The Expanding Role for ITAM-Based Signaling Pathways in Immune Cells

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The immunoreceptor tyrosine-based activation motif (ITAM) is the primary signaling domain used by classical immunoreceptors, such as the antigen receptors on B and T lymphocytes and the Fc receptors (FcRs) on myeloid cells. The ITAM is contained in the intracellular region of subunits associated with these receptors, often in pairs, or is part of the cytoplasmic domain of the receptors themselves. Data from many investigators have demonstrated that ITAMs are both necessary and sufficient for initiation of signaling downstream of all immunoreceptors. More recent reports indicate that ITAM signaling is used by additional receptors beyond the classical immunoreceptors : Cell adhesion molecules (integrins and PSGL-1), chemokine receptors (CXCR4), plexins, and lectin receptors all mediate immune cell function through ITAM-like signaling pathways. This convergence of intracellular signaling pathways in leukocytes illuminates the importance of tyrosine-based activation motifs in the immune system and suggests that inhibitors of ITAM signaling may have broader effects than originally envisioned.

Although T cell receptors (TCRs), B cell receptors (BCRs), FcRs, activating NK (natural killer) cell receptors, and TREM1 and 2 (triggering receptor expressed on myeloid cells 1 and 2) receptors respond to a diverse set of ligands and mediate a diverse set of responses, each of these immunoreceptors activates a common downstream signaling pathway (*1*–*5*). Receptor ligation leads to the Src-family kinase-mediated tyrosine phosphorylation of ITAM-containing protein domains, which in turn results in the recruitment and activation of spleen tyrosine kinase (Syk) or zeta-associated protein kinase (ZAP70), and the subsequent phosphorylation of downstream substrates such as LAT (linker for activation of T cells), SLP-76 [Src homology 2 (SH2) domain–containing leukocyte protein of 76 kD], and Vav guanine nucleotide exchange factors (Fig. 1). The immunoreceptors rely on different ITAM-containing adapter subunits for signaling: The TCR uses primarily the CD3ζ chain, the BCR uses associated immunoglobulin (Ig) α and β chains, the FcRs use mainly the FcRγ chain, and activating NK receptors and TREM1 and 2 rely primarily on DAP12 (Table 1). The "classical" ITAM consensus sequence is defined as $YxxI/Lx_{(6–12)}YxxI/L$ (where Y stands for tyrosine, I stands for isoleucine, L stands for leucine, and x can be any amino acid); Syk or ZAP70 binds to the dually phosphorylated tyrosines in the ITAM through their dual SH2 domains. Several nonclassical ITAM-like sequences have been described that appear to signal in a similar way, although in some cases a single tyrosine residue may be sufficient for Syk recruitment, perhaps with lower affinity (*6*, *7*). Mutation of critical residues within the ITAM or the SH2 domain blocks downstream signaling. ITAM-containing adapters associate with cell surface receptors through charged interactions between their transmembrane domains; single opposing charged amino acids contained within the transmembrane domains of the receptor and the ITAM adapter are critical for binding except in the case of the BCR, where a polar face mediates the interaction of Igα and Igβ with the receptor subunits.

It is now clear that ITAM-containing adapters are also involved in other nonimmunoreceptor signaling pathways in immune cells. Recent work has revealed that FcRγ and DAP12 participate in leukocyte integrin and plexin signaling (*8*–*10*), CD3ζ has been implicated in T cell CXCR4-mediated activation (*11*), and the lectin receptors either carry a novel ITAM-like sequence themselves or couple to FcRγ (*7*, *12*, *13*).

Leukocyte Integrins and ITAM Pathways

Two recent publications (*8*, *9*) have demonstrated that integrin "outside-in" signaling in leukocytes relies on an ITAM-based pathway. Integrins consist of transmembrane α and β chain heterodimers, which act as receptors for various vascular endothelial and extracellular matrix molecules. In resting blood cells, integrins adopt a folded conformation that restricts ligand binding. After leukocyte stimulation by chemokines, cytokines, or other activators of innate immune signaling, the integrins undergo a conformational change (referred to as "inside-out" signaling) that allows them to engage surface-bound ligands. Oligomerization of leukocyte integrins by their ligands leads to outside-in signals, which are critical for such processes as firm adhesion, cell spreading, migration, reactive oxygen species (ROS) production, and degranulation (*14*).

Although integrins are not known to associate with ITAM-containing adapters nor do they contain ITAMs in their cytoplasmic domains, there are many similarities between the signaling pathways downstream of classical immunoreceptors and those downstream of leukocyte integrins. Signaling through all the major integrins (β1, β2, and β3 types) in lymphocytes and myeloid cells (as well as in nonimmune cells such as platelets) depends on both Src family and Syk-ZAP70 family tyrosine kinases (*15*–*17*). Downstream signaling molecules such as SLP-76 and Vav family members, previously known to be associated with immunoreceptor signaling, are also required for integrin signaling; neutrophils and macrophages from knockout mice lacking these signaling molecules have integrin signaling defects that mirror those in cells from Src family—or Syk-deficient animals (*18*, *19*).

Two research groups (*8*, *9*) used retroviral infection of hematopoietic stem cells, followed by injection into irradiated recipient mice, to obtain genetically modified primary leuko-

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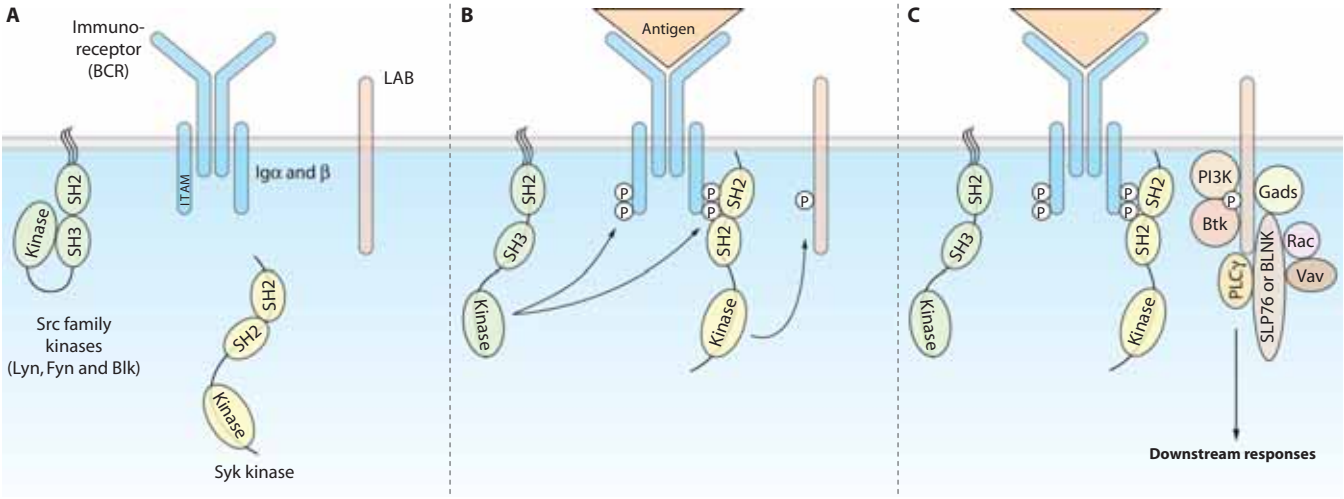

Fig. 1. Signal transduction by classical immunoreceptors. (**A**) Lymphocyte antigen receptor signaling, here exemplified by the BCR, is initiated after engagement of the receptor by antigen binding. (**B**) Through as-yet poorly defined mechanisms, antigen binding leads to activation of Src family kinases (in B cells, primarily Lyn, Fyn, and Blk) that in turn phosphorylate the ITAMs of the receptor-associated Igα and Igβ subunits. This phosphorylation creates a docking site for Syk (in B cells or ZAP70 in T cell signaling), which then associates with the phosphorylated ITAM adapters through the SH2 domains of the kinase. (**C**) Binding of phosphorylated ITAMs to Syk-SH2 domains activates the enzymatic activity of the kinase, leading to phosphorylation of other signaling adapter proteins, such as LAB (in B cells) or LAT (in T cells and platelets). These phosphorylated adapters then recruit a number of downstream molecules [such as SLP-76, phosphatidylinositol 3-kinase (PI3K), and Vav family members], some of which are also tyrosine phosphorylated by Syk to form a signaling complex at the membrane. Through activation of their individual functions (such as guanine nucleotide exchange by Vav proteins), downstream cellular responses occur, such as activation of MAPKs and actin cytoskeletal reorganization. This in turn induces cell-specific functional responses, such as proliferation and antibody secretion in B cells, proliferation and cytokine production in T cells, and degranulation and respiratory burst in myeloid cells.

cytes for testing whether integrin outside-in signaling depends on Syk SH2 function. By using this approach, both groups demonstrated that, although expression of wild-type Syk in Syk-deficient neutrophils restored normal β2 integrin signaling (as determined by adhesion-dependent ROS production), expression of an SH2 mutant of Syk did not. Furthermore, SH2 mutants of Syk failed to restore β3 integrin-dependent spreading responses of Syk-deficient platelets, indicating that different integrins from different cell types use a signaling pathway that depends on intact Syk SH2 domains (*6*). In both neutrophils and platelets, expression of kinase-inactive Syk also failed to rescue integrin signaling.

The requirement for intact SH2 domains in Syk for integrin signaling in leukocytes suggests that ITAM-containing molecules may be involved in the response. The major ITAM-containing adapters in myeloid cells are the FcRγ chain and the DAP12 molecule; myeloid cells lacking either FcRγ chain or DAP12 showed partial defects in β2 integrin signaling (as determined by cell spreading, ROS production, and degranulation), whereas cells lacking both adapters were completely defective in β2 integrin signaling and mimicked the phenotype of Syk-deficient cells (*7*). Expression of wild-type DAP12 in neutrophils deficient in both adapters restored integrin signaling (to the extent of that in FcRγ-deficient cells), whereas expression of an ITAM mutant of DAP12 was completely ineffective at restoring integrin signaling (*7*). Although neutrophils required both the FcRγ chain and DAP12 for integrin signaling, macrophages relied primarily on DAP12 (*7*). Overall, these studies demonstrate that outside-in signaling through the major integrins on myeloid leukocytes is mediated by the ITAM-containing proteins FcRγ and DAP12 in a process closely mimicking classical immunoreceptor signaling.

The mechanism linking leukocyte integrins to ITAM-containing adapters is unclear. Integrins do not possess charged residues in their transmembrane domains, as predicted by computer modeling (*20*), and no direct association between the β2 integrin and DAP12 or FcRγ has been detected. However, the ability of DAP12 to appropriately transmit integrin signals, like its association with classical immunoreceptors, appears to require its transmembrane charged residue. This suggests that an indirect association of integrins with a DAP12- or FcRγ-linked receptor may be involved in mediating the response (Fig. 2A). Alternatively, residues outside of the integrin transmembrane domain could mediate coupling to DAP12 and FcRγ, or association between integrins and ITAM adapters could occur through colocalization in lipid microdomains or intracellular compartments.

Although most responses downstream of leukocyte integrin signaling appear to be mediated through ITAM pathways, it is clear that some integrin-dependent responses use different mechanisms. For example, leukocyte migration is normal in mice lacking Src family kinases, Syk, Vav, SLP-76, or DAP12 and FcRγ (*9*, *16*, *18*, *19*). In nonimmune cells, integrin signaling is clearly important for many cellular functions, such as neurogenesis, tumor cell migration, and adhesion-mediated differentiation (*21*). Yet classical ITAM-containing adapters are not present in most nonimmune cells; therefore, the integrins in these cells must signal in different fashions. The development of distinct ITAM-mediated integrin signaling pathways in leukocytes is logical given the fact that these cells must rapidly adhere and become activated while exiting the circulation and

ITAM adapters	Sequence of ITAM	Expression	Couple to receptors	Recruit Syk or ZAP70	References
Classical ITAMs (Consensus: YxxI/Lx $_{(6-12)}$ YxxI/L)					
DAP12	ESPYQELQGQRSDVYSDL	Myeloid and NK cells (less abundant on some T and B cells, osteoclasts, microglia)	NKG2D-S, KIR-2D, Ly49, TREM1, 2, 3. (integrins, plexin A1)	Syk or ZAP70	(*4, 5, 9, 22*)
FcRγ	DGVYTGLSTRNQETYETL	Broad hematopoietic expression	FcεR, FcγR, OSCAR, PIR-A, Dectin-2, GPVI, TCR (integrins)	Syk	(*1, 9, 31, 38*)
Igα, Igβ	ENLYEGLNLDDCSMYEDI DHTYEGLDIDQTATYEDI	B cells	BCR, MHC class II	Syk	(*2, 33*)
CD3ζ	DGLYQGLSTATKDTYDAL	T cells	TCR, CXCR4	ZAP70	(*3, 19*)
Nonclassical ITAMs					
Moesin	VLEYLKIAQDLEMYGVNYFSI	Broad expression, hematopoietic, endothelial, epithelial	PSGL-1	Syk	(*27*)
Dectin-1	MEYHPDLENLDEDGYTQL	Myeloid cells (less abundant in DCs and T cells)		Syk	(*7*)
CLEC2	MQDEDGYITL	Myeloid cells, DCs, platelets		Syk	(*6*)
RhoH	PLSYQQADVVLMCYSVA	Hematopoietic cells (most abundant in thymus and T cells)		ZAP70	(*30*)
MMTV Env	AYDYAAIIVKRPPYVLL	Viral envelope protein of MMTV		Syk	(*35, 36*)
EBV LMP2A	HSDYQPLGTQDQSLYLGL	Infected B cells (required for latency)		Syk	(*37*)

Table 1. Examples of ITAM-containing proteins used for signaling in immune cells. The table lists classical and nonclassical ITAM-containing adapters, the amino acid sequence of the ITAM itself (taken from the human gene), the cell types in which the adapter is expressed, the receptors with which they couple, and the downstream kinases they recruit.

entering into inflammatory sites. The potential role of nonclassical ITAM-based pathways downstream of integrins in nonimmune cells has not been investigated.

Chemokine Receptors and ITAM Pathways

Chemokine receptors are seven transmembrane domain–containing heterotrimeric guanine nucleotide–binding protein (G-protein)–coupled receptors that initiate downstream signaling through Gα and βγ subunits. The ligand stromal cell-derived factor 1α (SDF-1α) acts through the CXCR4 receptor on various cell types; in T cells, SDF-1α mediates adhesion, chemotaxis, and TCR costimulation. In particular, SDF-1α stimulation of T cells results in prolonged activation of the mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinase (ERK) 1 and 2.

New evidence suggests that this effect may be mediated by an ITAM-dependent pathway (Fig. 2B). Stimulation of Jurkat cells lacking either ZAP70 or SLP-76 demonstrated a role for these signaling molecules in the prolonged ERK activation (*22*). The major ITAM-containing proteins in T cells are subunits of the TCR (ε, δ, γ, and ζ), and a recent study examined whether these molecules are also involved in prolonged ERK activation (*11*). This study showed that CXCR4 coimmunoprecipitates and colocalizes with the ITAM adapter CD3ζ after SDF-1α treatment of Jurkat T cells. TCRβ-deficient Jurkat cells, which lack the surface TCR, failed to show prolonged ERK activation in response to SDF-1α. Expression of the CD3ζ cytoplasmic domain in these cells, as a chimera with the extracellular and transmembrane regions of CD8, rescued the defect in ERK activation, but expression of CD3ζ containing mutant ITAMs did not. These data suggest that the CXCR4 receptor can signal through an ITAM-dependent pathway by using subunits of the TCR.

The mechanism of CXCR4 coupling to downstream ITAM pathways is unclear. No phosphorylation of ZAP70 or CD3ζ in response to SDF-1α stimulation was detected. The authors suggested that a pool of constitutively phosphorylated ZAP70 is used, but it is perhaps more likely that only a small fraction of these molecules are involved. Nevertheless, alterations in signaling downstream of the TCR as a result of SDF-1α signaling could have important consequences for thymic selection or T cell responses to antigenic stimulation.

The convergence of chemokine and other ITAM-dependent pathways, such as those involving BCR and FcR signaling, may

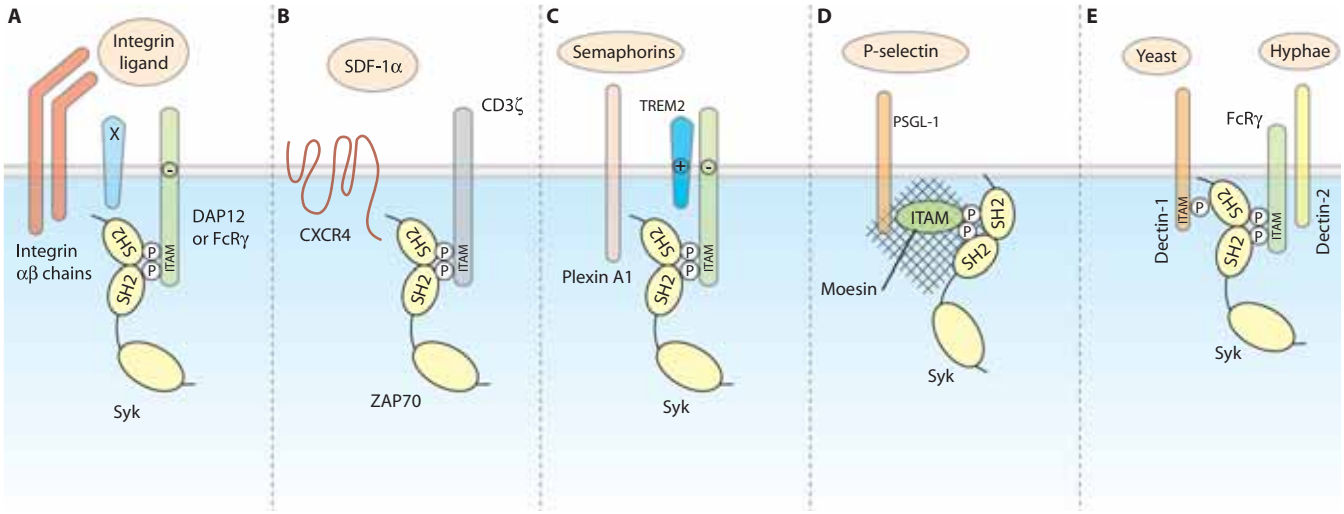

Fig. 2. Nonimmunoreceptors that use ITAM-containing adapters for signaling. Examples of cell surface receptors, unrelated to classical immunoreceptors, that activate Syk or ZAP70 kinases through ITAM-dependent pathways. (**A**) Signaling through leukocyte integrin β2 involves phosphorylation of the ITAM adapters FcRγ and DAP12, which leads to Syk activation. The mechanism of ITAM adapter recruitment by integrins is unclear, hence the use of protein X to designate a potential role of a yet-unidentified immunoreceptor in integrin signaling. (**B**) The chemokine receptor CXCR4 uses classical immunoreceptor components, such as CD3ζ, to activate ZAP70 upon ligand (SDF-1α) binding. (**C**) The semaphorin receptor plexin-A1 facilitates Syk activation through DAP12 by recruiting classical immunoreceptors themselves, such as TREM2. (**D**) The receptor for P-selectin, PSGL-1, recruits the nonclassical ITAM-containing actin-binding protein moesin to mediate Syk activation. (**E**) The C-type lectin receptors activate Syk either through a nonclassical ITAM in the cytoplasmic domain of the receptor itself (as in the case of dectin-1) or through the recruitment of the ITAM adapter FcRγ.

play important roles in other cell types as well. For instance, Syk is tyrosine phosphorylated after SDF-1α treatment of the pro B cell line BAF3 (*23*). In addition, negative regulation of neutrophil chemokine signaling occurs through an immunoreceptor tyrosine-based inhibitory motif (ITIM) pathway similar to negative regulation of classical immunoreceptors (*24*).

Plexin-A1 and ITAM Pathways

Plexin-A1 is a receptor for semaphorins, which are secreted, transmembrane, or glycosylphosphatidylinositol (GPI)-linked proteins defined by cysteine-rich protein domains that regulate cell attachment and motility. Despite its wide expression in various tissues, mice deficient in plexin-A1 show defects mainly in immune and skeletal tissues (*10*). The immune dysfunction in plexin-A1–deficient animals manifests as an impaired ability of dendritic cells (DCs) to induce antigen-specific T cell responses in vitro or in vivo. The immunoreceptor TREM2, which is highly expressed in DCs, has recently been identified as a plexin-A1–associating receptor (Fig. 2C), potentially explaining the reduced antigen presentation in plexin-A1–deficient mice. The association of plexin-A1 with TREM-2 thus links the semaphorin receptor to DAP12- and ITAM-dependent signaling pathways (*10*). Stimulation of RAW264.7 macrophages overexpressing plexin-A1, TREM2, and DAP12 with soluble sema6D, a ligand for plexin-A1, results in tyrosine phosphorylation of DAP12. Additionally, incubation of bone marrow DCs with sema6D induces maturation [similar to other agonists of DAP12 signaling (*25*)].

Sema6D stimulation of myeloid precursors also induced their development into osteoclasts. Indeed, loss of hematopoietic expression of plexin-A1 produces a defect in bone development (osteopetrosis) very similar to that seen in mice lacking TREM2 or DAP12 (*26*). Previous evidence had indicated that phosphorylation of DAP12 and the ability of DAP12 to form phospho-ITAM-SH2 interactions with Syk are also crucial for osteoclast development (*27*). Therefore, it appears that the nonimmunoreceptor plexin-A1, which is expressed in various cells and has predominately been implicated in axon guidance and skeletal muscle development, uses ITAM-mediated signaling pathways for activation of DCs and osteoclast precursors. In this case, the plexin-A1 receptor activates the ITAM pathway indirectly, by association with a classical immunoreceptor, TREM2. The mechanism linking plexin-A1 to TREM2 is unclear.

PSGL-1 and ITAM Pathways

The leukocyte adhesion molecule P-selectin glycoprotein ligand (PSGL-1) recognizes endothelial P-selectin and mediates tethering and rolling of leukocytes during the initial steps of inflammation. Engagement of P-selectin by PSGL-1 initiates a number of signaling responses in the leukocyte, including activation of both Syk kinase and the MAPK cascade, rearrangement of the actin cytoskeleton, and expression of various pro-inflammatory chemokines (*28*). During leukocyte attachment to vascular P-selectin, PSGL-1 physically associates with the actin cytoskeleton through the actin-binding proteins ezrin and moesin (*29*). In addition, PSGL-1 associates with Syk in myeloid cell lysates. Experiments using ^{35}S-labeled Syk produced in an in vitro reticulocyte lysate and a moesin–glutathione *S*-transferase (GST) fusion protein suggested that the interaction between PSGL-1 and Syk might be mediated through moesin. Mutation of an ITAM-like sequence present in moesin prevents its association with Syk

and blocks the ability of PSGL-1 to signal after ligand engagement. Thus, activation of Syk kinase by PSGL-1 occurs through a nonclassical ITAM-like sequence present in the actin-binding protein moesin (Fig. 2D). Like immunoreceptor signaling, the PSGL-1–Syk interaction depends on intact lipid raft structures; depletion of raft-associated cholesterol blocks the ability of PSGL-1 to activate Syk kinase and reduces the capacity of leukocytes to roll on P-selectin–coated surfaces (*30*).

Lectin Receptors and ITAM Pathways

Recently, the C-type lectin receptor dectin-1 has been found to activate immune cell function through a Syk kinase–ITAM–like pathway (Fig. 2E) (*7*, *12*). Dectin-1, which binds β-glucan structures in the yeast cell wall, is the main receptor used by macrophages and DCs to phagocytose yeast particles. Engagement of dectin-1 also initiates cytokine and ROS production in macrophages and DCs in a signaling reaction that depends on Syk.

Syk-deficient macrophages can still phagocytose yeast particles, but they fail to produce ROS. Syk-deficient DCs show defects in phagocytosis, in addition to their inability to release interleukin-2 (IL-2) or IL-10 upon dectin-1 engagement. The ability of dectin-1 to activate Syk is thought to be mediated by a nonclassical ITAM-like sequence in the cytoplasmic tail of the receptor. The interaction between dectin-1 and Syk appears not to require the first tyrosine in the ITAM; however, mutation of the second tyrosine blocked the ability of the receptor to activate Syk and resulted in loss of cytokine release after receptor engagement.

The platelet lectin receptor CLEC-2 (C-type lectin-like receptor 2) has a single tyrosine–containing ITAM-like sequence similar to that of dectin-1. CLEC-2 becomes tyrosine phosphorylated by Src kinases upon ligand engagement and induces platelet activation that depends on Syk (*6*). These data suggest that monophosphorylation of an ITAM may be sufficient to recruit Syk, perhaps with a lower binding affinity. A suboptimal ITAM-like sequence has also been identified within the small guanine triphosphatase (GTPase) RhoH (*31*). RhoH may bind to ZAP70, although how tyrosine phosphorylation regulates this interaction in resting cells is unclear. Upon TCR stimulation, RhoH could shuttle ZAP70 to the membrane, where the predicted higher-affinity phosphorylated CD3ζ ITAMs would effectively compete for ZAP70 binding (*31*).

A second lectin receptor, dectin-2, appears to engage ITAM signaling pathways by directly associating with the FcRγ chain (*13*). Dectin-2, which is highly expressed by DCs and activated macrophages, recognizes the hyphal forms of various organisms, including *Candida albicans* and the dermatophytes *Microsporum* and *Trichophyton*. Binding of hyphae from these organisms to macrophages through dectin-2 activates a tyrosine kinase signaling pathway that leads to pro-inflammatory cytokine release. Coimmunoprecipitation analysis revealed that dectin-2 is physically associated with the FcRγ chain (*13*) and that cross-linking of dectin-2 leads to Src family kinase–dependent phosphorylation of FcRγ. Pharmacologic blockade of Src family kinases in macrophages impaired their ability to respond to *C. albicans* hyphae. Together, these data suggest that the lectin receptors dectin-1 and dectin-2 both couple to ITAM pathways to affect leukocyte activation.

Major Histocompatibility Complex (MHC) Class II and ITAM Pathways

Engagement of MHC class II molecules on the surface of antigen-primed B cells leads to increased total cellular protein tyrosine phosphorylation (*32*). The cytoplasmic tail of MHC class II proteins is very short and is not required for this phenomenon (*32*). Recent data have identified the ITAM adapters Igα and Igβ, normally thought to be used exclusively by the BCR, as important for transducing signals from MHC class II molecules, leading to tyrosine kinase activation and calcium mobilization (*33*). The mechanism coupling the MHC class II molecules to the ITAM adapters is unclear, although this complex is distinct from BCR complexes containing Igα and Igβ. The requirement for the ITAM tyrosines has not been tested.

Use of ITAM Adapters by Viral Proteins

ITAM-like sequences have been identified in a number of viral proteins (34), including the env gene of mouse mammary tumor virus (MMTV), which encodes an envelope protein that mediates viral entry (35). Mutation of this ITAM-like sequence blocks the ability of the virus to induce cellular transformation in cell lines and in vivo without affecting viral replication (36). MMTV uses its own ITAM-like sequence to hijack a cellular signaling pathway and activate Syk, leading to tumorigenesis. The Epstein-Barr virus encoded protein LMP2A (latent membrane protein 2A) also has an ITAM-like sequence, which has recently been shown to be required for induction of epithelial cell migration through activation of Syk (37). In this context, it is possible that Syk-ITAM–mediated signaling pathways extend beyond the immune system and may involve nonhematopoietic cells as well.

Summary

It has become abundantly clear that activation of immune cells by many different receptors, not just those of the immunoreceptor family, depends on a common ITAM-based signaling pathway (Fig. 2). In some cases, receptors use ITAM-containing adapters such as FcRγ or CD3ζ, previously thought to associate only with immunoreceptors, and in other cases receptors use ITAM-like sequences present in what were thought to be nonsignaling molecules (like the actin-binding protein moesin). Indeed, it even appears that the TCR can use ITAM-containing adapters generally not considered to be part of the receptor complex, based on the recent description of the requirement for FcRγ-mediated Syk activation downstream of the TCR in $CD4^{-}/CD8^{-}$ T regulatory cells (*38*). It is likely that additional signaling receptors may rely on ITAM-like mechanisms, because simple computer searches demonstrate that ITAM-like sequences are found in many intracellular molecules (*39*).

For both nonimmunoreceptors and viral proteins using ITAM-based signaling pathways as described above, it remains unclear how well the full ITAM paradigm is preserved; for example, is Src family kinase–mediated ITAM phosphorylation involved in all cases? Similarly, for most of the nonimmunoreceptors, it remains unclear how activation of the ITAM pathway is linked to ligand binding of the receptor. Linkage may occur through binding to ITAM-associated receptors (as suggested for plexin-A1 and TREM2) or through colocalization in membrane raft domains (as suggested for PSGL-1 and moesin).

The molecular details of how engagement of a nonimmunoreceptor leads to ITAM phosphorylation and Syk acti-

vation are also murky; indeed, these first steps are not fully understood downstream of classical immunoreceptors either. Nevertheless, there is a growing recognition that numerous receptors beyond just the classical immunoreceptors use ITAM-containing molecules to recruit and activate Syk and ZAP70 for initiation of downstream signals. In this light, therapeutic modulation of ITAM-based signaling pathways may have broader implications than originally envisioned.

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