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T-cell signalling and immune system disorders

Beverley Wilkinson, Jocelyn S. Downey and Christopher E. Rudd

T-cell receptor (TCR) engagement initiates intracellular signalling cascades that lead to T-cell proliferation, cytokine production and differentiation into effector cells. These cascades comprise an array of protein-tyrosine kinases, phosphatases, GTP-binding proteins and adaptor proteins that regulate generic and specialised functions. The integration of these signals is essential for the normal development, homeostasis and function of T cells. Defects in a single mediator can produce T cells that are unable to participate fully in an immune response and/or that mount an inappropriate response, which leads to immunodeficiency, autoimmunity or leukaemia/lymphomas. This review highlights some of the key players in T-cell signalling and their involvement in the development of various clinical disease states. Some of these immune-specific signalling proteins are attractive potential targets in the development of therapies to augment T-cell responses to antigen or tumours, and to treat immune cell disorders.

T cells are of central importance to the immune system, orchestrating functions as diverse as cytokine and antibody production, the generation of cytotoxic T lymphocytes (CTLs), and tolerance to self-antigen. They express an array of unique surface molecules that include the T-cell receptor complex (TCRζ–CD3), co-receptors such as CD28, ICOS (inducible co-stimulator) and CTLA-4 (cytotoxic T-lymphocyte antigen 4), and adhesion receptors such as LFA-1 (leukocyte

Beverley Wilkinson
Research Associate, Molecular Immunology Section, Department of Immunology, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK. Tel: +44 (0)20 8383 8421; Fax: +44 (0)20 8383 8434

Jocelyn S. Downey
Research Fellow, Molecular Immunology Section, Department of Immunology, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK. Tel: +44 (0)20 8383 8421; Fax: +44 (0)20 8383 8434

Christopher E. Rudd (corresponding author)
Professor of Haematology, Molecular Immunology Section, Department of Immunology, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK. Tel: +44 (0)20 8383 8421; Fax: +44 (0)20 8383 8434; E-mail: c.rudd@imperial.ac.uk

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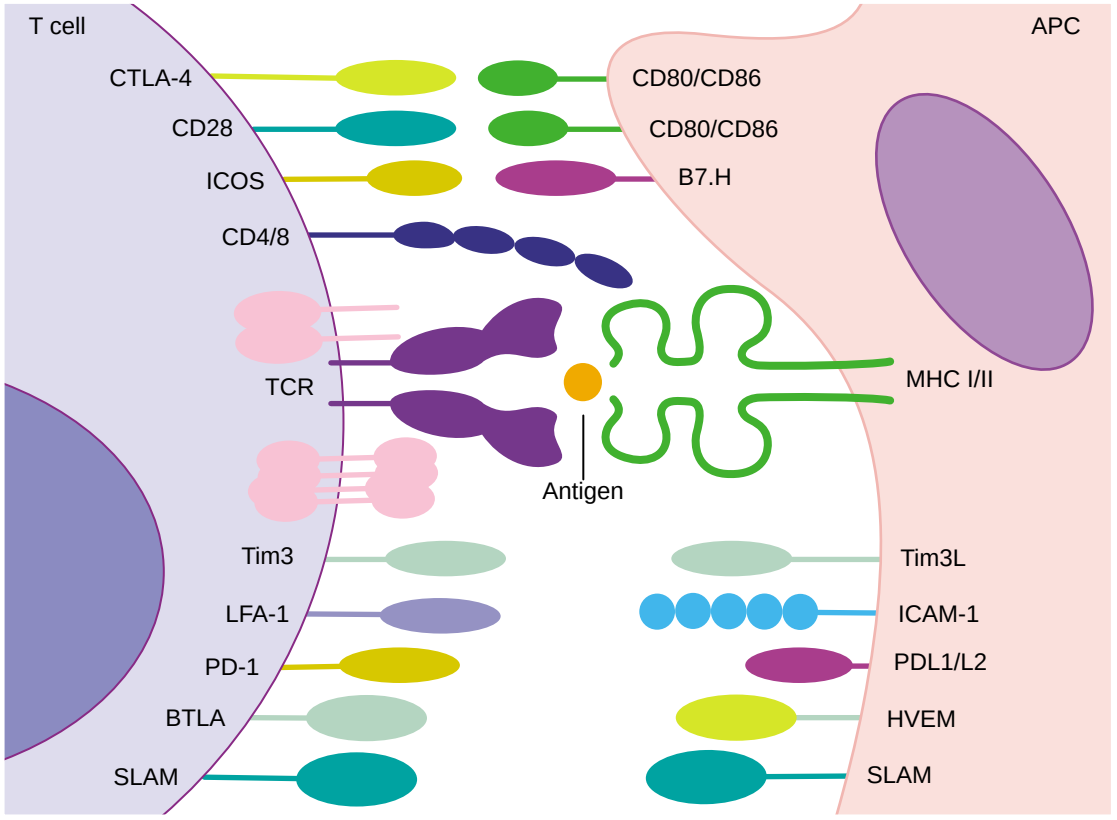

Receptors on T cells and their ligands on antigen-presenting cells

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Figure 1. Receptors on T cells and their ligands on antigen-presenting cells. T cells express an array of surface receptors that interact with ligands on antigen-presenting cells (APCs). The T-cell receptor (TCR) and associated CD3 subunits (shown in pink) are engaged by a specific peptide antigen presented by the major histocompatibility complex (MHC). CD4 and CD8 bind to non-polymorphic determinants in class II and I antigens, respectively. Co-signals are provided by CD80/CD86 binding to CD28 and CTLA-4, ICOS binding to B7.H, Tim3 binding to Tim3L, SLAM–SLAM binding, PD-1 binding to PDL1/L2, and BTLA binding to HVEM; other interactions such as LFA-1 binding to ICAM-1 and CD2 binding to CD48/58 (not shown) are important for the adhesion between T cells and APCs. Abbreviations: BTLA, B- and T-lymphocyte attenuator; CTLA-4, cytotoxic T-lymphocyte antigen 4; HVEM, herpesvirus entry mediator; ICAM-1, intercellular cell adhesion molecule 1; ICOS, inducible co-stimulator; LFA-1, leukocyte function-associated antigen 1; PD-1, program death 1 receptor; SLAM, signalling lymphocyte activation molecule; Tim3, T-cell immunoglobulin- and mucin-domain-containing molecule 3.

function-associated antigen 1) (Fig. 1). The T-cell compartment comprises subsets of cells such as T helper 1 (Th1) and T helper 2 (Th2) cells (Ref. 1). Each subset expresses different cytokines and regulates distinct functions. Th1 cells produce interferon (IFN)-γ, interleukin (IL)-2 and tumour necrosis factor (TNF)-α, and are involved in cell-mediated immunity and delayed-type hypersensitivity reactions. These responses are important against intracellular infections such as tuberculosis, and a failure to overcome this infection is strongly associated with an inability to mount a competent Th1 response (Ref. 2). Autoimmune and chronic inflammatory diseases such as multiple sclerosis, type II diabetes and rheumatoid arthritis have also been described as Th1-dominant diseases. By contrast, Th2 cells are characterised by the production of interleukins

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IL-4, IL-5, IL-10 and IL-13, and regulate humoral responses. Th2 responses dominate in defence against parasitic infections, such as helminth infections, effect the activation of mast cells and eosinophils, and are associated with atopy and allergy (Ref. 1). Clinical outcomes are determined by the different cell-surface receptors and signalling events that account for distinct T-cell functions. Altered signalling therefore impacts on molecular medicine and the development of immune-cell-based pathologies.

Kinases and the T-cell signalling paradigm

T-cell signalling is initiated by the coordinate binding of the TCRζ–CD3 complex on T cells to peptide presented by major histocompatibility complex (MHC) antigens (class I and II) on antigen-presenting cells (APCs). The concomitant binding of CD4 and CD8 to conserved sites on their respective class II and I antigens brings the initiator signalling complexes, CD4–Lck and CD8–Lck , into the proximity of the cytoplasmic domains of the TCRζ and CD3 chains (Refs 3, 4, 5) (Fig. 2a). CD4/CD8-associated Lck ($p56^{lck}$) is a protein-tyrosine kinase (PTK) that phosphorylates immunoreceptor-based tyrosine activation motifs (ITAMs) of the TCR complex. These sites in turn bind to two Src-homology 2 (SH2) domains of other PTKs: zeta-associated protein 70 (ZAP-70) or related SYK (Refs 6, 7). Other PTKs such as the Tec-family kinases IL-2-inducible kinase (ITK) and resting T-cell kinase (RLK) also become activated (Ref. 8).

These phosphorylation events are required for the activation of phospholipase Cγ1 (PLCγ1), an enzyme that hydrolyses phosphatidylinositol (4,5)-bisphosphate [PtdIns(4,5)P_2], generating the second messengers diacylglycerol (DAG) and inositol (1,4,5)-trisphosphate [Ins(1,4,5)P_3]. DAG activates the serine/threonine protein kinase C (PKC) family, whereas the production of Ins(1,4,5)P_3 induces the release of intracellular Ca^{2+}, which activates the serine/threonine phosphatase calcineurin. Calcineurin dephosphorylates the transcription factor NFAT (nuclear factor for the activation of T cells), allowing it to translocate to the nucleus where it activates IL-2 transcription (Ref. 9) Other downstream signalling effectors include: the Rho family of GTPases; mitogen-activated protein kinases (MAPKs) including the extracellular-signal-regulated kinases (ERKs), p38 and c-Jun N-terminal kinase (JNK); serine/threonine protein kinases such as protein kinase C θ (PKC-θ); and the transcription factors nuclear factor κB (NF-κB) and activator protein 1 (AP-1).

Co-receptors such as CD28, ICOS, CTLA-4, PDL1 and Tim3 provide overlapping and unique signals (Refs 10, 11, 12). CD28, ICOS and CTLA-4 bind and activate the lipid kinase phosphoinositide 3-kinase (PI3K), which produces D3-lipids needed for the membrane localisation of numerous proteins with pleckstrin homology (PH) domains (Ref. 11). One classic pathway triggered by these co-receptors involves the activation of 3-phosphoinositide-dependent protein kinase 1 (PDK1), protein kinase B (PKB)/AKT and glycogen synthase kinase 3 (GSK-3) (Ref. 13).

Collectively, the combination of signals provided by an array of different mediators and surface receptors determines the ultimate nature of the T-cell response.

Tyrosine phosphatases

In addition to PTKs, over 60 protein-tyrosine phosphatases (PTPs) are expressed in T cells (Refs 14, 15, 16, 17). Contrary to PTKs, PTPs

Figure 2. The T-cell signalling paradigm. *(Legend; see next page for figure.)* (a) Initial phosphorylation events. Ligation of the TCRζ–CD3 complex and CD4/CD8–Lck induces phosphorylation of ITAMs on the TCRζ and CD3 chains. Phosphorylated ITAMs then bind in tandem to two SH2 domains of ZAP-70. Tyrosine phosphatase CD45 maintains activation of Lck by dephosphorylation of an inhibitory C-terminal phosphate. Subsequent events include Lck phosphorylation and binding to ZAP-70, resulting in ZAP-70 activation and the regulation of downstream substrates (i.e. adaptors LAT and SLP-76). (b) Regulation of Lck. The phosphorylated C-terminal tyrosine residue Y505 of Lck interacts with the internal SH2 domain, holding it in a closed, inactive state. In resting T cells, Cbp (Csk-binding protein)/PAG (phosphoprotein associated with glycosphingolipid-enriched microdomain) is tyrosine phosphorylated and recruits the kinase Csk, leading to increased phosphorylation of the Y505 site, which inhibits Lck activity. In response to TCR stimulation, these modifications are lost. By contrast to Cbp/PAG, CD45 dephosphorylates the regulatory tyrosine residue Y505, resulting in an unfolding and activation of the kinase. Cbp/PAG–Csk and CD45 therefore compete in the regulation of Lck. Abbreviations: ITAM, immunoreceptor-based tyrosine activation motifs; LAT, linker for activation of T cells; MHC, major histocompatibility complex; PTK, protein tyrosine kinase; SLP-76, SH2-domain-containing leukocyte protein of 76 kDa; TCR, T-cell receptor; SH2, Src-homology 2; ZAP-70, zeta-associated protein 70.

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remove the phosphate moiety from the tyrosine residue, either inhibiting or activating protein function. Among the PTPs, PTPN7 (protein-tyrosine phosphatase, non-receptor type 7; otherwise known as haematopoietic protein-tyrosine phosphatase, HePTP) inhibits TCR signalling by binding and inhibiting ERKs 1 and 2 (Ref. 18). The same PTP has no effect on JNK, or on events upstream of the MAPKs. Similarly, PTPN22 (otherwise known as Lyp1/Lyp2/PEP) is a powerful inhibitor of T-cell activation by the dephosphorylation of Lck, Fyn and ZAP-70 (Refs 19, 20).

Another key PTP is transmembrane CD45, an enzyme with seemingly paradoxical effects (Refs 14, 15, 16, 17). CD45 is an abundant surface

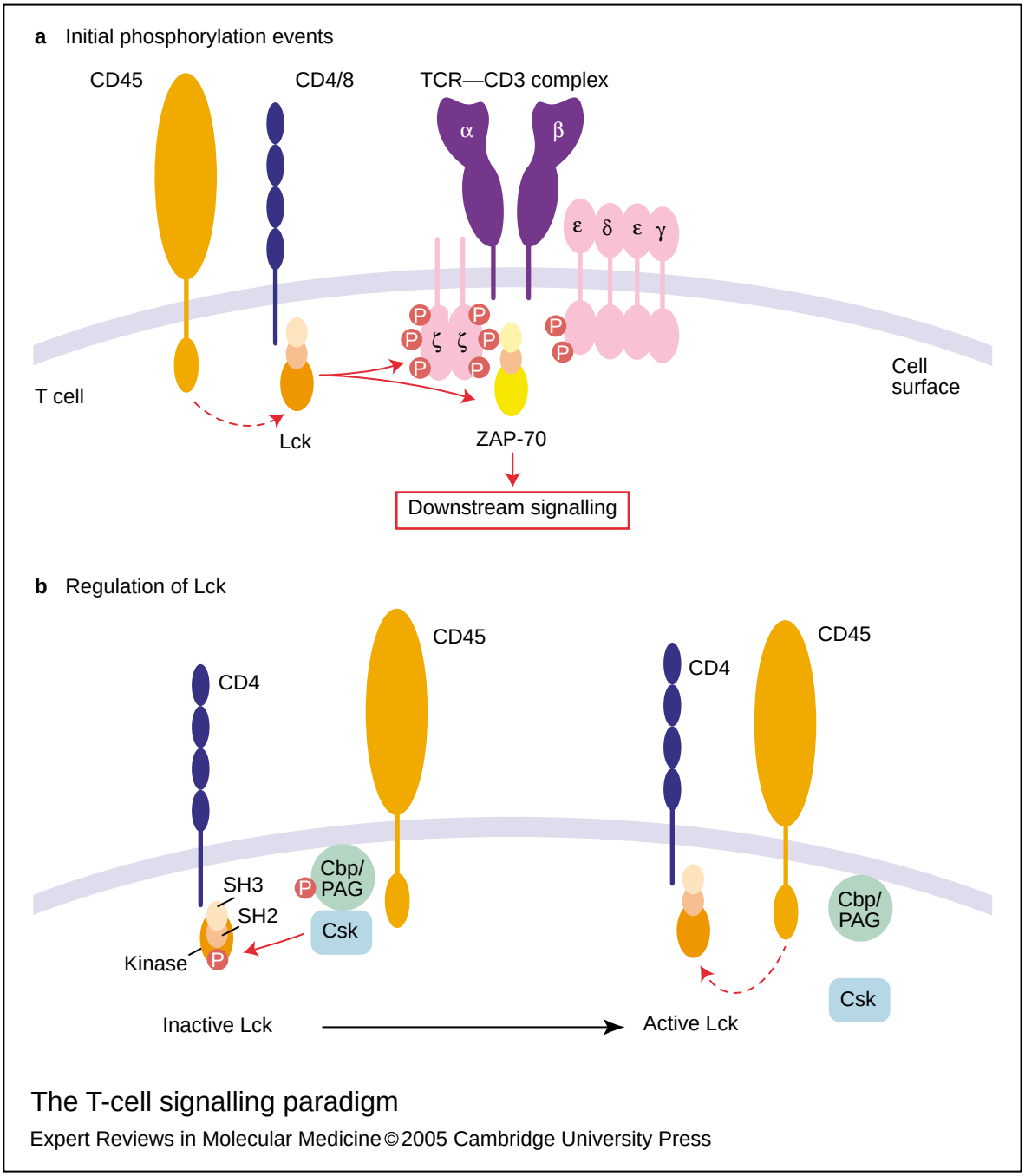

Figure 2. The T-cell signalling paradigm. *(See previous page for legend.)*

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protein with an extended ectodomain linked to a transmembrane region followed by a cytoplasmic tail with a PTP domain. Multiple isoforms are generated by alternative splicing and are expressed in an activation-state-specific manner. Naive T cells express all isoforms including CD45RA, whereas activated T cells express mainly the lower molecular weight CD45R0 isoforms. CD45-deficient T-cell lines are unresponsive to antigen-receptor stimulation (Ref. 21) and mice deficient in CD45 exhibit a block in B- and T-cell development and function (Ref. 22). Such studies support a crucial positive role for CD45 in antigen-receptor-mediated signalling during lymphocyte development and function.

The molecular basis underlying CD45 function has been the subject of much investigation over the past decade. One clear pathway involves CD45 dephosphorylation of a key conserved tyrosine at the C-terminal end of Src kinases (i.e. Y505 for Lck and Y528 for Fyn). The kinase is normally held in a closed, inactive conformation by an interaction between the phosphorylated tyrosine and the internal SH2 domain of the kinase. Dephosphorylation by CD45 unfolds and activates the kinase. This is thought to maintain a steady-state pool of dephosphorylated Lck (Fig. 2b). Lck and Fyn are hyperphosphorylated at the negative regulatory tyrosine residue in many $CD45^{-/-}$ cell lines (Ref. 23). Further, expression of the constitutively active Lck (i.e carrying the mutation Y505F) in CD45-deficient mice overcomes the block in T-cell development (Refs 24, 25).

By contrast, another PTK, Csk (C-terminal Src kinase), can phosphorylate the C-terminal tyrosines, thereby inactivating Lck and Fyn. Cbp (Csk-binding protein)/PAG (phosphoprotein associated with glycosphingolipid-enriched microdomain) regulates Csk function by recruiting the enzyme to the membrane and promoting its catalytic activity (Refs 26, 27) (Fig. 2b). Phosphorylated Cbp/PAG binds and activates Csk by reducing the K_m for Src kinases relative to free Csk. In resting T cells, PAG is tyrosine-phosphorylated and associated with Csk, and these modifications are lost in response to TCR stimulation. Cbp/PAG therefore competes with CD45 for the regulation of Lck and Fyn (Refs 14, 15, 16, 17, 25). CD45 may play a role in dephosphorylating Cbp/PAG. Since the Cbp knock-out mouse shows normal T-cell development and function, other, redundant mechanisms also appear to inhibit Lck kinase function.

Despite its positive regulatory role, an understanding of CD45 is complicated by its additional ability to dephosphorylate other sites with inhibitory effects. For example, CD45 can also dephosphorylate the autoregulatory site of Lck and Fyn (i.e. Lck 314 and Fyn 420) (Ref. 28), and can down-regulate Lck/Fyn kinase activity in thymocytes and during integrin-mediated adhesion in macrophages (Ref. 29). More revealing, mice expressing active Lck Y505F at non-oncogenic levels in normal mice develop aggressive thymic lymphomas on a $CD45^{-/-}$ background (Ref. 30). CD45 suppresses the kinase by dephosphorylating the Y394 autophosphorylation site. It can also indirectly inhibit T-cell function by up-regulating the expression of the inhibitory co-receptor CTLA-4 (Ref. 31). In addition, CD45 suppresses JAKs (Janus kinases) and negatively regulates cytokine receptor signalling. The targeted disruption of the CD45 gene enhances cytokine- and IFN-receptor-mediated activation of JAKs and STAT (signal transducer and activators of transcription) proteins (Ref. 32).

The conditions that regulate a net positive or negative role for CD45 in T cells remain to be determined. Future experiments on the spatiotemporal localisation of CD45 in T cells following activation might be useful to resolve this issue. Following TCR ligation, there is a re-arrangement of surface receptors that leads to the formation of the supramolecular complex (SMAC) in the immunological synapse (IS). The SMAC comprises a central cluster (c-SMAC) with TCR–CD3 and co-stimulatory receptors, such as CD4, CD2 and CD28, and a peripheral ring (p-SMAC) with LFA-1. Upon activation, CD45 may transiently enter the c-SMAC, the site of Src-family kinases (Ref. 33). CD45 activity might also be regulated by receptor dimerisation (Ref. 34). To date, a specific ligand for CD45 has yet to be identified.

Adaptors: integrators of T-cell signalling

In concert with the kinases and phosphatases, another group of proteins, known as adaptor proteins or molecular scaffolds, are also required for T-cell signalling. These proteins lack enzymatic activity but contain multiple motifs and domains that mediate binding to other proteins, enabling the formation of multiprotein complexes and the integrating of signals from the TCR (Refs 35, 36, 37). One central adaptor is the transmembrane adaptor LAT (linker for activation of T cells),

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which regulates PLCγ1 activation and Ca^{2+} mobilisation (Refs 38, 39). Other adaptors such as Wiskott Aldrich syndrome protein (WASP) and adhesion-and degranulation-promoting protein (ADAP) play more specialised and restricted functions such as integrin adhesion (Refs 36, 40).

Proximal adaptors in T cells

LAT

The ZAP-70 kinase, recruited to the TCR complex by CD4/CD8–Lck, can phosphorylate the adaptor proteins LAT and SLP-76 (SH2-domain-containing leukocyte protein of 76 kDa) (Refs 41, 42) (Fig. 3). LAT is a palmitoylated integral membrane protein composed of a short extracellular domain and a cytoplasmic tail with nine conserved tyrosine-based motifs (Refs 38, 39, 43). LAT-deficient mice are blocked at the pre-TCR stage in the thymus indicating that it is essential for pre-TCR signalling (Ref. 44). LAT-deficient Jurkat T cells show defects in TCR-induced Ca^{2+} mobilisation, ERK activation and in the activation of the transcription factors AP-1 and NFAT (Ref. 45). A more detailed view of LAT molecular pathways has come from the study of LAT mutants (Refs 46, 47, 48). LAT is phosphorylated by ZAP-70 on Y132, leading to the binding of PLCγ1, while other motifs in LAT bind to GADS (Grb2-related adaptor downstream of Shc) and Grb2 (growth-factor-receptor-bound protein 2). LAT knock-in mutant mice, in which LAT-deficient mice have been reconstituted with a form of LAT mutated in the PLCγ1-binding domain, exhibit a reduction in PLCγ1 phosphorylation and in Ca^{2+} mobilisation (Ref. 49). By contrast, ERK activation is intact. These knock-in mice show an increase in single-positive $CD4^+$ cells, and develop a polyclonal lymphoproliferative disorder with a skewed Th2 phenotype (Refs 49, 50).

SLP-76

GADS binding to LAT acts as a bridge to recruit the adaptor SLP-76 (Fig. 3). SLP-76 is composed of N-terminal tyrosine residues, a proline-rich region and a C-terminal SH2 domain (Ref. 51). GADS binds to a proline-rich region of SLP-76 (Ref. 52). The other regions can mediate further protein interactions. The N-terminal tyrosines can be phosphorylated by ZAP-70 and ITK/RLK (Refs 41, 42), and bind to three proteins: the guanine-nucleotide-exchange factor (GEF) VAV-1 (Refs 41, 53, 54), the adaptor NCK (Ref. 55) and the kinase ITK (Refs 56, 57). VAV-1 and NCK can re-model the cytoskeleton: VAV-1 can directly activate the GTP-binding protein Rac1, whereas NCK can recruit WASP to initiate actin re-modelling (Refs 55, 58). The importance of SLP-76 has been underscored by the phenotype of knock-out mice and cell lines. SLP-76-deficient Jurkat T cells show a selective defect in the phosphorylation of PLCγ1 that leads to defects in Ca^{2+} mobilisation and NFAT function (Refs 59, 60). The binding of ITK and RLK is thought to couple SLP-76 to PLCγ1 phosphorylation (Refs 56, 57, 60).

SLP-76-deficient mice also show a block at the CD4/CD8 double-negative stage of thymic development (Refs 61, 62). This is indicative of a role for SLP-76 in pre-TCR signalling. Reconstitution with transgenes has in turn demonstrated a differential requirement for specific domains in SLP-76 function (Refs 63, 64). Unlike the N-terminal tyrosines, the C-terminal SH2 domain is not needed for thymic differentiation, but rather is needed for the ability of T cells to respond to antigen. In this context, the SH2 domain binds to another adaptor termed ADAP, a regulator of integrin adhesion (Refs 65, 66). This raises the possibility that different regions of SLP-76 can be targeted in the treatment of immune-mediated diseases.

SAP

Another key adaptor on T cells is signalling lymphocytic activation molecule (SLAM)-associated protein (SAP). The SLAM family comprises a group of six immunoglobulin-like receptors named SLAM (or CD150), 2B4 (or CD244), Ly-9 (or CD229), NK-T-B antigen (NTB-A) (or Ly-108), CD84 and CD2-like receptor activating cytotoxic T cells (CRACC). In addition to serving as a self-ligand, SLAM in conjunction with CD46 may serve as the receptor for the human pathogen measles virus by binding to the virus haemagglutinin protein. SAP is a single-SH2-domain protein adaptor that binds to a unique motif (TxYxxV/I) on the cytoplasmic tail of SLAM and five SLAM-related receptors (Refs 67, 68, 69). While antibody ligation of SLAM augments T-cell proliferation and IFN-γ secretion, SLAM ligation in the presence of SAP promotes the recruitment and activation of kinase Fyn, thereby promoting the phosphorylation of SHIP-1 (SH2-domain-containing inositol polyphosphate phosphatase-1), Dok ('downstream of tyrosine kinases') and RasGAP, resulting in the inhibition of IFN-γ secretion (Refs 69, 70, 71). SAP operates in this pathway by binding to the SH3

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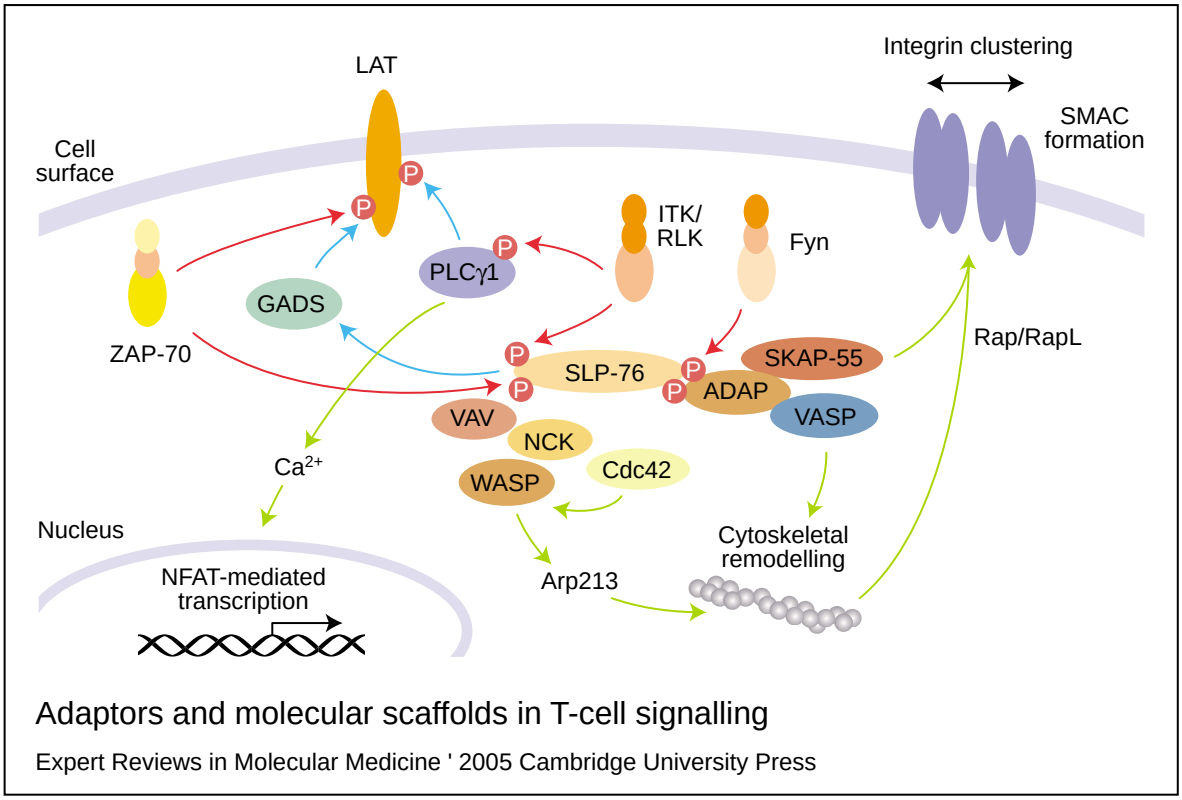

Figure 3. Adaptors and molecular scaffolds in T-cell signalling. Ligation of the T-cell receptor results in activation of the Syk-family protein tyrosine kinase ZAP-70 (see Fig. 2). ZAP-70 subsequently phosphorylates LAT (localised to a lipid raft) and SLP-76, allowing them to interact with SH2-containing proteins. SLP-76 and its associated molecules are recruited to LAT in the plasma membrane through an interaction with GADS. This leads to the SLP-76-dependent activation of PLCγ1, dependent on kinases ITK and RLK, which results in protein kinase C activation (not shown), intracellular Ca^{2+} mobilisation, and NFAT-mediated transcription. Phosphorylation of SLP-76 allows SH2-mediated binding to the adaptors VAV and NCK. The NCK–VAV–SLP-76 complex binds to WASP, which activates the Arp2/3 complex, leading to cytoskeletal reorganisation. SLP-76 also binds to ADAP in a pathway that is modulated by Fyn. ADAP in turn associates with SKAP-55, which is also needed for integrin clustering and adhesion. In addition, ADAP binds to Ena/VASP proteins, which, together with Cdc42 and WASP, influences actin remodelling. The putative SLP-76–ADAP–SKAP-55 complex is required for integrin (i.e. LFA-1) clustering and adhesion, and SMAC formation at the immunological synapse. The GTP-binding protein Rap-1 and its ligand RapL act further downstream in this pathway. In the figure, red arrows indicate the action of kinases; blue arrows indicate associations with adaptor proteins; and green arrows indicate downstream effector functions. Abbreviations: ADAP, adhesion-and degranulation-promoting protein; Arp2/3, actin-related proteins 2 and 3; GADS, Grb2-related adaptor downstream of Shc; ITK, IL-2-inducible kinase; LAT, linker for activation of T cells; LFA-1, leukocyte function-associated antigen 1; NCK, noncatalytic region of tyrosine kinase adaptor protein 1; NFAT, nuclear factor for the activation of T cells; PLCγ1, phospholipase Cγ1; RLK, resting T-cell kinase; SKAP-55, Src-family-kinase-associated phosphoprotein of 55 kDa; SH2, Src-homology 2; SLP-76, SH2-domain-containing leukocyte protein of 76 kDa; SMAC, supramolecular complex; VASP, vasodilator-stimulated phosphoprotein; WASP, Wiskott Aldrich syndrome protein; ZAP-70, zeta-associated protein 70.

domain of Fyn, through a second region in the SAP SH2 domain distinct from the phosphotyrosine-binding motif. This interaction is essential for SAP-mediated signalling in T cells, and for the capacity of SAP to modulate immune cell function (Refs 70, 71, 72, 73).

Adaptors and adhesion

TCR ligation leads to the rapid re-modelling of the actin cytoskeleton, which is needed for T-cell motility, adhesion and T-cell–APC conjugate formation. Control of this process is mediated by VAV-1, WASP, the GTP-binding protein Rap1 and

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other proteins (Refs 35, 36, 37, 40, 74, 75, 76, 77, 78, 79). VAV-1 is a multidomain protein that acts as a GEF for the Rho-family GTPase Cdc42, which, following activation, binds and activates WASP (Ref. 74). Tyrosine phosphorylation of LAT and SLP-76 is important for the recruitment of WASP and NCK and the polymerisation of actin (Refs 40, 58, 75). WASP consists of an N-terminal EVH1 domain, a Cdc42/Rac-GTPase-binding domain (GBD), a proline-rich region, and a C-terminal VCA domain ('verprolin homology, cofilin homology, acidic region'). Binding of an SH3 domain of NCK to WASP, together with binding of the VCA domain of WASP to the Arp2/3 complex (actin-related proteins 2 and 3), allows Arp2/3-complex-mediated actin polymerisation (Ref. 55) (Fig. 3). T cells lacking VAV-1 or WASP are defective in TCR clustering, which severely compromises T-cell activation and proliferation (Refs 80, 81).

Intimately connected to the cytoskeleton is the clustering of receptors on the surface of cells. Among these are the TCR complex and the adhesion receptor LFA-1. LFA-1 binds to the ligand ICAM-1/2, an event that is needed for the formation of T-cell conjugates with APCs and the migration of T cells to peripheral compartments. LFA-1 adhesion is induced by altered conformation and the clustering of receptors (Refs 82, 83). Clustering leads to the localisation of LFA-1 in the p-SMAC at the T-cell–APC interface (Refs 84, 85). Clustering requires multiple proteins: VAV-1, WASP, Rap1, its ligand RapL and the adaptors ADAP and SKAP-55 (Src-family-kinase-associated phosphoprotein of 55 kDa). VAV-1-deficient T cells are defective in LFA-1 clustering (Ref. 86). Rap1 is a GTP-binding protein with homology to Ras ($p21^{ras}$) and was initially found to act as a competitive inhibitor of the Ras–ERK pathway (Ref. 87). Binding of activated Rap1 to RapL is required for integrin clustering, and a dominant-negative form of RapL that abrogates LFA-1 interaction with ICAM-1 inhibits T-cell–APC conjugation (Ref. 88).

ADAP

SLP-76 plays a role in the regulation of LFA-1 clustering through its association with the downstream adaptor ADAP (Refs 35, 36, 37) (Fig. 3). ADAP contains several proline-rich regions and an SH3 domain that mediate binding to SKAP-55, along with 16 tyrosine-containing motifs, two putative nuclear localisation sequences (NLSs), and an EVH1 binding site [Ena (Enabled)/VASP (vasodilator-stimulated phosphoprotein)-homology-1-domain-binding site] that allows binding to proteins of the Ena/VASP family (Refs 65, 66). Two isoforms of ADAP, of 120 and 130 kDa, exist, with the 120 kDa isoform being preferentially expressed in the thymus and the 130 kDa in peripheral T cells (Ref. 89). Two YDDV motifs, beginning at residues 595 and 651, bind the SH2 domain of SLP-76, whereas the YDGI motif at residue 625 binds the SH2 domain of Fyn (Refs 90, 91). Fyn phosphorylates these signalling motifs following TCR ligation, regulating binding of SLP-76 and Fyn to ADAP, and this tyrosine phosphorylation is diminished in Fyn-deficient T cells (Refs 90, 91, 92).

The role of ADAP in the regulation of T-cell activation was initially unclear since transfection of Jurkat T cells revealed positive (Ref. 66) or negative effects (Ref. 65) on IL-2 production. Co-expression of ADAP with SLP-76 and Fyn acted synergistically to up-regulate IL-2 production in Jurkat T cells upon TCR ligation (Refs 89, 90, 91). In addition, ADAP was found to up-regulate integrin adhesion in basophils (Refs 93, 94). ADAP-deficient mice have demonstrated conclusively that ADAP is a positive regulator of T-cell activation, and is required for T-cell proliferation, cytokine production and LFA-1 clustering (Refs 95, 96). Although proximal TCR signalling events were normal in ADAP-deficient T cells, there was a marked impairment in TCR-induced integrin-mediated adhesion. Binding of the SH2 domain of SLP-76 to ADAP is required for integrin clustering/adhesion and p-SMAC formation in T cells (Ref. 97). Further downstream, ADAP binds to the actin regulator VASP (Ref. 98) and another adaptor, SKAP-55 (Refs 99, 100) (Fig 3).

SKAP-55

SKAP-55 has a PH domain for membrane localisation and a C-terminal SH3 domain for binding to ADAP (Refs 99, 100). SKAP-55 can potentiate LFA-1 clustering and adhesion in a manner dependent on its SH3 domain (Ref. 101), and a reduction of SKAP-55 expression via interfering RNAi reduces both LFA-1 adhesion and T-cell–APC conjugation (Ref. 102). Specificity was shown by the finding that multiple mutations in the putative ADAP EVH1 binding sites had no detrimental effect on conjugation (Ref. 99). VASP acts to prevent the termination of growing actin filaments by competing for the binding of capping

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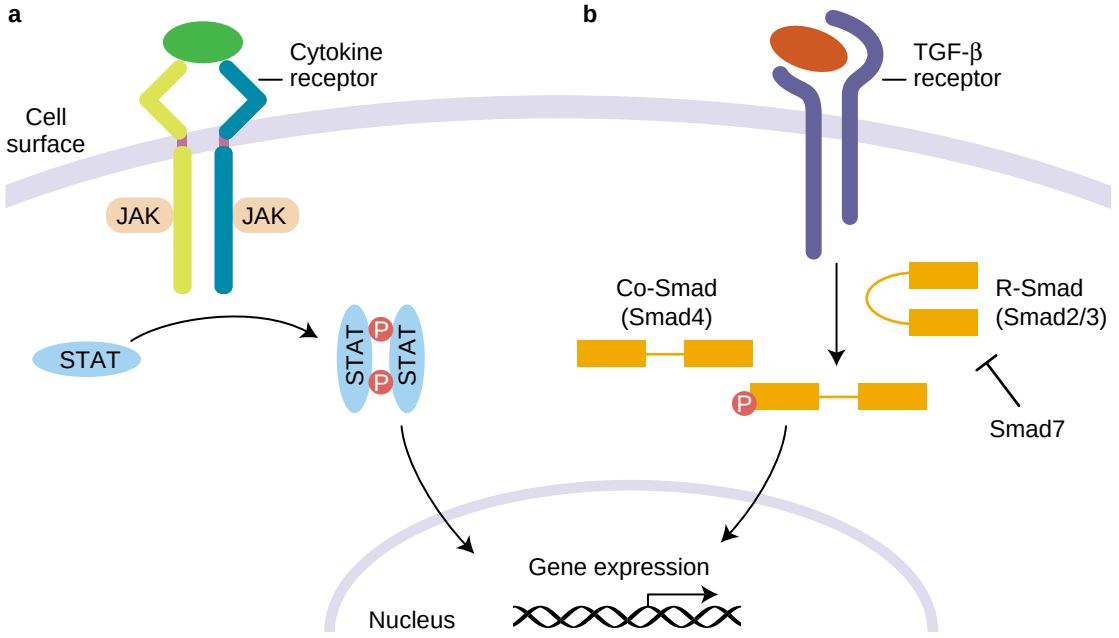
proteins (Ref. 103). VASP–ADAP binding might play other roles in conjugation, distinct from the regulation of LFA-1–ICAM1 binding. Another example where cytoskeleton re-modelling can be dissociated from conjugation is in the case of class II myosin, which modulates motility but not synapse formation (Ref. 104). Although the exact inside–out signalling pathway remains to be determined, a logical pathway would involve TCR–ZAP-70–LAT/SLP-76–ADAP–SKAP-55.

Cytokine signalling

JAKs and STATs

Cytokine receptors are needed for the full activation and progression of the T-cell response and the development of various effectors functions. Cytosolic PTKs of the JAK family, including JAK1, JAK2, Tyk and JAK3, are essential in coupling cytokine receptors to the activation of STAT proteins (Ref. 105). Following cytokine binding, JAKs phosphorylate STAT transcription factors found in the cytoplasm in an inactive state. Phosphorylation of STATs leads to their dimerisation and translocation to the nucleus where they activate gene transcription (Fig. 4a). JAK3 is primarily expressed by haematopoietic cells (Refs 106, 107), and associates with the common gamma chain (γc) (Ref. 108), which is essential for signalling by receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 (Refs 109, 110). Mice



JAK-STAT and Smad signalling cascades

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Figure 4. JAK–STAT and Smad signalling cascades. (a) Cytokine signalling via JAKs and STATs. Binding of cytokines to cytokine receptors leads to the activation of JAKs, which phosphorylate STAT transcription factors. Phosphorylation of STATs allows them to dimerise and translocate to the nucleus where they activate gene transcription. (b) TGF-β-receptor-mediated signalling via Smads. The TGF-β receptor comprises heterodimeric transmembrane serine/threonine kinases consisting of type I and type II receptor chains. Phosphorylated type I TGF-β receptors bind and phosphorylate the receptor-regulated Smads (R-Smads): Smad2 and Smad3. Once phosphorylated, the R-Smads dissociate from the receptor complex, form homotrimers, and bind to Smad4, the common mediator Smad (Co-Smad). The R-Smad–Co-Smad complex translocates into the nucleus and regulates gene transcription by interacting with tissue-specific transcriptional co-activators or co-repressors. Smad7 interferes with the phosphorylation of Smad2 and 3 phosphorylation. Abbreviations: JAK, Janus kinase; STAT, signal transducer and activators of transcription; TGF-β, transforming growth factor β.

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deficient in JAK3 show profound defects in lymphoid and myeloid development, B-cell maturation and T-cell activation, highlighting the importance of JAK3 in lymphocyte and natural killer (NK) cell development and function (Refs 111, 112, 113).

Smads

Another key cytokine receptor in T cells is the transforming growth factor β (TGF-β) receptor, which exists as a heterodimeric transmembrane protein consisting of TGF-β receptor type 1 and type II chains. It possesses serine/threonine kinase activity. Phosphorylated type I TGF-β receptors bind and phosphorylate the C-terminus of receptor-regulated Smads (R-Smads: Smad2 and Smad3 (Fig. 4b). Once phosphorylated, the R-Smads dissociate from the receptor complex, form trimers, and bind to Smad4. The R-Smad–Smad4 complex translocates into the nucleus and regulates gene transcription by interacting with tissue-specific transcriptional co-activators or co-repressors (Ref. 114).

T-cell signalling: immune system disorders and therapeutic implications

Given the importance of these mediators and networks, it is not surprising that deficiencies or mutations in key proteins have been linked to the development and pathogenesis of various diseases of the immune system (Table 1; Fig. 5). Mutations in ZAP-70, CD45, WASP and SAP, as well as JAKs and STATs, have been genetically linked to human immunodeficiency and autoimmune disorders; in addition, the loss of Lck, SLP-76 and ADAP expression in mouse models has produced phenotypes that suggest a possible link to human disease.

Lck and ZAP-70 kinases

Given their central roles in TCR signalling, it is not surprising that mutations and alterations in Lck and ZAP-70 expression have been linked to immunodeficiencies (Table 1; Fig. 5). Mice lacking Lck by homologous recombination show severe developmental defects leading to a severe combined immunodeficiency (SCID)-like phenotype (i.e. the absence of or defective function of T cells) (Refs 115, 116, 117). This invariably results in the onset of serious infections within the first few months of life, which commonly include gastrointestinal disease, atypical pneumonia, meningitis and septicaemia, and the failure to thrive. SCID encompassses a heterogeneous group of hereditary diseases, the most common of which is X-linked SCID, resulting from a defect in the gene for the γc common to cytokine receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 (Ref. 118). To date, immunodeficiencies due to Lck mutations or altered expression have not been documented in humans.

By contrast, ZAP-70 deficiency in humans leads to a rare form of SCID, with patients lacking peripheral $CD8^+$ T cells and having nonfunctional $CD4^+$ T cells (Refs 119, 120, 121). This might reflect a differential involvement of the kinase in human CD8 versus CD4 development, but contrasts with ZAP-$70^{-/-}$ mice, where both $CD4^+$ and $CD8^+$ T cells are absent (Ref. 122). Both homozygosity for splice mutations and compound heterozygous mutations in ZAP-70 have been linked to SCID. One intriguing mutation involves a G-to-A homozygous transition at nucleotide 1603 that results in an R465H substitution in the kinase domain (Ref. 123). Reported deletions include a 13 bp deletion involving nucleotides 1719–1731 (Ref. 119). ZAP-70-deficient patients fail to make antigen-specific antibodies, although a patient with specific IgE antibodies to food allergens has been reported (Ref. 123). Stimulation can induce IL-4, CD40 ligand (CD40L) expression, and expression of germ-line and mature IgE epsilon transcripts in B cells. The residual response in T cells is probably due to the expression of the related kinase Syk.

By contrast to immunodeficiency, ZAP-70 has also been implicated in the development of autoimmune arthritis. Sakaguchi and co-workers identified a spontaneous point mutation within the SH2 domain of ZAP-70 that results in chronic autoimmune arthritis in mice (Ref. 124). This chronic autoimmune arthritis in mice resembled human rheumatoid arthritis in many aspects. The underlying notion is that altered signal transduction from the TCR through the aberrant ZAP-70 changes the threshold thymic selection. This, in turn, leads to the positive selection of T cells that would otherwise be negatively selected. ZAP-70 function and the ability of the TCR to mobilise Ca^{2+} and induce tyrosine phosphorylation were impaired in these mice. It is thought that the generation of arthritogenic T cells as a result of a genetically determined selection shift of the T-cell repertoire towards high self-reactivity might eventually be found to play a causative

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Table 1. T-cell signalling proteins and human disease

Signalling protein	Function	Disease associations	Clinical applications
Kinases			
Lck	Regulation of T-cell development and activation	SCID (mice) (Refs 115, 116)	None described
ZAP-70	Regulation of T-cell development and activation	SCID (Refs 119, 120, 121, 122, 123) Autoimmune arthritis (Ref. 124)	None described Possible kinase modulators
Phosphatases			
CD45	Activates and inhibits Src kinases Required for T-cell development and activation	SCID (Refs 125, 126, 127, 128), SLE (Ref. 132), MS (Ref. 130), HIV (Refs 133, 134, 135), multiple myeloma (Ref. 37), Alzheimer's disease (Ref. 38), infantile cholestasis (Ref. 131), allograft rejection (Refs 31, 137, 138) Lymphocytic proliferation and autoimmunity (Ref. 141)	Treatment of Alzheimer's disease (Refs 38, 46), prevention of transplant rejection (Ref. 47), treatment of leukaemia patients with radioactive-labelled anti-CD45 antibodies (Ref. 48)
PTPN22	Inhibits Lck and ZAP-70	RA, type 1 diabetes, SLE (Refs 146, 147, 148, 149, 150, 151, 152, 153, 154, 155)	Potential PTP activators
E3 ligases			
Cbl GRAIL Itch	E3 ligases in the ubiquitination pathway	Spontaneous lympho-proliferative diseases and autoimmunty (Refs 180, 181, 182, 183, 184, 185, 186, 187)	None described; potential of E3 ligase stimulators to dampen autoimmuntiy
Cytokines			
γc	Regulation of cytokine signalling	SCID (Ref. 108)	Gene therapy for the treatment of X-SCID (Refs 154, 155)
JAK3		SCID (Refs 111, 112, 113)	
Adaptors			
LAT	Regulation of T-cell development and function; differentiation and homeostasis of Th1/Th2 cells	Autoimmune disease in mice (Ref. 49), RA in humans (Ref. 160)	None described

(Continued on next page)

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Table 1. T-cell signalling proteins and human disease *(continued)*

Signalling protein	Function	Disease associations	Clinical applications
Adaptors (continued)			
SLP-76	Regulation of T-cell development and function	None described	None described
ADAP	Regulation of integrin clustering and p-SMAC formation	None described	None described
SKAP-55	Regulation of integrin clustering/adhesion	None described	None described
WASP	Cytoskeletal remodelling	WAS (Refs 162, 163, 164, 165, 40) XLN (Ref. 168)	Gene therapy for the treatment of WAS (Refs 169, 170, 171, 172)
SAP	Regulation of immune cell activation	XLP (Refs 67, 175, 176)	Gene therapy for the treatment of XLP (Ref. 175)

Abbreviations: ADAP, adhesion-and degranulation-promoting protein; γc, gamma chain; HIV, human immunodeficiency virus; JAK3, Janus kinase 3; LAT, linker for activation of T cells; MS, multiple sclerosis; PTP, protein tyrosine phosphatase; PTPN22, protein tyrosine phosphatase, non-receptor type 22; RA, rheumatoid arthritis; SAP, SLAM-associated protein; SCID, severe combined immunodeficiency; SKAP-55, Src-family-kinase-associated phosphoprotein of 55 kDa; SLE, systemic lupus erythematosus; SLP-76, SH2-domain-containing leukocyte protein of 76 kDa; SLAM, signalling lymphocyte activation molecule; WAS, Wiscott–Aldrich syndrome; WASP, Wiskott Aldrich syndrome protein; XLP, X-linked lymphoproliferative disorder; ZAP-70, zeta-associated protein-70.

role in the development of disease in some human patients with rheumatoid arthritis.

PTPs and disease associations

In addition to PTKs, PTPs have been identified as major participants in the development of immunodeficiencies as well as lympho-proliferative disorders and autoimmunity. CD45-deficient mice are severely immunodeficient with few peripheral T cells (Ref. 125). In humans, CD45 deficiency and expression of different isoforms leads to a SCID-like phenotype and other human disease states (Refs 126, 127, 128) (Table 1; Fig. 5). CD45 polymorphisms have been associated with human multiple sclerosis, whereas CD45-deficient mice exhibit aberrant myelination of neurons (Ref. 129). However, although it may be up-regulated on microglial cells in patients with Alzheimer's disease (Ref. 130), the general connection between CD45 and multiple sclerosis has been questioned and might only pertain to some populations. Altered CD45 isoform expression has been associated with infantile cholestasis (Ref. 131), systemic lupus erythematosus (SLE) (Ref. 132) and infection by the human immunodeficiency virus (HIV-1) (Refs 133, 134, 135). The well-documented preferential replication of HIV-1 in $CD4^+$ $CD45R0^+$ activated/memory T cells (Refs 133, 134, 135) is likely related to the more metabolically active state of activated cells. Cellular activation facilitates viral replication.

CD45 is therefore a potentially important therapeutic target: a modification of function could be clinically beneficial in a range of inflammatory and immune disorders as well as preventing organ rejection in transplant patients (Table 1). The modulation of specific CD45 splice variants with antibodies was shown to

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suppress CD40L and β-amyloid-peptide-induced microglial activation in a model of Alzheimer's disease (Refs 130, 136), as well as prevent heart, kidney and islet transplant rejection (Refs 137, 138). Isotope-labelled anti-CD45 antibodies were successfully used to deliver a dose of radiation directly to neoplastic cells in patients suffering from acute myeloid leukaemia (Ref. 139). This approach is currently being tested in conjunction with conventional therapies in bone marrow transplant patients in an effort to minimise unwanted toxicity and reduce the risk of post-transplant relapse. The development of agents to selectively inhibit CD45 may provide a useful tool for future immunotherapy. However, although some potent and moderately selective CD45 inhibitors have been described (Ref. 140), future studies will determine whether such inhibitors have any real therapeutic value. One positive example involves an isoform-specific antibody to CD45RB that induces tolerance to renal graft transplants (Refs 31, 137, 138). Intriguingly, this effect is related to anti-CD45RB induction of CTLA-4 expression, leading to an inhibition of T-cell function by this co-receptor (Refs 31, 138).

In another case, a mutation in CD45 (i.e. E613R) has been linked to a lymphoproliferation syndrome leading to severe autoimmune nephritis with autoantibody production (Ref. 141). The mutation is dominant, such that heterozygotic E613R mice developed the pathology. Both B and T cells showed an activation phenotype with an elevated 35-fold production of IgA in homozygotic mice, and a selective increase in the expression of IL-10 and IFN-γ. Renal damage was confirmed by the presence of proteinuria in older mice. Intriguingly, the mutation occurred in a putative wedge region of CD45 that was thought to mediate receptor dimerisation. This notion was originally based on the dimer structure of the PTPase RPTPα. In this case, the N-terminal α1′-turn-α2′ segment prevents substrate access to the active site. As proposed by Weiss and colleagues, mutation within the wedge fits well with a dimeric model for the negative regulation of CD45 function (Ref. 17). However, the recently published crystal structure for CD45 intracellular domains failed to show dimerisation (even at high concentrations), and there is no evidence of a wedge region involved in intermolecular interactions (Ref. 142). Instead, the second inactive D2 domain prevents dimer formation of D1–D1 PTP domains. This molecular basis of the involvement of the E613R mutation in autoimmunity therefore remains an exciting question for future studies. In addition, whether CD45 is implicated in other autoimmune disorders (i.e. SLE) awaits future studies. In this context, SLE patients have been reported to have decreased CD45 expression and/or PTP activity (Ref. 143).

Perhaps the most striking example of a PTP link to an autoimmune phenotype is the *motheaten* mouse. This mouse has a single base pair

Figure 5. Immune disorders associated with T-cell signalling. *(Legend; see next page for figure.)* Depiction of the various disease states have been connected to signalling proteins in T cells. Mutations in CD45 or altered CD45 expression have been linked to SCID, HIV-1 infectivity and systemic lupus erythematosus (SLE)-like syndome. Mutations in PTPN22 (LYP/PEP) confer a predisposition to a range of autoimmune diseases such as rheumatoid arthritis (RA), type 1 diabetes, SLE, Graves' disease and Hashimoto thyroiditis. Loss of ZAP-70 expression causes severe combined immunodeficiency (SCID), while mutations in the kinase have been linked to a SCID-like syndrome as well as the onset of murine rheumatoid arthritis (RA). The loss of ubiquitin E3 ligases (Cbl-b, GRAIL, Itch and Nedd-4) can cause spontaneous autoimmunity as a result of an inability to degrade key signalling proteins. Mouse models have implicated the adaptor LAT in the development of RA, whereas loss of WASP expression has been causally linked to Wiscott–Aldrich syndrome (WAS) and X-linked severe congenital neutropenia (XLN). SLAM/SAP signalling defects are responsible for the development of X-linked lymphoproliferative disorder (XLP) in humans, while mutations in JAKs have been causally connected to the development of SCID via defects in cytokine signalling. Lastly, altered Smad signalling via TGF-β signalling has been linked to the onset of an inflammatory bowel disease (IBD)-like disorder in mice. Abbreviations: ADAP, adhesion-and degranulation-promoting protein; GADS, Grb2-related adaptor downstream of Shc; JAK, Janus kinase; NCK, noncatalytic region of tyrosine kinase adaptor protein 1; PLCγ1, phospholipase Cγ1; PTPN22, protein tyrosine phosphatase, non-receptor type 22; SAP, SLAM-associated protein; SH2, Src-homology 2; SKAP-55, Src-family-kinase-associated phosphoprotein of 55 kDa; SLP-76, SH2-domain-containing leukocyte protein of 76 kDa; SLAM, signalling lymphocyte activation molecule; STAT, signal transducer and activators of transcription; TCR, T-cell receptor; TGF-β, transforming growth factor β; VASP, vasodilator-stimulated phosphoprotein; WASP, Wiskott Aldrich syndrome protein; ZAP-70, zeta-associated protein 70.

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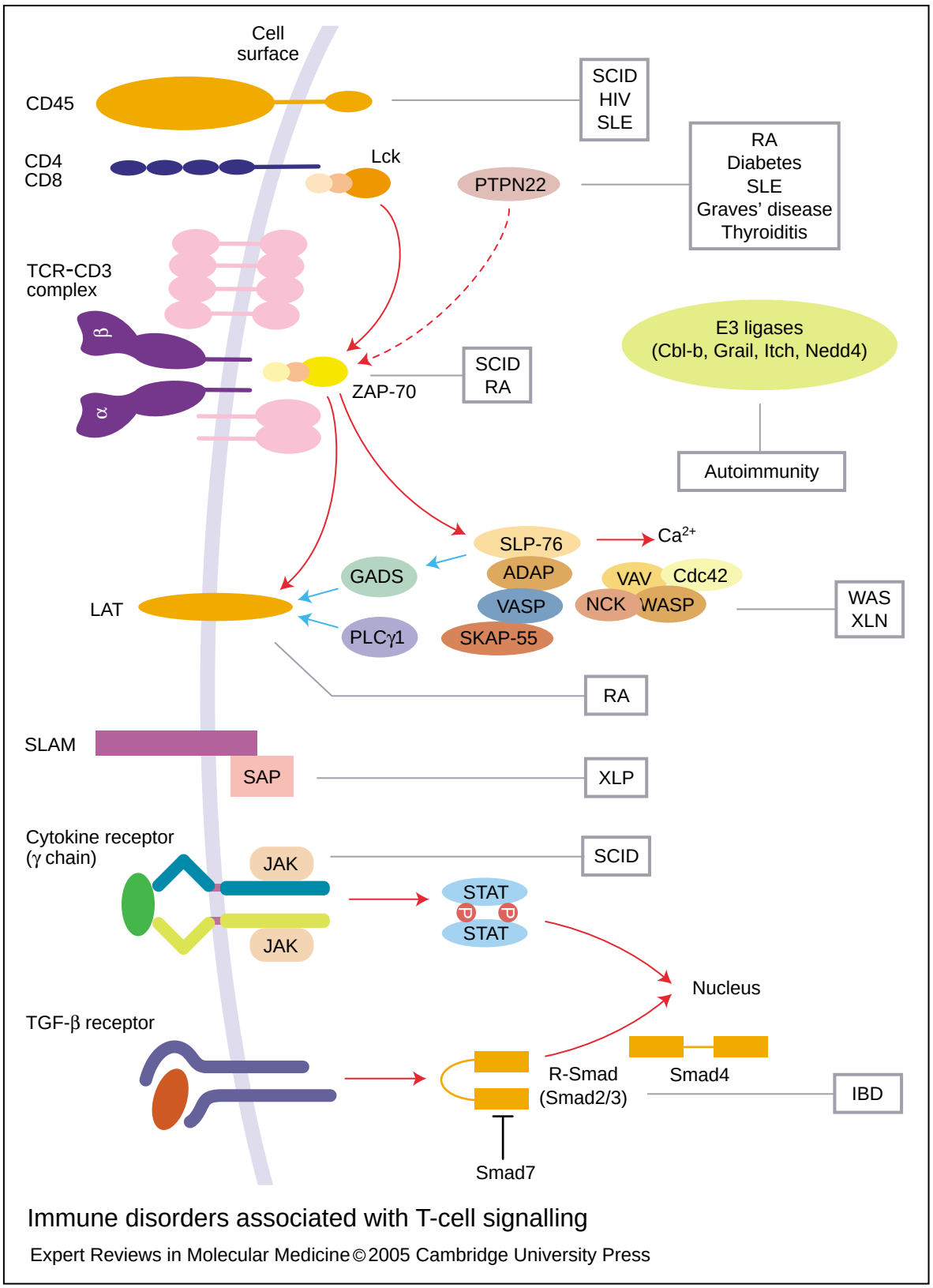

Immune disorders associated with T-cell signalling

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Figure 5. Immune disorders associated with T-cell signalling. *(See previous page for legend.)*

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substitution that interferes with normal splicing and prevents proper expression of SHP-1 (otherwise known as PTPN6/Ptp1C) (Refs 144, 145). The *Ptpn6* gene encodes an intracellular phosphatase with two N-terminal SH2 domains, a phosphatase domain, and a short tail enriched in basic amino acids. SHP-1 modulates the threshold of TCR signalling by dephosphorylating and inactivating ZAP-70 and other kinases. Homozygous mice develop a severe autoimmune disease with multiple disorders such as granulocytic skin lesions and pneumonitis. These mice have impaired humoral and cell-mediated immunity including deficient cytotoxic T-cell and NK activity. Homozygous mutant mice also exhibit hyperimmunoglobulinaemia, express multiple autoantibodies, and exhibit classic symptoms of osteoporosis as a result of an increased number and activity of osteoclasts in the bone marrow. The lifespan of homozygous *motheaten* mice is approximately three weeks, with death attributed to autoimmune pneumonitis.

Despite the importance of the mentioned associations of PTPs and specific diseases, an exciting new twist on the story has involved a connection between a single PTP and the generation of an array of different human autoimmune disorders. This suggests the provocative possibility that a single signalling event can account for an assortment of autoimmune disorders that have previously been considered to have distinct aetiologies. The PTP in question is PTPN22 [also known as PEST domain–enriched tyrosine phosphatase (PEP) in mice]. Bottini et al. first reported that the allele (T) at nucleotide 1858 of PTPN22 confers a predisposition to type 1 diabetes (Ref. 146). This was followed by reports documenting an association with rheumatoid arthritis (Ref. 147), type 1 diabetes (Refs 148, 149, 150), SLE (Ref. 151), Graves' disease and Hashimoto thyroiditis (Refs 152, 153). Several confirmations of the rheumatoid arthritis association have also been made (Refs 154, 155). By contrast, no associations with multiple sclerosis and Crohn's disease, where the appearance of autoantibodies is not a prominent feature, have been noted (Ref. 156). The linkage of a single PTP to multiple autoimmune disorders suggests the intriguing possibility that a common intracellular mediator and/or signalling pathway regulates a range of autoimmune diseases.

Consistent with this connection, T cells from PEP knock-out mice show a decrease in the threshold of T-cell signalling (Ref. 157). T cells from PEP knock-out mice are hyper-responsive, leading to an enlargement of the spleen and lymph nodes, and enhanced phosphorylation of Lck and ZAP-70. Interestingly, the PEP deficiency in mice does not induce autoimmunity, suggesting that other factors also contribute, and/or that humans and mice differ in their dependency on the PTP. Despite this, the nature of the PTPN22 mutations and disease imply a connection to a specific set of signalling events. The SH3 domain of the kinase Csk binds to two well-defined consensus sequences [class I (R/KxxPxxP) and class II (PxxPxR)] in a proline-rich region in PEP. Both charged R/K and nonpolar PxxP residues are needed for binding. Intriguingly, the PTPN22 R620W polymorphism is located within the SH3-binding site of PTPN22, leading to a disruption of binding to Csk (Ref. 146). The disease-associated R620W allele is therefore likely to disrupt the inter-molecular interaction, leading to change in the regulation of Lck, which the Csk–PEP complex normally holds in an inhibitory state. In the future, other disease-associated mutations might also be found linked to this PTP. The polymorphism does not eliminate all functions linked to PTPN22 since homozygous carriers of PTPN22 R620W do not exhibit a phenotype as potent as seen in the knock-out mouse.

Lastly, in addition to serving as intracellular regulators, PTPs can be processed as auto-antigen. PTPRN (IA-2) and PTPRN2 (phogrin) serve as auto-antigens in autoimmune diabetes (Refs 158, 159).

Adaptor proteins

Several studies have identified key adaptor proteins that play a role in the pathogenesis of immune-mediated diseases (Table 1; Fig. 5).

LAT and rheumatoid arthritis

As previously discussed, LAT plays a central role in generating pre-TCR and TCR signals. T-cell differentiation and the homeostasis of Th1/Th2 cells is LAT dependent (Refs 44, 45, 46, 47, 48, 49, 50, 51, 52). Mice expressing a mutant form of LAT develop a polyclonal lymphoproliferative disorder (Ref. 49) and an increase in Th2 cells (Ref. 50). The extent of this skewing is usually only accomplished by prolonged exposure to antigen in the presence of IL-4. In humans, a role for LAT in the development of rheumatoid arthritis was recently reported. LAT is displaced from the

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membrane in synovial fluid T cells from the inflamed joints of rheumatoid arthritis patients, as a consequence of chronic oxidative stress (Ref. 160). Residency in lipid rafts is crucial for LAT function, and displacement of LAT prevents phosphorylation and binding to associated proteins such as PLCγ1 and GADS. Ultimately, this may lead to T-cell hyporesponsiveness, a characteristic of rheumatoid arthritis. Understanding the role of LAT in disorders such as rheumatoid arthritis will facilitate the development of new therapeutic approaches to treat the disease.

WASP

WASP was one of the first adaptors to be linked to a human immunodeficiency syndrome (Ref. 161). WASP regulates actin modelling of the cytoskeleton via binding to the nucleation complex Arp2/3. Mutations in the gene encoding WASP impair the remodelling of the cytoskeleton in haematopoietic cells, leading to functional defects that result in X-linked Wiskott–Aldrich syndrome (WAS) and X-linked related thrombocytopenia (XLT). This defect in WASP function can result from reduced transcription or translation of the gene (Refs 162, 163, 164, 165). In T cells, the absence of WASP results in a marked reduction of TCR capping or clustering, an event that is needed for the activation of proximal kinases and intracellular signalling (Refs 165, 78). In addition, the formation of APC–T-cell conjugates and synapses in $WASP^{-/-}$ T cells is defective (Ref. 166). Similarly, the loss of a key regulatory phosphorylation site, Y291, abrogates actin polymerisation and conjugate formation (Ref. 167). Defective WASP function is also responsible for the immune system disorder X-linked severe congenital neutropenia (XLN). Neutropenia is the main clinical feature of XLN, usually associated with an arrest in haematopoietic maturation at the promyelocyte/myelocyte stage. Devriendt and co-workers have described a form of XLN that is caused by a mutation in WASP L270P in the region of the conserved GTPase-binding domain (GBD) (Ref. 168). This abrogates of the auto-inhibition function mediated by the GBD domain. This interesting connection points to the alteration of a precise intermolecular event involving WASP that is responsible for a distinct clinical phenotype. It is also the first example of a specific event linking the cytoskeleton to neutropenia.

The specificity of these connections have provided an opportunity to apply gene therapy as a cure for WAS. Defects in cytoskeletal remodelling and T-cell activation have been corrected with retroviral or lentiviral transfer of the gene encoding WASP into WASP-deficient T cells (Refs 169, 170, 171, 172). Further to these findings, a recent study reported that retroviral gene transfer into WASP-deficient haematopoietic stem cells (HSCs) led to the normal development of mature B and T cells and improved the defect in antigen-receptor-induced proliferation in T cells (Refs 171, 172). These results are encouraging for the development of gene therapy approaches for this disease and might promote future clinical gene therapy trials.

SAP and X-linked lymphoproliferative disease (XLP)

Highlighting its importance in cells, mutations in the gene encoding SAP have been shown to give rise to X-linked lymphoproliferative disease (XLP; also called Duncan's or Purtilo's syndrome). Not surprisingly, there is a great deal of interest in determining the role of this gene in T cells (Refs 58, 173, 174, 175) (Fig. 5). As its name suggests, XLP is characterised by a fatal lymphoproliferation, principally associated with an abnormal response to Epstein–Barr virus (EBV) infection (Refs 174, 175). Infection by EBV seems to act as a trigger leading to an unfavourable Th1-biased response and the massive accumulation of $CD8^+$ T cells, NK cells and macrophages; but, along with this viral-triggered lymphoproliferation, XLP is also associated with lymphoma, vasculitis, common variable immunodeficiency (CVID)-like syndromes, and hyper-IgM disease. However, despite a greater understanding of the structure of SAP and its molecular interactions in immune cells, the cellular pathogenesis of XLP remains poorly understood.

Several studies, in both mice and humans, suggest that the disruption of the Th1–Th2 cytokine balance and dysregulation of T-cell function might be of importance to the cellular pathogenesis of XLP (Refs 176, 177). Transformed $CD4^+$ T cells from XLP patients display high levels of early tyrosine phosphorylation of the CD3z chain, ZAP-70 and Cbl, together with altered MAPK activation and cytokine production (Ref. 72). Nontransformed T-cell lines derived from XLP patients were also shown to be defective in several

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activation events, leading to impaired IL-2 production, and these defects could be circumvented by phorbol myristate acetate (PMA)/ionomycin stimulation and corrected by retroviral-mediated expression of the *SAP* gene (Ref. 72). A more recent study reported that the pathophysiology of XLP was due to a T-cell defect, whereby the lack of SAP affects specific signalling pathways, resulting in the disruption of cytotoxic T-cell function (Ref. 178). Retroviral-mediated transfer of the *SAP* gene into EBV–T-cell lines reconstituted IFN-γ production and cytotoxic activity, confirming these SAP-dependent defects and further suggesting that SAP gene transfer in XLP patients could have some therapeutic value. Further studies are required to determine the precise molecular mechanisms causing XLP and to examine the role of SAP in the maintenance of immunosurveillance against EBV infection.

Ubiquitination (E3 ubiquitin ligases) and anergy

Superimposed on the array of signalling proteins that regulate T-cell function is a protein degradation pathway utilising the process of ubiquitination. This process involves adding a 76 amino acid globular glycopeptide called ubiquitin as a post-translational modification to proteins destined for degradation by the 26S proteasome complex (Ref. 179). Proteins are tagged by a series of events involving binding by an E3 ubiquitin ligase enzyme in the presence of an appropriate ubiquitin-conjugating enzyme, which is bound to ubiquitin through a reaction catalysed by an E1 enzyme. Ubiquitin alters the intracellular localisation of proteins and reduces their abundance in cells through degradation. Depending on the target protein, the process can either up-regulate or down-regulate signal events. Recent exciting studies have identified E3 ligases – c-Cbl, Cbl-b, GRAIL, Itch and Nedd4 – that control the balance between anergy and proliferation leading to autoimmunity (Ref. 180). In this manner, Cbl-b-deficient mice are resistant to anergy induction and develop a spontaneous systemic autoimmunity (Refs 181, 182). In addition, positional cloning in diabetes-prone Komeda mice has identified Cbl-b as a susceptibility gene for rat type 1 diabetes mellitus (Ref. 183). As with all E3 ligases, the nature of the exact downstream signalling proteins responsible for the disorder is unclear, although putative candidates include p85 of PI3K, ZAP-70, Crkl, PLCγ1 and PKC-θ. Another ligase, GRAIL, is induced by conditions that induce anergy (Ref. 184). Transfection with GRAIL inhibits IL-2 and IL-4 production, while transduction of naive $CD4^+$ T cells with otubain 1, a binding protein that increases GRAIL turnover, increases cytokine production (Ref. 185). Similar to Cbl-b and GRAIL, Itch levels are also increased in T cells following ionomycin exposure (Ref. 186). This depends on both an intracellular rise in Ca^{2+} and the activation of calcinuerin. Mutant animals lacking Itch activity spontaneously develop chronic and lethal systemic lymphoproliferative disease (Ref. 187). Down-regulation of PLCγ1 and PKC-θ after exposure to anergy-inducing conditions does not occur in T cells from $Itch^{-/-}$ mice suggesting a possible causal link.

Other SCIDs

IL-2 and JAKs

As mentioned, SCID is a primary immune deficiency characterised by a severe defect in the appearance or function of lymphocytes (Refs 104, 114, 122). While mutations or loss of ZAP-70, PTPs and SLAM/SAP define examples of SCID within this heterogeneous grouping, the most common is an X-linked SCID that results from a defect in the gene for the common γc to cytokine receptors for IL-2 and other cytokines such as IL-4, IL-7, IL-9, IL-15 and IL-21. This accounts for 50% of all cases of SCID. Given their central importance in driving the T-cell response, it is no surprise that defects in the expression of various mediators of cytokine signalling have been implicated in several immune pathologies. Key mediators are the JAKs, which couple cytokine receptors to STATs (Refs 104, 105, 106, 107, 108) (Fig. 4). Mice deficient in JAK3 show profound defects in lymphoid and myeloid development, B-cell maturation and T-cell activation, highlighting the importance of JAK3 in lymphocyte and NK-cell development and function (Refs 111, 112, 113).

JAK3 deficiency also leads to a form of SCID that is similar to X-linked SCID. Patients characteristically exhibit a paucity of NK and T cells with an elevated number of poorly functioning B cells (Refs 188, 189). HSC transplantation has been used as an effective treatment for JAK3-deficient SCID, since patients are highly immunocompromised and less susceptible to graft-versus-host disease (Refs 190, 191). Recent studies have investigated the potential advantages of gene therapy as an alternative treatment for patients with X-SCID or JAK3-

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deficient SCID (Refs 192, 193, 194, 195, 196, 197). Retroviral-mediated gene transfer of the γc in an X-SCID murine model showed a restoration of T-cell proliferation and the production of antigen-specific antigen upon immunisation (Ref. 192). Several preclinical studies have shown that retroviral-mediated gene transfer of γc or JAK3 can correct defects in lymphoid development and function (Ref. 194). Gene therapy for X-SCID was attempted in two infants by exposing collected bone marrow to a retroviral vector carrying a normal copy of the human γc gene, and then returning marrow cells by intravenous infusion. Over the subsequent months, both infants developed normal numbers of T cells and natural killer (NK) cells, which showed evidence of immunological function. Both infants have remained in good health, free of opportunistic infections, growing and developing without protective isolation. Initial evidence suggests they have also developed B-cell function with the presence of protective levels of antibodies, although the number of B cells remains low.

One major limitation involved in this approach, however, is the inappropriate clonal expansion of T cells due to insertion of the retrovirus into regions of the genome that regulate cell expansion. In one instance, patients were found to manifest the uncontrolled exponential clonal expansion and proliferation of mature T cells (both γ/δ and α/β) as a result of retroviral integration near the LMO2 proto-oncogene promoter (Ref. 198). Inappropriate retroviral insertion can trigger an unregulated pre-malignant cell proliferation with a high frequency. Sequence-targeted retroviral insertion should provide a way to obviate these negative effects in future studies.

SCID and ADA

The localisation of the γc gene on the X chromosome results in X-SCID affecting only males. It is also possible that other forms of SCID might develop from the inheritance of autosomal genetic factors or from germ-line mutation (Ref. 199). Of these, adenosine deaminase (ADA) deficiency, an enzyme responsible for adenosine and deoxyadenosine catabolism, is probably the most widely known, although other proteins involved in purine catabolism, such as purine nucleoside phosphorylase, can also result in severe immunodeficiency. ADA deficiency itself accounts for around 20% of SCID cases, with patients possessing critically low levels of functional T cells, B cells and NK cells, associated with increased lymphocyte apoptosis and an inhibition of TCR signalling (Ref. 200). Treatment of an ADA-SCID patient with transduced peripheral T cells showed a preferential expansion of T cells with the ADA gene, but this did not lead to a complete correction of the metabolic defect (Ref. 201). The use of stem cell gene therapy to correct ADA-SCID combined with nonmyeloablative conditioning has been used successfully for the treatment of the disorder (Ref. 202).

RAG1,2 deficiency and Artemis defects

The last group of regulators responsible for SCID involves the V(D)J recombination machinery. V(D)J recombination involves the somatic recombination of the variable (V), diversity (D) and joining (J) subexons to create a variable domain coding for immunoglobulins and TCRs (Ref. 203). V(D)J recombination starts with the binding of the RAG complex (including RAG1, RAG2 and HMG1) to the recombination signal sequences (RSSs). The complex then nicks between the coding end and the RSS and converts the nicks to double-strand DNA breaks. This creates hairpin-sealed coding ends and blunt signal ends (Ref. 204). The joining of the coding ends is then conducted by the nonhomologous-end-joining (NHEJ) machinery, which comprises Hu (Ku70 and Ku86), DNA-PKcs (catalytic subunit of the DNA-dependent protein kinase), Artemis and the DNA ligase IV–XRCC4 complex (Ref. 205). The absence of any of these components in vivo results in a SCID phenotype (Ref. 206). Artemis is the most recently discovered component in human patients that, when defective, leads to both radiosensitivity and a SCID phenotype (Ref. 207). The role of Artemis in hairpin opening and 5' and 3' overhang processing accounts for the dual role in the radiosensitivity and SCID phenotype. This feature distinguishes the role of deletions of the NHEJ machinery from other SCID-causing mutations.

Inflammatory bowel disease and TGF-β receptor signalling

Inflammatory bowel disease (IBD) is a chronic inflammation of the gastrointestinal tract caused by an abnormal and uncontrolled immune response to one or more normally occurring gut constituents. The two main forms of autoimmune IBD in humans are Crohn's disease, which affects

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the gastrointestinal tract, and ulcerative colitis, restricted to the large bowel. Although the exact causes are unknown, the disease involves infection and irregularities in the immune system. Recent studies have suggested that patients with Crohn's disease and ulcerative colitis have an increased prevalence of asthma, arthritis, multiple sclerosis, psoriasis and other disorders. In this way, there has been much recent focus on the role played by T cells in the regulation of inflammation in IBD. The initiation and continuation of IBD appears closely connected to the balance between pro- and anti-inflammatory cytokines secreted by T cells. TGF-β is one key multifunctional cytokine that negatively regulates mucosal inflammation. The importance of TGF-β signalling has been demonstrated by the fact that the inactivation of the receptor by expression of a dominant negative mutant resulted in the development of spontaneous colitis that presented with diarrhoea, haematochezia, and anal prolapse in non-pathogen free (SPF) conditions (Ref. 208). The transgenic mice also showed increased susceptibility to dextran sulphate sodium (DSS)-induced IBD, as well as increased expression of MHC class II and the generation of autoantibodies against intestinal goblet cells. In this context, suppressive T regulatory cells (Tregs) can elicit a protective effect on IBD through production of TGF-β (Ref. 209).

As previously outlined, the TGF-β receptor generates signals through R-Smads and Co-Smad (Ref. 114). Disruption of Smad3 expression results in diminished cell responses to TGF-β and resultant massive infiltration of T cells and pyogenic abscess formation in the stomach and intestine (Ref. 210) (Table 1; Fig. 5). Conversely, inhibition of Smad7 restored TGF-β1 signalling and enabled TGF-β1 to inhibit pro-inflammatory cytokine production (Ref. 211). Genes regulated by the transcription factor NF-κB, such as IL-1β, TNF-α, IL-8 and IL-12, are also believed to be involved in the pathogenesis of IBD. Increased activation of NF-κB was detected in lamina propria mononuclear cells from patients with active IBD (Ref. 212). Furthermore, mutations in a regulator of NF-κB – NOD2/CARD15 – have been identified in patients with adult-onset Crohn's disease (Ref. 213). Inhibitors of NF-κB signalling have proven effective in reducing the severity of IBD in animal models of the disease.

In the context of Th1/Th2 cells, the transcription factor T-bet serves as a master switch for Th1-cell development and effector function (Ref. 214). T cells from mice deficient in T-bet fail to induce Th1-mediated disease, whereas disease mediated by IL-4 (i.e. a Th2 cytokine) was exacerbated. Conversely, Treg cells from T-bet-deficient mice show enhanced protection, most probably owing to the increase in TGF-β production. Therapeutic manipulation of T-bet function might prove useful in treating IBD, although the loss of Th1 cells in T-bet-deficient mice leads to a profound loss of IFN-γ production, rendering mice more susceptible to infection and spontaneous asthma, a sign of excess Th2 activity.

Research in progress and outstanding research questions

Our knowledge of the role of T-cell signalling proteins in the normal development and function of T cells and in the pathogenesis of human disease has greatly expanded over the past two decades. Furthermore, the recent identification of adaptor proteins has greatly contributed to our understanding of the way in which membrane-proximal signalling events lead to the initiation and integration of downstream signalling pathways in T cells. A number of studies in recent years have pinpointed several T-cell signalling proteins in human disease states such as immune deficiency disorders, autoimmune disease, AIDS, cancer and Alzheimer's disease, paving the way for the development of new therapeutic strategies to treat these disorders.

Although many T-cell signalling proteins have been well characterised, the biological functions of many others need to be determined. In particular, a greater understanding of the function of adaptors in the immune system will come as new techniques and approaches are applied to the field. New imaging technologies, coupled with the development of new fluorescent labels and sensors and the use of more-sophisticated computer software for image acquisition will further our understanding of the assembly, spatial dynamics and intracellular location of adaptors (Refs 215, 216, 217). These novel approaches could provide insights into the dynamics of adaptor proteins and their interactions with other signalling molecules in living cells and might help us to identify the precise molecular mechanisms by which adaptors integrate diverse signalling networks. Such studies should result in a better understanding of the complex molecular interactions underlying TCR signalling, and

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lead to the development of new therapeutic targets for the treatment of immunodeficiency disorders, infectious diseases, autoimmunity and cancer, and for the modulation of transplantation.

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References

1 O'Garra, A. and Arai, N. (2000) The molecular basis of T helper 1 and T helper 2 cell differentiation. Trends Cell Biol 10, 542-550, PubMed: 11121747
2 Raja, A. (2004) Immunology of tuberculosis. Indian J Med Res 120, 213-232, PubMed: 15520479
3 Rudd, C.E. et al. (1988) The CD4 receptor is complexed in detergent lysates to a protein-tyrosine kinase (pp58) from human T lymphocytes. Proc Natl Acad Sci U S A 85, 5190-5194, PubMed: 2455897
4 Veillette, A. et al. (1989) Signal transduction through the CD4 receptor involves the activation of the internal membrane tyrosine-protein kinase p56lck. Nature 338, 257-259, PubMed: 2784195
5 Rudd, C.E. (1990) CD4, CD8 and the TCR-CD3 complex: a novel class of protein-tyrosine kinase receptor. Immunol Today 11, 400-406, PubMed: 1964053
6 Weiss, A. and Littman, D.R. (1994) Signal transduction by lymphocyte antigen receptors. Cell 76, 263-274, PubMed: 8293463
7 Wange, R.L. and Samelson, L.E. (1996) Complex complexes: signaling at the TCR. Immunity 5, 197-205, PubMed: 8808675
8 Lewis, C.M. et al. (2001) Tec kinases: modulators of lymphocyte signaling and development. Curr Opin Immunol 13, 317-325, PubMed: 11406363
9 Rao, A., Luo, C. and Hogan, P.G. (1997) Transcription factors of the NFAT family: regulation and function. Annu Rev Immunol 15, 707-747, PubMed: 9143705
10 Riley, J.L. and June, C.H. (2005) The CD28 family: a T-cell rheostat for therapeutic control of T-cell activation. Blood 105, 13-21, PubMed: 15353480
11 Rudd, C.E. and Schneider, H. (2003) Unifying concepts in CD28, ICOS and CTLA4 co-receptor signalling. Nat Rev Immunol 3, 544-556, PubMed: 12876557
12 Greenwald, R.J., Freeman, G.J. and Sharpe, A.H. (2005) The B7 family revisited. Annu Rev Immunol 23, 515-548, PubMed: 15771580
13 Mora, A. et al. (2004) PDK1, the master regulator of AGC kinase signal transduction. Semin Cell Dev Biol 15, 161-170, PubMed: 15209375
14 Mustelin, T., Vang, T. and Bottini, N. (2005) Protein tyrosine phosphatases and the immune response. Nat Rev Immunol 5, 43-57, PubMed: 15630428
15 Neel, B.G. (1997) Role of phosphatases in lymphocyte activation. Curr Opin Immunol 9, 405-420, PubMed: 9203419
16 Trowbridge, I.S. and Thomas, M.L. (1994) CD45: an emerging role as a protein tyrosine phosphatase required for lymphocyte activation and development. Annu Rev Immunol 12, 85-116, PubMed: 8011300
17 Hermiston, M.L., Xu, Z. and Weiss, A. (2003) CD45: a critical regulator of signaling thresholds in immune cells. Annu Rev Immunol 21, 107-137, PubMed: 12414720
18 Saxena, M. et al. (1999) Inhibition of T cell signaling by mitogen-activated protein kinase-targeted hematopoietic tyrosine phosphatase (HePTP). J Biol Chem 274, 11693-11700, PubMed: 10206983
19 Cloutier, J.F. and Veillette, A. (1999) Cooperative inhibition of T-cell antigen receptor signaling by a complex between a kinase and a phosphatase. J Exp Med 189, 111-121, PubMed: 9874568
20 Gjorloff-Wingren, A. et al. (1999) Characterization of TCR-induced receptor-proximal signaling events negatively regulated by the protein tyrosine phosphatase PEP. Eur J Immunol 29, 3845-3854, PubMed: 10601992
21 Koretzky, G.A. et al. (1990) Tyrosine phosphatase CD45 is essential for coupling T-cell antigen receptor to the phosphatidyl inositol pathway. Nature 346, 66-68, PubMed: 2164155
22 Kawai, K. et al. (1995) Impaired development of V gamma 3 dendritic epidermal T cells in p56lck protein tyrosine kinase-deficient and CD45 protein tyrosine phosphatase-deficient mice. J Exp Med 181, 345-349, PubMed: 7807014
23 Mustelin, T., Coggeshall, K.M. and Altman, A. (1989) Rapid activation of the T-cell tyrosine protein kinase pp56lck by the CD45 phosphotyrosine phosphatase. Proc Natl Acad Sci U S A 86, 6302-6306, PubMed: 2548204
24 Pingel, S. et al. (1999) The CD45 tyrosine phosphatase regulates CD3-induced signal

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transduction and T cell development in recombinase-deficient mice: restoration of pre-TCR function by active p56(lck). Eur J Immunol 29, 2376-2384, PubMed: 10458749
25 Seavitt, J.R. et al. (1999) Expression of the p56(Lck) Y505F mutation in CD45-deficient mice rescues thymocyte development. Mol Cell Biol 19, 4200-4208, PubMed: 10330160
26 Kawabuchi, M. et al. (2000) Transmembrane phosphoprotein Cbp regulates the activities of Src-family tyrosine kinases. Nature 404, 999-1003, PubMed: 10801129
27 Brdicka, T. et al. (2000) Phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG), a novel ubiquitously expressed transmembrane adaptor protein, binds the protein tyrosine kinase csk and is involved in regulation of T cell activation. J Exp Med 191, 1591-1604, PubMed: 10790433
28 D'Oro, U. and Ashwell, J.D. (1999) Cutting edge: the CD45 tyrosine phosphatase is an inhibitor of Lck activity in thymocytes. J Immunol 162, 1879-1883, PubMed: 9973453
29 Shenoi, H. et al. (1999) Regulation of integrin-mediated T cell adhesion by the transmembrane protein tyrosine phosphatase CD45. J Immunol 162, 7120-7127, PubMed: 10358156
30 Baker, M. et al. (2000) Development of T-leukaemias in CD45 tyrosine phosphatase-deficient mutant lck mice. Embo J 19, 4644-4654, PubMed: 10970857
31 Fecteau, S. et al. (2001) CTLA-4 up-regulation plays a role in tolerance mediated by CD45. Nat Immunol 2, 58-63, PubMed: 11135579
32 Irie-Sasaki, J. et al. (2001) CD45 is a JAK phosphatase and negatively regulates cytokine receptor signalling. Nature 409, 349-354, PubMed: 11201744
33 Johnson, K.G. et al. (2000) A supramolecular basis for CD45 tyrosine phosphatase regulation in sustained T cell activation. Proc Natl Acad Sci U S A 97, 10138-10143, PubMed: 10963676
34 Majeti, R. et al. (1998) Dimerization-induced inhibition of receptor protein tyrosine phosphatase function through an inhibitory wedge. Science 279, 88-91, PubMed: 9417031
35 Samelson, L.E. (1999) Adaptor proteins and T-cell antigen receptor signaling. Prog Biophys Mol Biol 71, 393-403, PubMed: 10354706
36 Rudd, C.E. (1999) Adaptors and molecular scaffolds in immune cell signaling. Cell 96, 5-8, PubMed: 9989491
37 Koretzky, G.A. and Myung, P.S. (2001) Positive and negative regulation of T-cell activation by adaptor proteins. Nat Rev Immunol 1, 95-107, PubMed: 11905825
38 Zhang, W. et al. (1998) LAT: the ZAP-70 tyrosine kinase substrate that links T cell receptor to cellular activation. Cell 92, 83-92, PubMed: 9489702
39 Weber, J.R. et al. (1998) Molecular cloning of the cDNA encoding pp36, a tyrosine-phosphorylated adaptor protein selectively expressed by T cells and natural killer cells. J Exp Med 187, 1157-1161, PubMed: 9529333
40 Badour, K., Zhang, J. and Siminovitch, K.A. (2004) Involvement of the Wiskott-Aldrich syndrome protein and other actin regulatory adaptors in T cell activation. Semin Immunol 16, 395-407, PubMed: 15541654
41 Raab, M. et al. (1997) Regulation of Vav-SLP-76 binding by ZAP-70 and its relevance to TCR zeta/CD3 induction of interleukin-2. Immunity 6, 155-164, PubMed: 9047237
42 Wardenburg, J.B. et al. (1996) Phosphorylation of SLP-76 by the ZAP-70 protein-tyrosine kinase is required for T-cell receptor function. J Biol Chem 271, 19641-19644, PubMed: 8702662
43 Zhang, W., Trible, R.P. and Samelson, L.E. (1998) LAT palmitoylation: its essential role in membrane microdomain targeting and tyrosine phosphorylation during T cell activation. Immunity 9, 239-246, PubMed: 9729044
44 Zhang, W. et al. (1999) Essential role of LAT in T cell development. Immunity 10, 323-332, PubMed: 10204488
45 Finco, T.S. et al. (1998) LAT is required for TCR-mediated activation of PLCgamma1 and the Ras pathway. Immunity 9, 617-626, PubMed: 9846483
46 Zhang, W. et al. (1999) Functional analysis of LAT in TCR-mediated signaling pathways using a LAT-deficient Jurkat cell line. Int Immunol 11, 943-950, PubMed: 10360968
47 Lin, J. and Weiss, A. (2001) Identification of the minimal tyrosine residues required for linker for activation of T cell function. J Biol Chem 276, 29588-29595, PubMed: 11395491
48 Paz, P.E. et al. (2001) Mapping the Zap-70 phosphorylation sites on LAT (linker for activation of T cells) required for recruitment and activation of signalling proteins in T cells. Biochem J 356, 461-471, PubMed: 11368773
49 Sommers, C.L. et al. (2002) A LAT mutation that inhibits T cell development yet induces lymphoproliferation. Science 296, 2040-2043, PubMed: 12065840

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50 Aguado, E. et al. (2002) Induction of T helper type 2 immunity by a point mutation in the LAT adaptor. Science 296, 2036-2040, PubMed: 12065839
51 Jackman, J.K. et al. (1995) Molecular cloning of SLP-76, a 76-kDa tyrosine phosphoprotein associated with Grb2 in T cells. J Biol Chem 270, 7029-7032, PubMed: 7706237
52 Berry, D.M. et al. (2002) A high-affinity Arg-X-X-Lys SH3 binding motif confers specificity for the interaction between Gads and SLP-76 in T cell signaling. Curr Biol 12, 1336-1341, PubMed: 12176364
53 Onodera, H. et al. (1996) Differential regulation of activation-induced tyrosine phosphorylation and recruitment of SLP-76 to Vav by distinct isoforms of the CD45 protein-tyrosine phosphatase. J Biol Chem 271, 22225-22230, PubMed: 8703037
54 Tuosto, L., Michel, F. and Acuto, O. (1996) p95vav associates with tyrosine-phosphorylated SLP-76 in antigen-stimulated T cells. J Exp Med 184, 1161-1166, PubMed: 9064333
55 Bubeck Wardenburg, J. et al. (1998) Regulation of PAK activation and the T cell cytoskeleton by the linker protein SLP-76. Immunity 9, 607-616, PubMed: 9846482
56 Bunnell, S.C. et al. (2000) Biochemical interactions integrating Itk with the T cell receptor-initiated signaling cascade. J Biol Chem 275, 2219-2230, PubMed: 10636929
57 Su, Y.W. et al. (1999) Interaction of SLP adaptors with the SH2 domain of Tec family kinases. Eur J Immunol 29, 3702-3711, PubMed: 10556826
58 Zeng, R. et al. (2003) SLP-76 coordinates Nck-dependent Wiskott-Aldrich syndrome protein recruitment with Vav-1/Cdc42-dependent Wiskott-Aldrich syndrome protein activation at the T cell-APC contact site. J Immunol 171, 1360-1368, PubMed: 12874226
59 Yablonski, D. et al. (1998) Uncoupling of nonreceptor tyrosine kinases from PLC-gamma1 in an SLP-76-deficient T cell. Science 281, 413-416, PubMed: 9665884
60 Schneider, H. et al. (2000) Resting lymphocyte kinase (Rlk/Txk) targets lymphoid adaptor SLP-76 in the cooperative activation of interleukin-2 transcription in T-cells. J Biol Chem 275, 3835-3840, PubMed: 10660534
61 Clements, J.L. et al. (1998) Requirement for the leukocyte-specific adapter protein SLP-76 for normal T cell development. Science 281, 416-419, PubMed: 9665885
62 Pivniouk, V. et al. (1998) Impaired viability and profound block in thymocyte development in mice lacking the adaptor protein SLP-76. Cell 94, 229-238, PubMed: 9695951
63 Kumar, L. et al. (2002) Differential role of SLP-76 domains in T cell development and function. Proc Natl Acad Sci U S A 99, 884-889, PubMed: 11792851
64 Myung, P.S. et al. (2001) Differential requirement for SLP-76 domains in T cell development and function. Immunity 15, 1011-1026, PubMed: 11754821
65 da Silva, A.J. et al. (1997) Cloning of a novel T-cell protein FYB that binds FYN and SH2-domain-containing leukocyte protein 76 and modulates interleukin 2 production. Proc Natl Acad Sci U S A 94, 7493-7498, PubMed: 9207119
66 Musci, M.A. et al. (1997) Molecular cloning of SLAP-130, an SLP-76-associated substrate of the T cell antigen receptor-stimulated protein tyrosine kinases. J Biol Chem 272, 11674-11677, PubMed: 9115214
67 Sayos, J. et al. (1998) The X-linked lymphoproliferative-disease gene product SAP regulates signals induced through the co-receptor SLAM. Nature 395, 462-469, PubMed: 9774102
68 Coffey, A.J. et al. (1998) Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. Nat Genet 20, 129-135, PubMed: 9771704
69 Latour, S. and Veillette, A. (2003) Molecular and immunological basis of X-linked lymphoproliferative disease. Immunol Rev 192, 212-224, PubMed: 12670406
70 Chan, B. et al. (2003) SAP couples Fyn to SLAM immune receptors. Nat Cell Biol 5, 155-160, PubMed: 12545174
71 Latour, S. et al. (2001) Regulation of SLAM-mediated signal transduction by SAP, the X-linked lymphoproliferative gene product. Nat Immunol 2, 681-690, PubMed: 11477403
72 Sanzone, S. et al. (2003) SLAM-associated protein deficiency causes imbalanced early signal transduction and blocks downstream activation in T cells from X-linked lymphoproliferative disease patients. J Biol Chem 278, 29593-29599, PubMed: 12766168
73 Simarro, M. et al. (2004) SAP increases FynT kinase activity and is required for phosphorylation of SLAM and Ly9. Int Immunol 16, 727-736, PubMed: 15096483

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https://doi.org/10.1017/S1462399405010264 Published online by Cambridge University Press

74 Bustelo, X.R. (2000) Regulatory and signaling properties of the Vav family. Mol Cell Biol 20, 1461-1477, PubMed: 10669724
75 Barda-Saad, M. et al. (2005) Dynamic molecular interactions linking the T cell antigen receptor to the actin cytoskeleton. Nat Immunol 6, 80-89, PubMed: 15558067
76 Machesky, L.M. and Insall, R.H. (1998) Scar1 and the related Wiskott-Aldrich syndrome protein, WASP, regulate the actin cytoskeleton through the Arp2/3 complex. Curr Biol 8, 1347-1356, PubMed: 9889097
77 Higgs, H.N. and Pollard, T.D. (2000) Activation by Cdc42 and PIP(2) of Wiskott-Aldrich syndrome protein (WASp) stimulates actin nucleation by Arp2/3 complex. J Cell Biol 150, 1311-1320, PubMed: 10995437
78 Zhang, J. et al. (1999) Antigen receptor-induced activation and cytoskeletal rearrangement are impaired in Wiskott-Aldrich syndrome protein-deficient lymphocytes. J Exp Med 190, 1329-1342, PubMed: 10544204
79 Kim, A.S. et al. (2000) Autoinhibition and activation mechanisms of the Wiskott-Aldrich syndrome protein. Nature 404, 151-158, PubMed: 10724160
80 Holsinger, L.J. et al. (1998) Defects in actin-cap formation in Vav-deficient mice implicate an actin requirement for lymphocyte signal transduction. Curr Biol 8, 563-572, PubMed: 9601640
81 Fischer, K.D. et al. (1998) Vav is a regulator of cytoskeletal reorganization mediated by the T-cell receptor. Curr Biol 8, 554-562, PubMed: 9601639
82 Hogg, N. et al. (2003) T-cell integrins: more than just sticking points. J Cell Sci 116, 4695-4705, PubMed: 14600256
83 Shimaoka, M. et al. (2003) Structures of the alpha L I domain and its complex with ICAM-1 reveal a shape-shifting pathway for integrin regulation. Cell 112, 99-111, PubMed: 12526797
84 Monks, C.R. et al. (1998) Three-dimensional segregation of supramolecular activation clusters in T cells. Nature 395, 82-86, PubMed: 9738502
85 Dustin, M.L. and Shaw, A.S. (1999) Costimulation: building an immunological synapse. Science 283, 649-650, PubMed: 9988658
86 Krawczyk, C. et al. (2002) Vav1 controls integrin clustering and MHC/peptide-specific cell adhesion to antigen-presenting cells. Immunity 16, 331-343, PubMed: 11911819
87 Bos, J.L. (2005) Linking Rap to cell adhesion. Curr Opin Cell Biol 17, 123-128, PubMed: 15780587
88 Katagiri, K. et al. (2002) Rap1 functions as a key regulator of T-cell and antigen-presenting cell interactions and modulates T-cell responses. Mol Cell Biol 22, 1001-1015, PubMed: 11809793
89 Veale, M. et al. (1999) Novel isoform of lymphoid adaptor FYN-T-binding protein (FYB-130) interacts with SLP-76 and up-regulates interleukin 2 production. J Biol Chem 274, 28427-28435, PubMed: 10497204
90 Geng, L., Raab, M. and Rudd, C.E. (1999) Cutting edge: SLP-76 cooperativity with FYB/FYN-T in the Up-regulation of TCR-driven IL-2 transcription requires SLP-76 binding to FYB at Tyr595 and Tyr651. J Immunol 163, 5753-5757, PubMed: 10570256
91 Raab, M. et al. (1999) FYN-T-FYB-SLP-76 interactions define a T-cell receptor zeta/CD3-mediated tyrosine phosphorylation pathway that up-regulates interleukin 2 transcription in T-cells. J Biol Chem 274, 21170-21179, PubMed: 10409671
92 da Silva, A.J. et al. (1997) Biochemical analysis of p120/130: a protein-tyrosine kinase substrate restricted to T and myeloid cells. J Immunol 158, 2007-2016, PubMed: 9036943
93 Geng, L. et al. (2001) Adaptor FYB (Fyn-binding protein) regulates integrin-mediated adhesion and mediator release: differential involvement of the FYB SH3 domain. Proc Natl Acad Sci U S A 98, 11527-11532, PubMed: 11553777
94 Geng, L. and Rudd, C. (2001) Adaptor ADAP (adhesion- and degranulation-promoting adaptor protein) regulates beta1 integrin clustering on mast cells. Biochem Biophys Res Commun 289, 1135-1140, PubMed: 11741310
95 Peterson, E.J. et al. (2001) Coupling of the TCR to integrin activation by Slap-130/Fyb. Science 293, 2263-2265, PubMed: 11567141
96 Griffiths, E.K. et al. (2001) Positive regulation of T cell activation and integrin adhesion by the adapter Fyb/Slap. Science 293, 2260-2263, PubMed: 11567140
97 Wang, H. et al. (2004) ADAP-SLP-76 binding differentially regulates supramolecular activation cluster (SMAC) formation relative to T cell-APC conjugation. J Exp Med 200, 1063-1074, PubMed: 15477347
98 Krause, M. et al. (2000) Fyn-binding protein (Fyb)/SLP-76-associated protein (SLAP), Ena/vasodilator-stimulated phosphoprotein (VASP) proteins and the Arp2/3 complex link T cell receptor (TCR) signaling to the actin

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https://doi.org/10.1017/S1462399405010264 Published online by Cambridge University Press

cytoskeleton. J Cell Biol 149, 181-194, PubMed: 10747096
99 Liu, J. et al. (1998) FYB (FYN binding protein) serves as a binding partner for lymphoid protein and FYN kinase substrate SKAP55 and a SKAP55-related protein in T cells. Proc Natl Acad Sci U S A 95, 8779-8784, PubMed: 9671755
100 Marie-Cardine, A. et al. (1997) Molecular cloning of SKAP55, a novel protein that associates with the protein tyrosine kinase p59fyn in human T-lymphocytes. J Biol Chem 272, 16077-16080, PubMed: 9195899
101 Wang, H. et al. (2003) SKAP-55 regulates integrin adhesion and formation of T cell-APC conjugates. Nat Immunol 4, 366-374, PubMed: 12652296
102 Jo, E.K., Wang, H. and Rudd, C.E. (2005) An essential role for SKAP-55 in LFA-1 clustering on T cells that cannot be substituted by SKAP-55R. J Exp Med 201, 1733-1739, PubMed: 15939789
103 Bear, J.E. et al. (2002) Antagonism between Ena/VASP proteins and actin filament capping regulates fibroblast motility. Cell 109, 509-521, PubMed: 12086607
104 Jacobelli, J. et al. (2004) A single class II myosin modulates T cell motility and stopping, but not synapse formation. Nat Immunol 5, 531-538, PubMed: 15064761
105 Ihle, J.N. and Kerr, I.M. (1995) Jaks and Stats in signaling by the cytokine receptor superfamily. Trends Genet 11, 69-74, PubMed: 7716810
106 Kawamura, M. et al. (1994) Molecular cloning of L-JAK, a Janus family protein-tyrosine kinase expressed in natural killer cells and activated leukocytes. Proc Natl Acad Sci U S A 91, 6374-6378, PubMed: 8022790
107 Gurniak, C.B. and Berg, L.J. (1996) Murine JAK3 is preferentially expressed in hematopoietic tissues and lymphocyte precursor cells. Blood 87, 3151-3160, PubMed: 8605329
108 Russell, S.M. et al. (1994) Interaction of IL-2R beta and gamma c chains with Jak1 and Jak3: implications for XSCID and XCID. Science 266, 1042-1045, PubMed: 7973658
109 Leonard, W.J. (1994) The defective gene in X-linked severe combined immunodeficiency encodes a shared interleukin receptor subunit: implications for cytokine pleiotropy and redundancy. Curr Opin Immunol 6, 631-635, PubMed: 7946053
110 Asao, H. et al. (2001) Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol 167, 1-5, PubMed: 11418623
111 Park, S.Y. et al. (1995) Developmental defects of lymphoid cells in Jak3 kinase-deficient mice. Immunity 3, 771-782, PubMed: 8777722
112 Thomis, D.C. et al. (1995) Defects in B lymphocyte maturation and T lymphocyte activation in mice lacking Jak3. Science 270, 794-797, PubMed: 7481767
113 Nosaka, T. et al. (1995) Defective lymphoid development in mice lacking Jak3. Science 270, 800-802, PubMed: 7481769
114 Reguly, T. and Wrana, J.L. (2003) In or out? The dynamics of Smad nucleocytoplasmic shuttling. Trends Cell Biol 13, 216-220, PubMed: 12742164
115 Molina, T.J. et al. (1992) Profound block in thymocyte development in mice lacking p56lck. Nature 357, 161-164, PubMed: 1579166
116 Levin, S.D. et al. (1993) The protein tyrosine kinase p56lck regulates thymocyte development independently of its interaction with CD4 and CD8 coreceptors [corrected]. J Exp Med 178, 245-255, PubMed: 8391060
117 Fischer, A. (2000) Severe combined immunodeficiencies (SCID). Clin Exp Immunol 122, 143-149, PubMed: 11091267
118 Boulanger, M.J. and Garcia, K.C. (2004) Shared cytokine signaling receptors: structural insights from the gp130 system. Adv Protein Chem 68, 107-146, PubMed: 15500860
119 Elder, M.E. et al. (1994) Human severe combined immunodeficiency due to a defect in ZAP-70, a T cell tyrosine kinase. Science 264, 1596-1599, PubMed: 8202712
120 Arpaia, E. et al. (1994) Defective T cell receptor signaling and CD8+ thymic selection in humans lacking zap-70 kinase. Cell 76, 947-958, PubMed: 8124727
121 Chan, A.C. et al. (1994) ZAP-70 deficiency in an autosomal recessive form of severe combined immunodeficiency. Science 264, 1599-1601, PubMed: 8202713
122 Gelfand, E.W. et al. (1995) Absence of ZAP-70 prevents signaling through the antigen receptor on peripheral blood T cells but not on thymocytes. J Exp Med 182, 1057-1065, PubMed: 7561679
123 Toyabe, S. et al. (2001) Specific immunoglobulin E responses in ZAP-70-deficient patients are mediated by Syk-dependent T-cell receptor signalling. Immunology 103, 164-171, PubMed: 11412303
124 Sakaguchi, N. et al. (2003) Altered thymic T-cell selection due to a mutation of the ZAP-70 gene

Accession information: DOI: 10.1017/S1462399405010264; Vol. 7; Issue 29; 20 December 2005
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https://doi.org/10.1017/S1462399405010264 Published online by Cambridge University Press

causes autoimmune arthritis in mice. Nature 426, 454-460, PubMed: 14647385
125 Kishihara, K. et al. (1993) Normal B lymphocyte development but impaired T cell maturation in CD45-exon6 protein tyrosine phosphatase-deficient mice. Cell 74, 143-156, PubMed: 8334701
126 Kung, C. et al. (2000) Mutations in the tyrosine phosphatase CD45 gene in a child with severe combined immunodeficiency disease. Nat Med 6, 343-345, PubMed: 10700239
127 Tchilian, E.Z. et al. (2001) A deletion in the gene encoding the CD45 antigen in a patient with SCID. J Immunol 166, 1308-1313, PubMed: 11145714
128 Cale, C.M. et al. (1997) Severe combined immunodeficiency with abnormalities in expression of the common leucocyte antigen, CD45. Arch Dis Child 76, 163-164, PubMed: 9068311
129 Jacobsen, M. et al. (2000) A point mutation in PTPRC is associated with the development of multiple sclerosis. Nat Genet 26, 495-499, PubMed: 11101853
130 Tan, J. et al. (2000) CD45 opposes beta-amyloid peptide-induced microglial activation via inhibition of p44/42 mitogen-activated protein kinase. J Neurosci 20, 7587-7594, PubMed: 11027218
131 Socha, P. et al. (2001) Deficiency of the expression of CD45RA isoform of CD45 common leukocyte antigen in CD4+ T lymphocytes in children with infantile cholestasis. Immunol Lett 75, 179-184, PubMed: 11166373
132 Neidhart, M. et al. (1996) CD45 isoforms expression on CD4+ and CD8+ peripheral blood T-lymphocytes is related to auto-immune processes and hematological manifestations in systemic lupus erythematosus. Schweiz Med Wochenschr 126, 1922-1925, PubMed: 8946597
133 Spina, C.A., Prince, H.E. and Richman, D.D. (1997) Preferential replication of HIV-1 in the CD45RO memory cell subset of primary CD4 lymphocytes in vitro. J Clin Invest 99, 1774-1785, PubMed: 9120023
134 Helbert, M.R. et al. (1997) HIV infection of CD45RA+ and CD45RO+ CD4+ T cells. Clin Exp Immunol 107, 300-305, PubMed: 9030867
135 Barbeau, B. et al. (2001) Negative regulation of the NFAT1 factor by CD45: implication in HIV-1 long terminal repeat activation. J Immunol 167, 2700-2713, PubMed: 11509614
136 Tan, J., Town, T. and Mullan, M. (2000) CD45 inhibits CD40L-induced microglial activation via negative regulation of the Src/p44/42 MAPK pathway. J Biol Chem 275, 37224-37231, PubMed: 10978311
137 Lazarovits, A.I. et al. (1996) Prevention and reversal of renal allograft rejection by antibody against CD45RB. Nature 380, 717-720, PubMed: 8614467
138 Sho, M. et al. (2005) Requirements for induction and maintenance of peripheral tolerance in stringent allograft models. Proc Natl Acad Sci U S A 102, 13230-13235, PubMed: 16150717
139 Countouriotis, A., Moore, T.B. and Sakamoto, K.M. (2002) Cell surface antigen and molecular targeting in the treatment of hematologic malignancies. Stem Cells 20, 215-229, PubMed: 12004080
140 Lee, K. and Burke, T.R., Jr. (2003) CD45 protein-tyrosine phosphatase inhibitor development. Curr Top Med Chem 3, 797-807, PubMed: 12678845
141 Majeti, R. et al. (2000) An inactivating point mutation in the inhibitory wedge of CD45 causes lymphoproliferation and autoimmunity. Cell 103, 1059-1070, PubMed: 11163182
142 Nam, H.J. et al. (2005) Structural basis for the function and regulation of the receptor protein tyrosine phosphatase CD45. J Exp Med 201, 441-452, PubMed: 15684325
143 Takeuchi, T. et al. (1997) Reduced protein tyrosine phosphatase (PTPase) activity of CD45 on peripheral blood lymphocytes in patients with systemic lupus erythematosus (SLE). Clin Exp Immunol 109, 20-26, PubMed: 9218819
144 Long, E.O. (1999) Regulation of immune responses through inhibitory receptors. Annu Rev Immunol 17, 875-904, PubMed: 10358776
145 Stefanova, I. et al. (2003) TCR ligand discrimination is enforced by competing ERK positive and SHP-1 negative feedback pathways. Nat Immunol 4, 248-254, PubMed: 12577055
146 Bottini, N. et al. (2004) A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. Nat Genet 36, 337-338, PubMed: 15004560
147 Begovich, A.B. et al. (2004) A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. Am J Hum Genet 75, 330-337, PubMed: 15208781
148 Smyth, D. et al. (2004) Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general

Accession information: DOI: 10.1017/S1462399405010264; Vol. 7; Issue 29; 20 December 2005
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https://doi.org/10.1017/S1462399405010264 Published online by Cambridge University Press

autoimmunity locus. Diabetes 53, 3020-3023, PubMed: 15504986
149 Onengut-Gumuscu, S. et al. (2004) A functional polymorphism (1858C/T) in the PTPN22 gene is linked and associated with type I diabetes in multiplex families. Genes Immun 5, 678-680, PubMed: 15526003
150 Ladner, M.B. et al. (2005) Association of the single nucleotide polymorphism C1858T of the PTPN22 gene with type 1 diabetes. Hum Immunol 66, 60-64, PubMed: 15620463
151 Kyogoku, C. et al. (2004) Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. Am J Hum Genet 75, 504-507, PubMed: 15273934
152 Velaga, M.R. et al. (2004) The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves' disease. J Clin Endocrinol Metab 89, 5862-5865, PubMed: 15531553
153 Criswell, L.A. et al. (2005) Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. Am J Hum Genet 76, 561-571, PubMed: 15719322
154 Orozco, G. et al. (2005) Association of a functional single-nucleotide polymorphism of PTPN22, encoding lymphoid protein phosphatase, with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Rheum 52, 219-224, PubMed: 15641066
155 Lee, A.T. et al. (2005) The PTPN22 R620W polymorphism associates with RF positive rheumatoid arthritis in a dose-dependent manner but not with HLA-SE status. Genes Immun 6, 129-133, PubMed: 15674368
156 Begovich, A.B. et al. (2005) The R620W polymorphism of the protein tyrosine phosphatase PTPN22 is not associated with multiple sclerosis. Am J Hum Genet 76, 184-187, PubMed: 15580548
157 Hasegawa, K. et al. (2004) PEST domain-enriched tyrosine phosphatase (PEP) regulation of effector/memory T cells. Science 303, 685-689, PubMed: 14752163
158 Solimena, M. et al. (1996) ICA 512, an autoantigen of type I diabetes, is an intrinsic membrane protein of neurosecretory granules. Embo J 15, 2102-2114, PubMed: 8641276
159 Kawasaki, E., Hutton, J.C. and Eisenbarth, G.S. (1996) Molecular cloning and characterization of the human transmembrane protein tyrosine phosphatase homologue, phogrin, an autoantigen of type 1 diabetes. Biochem Biophys Res Commun 227, 440-447, PubMed: 8878534
160 Malissen, B., Aguado, E. and Malissen, M. (2005) Role of the LAT adaptor in T-cell development and Th2 differentiation. Adv Immunol 87, 1-25, PubMed: 16102570
161 Snapper, S.B. and Rosen, F.S. (1999) The Wiskott-Aldrich syndrome protein (WASP): roles in signaling and cytoskeletal organization. Annu Rev Immunol 17, 905-929, PubMed: 10358777
162 MacCarthy-Morrogh, L. et al. (1998) Absence of expression of the Wiskott-Aldrich syndrome protein in peripheral blood cells of Wiskott-Aldrich syndrome patients. Clin Immunol Immunopathol 88, 22-27, PubMed: 9683546
163 Lemahieu, V., Gastier, J.M. and Francke, U. (1999) Novel mutations in the Wiskott-Aldrich syndrome protein gene and their effects on transcriptional, translational, and clinical phenotypes. Hum Mutat 14, 54-66, PubMed: 10447259
164 Shcherbina, A., Rosen, F.S. and Remold-O'Donnell, E. (1999) WASP levels in platelets and lymphocytes of wiskott-aldrich syndrome patients correlate with cell dysfunction. J Immunol 163, 6314-6320, PubMed: 10570326
165 Snapper, S.B. et al. (1998) Wiskott-Aldrich syndrome protein-deficient mice reveal a role for WASP in T but not B cell activation. Immunity 9, 81-91, PubMed: 9697838
166 Badour, K. et al. (2003) The Wiskott-Aldrich syndrome protein acts downstream of CD2 and the CD2AP and PSTPIP1 adaptors to promote formation of the immunological synapse. Immunity 18, 141-154, PubMed: 12530983
167 Badour, K. et al. (2004) Fyn and PTP-PEST-mediated regulation of Wiskott-Aldrich syndrome protein (WASp) tyrosine phosphorylation is required for coupling T cell antigen receptor engagement to WASp effector function and T cell activation. J Exp Med 199, 99-112, PubMed: 14707117
168 Devriendt, K. et al. (2001) Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia. Nat Genet 27, 313-317, PubMed: 11242115
169 Thrasher, A.J. (2002) WASp in immune-system organization and function. Nat Rev Immunol 2, 635-646, PubMed: 12209132
170 Wada, T. et al. (2002) Retrovirus-mediated WASP gene transfer corrects Wiskott-Aldrich syndrome T-cell dysfunction. Hum Gene Ther 13, 1039-

Accession information: DOI: 10.1017/S1462399405010264; Vol. 7; Issue 29; 20 December 2005
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https://doi.org/10.1017/S1462399405010264 Published online by Cambridge University Press

1046, PubMed: 12067437
171 Strom, T.S. et al. (2003) Functional correction of T cells derived from patients with the Wiskott-Aldrich syndrome (WAS) by transduction with an oncoretroviral vector encoding the WAS protein. Gene Ther 10, 803-809, PubMed: 12704420
172 Klein, C. et al. (2003) Gene therapy for Wiskott-Aldrich syndrome: rescue of T-cell signaling and amelioration of colitis upon transplantation of retrovirally transduced hematopoietic stem cells in mice. Blood 101, 2159-2166, PubMed: 12433691
173 Nichols, K.E. et al. (1998) Inactivating mutations in an SH2 domain-encoding gene in X-linked lymphoproliferative syndrome. Proc Natl Acad Sci U S A 95, 13765-13770, PubMed: 9811875
174 Howie, D. et al. (2000) The gene defective in X-linked lymphoproliferative disease controls T cell dependent immune surveillance against Epstein-Barr virus. Curr Opin Immunol 12, 474-478, PubMed: 10899030
175 Nelson, D.L. and Terhorst, C. (2000) X-linked lymphoproliferative syndrome. Clin Exp Immunol 122, 291-295, PubMed: 11122230
176 Wu, C. et al. (2001) SAP controls T cell responses to virus and terminal differentiation of TH2 cells. Nat Immunol 2, 410-414, PubMed: 11323694
177 Nakamura, H. et al. (2001) Abnormal T cell receptor signal transduction of CD4 Th cells in X-linked lymphoproliferative syndrome. J Immunol 167, 2657-2665, PubMed: 11509608
178 Sharifi, R. et al. (2004) SAP mediates specific cytotoxic T-cell functions in X-linked lymphoproliferative disease. Blood 103, 3821-3827, PubMed: 14726378
179 Weissman, A.M. (2001) Themes and variations on ubiquitylation. Nat Rev Mol Cell Biol 2, 169-178, PubMed: 11265246
180 Mueller, D.L. (2004) E3 ubiquitin ligases as T cell anergy factors. Nat Immunol 5, 883-890, PubMed: 15334084
181 Bachmaier, K. et al. (2000) Negative regulation of lymphocyte activation and autoimmunity by the molecular adaptor Cbl-b. Nature 403, 211-216, PubMed: 10646608
182 Chiang, Y.J. et al. (2000) Cbl-b regulates the CD28 dependence of T-cell activation. Nature 403, 216-220, PubMed: 10646609
183 Yokoi, N. et al. (2002) Cblb is a major susceptibility gene for rat type 1 diabetes mellitus. Nat Genet 31, 391-394, PubMed: 12118252
184 Anandasabapathy, N. et al. (2003) GRAIL: an E3 ubiquitin ligase that inhibits cytokine gene transcription is expressed in anergic CD4+ T cells. Immunity 18, 535-547, PubMed: 12705856
185 Soares, L. et al. (2004) Two isoforms of otubain 1 regulate T cell anergy via GRAIL. Nat Immunol 5, 45-54, PubMed: 14661020
186 Heissmeyer, V. et al. (2004) Calcineurin imposes T cell unresponsiveness through targeted proteolysis of signaling proteins. Nat Immunol 5, 255-265, PubMed: 14973438
187 Fang, D. et al. (2002) Dysregulation of T lymphocyte function in itchy mice: a role for Itch in TH2 differentiation. Nat Immunol 3, 281-287, PubMed: 11828324
188 Buckley, R.H. et al. (1997) Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J Pediatr 130, 378-387, PubMed: 9063412
189 Buckley, R.H. et al. (1999) Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 340, 508-516, PubMed: 10021471
190 Haddad, E. et al. (1998) Long-term immune reconstitution and outcome after HLA-nonidentical T-cell-depleted bone marrow transplantation for severe combined immunodeficiency: a European retrospective study of 116 patients. Blood 91, 3646-3653, PubMed: 9573000
191 Patel, D.D. et al. (2000) Thymic function after hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 342, 1325-1332, PubMed: 10793165
192 Otsu, M. et al. (2000) Lymphoid development and function in X-linked severe combined immunodeficiency mice after stem cell gene therapy. Mol Ther 1, 145-153, PubMed: 10933924
193 Cavazzana-Calvo, M. et al. (2000) Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science 288, 669-672, PubMed: 10784449
194 Fischer, A., Hacein-Bey, S. and Cavazzana-Calvo, M. (2002) Gene therapy of severe combined immunodeficiencies. Nat Rev Immunol 2, 615-621, PubMed: 12154380
195 O'Shea, J.J. et al. (2004) A new modality for immunosuppression: targeting the JAK/STAT pathway. Nat Rev Drug Discov 3, 555-564, PubMed: 15232577
196 Gaspar, H.B. et al. (2004) Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector. Lancet 364, 2181-2187, PubMed: 15610804

Accession information: DOI: 10.1017/S1462399405010264; Vol. 7; Issue 29; 20 December 2005
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https://doi.org/10.1017/S1462399405010264 Published online by Cambridge University Press

197 Hacein-Bey-Abina, S. et al. (2002) Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med 346, 1185-1193, PubMed: 11961146
198 Hacein-Bey-Abina, S. et al. (2003) LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 302, 415-419, PubMed: 14564000
199 Hershfield, M.S. (2004) Combined immune deficiencies due to purine enzyme defects. In Immunologic Disorders in Infants and Children (Stiehm, E.R., Ochs, H.D.and Winkelstein, J.A., eds), pp. 480-504, W.B. Saunders, Philadelphia
200 Apasov, S.G. et al. (2001) Adenosine deaminase deficiency increases thymic apoptosis and causes defective T cell receptor signaling. J Clin Invest 108, 131-141, PubMed: 11435465
201 Aiuti, A. et al. (2002) Immune reconstitution in ADA-SCID after PBL gene therapy and discontinuation of enzyme replacement. Nat Med 8, 423-425, PubMed: 11984564
202 Aiuti, A. et al. (2002) Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. Science 296, 2410-2413, PubMed: 12089448
203 Gellert, M. (2002) V(D)J recombination: RAG proteins, repair factors, and regulation. Annu Rev Biochem 71, 101-132, PubMed: 12045092
204 Fugmann, S.D. et al. (2000) The RAG proteins and V(D)J recombination: complexes, ends, and transposition. Annu Rev Immunol 18, 495-527, PubMed: 10837067
205 Rooney, S., Chaudhuri, J. and Alt, F.W. (2004) The role of the non-homologous end-joining pathway in lymphocyte development. Immunol Rev 200, 115-131, PubMed: 15242400
206 de Villartay, J.P. (2002) V(D)J recombination and DNA repair: lessons from human immune deficiencies and other animal models. Curr Opin Allergy Clin Immunol 2, 473-479, PubMed: 14752329
207 Moshous, D. et al. (2001) Artemis, a novel DNA double-strand break repair/V(D)J recombination protein, is mutated in human severe combined immune deficiency. Cell 105, 177-186, PubMed: 11336668
208 Hahm, K.B. et al. (2001) Loss of transforming growth factor beta signalling in the intestine contributes to tissue injury in inflammatory bowel disease. Gut 49, 190-198, PubMed: 11454793
209 Maloy, K.J. and Powrie, F. (2001) Regulatory T cells in the control of immune pathology. Nat Immunol 2, 816-822, PubMed: 11526392
210 Yang, X. et al. (1999) Targeted disruption of SMAD3 results in impaired mucosal immunity and diminished T cell responsiveness to TGF-beta. Embo J 18, 1280-1291, PubMed: 10064594
211 Monteleone, G. et al. (2001) Blocking Smad7 restores TGF-beta1 signaling in chronic inflammatory bowel disease. J Clin Invest 108, 601-609, PubMed: 11518734
212 Schreiber, S., Nikolaus, S. and Hampe, J. (1998) Activation of nuclear factor kappa B inflammatory bowel disease. Gut 42, 477-484, PubMed: 9616307
213 Stoll, M. et al. (2004) Genetic variation in DLG5 is associated with inflammatory bowel disease. Nat Genet 36, 476-480, PubMed: 15107852
214 Neurath, M.F., Finotto, S. and Glimcher, L.H. (2002) The role of Th1/Th2 polarization in mucosal immunity. Nat Med 8, 567-573, PubMed: 12042806
215 Lippincott-Schwartz, J. and Patterson, G.H. (2003) Development and use of fluorescent protein markers in living cells. Science 300, 87-91, PubMed: 12677058
216 Zimmermann, T., Rietdorf, J. and Pepperkok, R. (2003) Spectral imaging and its applications in live cell microscopy. FEBS Lett 546, 87-92, PubMed: 12829241
217 Eils, R. and Athale, C. (2003) Computational imaging in cell biology. J Cell Biol 161, 477-481, PubMed: 12743101

Accession information: DOI: 10.1017/S1462399405010264; Vol. 7; Issue 29; 20 December 2005
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Further reading, resources and contacts

Other excellent reviews on signalling proteins in T cells and disease associations include:

Jordan, M.S., Singer, A.L. and Koretzky, G.A. (2003) Adaptors as central mediators of signal transduction in immune cells. Nat Immunol 4, 110-116, PubMed: 12555096

Samelson, L.E. (2002) Signal transduction mediated by the T cell antigen receptor: the role of adapter proteins. Annu Rev Immunol 20, 371-394, PubMed: 11861607
Reviews the identity of adapters and their control of the cytoskeleton organisation and T-cell function.

Fathman, C.G. et al. (2005) An array of possibilities for the study of autoimmunity. Nature 435, 605-611, PubMed: 15931213
Discusses how genomic and proteomic technologies are providing useful information about autoimmune disease, and how they are likely to lead to important discoveries within the next decade.

Macian, F. et al. (2004) T-cell anergy. Curr Opin Immunol 16, 209-216, PubMed: 15023415
Reviews recent studies that have provided new insights into the mechanisms responsible for the induction and maintenance of T-cell anergy.

Hermiston, M.L., Xu, Z. and Weiss, A. (2003) CD45: a critical regulator of signaling thresholds in immune cells. Annu Rev Immunol 21, 107-137, PubMed: 12414720
Reviews how CD45 regulates threshold of responses to external stimuli and may contribute to autoimmunity, immunodeficiency and malignancy.

Rudd, C.E. and Schneider, H. (2003) Unifying concepts in CD28, ICOS and CTLA4 co-receptor signalling. Nat Rev Immunol 3, 544-556, PubMed: 12876557

Mustelin, T., Vang, T. and Bottini, N. (2005) Protein tyrosine phosphatases and the immune response. Nat Rev Immunol 5, 43-57, PubMed: 15630428
Highlights recent evidence that subtle alterations in protein tyrosine phosphatases can cause immune dysfunction and human disease.

Buckley, R.H. et al. (1999) Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 340, 508-516, PubMed: 10021471

Features associated with this article

Figures

Figure 1. Receptors on T cells and their ligands on antigen-presenting cells.
Figure 2. The T-cell signalling paradigm.
Figure 3. Adaptors and molecular scaffolds in T-cell signalling.
Figure 4. JAK–STAT and Smad signalling cascades.
Figure 5. Immune disorders associated with T-cell signalling.

Table

Table 1. T-cell signalling proteins and human disease.

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