SH2 domains: role, structure and implications for molecular medicine

Gabriel Waksman, Sangaralingam Kumaran and Olga Lubman

Src homology 2 (SH2) domains are protein modules (of ~100 amino acids) found in many proteins involved in tyrosine kinase signalling cascades. Their function is to bind tyrosine-phosphorylated sequences in specific protein targets. Binding of an SH2 domain to its cognate tyrosine-phosphorylated target links receptor activation to downstream signalling, both to the nucleus to regulate gene expression and throughout the cytoplasm of the cell. This review recapitulates the roles that SH2 domains play in normal and diseased states, describes the successes of SH2 domain research in deciphering their mechanism of action, and provides an overview of the use of SH2 domains as structural templates for the design of inhibitor drugs.

Signal transduction is a key event in the response of the cell to changes in its extracellular environment. The cell responds to extracellular signals by transducing through its membrane the molecular message that these signals contain (Ref. 1). One well-documented signal transduction pathway is that induced by platelet-derived growth factor (PDGF). PDGF receptors play important roles during embryogenesis, particularly in the development of the kidneys, blood vessels, lungs and the central nervous system (Refs 2, 3, 4, 5). PDGF receptors also

Gabriel Waksman (corresponding author)
Currently, Professor of Structural Molecular Biology, Director of the Institute of Structural Molecular Biology at Birkbeck/UCL, Birkbeck College, School of Crystallography, Malet Street, London, WC1E 7HX, UK, and University College London, Department of Biochemistry and Molecular Biology, Gower Street, London, WC1E 6BT, UK. Tel: +44 (0) 207 631 6833; Fax: +44 (0) 207 631 6803; E-mail: g.waksman@bbk.ac.uk or g.waksman@ucl.ac.uk
Formerly, Roy and Diana Vagelos Professor of Biochemistry and Molecular Biophysics, Washington University School of Medicine, Department of Biochemistry and Molecular Biophysics, Saint Louis, MO, USA.

Sangaralingam Kumaran
Postdoctoral Associate, Washington University School of Medicine, Department of Biochemistry and Molecular Biophysics, 660 South Euclid Avenue, Saint Louis, MO 63110, USA. Tel: +1 314 362 4565; Fax: +1 314 362 7813; E-mail: kumaran@biochem.wustl.edu

Olga Lubman
W. Keck Postdoctoral Fellow, Washington University School of Medicine, Department of Molecular Biology and Pharmacology, 660 South Euclid Avenue, Saint Louis, MO 63110, USA. Tel: +1 314 362 4565; Fax: +1 314 362 7183; E-mail: olubman@molecool.wustl.edu

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

SH2 domains: role, structure and implications for molecular medicine

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

have a role in wound healing in adults (Ref. 6). The PDGF receptor belongs to the family of receptor tyrosine kinases. Each contains a large extracellular region involved in growth factor binding and an intracellular region that contains a kinase domain responsible for propagation of the signal (Refs 7, 8, 9). Ligand binding to the PDGF receptor induces an increased catalytic activity of its receptor kinase activity, leading to the addition of phosphate groups on specific tyrosine residues located in its intracellular domain. Thus, the extracellular 'signal' that PDGF constitutes is 'translated' to the other side of the cell membrane by the specific phosphorylation of tyrosine residues. What happens next is the transmission of the phosphate signal from one protein to another through a succession of protein–protein interactions that ultimately leads to a cellular response such as gene activation or enzyme activation. Such a mechanism implies that tyrosine residues that are phosphorylated upon receptor activation are in some way recognised and serve as docking sites for downstream signal transduction molecules. Such a recognition process is made possible by small protein modules that are contained within signal transduction molecules and bind to phosphorylated tyrosine residues in a sequence-specific manner. These domains are called Src homology 2 (SH2) domains (Ref. 10).

The initial discovery of the SH2 domain identified it as a ~100 amino acid block that was conserved in several cytoplasmic tyrosine kinases, including Src, and that, when mutated, appeared to be involved either in regulating kinase activity or in promoting interactions of kinases with other components of the cell (Ref. 11). Subsequent breakthroughs identified SH2 domains as binding specifically to tyrosine-phophorylated sites (reviewed in Ref. 12). Since this pioneering work, SH2 domains have been identified in numerous proteins of various origins and with various activities, which include protein tyrosine kinases, transcription factors and molecular adaptors (Fig. 1). SH2-domain-containing proteins are involved in pathways regulating numerous essential cellular processes, such as cytoskeletal rearrangement, homeostasis, immune responses and development. Although mutations in SH2 domains are rarely the cause of pathological conditions (see section 'SH2 domains: clinical implications'), the involvement of these domains in such a variety of pathways makes them ideal candidates as drug targets (see section 'SH2 domains: clinical applications'). Indeed, disease states often result from alterations in signal transduction proteins; thus, the hope that SH2-domain-binding inhibitors could be designed to inhibit a faulty signal transduction pathway has in the past 15 years justified substantial investments by the pharmaceutical industry (Refs 13, 14).

SH2 domains: clinical implications

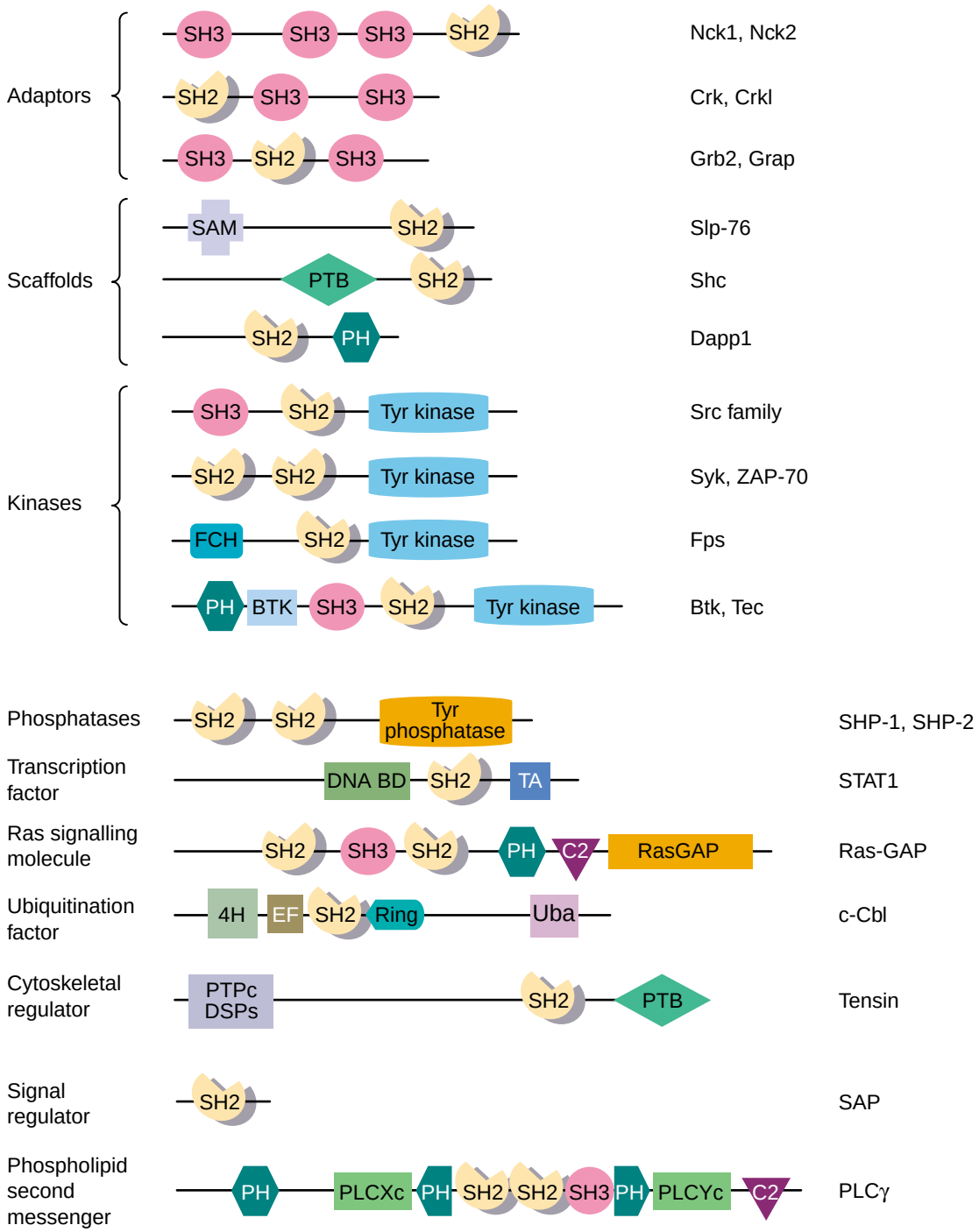
SH2 domain mutation and disease

To date, only three SH2 domains have been directly implicated in human diseases. Mutations in the SH2 domain of SAP [SLAM (signalling lymphocyte activation molecule)-associated protein; also known as SH2D1A or DSHP] cause X-linked lymphoproliferative disease (XLP) (Refs 15, 16, 17). This disorder is characterised by an extreme sensitivity to Epstein–Barr virus, with infection resulting in uncontrolled B-cell proliferation. The average age of onset in affected young boys is 2.5 years, with 75% mortality by age 10 and 100% mortality by age 40. SAP functions in immune cell signalling, with its expression restricted primarily to T cells. It

Figure 1. Examples of Src homology 2 (SH2)-domain-containing proteins and their modular primary structure. *(Legend; see next page for figure.)* The biological functions of the proteins are indicated on the left, and the names of the proteins are given on the right. The various homology domains that are found in these proteins are represented by different shapes and colours, and are labelled accordingly. Abbreviations: C2, protein kinase C conserved region 2 calcium-dependent phospholipid binding; Dapp1, dual adaptor for phosphotyrosine and 3-phosphoinositide; DNA BD, DNA-binding domain; EF, EF-hand; FCH, Fes/CIP4 homology domain; Grap, Grb2-related adaptor protein; 4H, four-helix bundle; Nck, noncatalytic region of tyrosine kinase; PLC, phospholipase C; PH, pleckstrin homology domain; PTB, phosphotyrosine-binding domain; PTPc DSPs, protein tyrosine phosphatase; SAM, sterile alpha motif domain; SAP, SLAM (signalling lymphocyte activation molecule)-associated protein; Slp-76, SH2-domain-containing leukocyte protein of 76 kDa; TA, transcriptional activation domain; Tyr kinase, tyrosine kinase domain; Tyr phosphatase, tyrosine phosphatase domain; Uba, ubiquitin association domain. Cbl, Crk, Fps, Ras, Src are products of homologues of viral oncogenes, and their abbreviations are derived from the viral oncogene names. For other abbreviations see Table 1. Figure drawn according to Ref. 117.

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press



Examples of Src homology 2 (SH2)-domain-containing proteins and their modular primary structure

Expert Reviews in Molecular Medicine ©2004 Cambridge University Press

Figure 1. Examples of Src homology 2 (SH2)-domain-containing proteins and their modular primary structure. *(See previous page for legend.)*

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

interacts with the protein SLAM, a 70 kDa glycoprotein expressed on many lymphocyte cell surfaces. SLAM is a self-ligand type of receptor that operates in bidirectional signalling between B and T cells, perhaps functioning in the switching of helper T-cell phenotype. Thus, mutations in the SAP SH2 domain appear to impair the normal signalling between B and T cells following viral infection, and result in the uncontrolled proliferation of B cells.

A point mutation in the SH2 domain of the Bruton tyrosine kinase (Btk) has been shown to cause cases of X-linked agammaglobulinaemia (XLA), which is the prototypical humoral immunodeficiency first described by Bruton in 1952 (Ref. 18). It is characterised by a paucity of circulating B cells and a drastic reduction in the serum concentrations of immunoglobulins. Studies analysing patterns of X chromosome inactivation showed that the genetic defect was intrinsic to the B-cell lineage, and mapping studies localised the defect in the midportion of the long arm of the X chromosome at Xq225. Subsequent studies demonstrated that mutations in the gene encoding the cytoplasmic tyrosine kinase Btk are responsible for X-linked agammaglobulinaemia (Ref. 18). Like other cytoplasmic tyrosine kinases, Btk contains a unique N-terminal region, in addition to SH3 and SH2 domains (SH3 domains are homology domains that specifically bind to polyproline sequences), and a C-terminal tyrosine kinase domain. Saffran and co-workers (Ref. 18) identified a mutation (at residue 361) in the SH2 domain of Btk that causes the disease and that appears to destabilise the full-length protein or interfere directly with SH2 domain function.

Finally, mutations in the N-terminal SH2 domain of the nonreceptor protein tyrosine phosphatase 2 (SHP-2) (Fig. 1) cause a relatively common autosomal dominant disorder called Noonan's syndrome (Ref. 19). This disease is characterised by dysmorphic facial features, short stature and heart disease. Webbed neck, chest deformity and mental retardation are also frequently associated with this disease. Missense mutations in *PTPN11*, the gene that encodes SHP-2, cause Noonan's syndrome and account for more than 50% of the cases examined (Ref. 19). SHP-2 contains two SH2 domains. All mutations locate in the interacting portions of the N-terminal SH2 domain, which is involved in downregulating phosphatase activity. Thus, the disease state might result from excessive phosphatase activity.

Potential drug targets

Although examples of direct implication of SH2 domains in diseases are few, their involvement in pathways altered by disease-causing mutations makes them attractive targets for pharmaceuticals. Table 1 summarises diseases in which SH2 domains have potential as drug targets (Ref. 20), ranging from cancer, allergy and AIDS (acquired immune deficiency syndrome) to osteoporosis. Several SH2 domains have been, and continue to be, the subjects both of extensive drug design effort in the pharmaceutical industry and of academic research – for potential uses in cancer [Grb2 adaptor, phosphoinositide 3-kinase (PI3K)], autoimmune diseases (the ζ-chain-associated protein kinase ZAP-70), allergy and asthma (Syk kinase) and osteoporosis (Src kinase). The cellular biology in which Src, Syk and Grb2 are involved is discussed below. The effort expended in designing efficacious Src and Grb2 SH2-domain-binding inhibitors has been met with some measure of success and will be described in the section 'SH2 domains: clinical applications' below.

Src kinase

The Src kinase consists of four domains: a short myristylation domain that anchors Src to the membrane, an SH3 domain that binds polyproline-rich sequences, an SH2 domain and a kinase domain (Fig. 1) (Ref. 21). Src has been shown to be involved in a variety of cellular processes including bone resorption, tumour growth and angiogenesis, and tumour metastasis (Ref. 21). However, the major phenotype of a Src-knockout mutant mouse is an excessive accumulation of bone in marrow cavities during bone development resulting from excessive bone resorption (osteopetrosis) (Ref. 22). A more severe form of osteopetrosis is observed in the double Src–Hck-knockout mouse (Ref. 23), suggesting that these Src-family kinases have partially overlapping functions in osteoclasts. Osteoclasts are the cells specialised in bone resorption, and although osteoclasts derived from Src-deficient mice are viable, they fail to form ruffled borders, and thus are unable to secrete acid proteases and bone-metabolising enzymes (Refs 24, 25). Osteoblasts are the cells that produce bones, and Src-deficient osteoblasts appear to have increased activity (Ref. 26), thus possibly contributing to the osteopetrotic phenotype observed in Src-deficient mice. Partial rescue of the osteopetrosis phenotype

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

Table 1. Diseases in which Src homology 2 (SH2) domains have potential as pharmaceutical targets[a]

Disease	SH2 domain-containing target
AIDS	Lck, Hck
Allergy and asthma	Syk, Lyn
Anaemia	SHP-1
Autoimmune disease	ZAP-70
Breast cancer	Grb2, Grb7, Src
Cancer	p85, Shc, Grb2, GAP
CML and ALL	Grb2, Crkl
Erythroleukaemia	Shc
Inflammatory disease	STATs
Pre-B-cell leukaemia	Btk
Myelodysplastic syndrome	Tec
Osteoporosis	Src

[a] For further information, see Ref. 20.

Abbreviations: AIDS, acquired immune deficiency syndrome; ALL, acute lymphoblastic leukaemia; Btk, Bruton tyrosine kinase; CML, chronic myeloid leukaemia; Crkl, Crk-like protein; GAP, GTPase-activating protein; Grb, growth-receptor-binding protein; Hck, haematopoietic cell kinase; Lck, lymphocyte-specific protein tyrosine kinase; p85, p85 subunit of the phosphoinositide 3-kinase; Shc, Src homologous and collagen protein; SHP-1, SH2-domain-containing protein tyrosine phosphatase 1; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase; Tec, tyrosine-protein kinase Tec; ZAP-70, zeta-chain associated protein kinase. Crk, Lyn and Src are products of homologues of viral oncogenes, and their abbreviations are derived from the viral oncogene names.

in Src-deficient mice by transgenic expression of the kinase-deficient K295M Src mutant suggests that the role of Src in osteoclasts is mediated by its SH2 or SH3 domains (Ref. 27). Thus, an SH2-domain-binding inhibitor of the Src kinase could potentially inhibit bone resorption and serve as a treatment for osteoporosis, a condition that results in the weakening of the bone structure (Ref. 28).

Syk kinase

The Syk kinase consists of two SH2 domains in tandem, collectively named 'tandem SH2 domain', and a tyrosine kinase domain (Fig. 1) (Ref. 29). Syk is a member of the Syk family of cytosolic protein tyrosine kinases that also includes the ZAP-70 kinase (Refs 30, 31). Syk is expressed ubiquitously in haematopoietic cells such as B cells, mast cells, polymorphonuclear leukocytes, platelets, macrophages and immature T cells. Syk is also present in nonhaematopoietic cells such as epithelial cells, hepatocytes, fibroblasts and neuronal cells. The absence of either Syk-family kinase results in arrested T- and B-cell development and functional defects for a variety of immune receptors, including the T-cell receptor, the B-cell receptor, and receptors for IgG and IgE (Refs 32, 33, 34, 35, 36, 37, 38). In addition, Syk-family kinases have been implicated in activating natural killer (NK) cells (Refs 39, 40) and signalling by nonimmune receptors such as cytokine and thrombin receptors, integrins and G-protein-coupled receptors (Refs 41, 42, 43, 44, 45, 46). The involvement of Syk in immune cell biology suggests that SH2 domain inhibitors targeting the tandem SH2 domain of this enzyme could be used for the treatment of allergy.

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

Grb2 adaptor

Grb2 is a small adaptor protein that consists of one SH2 domain flanked by two SH3 domains (Ref. 47) (Fig. 1). The function of Grb2 was elucidated in a series of outstanding publications where it was reported that Grb2 serves to link receptor tyrosine kinases to Ras signalling (Refs 47, 48, 49, 50, 51). The SH2 domain of Grb2 binds to specific phosphorylated tyrosine residues on activated receptors, whereas its SH3 domains bind to the guanine-nucleotide-exchange factor specific to the low-molecular-weight GTP-binding protein Ras, thereby activating Ras and the downstream Ras-dependent mitogen-activated protein (MAP) kinases. As Ras is known to play a key role in the regulation of cellular growth and differentiation (Ref. 1), one means to control Ras is through indirect inhibition of Grb2.

Structure and ligand binding

Because of their importance in some of the most essential biological processes in humans, SH2 domains have been the subjects of extensive investigations aimed at understanding the structure–function relationship and/or at designing SH2-domain-binding inhibitors.

The structures of a large number of SH2 domains have been determined (reviewed in Ref. 52). These studies have revealed a common fold consisting of a central β-sheet flanked by two α-helices (Fig. 2a). A remarkable feature of the structure, which was revealed by the determination of the first structure of a binary complex of the Src SH2 domain bound to a tyrosine-phosphorylated peptide, is the definition of two regions, each with a distinct functional role. The region between the first α-helix and the β-sheet is the site of phosphotyrosine recognition, whereas the region between the β-sheet and the C-terminal helix forms the so-called 'specificity-determining region' as it forms the interacting surface for the residues C-terminal to the phosphotyrosine (Fig. 2a) (Ref. 53).

Phosphotyrosine binding

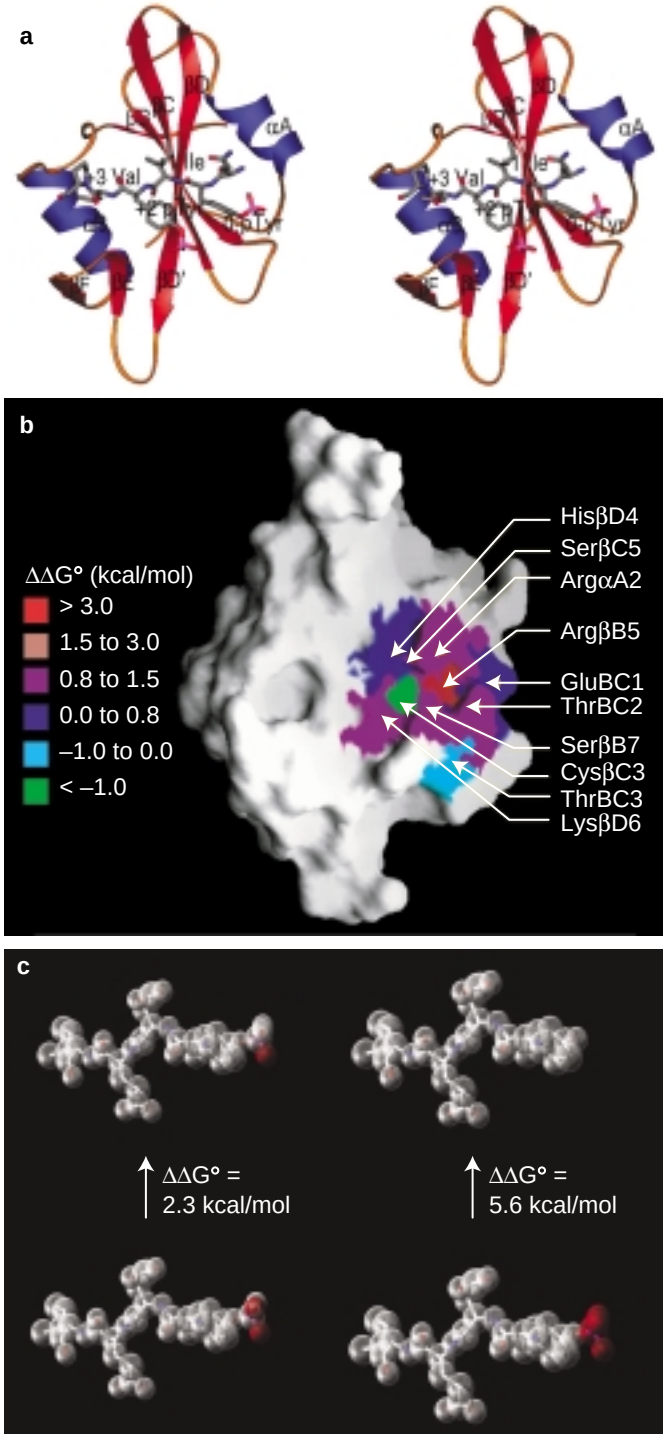
In vivo and in vitro studies have shown that phosphorylation of tyrosine residues of the ligand is a requirement for SH2-domain binding (reviewed in Ref. 54). However, exactly how stringent the requirement for phosphate is has only recently been rigorously evaluated (Ref. 55). This study showed that more than a half of the binding free energy of the interaction of the SH2 domain of the Src kinase with its cognate tysosine-phosphorylated peptide target (sequence pYEEI where pY indicates phosphotyrosine) is contributed by phosphorylation. Other studies have shown that no other residue in the tyrosine-phosphorylated ligand is nearly as important (Ref. 56). Thus, as suspected and now rigorously determined, the phosphate group is by far the most essential structural requirement for binding. One exception is binding of the SH2 domain of SAP, which appears to be much less dependent on phosphorylation (see below).

The region that binds phosphotyrosine forms a deep positively charged pocket – the so-called 'phosphotyrosine (pY or pTyr or 0-pTyr)-binding pocket' (Ref. 53). A vast array of interactions is observed between the pocket and the phosphotyrosine. They include: (1) a salt bridge between the phosphate and an arginine residue,

Figure 2. Structural and thermodynamic characterisation of the Src homology 2 (SH2) domain of Src kinase. *(Legend; see next page for figure.)* (a) Structure of the SH2 domain bound to its physiological tyrosine-phosphorylated target on the platelet-derived growth factor (PDGF) receptor (motif pYIpYV). The SH2 domain is in stereoribbon representation with α-helices in blue and β-strands in red. The peptide ligand is shown in stick representation with carbon, oxygen, phosphorus and nitrogen atoms coloured in grey, red, pink and blue, respectively. Notations of secondary structures are according to Refs 60 and 61. (b) Energetic contribution of each of the residues in the pY-binding pocket. Each residue indicated in the diagram has been mutated to a single-site Ala residue and the difference in binding free energy of the resulting mutants compared with wild-type ($\Delta\Delta G^{o}$) is shown by ranges colour coded as indicated in the scale to the left. Binding was assessed against the pYEEI motif. As can be seen, ArgβB5 is the single most important residue in the phosphotyrosine-binding pocket. Image reproduced from Ref. 55, with permission from Elsevier (Copyright © 1999, Elsevier Science). (c) Contribution of phosphate and charges to the binding free energy. The pYEEI motif peptide is in ball-and-stick representation with sticks in white and balls in semitransparent white. On the left, the red colouring of the oxygen atoms illustrates the presence of a charge on these atoms; on the right, the phosphate group atoms are in red. The most important contributor to binding free energy in the ligand is the phosphate, which contributes 5.6 kcal/mol out of the 9.2 kcal/mol binding free energy of the entire pYEEI ligand (Ref. 55). Out of the 5.6 kcal/mol contributed by the phosphate, nearly a half is contributed by a single charge (Ref. 55).

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press



Structural and thermodynamic characterisation of the Src homology 2 (SH2) domain of Src kinase

Expert Reviews in Molecular Medicine ©2004 Cambridge University Press (parts a and c)

Figure 2. Structural and thermodynamic characterisation of the Src homology 2 (SH2) domain of Src kinase. *(See previous page for legend.)*

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

ArgβB5; (2) an amino–aromatic interaction between the guanidinium group of another arginine, ArgαA2, and the aromatic ring of the phosphotyrosine; and (3) numerous hydrogen bonds contributed by residues in the BC loop between the βB and βC strands (see notation for secondary structures in Fig. 2a). Remarkably, of the myriad of interactions that the SH2 domain makes with the phosphate, only one contributes significant binding free energy: that of ArgβB5 with the phosphate (Fig. 2b, c) (Ref. 55). Thus, the binding interface in this region of the structure is a classical hot-spot interface where only one interaction appears to be critical (Ref. 57).

Peptide-binding specificity of single SH2 domains

The first evidence that SH2-domain-containing proteins are recruited specifically to certain tyrosine-phosphorylated sites on activated receptors emerged in early work on such proteins (reviewed in Ref. 54). Subsequent studies defined the residues C-terminal to the phosphotyrosine as being specifically involved in providing discrimination between phosphorylation sites (Refs 58, 59). These studies defined binding motifs specific to classes of SH2 domains. For example, the SH2 domains of Src-family members have a binding preference for the motif pYEEI (i.e. glutamic acid residues at the +1 and +2 position C-terminal to the phosphotyrosine, followed by isoleucine at the +3 position). The N-terminal SH2 domain of the p85 subunit of PI3K has a distinct binding motif, pYXXM (where X can be any amino acid); thus, the +3 position defines the selective recruitment of these SH2 domains. The SH2 domain of Grb2 distinguishes itself by requiring an asparagine residue at the +2 position, whereas the +1 and +3 positions appear to play minor roles (Ref. 59).

Role of residues C-terminal to pTyr

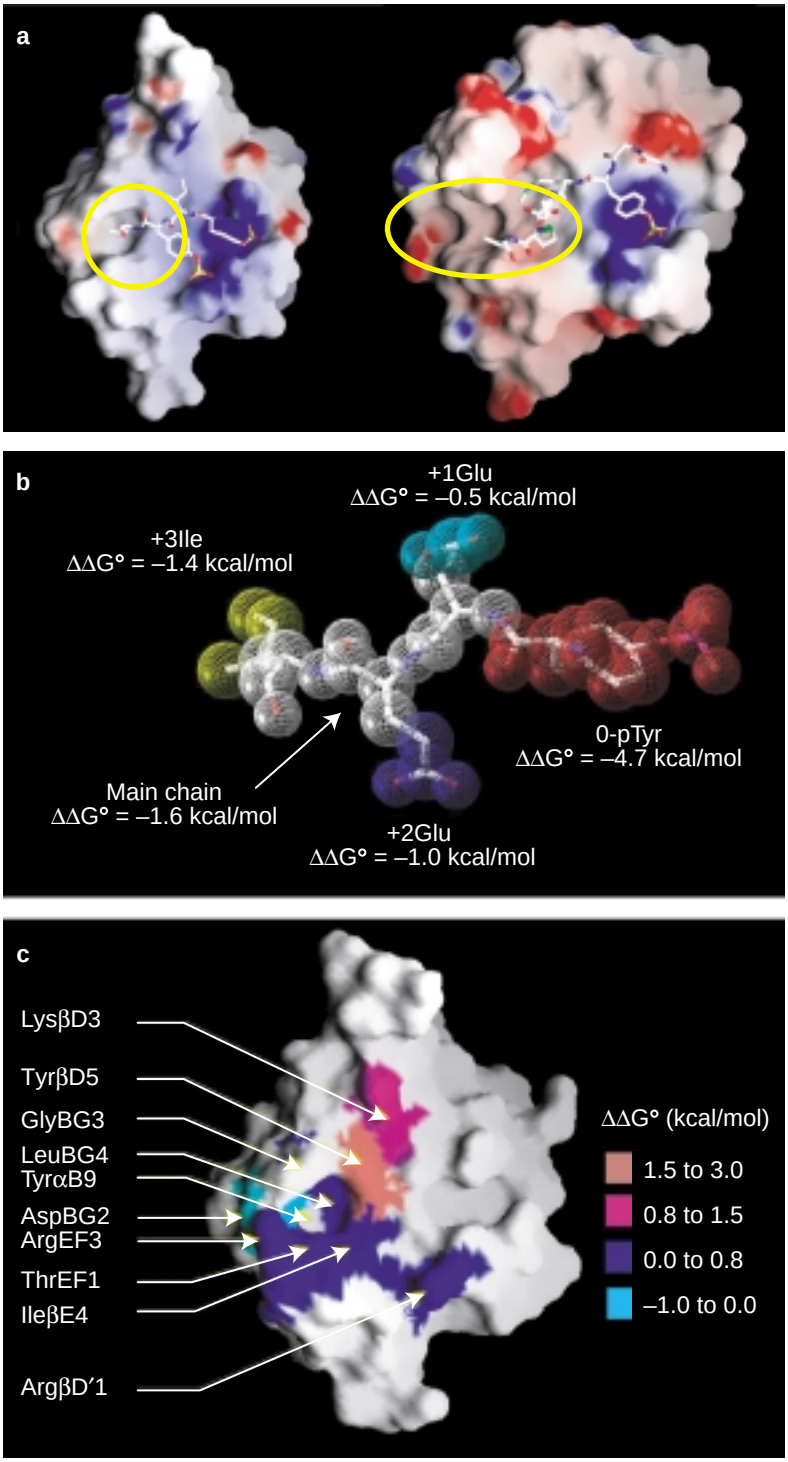
The structural characterisation of selective peptide binding was first approached by the crystallisation of SH2 domains of Src-family members with the pYEEI motif (Refs 60, 61). A central feature of the contact interface for the +1Glu, +2Glu and +3Ile residues is a deep hydrophobic pocket formed by residues of the central β-sheet, the C-terminal helix αB, and the EF and BG loops (Fig. 3a). The +3Ile of the pYEEI motif fits snugly into this pocket. The N- and C-terminal SH2 domains of the p85 subunit of the PI3K are also characterised by a well-defined +3-binding pocket where the +3Met of the pYXXM cognate motif inserts (Refs 62, 63). However, such a feature is not universal. The structure of the C-terminal SH2 domain of phospholipase Cγ (C-PLCγ) in a complex with a tyrosine-phosphorylated peptide shows a peptide-binding interface that is extended to the residue +5 positions C-terminal to the phosphotyrosine (Ref. 64). A similar extended binding interface is seen in the N-terminal SH2 domain of the SHP-2 phosphatase (Fig. 3a) (Ref. 65). It might have been expected that the interactions between residues throughout this extended interface would be critical for high-affinity binding. However, binding experiments using a series of truncated peptides have indicated that only the residue immediately C-terminal to the phosphotyrosine is required to maintain the majority of binding energy of the C-PLCγ SH2-domain binding interaction (Ref. 66).

The fact that many interactions observed in the crystal or nuclear magnetic resonance (NMR)

Figure 3. Peptide-binding specificity of Src homology 2 (SH2) domains. *(Legend; see next page for figure.)* (a, left) Surface diagram of the Src SH2 domain generated using the programme GRASP (Ref. 116). The surface is colour-coded according to electrostatic potential, with blue and red indicating positive and negative potentials, respectively. The peptide pYIpYV ligand is shown in ball and stick representation. The +3-binding pocket is identified by the yellow circle. (a, right) Surface diagram of the N-terminal SH2 domain of the SHP-2 phosphatase. Representation of the SH2 domain and its ligand is as in the left panel. Here, specificity-determining residues form an open groove located by the yellow oval. (b) Respective contribution of the various constituents of the pYEEI motif to the binding free energy of the pYEEI peptide. Side chains for each of the four residues of the motif are colour-coded differently and labelled accordingly. The $\Delta\Delta G^{o}$ between mutant (to Ala) and wild-type peptides are indicated under each label. The contribution of pY was assessed using phosphotyrosine alone. (c) Energetic contribution of each of the residues in the specificity-determining region. Each residue indicated in the diagram has been mutated to single-site Ala residue and the difference in binding free energy of the resulting mutants compared with wild type ($\Delta\Delta G^{o}$) is indicated by ranges colour-coded as indicated in the scale to the right. TyrβD5 and LysβD3 are the main contributors to the binding free energy. The origin of the effect of the LysβD3Ala mutation has been studied in detail elsewhere (Ref. 68).

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press



Peptide-binding specificity of Src homology 2 (SH2) domains

Expert Reviews in Molecular Medicine ©2004 Cambridge University Press

Figure 3. Peptide-binding specificity of Src homology 2 (SH2) domains. *(See previous page for legend.)*

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

structures appear to be of little importance is emphasised by a study aimed at assessing the importance of the +1, +2 and +3 positions of the pYEEI motif (Ref. 56). Conservative substitutions in this motif induce only very minor (threefold or less) decreases in affinity compared with the wild-type pYEEI peptide. The effect of alanine substitutions is generally small; the pYAEI, pYEAI and pYEEA peptides bound only twofold, sixfold and tenfold, respectively, weaker than the pYEEI peptide (Fig. 3b). A mutational investigation of the Src SH2 domain itself has probed the importance of the residues in the SH2 domain responsible for coordinating the EEI motif (the so-called specificity-determining residues) and determined that the majority of these residues make only small energetic contributions to binding (Fig. 3c) (Ref. 67). In this region, only mutation of TyrβD5, the residue that forms a platform for the peptide backbone and contributes part of the hydrophobic +3-binding pocket as well as interaction with the C_β of the +1Glu, induced a greater than tenfold loss in affinity upon mutation. Also, mutation of LysβD3, the residue that coordinates the +1Glu of the peptide, caused a sevenfold reduction in affinity. Interestingly, subsequent studies showed that the effect of the LysβD3 mutation to Ala is actually caused by the indirect effect of two aspartate residues that are not part of the interface (Ref. 68). Thus, LysβD3 appears to have nothing to do with peptide binding but rather acts to neutralise the negative charges emanating from other regions of the structure.

Thus, based on studies of the pYEEI motif binding by the Src SH2 domain, single SH2 domains appear to be unable to discriminate radically between tyrosine-phosphorylated ligands. However, the pYEEI motif is not a physiological substrate for the Src SH2 domain. Instead, one established binding site for Src recruitment is that located on the PDGF receptor (Refs 21, 69, 70, 71). The site has been mapped to two tyrosines, Tyr579 and Tyr581, in the juxtamembrane region of PDGF receptor β, and to Tyr572 and Tyr574 of the α receptor isoform (Refs 72, 73). Although phosphorylation of the second tyrosine is not essential for binding of the Src SH2 domain, it has been shown that tyrosine phosphorylation at the +2 position considerably enhances the free energy window for specific interaction (Ref. 74). In fact, the predominant contributors to binding free energy are no longer the 0-pTyr and the +3 position but the 0-pTyr and the +2pTyr. Thus, in the physiologically relevant interaction, the two residues anchoring the ligand to the peptide-binding interface are the 0-pTyr and the +2 position (Ref. 74). How +2pTyr recognition occurs remains a puzzle: the crystal structure of the Src SH2 domain bound to its binding site on the PDGF receptor and further mutation studies showed that: (1) an arginine nearby ideally positioned to form a salt bridge with the phosphate group plays no role; and (2) most of the interactions between +2pTyr and the SH2 domain are mediated by water molecules (Refs 74, 75, 76).

The Grb2 SH2 domain has a strong requirement for a residue (Asn) at the position +2 C-terminal to the 0-pTyr (Ref. 59). A thermodynamic and mutational analysis of Grb2 SH2 domain binding has underscored the importance of this +2Asn for high-affinity binding to the tyrosine-phosphorylated peptide (Ref. 77). The +2Asn requirement is caused by a Trp residue at position EF1 of the SH2 domain of Grb2 that not only fills a potential +3-binding pocket but also redirects the peptide ligand at the +2 position (Fig. 4b) (Ref. 78). Mutation of the corresponding residue in the Src SH2 domain to Trp dramatically changes the binding properties of this SH2 domain and makes it remarkably similar to the Grb2 SH2 domain (Ref. 79).

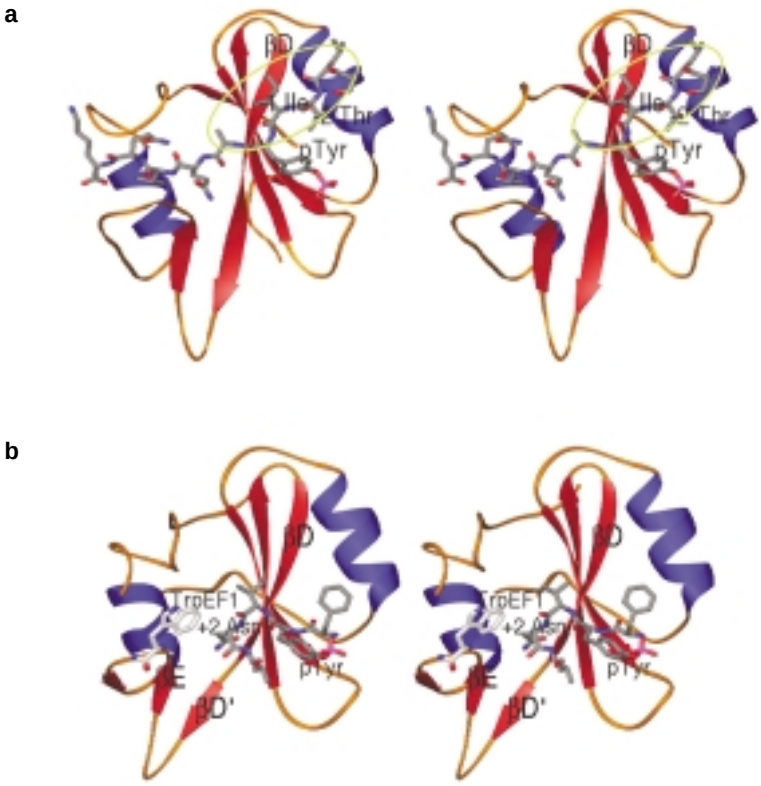
Role of residues N-terminal to pTyr

For the most part, the specificity of SH2 domain binding is determined by the residues of the target C-terminal to the 0-pTyr. However, for some SH2 domains, the residues N-terminal to the pTyr can be important. For example, it has been determined that the N-terminal SH2 domain of the SHP-2 phosphatase has a requirement for a hydrophobic residue (Val, Ile or Leu) at the position –2 (2d position N-terminal to 0-pTyr) (Refs 80, 81). This unusual requirement has been traced to the presence of a Gly at the αA2 position of the SH2 domain, a position that an Arg occupies in 80% of known SH2 domains (Ref. 82).

Another example of –2 position requirement is that of the SH2 domain of SAP; however, in this case, such a requirement appears to be the basis for a phosphorylation-independent interaction. The SAP SH2 domain is unusual in that it can bind targets in a phosphate-independent manner (Refs 17, 83). The structures of SAP in its unliganded form, as well as bound to both

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press



Structure of the SAP and Grb2 Src homology 2 (SH2) domains

Expert Reviews in Molecular Medicine ©2004 Cambridge University Press

Figure 4. Structure of the SAP and Grb2 Src homology 2 (SH2) domains. (a) Structure of the SH2 domain of SAP [SLAM (signalling lymphocyte activation molecule)-associated protein] bound to its cognate SLAM peptide. The SH2 domain is in ribbon representation with α-helices in blue and β-strands in red. The peptide ligand (motif TIpYAQVQK) is shown in stick representation with carbon, oxygen, phosphorus and nitrogen atoms colour-coded in grey, red, pink and blue, respectively. The yellow circle draws attention to the −1 and −2 interactions that appear to be responsible for the ability of the SAP SH2 domain to bind the unphosphorylated SLAM motif. (b) Structure of the SH2 domain of Grb2 (growth-receptor-binding protein) bound to its cognate pYxNx motif. The SH2 domain and peptide ligand (motif pYxNx) are shown as in (a). TrpEF1 confers the +2 binding specificity and is indicated.

tyrosine-phosphorylated and -unphosphorylated peptides, have shown that the residues in the peptide N-terminal to 0-pTyr make specific contacts with SAP (Fig. 4a) (Ref. 84). These interactions may explain the requirement of the SAP SH2 domain for residues N-terminal to the pTyr.

Implications

The findings described above indicate that interactions between the 0-pTyr in the target and its binding pocket in the SH2 domain are those most crucial for the molecular recognition of SH2 domains; the interactions between other residues of the target and the specificity-determining residues of the SH2 domain appear to be secondary in importance. Furthermore, the level of specificity exhibited by SH2 domains, particularly those of the Src family, is modest. These results have profound implications for the mechanism by which SH2 domains specifically bind their targets within cells. In particular, they suggest that initial models of SH2 domain recognition, where single SH2 domains are able to recognise selectively their particular binding sites as a result of only a distinct set of interactions

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

between the SH2 domain and the target, might be overly simplistic.

If the interactions involving the specificity-determining residues are weak, how can SH2 domains be targeted to specific phosphotyrosine-containing sites within activated receptors? For single-SH2-domain-containing proteins, specific recruitment might be facilitated by other domains. For example, N-myristoylation of the Src kinase – and hence its association with the cell membrane – might facilitate the interaction of the Src SH2 domain with the most membrane-proximal phosphotyrosine of the PDGF receptor β. Another possibility stems from the fact that many SH2-domain-containing proteins do not contain just a single SH2 domain, but rather SH2 domains located in tandem (e.g. ZAP-70, Syk, PI3K and PLCγ). For these proteins, the concerted binding of multiple domains probably enhances overall specificity. This would be achieved in tandem SH2-domain binding for two reasons. First, the binding of two SH2 domains could be positively coupled, which would result in an increase in binding specificity. Second, improper targeting to tyrosine-phosphorylated sites might be reduced by the topological constraints imposed by the strict spacing between phosphotyrosines. Hence, although SH2 domains appear to have evolved only low levels of specificity, specific targeting of SH2-domain-containing proteins to signalling complexes could be achieved through cooperative interactions between these domains and other partners in the signalling complex.

Peptide-binding specificity of tandem SH2 domains

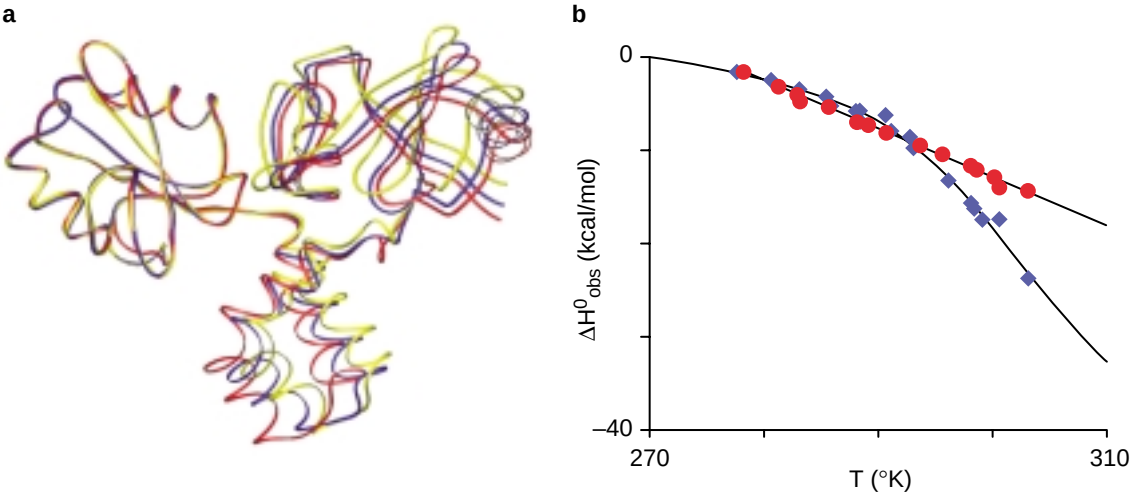
Syk-family kinases contain two SH2 domains positioned in tandem (Ref. 29). Syk-family kinases are recruited to cell-surface receptors through the interaction of their tandem SH2 domains with tyrosine-phosphorylated sequence motifs termed immunoreceptor tyrosine-based activation motifs (ITAMs) (Ref. 85). ITAMs typically have the consensus sequence YXX(L/I)-$X_{6/8}$-YXX(L/I) [i.e. two repeats of the sequence tyrosine, followed by two amino acids, followed by a hydrophobic residue (L or I) – with the two repeats separated by 6–8 amino acids] (Ref. 86). Remarkably, the tandem SH2 domain of Syk appears to be able to recognise a variety of doubly phosphorylated ITAMs (dpITAMS) that vary considerably not only in sequence but also in the length of the spacer region between the two phosphotyrosines (Refs 41, 87, 88). For example, the γ chain of the FcεRI receptor, an Fc receptor for IgE, contains an ITAM with a spacer region of 10 residues, whereas the spacer region of the ITAM on the single chain Fc receptor class IIA, an Fc receptor to IgG, is 15 residues in length (Ref. 89). Their sequences are also considerably different. Yet, doubly phosphorylated peptides derived from these dpITAMs bind equally well and with high affinity (2–4 nM) to the tandem SH2 domain of the Syk kinase (Ref. 88).

The mechanism by which the tandem SH2 domain of Syk can accommodate such structural variability in the ITAM was hinted at when the crystal structure of a complex of the Syk tandem SH2 domain bound to a dpITAM peptide derived from the CD3-ε chain of the T-cell receptor (K_d = 20 nM) was determined (Fig. 5a) (Ref. 90). The crystals contained six complexes in the asymmetric unit. Structural alignment of the six complexes revealed substantial flexibility in the relative orientation of the two SH2 domains. This feature, coupled with the fact that the interface between the SH2 domains is relatively small, suggested that, in the unbound state, there might even be larger fluctuations in the relative orientations of the two SH2 domains: the Syk tandem SH2 domain might fluctuate between an 'open' state where the two SH2 domains are far apart from each other and a 'closed' state where they are closer to one another. This hypothesis was supported by the results of a multifaceted biophysical study of dpITAM binding to the Syk tandem SH2 domain in solution (Ref. 91). In this study, an unusual nonlinear temperature dependence of the binding enthalpy [i.e a temperature-dependent heat capacity change (ΔC_p^o)] was observed that was interpreted as the thermodynamic signature of a pre-existing conformational equilibrium (between a closed and an open form) in the unbound state (Fig. 5b). These results provided a model for the ability of the Syk tandem SH2 domain to recognise dpITAMs with spacer regions of variable length: the two SH2 domains sample a continuum of relative orientations between an open and closed state, thus allowing the tandem SH2 domain to adapt and adjust to the various lengths of the interphosphotyrosine region. Although this model was consistent with the complexity of the binding data, direct confirmation was lacking.

This model can be tested by restricting the conformational ensemble accessible to the tandem

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press



Syk tandem Src homology 2 (SH2) domain structure and thermodynamics of binding

Expert Reviews in Molecular Medicine ©2004 Cambridge University Press (part a)

Figure 5. Syk tandem Src homology 2 (SH2) domain structure and thermodynamics of binding. (a) Structural flexibility in the relative orientation of the two SH2 domains in the tandem SH2 domain of Syk (spleen tyrosine kinase). The extreme orientations of the SH2 domains in the tandem SH2 domain bound to the CD3ε doubly phosphorylated immunoreceptor tyrosine-based activation motif (dpITAM) are shown in yellow and red. One intermediate is shown in blue. The orientations correspond to rigid body motion around the linker region between the two SH2 domains. In the unbound state, motions of even larger amplitude are expected. (b) Temperature dependence of the binding enthalpy of the Syk tandem SH2 domain-CD3ε dpITAM interaction. The heat of binding is monitored as a function of temperature. The curvature obtained with the wild-type protein (blue lozenges) is the thermodynamic signature of a conformational equilibrium, which is interpreted as taking place between a closed form where the SH2 domains are close to one another and an open form where the SH2 domains are apart. The additional heat observed at higher temperature is the result of not only binding but also of the conformational transition from open to closed (see Ref. 91 for details). When the SH2 domains are locked into a closed conformation by a disulphide bond, then a linear dependence of the enthalpy on temperature is observed (red circles) (Ref. 92). Panel (b) reproduced, with permission, from Ref. 92 (Copyright © 2003, National Academy of Sciences, U.S.A.).

SH2 domain in the unbound state. This was achieved by introducing a disulphide bridge at the interface between the two SH2 domains (Ref. 92). Remarkably, this double cysteine (2Cys) mutant displays all the binding properties that are expected from a Syk tandem SH2 domain locked into a closed conformation (i.e. the two SH2 domains locked close to one another and unable to open up): (1) the 2Cys mutant shows a temperature-independent heat capacity change (ΔC_p^o), which reflects a single species population as opposed to the previously observed temperature-dependent ΔC_p^o reflecting a multiconformer equilibrium (Fig. 5b); and (2) the affinity of this 2Cys mutant for a dpITAM sequence with a short spacer region is less affected than that for a dpITAM with a longer spacer region. Structural flexibility appears also to play a role in ZAP-70 tandem SH2 domain binding (Refs 93, 94, 95, 96).

It is at present not clear whether tandem SH2 domains demonstrate higher levels of sequence specificity. Grucza and colleagues have demonstrated that Syk tandem SH2 domain binding to the noncognate CD3-ε dpITAM peptide is only 20-fold weaker than binding to the biologically relevant (and similarly spaced) dpITAM derived from the γ chain of the FcεRI receptor (Ref. 88). Also, mutations at the +1, +2 or +3 positions C-terminal to both the N- and C-terminal phosphotyrosines do not dramatically affect binding to the Syk tandem SH2 domain (G. Waksman and R.A. Grucza, unpublished). Similarly, modest differences in affinity were

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

observed when binding of the Syk and ZAP-70 tandem SH2 domains to various dpITAM-based peptides was tested (Ref. 97). However, when doubly phosphorylated and similarly spaced peptides derived from the PDGF receptor were tested, binding was found to be three to four orders of magnitude weaker (Ref. 97). Therefore, it would appear from this example that SH2 domains in tandem might exhibit higher levels of sequence specificity than single SH2 domains.

Depending on the degree of receptor activation, ITAM sequences within the cell can be unphosphorylated, singly phosphorylated (mpITAM), or doubly phosphorylated. Hence, an additional issue regarding the specificity of tandem SH2 domain binding is the preferential binding of doubly phosphorylated, as opposed to singly or unphosphorylated, ITAM sequences. It has been experimentally observed that the Syk tandem SH2 domain displays dramatic differences in affinity between mpITAMs and dpITAMs (Ref. 88). For instance, the Syk tandem SH2 domain binds to the FcεRI ITAM with an affinity of about 2 nM, whereas affinities are about 1 mM and 10 mM for the corresponding ITAM with the N-terminal or C-terminal phosphate removed, respectively; loss of one phosphate of the ITAM causes about a 1000-fold loss in affinity (Ref. 88). This difference is similar to that observed for the binding of the Src SH2 domain to a phosphorylated versus dephosphorylated peptide (Ref. 55). Hence, tandem SH2 domains are highly specific for doubly phosphorylated sequences.

SH2 domains: clinical applications

As discussed above, the central role of SH2 domains in many tyrosine kinase signalling pathways makes them at least potentially attractive targets of pharmaceuticals (Refs 13, 14), and hence there have been significant efforts aimed at discovering SH2-domain-binding inhibitors. This section briefly discusses Src and Grb2 SH2-domain-binding inhibitors; further discussion of this field can be found in recent reviews (Refs 28, 98, 99, 100, 101, 102).

Src SH2-domain-binding inhibitors

The Src SH2 domain has a cysteine residue (CysβC3) located within its phosphotyrosine-binding cavity that is unique to Src; other SH2 domains have a serine, threonine, valine or alanine at this position. Cysteine residues such as CysβC3 are potentially good targets for pharmaceuticals because of their nucleophilic character: these residues can in certain cases be induced to form covalent bonds with aldehyde groups on pharmaceutical targets, as has been shown for cysteine proteases (Ref. 103). In particular, CysβC3 might be particularly reactive owing to the fact that the positively charged environment of the phosphotyrosine-binding cavity lowers its pKa (Ref. 104). It has indeed been shown using X-ray crystallography and titration microcalorimetry that CysβC3 can form a covalent bond with aldehyde groups on pharmaceutical-like compounds, implying that it might be possible to target the Src SH2 domain selectively with specific compounds in vivo (Refs 105, 106). This possibility has been further advanced by studies that have examined the effect of a CysβC3-targeting compound in living cells. As indicated above, mice lacking the *src* gene demonstrate osteopetrosis (thickened bones), indicating that Src plays a role in bone formation and suggesting that Src might be a useful target for treatment of osteoporosis. A compound that targets CysβC3 of the Src SH2 domain has been shown to bind preferentially to the Src SH2 domain in vitro (Ref. 107). This compound inhibits interactions between the Src SH2 domain and phosphopeptide within cells and also diminishes the resorptive activity of rabbit osteoclasts (Ref. 107).

More recently, second-generation compounds have been designed that appear to have been inspired by the crystal structure of a citrate-bound Src SH2 domain complex (Ref. 108). In this structure, citrate appears to make hydrogen bonding interactions with residues that had not previously been exploited for design of phosphotyrosine mimics (Ref. 108). Incorporation of diphosphonomethyl-phenylalanine into the design of inhibitory peptides targeting the Src SH2 domain led to the discovery of another potent active molecule exhibiting bone-targeting properties and antiresorptive activity in a cell-based assay utilising osteoclasts and bone (Ref. 109).

Grb2 SH2-domain-binding inhibitors

The SH2 domain of Grb2 is perhaps the most selective SH2 domain in terms of target recognition: there is a strict requirement for Asn two residues C-terminal to the phosphotyrosine (Refs 59, 77). Furthermore, only in the Grb2 SH2 domain structure does the peptide bind in a β-turn conformation to accommodate interactions

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

between the +2Asn and the protein (Ref. 78). These findings might partially explain why non-tyrosine-phosphorylated peptidomimetics have been successfully designed and reported for the Grb2 SH2 domain, but not for any other SH2 domain (Ref. 110). These nonphosphorylated peptide inhibitors are very desirable given that the negatively charged phosphate group of phosphopeptides is a detriment to the cell permeability of pharmaceutical compounds. For instance, a cyclic, 11-residue nonphosphorylated peptide that contains the crucial Asn has been shown to bind specifically and with micromolar affinity to the Grb2 SH2 domain (Ref. 110). Other, noncyclic inhibitors of the Grb2 SH2 domain have also been found. Studies with these compounds have demonstrated how Grb2 couples activation of the Ras signalling pathway to cellular transformation (Ref. 111). Furthermore, Grb2 inhibitors have also demonstrated that this protein plays a role in the motility of tumour cells (Ref. 112). These results have highlighted how inhibition of the Grb2 SH2 domain could be an effective anticancer treatment.

Conclusions

Studies of SH2 domains have revealed their mode of action. Clearly, the most important binding property of SH2 domains is their selectivity for the phosphorylation state of their targets. Other recognition processes appear to play only minor roles. Receptor activation induces phosphorylation of numerous tyrosine residues and induces the recruitment of several SH2-domain-containing proteins; therefore, one would have expected some degree of specificity to be essential to prevent signal transduction pathways to cross. However, based on binding data, a back-of-the-envelope calculation of the degree of occupancy of any particular tyrosine-phosphorylated site by the Src SH2 domain shows that all sites would be at least partially occupied by this SH2 domain regardless of the sequence surrounding the site. Thus, a certain level of crosstalk between signal transduction pathways appears to be happening. Such crosstalks were in fact revealed in a study that used gene-array technology to monitor genes induced by phosphorylation of any particular tyrosine of the PDGF receptor upon activation by PDGFβ (Refs 113, 114). Using global expression monitoring, the relationship was investigated between signalling pathways activated by receptor tyrosine kinases and the transcriptional induction of immediate early genes (IEGs); 66 fibroblast IEGs induced by PDGFβ receptor signalling were identified. Mutant receptors lacking binding sites for activation of the PLCγ, PI3K, SHP-2 and Ras-GAP pathways still retain partial ability to induce 64 of these IEGs. Removal of the Grb2-binding site further broadly reduced induction. These results suggest that the diverse pathways exert broadly overlapping effects on IEG induction.

The fact that SH2 domains are involved in multiple cellular processes, some of which might be altered in diseases, has made them obvious targets for pharmaceuticals. Unfortunately, the investment that the pharmaceutical industry has made in the past 10–15 years towards finding suitable SH2-domain-binding inhibitors has not met with the anticipated success. Part of the problem is that the effort was not guided by a deep understanding of the relative importance of the various constituents of the phosphorylated sites that SH2 domains target. Although it had been realised early in the SH2 domain research that phosphorylation was an important determinant of binding affinity, the extent of the predominance of the phosphotyrosine in binding versus any other residues in the SH2 domain recognition sites was revealed only recently. It then became apparent that: (1) specificity in the targeting of the drug would be difficult to achieve as a phosphotyrosine derivative would need to be present, thus running the risk of targeting the drug to SH2-domain-containing proteins that play no role in the diseased state targeted for therapy; and (2) the large electrostatic field emanating from such an essential drug component would present an obstacle for the entire molecule to penetrate the hydrophobic environment of the cell membrane, and thus delivery to the cell might be prevented (Ref. 115). Whether a drug targeting an SH2 domain will appear on the market is still uncertain. However, the search for an efficacious and viable SH2-domain-binding inhibitor is actively continuing. Added specificity might be obtained by targeting sites that combine the recruitment of more than one SH2 domain, such as the tandem SH2 domain of the ZAP-70 and Syk kinases. A binding inhibitor targeting at the same time the two phosphotyrosine-binding pockets of the tandem SH2 domain with no other sequence specificity requirement would probably bind predominantly dpITAM recognition domains, thereby possibly

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

providing efficacious treatments of some immune diseases. In this regard, the details emerging on the binding properties of tandem SH2 domains will greatly facilitate the development of a successful strategy for designing binding inhibitors specific for the targeted immune-receptor-dependent pathways.

Acknowledgements and funding

We thank our anonymous peer reviewers for their comments. This work was funded by NIH grant GM60231 (G.W.).

References

1 Schlessinger, J. (2000) Cell signaling by receptor tyrosine kinases. Cell 103, 211-225, PubMed: 11057895
2 Bostrom, H. et al. (1996) PDGF-A signaling is a critical event in lung alveolar myofibroblast development and alveogenesis. Cell 85, 863-873, PubMed: 8681381
3 Leveen, P. et al. (1994) Mice deficient for PDGF B show renal, cardiovascular, and hematological abnormalities. Genes Dev 8, 1875-1887, PubMed: 7958863
4 Soriano, P. (1994) Abnormal kidney development and hematological disorders in PDGF beta-receptor mutant mice. Genes Dev 8, 1888-1896, PubMed: 7958864
5 Soriano, P. (1997) The PDGF alpha receptor is required for neural crest cell development and for normal patterning of the somites. Development 124, 2691-2700, PubMed: 9226440
6 Heldin, C.H. and Westermark, B. (1999) Mechanism of action and in vivo role of platelet-derived growth factor. Physiol Rev 79, 1283-1316, PubMed: 10508235
7 Claesson-Welsh, L. et al. (1989) cDNA cloning and expression of the human A-type platelet-derived growth factor (PDGF) receptor establishes structural similarity to the B-type PDGF receptor. Proc Natl Acad Sci U S A 86, 4917-4921, PubMed: 2544881
8 Matsui, T. et al. (1989) Isolation of a novel receptor cDNA establishes the existence of two PDGF receptor genes. Science 243, 800-804, PubMed: 2536956
9 Yarden, Y. et al. (1986) Structure of the receptor for platelet-derived growth factor helps define a family of closely related growth factor receptors. Nature 323, 226-232, PubMed: 3020426
10 Pawson, T. and Schlessinger, J. (1993) SH2 and SH3 domains. Current Biology 3, 434-442
11 Sadowski, I., Stone, J.C. and Pawson, T. (1986) A noncatalytic domain conserved among cytoplasmic protein-tyrosine kinases modifies the kinase function and transforming activity of Fujinami sarcoma virus P130gag-fps. Mol Cell Biol 6, 4396-4408, PubMed: 3025655
12 Pawson, T. and Gish, G.D. (1992) SH2 and SH3 domains: from structure to function. Cell 71, 359-362, PubMed: 1423600
13 Brugge, J.S. (1993) New intracellular targets for therapeutic drug design. Science 260, 918-919, PubMed: 8388123
14 Sawyer, T.K. (1998) Src homology-2 domains: structure, mechanisms, and drug discovery. Biopolymers 47, 243-261, PubMed: 9817027
15 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
16 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
17 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
18 Saffran, D.C. et al. (1994) Brief report: a point mutation in the SH2 domain of Bruton's tyrosine kinase in atypical X-linked agammaglobulinemia. N Engl J Med 330, 1488-1491, PubMed: 8164701
19 Tartaglia, M. et al. (2001) Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 29, 465-468, PubMed: 11704759
20 Botfield, M.C. and Green, J. (1995) SH2 and SH3 domains: choreographers of multiple signaling pathways. Ann Rep Med Chem 30, 227-237
21 Thomas, S.M. and Brugge, J.S. (1997) Cellular functions regulated by Src family kinases. Annu Rev Cell Dev Biol 13, 513-609, PubMed: 9442882
22 Soriano, P. et al. (1991) Targeted disruption of the c-src proto-oncogene leads to osteopetrosis in mice. Cell 64, 693-702, PubMed: 1997203
23 Lowell, C.A. et al. (1996) Deficiency of the Hck and Src tyrosine kinases results in extreme levels of extramedullary hematopoiesis. Blood 87, 1780-1792, PubMed: 8634424
24 Boyce, B.F. et al. (1992) Requirement of pp60c-src expression for osteoclasts to form ruffled borders

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

and resorb bone in mice. J Clin Invest 90, 1622-1627, PubMed: 1383278
25 Lowe, C. et al. (1993) Osteopetrosis in Src-deficient mice is due to an autonomous defect of osteoclasts. Proc Natl Acad Sci U S A 90, 4485-4489, PubMed: 7685105
26 Marzia, M. et al. (2000) Decreased c-Src expression enhances osteoblast differentiation and bone formation. J Cell Biol 151, 311-320, PubMed: 11038178
27 Schwartzberg, P.L. et al. (1997) Rescue of osteoclast function by transgenic expression of kinase-deficient Src in src-/- mutant mice. Genes Dev 11, 2835-2844, PubMed: 9353253
28 Sawyer, T. et al. (2001) Src inhibitors: genomics to therapeutics. Expert Opin Investig Drugs 10, 1327-1344, PubMed: 11772255
29 Chan, A.C. and Shaw, A.S. (1996) Regulation of antigen receptor signal transduction by protein tyrosine kinases. Curr Opin Immunol 8, 394-401, PubMed: 8794001
30 Reth, M. and Wienands, J. (1997) Initiation and processing of signals from the B cell antigen receptor. Annu Rev Immunol 15, 453-479, PubMed: 9143696
31 Kurosaki, T. (1997) Molecular mechanisms in B cell antigen receptor signaling. Curr Opin Immunol 9, 309-318, PubMed: 9203415
32 Chan, A.C. et al. (1994) ZAP-70 deficiency in an autosomal recessive form of severe combined immunodeficiency. Science 264, 1599-1601, PubMed: 8202713
33 Cheng, A.M. et al. (1997) The Syk and ZAP-70 SH2-containing tyrosine kinases are implicated in pre-T cell receptor signaling. Proc Natl Acad Sci U S A 94, 9797-9801, PubMed: 9275205
34 Costello, P.S. et al. (1996) Critical role for the tyrosine kinase Syk in signalling through the high affinity IgE receptor of mast cells. Oncogene 13, 2595-2605, PubMed: 9000133
35 Crowley, M.T. et al. (1997) A critical role for Syk in signal transduction and phagocytosis mediated by Fcgamma receptors on macrophages. J Exp Med 186, 1027-1039, PubMed: 9314552
36 Zhang, J. et al. (1996) Transfection of Syk protein tyrosine kinase reconstitutes high affinity IgE receptor-mediated degranulation in a Syk-negative variant of rat basophilic leukemia RBL-2H3 cells. J Exp Med 184, 71-79, PubMed: 8691151
37 Cheng, A.M. et al. (1995) Syk tyrosine kinase required for mouse viability and B-cell development. Nature 378, 303-306, PubMed: 7477353
38 Poole, A. et al. (1997) The Fc receptor gamma-chain and the tyrosine kinase Syk are essential for activation of mouse platelets by collagen. Embo J 16, 2333-2341, PubMed: 9171347
39 Brumbaugh, K.M. et al. (1997) Functional role for Syk tyrosine kinase in natural killer cell-mediated natural cytotoxicity. J Exp Med 186, 1965-1974, PubMed: 9396765
40 Lanier, L.L. et al. (1998) Immunoreceptor DAP12 bearing a tyrosine-based activation motif is involved in activating NK cells. Nature 391, 703-707, PubMed: 9490415
41 Corey, S.J. et al. (1994) Granulocyte colony-stimulating factor receptor signaling involves the formation of a three-component complex with Lyn and Syk protein-tyrosine kinases. Proc Natl Acad Sci U S A 91, 4683-4687, PubMed: 8197119
42 Lin, T.H. et al. (1995) Integrin-mediated tyrosine phosphorylation and cytokine message induction in monocytic cells. A possible signaling role for the Syk tyrosine kinase. J Biol Chem 270, 16189-16197, PubMed: 7541794
43 Yanaga, F. et al. (1995) Syk interacts with tyrosine-phosphorylated proteins in human platelets activated by collagen and cross-linking of the Fc gamma-IIA receptor. Biochem J 311 (Pt 2), 471-478, PubMed: 7487883
44 Wan, Y., Kurosaki, T. and Huang, X.Y. (1996) Tyrosine kinases in activation of the MAP kinase cascade by G-protein-coupled receptors. Nature 380, 541-544, PubMed: 8606776
45 Higuchi, M. et al. (1997) Regulation of IL-2 signaling. Leukemia 11 Suppl 3, 416-417, PubMed: 9209410
46 Gao, J. et al. (1997) Regulation of the pp72syk protein tyrosine kinase by platelet integrin alpha IIb beta 3. Embo J 16, 6414-6425, PubMed: 9351824
47 Lowenstein, E.J. et al. (1992) The SH2 and SH3 domain-containing protein GRB2 links receptor tyrosine kinases to ras signaling. Cell 70, 431-442, PubMed: 1322798
48 Rozakis-Adcock, M. et al. (1992) Association of the Shc and Grb2/Sem5 SH2-containing proteins is implicated in activation of the Ras pathway by tyrosine kinases. Nature 360, 689-692, PubMed: 1465135
49 Olivier, J.P. et al. (1993) A Drosophila SH2-SH3 adaptor protein implicated in coupling the sevenless tyrosine kinase to an activator of Ras guanine nucleotide exchange, Sos. Cell 73, 179-

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

191, PubMed: 8462098
50 Egan, S.E. et al. (1993) Association of Sos Ras exchange protein with Grb2 is implicated in tyrosine kinase signal transduction and transformation. Nature 363, 45-51, PubMed: 8479536
51 Simon, M.A., Dodson, G.S. and Rubin, G.M. (1993) An SH3-SH2-SH3 protein is required for p21Ras1 activation and binds to sevenless and Sos proteins in vitro. Cell 73, 169-177, PubMed: 8462097
52 Kuriyan, J. and Cowburn, D. (1997) Modular peptide recognition domains in eukaryotic signaling. Annu Rev Biophys Biomol Struct 26, 259-288, PubMed: 9241420
53 Waksman, G. et al. (1992) Crystal structure of the phosphotyrosine recognition domain SH2 of v-src complexed with tyrosine-phosphorylated peptides. Nature 358, 646-653, PubMed: 1379696
54 Pawson, T. (1992) SH2 and SH3 domains. Curr Opin Struct Biol 2, 432-437
55 Bradshaw, J.M., Mitaxov, V. and Waksman, G. (1999) Investigation of phosphotyrosine recognition by the SH2 domain of the Src kinase. J Mol Biol 293, 971-985, PubMed: 10543978
56 Bradshaw, J.M. and Waksman, G. (1999) Calorimetric examination of high-affinity Src SH2 domain-tyrosyl phosphopeptide binding: dissection of the phosphopeptide sequence specificity and coupling energetics. Biochemistry 38, 5147-5154, PubMed: 10213620
57 Clackson, T. and Wells, J.A. (1995) A hot spot of binding energy in a hormone-receptor interface. Science 267, 383-386, PubMed: 7529940
58 Songyang, Z. et al. (1993) SH2 domains recognize specific phosphopeptide sequences. Cell 72, 767-778, PubMed: 7680959
59 Songyang, Z. et al. (1994) Specific motifs recognized by the SH2 domains of Csk, 3BP2, fps/fes, GRB-2, HCP, SHC, Syk, and Vav. Mol Cell Biol 14, 2777-2785, PubMed: 7511210
60 Waksman, G. et al. (1993) Binding of a high affinity phosphotyrosyl peptide to the Src SH2 domain: crystal structures of the complexed and peptide-free forms. Cell 72, 779-790, PubMed: 7680960
61 Eck, M.J., Shoelson, S.E. and Harrison, S.C. (1993) Recognition of a high-affinity phosphotyrosyl peptide by the Src homology-2 domain of p56lck. Nature 362, 87-91, PubMed: 7680435
62 Nolte, R.T. et al. (1996) Crystal structure of the PI 3-kinase p85 amino-terminal SH2 domain and its phosphopeptide complexes. Nat Struct Biol 3, 364-374, PubMed: 8599763
63 Breeze, A.L. et al. (1996) Structure of a specific peptide complex of the carboxy-terminal SH2 domain from the p85 alpha subunit of phosphatidylinositol 3-kinase. Embo J 15, 3579-3589, PubMed: 8670861
64 Pascal, S.M. et al. (1994) Nuclear magnetic resonance structure of an SH2 domain of phospholipase C-gamma 1 complexed with a high affinity binding peptide. Cell 77, 461-472, PubMed: 8181064
65 Lee, C.H. et al. (1994) Crystal structures of peptide complexes of the amino-terminal SH2 domain of the Syp tyrosine phosphatase. Structure 2, 423-438, PubMed: 7521735
66 Kay, L.E. et al. (1998) Correlation between binding and dynamics at SH2 domain interfaces. Nat Struct Biol 5, 156-163, PubMed: 9461082
67 Bradshaw, J.M., Mitaxov, V. and Waksman, G. (2000) Mutational investigation of the specificity determining region of the Src SH2 domain. J Mol Biol 299, 521-535, PubMed: 10860756
68 Lubman, O.Y. and Waksman, G. (2002) Dissection of the energetic coupling across the Src SH2 domain-tyrosyl phosphopeptide interface. J Mol Biol 316, 291-304, PubMed: 11851339
69 Erpel, T. and Courtneidge, S.A. (1995) Src family protein tyrosine kinases and cellular signal transduction pathways. Curr Opin Cell Biol 7, 176-182, PubMed: 7612268
70 Kypta, R.M. et al. (1990) Association between the PDGF receptor and members of the src family of tyrosine kinases. Cell 62, 481-492, PubMed: 1696179
71 Ralston, R. and Bishop, J.M. (1985) The product of the protooncogene c-src is modified during the cellular response to platelet-derived growth factor. Proc Natl Acad Sci U S A 82, 7845-7849, PubMed: 2415973
72 Alonso, G. et al. (1995) Sequence requirements for binding of Src family tyrosine kinases to activated growth factor receptors. J Biol Chem 270, 9840-9848, PubMed: 7730365
73 Mori, S. et al. (1993) Identification of two juxtamembrane autophosphorylation sites in the PDGF beta-receptor; involvement in the interaction with Src family tyrosine kinases. Embo J 12, 2257-2264, PubMed: 7685273
74 Lubman, O.Y. and Waksman, G. (2003) Structural and thermodynamic basis for the interaction of the Src SH2 domain with the activated form of the PDGF beta-receptor. J Mol Biol 328, 655-668,

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

PubMed: 12706723
75 Renzoni, D.A. et al. (1997) Exploring uncharted waters: water molecules in drug design strategies. In Structure-based Drug Design (Ladbury, J.E. and Connelly, P.R., eds), pp. 160-184, R.G. Landes Inc., Austin TX, USA
76 Ladbury, J.E. (1996) Just add water! The effect of water on the specificity of protein-ligand binding sites and its potential application to drug design. Chem Biol 3, 973-980, PubMed: 9000013
77 McNemar, C. et al. (1997) Thermodynamic and structural analysis of phosphotyrosine polypeptide binding to Grb2-SH2. Biochemistry 36, 10006-10014, PubMed: 9254595
78 Rahuel, J. et al. (1996) Structural basis for specificity of Grb2-SH2 revealed by a novel ligand binding mode. Nat Struct Biol 3, 586-589, PubMed: 8673601
79 Marengere, L.E. et al. (1994) SH2 domain specificity and activity modified by a single residue. Nature 369, 502-505, PubMed: 7515480
80 Huyer, G. et al. (1995) Direct determination of the sequence recognition requirements of the SH2 domains of SH-PTP2. Biochemistry 34, 1040-1049, PubMed: 7530043
81 Burshtyn, D.N. et al. (1997) A novel phosphotyrosine motif with a critical amino acid at position -2 for the SH2 domain-mediated activation of the tyrosine phosphatase SHP-1. J Biol Chem 272, 13066-13072, PubMed: 9148918
82 Huyer, G. and Ramachandran, C. (1998) The specificity of the N-terminal SH2 domain of SHP-2 is modified by a single point mutation. Biochemistry 37, 2741-2747, PubMed: 9485424
83 Li, S.C. et al. (1999) Novel mode of ligand binding by the SH2 domain of the human XLP disease gene product SAP/SH2D1A. Curr Biol 9, 1355-1362, PubMed: 10607564
84 Poy, F. et al. (1999) Crystal structures of the XLP protein SAP reveal a class of SH2 domains with extended, phosphotyrosine-independent sequence recognition. Mol Cell 4, 555-561, PubMed: 10549287
85 Reth, M. (1989) Antigen receptor tail clue. Nature 338, 383-384, PubMed: 2927501
86 Cambier, J.C. (1995) Antigen and Fc receptor signaling. The awesome power of the immunoreceptor tyrosine-based activation motif (ITAM). J Immunol 155, 3281-3285, PubMed: 7561018
87 Chacko, G.W. et al. (1996) Phosphoinositide 3-kinase and p72syk noncovalently associate with the low affinity Fc gamma receptor on human platelets through an immunoreceptor tyrosine-based activation motif. Reconstitution with synthetic phosphopeptides. J Biol Chem 271, 10775-10781, PubMed: 8631888
88 Grucza, R.A. et al. (2000) Role of electrostatic interactions in SH2 domain recognition: salt-dependence of tyrosyl-phosphorylated peptide binding to the tandem SH2 domain of the Syk kinase and the single SH2 domain of the Src kinase. Biochemistry 39, 10072-10081, PubMed: 10955995
89 Daeron, M. (1997) Fc receptor biology. Annu Rev Immunol 15, 203-234, PubMed: 9143687
90 Futterer, K. et al. (1998) Structural basis for Syk tyrosine kinase ubiquity in signal transduction pathways revealed by the crystal structure of its regulatory SH2 domains bound to a dually phosphorylated ITAM peptide. J Mol Biol 281, 523-537, PubMed: 9698567
91 Grucza, R.A. et al. (1999) Thermodynamic study of the binding of the tandem-SH2 domain of the Syk kinase to a dually phosphorylated ITAM peptide: evidence for two conformers. Biochemistry 38, 5024-5033, PubMed: 10213605
92 Kumaran, S., Grucza, R.A. and Waksman, G. (2003) The tandem Src homology 2 domain of the Syk kinase: a molecular device that adapts to interphosphotyrosine distances. Proc Natl Acad Sci U S A 100, 14828-14833, PubMed: 14657388
93 Hatada, M.H. et al. (1995) Molecular basis for interaction of the protein tyrosine kinase ZAP-70 with the T-cell receptor. Nature 377, 32-38, PubMed: 7659156
94 Labadia, M.E. et al. (1997) Interaction between the SH2 domains of ZAP-70 and the tyrosine-based activation motif 1 sequence of the zeta subunit of the T-cell receptor. Arch Biochem Biophys 342, 117-125, PubMed: 9185620
95 Grazioli, L. et al. (1998) Anti-peptide antibodies detect conformational changes of the inter-SH2 domain of ZAP-70 due to binding to the zeta chain and to intramolecular interactions. J Biol Chem 273, 8916-8921, PubMed: 9535874
96 O'Brien, R. et al. (2000) Alternative modes of binding of proteins with tandem SH2 domains. Protein Sci 9, 570-579, PubMed: 10752619
97 Ottinger, E.A., Botfield, M.C. and Shoelson, S.E. (1998) Tandem SH2 domains confer high specificity in tyrosine kinase signaling. J Biol Chem 273, 729-735, PubMed: 9422724
98 Lung, F.D. and Tsai, J.Y. (2003) Grb2 SH2 domain-binding peptide analogs as potential anticancer agents. Biopolymers 71, 132-140,

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

PubMed: 12767115
99 Burke, T.R., Jr. et al. (2001) Phosphoryltyrosyl mimetics in the design of peptide-based signal transduction inhibitors. Biopolymers 60, 32-44, PubMed: 11376431
100 Shakespeare, W.C. (2001) SH2 domain inhibition: a problem solved? Curr Opin Chem Biol 5, 409-415, PubMed: 11470604
101 Dunican, D.J. and Doherty, P. (2001) Designing cell-permeant phosphopeptides to modulate intracellular signaling pathways. Biopolymers 60, 45-60, PubMed: 11376432
102 Sawyer, T.K. et al. (2002) SRC homology-2 inhibitors: peptidomimetic and nonpeptide. Mini Rev Med Chem 2, 475-488, PubMed: 12370048
103 Rich, D.H. (1986) Proteinase Inhibitors, Elsevier, Amsterdam
104 Bradshaw, J.M. and Waksman, G. (1998) Calorimetric investigation of proton linkage by monitoring both the enthalpy and association constant of binding: application to the interaction of the Src SH2 domain with a high-affinity tyrosyl phosphopeptide. Biochemistry 37, 15400-15407, PubMed: 9799501
105 Charifson, P.S. et al. (1997) Peptide ligands of pp60(c-src) SH2 domains: a thermodynamic and structural study. Biochemistry 36, 6283-6293, PubMed: 9174343
106 Alligood, K.J. et al. (1998) The formation of a covalent complex between a dipeptide ligand and the src SH2 domain. Bioorg Med Chem Lett 8, 1189-1194, PubMed: 9871733
107 Violette, S.M. et al. (2000) A Src SH2 selective binding compound inhibits osteoclast-mediated resorption. Chem Biol 7, 225-235, PubMed: 10712930
108 Bohacek, R.S. et al. (2001) X-Ray structure of citrate bound to Src SH2 leads to a high-affinity, bone-targeted Src SH2 inhibitor. J Med Chem 44, 660-663, PubMed: 11262076
109 Shakespeare, W. et al. (2000) Structure-based design of an osteoclast-selective, nonpeptide src homology 2 inhibitor with in vivo antiresorptive activity. Proc Natl Acad Sci U S A 97, 9373-9378, PubMed: 10944210
110 Oligino, L. et al. (1997) Nonphosphorylated peptide ligands for the Grb2 Src homology 2 domain. J Biol Chem 272, 29046-29052, PubMed: 9360978
111 Gay, B. et al. (1999) Selective GRB2 SH2 inhibitors as anti-Ras therapy. Int J Cancer 83, 235-241, PubMed: 10471533
112 Gay, B. et al. (1999) Effect of potent and selective inhibitors of the Grb2 SH2 domain on cell motility. J Biol Chem 274, 23311-23315, PubMed: 10438507
113 Fambrough, D. et al. (1999) Diverse signaling pathways activated by growth factor receptors induce broadly overlapping, rather than independent, sets of genes. Cell 97, 727-741, PubMed: 10380925
114 Pawson, T. and Saxton, T.M. (1999) Signaling networks—do all roads lead to the same genes? Cell 97, 675-678, PubMed: 10380918
115 Bradshaw, J.M. and Waksman, G. (2002) Molecular recognition by SH2 domains. Adv Protein Chem 61, 161-210, PubMed: 12461824
116 Nicholls, A. and Honig, B. (1991) A rapid finite difference algorithm, utilizing successive over-relaxation to solve the Poisson-Boltzman equation. Journal of Computational Chemistry 12, 435-445
117 Pawson, T., Gish, G.D. and Nash, P. (2001) SH2 domains, interaction modules and cellular wiring. Trends Cell Biol 11, 504-511, PubMed: 11719057

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press

Further reading, resources and contacts

Reviews on SH2-domain-binding inhibitors:

Sawyer, T. et al. (2001) Src inhibitors: genomics to therapeutics. Expert Opin Investig Drugs 10, 1327-1344

Lung, F.D. and Tsai, J.Y. (2003) Grb2 SH2 domain-binding peptide analogs as potential anticancer agents. Biopolymers 71, 132-140, PubMed: 12767115

Burke, T.R., Jr. et al. (2001) Phosphoryltyrosyl mimetics in the design of peptide-based signal transduction inhibitors. Biopolymers 60, 32-44, PubMed: 11376431

Shakespeare, W.C. (2001) SH2 domain inhibition: a problem solved? Curr Opin Chem Biol 5, 409-415, PubMed: 11470604

Dunican, D.J. and Doherty, P. (2001) Designing cell-permeant phosphopeptides to modulate intracellular signaling pathways. Biopolymers 60, 45-60, PubMed: 11376432

Sawyer, T.K. et al. (2002) SRC homology-2 inhibitors: peptidomimetic and nonpeptide. Mini Rev Med Chem 2, 475-488, PubMed: 12370048

Features associated with this article

Figures

Figure 1. Examples of Src homology 2 (SH2)-domain-containing proteins and their modular primary structure.
Figure 2. Structural and thermodynamic characterisation of the Src homology 2 (SH2) domain of Src kinase.
Figure 3. Peptide-binding specificity of Src homology 2 (SH2) domains.
Figure 4. Structure of the SAP and Grb2 Src homology 2 (SH2) domains.
Figure 5. Syk tandem Src homology 2 (SH2) domain structure and thermodynamics of binding.

Table

Table 1. Diseases in which Src homology 2 (SH2) domains have potential as pharmaceutical targets.

Citation details for this article

Gabriel Waksman, Sangaralingam Kumaran and Olga Lubman (2004) SH2 domains: role, structure and implications for molecular medicine. Expert Rev. Mol. Med. Vol. 6, Issue 3, 30 January, DOI: 10.1017/S1462399404007331

Accession information: DOI: 10.1017/S1462399404007331; Vol. 6; Issue 3; 30 January 2004
©2004 Cambridge University Press

https://doi.org/10.1017/S1462399404007331 Published online by Cambridge University Press