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The Y's that bind: negative regulators of Src family kinase activity in platelets

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Summary

Members of the Src family of protein tyrosine kinases play important roles in platelet adhesion, activation, and aggregation. The purpose of this review is to summarize current knowledge regarding how Src family kinase activity is regulated in general, to describe what is known about mechanisms underlying SFK activation in platelets, and to discuss platelet proteins that contribute to SFK inactivation, particularly those that use phosphotyrosine-containing sequences to recruit phosphatases and kinases to sites of SFK activity.

Keywords

blood platelets; phosphorylation; platelet activation; protein tyrosine phosphatases; protein-tyrosine kinases; signal transduction

Regulation of Src family kinase (SFK) activity: general mechanisms

Structure of inactive SFKs

All SFKs share a similar modular domain structure (Fig. 1A) that comprises, in order, from the amino (N)- to the carboxy (C)-terminus: (i) a unique N-terminal sequence, also referred to as the Src homology (SH) 4 domain, that contains myristoylation and sometimes also palmitoylation sites that influence sub-cellular localization, (ii) the SH3 domain that binds proline-rich sequences, (iii) a short connector that joins the SH3 and the SH2 domains, (iv) the SH2 domain that binds phosphotyrosine (pY)-containing sequences, (v) the SH2-kinase linker sequence, (vi) a kinase, or SH1, domain that is responsible for enzymatic activity and is comprised of a smaller N-terminal catalytic lobe that is connected to a larger C-terminal regulatory lobe by a flexible activation loop that contains a regulatory tyrosine (Y) residue (Y₄₁₆ in human Src), and (vii) a C-terminal tail that also contains a regulatory Y residue (Y₅₂₇ in human Src) [1]. Maintenance of SFKs in an inactive conformation requires synergy amongst a number of intra-molecular interactions that involve the SH3 and SH2 domains [2,3]. In fully assembled, inactive SFKs (Fig. 1A), the ligand-binding surface of the SH3 domain is occupied by a polyproline type II-like sequence within the SH2-kinase linker,

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whereas the SH2 domain is occupied by a phosphorylated tyrosine residue located in the C-terminal tail. In addition, the SH3 domain and SH2-kinase linker of inactive SFKs contact residues in the N lobe of the kinase domain, whereas the SH2 domain interacts with residues of C lobe. Together, these interactions inhibit kinase activity by forcing the N and C lobes of the kinase domain together, which displaces the activation loop of the N lobe away from the position it occupies in active kinases and leads to rearrangement of residues that would otherwise participate in catalysis.

Structures of active SFKs

To paraphrase Anna Karenina, whereas all *inactive* SFKs are alike, *active* kinases can be active in different ways. Fully active, fully disassembled SFKs (Fig. 1B) are characterized by: (i) disruption of intra-molecular interactions in which both the SH3 and SH2 domains participate, (ii) the presence of a phosphotyrosine (pY) residue within the activation loop of the kinase domain (which arises as a consequence of autophosphorylation), and (iii) the presence of an unphosphorylated Y residue within the C-terminal tail of the enzyme [2,3]. However, SFKs need not be fully disassembled to be active. Thus, dissociation of the SH3 domain from its inhibitory intra-molecular interactions is alone sufficient to activate an SFK. Such dissociation can be driven by artificial or naturally occurring mutations, within either the SH3 domain, the SH2-kinase linker, or the kinase domain [2,3]. In addition, because the proline-rich sequence in the SH2-kinase linker (PX₄PX₁₂P) binds to the SH3 domain with low affinity, it can be displaced by inter-molecular interaction of the SH3 domain with higher affinity proline-rich sequences (e.g., PXXPXR) in other proteins (Fig. 1C) [2,3]. Interestingly, SFKs that are activated by disruption of their SH3 domain-dependent intra-molecular interactions may retain the intra-molecular interaction between the C-terminal pY residue and the SH2 domain, because the latter interaction is required for inhibition, but need not be disrupted for activation, of the SFK [4]. Dissociation of the SH2 domain from its intra-molecular interaction with the inhibitory C-terminal pY residue, which is accompanied by dissociation of the SH3 domain from its intra-molecular interactions [5], is also sufficient to activate SFKs (Fig. 1D). Although such dissociation has been artificially driven by substitution of the C-terminal Y residue with phenylalanine [6] or by elimination of the C-terminal tail of the enzyme altogether [7], this interaction can be disrupted upon dephosphorylation of the C-terminal pY residue [Fig. 1D(i)], which can be accomplished by a number of different phosphatases, including proline-enriched tyrosine phosphatase (PEP), T-cell protein tyrosine phosphatase (TCPTP), tandem SH2 domain-containing protein tyrosine phosphatase-1 (SHP-1), and CD45 [3]. In addition, as is the case with the SH3 domain, the pY-containing sequence in the C-terminal tail (pYQPG, pYQQQ, or pYQPQ) binds to the SH2 domain with relatively low affinity, and can be easily overcome by pY-containing sequences (e.g. pYEEI) in other proteins for which the SH2 domain has higher affinity [Fig. 1D(ii)] [2,3]. In this latter case, the active SFK may, but need not, be dephosphorylated on its C-terminal Y residue [8].

Regulation of SFK activity in platelets

In this context, it is clear that a complete understanding of how SFKs regulate platelet activation requires knowledge at several levels. First, it is necessary to identify the SFKs

that are involved in important platelet activation pathways. Second, for each of these pathways, the types of inter-molecular interactions that support binding of the SFKs to the receptors that initiate these pathways must be characterized. For those pathways that involve SH2 domain-dependent interactions with pY-containing sequences in other proteins, the phosphatases that dephosphorylate those proteins and the adaptor molecules that recruit relevant phosphatases to the site of SFK activation have to be identified. Finally, for those pathways that require re-phosphorylation of the SFK C-terminal inhibitory Y residue, it is necessary to identify the kinase responsible and define how it gets to the site of SFK activation.

SFK-dependent platelet activation pathways

Platelets express at least six SFKs, including Fgr, Fyn, Lck, Lyn, Src, and Yes [9,10]. Fyn and Lyn are involved in activation of platelets following binding of collagen or laminin to the platelet-specific GPVI/Fc receptor (FcR) γ -chain complex [11]. The SH3 domains of Fyn and Lyn both associate with a proline-rich sequence in the cytoplasmic domain of the GPVI subunit [12]. Activation of Fyn and Lyn following ligand binding to GPVI initiates a signal transduction pathway that involves phosphorylation of an immunoreceptor tyrosine-based activation motif (ITAM) in the FcR γ -chain, and recruitment of the tyrosine kinase, Syk, to the phosphorylated ITAM [13,14]. Subsequent phosphorylation of adaptor molecules results in recruitment and activation of other enzymes that ultimately lead to generation of second messengers required for platelet granule release and cytoskeletal rearrangement [15]. Fyn and Lyn have been found to co-precipitate with the FcR γ -chain following GPVI-mediated platelet activation [16]; however, it is not known whether the SH2 domains of Fyn and Lyn are involved in these interactions and, if so, whether such interactions stabilize the kinases in active conformations. Down-regulation of the GPVI/FcR γ -chain complex has been observed following activation of both mouse and human platelets [17,18]. Whether such receptor down-regulation plays a role in inactivation of Fyn and Lyn following GPVI-mediated platelet activation remains to be determined.

Another important platelet activation pathway that involves SFKs, specifically Src itself and Fyn, is that of outside-in signaling by the platelet-specific integrin, $\alpha_{IIb}\beta_3$ [19,20]. Src has been reported to associate with an arginine-glycine-threonine sequence at the extreme C-terminus of the integrin β_3 subunit [21], whereas Fyn is thought to bind to a sequence in β_3 that is nearer the inner face of the plasma membrane [20]. SFK activation following ligation of $\alpha_{IIb}\beta_3$ on human platelets initiates a signal transduction pathway very similar to that of the GPVI/FcR γ -chain complex [22], except that it begins with phosphorylation of an ITAM in the cytoplasmic domain of Fc γ RIIA [23]. Additional studies are needed to determine the extent to which the SH3 and/or SH2 domains of Src and Fyn are involved in their interactions with $\alpha_{IIb}\beta_3$ and components of the $\alpha_{IIb}\beta_3$ signal transduction pathway, whether such interactions contribute to activation of these SFKs, and how the activity of these enzymes is controlled following $\alpha_{IIb}\beta_3$ engagement. Finally, SFKs, Lyn in particular [24], have also been shown to be involved in activation of platelets by the GPIb/V/IX receptor for von Willebrand Factor [25]. However, the mechanism by which SFKs are activated following VWF binding to GPIb/V/IX remains to be determined.

Phosphotyrosine-containing proteins that contribute to SFK inactivation in platelets

Inactivation of SFKs activated by SH2 domain-dependent inter-molecular interactions

The SH2 domain-dependent inter-molecular interactions in which SFKs participate in platelets, and the identities of the phosphatases that negatively regulate these interactions, are incompletely characterized at present. Scaffolding molecules that may regulate the platelet activation state by recruiting protein tyrosine phosphatases to sites of SFK activation have, however, begun to be identified. One such scaffolding molecule is Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1 or CD31). PECAM-1 possesses a long cytoplasmic tail that contains two immunoreceptor tyrosine based inhibitory motifs (ITIMs), phosphorylation of which supports recruitment to the membrane and activation of the tandem SH2 domain-containing, non-receptor protein tyrosine phosphatases, SHP-2 and SHP-1 [26]. PECAM-1 deficiency in mice results in platelet hyper-responsiveness, especially to GPVI-specific stimuli [27,28]. Recently, Carcinoembryonic Antigen-related Cell Adhesion Molecule-1 (CEACAM-1), which possesses cytoplasmic ITIMs that support recruitment and activation of SHP-1, has been shown to behave similarly to PECAM-1 in that its deficiency in mice also results in platelet hyper-responsiveness to GPVI-specific agonists [29]. Platelets also express additional ITIM-containing molecules, including G6b-B [30] and TREM-like Transcript-1 (TLT-1) [31]. Although there is evidence that G6b-B can modulate GPVI signaling [32,33] and that TLT-1 is functionally important in platelets [34,35], the mechanisms by which these molecules function in platelets remain to be determined.

Inactivation of SFKs activated by disruption of the SH2 domain-dependent intra-molecular interaction with the C-terminal inhibitory pY residue

The steps involved in re-establishment of the intra-molecular interaction between the SFK SH2 domain and its C-terminal inhibitory pY residue have also not been completely delineated for any of the SFK-dependent platelet activation pathways. However, much is known about the kinases responsible for phosphorylation of the C-terminal Y residue, and also about the mechanism by which these kinases are activated at sites of SFK activity. The kinases involved include the aptly named C-terminal Src kinase (Csk) itself and its close relative, Csk-homologous kinase (Chk) [36]. Both of these enzymes are known to be expressed in platelets [19,37]. Csk and Chk have a domain organization similar to that of SFKs, except for the absence of both the N-terminal SH4 domain and a C-terminal inhibitory Y residue [36]. Consequently, Csk and Chk are cytoplasmic enzymes that are not regulated directly by tyrosine phosphorylation; instead, they are recruited to the membrane and activated upon binding of their SH2 domains to pY residues within Csk binding proteins, which are themselves phosphorylated by SFKs [36]. Although many molecules with Csk or Chk binding functions have been identified [38], the only protein thus far shown to have such function in platelets is paxillin, which regulates Lyn activity downstream of $\alpha_{IIb}\beta_3$ engagement [39]. Other well-characterized Csk binding proteins that are expressed in platelets include Csk binding protein (Cbp)/Phosphoprotein Associated with glycosphingolipid-enriched membrane microdomains (PAG) [40], caveolin-1 [41], and

insulin receptor substrate-1[42]. The extent to which these molecules function as Csk binding proteins in platelets and the stages of the platelet activation process at which they regulate SFK activity remains to be determined.

In summary, although progress has been made toward developing a complete understanding of how SFK activity is regulated during platelet activation, much remains to be learned. Specifically, whereas the SFKs that are involved in platelet activation by GPVI and $\alpha_{IIb}\beta_3$ have been identified, the types of inter-molecular interactions that maintain these SFKs in an active conformation downstream of receptor engagement have yet to be fully characterized. Similarly, whereas we have begun to identify the tyrosine phosphatases (and the scaffolding molecules that recruit these phosphatases to sites of SFK activity, where necessary) that are capable of interfering with SH2-dependent, SFK-activating interactions, the substrates that must be dephosphorylated to return SFKs to an inactive conformation remain to be identified. Finally, more information is needed regarding the inventory of molecules that can serve as Csk binding proteins in platelets, the extent to which these molecules recruit Csk vs. Chk to sites of SFK activity, and the identities of the pathways that require re-phosphorylation of the SFK C-terminal inhibitory Y residue to effect SFK inactivation. It is hoped that significant advances will be made in these areas in the coming years.

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Fig. 1.
Structures of inactive (A) and active (B--D) forms of Src family kinases.