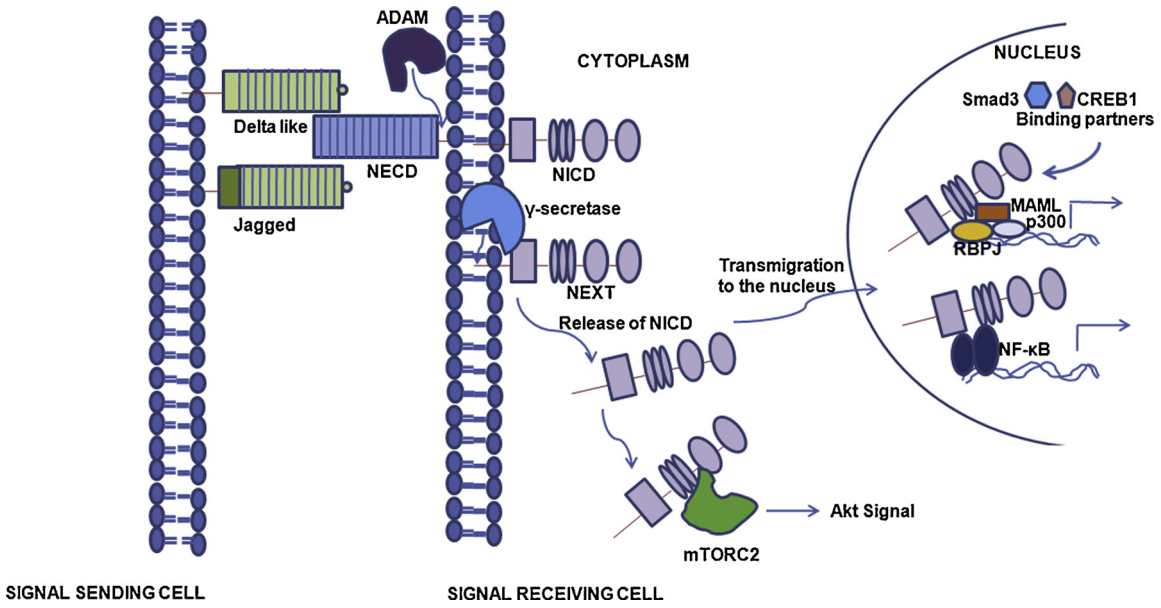

Fig. 1. Canonical and Non-canonical Notch signaling Pathway. Ligand binding to the Notch extracellular domain (NECD) brings conformational changes in the bound Notch receptor. This conformational change is required to expose a metalloprotease site allowing its cleavage by disintegrin and metallopeptidase/tumor necrosis factor-α converting enzyme (ADAM/TACE) proteins. Notch cleavage by ADAM generates the membrane-anchored Notch extracellular truncation (NEXT) fragment, a substrate for γ-secretase. Subsequently, γ-secretase cleaves the Notch transmembrane domain to release the Notch intracellular domain (NICD). **(A)** In canonical Notch signal, the cleaved NICD migrates into the nucleus where it associates with the DNA-binding protein RBPJ and act as a transcription factor after recruiting the co-activator mastermind-like (MAML) and the histone acetyltransferase p300. In the absence of NICD, RBPJ associates with ubiquitous co-repressor (Co-R) proteins to repress transcription of target genes. Additional binding partners of NICD such as Smad3 and CREB1 increases the diversity of functional outputs of Notch pathway. **(B)** In non-canonical Notch signal, NICD interacts with NF-κB and facilitates its sustained activity. Additionally, non-canonical and non-nuclear Notch signal occurs in the cytoplasm, where NICD along with mTORC2 activates Akt signaling to promote cell survival.

activation of T lymphocytes can also lead to the release of NICD that results in Notch ligand-independent Notch signaling [22,23]. The mechanism of receptor processing in ligand-independent Notch activation has been described to be triggered via cell-internal signals [24]. Interestingly, non-canonical Notch signaling also occurs in the absence of RBPJ (Fig. 1). The non-canonical Notch signaling was first reported in Drosophila for its role in axon guidance [25]. Subsequently, it was observed that stemness-related KLF4-transcription factor binds to the proximal Notch1 promoter to induce Notch1 expression and promote the epithelial transformation of mammary cancer cells through a non-canonical Notch signaling pathway [26]. This RBPJ-independent Notch signal can also regulate expression of IFN-γ in peripheral T cells by associating with NF-κB proteins, p50 and c-rel [27]. Likewise, the non-canonical Notch signal is required for the activation and proliferation of $CD4^+$ T cells as well as differentiation to Th1 and induced regulatory (iTreg) T cell lineages [28]. Additionally, non-canonical and non-nuclear Notch signaling occurs in T cell, wherein NICD interacts with mTORC2 in the cytosol to activate Akt signal and prevent loss of mitochondrial function and consequent nuclear damage to promote cell survival [29,30].

3. Notch signal in development and maturation of T cell

Notch signaling is essential in lineage specification of hematopoietic progenitor cells. This signal is involved in the differentiation of T versus B lymphocyte from a common lymphocyte precursor in the bone marrow and has been shown to favor differentiation of the thymus independent T cell against B cell lymphopoiesis in an experimental model [31]. Due to the presence of integrins, selectins and chemokine receptors, the thymus-settling progenitors (TSPs) migrate from bone marrow to thymus where they experience powerful Notch signal (Fig. 2). The presence of Notch signal is essential for maintaining T cell lineage fate and dampening of both B and NK cell lineage commitment. Thymus is rich in Notch ligands that interacts with TSPs to promote the development of $CD44^+CD25^-CD4^-CD8^-$ double-negative1 (DN1) precursors [32–34]. These DN1 precursors proliferate and differentiate to DN2 cells and express higher level of CD25 as a result of increased Notch signal [35]. The subsequent transition from DN2 to DN3 ($CD44^-CD25^+$) subsets is characterized by a marked decrease in proliferation and increase in expression of Notch target genes-*HES1* and *DTX* [36,37]. Other critical T cell genes, including *GATA3, Tcf7, Runx1, Ets1* and *Lef1* are also upregulated to their maximum levels at the DN3 stage [36]. The DN3 cells can be further subdivided into DN3a and DN3b on the basis of cell size and CD27 expression; with DN3b having larger size and upregulated CD27 expression [38–40]. These cells at DN3 stage undergo extensive DNA rearrangements at the β, γ and δ loci in order to generate functional TCR chains [41]. The decision of the progenitor T cells to generate either αβ T cell subsets or γδ T cells take place at this stage. The generation of αβ T subsets is preceded with the expression of TCR-β and invariant pre-Tα chains resulting in a process called β-selection, whereas, the expression of TCR-γ along with TCR-δ chains directs the formation of γδ T cell subsets, a process known as γδ-selection [42,43]. Notch signaling is known to be intimately involved in γδ versus αβ T cell lineage decision [44]. Several reports on mice suggest that Notch signal favors αβ T cell lineage over γδ T cell [31,44,45]. The expression of complete pre TCR complex consisting of pre-Tα and TCR β chains at DN3 stage results in a transition to $CD44^-CD25^-$ DN4 stage. Subsequently, signaling through the Notch and pre TCR complex induces survival and differentiation of DN4 progenitor cells to $CD4^+CD8^+$ double-positive (DP) αβ T cells. The generation of DP cells from DN3 and DN4 progenitors are hindered in the absence of Notch signal [46–49]. The binding of CD4 coreceptor and TCR to MHC class II ligands promote transition of DP progenitors into the $CD4^+$ single-positive (SP) T cells, while binding between $CD8^+$ coreceptor and TCR to MHC class I ligands promote maturation into the $CD8^+$ SP T cells. This final step in the maturation of both $CD4^+$ and $CD8^+$ αβ T cells in the thymus is also mediated by Notch signal [18,50]. Alternatively, the γδ T cell lineage commitment and

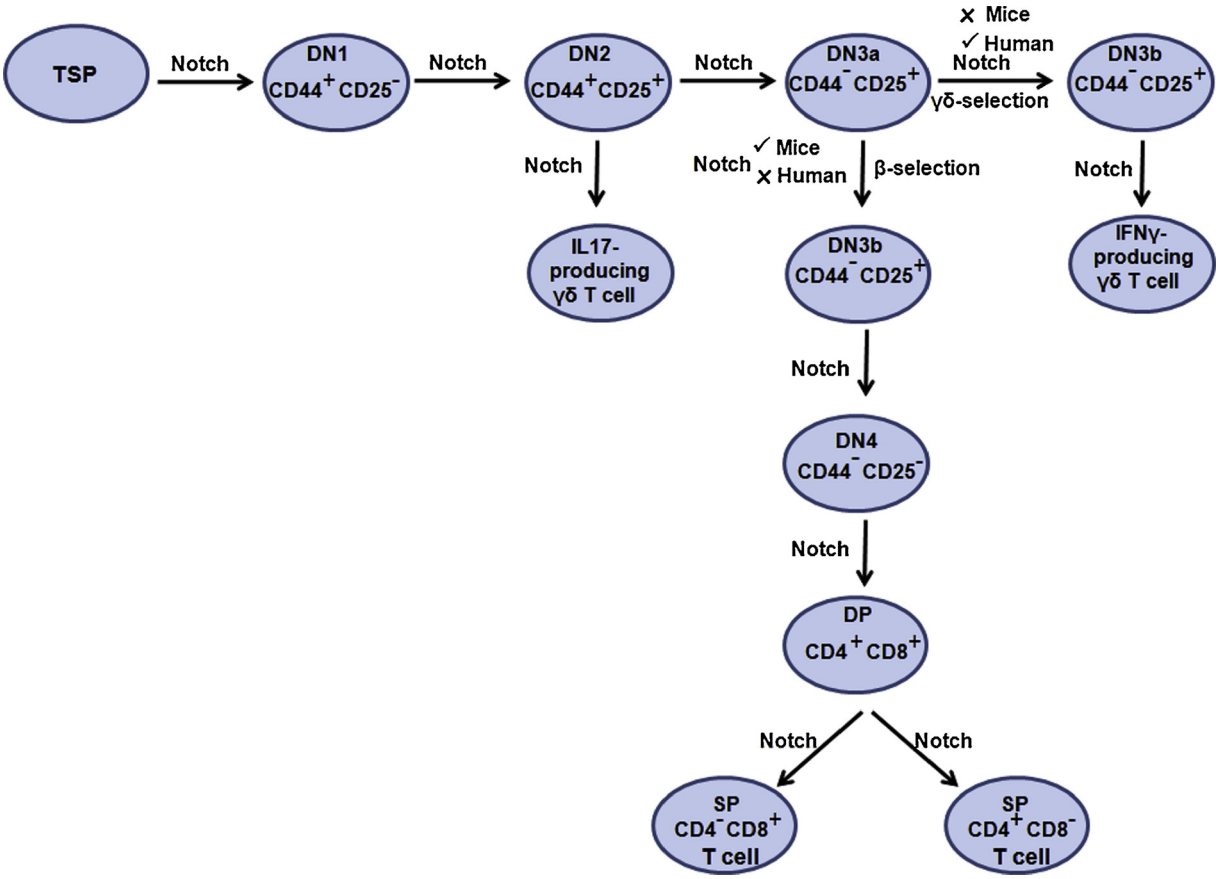

Fig. 2. Notch signaling in T cell development and maturation. The development of T cells from thymus-settling progenitors (TSPs) occurs in the thymus. In the presence of strong Notch signal, TSPs develop into several stages of $CD4^-$ $CD8^-$ double negative (DN) T progenitor cells that differs from each other based on cell surface expression of CD44 and CD25 markers. With the exception of IL17-producing γδ T cells that differentiate from DN2 stage, the differentiation of both αβ and γδ T cells takes place at DN3 stage. In mice, the commitment of the αβ T cell lineage into DP T cells and then subsequently into either $CD4^+$ T cell or $CD8^+$ T cell requires a higher level of Notch signal and that of γδ T cell lineage commitment occurs in the absence of Notch signal. On the contrary, in human, the activation of Notch signal results in increased generation of γδ T cells and a decreased in Notch signal favors αβ T cell lineage commitment.

bifurcation from αβ T cells occurs at the DN3 stage. Unlike αβ T cells, the development of γδT cells from γδ TCR-expressing progenitor takes place in the absence of Notch signal in mice [39,51,52]. Strikingly, the IL-17– producing γδ T cells differentiate from DN2 stage, and Notch signal is essential for the development of IL-17–producing γδ T cells in mice fetal thymus [53,54]. Compared to the mice, human αβ/γδ T cell lineage specification is characterized by distinct thymic environment and developmental stages. The TCR-γδ recombination events in human precede αβ lineage differentiation stages [55,56]. It is interesting to note that the Notch-mediated molecular events that trigger T cell development is essentially different for human and mice (Fig. 2). There is an opposing role of Notch signal in determining human αβ/γδ lineage decision. Constitutive expression of Notch in human thymocyte progenitors impairs progression of αβ T cells and efficiently generates γδ T cells [57]. These results were further confirmed by using OP9-DLL1 and human thymocytes co-culture system, where it was found that Notch activation promotes generation of γδ T cells, and development of αβ T cells takes place in the absence of Notch signal, which is in sharp contrast to T cell development in mice [58]. The differential requirements of Notch signal for αβ and γδ T cell development in mice and human could be mainly due to the differences in the expression patterns of the Notch ligands in the thymocytes of human and mouse. The expression Dll4 is high in the murine thymus and is crucial for promoting αβ T cell fate specification and maturation in a Notch1 dependent manner [59]. Unlike the mouse cortical thymic epithelial cells (TECs), most post natal human cortical TECs express Jag2 and lacked Dll4 for inducing γδ T-lineage differentiation, suggesting species-specific role of the ligands in T cell development [60,61]. In human, Jag2 mediated Notch3 signaling is involved in γδ T-cell commitment and development, but impairs αβ T-cell development by inhibiting TCR-β formation [62,63]. Consequently, Notch mediated differential tuning of T cell development in mice and human creates further complications in addressing aberrations associated with T cell maturation that can result in T cell malignancies in human. It would therefore be critical to carefully evaluate whether the studies using mouse models could contribute to therapeutic approaches targeting anomalies linked to human T cell development.

4. Notch signaling in regulation of T cell function

Combinatorial use of several signaling pathways enables T cells to execute effector functions. Among these, Notch signal plays an important role in T cell function. Early studies showed that TCR-mediated signaling can activate Notch signal in both $CD4^+$ and $CD8^+$ T cells in a ligand independent manner [22,64]. Activated Notch signaling in turn regulates proliferation and IFN-γ production in peripheral T cells [22]. We have recently reported that Notch signaling regulates expression of CD3-ζ chain to support proliferation and activation of αβ T cells [65]. Notch signal also reduces the threshold for the responsiveness of T cells by enhancing CD25 expression [66]. In addition to the TCR-mediated signaling, DLL4 mediated Notch signaling promotes naive $CD4^+$ T cells to react to a lower intensity of the antigen by potentiating downstream PI3K-dependent signaling [67]. Notch signaling regulates the expression of key effector molecules-perforin and granzyme B, which are

known to be directly linked to the cytolytic effector function of $CD8^+$ T cells [64,68]. The integration of Notch2 intracellular domain (N2ICD) with transcriptional factor CREB1 and RBP-J on the promoter of granzyme B was able to induce T cell cytotoxicity. Our previous study showed that Notch signaling plays an important role in modulating the antigen-specific proliferation of γδ T cells, their ability to lyse tumor targets and secrete IFN-γ upon stimulation [23]. Accumulating data also supports a function of Notch signal in modulating cross talk between antigen presenting cell (APC) and T cell. A stimulus that in general induces a Th1 response, e.g., bacterial lipopolysaccharide (LPS), dengue virus and respiratory syncytial virus results in upregulation of Dll1/Dll4 on APCs, whereas a type2 stimulus such as cholera toxin and allergens induces the expression of Jag2 on APCs [69–73]. Depending on the polarizing cytokine milieu and Notch ligands expressed by the signal-sending cells such as APCs, $CD4^+$ T cells can differentiate into different Th subsets. Notch pathway can promote differentiation of both Th1 and Th2 cells by inducing the expression of *Tbx2* and *Gata3* respectively [74,75]. Non-canonical Notch signaling was suggested to be involved in functional Th1 immune response, while Th2 differentiation was found to be regulated by canonical Notch pathway [22,69,76]. Canonical Notch signaling can also mediate differentiation and function of Th17 and Th9 cells. Notch pathway has emerged as an essential regulator of *RORγt* and *IL23r* genes leading to differentiation and activation of Th17 cells [77,78]. Besides, induction of Notch signaling by Jag2 in the presence of TGF-β results in binding of SMAD3 to NICD and RBP-Jκ to promote Th9 cell generation [79]. APCs in different lymphoid tissues showed a distinct pattern of Notch ligand expression, suggesting its physiological relevance in different organs [80].

Nevertheless, Notch signaling also function as an opposite force by dampening the T cell response. Notch signal is essential for regulatory T cells (Tregs) that are known to be involved in the suppression of immune responses. The phosphorylated Smad3 arising from TGF-β signaling binds to NICD and this complex move to the nucleus for regulating Foxp3 expression in Tregs [81]. Notch also controls the plasticity of proinflammatory and antiinflammatory Th1 cell function and can mediate conversion of Th1 cells into IL10 producing Tregs by a STAT4-dependent process [82]. Moreover, Notch signal is capable of spurring exhaustion or inhibition of T cell function by enhancing PD-1 expression on activated $CD8^+$ T cell [83]. Recent work has shown that Dll4/Notch signaling can epigenitically control differentiation and function of induced Tregs (iTregs) by supporting IL10 production and Lag-3 expression [84]. There is also evidence that Dll4 mediated Notch signaling promotes Treg cell development and function during Respiratory syncytial virus (RSV) infection, which is critical for maintaining T cell homeostasis [85]. The suppression of immune responses is essential to minimize tissue damage and immunopathology in the host. Thus, Notch signaling might be playing a key role in shutting down the immune responses after effector T cells achieve their goal of removing a pathogenic threat in order to avoid collateral tissue damage.

5. Concluding remarks

The unique feature of Notch is that it acts as a transmembrane receptor as well as a transcription factor. The Notch signaling pathway is crucial to T cell development and maturation. The decisive role played by Notch signaling in the αβ versus the γδ lineage decision is fundamentally different in the human and mice. In mice, Notch signal is required for αβ T cell lineage commitment and inhibits maturation towards the γδ T cell, whereas, the opposite holds true for the human. Accordingly, the differential regulation of T lineage specification in mice and human have complicated extrapolation of mouse thymic T cell development biology to humans. Notch signaling pathway also contributes as an additional signal for the activation and regulation of T cell functions. Conversely, Notch signaling supports suppressive potential of Tregs as well as promotes exhaustion of T cells that results in dampening of T cell responses. Notch, thus, plays a critical role in modulating both activation and inhibition of T cell functions, and helps in maintaining the balance of immune reactions in the host. A proper understanding of specific conditions required for the regulation of Notch signaling that determine "activation/suppression" of immune responses would fuel the interest in understanding the clinical relevance of Notch signal and deeper investigations of the Notch signaling pathway.

Conflicts of interest

The authors have no financial conflicts of interest.

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