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Signal Transduction via the T cell Antigen Receptor in naïve and effector/memory T cells

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Abstract

T cells play an indispensable role in immune defense against infectious agents, but can also be pathogenic. These T cells develop in the thymus, are exported into the periphery as naïve cells and participate in immune responses. Upon recognition of antigen, they are activated and differentiate into effector and memory T cells. While effector T cells carry out the function of the immune response, memory T cells can last up to the life time of the individual, and are activated by subsequent antigenic exposure. Throughout this life cycle, the T cell uses the same receptor for antigen, the T cell Receptor, a complex multi-subunit receptor. Recognition of antigen presented by peptide/MHC complexes on antigen presenting cells unleashes signaling pathways that control T cell activation at each stage. In this review, we discuss the signals regulated by the T cell receptor in naïve and effector/memory T cells.

Introduction

T cells are critical regulators of the mammalian immune system and express a very unique receptor that is exquisitely specific for antigen, but conventional T cells only recognize peptide antigens presented by Major Histocompatibility complex proteins (MHC) I or II presented by antigen presenting cells (APCs) (Anderson et al., 1996a). T cells undergo different stages of maturation, from antigen driven development in the thymus, to the response of naïve T cells to specific antigen in the periphery during an immune response to generate effector and memory T cells, and the response of the latter cells during antigen re-exposure. Throughout this process, they use the same TcR for signaling antigen recognition, with different outcomes for each stage of the T cell's life (Anderson et al., 1996a). This review will discuss those early signaling pathways used by the TcR upon recognition of antigen in naïve and effector/memory T cells.

Functions

The TcR is a complex receptor with 5–6 proteins, two receptor subunits that recognize antigen (αβ or γδ), and 3–4 proteins that signal (ε, δ, γ and ζ homodimers or ζ/η heterodimers, the CD3 complex)(van der Merwe and Dushek, 2011). In the thymus,

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developing T cells undergo maturation and express one of the two types of TcRs, either αβ or γδ. αβ TcR-bearing T cells represent greater than 95% of all peripheral T cells and significantly more is known about its function, and this review will address this receptor, although γδ TcRs may use similar signaling pathways (Hayes et al., 2010). Immature T cell precursors rearrange gene segments within the TcR locus, placing unique V region segments upstream of the α and β chains (to generate αβ T cells), or the γ and δ chains (to generate γδ T cells). This results in T cells bearing between $2x10^6$ and $2.5x10^8$ unique TcRs in the periphery of mouse and humans respectively (Casrouge et al., 2000, Robins et al., 2009). While these αβ proteins recognize antigen, they have a very short cytoplasmic tails and so are thought to be unable to signal on their own. Instead, they use the associated common CD3 signaling chains for this purpose. The CD3 chains contain one (ε, δ, γ) or three (ζ) Immunoreceptor Tyrosine based activation motifs (ITAMs). The combination of 4 ITAMs in ε, δ, γ, δ/ε chains and 6 in the ζ homodimers make up a total of 10 of these motifs that connect to signaling proteins inside the T cell (Guy and Vignali, 2009, Wucherpfennig et al., 2010). In the thymus, the TcR interacts with MHC proteins carrying self-antigen resulting in positive or negative selection (Kisielow et al., 1988, Anderson et al., 1996b). If this process is not well controlled, auto reactive T cells will be allowed to leave the thymus and may cause autoimmune disease (von Boehmer and Melchers, 2010). This selective event is controlled by the strength of TcR signal; strong signals lead result in negative selection and apoptosis, while weak signals result in survival and export to the periphery (Hogquist et al., 1994, Sebzda et al., 1996). In the periphery by contrast, weak TcR signals are required for maintenance of these cells, while strong signals generate an immune response (Ernst et al., 1999, Viret et al., 1999).

Cascades and Key Molecules

TcR interaction with MHC/peptide complexes on APCs results in clustering of the TcR, and it has been suggested that a single peptide/MHC molecule can serially trigger up to 200 TcRs for productive activation (Valitutti et al., 1995). The participation of co-receptors such as CD4 (on T helper cells) and CD8 (on cytotoxic T cells) are critical for binding to MHC molecules (CD4 to MHC II and CD8 to MHC I), and provide the TcR with the Src kinase Lck, which is associated with these co-receptors (van der Merwe and Dushek, 2011). Lck, and the related Src kinase Fyn initiate tyrosine phosphorylation of the CD3 ITAMs (Smith-Garvin et al., 2009a)(Fig. 1). Early signaling is accompanied by recruitment of the TcR into lipid rafts and a higher order structure referred to as a cSMAC. This is surrounded by a peripheral or pSMAC or ring of other cell surface proteins such as the integrins (also called distal or dSMAC) (Grakoui et al., 1999). The function of this cSMAC is controversial, but is thought to be involved in distinguishing the TcR signal (Alarcon et al., 2011).

Early phosphorylation of the ITAMs leads to recruitment of ZAP-70, a Syk-family non-receptor tyrosine kinase. ZAP-70 is tyrosine phosphorylated and activated by Lck, going on to phosphorylate the adaptor protein LAT (Fig. 1). Lck is negatively regulated by the balanced actions of the kinase Csk, and the phosphatases CD45 and PEP (Rhee and Veillette, 2012). ZAP-70 is regulated by the E3-ubiquitin ligase c-Cbl, which targets it for proteasomal degradation and attenuates its signal (Rao et al., 2002). The phosphorylation of LAT initiates the assembly of a ‘proximal signaling complex’ that includes LAT, which binds the adapters Grb2 and GADs. These two proteins bind to the adaptor SLP-76 (Smith-Garvin et al., 2009a). SLP-76 is phosphorylated by ZAP-70, allowing it to bind to the guanine nucleotide exchange factor Vav1 and the Tec kinases Itk and Txk/Rlk. Itk is recruited to the signaling complex via its PH domain interacting with phosphatidylinositol (3,4,5) triphosphate (PIP_3), generated at the plasma membrane by the enzyme PI3K, activated by Lck and regulated by ItpkB (Huang et al., 2007, August and Ragin, 2012). Itk is also activated by direct tyrosine phosphorylation by Lck (Gibson. et al., 1996). PLCγ is also

brought to the complex through its interaction with LAT and SLP-76 and is activated by tyrosine phosphorylation via both ZAP-70 and Itk (Smith-Garvin et al., 2009a, Schwartzberg et al., 2005). Lipids phosphorylated by activated PI3K also recruit and activate the kinase PDK, which further activates AKT/PKB via (Fayard et al., 2010). AKT/PKB is an important node that regulates multiple downstream pathways, including the activation of the transcription factors NFκB and those of the FoxO family, and in the activation of the mTOR pathway (Sheppard et al., 2012, Song et al., 2008). PI3K regulated pathways are counteracted by the lipid phosphatase PTEN (Song et al., 2012).

TcR-induced increases in intracellular calcium and the activation of MAPK pathways are critical in the activation of T cells. Phosphorylated PLCγ catalyzes the breakdown of PI4,5P to second messengers- IP_3 and DAG. Tec kinases also enhance this process by recruiting the enzyme PIP5K to the membrane, which is able to replenish PI4,5P at the site of action (Saito et al., 2003). IP_3 binds to the IP_3 receptor in the membrane of ER, resulting in the release of Ca^{2+} from the ER. This depletion of ER Ca^{2+} stores results in the opening of Ca^{2+} channels in the plasma membrane, triggered through the sensor STIM1 communicating with CRAC channels in the plasma membrane, including the Orai1 channels (reviewed in (Hogan et al., 2010)). The resulting Ca^{2+} influx leads to the activation and nuclear translocation of NFAT through calcineurin and calmodulin (Smith-Garvin et al., 2009b). DAG on the other hand activates PKCθ as well as the RAS guanine nucleotide releasing protein, RASGRP. The CARMA proteins are also recruited to ADAP (which also interacts with SLP-76), and are phosphorylated by PKCθ, along with AKT, leading to activation of the NFκB transcription factor via the PKCθ/CARMA/MALT/Bcl10/NEMO/IKK pathway (Wegener et al., 2006, Narayan et al., 2006, Blonska and Lin, 2011). RASGRP on the other hand, initiates the MAPK pathway by activating Ras, leading to Raf and ERK/MAPK. Ras can also activate JNK and p38 MAPKs downstream of the TcR (Smith-Garvin et al., 2009a). The activation of other small G-proteins by TcR signals occur in part by the guanine nucleotide exchange factor Vav, which can activate CDC42 and Rac, both of which are upstream of MAPKs JNK and p38. CDC42 and Rac, along with the actin regulators Arp2/3 and WASP, are also important for regulating actin polymerization downstream of the TcR (for review see (Andreotti et al., 2010)). This TcR regulation of F-actin and retrograde actin flow also sustains the phosphorylation of PLCγ and the release of intracellular Ca^{2+} store (Babich et al., 2012). Antigen induced TcR clusters generates SLP-76 containing signaling complexes, which emanate from activated TcRs (Seminario and Bunnell, 2008). These SLP-76 complexes forms unique microclusters within the cell that is separate from the TcR clusters, and includes LAT, Grb-2 and GADS, along with kinases ZAP-70, Itk and HPK, and other signaling mediators Vav and PLCγ (Seminario and Bunnell, 2008). These microclusters are important for activation of downstream pathways critical for activating the T cell (Seminario and Bunnell, 2008).

Activation of the mTOR pathway is another critical event during T cell activation, controlling differentiation of multiple T cell lineages (Waickman and Powell, 2012). This pathway, composed of two complexes, mTORC1 and mTORC2, is suggested to lie downstream of the kinase AKT, although exactly how mTOR is activated downstream of the TcR remains to be determined, since AKT also lies downstream of mTORC2 (Sarbassov et al., 2006, Sarbassov et al., 2005). It is likely that mTOR activation occurs via the inactivation of a negative regulator of AMPK by CAMKKβ, acting downstream of calcium signals (Anderson et al., 2008). mTOR can also be activated by nutrient sensing and cytokine signals (Russell et al., 2011), and the mTOR complexes regulate a wide range of processes including autophagy, metabolism and transcription factor expression (such as T-bet, Eomesodermin and FoxO) and function (for review see (Chi, 2012)).

Distal TcR signaling events

The early biochemical signals from the TcR leads to the activation of a number of transcription factors that play critical roles in regulating T cell responses. These transcription factors sense the activation of the MAPK pathway (such as AP1 and Egr family members), Ca^{2+} increase and accompanying PKC activation (the NFAT and NFκB family members) (Smith-Garvin et al., 2009a). Increases in intracellular Ca^{2+} results in the activation of calcineurin, which leads to activation of NFAT and enhances NFκB activation (Hogan et al., 2010). Thus early TcR induced gene expression, including cytokines and their receptors, is largely driven by transcription by AP1, Egr, NFAT and NFκB family members (Fig. 1, (Smith-Garvin et al., 2009a)). In addition, dependent on whether the T cell is $CD4^+$ or $CD8^+$, effector cell specific transcription factors such as T-bet ($CD4^+$ Th1 cells, effector $CD8^+$ T cells), Eomesodermin (Memory $CD8^+$ T cells), GATA3 ($CD4^+$ Th2 cells), Rorγt ($CD4^+$ Th17 cells), FoxO family (naïve and effector $CD4^+$ and $CD8^+$ T cells), and Foxp3 ($CD4^+$ regulatory T cells), play critical roles in the function of subsequent responses (Waickman and Powell, 2012, Chi, 2012).

TcR signaling in naïve versus effector and memory T cells

During the generation of an immune response, naïve T cells utilize TcR signals, along with other environment cues/signals, including cytokines and chemokine signals, to differentiate into effector T cells and memory T cells, the latter being responsible for responses to subsequent antigenic exposure (Farber, 2009, Curtsinger et al., 1998). Manipulation of these signals can alter the activation and development of effectors versus long-term memory T cells (Araki et al., 2009, Rao et al., 2010, Waickman and Powell, 2012). Indeed, the strength of the initial TcR signal in naïve T cells may dictate the subsequent generation of effector and memory T cell populations (Williams et al., 2008). Activation of naive T cells differs from activation of effector and memory T cells, but less is known about these differences in $CD4^+$ T cells compared to $CD8^+$ T cells. We will discuss differences in both populations based on what is currently understood, although in some cases, effector and memory T cells have not been distinguished and so we conflate discussion of the two types. In some cases, differences in activation may be due to differential expression of signaling molecules and transcription factor family members, while in other cases, the sensitivity of the TcR is increased, such that they are less reliant on some signaling pathways for their activation, or for example due to changes in avidity of the receptor in $CD8^+$ T cells (Hussain et al., 2002, Farber, 2009, Fahmy et al., 2001). While tyrosine phosphorylation of the CD3 complex is similar to that seen in naïve T cells, memory $CD4^+$ and $CD8^+$ T cells seem to have more extensive lipid rafts and phosphoprotein content, and the TcR in these cells may be more efficient at inducing tyrosine phosphorylation and/or activation of proteins such as LAT, ERK, JNK, and p38 (Kersh et al., 2003). Effector $CD4^+$ T cells show reduced expression of c-cbl and higher basal levels of overall tyrosine phosphorylation (Krishnan et al., 2001, Brembilla et al., 2008), and in human but not mouse, $CD4^+$ effectors express an altered CD3 signaling complex with the FcRγchain replacing the CD3-ζ chain, allowing recruitment of Syk rather than ZAP-70 (Krishnan et al., 2003). Syk has been demonstrated to be more efficient at phosphorylating downstream targets than ZAP-70 (Oliver et al., 1994). Murine memory $CD4^+$ T cells also utilize Syk instead of ZAP-70 (Farber et al., 1997). SLP-76 expression and phosphorylation also differs between naïve and effector/memory $CD4^+$ T cells, with reduced expression in memory cells, although it is still required for effective function of these cells (Bushar et al., 2010). SLP-76 and LAT are however, hyper phosphorylated in response to TcR signals in effector $CD4^+$ T cells, with accompanying increases in ERK activation (Bushar et al., 2010). Naïve and memory $CD4^+$ T cells also differ in their ability to rapidly activate NFAT, perhaps due to differences in expression of family members of this transcription factor (Dienz et al., 2007). In addition, activation of the NFκB pathway also differs between naïve and memory $CD4^+$ T cells, with the upstream

kinase IKK2 being dispensable for activation of naïve cells, but required for activation of memory T cells (Schmidt-Supprian et al., 2003). mTOR complexes also regulate the activation and/or differentiation of $CD4^+$ effector Th cells in a differential fashion. mTORC1 and 2 are both required for the development of Th1 cells, while mTORC2 but not 1 is required for development of Th2 cells, and mTORC1 but not 2 for the development of Th17 cells. By contrast, neither mTORC1 nor 2 is required for the development of T regulatory cells (Waickman and Powell, 2012). However, it is not clear whether the upstream source of activation of the mTOR complexes is the initial or continuing TcR signal, or subsequent cytokine signals driving these cells. In addition, it is not clear whether these mTOR complexes are required (or not) for the subsequent activation of these cells once they have differentiated.

In $CD8^+$ T cells, Lck seems to be dispensable for the activation of effector/memory T cells (Tewari et al., 2006). In addition, while the expression of ZAP-70 is not different between effector/memory and naïve $CD8^+$ T cells, its activity is required for $CD8^+$ effector/memory T cell activation (Bachmann et al., 1999, Slifka and Whitton, 2001, Kaech et al., 2002). mTOR complexes regulate the switch from catabolic to anabolic metabolism in effector $CD8^+$ T cells, and the switch back to catabolic metabolism in memory $CD8^+$ T cells (Pearce et al., 2009, Tamas et al., 2006, Peter et al., 2010, Gwinn et al., 2008). However while mTOR pathways plays a critical role in the activation of naïve $CD8^+$ T cells to effector cells, and negatively regulate the development of $CD8^+$ memory T cells, it is not clear which mTOR complexes are involved (Chi, 2012). In addition, as in $CD4^+$ T cells, it is not clear which upstream source of activation of the mTOR complexes is critical for these processes, nor whether these mTOR complexes are required (or not) for the subsequent activation of these cells once they have differentiated. Nevertheless regulators of mTOR complexes such as Rapamycin could play critical roles in the activation of naïve T cells and subsequent development to and effector and memory T cells.

Associated pathologies and therapeutic implications

T cells regulate the development of vaccine induced immune memory, as well as autoimmune and other pathologies including transplant rejection, lupus, asthma and other airway inflammatory diseases, diabetes. T cells are therefore targets of a number of drugs that target the immune response, including enhancing vaccine efficacy, but also in preventing transplant rejection and other autoimmune diseases. The monoclonal antibodies against the CD3 proteins (e.g. Muromonab-CD3, Orthoclone OKT3©) has also been used effectively in the clinic to reduce T cell activation (most likely by depleting T cells or inducing immune tolerance) and reduce transplant rejection and type I diabetes (Isaacs, 2007). Two of the first significant immunosupressants, Tacrolimus (FK506, Prograf©, Advagraf© or Protopic©) and Cyclosporin A (Neoral© or Sandimmune©), target calcineurin, regulating NFAT activation (Martinez-Martinez and Redondo, 2004). These drugs are potent immunosuppressants used in the clinic to decrease the incidence of transplant rejection (Kahan, 2008). In addition, the immunosuppressant Rapamycin (Sirolimus, Rapamune©), targets mTOR, which reduces T cell proliferation (Sigal and Dumont, 1992). However, more recent exciting findings suggest that Rapamycin may be able to manipulate $CD8^+$ T cell responses, enhancing long term development of $CD8^+$ memory T cells, In addition, Rapamycin may be able to alter the development of $CD4^+$ T helper subsets (Th1/2/17/Treg) (Waickman and Powell, 2012, Chi, 2012). More recent efforts have focused on targeted ZAP-70, Itk, PI3K, and MAPK (Hirabayashi et al., 2009, Lo, 2010, Norman, 2011, Chung, 2011, Trujillo, 2011). Expression of some of these targets such as ZAP-70, Lck, Fyn, and Itk are T cell specific or selective and so are much more likely to have specific effects on T cells without affecting other cell types.

The TcR is one of the most important receptors in the immune system, and signal critical events in the life of a T cell in control of the immune response. These pathways represent a rich array of targets for manipulating T cell activation and differentiation, and thus immune function in disease.

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Abbreviations Used

APC	Antigen Presenting Cell
AP1	Activated Protein 1
ADAP	adhesion and degranulation-promoting adaptor protein
AMPK	AMP activated kinase
AKT	RAC-alpha serine/threonine-protein kinase/Protein kinase B
CAMKKβ	Calcium /calmodulin activated kinase kinase beta
c-cbl	cellular Casitas B-lineage Lymphoma
CARMA	Caspase recruitment domain (CARD)- and membrane-associated guanylate kinase-like domain-containing protein
cSMAC	Central Supramolecular Activation Cluster
CRAC	Calcium release activated calcium current
DAG	diacylglycerol
Egr	Early growth response gene
ER	endoplasmic reticulum
FoxO	Forkhead protein O
FcRγ	Fc receptor gamma chain
HPK	Hematopoietic cell kinase
IKK	Inhibitor of nuclear factor kappa-B kinase
Itk	Interleukin-2 inducible T cell kinase
IP_3	inositol 1,4,5-trisphosphate
ItpkB	IP_3 3-kinase B
MHC	Major Histocompatibility Complex
mTOR	murine Target of Rapamycin
mTORC	murine Target of Rapamycin Complex
NFAT	Nuclear Factor of Activated T cell
NFκB	Nuclear Factor kappa B
NEMO	NFκB essential modulator
PH	Pleckstrin Homology

PLCγ	Phospholipase C-γ
PKCθ	Protein Kinase C theta
PDK	3-phosphoinositide-dependent protein kinase
PIP_2	phosphatidylinositol-4,5-bisphosphate
PI3K	phosphatidylinositol-3-kinase
PIP5K	1-phosphatidylinositol-5-kinase
PEP	PEST domain enriched tyrosine phosphatase
PTEN	Phosphatase and Tensin homolog
pSMAC	peripheral Supramolecular Activation Cluster
RORγt	retinoic Acid related orphan receptor gamma T
SH2	Src Homology domain 2
SH3	Src Homology Domain 3
SLP-76	SH3 containing Lymphocyte protein
STIM1	Stromal Interaction molecule 1
Tec	Tyrosine kinase expressed in hepatocellular carcinoma
Txk/Rlk	Tyrosine protein kinase/Resting lymphocyte kinase
TcR	T cell Receptor
ZAP-70	Zeta–chain-associated kinase

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Signaling Network Facts

- T cell Receptor (TcR) – the antigen specific receptor carried by all T cells. TcRs recognize antigenic peptides only when presented by peptide/Major Histocompatibility (MHC) protein complexes found on antigen presenting cells.
- The antigen specific component of the TcR is generated by rearrangements of the TcR genomic locus in each developing T cell to generate a unique TcR in association with the common CD3 signaling chains.
- The TcR signals differently dependent on the differentiation state of the T cells, naïve vs. effector/memory.
- Targeting TcR signaling pathways are beneficial in a number of autoimmune diseases and in transplant rejection.

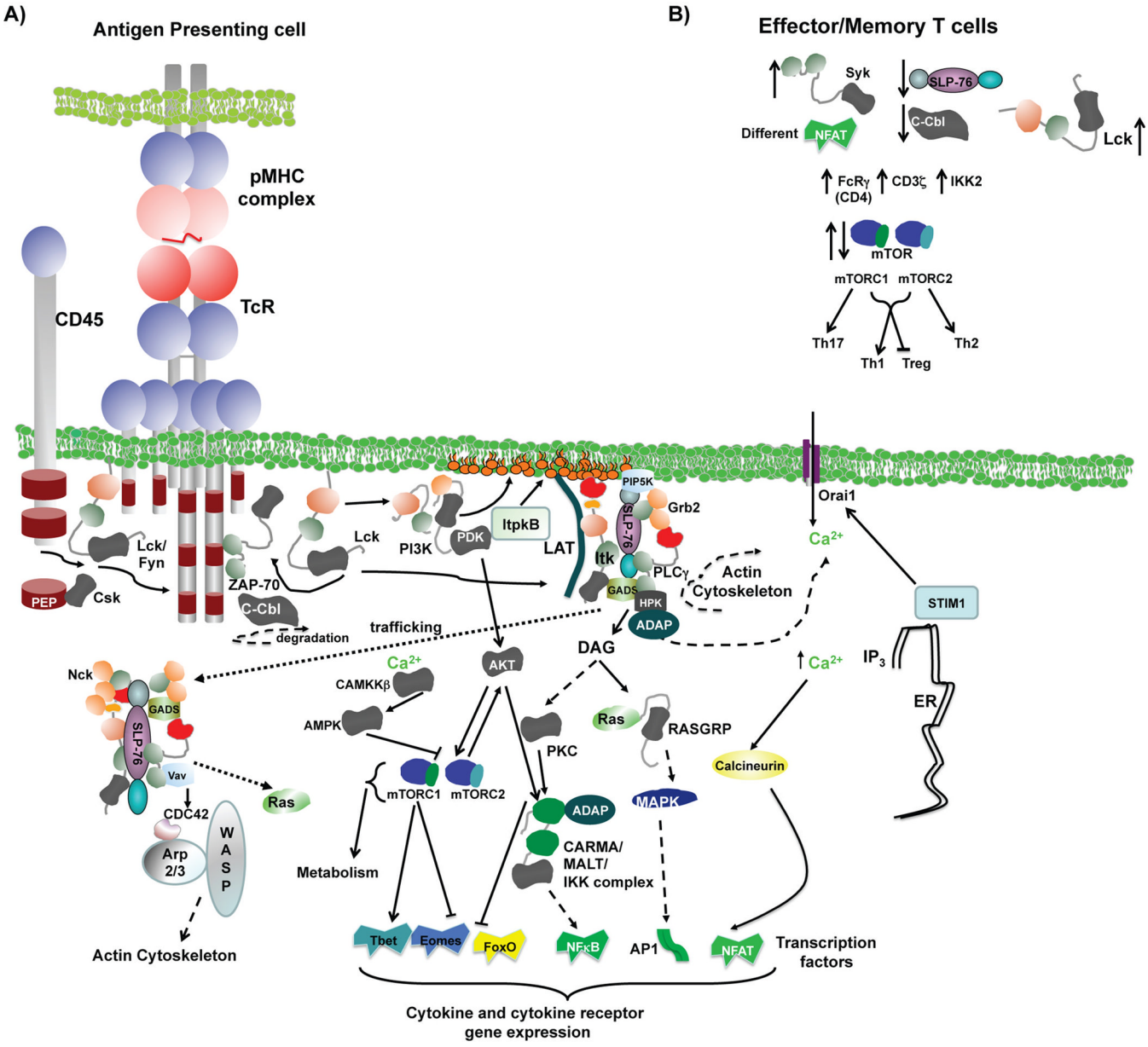

Figure 1. Signaling pathways used by the TcR in naïve and effector/memory T cell activation

A) Signaling pathways used by the TcR to activate T cells. Dashed lines indicate indirect interactions or connections. **B**) Changes in the indicated signaling molecules in the activation of effector/memory T cells compared to naïve T cells. Further details are found in the text.