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Structure of the Carboxyl-terminal Src Kinase, Csk*

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The carboxyl-terminal Src kinase (Csk) is an indispensable negative regulator for the Src family tyrosine kinases (SFKs) that play pivotal roles in various cell signalings. To understand the molecular basis of the Csk-mediated regulation of SFKs, we elucidated the crystal structure of full-length Csk. The Csk crystal consists of six molecules classified as active or inactive states according to the coordinations of catalytic residues. Csk assembles the SH2 and SH3 domains differently from inactive SFKs, and their binding pockets are oriented outward enabling the intermolecular interaction. In active molecules, the SH2-kinase and SH2-SH3 linkers are tightly stuck to the N-lobe of the kinase domain to stabilize the active conformation, and there is a direct linkage between the SH2 and the kinase domains. In inactive molecules, the SH2 domains are rotated destroying the linkage to the kinase domain. Cross-correlation matrices for the active molecules reveal that the SH2 domain and the N-lobe of the kinase domain move as a unit. These observations suggest that Csk can be regulated through coupling of the SH2 and kinase domains and that Csk provides a novel built-in activation mechanism for cytoplasmic tyrosine kinases.

The Src family tyrosine kinases (SFKs),[1] benign relatives of the oncogenic v-*src* gene product, are non-receptor types of protein tyrosine kinases (PTKs) that are associated with the plasma membrane through their fatty acylated N termini (1). The SFKs serve as molecular switches involved in the initiation of a variety of cellular events in the multicellular animals, including cell growth and division, cell attachment and movement, differentiation, survival, and death (2). The SFKs are ordinarily present in an inactive state in which the phosphorylated C-terminal regulatory tyrosine binds to its own SH2 domain (3). In response to an external stimulus, an SFK becomes activated through dephosphorylation of the C-terminal tyrosine or through binding to another protein that displaces the intramolecular interaction. The phosphorylation of the regulatory tyrosine of SFK is strictly controlled by another PTK, the C-terminal Src kinase (Csk) (4, 5). The loss-of-function of Csk leads to constitutive activation of SFKs, accompanied by severe defects in embryonic development (5). In contrast, gain-of-function of Csk can readily down-regulate SFK-mediated cell signaling (6). Therefore, to understand the function and regulation of SFKs, it is essential to clarify the regulation mechanism controlling the phosphorylation of the critical C-terminal tyrosine.

Csk is a cytoplasmic PTK consisting of an SH3, an SH2, and a kinase domain (4). Because it lacks an N-terminal acylation signal, an autophosphorylation site, and a C-terminal regulatory tyrosine, all of which are conserved among SFKs, the regulatory mechanism of Csk appears to be quite different from those of SFKs. The molecular basis of Csk regulation has so far been studied using mutated molecules and isolated domains (7, 8). However, lack of the entire structure of Csk has hampered the evaluation of their physiological roles. Some evidence suggests that the SH2 and/or SH3 domain of Csk is essential for SFK regulation (7, 9) and that recruitment to the membrane is required for Csk function (6, 10). In this context, we and others have recently identified a membrane phosphoprotein that can tightly bind to the SH2 domain of Csk (Cbp or PAG) (11, 12). Upon phosphorylation, Cbp/PAG can recruit Csk to a membrane microdomain, so-called lipid Rafts, to terminate SFK signaling. More recently, we found that the binding to the phosphorylated Cbp/PAG could directly activate Csk (13). Thus it is likely that Cbp/PAG plays an important role in Csk regulation. On the other hand, other proteins that could functionally bind to the SH2 domain of Csk, such as Paxillin and FAK, have been identified previously (7). These findings suggest that Csk is regulated through its SH2 domain *in vivo*, although the molecular basis of this regulation remains thoroughly unknown. To address this issue, we here elucidated the entire structure of Csk by crystallographic analysis.

EXPERIMENTAL PROCEDURES

Expression and Purification of Csk—The full-length (amino acids 1–450) rat Csk was expressed using baculovirus vector in insect cells and purified essentially by the same methods as described previously (13), except that β-octyl-D-glucoside was added (instead of Nonidet P-40) to the buffer during chromatography processes and that the final gel filtration chromatography was performed in a buffer consisting of 100 mM Tris-HCl (pH 8.5), 150 mM NaCl, 5 mM β-mercaptoethanol, 1 mM EDTA, 5% glycerol, and 0.02% β-octyl-D-glucoside. Size estimation was carried out on a Superdex200 HR10/30 column equilibrated with phosphate-buffered saline. Sedimentation equilibrium was performed by ultracentrifugation at 17,000 rpm for 22 h. Concentration distributions were measured using the Rayleigh interference optics.

Crystal Structure Analysis—The purified Csk was concentrated to ~12 mg/ml, mixed with 50 mM Hepes-NaOH (pH 7.4) containing 1.90–1.95 M ammonium sulfate, and crystallized in a sitting drop by vapor diffusion at 288 K for 1–2 months. All data were collected at the

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The atomic coordinates and structure factors (code 1K9A) have been deposited in the Protein Data Bank, Research Collaboratory for Structural Bioinformatics, Rutgers University, New Brunswick, NJ (http://www.rcsb.org/).

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[1] The abbreviations used are: SFK, Src family tyrosine kinase; PTK, protein tyrosine kinase.

TABLE I
Summery of crystallographic data and refinement statistics

	Native1	Native2	CH_3HgBr
Space group	$P2_12_12_1$		
Cell parameters			
a (Å)	115.0	115.0	115.1
b (Å)	162.6	162.6	162.9
c (Å)	232.4	232.4	232.5
Wavelength (Å)	0.900	1.000	1.007
Resolution range[a] (Å)	73–2.5 (2.64–2.50)	30–2.6 (2.69–2.60)	49–2.9 (3.0–2.9)
Number of unique reflections[a]	150,489 (17,029)	136,322 (13,573)	93,131 (9,172)
Completeness[a]	98.2 (98.2)	99.4 (99.9)	99.9 (98.8)
Multiplicity[a]	5.0 (4.5)	5.2 (4.9)	5.9 (5.1)
I/σ[a]	6.9 (1.7)	8.8	12.1
R_{sym}[a] (%)	7.3 (39.8)	5.9 (39.0)	6.9 (36.2)
R_{cryst}/R_{free} (%)	24.6/28.8		
Root mean square deviation			
Bond lengths (Å)	0.007		
Bond angles (°)	1.427		

[a] Values in parentheses are for the last resolution shell.

cryogenic temperature (around 100 K) using 25% (v/v) ethylene glycol as a cryoprotectant. The native1, native2, and Hg data were collected on the PX210 (Oxford) at BL44XU, Quantum4 (adsc) at BL40B2, and on the marCCD (Mar research) at BL41XU in SPring-8, respectively. The diffraction images were reduced and scaled with Mosflm (ccp4 (14)) and Scala (ccp4) in native1 and Denzo/Scalepack (15) in native2 and Hg data sets. The intensities were converted to the structure factor amplitudes with TRUNCATE (ccp4). Subsequent phasing calculations were performed using native2 and Hg data. The six Hg positions were first located using SHELXS-97 (16), followed by the minor site specification, heavy atom parameter refinement, and the SIRAS phase calculation with SHARP (17). The density modification with SOLOMON (ccp4) permitted us clear interpretation of the electron density map. The atomic model was built using O (18) and refined with the native1 data set using CNS (19). Of the 2,298 non-glycine and non-proline residues, 83.0% fell into the most favored regions, 16.1% into the additional allowed regions, 0.9% into the generously allowed regions, and no residue into the disallowed regions of Ramachandran plot as defined in PROCHECK. Coordinates have been deposited with the Protein Data Bank under accession codes 1K9A.

RESULTS AND DISCUSSION

Overview of Csk Structure—The full-length rat Csk was produced using a baculovirus vector in insect cells and purified through sequential column chromatography. Although Csk from the brain tissue (<0.01 mg/ml) behaved as a monomer (50 kDa) on gel filtration chromatography (20), the highly concentrated Csk from insect cells (>1 mg/ml) was eluted with an apparent molecular size around 100 kDa (data not shown). Sedimentation equilibrium analysis also revealed that Csk is present as a dimer at concentrations around 1 mg/ml (data not shown). These findings demonstrate that Csk tends to dimerize at high protein concentrations *in vitro*. The crystal structure of Csk was solved by the heavy atom single isomorphous replacement method. Crystallographic data and refinement statistics are shown in Table I. An interesting feature of Csk crystal is that it consists of six molecules divided into three pairs of putative dimers per asymmetric unit. This is probably because of oligomerization of Csk dimers during crystallization processes. The dimers are made with loose interactions through the backside of the kinase domains and the SH3 domains. Two of the six molecules, in distinct dimers, make further contact with each other and appear to have some distortions in their structures as described later. In every molecule, however, the three functional domains, SH2, SH3, and kinase, are arranged in a similar manner with the SH2 and SH3 domains diametrically opposite on the top of the N-lobe of the kinase domain (Fig. 1, *A* and *C*). Although the position of the SH3 domain resembles the position of the SH3 domain of inactive forms of SFKs, the position of the SH2 domain is entirely different (3). In addition, there is no direct contact between the SH2 and SH3 domains of Csk.

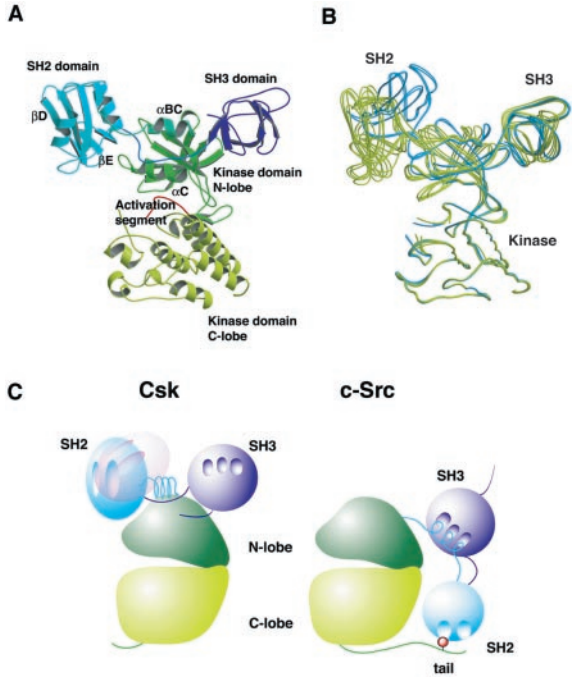
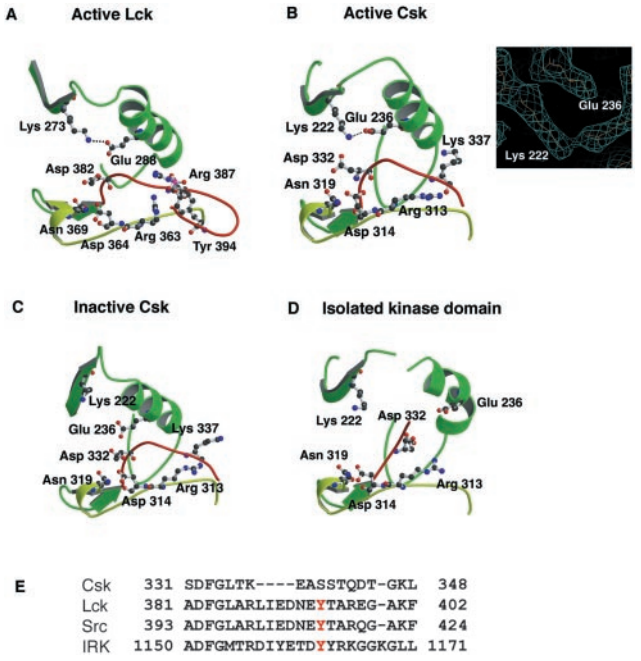


FIG. 1. *A*, ribbon diagram of a representative Csk structure (active molecule) in the crystal. Domain structures are distinctively colored: SH2 in *blue*, SH3 in *purple*, N-lobe in *dark green*, C-lobe in *light green*, and the activation segment in *red*. *B*, superimposed model of the six Csk molecules in an asymmetric unit. Active molecules are shown in *green* and inactive molecules are in *blue*. *C*, schematic models of the structures of Csk (*left*) and c-Src (*right*). Peptide binding pockets of the SH2 and SH3 domains are shown by *hollows*. The rotated SH2 domain of the inactive molecule is colored *pink*. Phosphate on the tail tyrosine (Tyr-527) of c-Src is colored *red*.

Arrangements of the SH2 and SH3 Domains—The SH3 domains fold canonically with two anti-parallel sheets of five β-strands sandwiched into a compact structure. There are virtually no differences from the structure of an isolated Csk-SH3 domain (21) except that the N-terminal region is disordered in the isolated SH3 domain (Fig. 1*A*). The peptide-binding pocket of the SH3 domain is oriented outward (Fig. 1*C*) enabling the intermolecular interaction, and the interactions between the SH3 and SH2-kinase linker observed in inactive SFK structures are absent. The SH2 domains are also canonical, consisting of a central β-sheet flanked by two α-helices as in c-Src (Fig. 1*A*), although an insertion is present in the loop region of the c-Src SH2 domain. However, a significant difference can be observed in the orientations of the SH2 domains when all six Csk molecules are superimposed (Fig. 1*B*). In four Csk mole-



E

Csk	331	SDFGLTK----EASSTQDT-GKL 348
Lck	381	ADFGLARLIEDNEYTAREG-AKF 402
Src	393	ADFGLARLIEDNEYTARQG-AKF 424
IRK	1150	ADFGMTRDIYETDYYRKGGKGLL 1171

FIG. 2. Arrangements of the catalytically important residues in Lck (*A*), active Csk and a simulated annealing omit map at 1.5 σ in the vicinity of the salt bridge between Lys-222 and Glu-236 (*B*), inactive Csk (*C*), and the isolated kinase domain of Csk (27) (*D*) are shown. The salt bridge between Lys-222 and Glu-236 is indicated by *dotted line* in *A* and *B*. *E*, sequence alignment of the activation loops of Csk, Lck, c-Src (*Src*) and insulin receptor kinase (*IRK*). Autophosphorylated tyrosines are colored *red*.

cules, the ligand binding surfaces face to the *left* in Fig. 1*B*, whereas those of the other two are rotated upward ~60° (Fig. 1*B*). This disorientation may reflect an unusual flexibility of the SH3-SH2 linker and SH2-kinase linker, which form a hinge about which the SH2 domain pivots. These two linkers make extensive hydrophobic contacts with the N-lobe of the kinase domain (Fig. 1*A* and Fig. 3). In the SH2-kinase linker, there is an α-helix, which is designated as αBC, that is absent from SFKs (Fig. 1*A*). All the hydrophobic residues involved in engaging the SH2 and kinase domains are highly conserved among Csks derived from various species, suggesting that docking of the SH2 linkers into the kinase domain is important for regulation.

Active Conformation of the Kinase Domain—The kinase domains of the four Csk molecules whose SH2 domains face to the *left* in Fig. 1*B* can be readily superimposed on the kinase domain of an active SFK, Lck (22). The positions of residues crucial for catalytic activity (Asp-314, Asn-319, and Asp-332) and the critical ion bridge that orients the γ-phosphate of ATP (Glu-236 in αC and Lys-222 in β3) are consistent with those of Lck (Fig. 2, *A* and *B*). All these features suggest that the four molecules are most likely to be enzymatically active. The active site similarity with Lck is rather remarkable considering that Csk differs from SFKs in its activation loop (Fig. 2, *red*). The activation loop of Csk (331–348) is four residues shorter than and diverged from that of Lck, and, critically, it lacks a phosphorylated tyrosine residue (Fig. 2*E*). In addition, Csk residues are either substantially displaced as compared with their counterparts in Lck (338–342, 346–349) or disordered (343–345). In SFKs, autophosphorylation of the activation loop tyrosine is regulatory and essential for full catalytic activity and for transforming potential (23, 24). In Lck, this phosphotyrosine (Tyr-394) is essential to coordinate Arg-363 and Arg-387 and thus stabilize the active structure. In Csk, however, the side chain of Lys-337, which corresponds to Arg-387 in Lck, has no

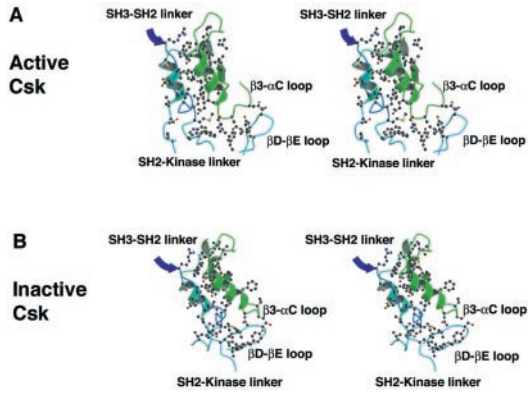


FIG. 3. **Stereo representations of the interaction between the SH3-SH2 linker, SH2-kinase linker, and the kinase domain in active Csk (*A*) and inactive Csk (*B*).** The interaction between the βD-βE loop and β3-αC loop cannot been seen in the inactive Csk.

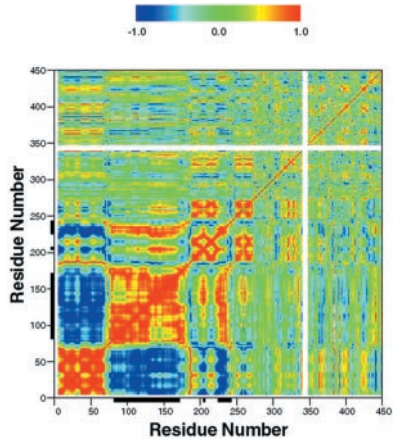


FIG. 4. **Cross-correlation matrices for the four active Csk molecules.** The SH2 domain (82–172), β1-β2 and β3-αC loop (204–207), and β3-αC loop and αC (225–243) are emphasized by the *bold lines*. The C-lobes of four molecules were superimposed prior to the calculation. The correlation coefficients c_{ij}, which are plotted according to the scale indicated on the *top*, are defined as $c_{ij} = \Sigma(r_i \cdot r_j)/((\Sigma|r_i|^2)^{1/2}(\Sigma|r_j|^2)^{1/2})$, where r_i is the deviation of the backbone carbon position from the average position of the "*i*"th residue.

apparent coordinations to a specific partner, yet the main chain lies within 1.5 Å of Lck Arg-337 when the C-lobes are superimposed.

The similarity in active sites despite the absence of phosphate in the activation loop suggests that another mechanism maintains the active conformation of Csk. Previously it has been reported that deletion of sequences preceding the kinase domain significantly reduces Csk activity (7, 8, 25, 26), and a role of the SH3-SH2 linker in Csk activation has been suggested (8). In a structure of the isolated kinase domain bound to staurosporine, the helix αC is kinked and flexible, destroying the critical salt bridge between Lys-222 and Glu-236 (Fig. 2*D*) (27). In the case of Lck, however, an isolated kinase domain retains full activity (28). As already mentioned, in Csk there are tight interactions between the two linkers and the N-lobe of the kinase domain. Notably, the helix αC, which positions Glu-236, is oriented by extensive contacts with the linkers (Fig. 3). This resembles the case of CDK2 that is partially activated through binding to cyclin A (29). The binding of cyclin A to the helix αC (containing PSTAIRE motif) of CDK2 induces a dramatic change in the orientation of the helix αC so that the catalytic residues are appropriately coordinated for the catalysis. Therefore, instead of the activating phosphotyrosine, Csk may require the interaction between the kinase domain and the linkers to stabilize the active conformation.

Inactive Conformation of the Kinase Domain—In contrast with the active molecules, the two Csk molecules with rotated SH2 domains appear to be inactive. These molecules are substantially different from the active molecules in the backbone carbon positions of the N-lobe of the kinase domain (Fig. 1*B*). Importantly, the critical ion pair (between Glu-236 and Lys-222) is absent (Fig. 2*C*) although the conformation of the catalytic domain is apparently different from that of the isolated kinase domain bound to staurosporine (27). Furthermore, there is a major difference between the active and inactive molecules in the SH2-kinase interface (Fig. 3); the interactions between the βD-βE loop of the SH2 domain and β3-αC loop in the N-lobe of kinase domain are absent in the inactive molecules. These indicate that rotation of the SH2 domain could affect the conformation of the N-lobe of the kinase domain, implicating the functional relationship between the SH2 domain and the kinase domain.

Regulatory Feature of Csk—To address the above issue, we calculated cross-correlation matrices for the deviations of the backbone carbon atoms of the molecules in the crystal. The cross-correlation matrix was recently found to be useful to assess interdomain interactions in molecular dynamics studies (30). Fortunately, our crystal contained multiple copies of Csk molecules in an asymmetric unit, and we used four crystallographically independent copies instead of conformational snapshots in the molecular dynamics study. The C-lobes of the kinase domains were first superimposed by the program LSQKAB (14), and then we generated a set of averaged positions of the α carbon. The correlation between two atoms can be defined using the deviations from their respective average positions. It is obvious that the correlation value for two atoms in the same domain shows an absolute value close to 1 as the domain moves en bloc. If two residues move independently, the correlation will be near 0. It is usually observed that the correlation between two atoms in the "superimposed" region is flattened to 0. As shown in Fig. 4, for four active-state molecules, clusters of positive correlations between two atoms lie in the regions indicating correlations between the SH2 domain and β1-β2 and β3-αC regions of the kinase domain. This indicates that these segments deviate en bloc in the crystal, representing a functional coupling between the SH2 and the kinase domain.

The structure of Csk presented here highlights the functional interactions of the catalytic domain with the SH2 domain and its linkers and suggests a novel activation mechanism that is distinct from the phosphorylation-dependent regulation of SFKs. The presence of an inactive conformation of Csk, which is probably produced by the unusual flexibility of the hinge region of the SH2 domain, also suggests that there may be a dynamic equilibrium between active and inactive Csk. It is known that a strong ligand of the SH2 domain, the phosphorylated Cbp/PAG, could elicit potentially full activity of Csk (13). Therefore, it is probable that binding of Cbp/PAG ligand to the SH2 domain could fix the active state to make the kinase constitutively active. It is also possible that the conformation change induced by the SH2 ligand could affect the region responsible for the substrate recognition. To verify these hypotheses, the structural details of Csk association with Cbp/PAG are now under investigation.

Among the many types of cytoplasmic protein tyrosine kinases, including the Fes, Abl, Syk, Tec, and Csk families, the SFKs are unusual in that they are negatively regulated by phosphorylation of the C-terminal regulatory site. The SH2 domain of the SFK serves as an acceptor for the phosphorylated regulatory tyrosine. All the aforementioned cytoplasmic tyrosine kinases also possess an SH2 domain adjacent to the catalytic domain but have no C-terminal phosphotyrosine. Although the actual roles of SH2 domains in these enzymes remain to be studied at the molecular level, the structures of Csk presented here could be representative of cytoplasmic tyrosine kinases other than SFKs.

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