Lipid Signaling in T-Cell Development and Function

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Second messenger molecules relay, amplify, and diversify cell surface receptor signals. Two important examples are phosphorylated D-myo-inositol derivatives, such as phosphoinositide lipids within cellular membranes, and soluble inositol phosphates. Here, we review how phosphoinositide metabolism generates multiple second messengers with important roles in T-cell development and function. They include soluble inositol(1,4,5)trisphosphate, long known for its Ca²⁺-mobilizing function, and phosphatidylinositol(3,4,5)trisphosphate, whose generation by phosphoinositide 3-kinase and turnover by the phosphatases PTEN and SHIP control a key “hub” of TCR signaling. More recent studies unveiled important second messenger functions for diacylglycerol, phosphatidic acid, and soluble inositol(1,3,4,5)tetrakisphosphate (IP₄) in immune cells. Inositol(1,3,4,5)tetrakisphosphate acts as a soluble phosphatidylinositol(3,4,5)trisphosphate analog to control protein membrane recruitment. We propose that phosphoinositide lipids and soluble inositol phosphates (IPs) can act as complementary partners whose interplay could have broadly important roles in cellular signaling.
PIP2-hydrolysis by phospholipases such as PLCγ1/2 in lymphocytes generates the lipid diacylglycerol (DAG) and the soluble IP inositol(1,4,5)trisphosphate (IP3). PIP3, DAG, and IP3 have essential second messenger functions in many cells, including lymphocytes. Here, we review the importance of phosphoinositide signaling in T cells and highlight the importance of a recently identified, intriguing molecular interplay between second messenger lipids and their soluble IP counterparts.

**PHOSPHOINOSITIDES CONTROL SIGNALING BY BINDING TO SPECIFIC PROTEIN DOMAINS**

All phosphoinositides contain a hydrophobic membrane-embedded diacylglyceride and a hydrophilic solvent-exposed IP moiety. The inositol ring hydroxyl groups can be stereo-specifically phosphorylated by phosphoinositide-kinases. Most phosphatidylinositol-bisphosphate in the plasma membrane of unstimulated cells is phosphatidylinositol(4,5)trisphosphate (PIP2), which is converted into phosphatidylinositol(3,4,5)trisphosphate (PIP3) by phosphatidylinositol-3-kinases. PIP3 is then hydrolyzed by PLCγ1/2 into DAG and IP3. IP3 binding to calcium channels mobilizes calcium ions, which activate various downstream signaling pathways.

IP3 3-kinases convert IP3 into IP4, which acts as a soluble PIP3 analog and controls the abilities of certain PH domains to bind to PIP3 either positively (green arrow) or negatively (red arrow). An unknown 5-phosphatase metabolizes IP4 into I(1,3,4)P3, a precursor for higher-order IPs. In vitro, SHIP1 and PTEN can dephosphorylate IP4 at the 5- or 3-positions, respectively (Erneux et al. 1998; Maehama and Dixon 1998; Pesesse et al. 1998; Caffrey et al. 2001). Whether this occurs physiologically is unknown. Finally, DAG kinases (DGKs) down-regulate DAG function by phosphorylating it into PA, itself a ligand for certain proteins. Further metabolism of all these second messengers results in the generation of many lipid and soluble metabolites. Several of these have important signaling functions (Irvine 2001; Irvine and Schell 2001; York and Hunter 2004; York 2006; Alcazar-Roman and Wente 2008; Huang et al. 2008; Jia et al. 2008b; Miller et al. 2008; Burton et al. 2009; Shears 2009; Sauer and Cooke 2010; Schell 2010). Their functions in immunocytes are unknown.
cells is phosphorylated at the inositol 4- and 5-positions. This PIP₂ comprises <1% of the inner leaflet of the plasma membrane, contrasting with much more abundant phospholipids such as phosphatidylserine and phosphatidic acid (PA) (Lemmon 2008). Despite its low abundance, PIP₂ is an important second messenger. It recruits and regulates multiple signaling proteins by binding to their pleckstrin homology (PH), epsin N-terminal homology (ENTH), 4.1, ezrin, radixin, moesin (FERM), Tubby, or Phox-homology (PX) domains with varying affinities and specificities (McLaughlin et al. 2002). Due to the constitutive PIP₂ availability in resting cells, these PIP₂-associated proteins likely maintain signaling pathways in a preactivation state. Evidence supporting this notion in T cells comes from the inhibitory effects of PIP₂ binding to the guanine nucleotide exchange factor, Vav (Han et al. 1998), and the guanine nucleotide activating factor, ArhGAP9, which maintains Rho-family GTPases in an inactive state (Ang et al. 2007; Ceccarelli et al. 2007).

**PHOSPHOINOSITIDE 3-KINASES CONVERT PIP₂ INTO PHOSPHATIDYLINOSITOL(3,4,5) TRIPHOSPHATE**

Despite the importance of PIP₂, much greater attention has been given to the products of PIP₂ phosphorylation or PIP₂ hydrolysis that are induced following receptor activation. PIP₂ phosphorylation is mediated by PI3Ks. PI3Ks fall into four classes based upon their substrate specificity. Each class comprises one or more regulatory and catalytic subunits with partially distinct and overlapping functions (Fig. 2). Class II and III PI3Ks phosphorylate phosphatidylinositol (PI) into PI(3)P and PI(3,4)P₂. Their functions in lymphocytes are largely unexplored. Class I PI3Ks phosphorylate PIP₂ into PIP₃, an inducible ligand that mediates recruitment and activation of various important signaling proteins. Class IA PI3Ks are activated by most stimulatory receptors on lymphocytes including T- and B-cell antigen receptors (TCR, BCR), and co-stimulatory; Toll-like, and cytokine receptors (Vanhaesebroeck et al. 2005; Buitenhuis and Coffer 2009; Fruman and Bismuth 2009). Five regulatory (p55α, p55γ, p55γ, p85α, p85β) and three catalytic (p110α, β, and δ) subunits participate in Class IA PI3K signaling. Recruitment of Class IA regulatory subunits via binding of their SH2 domains to receptor-induced tyrosine-phosphorylated ITAM motifs leads to colocalization of PI3K catalytic subunits with their substrate, membrane PIP₂. In contrast, Class IB PI3Ks are activated downstream of G-protein-coupled receptors, including chemokine receptors. Class IB comprises two regulatory subunits (p101, p84/87) and one catalytic (p110γ) subunit (Stephens et al. 1994; Stoyanov et al. 1995; Stephens et al. 1997; Suire et al. 2005). Following GPCR engagement, class IB PI3K regulatory subunits bind through their C-terminal domains to GBγ subunits. Both class IA (Okkenhaug et al. 2002; Okkenhaug et al. 2006; Patton et al. 2006; Matheu et al. 2007; Liu et al. 2009a; Liu and Uzonna 2010; Soond et al. 2010) and class IB (Sasaki et al. 2000; Swat et al. 2006; Alcazar et al. 2007) PI3Ks have important functions in T-cell development and function. The T-cell phenotypes of mice with individual or combined PI3K subunit deficiencies are summarized in Table 1.

**THE SECOND MESSENGER PIP₃ RECRUITS PROTEINS TO MEMBRANES BY BINDING TO THEIR PH DOMAINS**

Taken together, immunoreceptor-induced PIP₃ generation is important for lymphocyte proliferation and differentiation (for reviews, see Juntilla and Koretzky 2008; Buitenhuis and Coffer 2009; Fruman and Bismuth 2009). PIP₃ mediates the cellular effects of PI3K activation by recruiting effector proteins that stereospecifically bind to PIP₃ through a subclass of pleckstrin homology or PH domains—protein modules of approximately 120 amino acids that were originally identified as a repeated domain in Pleckstrin (Haslam et al. 1993; Mayer et al. 1993). The mammalian genome contains approximately 250 PH domain proteins. Although there is little amino acid sequence conservation among PH domains, they share a common β-barrel fold comprised of two β
sheets and a C-terminal α-helical cap (Downing et al. 1994; Ferguson et al. 1994; Macias et al. 1994; Timm et al. 1994; Yoon et al. 1994). In approximately 60 PH domains, the N-terminal portion contains a pocket that binds phosphoinositols (Cozier et al. 2004; Hirata et al. 1998). These PH domains are divided into two classes. Class I PH domains bind with high affinity and specificity to PI(4,5)P₂, PI(3,4)P₂, PIP₃, and/or IP₄. Class II PH domains bind PIs more promiscuously and with lower affinity.

Different positively charged amino acid side chains in the PI-binding pocket of a PH
Table 1. Phenotypic consequences of deficiencies in phosphoinositol lipid metabolizing enzymes in lymphocytes.

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<thead>
<tr>
<th>Deficient- or functionally-impaired protein(s)</th>
<th>T-cell phenotype</th>
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<tr>
<td><strong>PI3 Kinase Regulatory Subunits</strong></td>
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<tr>
<td>p85α-(<em>pik3r1</em>) deficient mice</td>
<td>Reduced T-cell development, reduced migrational velocity, normal mature T-cell function.</td>
<td>(Matheu et al. 2007; Shiroki et al. 2007)</td>
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<td>p85β-(<em>pik3r2</em>) deficient mice</td>
<td>Normal T-cell development, reduced cell velocity. Elevated anti-CD3/IL-2-induced proliferation in one study. Defective peripheral T cell recall responses and CD28 signaling in another study.</td>
<td>(Deane et al. 2004; Matheu et al. 2007; Alcazar et al. 2009)</td>
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<td>p85α, p55α, p50α (<em>pik3r1</em>) multi-deficient mice</td>
<td>None reported. Perinatal lethality.</td>
<td>(Fruman et al. 2000)</td>
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<td>p85α, p55α, p50α (<em>pik3r1</em>) &amp; p85β (<em>pik3r2</em>) multi-deficient T cells</td>
<td>Largely normal T-cell development. Impaired T cell Ca2+ signaling, proliferation and cytokines, defective Treg function and Th2 responses but normal Th1 responses, reduced cell velocity and polarization. Sjoegren’s like autoimmune disease.</td>
<td>(Oak et al. 2006; Deane et al. 2007; Matheu et al. 2007; Fruman and Bismuth 2009)</td>
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<td><strong>PI3 Kinase Catalytic Subunits</strong></td>
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<tr>
<td>p110α−/− mice or p110β−/− mice</td>
<td>Not determined. Embryonic lethal.</td>
<td>(Buitenhuis and Coffer 2009)</td>
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<td>p110β−/− mice</td>
<td>No major abnormalities.</td>
<td>(Clayton et al. 2002)</td>
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<tr>
<td>p110δ D910A catalytically inactive mutant expressing mice</td>
<td>Impaired TCR-induced Ca2+ signaling, proliferation, migration and cytokine production, reduced Th1, Th2 and Treg function. Protection from type 2 cytokine responses like airway hyperresponsiveness. Colitis, widespread autoimmunity.</td>
<td>(Okkenhaug et al. 2002; Okkenhaug et al. 2006; Patton et al. 2006; Nashed et al. 2007; Jarmin et al. 2008)</td>
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<tr>
<td>p110γ−/− mice</td>
<td>Some controversies between groups. Impaired T-cell development and activation, proliferation, actin polymerization. Normal activation but impaired migration in another study. Similar cell velocity but with more turning. Reduced CD4+ memory cell survival, autoantibody production, glomerulonephritis, and systemic lupus.</td>
<td>(Sasaki et al. 2000; Rodriguez-Borlado et al. 2003; Barber et al. 2006; Alcazar et al. 2007; Martin et al. 2008; Thomas et al. 2008; Fruman and Bismuth 2009)</td>
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<tr>
<td>p110γ−/− p110δ−/− or p110γ−/− p110δ D910A mice</td>
<td>Impaired T-cell development, proliferation and cell survival, exaggerated Th2 over Th1 responses, high serum IgE levels.</td>
<td>(Webb et al. 2005; Swat et al. 2006; Ji et al. 2007)</td>
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<tr>
<td><strong>IP$_3$ 3-Kinases</strong></td>
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<td>Itpk$A^{-/-}$ mice</td>
<td>None reported.</td>
<td>(Jun et al. 1998; Kim et al. 2009)</td>
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<tr>
<td>ItpkB$^{-/-}$ mice</td>
<td>Blocked T-cell development and thymocyte positive selection. Normal IP$_3$-accumulation and Ca$^{2+}$ signaling, but defective DAG production, Itk recruitment, and activation in thymocytes.</td>
<td>(Pouillon et al. 2003; Wen et al. 2004; Chamberlain et al. 2005; Huang et al. 2006; Huang et al. 2007; Jia et al. 2007; Marechal et al. 2007; Miller et al. 2007b; Huang et al. 2008; Jia et al. 2008a; Jia et al. 2008b; Miller et al. 2008; Miller et al. 2009)</td>
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<tr>
<td>ItpkB$^{-/-}$/ItpkC$^{-/-}$ mice</td>
<td>Same T-cell developmental block as ItpkB$^{-/-}$ mice.</td>
<td>(Pouillon et al. 2003)</td>
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<td>ITPKC loss-of-function polymorphism, humans</td>
<td>Associated with Kawasaki disease susceptibility.</td>
<td>(Onouchi et al. 2008)</td>
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<td>ITPKC knockdown, Jurkat cells</td>
<td>Hyperactivation.</td>
<td>(Onouchi et al. 2008)</td>
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<tr>
<td>ITPKC overexpression, Jurkat cells</td>
<td>Reduced activation.</td>
<td>(Onouchi et al. 2008)</td>
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<tr>
<td>IPMK$^{-/-}$ mice</td>
<td>None reported. Embryonic lethal.</td>
<td>(Frederick et al. 2005)</td>
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<td><strong>PIP$_3$/IP$_4$ Phosphatases</strong></td>
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<td>SHIP$^{-/-}$ mice</td>
<td>Altered Th1/Th2 ratio, reduced CD8 cytotoxicity. Shortened lifespan, splenomegaly, autoimmunity.</td>
<td>(Helgason et al. 1998; Tarasenko et al. 2007)</td>
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<td>PTEN$^{+/+}$ mice</td>
<td>Hyperproliferative T cells. Increased tumor incidence, autoimmunity.</td>
<td>(Di Cristofano et al. 1999; Di Cristofano and Pandolfi 2000)</td>
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<tr>
<td>Conditional PTEN knockout in T cells in mice</td>
<td>Impaired T-cell development, hyperresponsive to suboptimal TCR signals, increased cytokine production, Th2 bias, autoimmune pathology.</td>
<td>(Suzuki et al. 2001; Hagenbeck et al. 2004; Buckler et al. 2008)</td>
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<td>PLC$\gamma 1^{-/-}$ mice</td>
<td>Conditional knockout: Impaired thymocyte positive and negative selection, regulatory T$_{reg}$ cell development and function, TCR-induced peripheral T-cell proliferation and cytokine production. Autoimmune disease. Conventional knockout is embryonic lethal. Chimeric mice: Severe defects in early hematopoiesis.</td>
<td>(Ji et al. 1997; Shirane et al. 2001; Fu et al. 2010)</td>
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<tr>
<td>PLC$\gamma 2^{-/-}$ mice</td>
<td>No T-cell defect reported. Defects in mast cells, dendritic cells, osteoclasts, and neutrophils.</td>
<td>(Wang et al. 2000; Graham et al. 2007; Cremasco et al. 2008; Eppe et al. 2008; Cremasco et al. 2010)</td>
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domain determine its ligand specificity by interacting with specific negatively charged phosphate groups within the inositol ring. The Akt (Protein kinase B) and Tec protein kinase families are part of a small but immunologically important subset of PH-domain-containing proteins whose activities are regulated by PIP3 binding, which colocalizes the kinases with their upstream activators (August et al. 1997; Heyeck et al. 1997; Stokoe et al. 1997). In addition, the Akt PH domain can also bind to PI(3,4)P2 (Cozier et al. 2004; DiNitto and Lambright 2006; James et al. 1996; Lemmon 2008).

**Table 1. Continued**

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<tr>
<td>DGKα−/− mice</td>
<td>Hyper-responsive T cells.</td>
<td>(Outram et al. 2002; Olenchock et al. 2006)</td>
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<tr>
<td>DGKε−/− mice</td>
<td>Hyper-responsive T cells.</td>
<td>(Zhong et al. 2003; Olenchock et al. 2006)</td>
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<tr>
<td>DGKα−/− DGKε−/− mice</td>
<td>Lymphopenia due to a partial block in T-cell development. Reduced T&lt;sub&gt;reg&lt;/sub&gt;, peripheral T cell resistant to anergy-induction.</td>
<td>(Olenchock et al. 2006; Zha et al. 2006; Guo et al. 2008)</td>
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**PI3K CONTROLS AKT FUNCTION IN LYMPHOCYTES**

Akt and its upstream activator PDK1 (Phosphoinositide-dependent kinase 1) are nonreceptor serine/threonine kinases of the AGC family. They regulate survival and proliferation of many cell types (Manning and Cantley 2007). Both kinase families are structurally relatively simple—containing only a kinase domain, a PH domain, and in the case of Akt1, a short hydrophobic motif. Before activation, the Akt and PDK1 PH domains seem to function in an inhibitory manner that is released upon membrane PIP3 binding (Stokoe et al. 1997; Gao and Harris 2006). Full PDK1 activation requires PIP3 binding to the PDK1 PH domain, which allows trans-phosphorylation of a C-terminal residue (Gao and Harris 2006). In the absence of lipid ligands, the Akt1 PH domain occludes access to the activation site, prohibiting its phosphorylation by PDK1 (Stokoe et al. 1997; Calleja et al. 2007). PH-domain-mediated PDK1 and Akt recruitment to membrane PIP3 leads to phosphorylation of the catalytic T-loop of Akt by PDK1, activating Akt (Stephens et al. 1998). A second kinase of uncertain identity phosphorylates the Akt C-terminal hydrophobic motif, leading to optimal Akt kinase activity.

There are three Akt paralogs in mammals (Akt1/2/3). All are expressed in lymphocytes and have partially redundant functions. Akt promotes cell survival primarily through inhibition of apoptosis. Akt can directly or indirectly inhibit the function of proapoptotic Bcl-2 family members by phosphorylation (del Peso et al. 1997; Gardai et al. 2004; Qi et al. 2006; Hubner et al. 2008). Akt also activates the transcription factor NF-kB (Madrid et al. 2000) and induces expression of antiapoptotic Bcl-2, FLIP, and IAP proteins (Wang et al. 1998; Panka et al. 2001). Akt, moreover, promotes cell proliferation by increasing cell metabolism (Frauwirth et al. 2002; Rathmell et al. 2003; Jacobs et al. 2008), facilitating protein translation (Dufner et al. 1999), and cell cycle progression (Liang et al. 2002; Shin et al. 2002; Viglietto et al. 2002). Consequently, genetic alterations that enhance Akt activity either directly or indirectly via amplification of PI3K activity often lead to cellular transformation (Liu et al. 2009b).

Akt1 and Akt2 are particularly important during early T-cell development (Juntilla et al. 2007; Juntilla and Koretzky 2008). CD4 and CD8 T cells develop from a common thymic
progenitor through a series of developmental stages that can be partially characterized by differential cell-surface expression of the CD4 and CD8 coreceptors. At the early, CD4⁻CD8⁻ double-negative (DN) stage, productive TCRβ gene rearrangement results in a pre-TCR signal that suppresses rearrangement of the second TCRβ allele and triggers proliferative expansion and progression to the CD4⁺CD8⁺ double-positive (DP) stage. During this process, the cells rearrange their TCRα chain genes. Successful TCRα protein expression results in pre-TCR replacement by a mature TCR composed of α and β chains. Akt1 or Akt2 deficiency results in a two-fold reduction in thymic cellularity due to a partial block between DN and DP cells. In contrast, Akt1 and Akt2 double-deficiency results in a 45-fold decrease in thymic cellularity (Juntilla et al. 2007). This highlights the importance of Akt kinases during the highly proliferative stage of thymic development.

TEC FAMILY PROTEIN TYROSINE KINASES ARE KEY PIP₃ EFFECTORS IN LYMPHOCYTES

The expression of certain Tec family non-receptor protein–tyrosine–kinases (TFKs) is restricted to specific immune cell types (Readinger et al. 2009). Itk and Rlk are largely restricted to T cells and NK cells. Btk is not expressed in these, but enriched in B cells, mast cells, and myeloid cells. Tec is broadly expressed in hematopoietic cells. Despite some functional redundancies, deficiency in individual TFKs causes profound functional defects (for a review, see Readinger et al. 2009). Itk deficiency causes defects in T-cell development and in certain peripheral T-cell functions (Liao and Littman 1995; Fowell et al. 1999; Schaeffer et al. 1999; Schaeffer et al. 2000; Schaeffer et al. 2001; Tomlinson et al. 2004; Finkelstein et al. 2005; Atherly et al. 2006; Broussard et al. 2006; Horai et al. 2007; Lucas et al. 2007).

At the DP stage, thymocytes are evaluated for the ability of their TCR to interact with self MHC/peptide complexes on the surfaces of thymic antigen-presenting cells. DP cells whose TCRs do not interact with sufficient strength or duration die by “neglect.” DP cells whose TCRs interact moderately with self-MHC class I or II are positively selected to mature into CD8 or CD4 single positive T cells, respectively. DP cells carrying potentially autoreactive TCRs that interact too strongly or for an inappropriate duration with self-MHC are induced to die by “negative selection.” A major unresolved question in immunological research is how TCR engagement can have such different outcomes.

Positively and negatively selecting TCR signals appear to activate the same proximal signaling molecules, including Itk. In Itk-deficient mice, the efficiencies of positive and negative selection are dramatically decreased (Liao and Littman 1995; Schaeffer et al. 2000). In contrast, Itk deficiency favors the accumulation of a nonconventional thymic T cell subset with an effector/memory or “innate” phenotype, particularly in the CD8 lineage (Atherly et al. 2006; Broussard et al. 2006; Horai et al. 2007). In addition, TCR signals that normally induce negative selection can, under some circumstances, promote positive selection in Itk-deficient mice (Schaeffer et al. 2000). In mature T cells, Itk appears to be required to sustain T₂H2 responses (Fowell et al. 1999; Schaeffer et al. 2001).

TFKs have a relatively complex domain structure with an N-terminal PH domain, followed by a proline-rich Tec homology domain, Src homology 3 (SH3) and SH2 domains, and a C-terminal kinase domain. In Rlk, a missing N-terminal PH domain is functionally substituted by palmitoylation, resulting in constitutive membrane association (Debnath et al. 1999). Membrane recruitment of the other TFKs predominantly depends on interactions between their PH domains and membrane PIP₃ (Ching et al. 1999; Shan et al. 2000), together with interactions between their SH2 domains and adaptor proteins such as SLP-76 in T cells (Ching et al. 1999; Su et al. 1999). However, recent data may suggest that Btk membrane recruitment can also occur in a PH-domain-independent manner (Fruman and Bismuth 2009). Activation-induced association with cytosolic SLP-76 and the membrane adaptor LAT colocalizes TFKs with their upstream activators, Src kinases, and their downstream target, PLCγ1.
Mechanistically, the consequences of TFK deficiency have primarily been attributed to defective PLCγ phosphorylation and activation (Liu et al. 1998). In addition, TFKs appear required for Vav-dependent cytoskeletal organization and cell adhesion (Gomez-Rodriguez et al. 2007). However, TFK promotion of Vav function appears to involve TFK adaptor functions, rather than their kinase activities (Grasis et al. 2003; Dombroski et al. 2005).

**PHOSPHOLIPASE-Cγ HYDROLYZES PIP2 INTO THE SECOND MESSENGERS DIACYLGLYCEROL AND INOSITOL(1,4,5)TRISPHOSPHATE**

PI(4,5)P2 is a substrate for another immunologically important enzyme, phosphatidylinositol-specific phospholipase-Cγ (PLCγ). PLCγ hydrolyzes PIP2 into its hydrophobic and hydrophilic components, the membrane-lipid diacylglycerol (DAG) and soluble inositol(1,4,5)trisphosphate (IP3). Both are second messengers that regulate proteins through specific binding domains.

The two mammalian PLCγ isoforms, PLCγ1 and 2, have partially overlapping expression patterns and functions (Wilde and Watson 2001). T cells exclusively express PLCγ1. T-cell-specific PLCγ1-deletion impaired thymocyte positive and negative selection, regulatory Treg cell development and function, TCR-induced peripheral T-cell proliferation, and cytokine production (Fu et al. 2010). Defective TCR activation of the MAP kinases Erk and Jnk, and of the transcription factors NFAT, AP-1, and NF-κB indicates the broad importance of PLCγ1 in TCR signaling through several pathways. Autoimmune disease symptoms show the physiological importance of PLCγ1 in T cells (Fu et al. 2010). Severe blocks in T-cell development and late onset autoimmunity in mice expressing a PLCγ1-binding-deficient LAT allele indicate the importance of LAT interactions for PLCγ1 function (Sommers et al. 2002; Sommers et al. 2005). Finally, severe defects in early hematopoiesis in chimeric mice generated with PLCγ1-deficient embryonic stem cells suggest important PLCγ1 functions in hematopoietic stem or progenitor cells (Shirane et al. 2001). In contrast, PLCγ2-deficient mice are viable with specific defects in B cells, mast cells, dendritic cells, osteoclasts, and neutrophils (Wang et al. 2000; Graham et al. 2007; Cremasco et al. 2008; Epple et al. 2008; Cremasco et al. 2010).

PLCγ1/2 have complex domain structures with an N-terminal PH domain, followed by a number of EF hands, a catalytic domain that is split by an internal regulatory domain, and a C-terminal Ca²⁺-binding-C2 domain (Fig. 2). The regulatory domain contains a core of two tandem SH2 domains and an SH3 domain that is flanked by a split PH domain. This split PH domain can self-associate to form a functional PH domain, or associate in trans with a split PH domain in TRPC-family Ca²⁺ channels (van Rossum et al. 2005). Either one or both PH domains contribute to PLCγ1 membrane association by binding to PIP3 (Bae et al. 1998; Falasca et al. 1998). Additional interactions are provided by the other modular domains. Once PLCγ1 is at the membrane, phosphorylation of tyrosine residues within its regulatory domain by TFKs induces PLCγ1 activation. Recent studies suggest that this requires phosphotyrosine-independent PLCγ1 SH2 domain binding to a noncanonical ligand motif in Itk (Joseph et al. 2007; Min et al. 2009).

**DIACYLGLYCEROL CONTROLS Ras AND PKC ACTIVATION IN LYMPHOCYTES**

The membrane second messenger, DAG, propagates signals via membrane recruitment of cytosolic signaling proteins by binding to their C1 domains, cysteine-rich domains of approximately 50 amino acids. Two β-sheets harbor the DAG-binding cavity.

Several well-characterized DAG-effector families include Ras guanine-nucleotide-exchange-factors/relasing proteins (RasGRPs), protein kinase C-related kinases (PKCs, PKD), chimaerin Rho/Rac-GTPase-activating proteins (Yang and Kazanietz 2007), Munc13 proteins (Betz et al. 1998), and diacylglycerol kinases (DGKs). There is some effector selectivity for different DAG species that differ in their subcellular localization.
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For example, RasGRPs preferentially bind to DAG in Golgi membranes (Carrasco and Merida 2004). PKCs preferentially bind to DAG in the plasma membrane (Spitaler et al. 2006). RasGRP membrane recruitment by DAG colocalizes these Ras activators with their substrate, inducing release of Ras-bound GDP, GTP binding, and Ras activation. Ras then activates the kinase Raf, which activates the downstream Erk cascade. The four mammalian RasGRPs1–4 have partially overlapping expression patterns and partially redundant functions. T cells predominantly express RasGRP1, the main mediator of TCR-induced Ras/Erk activation (Dower et al. 2000; Priatel et al. 2002). RasGRP1 deficiency causes a significant block of T-cell development with strong defects in positive, and some defects in negative selection (Dower et al. 2000; Priatel et al. 2002). However, this developmental block is incomplete and can be partially rescued by strong TCR activation (Priatel et al. 2006). Nevertheless, a moderate lymphopenia occurs due to T-cell exhaustion (Priatel et al. 2007). Interestingly, Treg cells accumulate in the periphery of RasGRP1-deficient mice, despite perturbed Treg development (Chen et al. 2008).

In contrast to RasGRPs, DAG-mediated membrane recruitment allosterically induces PKC activation by abrogating an auto-inhibitory association between the PKC pseudo-substrate and substrate-binding domains (Rosse et al. 2010). DAG promotes activation of classic (PKCa, PKCbI, PKCbII, PKCy), novel (PKCd, PKCe, PKCn, PKCb), and atypical PKCs (PKCe, b/4). However, classic and novel PKCs also require Ca$^{2+}$ binding to their C2 domains (Rosse et al. 2010). Multiple studies have shown essential PKC roles in lymphocyte development and function (for reviews, see Isakov and Altman 2002; Barouch-Bentov and Altman 2006; Manicassamy et al. 2006). In particular, PKCδ is important for TCR signaling and required for thymocyte-positive selection (Morley et al. 2008). Incomplete developmental defects likely reflect redundancy among thymocyte-expressed PKCs.

Several recent publications suggest important functions for chimaerins in TCR signaling, T-cell adhesion, and chemotaxis that involve their ability to inactivate Rac (Siliceo et al. 2006; Caloca et al. 2008; Siliceo and Merida 2009). No munc13 protein roles in the immune system have been reported.

**DIACYLGLYCEROL KINASES CONVERT DAG INTO PHOSPHATIDIC ACID**

Aside from their production by PLCγ in lymphocytes, DAG levels are also regulated through their phosphorylation into phosphatidic acid (PA) by DAG kinases (DGKs). In T cells, this down regulates PKC and RasGRP functions and TCR-induced-Erk activation (reviewed in Zhong et al. 2008). However, in many cell types, receptor-induced PA generation activates a series of PA-effector proteins with various functions, including vesicular trafficking, cell survival, and proliferation (Wang et al. 2006).

The ten mammalian DGKs form five groups based on their domain structure (Fig. 3). All DGKs have two to three C1 domains and a kinase domain. However, these C1 domains do not necessarily participate in DAG binding. Instead, the domains that distinguish the DGK types direct differential localization or activation requirements. T cells express at least three DAG kinases: DGKa (type I), δ (type II), and ε (type IV). DGKa has an N-terminal RVH domain and two EF hands. Ca$^{2+}$ binding to these three domains induces DGKa activation. DGKδ has an N-terminal PH domain, two EF hands, and a C-terminal SAM domain. The PH domain facilitates DAG binding. The SAM domain mediates DGKδ oligomerization and ER targeting. DGKE has a central MARCKS domain, multiple ankyrin repeats, and a C-terminal PDZ-BM domain. The MARCKS domain contains a nuclear localization sequence. The PDZ-BM domain of DGKE regulates Rac activity and membrane ruffling. DGKa and DGKE cooperatively down-regulate T-cell activation and facilitate T-cell tolerance (Guo et al. 2008). Different T-cell developmental and activation stages express different DGKa and DGKE splice variants (Macian et al. 2002). DGKa- (Outram et al. 2008).
2002; Olenchock et al. 2006) or DGKξ- (Zhong et al. 2003; Olenchock et al. 2006) deficient mice have increased DAG-dependent signaling and produce hyper-responsive T cells. DGKα/ξ double deficiency causes lymphopenia due to a partial block in T-cell development (Guo et al. 2008). The peripheral T cells contain reduced Treg proportions and are resistant to anergy induction (Olenchock et al. 2006; Zha et al. 2006). Therefore, limiting DAG function in T cells is of great physiological importance, although defective PA production may contribute to the phenotype (Zhong et al. 2008).

Ca2+ is a rapid and robust, soluble second messenger with multiple downstream effectors (Feske 2007; Oh-hora and Rao 2008; Vig and Kinet 2009). mM extracellular Ca2+ concentrations contrast with nM cytosolic Ca2+ concentrations that are tightly maintained by pumps, which sequester Ca2+ into the extracellular space or intracellular storage compartments (Feske 2007; Oh-hora and Rao 2008). Following TCR engagement, Ca2+ signaling is initiated by the soluble product of PIP2 hydrolysis, Ins(1,4,5)P3 (here IP3). IP3 binding to receptors in the ER membrane releases the stored Ca2+ into the cytosol (Taylor et al. 2009). Subsequent sensing of the store depletion by STIM proteins induces STIM translocation to the plasma membrane, where STIM-induced opening of ORAI-family Ca2+ channels triggers a store-operated Ca2+ entry (SOCE). This causes a sustained increase of the cytoplasmic Ca2+ concentration that is essential for T-cell activation (Feske 2007; Oh-hora and Rao 2008; Vig and Kinet 2009).

Cytosolic Ca2+ binds to proteins with C2 domains and EF hands, inducing conformational changes that alter activity (Niki et al. 1996). Important examples with EF hands are the cytosolic adapter Calmodulin and STIM proteins (Feske 2007; Oh-hora and Rao 2008; Vig and Kinet 2009).

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Figure 3. Schematic structures of key PIP3 or IP4 phosphatases and DAG kinases in lymphocytes. For details, see text.
IP3 CONVERSION INTO INOSITOL(1,3,4,5)TETRAKISPHOSPHATE BY IP3 3-KINASES CONTROLS LYMPHOCYTE DEVELOPMENT AND FUNCTION

Aside from mediating receptor-induced Ca2+ mobilization, IP3 can also act as a precursor for other IPs. A key step in their generation is IP3 phosphorylation at its 3-position into IP4 by IP3 3-kinases (IP3Ks). Mammals have four IP3Ks: the closely related ITPK-family members ItpkA/B/C and the unrelated IP multikinase (IPMK).

Genetic studies in yeast and biochemical data have suggested many potential IP4 functions (Irvine 2001; Irvine and Schell 2001; Nalaskowski and Mayr 2004; Pattni and Banting 2004; Irvine 2005; Irvine et al. 2006; York 2006; Otto et al. 2007; Huang et al. 2008; Jia et al. 2008b; Miller et al. 2008; Sauer and Cooke 2010; Schell 2010). Much research has explored potential IP3K roles in regulating Ca2+ mobilization either by controlling IP3 turnover, or through distinct functions of IP4 or IP4-derived other IPs. The results caused a long-standing controversy that could be attributed to differences in cell type, stimulation regimen, or experimental conditions. Studies with human Jurkat T cells suggest that IP4 can sustain TCR-induced IP3 accumulation and Ca2+ mobilization through competitive inhibition of an inositol 5-phosphatase (Hermosura et al. 2000). Moreover, a recent study suggested that ITPKC knockdown in Jurkat cells promotes TCR-induced activation of the Ca2+-effector NFAT and IL-2 production (Onouchi et al. 2008). These data are consistent with one IP3K role in controlling IP3 levels or function. The precise mechanism, identity of the 5-phosphatase, and physiological relevance remain unclear. Normal anti-TCR antibody-induced IP3 accumulation and Ca2+ mobilization is mediated by competitive inhibition of an inositol 5-phosphatase (Hermosura et al. 2000). Moreover, a recent study suggested that ITPKC knockdown in Jurkat cells promotes TCR-induced activation of the Ca2+-effector NFAT and IL-2 production (Onouchi et al. 2008). These data are consistent with one IP3K role in controlling IP3 levels or function. The precise mechanism, identity of the 5-phosphatase, and physiological relevance remain unclear. Normal anti-TCR antibody-induced IP3 accumulation and Ca2+ mobilization is mediated by competitive inhibition of an inositol 5-phosphatase (Hermosura et al. 2000). However, IP4 levels and total IP3K activity were only approximately 50% reduced. Thus, other IP3Ks likely contribute to IP4 production in thymocytes, and the consequences of complete IP3K/IP4 deficiency on Ca2+ mobilization still needs to be determined.

IP4 chemically resembles the PH-domain-binding headgroup of PIP3, and less well those of PI(4,5)P2 and PI(3,4)P2. Not surprisingly, IP4 can bind to some of the protein domains that bind to these phosphoinositides. This property is often used to facilitate PH domain crystallization for X-ray structure determination (Lemmon 2008). Biochemical data suggest that IP4 binding to the PH domains of Ras GTPase-activating proteins (RASA2/GAP1m, RASA3/GAP1p4IP4B) (Cullen et al. 1995; Cozier et al. 2000b), BTK, AKT, or certain regulators of vesicular trafficking (synaptotagmins, centaurin-α1/p42IP4), might inhibit their membrane recruitment, activation, or protein interactions. However, until recently, the physiological relevance of these findings was unknown.

Lymphocytes predominantly express two Itpks, ItpkB and ItpkC (Vanweyenberg et al. 1995; Wen et al. 2004). ItpkC is broadly expressed by many tissues. ItpkB expression appears restricted to hematopoietic cells and the brain (Wen et al. 2004; Jia et al. 2008a). ItpkB-deficient mice recently unveiled the physiological importance of ItpkB in lymphocyte development and activation (Table 1) (Pouillon et al. 2003; Wen et al. 2004). These mice are profoundly immunocompromised due to severe peripheral T-cell deficiency (Pouillon et al. 2003; Wen et al. 2004), reduced numbers and defective activation of B cells (Marchal et al. 2007; Miller et al. 2007a; Miller et al. 2009), and increased numbers of functionally perturbed neutrophils (Jia et al. 2007). Several recent reviews describe current models for ItpkB function in B cells and neutrophils (Huang et al. 2008; Jia et al. 2008b; Miller et al. 2008; Sauer and Cooke 2010). Here, we highlight the function of IP4 in T cells.

ItpkB-deficient mice have a block of T-cell development due to defective positive selection (Pouillon et al. 2003; Wen et al. 2004). Whether negative selection is affected is still unclear (Sauer and Cooke 2010). Selected effectors of both IP3 (Ca2+) and DAG are specifically required for positive selection. Deficiency in Calcineurin B, a Ca2+-dependent phosphatase
that activates NFAT (Neilson et al. 2004; Gallo et al. 2007), or in RasGRP1, partially blocks positive selection (Dower et al. 2000; Priatel et al. 2002). Intriguingly, ItpkB deficiency blocks positive selection much more profoundly in a manner that depends on the ability of ItpkB to generate IP4 (Huang et al. 2007). Normal IP3 levels and Ca2+ mobilization in ItpkB-deficient thymocytes argue against significant contributions by these messengers. Instead, the block results from an inability of ItpkB-deficient thymocytes to produce sufficient DAG amounts in response to mild, positively selecting TCR stimuli (Huang et al. 2007). Consequently, mild TCR engagement induced Ras/Erk activation is impaired in ItpkB-deficient DP cells. This likely contributes to defective positive selection (Starr et al. 2003; McGargill et al. 2009). Addition of the DAG analog, PMA, restored Erk activation and allowed ItpkB-deficient CD4 and CD8 T-cell maturation (Huang et al. 2007). Thus, IP4 is required for DAG-induced Erk activation in response to positively selecting TCR stimuli. Yet, how does IP4 promote DAG accumulation?

SOLUBLE IP4 CONTROLS ITK-PH-DOMAIN BINDING TO PIP3 IN THYMOCYTES

Mechanistic analyses revealed that IP4 is required for membrane recruitment and subsequent activation of the TFK Itk following mild TCR stimulation (Huang et al. 2007). This was surprising since generation of PIP3, the established membrane ligand for the Itk PH domain, was thought to be the limiting factor for Itk membrane localization. In vitro analyses then showed that low μM IP4 concentrations, as previously found in TCR-stimulated T cells (Imboden and Pattison 1987), promoted Itk or Itk-PH-domain binding to PIP3 (Huang et al. 2007). Very high, likely super-physiological IP4 concentrations, competed with PIP3 binding. The ability of the Itk-PH domain to oligomerize (Huang et al. 2007) then resulted in a model where IP4 binding to one Itk-PH domain in a multimeric Itk complex induced conformational changes in all PH domains within the complex that allosterically increase their affinities for PIP3 and IP4. This promotes PIP3 binding, as long as IP4 is not in excess over PIP3. Here, IP4 catalyzes PIP3 binding at low, but competes with it at very high concentrations (Sauer and Cooke 2010). These findings identified Itk as the first physiological IP4 “receptor” and unveiled the first physiological IP4 function as a second messenger that controls Itk membrane recruitment and activation downstream of the TCR (Irvine 2007). They suggest that IP4 and PIP3 act as partners where soluble IP4 controls the ability of its membrane lipid counterpart to interact with the Itk-PH domain. It is exciting to hypothesize that this new principle of regulating PH-domain function through an interplay of a soluble IP and its phosphoinositide-lipid partner has broader relevance in biological signaling. Indeed, IP4 could have similar bimodal effects on PIP3 binding to the Tec- and RASA3-PH domains, but whether this is physiologically relevant still needs to be determined (Huang et al. 2007). In neutrophils, IP4 has recently been suggested to inhibit Akt-PH domain interactions with membrane PIP3 or PI(3,4)P2 (Jia et al. 2007). Loss of this function may contribute to an accumulation of granulocyte-macrophage progenitors and functionally-impaired neutrophils in ItpkB−/− mice (Jia et al. 2007; Jia et al. 2008a; Jia et al. 2008b). On the other hand, IP4 did not affect PLCγ1 binding to PIP3, which is mediated through its classic- and split-PH domains (Fig. 2) (Huang et al. 2007). Thus, not all PIP3-binding PH domains may be subject to IP4 control. One possible explanation is that the affinities of a given PH domain for PIP3 and IP4 can differ, with some PH domains preferring IP4 or PIP3, possibly due to differential contributions of the 1-phosphate or the lipid environment to the binding free energy (DiNitto and Lambright 2006).

Finally, it is important to keep in mind that IP4 can be a precursor for multiple soluble IPs in mammalian cells. Some of these have been found in lymphocytes (for reviews, see Sauer et al. 2009; Sauer and Cooke 2010). Hence, some aspects of the ItpkB−/− phenotype might reflect deficiencies in other IPs.

Due to the blocked T-cell development in ItpkB-deficient mice, analyses of specific ItpkB
functions in peripheral T cells will require conditionally ItpkB-deficient mice. However, studies linking ItpkC loss-of-function to augmented Jurkat cell activation and human Kawasaki disease support an IP₄ role in regulating peripheral T-cell activation (Onouchi et al. 2008).

**PHOSPHATASES CONTROL PIP₃ AND IP₄ TURNOVER**

PIP₃ levels are down-regulated by lipid phosphatases, including PTEN and SHIP1/2 in lymphocytes (Figs. 1 and 3; Table 1) (Harris et al. 2008). PTEN reverses the PI3K reaction and is generally thought to limit PI3K function. SHIP1/2 remove the PIP₃ 5-phosphate, generating PI(3,4)P₂ and also down-modulating PIP₃ levels (Damen et al. 1996; Kavanaugh et al. 1996; Lioubin et al. 1996). However, effectors such as Akt that predominantly bind to the inositol 3/4-phosphates may continue to be recruited and activated by PI(3,4)P₂. Thus, differential use of PTEN and SHIP1/2 can selectively alter the activities of a subset of PIP₃ effectors, qualitatively changing PI3K responses.

Complete PTEN deficiency in mice results in embryonic lethality (Di Cristofano et al. 1998). PTEN hemizygosity, or conditional deficiency caused T-cell hyperproliferation, autoimmunity, and increased tumor incidence (Di Cristofano et al. 1999; Di Cristofano and Pandolfi 2000). PTEN deletion in T cells revealed the importance of precise PIP₃ regulation for T-cell development through defective positive and negative selection (Suzuki et al. 2001). PTEN-deficient peripheral T cells were hyper-responsive to suboptimal TCR stimulation and less dependent on co-stimulation, resulting in autoimmune pathology (Suzuki et al. 2001). Activated T cells secreted increased cytokine amounts (Suzuki et al. 2001) and showed a bias toward the Th1/2 lineage (Buckler et al. 2008). Thus, PIP₃ down-regulation by PTEN is required for limiting T-cell responses and maintaining self-tolerance.

PIP₃ dephosphorylation at the 5-position by SHIP1/2 is also important for T-cell tolerance. However, while the effects of SHIP deficiency partially overlap with those of PTEN deficiency, the additional importance of generating PI(3,4)P₂ is evident from the additional shortened lifespan of SHIP-deficient mice (Helgason et al. 1998). SHIP-deficient CD4 T cells have an altered Th1/Th2 cell ratio. SHIP-deficient CD8 T cells are less cytotoxic (Tarsenko et al. 2007). Thus far, these phenotypes have been attributed to defective PIP₃ conversion into PI(3,4)P₂.

However, in vitro, both SHIPs and PTEN can dephosphorylate IP₄ into I(1,3,4)P₃ or Ins(1,4,5)P₃, respectively (Fig. 1) (Erneux et al. 1998; Maehama and Dixon 1998; Pesesse et al. 2001). Whether this is relevant in vivo is unknown. If it were, then the phenotypes of PTEN⁻/⁻ or SHIP⁻/⁻ mice might need reinterpretation to consider potential contributions of perturbed IP₄ down-regulation. On the other hand, the presence of an IP₄-inhibited 5-phosphatase in Jurkat cells that lack SHIP and PTEN (and also show hyper-activation) suggests that other phosphatases might also regulate IP₄ levels in T cells (Hermosura et al. 2000).

**CONCLUDING REMARKS**

We have highlighted the importance of phosphoinositide signaling in lymphocytes, focusing on T cells. The importance of phosphoinositide lipids and of the Ca²⁺-mobilizing soluble I(1,4,5)P₃ in lymphocyte signaling have long been established, although many open questions remain. For example, what influence do the specific fatty acids in a phosphoinositide have? There is evidence that many different fatty acids can be found in a given phosphoinositide isomer. They might control where it is located or other aspects of its function. Is PIP₃ really a universe of diverse molecules that differ in their fatty acid moieties and, possibly, functions?

More recent data unveiled important functions for the lipids DAG and PA, and for soluble IP₄ in lymphocyte development and function. Some insight into the molecular mechanisms through which these novel messengers act has been gained, but our understanding of their molecular functions is far from complete. In
particular, the roles of additional DAG effectors other than RasGRPs and PKCs in T cells need assessment, and the molecular mechanisms through which PA contributes to DGK function in lymphocytes are only beginning to be understood (Zhong et al. 2008).

One of the most intriguing, possibly broadly relevant, recent findings is the ability of IP₄ to control PIP₃ interactions with its effectors. Because PIP₃ is the key mediator of PI3K, PTEN, and SHIP function, IP₄ might ultimately act to control the functions of these important enzymes. Biochemically, PI3K and IP3Ks catalyze the same very reaction: phosphorylation of the inositol 3-position. Physiologically, they create the Tessa Virtue and Scott Moir, respectively, of a couple of second messengers whose dance in the cellular ice ring is reminiscent of the intricacy and elegance of its 2010 Winter Olympics counterpart. In DP thymocytes, the dance establishes a feedback loop of Itk-membrane recruitment and PLCγ₁ activation that is essential to allow mild TCR stimuli to cause sufficient DAG production, such that Ras/Erk can be activated and trigger positive selection (Huang et al. 2007; Sauer and Cooke 2010). It will be important to explore how broadly relevant PIP₃ control through soluble IP₄ is in other cell types and downstream of other receptors. Moreover, clarifying what determines whether a PIP₃-binding protein domain is subject to IP₄ control remains a challenging and important question. Finally, it will be exciting to determine the functions of the other higher-order IPs found in lymphocytes (Sauer et al. 2009; Sauer and Cooke 2010), and to determine which ones are IP₄-derived and might, thus, mediate aspects of IP₄ function. Clearly, exploring phosphoinositide-lipid signaling and the functions of the soluble IP code in lymphocytes will remain an exciting and important research area for years to come.

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Lipid Signaling in T-Cell Development and Function

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