including HIV-2, feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), EIAV, and MLV [297]. Collectively, these results demonstrated that SAMHD1 is a Vpx target that strongly blocks viral replication in non-dividing cells by depleting the intracellular dNTP pool. SAMHD1 is a nuclear protein, but its nuclear localization is not required for its enzymatic activity and/or antiviral activity [293,294]. Because cellular dNTPs are not compartmentalized, SMAHD1 should be able to degrade dNTPs in both the cytoplasm and the nucleus (Figure 1). Although SAMHD1 imposes an important block to HIV-1 infection, disruption of this block cannot restore HIV-1 replication in resting $CD4^+$ T cells, indicating that there are additional blocks in these cells [301,302]. In addition, another type I IFN-inducible unknown restriction factor in dendritic cells, which also blocks HIV-1 replication at an early step and is counteracted by Vpx, needs to be identified [328].

An important feature of SAMHD1's antiviral activity is that it requires cells to stay in a resting or non-dividing state. The SAMHD1 activity is only detectable in the myeloid cell lines THP1 and U937 after they are fully differentiated into macrophages by treatment with phorbol myristate acetate (PMA) [323]; although activated primary $CD4^+$ T cells still express SAMHD1, this expression neither reduces intracellular dNTP levels, nor does it inhibit HIV-1 replication [302,323]. In addition, ectopic expression of SAMHD1 in a human T cell line did not show these restrictive activities, either [317,323]. Because dividing cells maintain high levels of dNTPs, SAMHD1 may not sufficiently reduce dNTPs to restrict viral replication. Thus, SAMHD1-mediated dNTP hydrolysis and inhibition of viral reverse transcription stand as a very attractive model for SAMHD1 antiviral mechanism in non-dividing cells. Alternatively, the SAMHD1 antiviral activity may not be completely dependent on the dNTP triphosphohydrolase activity. Because SAMHD1 has nucleic acid binding activity, it may interact with viral reverse transcription complex and inhibit production of full-length viral DNA, and this activity may require other cellular factor that is only expressed in non-dividing cells. Thus, the regulation of SAMHD1 antiviral activity remains an important area of future study.

Action of Vpx

As introduced earlier, Vpx tightly associates with DCAF1, which is a substrate receptor subunit of the Cul4A E3 ubiquitin ligase complex, and this interaction is linked to Vpx activity to relieve SAMHD1 restriction in non-dividing cells [307]. Like Vpr, the Vpx protein has three central α-helices connected by two flexible loops and unstructured amino and carboxy termini (Figure 6) [329,330]. Like SAMHD1, Vpx is also a nuclear protein, which is determined by a C-terminal proline-repeat and a NLS motif crossing the end of second loop and the beginning of the α-helix 3 region [329]. Vpx binds DCAF1 through the α-helix 3 region where the Q76 residue is located [312], and it binds to SAMHD1 through the N-terminal unstructured region, where the T17 residue is located [331,332]. Vpx recognizes the C-terminal 31 amino acid residues of SAMHD1, loads this protein onto the Cul4A-DCAF1 complex, and triggers SAMHD1 proteasomal degradation [331,333]. Indeed, the SAMHD1 C-terminal tail is highly divergent among vertebrate species; so the neutralization of SAMHD1 by Vpx is highly species-specific. For example, Vpx from SIVmac239 can effectively neutralize human but not mouse and zebrafish SAMHD1 [331]. In addition, this domain is the target for strong positive selection during primate evolution, which contains a cluster of five positively selected sites. Among these, the last M626 residue critically determines human and primate SAMHD1 sensitivity to Vpx [333]. Several other positively selected residues are also found in the N-terminal region, and among these, the G46 and R69 also contribute to this species-specific interaction [334]. Notably, although SAMHD1 still retains antiviral activity when it is relocated to cytoplasm, the cytoplasmic SAMHD1 becomes resistant to Vpx-induced degradation [293,294]. Because Cul4A and DCAF1 are also nuclear proteins, which can induce polyubiquitylation of proteins associated with chromatin [335], it is possible that Vpx loads SAMHD1 onto the Cul4A/DCAF1 E3 ligase complex in the nucleus. However, it is still inconclusive whether SAMHD1 is degraded in the nucleus [294], or it is re-targeted to the cytoplasm for degradation [293,333].

HIV-1 does not have the capability to neutralize SAMHD1, because its Vpr does not degrade SAMHD1 and it does not encode a Vpx protein. However, an evolutionary study has uncovered that the ancestral Vpr gene had the ability to antagonize SAMHD1 before it gave rise to the Vpx gene [334]. Accordingly, Vpr proteins from several SIV strains isolated from different old world monkey species are still able to degrade SAMHD1 [294,334]. SAMHD1 may have exhibited evolutionary pressure to differentiate Vpr and Vpx, so that the two proteins have divergent functions. HIV-1 is originally from SIVcpz, whose Vpr does not have SAMHD1-degrading ability [334]. This and other factors may explain why HIV-1 replicates in macrophages at very low levels, and why it cannot infect efficiently dendritic cells [336]. In fact, by not infecting dendritic cells, HIV-1 could avoid activating a cryptic sensor, which induces type I IFNs and thus activates an antiviral response [337]. By evading detection by this sensor, HIV-1 is able to replicate in macrophages at a low level

that is sufficient to transmit the virus to activated $CD4^+$ T cells. This covert replication strategy may help HIV-1 to establish a persistent infection in humans. In addition, although HIV-1 Vpr does not overcome SAMHD1, it may target another unknown restriction factor in human $CD4^+$ T cells, and this mechanism needs to be clarified [338-340].

MOV10

The Moloney Leukemia Virus 10 inactivated gene *MOV10* was first discovered from the Moloney murine leukemia virus (M-MLV)-carrying mouse strains (Mov mice), which have a single copy of M-MLV provirus at different loci after germline infection [341]. These MOV mice show three different levels of viral replication during development: viremic, conditional viremic, and non-viremic. The MOV10 mouse is non-viremic, because the provirus has mutations in the *gag-pol* region and does not produce infectious particles [342]. The provirus is integrated into a gene locus on chromosome 3, which encodes a 110-kDa protein. Since this protein contains three consensus elements for GTP-binding proteins, it was named gb110 [343]. Later, it was found that this protein has seven conserved helicase motifs, which classified it as a SF-1 helicase [344]. Helicases have purine nucleoside triphosphate phosphatase (ATPase or GTPase) activity, which catalyzes the separation of DNA and/or RNA duplex into single strands in an ATP-dependent reaction [345]. They may have up to seven helicase motifs (I, Ia, II, III, IV, V, and VI) and are classified into three super families (SF-1, SF-2, SF-3) and two small families (F-4, F-5) [346]. Motif I has a GxxxxGKT/S consensus and binds to phosphates; and motif II has a DExx consensus and binds to magnesium (Figure 7). These two motifs catalyze the hydrolysis of purine nucleoside triphosphate, providing energy for helicase activity. The other five motifs are more diverse, and they could contribute to RNA or DNA binding [346]. All helicases have motifs I and II, but only SF-1 and SF-2 helicases have all seven motifs [347]. MOV10 has all seven motifs, and its motif II has a DEAG fingerprint, which qualifies it as a SF-1 helicase [344]. The physiological function of MOV10 was not clear until its ortholog in *Arabidopsis*, the silencing defective gene 3 (SDE3), was found to be required for the RNA silencing pathway [348]. This activity was confirmed by another ortholog in *Drosophila*, the *Armitage* (*Armi*) gene, which is also required for the RNA silencing pathway [349,350]. In addition, MOV10 interacts with the RNA interference machinery through the Argonaute 2 (Ago2) protein in mammalian cells, which further highlights its important role in the regulation of gene expression [351,352].

Discovery of MOV10 antiretroviral activity

Because the RNA interference (RNAi) pathway defends viral infection in plants, invertebrate, and vetebrate animals [353-355], several components of the mammalian RNAi machinery have been tested for anti-HIV activity [356-360]. Among these proteins, MOV10 was consistently found to have very potent and direct anti-HIV-1 activity when it was ectopically expressed [356,358,360,361]. MOV10 additionally inhibits SIV [360], MLV [360], EIAV [358], hepatitis C virus (HCV) [362], and vesicular stomatitis virus (VSV) [363]. Thus, MOV10 has very broad antiretroviral activity, and this activity may extend to several RNA viruses.

MOV10 has a mammalian paralog, which is called MOV10-like-1 (MOV10L1). MOV10L1 shares 45% amino

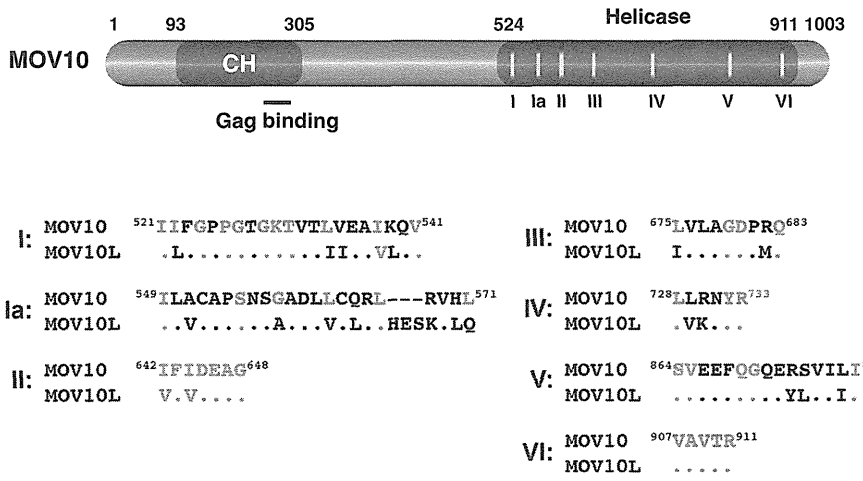

Figure 7 Schematic illustration of human MOV10 protein. Numbers indicate amino acid positions. The Cys-His-rich (CH) domain, helicase domain, and seven helicase motifs (I, Ia, II, III, IV, V, VI) are indicated. The amino acid sequences of these motifs from MOV10 and MOV10L proteins are aligned. Dots indicate identical residues, and critical residues in each motif are in orange color.

acid identity with MOV10 in the C-terminal helicase region (Figure 7), and it is specifically expressed in the mouse germ cells [364]. Knockout studies demonstrate that MOV10L1 is required for spermatogenesis by serving as one critical component of the Piwi-interacting RNA (piRNA) pathway, which specifically inhibits retrotransposon activity [365,366]. ~41% of the human genome is constituted from retrotransposons [367], including endogenous retroviruses (ERVs), long-interspersed-element 1 (LINE1), short-interspersed-elements (SINEs)/Alu, and SINE-VNTR-Alu (SVA) [368]. Like retroviruses, the ERVs have two long terminal repeats (LTRs), so they are also called LTR-retrotransposons, and the others are called non-LTR retrotranspnosons (LINE1, SINE-Alu, SINE-SVA). The LTR and LINE1 retrotransposons are strongly activated in the primary spermatocytes of MOV10L1 knockout mice, followed by death of these cells, indicating that MOV10L1 plays a critical role in genome integrity in germ cells. Indeed, MOV10 exhibits similar anti-retrotransposon activity *in vitro*, which inhibits both LTR and non-LTR retrotransposons [361,369,370]. Thus, like A3 proteins, the MOV10 antiviral activity also applies to endogenous retroviral elements. Notably, although both exogenously and endogenously expressed MOV10 proteins inhibit retrotransposon replication [361,369], the endogenous MOV10 was found unable to inhibit HIV-1 replication [361]. This puzzle needs to be solved.

Action of MOV10

The human MOV10 has 1,003 amino acids, which are translated from 20 or 21 exons in chromosome 1 (Figure 7). Its seven helicase motifs are located in the C-terminal region from residues 524–911. Notably, its N-terminal region from residues 93–305 contains a structurally exposed Cys-His-rich (CH) domain [371], which has been recently recognized as a novel class of protein-protein interaction module [372]. MOV10 decreases both the quantity and quality of the HIV-1 infectious particles in viral producer cells. MOV10 reduces HIV-1 production, possibly by decreasing Gag expression and processing, but this mechanism is still unclear [356]. In addition, MOV10 is packaged into virions and inhibits HIV-1 replication from the 2nd cycle by interfering with viral reverse transcription (Figure 1) [356,358,360]. The MOV10 packaging involves a specific interaction with Gag. MOV10 interacts with Gag in the NC region, probably via the basic linker domain [371]. On the other hand, Gag binds to the MOV10 CH domain via a region from amino acid 261–305 [371]. However, the CH-domain is not sufficient for packaging of the full-length MOV10 protein, and its packaging also requires the C-terminal helicase motifs [371]. Because these helicase motifs have high-affinity for RNA, unknown cellular RNAs are required for MOV10 packaging. In fact, MOV10 is packaged inside the core [360], which allows MOV10 to directly interact with viral RNA and block viral reverse transcription in the target cells. Compared to its reduction of viral production, the reduction of viral infectivity by MOV10 is more significant, leading to over 100-fold inhibition of viral replication. MOV10 also associates with retrotransposon ribonucleoprotein particles (RNPs) and inhibits their replication in a similar manner [369,370]. LINE1 produces two proteins: a 40-kDa RNA-binding protein ORF1p, and a 150-kDa ORF2p protein that has endonuclease and reverse transcriptase activities. MOV10 tightly interacts with ORF1p, which mediates its strong anti-LINE1 activity [369]. Because all these inhibitory activities require its helicase domain, MOV10 likely recognizes a common RNA secondary structure to exhibit its inhibitory effect. Unlike other restriction factors, MOV10 has not been subjected to positive selection, indicating that it may not participate into the co-evolutionary arms race with exogenous pathogens. However, its strong sequence conservation across species suggests that MOV10 may play an important role *in vivo* [369].

MicroRNAs

While the primary aim of this review is to survey protein restriction factors, one should be mindful that non-coding RNAs and RNAi activities have also been found to play increasingly significant regulatory and effector roles in eukaryotic biology. Indeed, RNAi activity is ubiquitously involved in normal and diseased physiology including cancers, metabolic disorders, and infectious diseases [373-375]. In the realm of host-virus interaction, it was originally thought that RNAi only serves host defense against viral infection in plants and invetebrate animals [376,377]; however, emerging evidence suggests that this defense also functions in mammals [353,378]. Significant findings supportive of this notion arise from evidence that the virulence of viral infection in mammals is exacerbated by a reduction in host RNAi function [348,355,379-381].

MicroRNAs (miRNAs) represent a major class of small non-coding RNAs in the human genome. Humans encode for more than 1,600 characterized miRNAs (miRbase.org). Relevant to HIV-1, many human miRNAs have been found to directly target HIV-1 sequences and to attenuate virus replication in cells. These include miR-28, miR-29a, miR, miR-125b, miR-150, miR-223, miR-382, miR-133b, miR-138, miR-149, and miR-326 [382-388]. Other cellular miRNAs have also been shown to indirectly target factors such as PCAF and cyclin T1 that are needed by HIV-1 to replicate [355,389,390]. In this manner, these miRNAs can indirectly repress HIV-1 replication in cells [391]. MiRNA-repression of the intracellular replication of mammalian viruses appears to be a common theme; indeed, an increasingly large number of published reports document the suppression by

various human miRNAs of Epstein Barr Virus (EBV) [392,393], Kaposi's sarcoma Herpes virus (KSHV) [394], hepatitis B virus [395,396], coxsackie virus [397], human papilloma virus [398], amongst others. This list of examples promises to grow longer over time.

In view of the above, how do viruses counter the host cell's RNAi restriction? In principle, there are several means that viruses can employ, including the shielding of viral genomes from access by RNAi, the mutation of viral sequences to evade RNAi, the encoding of viral RNAi suppressor moieties, and changing the miRNA expression profile of the infected cells [399]. For HIV-1, several published reports have shown that the virus can explicitly alter the cellular profile of miRNA expression [400,401], presumably to benefit viral replication. Other reports have implicated that the HIV-1 Tat protein [402-407] and the viral TAR RNA [408] serve RNAi-suppressing activities. Tat, like the HTLV-1 Rex protein, likely suppresses RNAi through sequestration of RNA via its basic amino acids [409]. Nevertheless, the RNAi-suppressing activity of Tat appears to be modest and has been difficult to measure in some assays [410].

Several HIV-1 encoded small non-coding RNAs (ncRNAs) have also been identified in infected cells using next generation pyrosequencing; and the over expression of these ncRNAs represses viral replication [411-413]. HIV-1, like HTLV-1 [414,415], also expresses antisense non-coding RNAs [416,417]. Currently, we do not fully understand the roles of these non-coding HIV-1 RNAs. The clarification of their biological functions in virus replication represents an important future challenge for investigators.

Conclusions

Over the past decade much progress has been made in generating insights into HIV-1 virus-host interactions. In this respect, several hundred host dependency factors have been identified that act positively to regulate HIV-1 replication in human cells [418-423]. As a counterweight to the study of positive host factors, it is also instructive and important to appreciate the role that restriction factors play in moderating HIV-1 replication. Our survey here of several examples of HIV-1 restriction factors is not intended to be complete or fully comprehensive. We hope the review provides a platform that introduces this topic to those readers interested in further studies of viral restriction factors.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YHZ, KTJ, and KT wrote different sections of this manuscript. YHZ and KT prepared the figures. All authors read and approved the final manuscript.

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Review Article Open Access

New Paradigm of T cell Signaling: Learning from Malignancies

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Abstract

T cells are key mediators of cell-mediated immunity. Their functions and proliferation result from T cell-specific receptor signaling (TCR/CD28) that activates the NF-κB, NFAT, Ras-MAPK, and PI3K-Akt pathways. Their development and activation also involve a complex array of signaling pathways that regulate gene expression networks, including signaling of mTOR, Notch, Wnt, Hedgehog, TGF-β, and toll-like receptors. Furthermore, recent discoveries have provided two molecular hallmarks of potential generality: miRNA patterns and polycomb-mediated epigenetic reprogramming, which can strongly coordinate the balance between molecular networks in lymphocytes. Their deregulation apparently causes T cell disorders, such as T cell acute lymphoblastic leukemia (T-ALL), and human T cell leukemia virus (HTLV-1)-induced adult T cell leukemia (ATL). This review continues with a description of our understanding of crosstalk among the signaling pathways, which contribute to the highly orchestrated development of T cell fate specification under both normal physiological and pathological conditions.

Introduction

T cells use diverse genetic programs to direct the development of distinct lineages and the generation of several effector functions required for innate and adaptive immunity. The molecular networks in T cells are strictly controlled by the input from intercellular and extracellular signals. T cell activation is basically achieved by antigen-presenting cells (APCs). Antigen recognition by and signaling through the T cell receptor (TCR) are crucial processes for T cells and provide the molecular underpinning for the specificity and execution of immune system responses.

TCR-mediated signaling pathways are the bare bones of T cell activation. However, several other signaling pathways are intimately associated with T cell development, activation, and homeostasis. In addition, newly emerging molecular characteristics have been proposed on the basis of studies of normal T cells and T cell malignancies. This new paradigm includes miRNA-mediated gene regulation and epigenetic reprogramming.

In this review, by dissecting each signaling pathway, we summarize the molecular hallmarks of T cells. We first briefly introduce the fundamental molecular mechanisms involved in T cell activation and gene expression related to T cell functions [1,2]. These signaling pathways are also involved in T cell development and disorders. We next discuss the newly emerging signaling pathways involved in T cell biology. Genetic and physiological studies have indicated that the pathways primarily identified in the areas of development, regeneration, and innate immunity are also closely associated with T cell functions and their appropriate development. Finally, we discuss regarding a conceptual advance, i.e., crosstalk between several signaling pathways.

The complexity of signaling networks within T cells confers robustness to specific and diverse gene expressions and biological functions. The complex signaling regulation that is involved within different environments has been suggested from investigations in immature and mature T cell malignancies, including T cell acute lymphoblastic leukemia (T-ALL) and adult T cell leukemia/lymphoma (ATL).

Proximal Signaling of TCR-mediated T cell Activation

T cells are instructed to use their developmental and effector programs through stimulation of the TCR complex and costimulatory molecules, which are presented by professional APCs, e.g., macrophages, dendritic cells, and B cells. TCR signaling is initiated by CD3 phosphorylation. The CD3 proteins comprise a series of dimers, including γε, δε, and ζζ, which are associated with a single TCRαβ heterodimer (Figure 1). After the recognizing cognate complexes of foreign peptide and self major histocompatibility complex (MHC) class II (pMHC) molecules, TCR/CD3 affects signaling cascades, including phosphorylation of proximal TCR components, Ras–mitogen-activated protein kinase (MAPK) signaling, activation of nuclear factor κB (NF-κB) by protein kinase C θ (PKCθ), and Ca^{2+} flux-mediated signaling [1]. In response to stimulation, signaling through these mediators is integrated with input from other signaling pathways. This provides the biological output after TCR recognition of a ligand.

CD3 phosphorylation is regulated by the local balance of the tyrosine kinase Lck, which is associated with the monomorphic coreceptors CD4 and CD8 and phosphatases in the TCR signaling complex. Functional key motifs within CD3ε, γ, δ, and ζ chains, designated immunoreceptor tyrosine-based activation motifs (ITAMs), are phosphorylated by Lck after TCR ligation, which is an early, prerequisite step for TCR-directed T cell activation. Importantly, conformational changes in CD3 molecules are directly induced by CD3 phosphorylation after pMHC–TCR ligation. These conformational changes in CD3ε and CD3ζ make ITAMs more accessible for phosphorylation and are required for efficient T cell activation.

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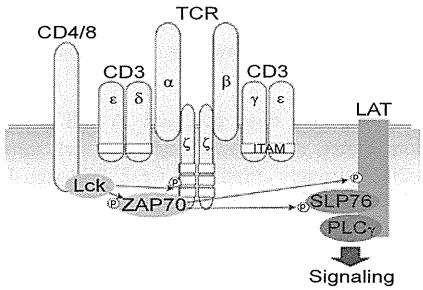

Figure 1: TCR/CD3-mediated proximal signaling. After engagement of TCR/CD3 complex, conformation change and following phosphorylation cascade is induced. Activated PLCγ coordinates the signaling required for T cell activation.

Phosphorylated CD3ζ (and other ITAM-containing proteins) provides recruitment sites of the 70-kDa phosphoprotein ZAP-70, a Syk kinase family member. That is, TCR engagement by pMHC leads to the activation of Src family PTK, such as Lck, which results in ITAM phosphorylation and ZAP-70 recruitment (Figure 1). The tandem SH2 domains of ZAP-70 are engaged by the phosphorylated ITAMs of CD3ζ, where in turn ZAP-70 is activated by Lck-mediated phosphorylation.

Among the most important ZAP-70 targets are the transmembrane adapter protein linker for the activation of T cells (LAT) and the cytosolic adapter protein Src homology 2 (SH2) domain-containing leukocyte phosphoprotein of 76 kDa (SLP-76). Phosphorylated LAT in turn serves as a docking site to which a number of signaling proteins can bind. These two adapters form the backbone of a complex that includes several effector molecules to allow for the activation of multiple signaling pathways. Proteins that are incorporated in these assemblies include other scaffold molecules, such as Grb2, Gads, and enzymes like phospholipase C γ1 (PLCγ1), and phosphoinositide 3-kinase (PI3K). The coordination of these interactions and the ensuing signaling result in a stable, but dynamic, zone of contact between APCs and T cells; this zone has been designated the immunological synapse (IS). IS has become a paradigm for studying the signals exchanged between the two cell types.

A lipid raft is a microdomain within the plasma membrane that is rich in cholesterol, glycosphingolipids, and sphingomyelin. Lipid rafts accumulate at IS. Initial TCR activation and an early phosphorylation cascade precedes the formation of IS, which not only provides the sustained signaling required for gene regulation in T cells but may also control the eventual halt of the signaling pathways. It is important that the ability of a kinase to support TCR signaling critically depend on its lipid modification. Indeed, the accumulation of lipid rafts and Lck in these areas can accelerate increased phosphorylation. Within a lipid raft, the signaling backbone established by LAT and SLP-76 coordinates downstream signaling by controlling PLCγ1 activity. However, a large amount of data suggests that the formation of this complex is more complicated. For its optimal activity, PLCγ1 directly binds to SLP-76, LAT, and Vav1 as well as to its activating kinase Itk. Lck, which binds to CD4/8 and activates ZAP-70, also phosphorylates Itk. Itk in turn phosphorylates PLCγ1. Activated PLCγ1 then hydrolyzes the membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP2), producing the second messengers inositol trisphosphate (IP3) and diacylglycerol (DAG), that are essential for T cell function (Figure 2).

TCR-mediated Gene Regulation via NFAT, NF-κB, and MAPK Cascades

TCR engagement results in the induction of expression of numerous genes required for T cell activation by triggering several signaling pathways. These pathways are described follows. Each of them acts specifically, but collaboratively, during T cell activation process.

Ras–MAPK pathway

TCR-induced DAG production results in the activation of two major key molecules: Ras and PKCθ. DAG recruits both RasGRP and PKCθ to the plasma membrane. Activated Ras, a guanine nucleotide-binding protein, initiates the MAPK phosphorylation and activation cascade by activating of the serine/threonine kinase Raf1 [1]. Raf1 is a MAPK kinase kinase (MAPKKK) that phosphorylates and activates MAPK kinases (MAPKKs), including MEK. This in turn phosphorylates and activates MAPK extracellular signal-regulated kinase 1 (Erk1) and Erk2 (Figure 2) [3]. Erk kinase activity is regulated by its phosphorylation. The transcription factor Elk1 is one of downstream molecule of Erk1 and induces Fos expression. Consequently, the activation of the activator protein-1 (AP1) complex constituted by Jun and Fos is sustained by the DAG–Ras pathway. Jun is activated via the Vav1–Rac pathway. In addition, Erk activation results in phosphorylation of signal transducer and activator of transcription 3 (STAT3) and Lck.

PKCθ-dependent NF-κB and AP1 pathways

Increased cellular concentrations of DAG also activates NF-κB signaling through PKCθ, a PKC family member that contains a lipid-binding domain specific for DAG. This domain is required for recruiting PKCθ to the lipid raft after TCR engagement. Moreover, Lck-mediated PKCθ phosphorylation appears to contribute to conformational changes required for binding of PKCθ to the lipid membrane. This concentration of PKCθ within the lipid raft enhances binding of PKCθ to DAG and results in PKCθ activation.

NF-κB plays its most important and evolutionarily conserved role in the immune system by regulating genes involved in inflammatory and immune responses as well as in some aspects of cell growth, survival and differentiation [4]. Both canonical (classical) and noncanonical (alternative) activation of this pathway in T cells are intimately involved in TCR-mediated T cell activation. PKCθ-mediated NF-κB induction has been shown to be selectively mediated by IKKβ that is

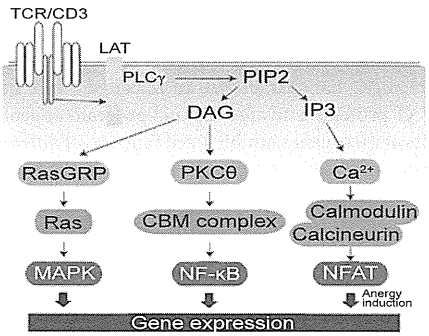

Figure 2: TCR-mediated signaling cascades. Engagement of TCR consequently induces expression of numerous genes required for T cell activation by triggering several signaling pathways, including Ras–MAPK pathway, NF-κB pathway, and NFAT pathway. Each of them specifically but collaboratively acts during T cell activation or anergy induction processes.

associated only with the canonical pathway, whereas noncanonical activation in T cells remains elusive. One study showed that MAP3K14 (also called NF-κB-inducing kinase; NIK), which is an essential factor for the noncanonical NF-κB cascade, was required for complete T cell activation [5].

Following TCR stimulation, PKCθ regulates the assembly of a CBM complex (CARMA1/Bcl10/MALT1) through its phosphorylation of CARMA1, which is required for CARMA1 oligomerization and association with Bcl10 [6]. MALT1 physically binds to Bcl10 and induces polyubiquitination of IKKγ, the regulatory subunit of the IKK complex, via activation of the E3 ubiquitin ligase TRAF6. K63 polyubiquitination appears to have a role in IKKγ activation, which results in IκB phosphorylation by IKK catalytic subunits and subsequent IκB degradation. Nuclear localization of NF-κB heterodimers induces gene activation (Figure 2). NF-κB activation is also regulated by costimulatory signaling (described below).

The original analysis of PKCθ knockout mice revealed that two transcription factors, NF-κB and AP1, are targets of PKCθ in TCR/CD28-costimulated T cells [7-9]. The pathway leading from PKCθ to AP1 activation is less clearly understood. One study has reported that SPAK, a Ste20-related MAP3K, is a direct substrate of PKCθ in the pathway leading to AP1, but not NF-κB, activation [10]. SPAK is most likely a mediator of PKCθ signals leading to AP1 activation, but intermediates downstream of SPAK in AP1 activation remain to be identified and functionally characterized.

Ca^{2+}-dependent NFAT pathway

PLCγ1-mediated IP3 generation stimulates Ca^{2+} permeable ion channel receptors (IP3R) located on the endoplasmic reticulum (ER). This leads to the release of ER Ca^{2+} stores into the cytoplasm. Because Ca^{2+} ions are universal second messengers in eukaryotic cells, TCR-induced increases in intracellular Ca^{2+} levels result in the activation of Ca^{2+}- and calmodulin-dependent transcription factors, including phosphatase calcineurin and the Ca^{2+}/calmodulin-dependent kinase (CaMK). Activated calcineurin then dephosphorylates members of the nuclear factor of activated T cells (NFAT) family, which results in their translocation to the nucleus. In the nucleus, NFATs form cooperative complexes with various other transcription factors, and this results in differential gene expression patterns and functional outcomes, depending on the context in which the TCR signal is delivered [11]. AP1 proteins are the main transcriptional partners of NFAT during T cell activation. Cooperation between NFAT and AP1 integrates two of the main signaling pathways i.e. the Ca^{2+} signaling and RAS-MAPK pathway. The NFAT-AP1 cooperation during T cell activation is responsible for a specific pattern of gene expression, which induces the functional changes that characterize an activated T cell. In the absence of AP1, NFAT proteins activate a distinct program of gene expression. The products of these genes inhibit T cell function at different levels and induce a status of T cell unresponsiveness, which is one of processes to induce the immune tolerance [12]. Thus, NFAT proteins control two opposing aspects of T cell function i.e. activation and anergy [13] (Figures 2 and 3).

Costimulation Signaling

A most important gene induced by TCR-mediated signaling is *IL-2*, which can activate STAT pathways. However, full induction of IL-2 expression is not achieved by TCR signaling alone, i.e., a nonresponsive state (anergy) exists in which T cells are refractory to restimulation. Additional engagement of other cell surface receptors provides and integrates signals required for anergy avoidance and productive T cell activation. Although many cell surface receptors can participate in costimulation signaling, CD28 provides more robust signals than other costimulatory molecules.

Weak TCR ligation does not lead to cell proliferation and differentiation; rather, it results in anergy or cell death. However, if engaged, CD28 strongly amplifies a weak TCR signal. In contrast, triggering of CD28 alone results in the transient expression of only a few genes and has no obvious biological consequences. A question has arisen whether TCR and the coreceptors induce separate signaling pathways (qualitative model) or whether the signaling pathways triggered by both receptor systems are entirely overlapping (quantitative model) [14].

Many studies have indicated that the signals generated by CD28 ligation have no unique effects. A microarray study showed that TCR-induced expression of thousands of genes in primary T cells was amplified (or suppressed) to varying degrees by CD28 costimulation, but that no new gene was induced by CD28 costimulation [15]. Indeed, all of the factors identified as components of the CD28 signaling pathway are those that are implicated in TCR-mediated signaling. These include PI3K, the Tec family of PTKs, such as Itk, Vav1, and the serine/threonine kinase Akt (also known as PKB), and NF-κB signaling.

CD28-mediated PI3K–Akt pathway

PI3K recruitment is a key event for coupling CD28 to several signaling pathways. Following engagement of CD28 with its ligands CD80 or CD86 expressed on APCs, the p85 regulatory subunit of PI3K associates with the phosphorylated cytoplasmic tail of CD28. This regulatory subunit recruits the p110 catalytic subunit of PI3K, which can convert PIP2 to PIP3 in the cell membrane. Then, the locally generated PIP3 serves as a docking site for the PH domains of PDK1 and its target Akt (Figure 3).

Akt phosphorylates multiple proteins involved in numerous cellular responses. Activated Akt enhances the nuclear translocation of NF-κB by associating with CARMA1 and facilitating the assembly of the CBM complex, a step critical for NF-κB activation [16]. In addition, one well-known Akt target is GSK-3, a serine/threonine kinase that influences the nuclear export of NFAT as well as the Wnt pathway. Thus, Akt-mediated GSK-3 inactivation might be a pathway responsible for prolonged NFAT nuclear localization and thus *IL-2* transcription following CD28 costimulation (Figure 3).

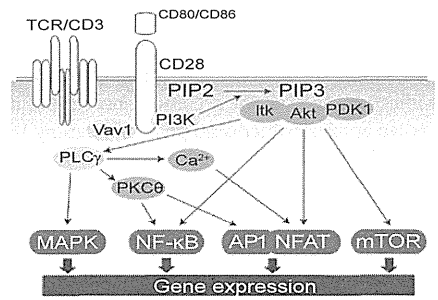

Figure 3: Costimulation signaling. Additional engagement of cell surface receptors such as CD28 provides and integrates signals required for anergy avoidance and productive T cell activation. The signaling generated by CD28 ligation has no unique effects but enhances the T cell signaling, including pathways of PI3K–Akt–mTOR, NF-κB, NFAT-AP1, and MAPK.

CD28/PI3K-generated PIP3 also provides a docking site for the PH domain of Itk. As described above, Itk associates with the TCR downstream complex consisting of LAT/SLP-76/Gads/PLCγ1 (Figure 3). Importantly, the localization and activation of this signaling complex depends on PI3K-generated PIP3.

A novel signaling mechanism has been suggested where by CD28 regulates cAMP degradation in T cell rafts through the recruitment of an Akt/β-arrestin/PDE4 complex [17]. CD28/PI3K-mediated PIP3 production recruits this supramolecular complex to lipid rafts, with recruitment occurring through the Akt PH domain.

Thus, although many of these pathways are activated by TCR ligation alone, the magnitude and maintenance of T cell activation signaling required for an appropriate response appear to be considerably regulated by costimulatory signals. This suggests that CD28 engagement primarily functions in a quantitative rather than a qualitative change in T cell activation.

CD28-mediated NF-κB pathway

Another important CD28 mediator is NF-κB signaling. CD28/PI3K generates the second messenger PIP3 that binds to various proteins harboring PH domains, including PDK1 and Akt. At present, we know that Akt is not an essential component of NF-κB signaling, at least in T cells. Akt appears to function as a rheostat; Akt can gently modulate the strength of the NF-κB cascade through its interaction with CARMA1 (Figure 3) [16]. Of note, PDK1, which is recruited to newly generated PIP3, can efficiently bind to both PKCθ and CARMA1 [18]. CD28 facilitates NF-κB activation by regulating the recruitment and phosphorylation of PDK1, which are necessary for the efficient binding of PDK1 to PKCθ and CARMA1 and thus for NF-κB induction. Furthermore, TCR/CD28 confers the noncanonical NF-κB activation in naïve T cells [19]. Taken together, NF-κB signaling is one of the major signaling pathways regulated by costimulation. Full activation of the NF-κB pathway requires CD28-mediated costimulatory signals in T cells.

CD28–Vav1 pathway

Vav1 is a guanosine exchange factor (GEF) for several small GTPases, including RAC1, RAC2, and RHOG. Vav1 controls several biochemical processes, such as those involved in cytoskeletal rearrangements. In addition, Vav1 strongly amplifies CD28-mediated costimulation-dependent activation of NFAT, NF-κB, CD28 response element, and JNK [20,21].

T cell development is markedly reduced in Vav1-deficient mice [22]. Of note, a CD28 mutant, which is unable to activate Vav1, does not alter TCR-directed ZAP-70 and LAT phosphorylation, but it does affect SLP-76, PLCγ1, and Itk phosphorylation and Akt activation [23]. This phenotype, which is remarkably similar to that of Vav1-deficient T cells [24], supports a role for Vav1 as a crucial signaling effector of CD28 costimulation.

TCR/CD28 and MAPK pathways

TCR engagement activates the ERK, JNK, and p38 cascades in T cells. With regard to costimulation effects, one study demonstrated that T cell activation involves these three MAPK cascades [25]. pMHC ligation directly activates the Ras–MEK–ERK pathway, as described above. JNK activation stimulated by TCR engagement requires CD28 coligation in T cell clones. However, JNK activation is not observed in mouse primary T cells. TCR and CD28 synergize after coligation to elicit enhanced p38 MAPK activation. p38 MAPK, but not JNK, is involved in signal integration during costimulation of naive mouse primary T cells. Indeed, the p38 MAPK inhibitor SB203580 blocks CD28-dependent proliferation and IL-2 production in human T cells [26]. We currently do not know how p38 modulates TCR signaling and IL-2 production.

Studies using both pharmacological and genetic manipulations have provided evidence that p38 is a crucial mediator of T cell development, activation, and inflammation [27]. In addition, p38α function in T and B cells has been addressed using the RAG-deficient blastocyst complementation method. Surprisingly, p38α-deficient T and B cells developed in normal numbers and proliferated normally in response to various stimuli, such as antigen–receptor ligation [28]. Moreover, mice that lack p38β appear to be completely normal with no obvious defects in T cell development or LPS-induced cytokine production [29]. To reconcile the genetic and pharmacological data with the paucity of observable abnormalities in p38 isoform-specific knockouts, further characterizations and detailed analyses of the p38 pathway in both normal T cells and T cell malignancies will be necessary.

Signaling Pathways Linking to T cell Activation, Development, and Disorder

In addition to TCR/CD28 engagements, several other signaling inputs participate in the regulation of T cell fates. These comprise pathways responsible for the development and differentiation of several cell types. Of note, deregulation of these signaling pathways lead to T cell disorders.

NF-κB signaling

In addition to TCR engagement-mediated NF-κB activation, pathological studies have strongly demonstrated that NF-κB activation is often sustained in T cell disorders. ATL cells show strong, constitutive NF-κB activation that contributes to their prolonged survival, proliferation, and invasiveness [30]. In particular, human T cell leukemia virus type 1 (HTLV-1) Tax is an intracellular stimulator of IKK. This stimulation is based on the physical interaction between Tax and IKK, which leads to the persistent activation of NF-κB-mediated transcription. Formation of the Tax/IKK complex relies on the physical interaction between Tax and the IKK regulatory subunit IKKγ. The Tax–IKKγ interaction is required for recruiting Tax to IKK catalytic subunits and for Tax-mediated IKK activation (Figure 4) [31].

In leukemic cells in which Tax is not expressed, a noncanonical NF-κB cascade appears to be important for the cellular characteristics of ATL. Both the canonical and noncanonical NF-κB pathways are persistently activated because NIK is aberrantly expressed in ATL cells [32]. NIK plays a central role in noncanonical NF-κB signaling through IKKα phosphorylation [33], and its constitutive expression leads to aberrant NF-κB activation in various malignancies, including B cell lymphoma, multiple myeloma, breast cancer, pancreatic cancer, and ATL [30].

Recently, we identified a novel molecular link between NF-κB activation and miRNA deregulation. Comprehensive gene expression analysis and *in vitro* experiments showed that miRNA-31 (miR-31) could regulate NIK expression through the 3′ untranslated region (UTR) in several cell types. In ATL cells, miR-31 expression was genetically and epigenetically silenced, which in turn induced constitutive NF-κB activation through NIK expression (Figure 4) [34]. Because current evidence clearly indicates that miR-31 dominates NF-κB activity in T cells, manipulating cellular miR-31 levels may be a novel molecular approach to reduce NF-κB activity and induce cellular apoptosis.

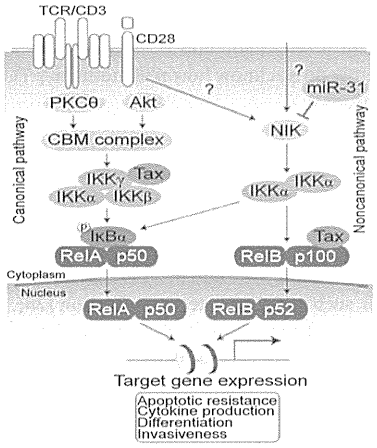

Figure 4: NF-κB signaling in T cell. Canonical and noncanonical pathways contribute to gene expression required for apoptotic resistance, inflammatory cytokine production, appropriate differentiation, and invasiveness. In HTLV-1 infected cells, viral protein Tax binds and drastically activates both pathways. In transformed leukemic cells, loss of miR-31 leads to NIK accumulation and persistent NF-κB activation.

Why is NF-κB signaling important for ATL cell survival? One of the target genes is Bcl-xl, which is expressed when NF-κB is activated. In HTLV-1-infected cell lines, Bcl-xl is expressed through the Tax–NF-κB pathway. Interestingly, fresh ATL samples exhibit Bcl-xl overexpression. Given that Bcl-xl is a principal anti-apoptotic protein as a Bcl-2 family member, persistent Bcl-xl expression is one of the molecular means to resist apoptosis, which may contribute to clinical chemoresistance. Indeed, inhibition of the NF-κB pathway by NIK depletion leads to impaired Bcl-xl expression and apoptotic death of ATL cells [34].

Because prevention of NF-κB activation showed good results in a xenograft model of cell lines with and without Tax [30], molecular targeting therapy based on the NF-κB pathway is a promising new treatment for ATL. Of note, we found that specific inhibition of NF-κB by DHMEQ could also remove virus-carrying cells from carrier peripheral blood mononuclear cell (PBMC) samples [35].

mTOR pathway

The signaling pathway target of rapamycin (TOR) is at the intersection between cell growth and starvation. The evolutionarily conserved kinase mammalian TOR (mTOR; officially known as the mechanistic target of rapamycin) controls cell growth and metabolism-related response to environmental inputs by regulating gene expression, which has been implicated in disease states, such as cancer, metabolic diseases and ageing. In T cell regulation, mTOR signaling is also involved in immune signals and metabolic cues for the proper maintenance and activation of T cells. Under resting conditions, mTOR signaling is strictly controlled by multiple inhibitory mechanisms, which enforces normal T cell homeostasis. T cell activation through antigen recognition triggers mTOR activation, which in turn influences the differentiation patterns of these cells.

mTOR, which belongs to the family of PI3K-related protein kinases (PIKK), is a conserved serine/threonine kinase and plays a central role in the regulation of cell growth and metabolism [36]. Diverse environmental signals, such as nutrients and growth factors, deliver their signaling inputs to the PI3K–Akt axis. Many upstream signals activate the mTOR complex 1 (mTORC1) via the GTP-loaded small GTPase RHEB. The activated PI3K–Akt pathway phosphorylates the Thr1462 residue of tuberous sclerosis 2 (TSC2), which in turn inhibits the TSC1/2 complex. Because RHEB is tightly regulated by the TSC1/2 complex, TCR/CD28 engagement activates RHEB/mTORC1 via the PI3K–Akt pathway. Recent studies have shown that RHEB deficiency in T cells reduced mTORC1 activation in response to TCR stimulation [37]. In addition, loss of TSC1 disrupts the TSC1/2 complex and enhances basal and TCR-induced mTORC1 activity [38,39]. Therefore, these results suggest a crucial role for the TSC–RHEB axis in T cell responses.

TCR engagement can activate both mTORC1 and mTORC2 within minutes. The strength of mTOR activation appears to be directly correlated with the duration of T cell–APC interaction and the cognate antigen dose. It should also be noted that mTOR activity is further conferred by costimulatory signals. CD28-mediated costimulation is a major driving force for the PI3K–AKT axis (described above), which in turn upregulates TCR-induced mTOR activity to facilitate productive T cell activation (Figure 5) [40,41]. In addition to CD28, another costimulatory receptor, OX40, which is a member of the tumor necrosis factor receptor (TNFR) family, assembles a signaling complex by recruiting PI3K–AKT to augment TCR-dependent Akt signaling; this may also affect mTOR signaling in T cells [42].

Several genetic studies have strongly suggested that the mTOR pathway is closely associated with T cell differentiation and homeostasis [43]. In particular, $CD8^+$ T cell differentiation is strictly regulated by mTOR signaling [44]. In addition, mTOR signaling appears to be involved in T helper (Th) cell differentiation and proliferation [43]. In sum, mTOR dictates the cell fate decisions of effector and regulatory T cells.

A common hematological malignancy, T-ALL, frequently harbors activating mutations in *NOTCH1* and/or loss-of-function mutations in a gene encoding phosphatase and tensin homolog deleted on chromosome 10 (PTEN). PTEN plays critical roles in cell growth, migration, and death because it can inhibit the PI3K–Akt pathway by catalyzing PIP3 dephosphorylation. It is noteworthy that both of these mutations can activate mTOR signaling, which suggests a pivotal role for mTOR in T-ALL development. Taken together, mTOR-mediated T cell fate decisions are of particular importance because of the unique functions of the mTOR pathway. Recent experimental advances have established that mTOR is a fundamental determinant of T cell homeostatic and functional fates. In addition, therapeutic targeting of mTOR may have beneficial effects for treating T cell disorders.

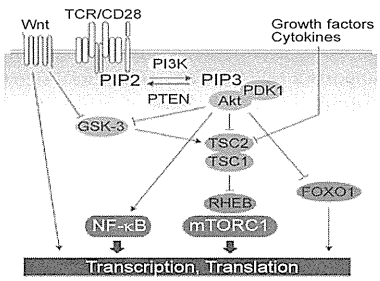

Figure 5: PI3K–Akt–mTOR axis. After TCR/CD28 stimulation, activated PI3K enhances phosphorylation of PDK1 and Akt. The Phosphorylated Akt in turn inhibits tumor suppressor TSC2, resulting in activation of mTORC1. In addition, Akt supports NF-κB signaling through CBM complex.

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Notch pathway

Notch proteins are cell-surface receptors and their expression is widely conserved in numerous species. It has been shown that Notch signaling is essential for T cell lineage development, thymocyte survival, and proliferation of T cell progenitors [45]. In addition, Notch signaling has been extensively studied in T-ALL because several lines of genetic evidence highlight the Notch signaling cascade as a central player in T-ALL pathogenesis [46].

Notch proteins are synthesized as a single polypeptide (approximately 300 kDa). After intracellular modifications that include fucosylation, glysocylation, and cleavage, a Notch heterodimer associates with the plasma membrane. Signaling is triggered by the interaction of Notch with Delta-like ligands (DLLs) or Jagged ligands on the surface of instructing cells. This ligation induces proteolytic cleavage of the Notch receptor by disintegrin and metalloproteinase (ADAM) and mono-ubiquitination of the intracellular portion of the transmembrane Notch fragment. This final cleavage leads to the release of the Notch intracellular domain from the plasma membrane and its translocation to the nucleus.

CBF1/suppressor of hairless/Lag1 (CSL) represses transcription of Notch target genes. Following activation by Notch, CSL is converted into a transcriptional activator and activates the transcription of the same genes. Intracellular Notch displaces the corepressors from CSL and recruits coactivators, such as Mastermind-like 1 (MAML1), to activate the expression of target genes (Figure 6). Intracellular Notch is then degraded by a polyubiquitination–proteasome pathway.

A landmark study published in 2004 changed our perspectives dramatically by showing that more than 50% of T-ALL cases harbored Notch1 mutations, which resulted in the hyperactivation of the Notch pathway. This finding implicated Notch1 has a very important role in the pathogenesis of T-ALL [47]. This suggests that Notch likely interacts with several important cellular pathways and can cooperate with other oncogenes during leukemogenesis.

Although the importance of Notch signaling activation in T-ALL is well established, the detailed molecular mechanisms by which NOTCH1 induces T cell transformation remain unclear. The best-characterized direct target genes are the bHLH transcriptional repressor Hes1 and the transcription factor c-Myc. Recently, Hes1 was shown to be a key regulator in the induction and maintenance of T-ALL. Notch-mediated c-Myc expression is also crucial for maintaining T-ALL.

Recently, activating mutations in Notch were identified in more than 30% of ATL patients [48]. Of note, compared with the activating frameshift mutations observed in T-ALL, ATL showed single substitution mutations activating the Notch pathway. These gene mutations could reduce CDC4/Fbw7-mediated degradation, which resulted in stabilization of the intracellular NOTCH1. They also resulted in Hes1 expression in ATL patient samples. In addition, γ-secretase inhibitors reduced tumor cell proliferation and tumor formation in ATL-engrafted mice. Collectively, these findings suggest that activated Notch may be important for ATL leukemogenesis.

There is mounting evidence that Notch signaling is also an important pathway for mediating cell fate decisions in developing thymocytes and peripheral T cells. Strong Notch signaling restricts the multilymphoid progenitors of the T cell lineage and promotes thymocyte development [49]. Results from several studies support a role for Notch in the generation of single-positive cells from double-positive precursor thymocytes [50].

Notch proteins are now emerging as potentiators of TCR/CD28 signaling in mature T cells. Some studies have confirmed the roles for Notch receptors in T cell activation, proliferation, and cytokine production. Pharmacological inhibition of the Notch pathway in $CD4^+$ and $CD8^+$ T cells significantly inhibited their proliferation and IFNγ production after TCR stimulation [51]. In addition, Notch signaling was shown to be involved in a positive-feedback loop of IL2–IL2R that regulated T cell proliferation [52]. Important pathways activated through Notch1 signaling include the PI3K–Akt and mTOR signaling cascades. In addition, NF-κB signaling, which can be activated through TCR/CD28 signaling, appears to be sustained by the Notch pathway. These details are discussed in a later chapter.

Wnt pathway

Wnt signaling is subject to strict molecular control. Thus, deregulated Wnt signaling has been implicated in the development of several malignancies, including the leukemias and lymphomas [53]. To date, at least three different Wnt pathways have been identified: the canonical Wnt pathway, which involves β-catenin and the T cell factor (TCF)/lymphocyte-enhancer-binding factor (LEF) family; the planar cell polarity pathway; and the Wnt/Ca^{2+} pathway. Among these, the canonical (Wnt/β-catenin) pathway is primarily involved in T cell development and proliferation [54].

One important study demonstrated that a T cell-specific defect in Wnt signaling by deletion of β-catenin impaired T cell development at the β-selection checkpoint, which resulted in a decrease in splenic T cells. In addition, β-catenin appeared to be a target of TCR signals in thymocytes and mature T cells. These results indicate that β-catenin-mediated signals are required for normal T cell development [55].

TCF1 is highly expressed in T cells. A recent study showed that β-catenin expression was stabilized after TCR-mediated T cell stimulation, resulting in the upregulation of TCF1-dependent gene expression in T cells [56]. It also suggested that TCF1 initiated Th2 differentiation of activated $CD4^+$ T cells by promoting GATA-3 expression and suppressing IFN-γ expression. In addition, during T cell development, TCR signaling was shown to stabilize β-catenin and regulate the response to αβTCR engagement [57]. In sum, several genetic studies have suggested that the canonical Wnt pathway participates in T cell development. In $CD8^+$ T cells, activation of Wnt/

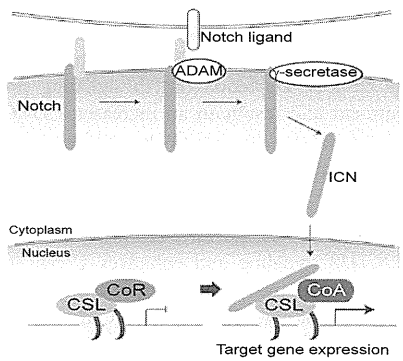

Figure 6: Notch signaling. After intracellular modifications, the Notch heterodimer associates with the plasma membrane. Signaling is triggered by the interaction with Notch ligands, which induces proteolytic cleavage of the Notch and leads to the nuclear translocation of the Notch intracellular domain (ICN). The intracellular Notch displaces the co-repressors (CoR) from CSL and recruits co-activators (CoA) to activate the expression of target genes.