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NON-RECEPTOR PROTEIN TYROSINE KINASES

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1. ABSTRACT

The protein tyrosine kinases (PTKs) are enzymes catalyzing the transfer of the gamma-phosphate group of ATP to the hydroxyl groups of specific tyrosine residues in peptides. Although phosphotransfer reactions catalyzed by various PTKs are similar with regard to their basic mechanisms, their biological functions demonstrate a considerable degree of specificity. PTKs are divided into two groups according to the presence of transmembrane and extracellular domains. Whereas most PTKs possess these domains, which render them capable of recognizing extracellular ligands, many PTKs lack these sequences and are therefore referred to as non-receptor or non-transmembrane PTKs. Thirty-two genes encoding for non-receptor PTKs are present in the human genome. The current review focuses on the composition, structure, expression, functions and regulation of the mammalian non-receptor PTK families.

2. INTRODUCTION

The protein tyrosine kinases (PTKs) are enzymes catalyzing the transfer of the gamma-phosphate group of ATP to the hydroxyl groups of specific tyrosine residues in peptides. Although phosphotransfer reactions catalyzed by various PTKs are similar with regard to the basic mechanisms, the recognition of substrates by PTKs and, therefore, subsets of proteins phosphorylated by them show a considerable degree of specificity.

In agreement with the general prevalence of serine/threonine phosphorylation over tyrosine phosphorylation in the cells, the genes encoding for PTKs are notably fewer than those encoding for serine/threonine protein kinases, only about 1/6 of all protein kinase genes of the human genome are PTKs (1-4). The PTK superfamily is enormously diverse. First of all, PTKs are clearly divided into two groups according to the presence of transmembrane and extracellular domains, which enable PTKs possessing them to recognize extracellular ligands, in particular, various peptide growth factors. Specific ligands and intracellular signaling pathways induced by them have been identified for many, albeit not for all, membrane-spanning PTKs (5). Whereas most PTKs are of receptor nature, many PTKs lack the transmembrane and extracellular sequences and are therefore referred to as non-receptor or non-transmembrane PTKs. Thirty-two genes encoding for non-receptor PTKs are present in the human genome. The current review, focussing on mammalian non-receptor PTKs, is not intended to replace a number of excellent reviews on this subject (see above), but to give a brief overview of these proteins for the current special issue on protein tyrosine phosphorylation. The information on receptor PTKs can be obtained in a number of recent reviews (5-18).

PTKs have been found only in the multicellular animal organisms. This peculiarity appears to make biological sense, since PTKs are primarily involved in the regulation of the cellular functions that are directly related to the multicellular status of the organism, such as growth, differentiation, and cell-cell and cell-extracellular matrix interactions. However, the significance of the apparent lack of PTKs in the multicellular plant organisms is not clear (19).

Each PTK possesses a functional kinase domain capable of catalyzing the transfer of phosphate from ATP to tyrosine residues essentially independent of the presence

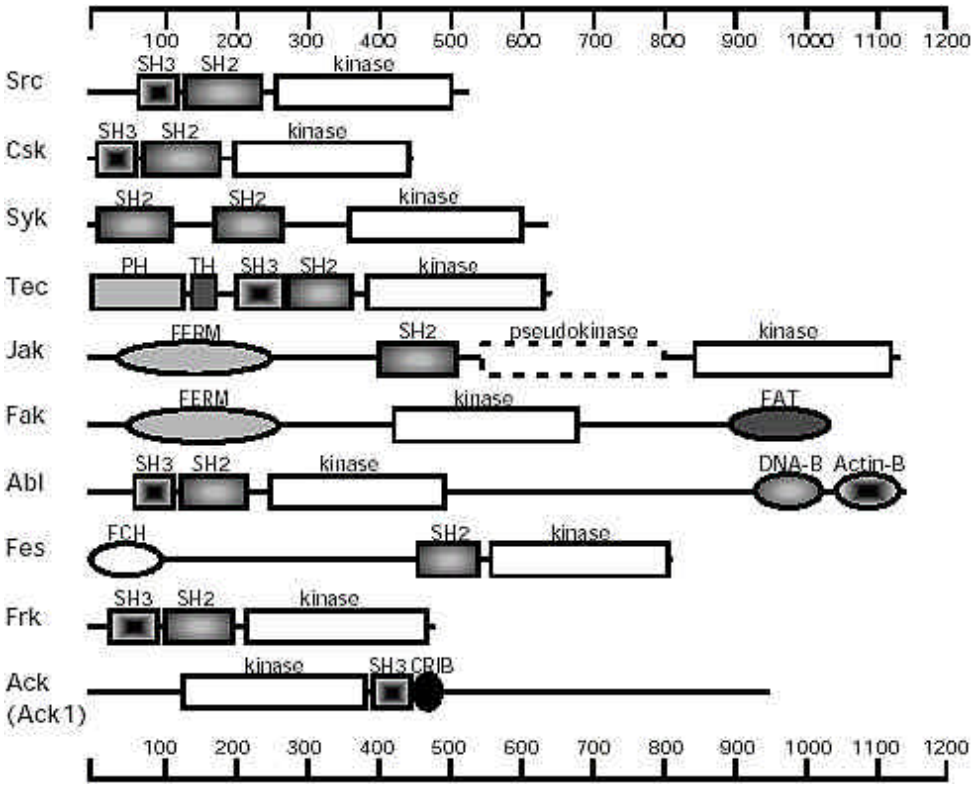

Figure 1. Domain structure of non-receptor protein tyrosine kinase families. The overall length of kinases and the positions of their domains (rulers at the top and at the bottom of the figure are graduated in amino acid residues) have been averaged for each family, unless substantial differences exist between family members. Thus, Tec-family structure is based on the typical members (Tec, Btk, Itk, and Bmx), while Txk lacking both PH and TH domains has been omitted from averaging. The DNA binding domain in the Abl-family structure is shown, although it is not conserved in Arg. The presented structure of Ack family is that of Ack1, because including Tnk1 in the averaging would not be meaningful, since Tnk1 is substantially shorter than Ack1 and lacks the CRIB domain. The details of the domain structure and interactions are given in the text.

of other structural elements of PTKs. The kinase domains are highly conserved among receptor and non-receptor PTKs. Furthermore, PTK catalytic domains are similar to those of serine/threonine and dual-specificity protein kinases, although several subdomain motifs appear to be unique for PTKs (20).

Based on the solved crystal structures of several PTKs, the catalytic domain of PTKs is similar to that of Ser/Thr protein kinases consisting of two lobes, N-terminal, which interacts with the phosphate groups of ATP, and C-terminal, which provides substrate-binding sites for ATP and peptides. The C-terminal domain includes the activation loop, a segment typically containing Tyr, Ser or Thr residues that can be phosphorylated. In its non-phosphorylated state, the activation loop tends to hinder substrate binding. Phosphorylation of these residues increases kinase activity (reviewed in (21-24)).

In addition to catalytic domains, the structure of PTKs includes other well-characterized protein domains. Typically, these domains mediate inter- and intramolecular interactions of PTKs, thus playing an important role in their functional regulation. Of these non-catalytic domains, SH2 and SH3 domains are most frequently present in non-receptor PTKs. The SH2 domain is capable of specific binding to phosphotyrosyl residues (25, 26), whereas SH3 binds to specific proline-rich motifs present in many proteins (27, 28). These domains are not unique for PTKs, but are present instead in numerous eukaryotic proteins.

The PTKs may be grouped into distinct families based on their overall domain structure, divergence of amino acid sequences of their kinase domains and the exon/intron organization of their genes. As a result of this analysis, the mammalian non-receptor PTKs are clustered into 10 families (figure 1). In the current review, a brief overview of structure, expression, role in signal transduction, biological functions and regulation is given for each family.

3. FAMILIES OF NON-RECEPTOR PTKs

3.1. Src

The Src family of PTKs with its eight members is the largest one among non-receptor PTKs. Mouse orthologs are known for all eight human Src-family members, as they are for almost all other human PTKs. A substantial number of rat and chicken orthologs of human Src-family PTKs have been identified. However, it is possible that non-mammalian species, such as the chicken, may have Src-family PTKs that lack human or mammalian orthologs. For

example, it appears that no mammalian ortholog exists for the Yrk kinase of Src-family from chicken (1, 29).

All PTKs of Src-family have a common structure consisting of the N-terminal sequence containing fatty acid-modification sites followed by a region in which the sequences of Src-family PTKs show the lowest degree of intra-family homology or the so-called "unique domain." Next to the N-terminal region is located an SH3 domain followed by an SH2 domain, which is followed, in turn, by a tyrosine kinase domain. The C-terminal part of Src-family PTKs contains the tyrosine residue that plays an important role in the regulation of their activity (see below).

Comparison of amino acid sequences of Src-family PTKs allows us to separate them into two subfamilies. The first subfamily includes Src, the prototypical member of the family, Fyn, Yes and Fgr. (Here and throughout the entire text, the prefix "c" is omitted for all cellular PTKs. If no prefix denoting a viral or another deregulated PTK form is used, it is presumed that a cellular form of PTK is mentioned.) The second one includes Lck, Blk, Lyn and Hck. Interestingly, this division corresponds to the tissue expression of these PTKs. Kinases of the first subfamily are widely expressed in various tissues, whereas expression of the second subfamily is restricted to hematopoietic cells. Furthermore, expression of each PTK of the second family is specific for certain cell types. For instance, expression of Lck is restricted to T and NK cells, whereas Blk is expressed in B cells only (reviewed in (30, 31)).

Although Src-family PTKs lack a transmembrane domain, they are localized primarily to cellular membranes, including plasma, perinuclear and endosomal membranes (32-34). The membrane localization of Src-family PTKs is due, to a substantial extent, to their N-terminal post-translation modifications with fatty acid moieties, myristoylation (35-37) and palmitoylation (38-40). The former appears to be irreversible, whereas the latter is reversible, making it possible to regulate the degree of hydrophobicity of Src-family PTKs.

Localization of individual Src-family PTKs is also dependent on their specific interactions with other cellular proteins. For example, Lck binds to the cytosolic tails of the CD4 and CD8 co-receptors in T lymphocytes (41, 42) and is, therefore, localized in the proximity of the T-cell receptor complex (TCR/CD3) (43-45), where it plays an important role in TCR/CD3-induced signaling (44, 46, 47). Fyn is another Src-family PTK participating in TCR/CD3-induced signaling (48-51). However, unlike Lck, Fyn is associated directly with the cytoplasmic tails of TCR/CD3 (52, 53). Other Src-family PTKs expressed in the cells of the immune system have also been shown to physically associate with multi-chain immune recognition receptors (MIRRs), including the B-cell antigen receptor complex (BCR) (54-57) and the receptors for the Fc portions of IgG (58-64) and IgE (65-68).

The function of Src-family PTKs associated with these and other surface receptors of immune cells appears to be the triggering of signal transduction pathways that emanate from the corresponding receptors (48, 49, 69-78). In many cases, the first and the most critical target of Src-family PTKs are the tyrosine residues within the immune receptor tyrosine-based activation motifs (ITAMs) of the MIRRs (79-82). Each of these motifs includes two Tyr-X-X-Leu/Ile sequences separated by 7-9 amino acid residues. Both tyrosines should become phosphorylated on a single ITAM to form a docking site for the Syk-family PTKs, which tightly bind to doubly phosphorylated ITAMs with their double SH2 domains position in tandem to each other (see below). In addition to phosphorylating ITAMs, Src-family PTKs appear to phosphorylate a number of other substrates, including other PTKs, thus playing an important role in the regulation of the latter (see below).

It should be noted that in spite of certain similarities between members of Src-family PTKs regarding the molecular basis of their involvement in receptor signaling and in spite of some redundancy and overlapping of their functions, the roles of these PTKs in signaling are highly specific. This conclusion is supported by numerous biochemical and genetic studies quoted above, as well as by gene-targeting experiments with Src-family PTKs (see below).

An interesting characteristic of the localization of Src-family PTKs is that they are preferentially localized to cholesterol- and glycolipid-enriched membrane microdomains frequently referred to as lipid rafts (83-86). Localization of Src-family PTKs, as well as other PTKs and their substrates, to the lipid rafts is likely to be important for the activation of immune cells (87-96).

Signal transduction through MIRRs is not the only function of Src-family PTKs. They also participate in signaling through other receptors, including the cytokine receptors (97-105) and the receptor PTKs (106-111). Participation of Src-family PTKs in cytokine signaling may involve functional interactions with Jak-family PTKs (112-114).

Src-family PTKs are also involved in the regulation of cytoskeletal rearrangements in various cell types. This involvement is due to the ability of Src-family PTKs to associate with various cytoskeletal proteins, including focal adhesion kinase (Fak) (115-125). These interactions appear to be critical for the regulation of assembly/disassembly of focal adhesion complexes and for the transmission of signals from the focal adhesions-linked integrins to the system regulating actin cytoskeleton assembly.

In the above-discussed phenomena, activation of PTKs appeared to be the first step of signaling pathways. Initiation of MIRR-mediated signaling by Src-family PTKs may be considered the "classical" example of such a role. However, Src-family PTKs may also function as downstream elements of signal transduction pathways. For instance, substantial evidence has been accumulated that Src-family PTKs may act as effectors of trimeric G proteins (126, 127). Furthermore, the naturally occurring form of Fgr lacking a myristoylation site (128) and, under certain

conditions, the full-length Src (129) have been found in the nucleus. Although the functions of nucleus-localized Src-family PTKs are still unclear, Src has been implicated in regulation of cell cycle progression and mitosis (130-135).

Targeted disruptions of Src-family PTK genes confirmed their biological importance and highlighted specific functions of individual Src-family PTKs. The biological consequence of the loss of Src turned out to be osteopetrosis due to a defective osteoclast function (136, 137). Consistent with the involvement of Lck in T-cell signaling, Lck-deficient mice demonstrated a profound block in T-cell development along with the impaired signaling and biological responses of the remaining few mature T cells (138-140). The effect of Lck disruption on T-cell development is apparently due to the essential role of this kinase in transducing signals from the pre-TCR that are required for the progression of thymocytes from the double-negative to the double-positive stage (141, 142). In contrast, targeted disruption of Fyn, which is also involved in lymphocyte signaling, caused no effects in T-cell development and only mild defects in T-cell signaling (48, 49). However, Fyn-negative mice show numerous and quite severe defects in the architecture and functions of the central nervous system (143-146), as well as the defect in keratinocyte development (147). A deficiency in Lyn resulted in a substantial reduction in the number of peripheral B cells and the level of their BCR-mediated responses, as well as in developing autoimmunity (148, 149). The latter can be explained by possible defects in negative selection of autoreactive B-cell progenitors.

No overt phenotypic changes have been observed in *yes*-, *hck*-, *fgr*- or *blk*-null mice (reviewed in (150)). These findings suggest that a high degree of redundancy exists between different members of the Src family. This notion is supported by findings indicating that double knock-out mutations can dramatically exacerbate phenotypical defects caused by single knock-outs. For example, *hck/src*-null mice exhibit substantially more severe osteopetrosis than *src*-null mice (151). Likewise, *fyn/lck*-null mice show a dramatic further reduction in thymocyte development as compared to *lck*-null mice (152). Furthermore, neutrophils of *hck*/*fgr*-null mice demonstrate susceptibility to *Listeria*, which is not seen in single knock-outs (153). Consistent with this finding, neutrophils of these double mutants, but not those of the corresponding single mutants, are impaired in adhesion and spreading on extracellular matrix (154). Likewise, monocytes of the *hck*/*fgr*/*lyn* triple null-mutant mice are defective in adhesion and spreading (155). Finally, many of the double mutations, such as *src/fyn*-null and *src/yes*-null, are lethal (reviewed in (150)).

The kinase activity of Src-family PTKs is regulated by their tyrosine phosphorylation. There are two major tyrosine phosphorylation sites in Src-family PTKs, the autophosphorylation site and the C-terminal negative regulatory site, corresponding to tyrosines 419 and 530 of human Src. Autophosphorylation of Src-family PTKs appears to be an intermolecular process (156-158). Furthermore, based on their consensus sequence, the autophosphorylation sites of Src-family PTKs represent potential substrates for other PTKs (159). Indeed, phosphorylation of tyrosine 394 of Lck that corresponds to Tyr-419 of human Src has been observed in inactive Lck in cells lacking endogenous wild-type Lck (160), as well as in the cells lacking any Src-family PTKs (161). Phosphorylation of the tyrosine residue corresponding to Tyr-419 of human Src, regardless of the specific mode by which it is achieved, causes displacement of this tyrosine from a hydrophobic pocket formed by both lobes of the PTK catalytic domain and results in the correct positioning of all key catalytic residues and in the formation of the substrate binding surfaces, thus leading to the full activation of the Src-family enzymes (162-167).

The second major tyrosine phosphorylation site of Src-family PTKs, which is located in their C-terminal domain, is phosphorylated by Csk-family PTKs (see below). Phosphorylation of this tyrosine causes its intramolecular interaction with an SH2 domain (168-171). The binding between the SH2 domain and the C-terminal phosphorylated tyrosine *per se* does not block or alter the active site of the kinase domain. Instead, it induces the binding of the SH3 domain to the linker region connecting the SH2 domain and the kinase domain accompanied by the binding of the linker region to the kinase domain. These intramolecular interactions prevent binding of ATP to the critical catalytic residues rendering Src-family PTKs inactive. The residue corresponding to Tyr-419 of human Src is located in the hydrophobic pocket and is protected from phosphorylation in the inactive form of Src-family PTKs (163-167, 172).

Consistent with these findings, disruption of the interactions that negatively regulate Src-family PTKs increases their enzymatic activity and cell-transformation potential. Such disruption may be achieved by mutating the C-terminal negative regulatory region (173-176), the SH2/SH3 domains (177-180), or the residues responsible for the interactions between the linker region and the kinase domain (172). Physiological regulation of Src-family PTKs is mediated by modulation of the interactions described above achieved by (a) phosphorylation/dephosphorylation of the C-terminal regulatory site, and (b) binding of the SH2 and SH3 domains of Src-family PTKs to various phosphotyrosine- or polyproline-containing proteins.

The C-terminal tyrosine is thought to be phosphorylated primarily by Csk-family PTKs (181-188) and dephosphorylated by several protein tyrosine phosphatases (PTPs), including CD45 (189-195), PTP-alpha and -lambda (196-198). Although it is clear that the removal of a phosphate from the autophosphorylation site should inhibit Src-family PTK activity, the nature of PTPs involved in this process is less clear. PEP and SHP-1 PTPs are possible candidate for this role (199-202).

Binding of the SH2 and SH3 domains of Src-family PTKs to phosphotyrosine- or polyproline-containing ligands may disrupt the intramolecular interactions of Src-family PTKs that negatively regulate Src-family PTKs and,

hence, activate these kinases. For example, phosphorylated forms of PDGF receptor (203), Cas adaptor protein (204) and Fak (124, 125) activate Src-family PTKs by binding to their SH2 domains. Similarly, several proteins, including the HIV protein Nef, activate Src-family PTKs by binding to their SH3 domains (205-207). Furthermore, interactions of Src-family PTKs with protein ligands may cause translocation of the former to the sites of action. Such interactions include above-mentioned binding of Src-family PTKs to various cell surface receptors, proteins of the cytoskeleton and adhesion complexes and nuclear proteins.

Other phosphorylation sites have also been identified on Src-family PTKs. Several serine residues are phosphorylated within the unique domain of Lck upon TCR- or IL-2-dependent stimulation, as well as PMA treatment. This phosphorylation, most likely mediated by Erk kinases, does not seem to substantially affect Lck kinase activity, although it has been proposed that it might work as a negative feedback (208-213). In contrast, serine phosphorylation of the unique domain of Src by PKA has recently been shown to activate this PTK (214).

Furthermore, sites of tyrosine phosphorylation have been identified within the SH2 domains of Lck and Src (215-217) and within the SH3 domain of Src (218). Phosphorylation of these sites may disrupt SH2- and SH3-mediated interactions of Src-family PTKs with their protein ligands.

Finally, the activity of Src-family PTKs has been shown to be regulated by ubiquitylation-induced degradation of their activated forms (219-222). In some cases, this degradation has been shown to be dependent on c-Cbl, an E3 ubiquitin ligase capable of interacting with Src-family PTKs (221, 222).

3.2. Csk

The Csk family of PTKs has two members, Csk and Matk. The latter is also known as Ctk, Ntk, Chk, Hyl and Lsk. Csk is expressed ubiquitously, but predominantly in thymus and spleen, while Matk is expressed primarily in brain and hematopoietic cells (reviewed in (223)).

Amino acid sequences of Csk- and Src-family PTKs are highly homologous. The domain structure of Csk-family PTKs includes an SH3 domain, followed by an SH2 domain and then by a tyrosine kinase domain, and therefore, closely resembles that of Src-family PTKs. Moreover, the crystal structure of Csk is very similar to those of Src-family PTKs (224). However, there are several important points of divergence between Src- and Csk-family PTKs. First, Csk-family PTKs lack the N-terminal unique domain carrying fatty-acid modification sites, which anchors Src-family PTKs in the membrane. Likewise, the C-terminal regulatory site is absent from Csk-family PTKs. Furthermore, there is no tyrosine residue in the activation loop of Csk. In agreement with this feature, Csk is incapable of autophosphorylation (see (223)). Because of the lack of these important tyrosine residues, regulation mechanisms for Src- and Csk-families of PTKs are very different (see below).

The main function of Csk-family PTKs appears to be the negative regulation of Src-family PTKs mediated by phosphorylation of their inhibitory tyrosine residue, which has been shown in multiple experimental systems (225-229). Consistent with this notion, the C-terminal regulatory domain of full-length Src-family PTKs is the most catalytically efficient substrate known to date (230), although CD45 also appears to be phosphorylated by Csk (231). Phosphorylation of CD45 by Csk activates CD45 and creates on it an Lck-binding site.

The targeted disruption of *csk* has confirmed that Csk plays a crucial regulatory role, since *csk*-null embryos die due, apparently, to a defect in the neural tube (185, 232). Cells derived from these embryos exhibit a dramatic increase in the kinase activity of Src, Fyn and Lyn (185, 232). Furthermore, the generation of chimeric mice using *csk*-null embryonic stem cells has shown that T- and B-cell differentiation of *csk*-null progenitors is blocked at very early stages, whereas the development of myelomonocytic cells remains normal (233). It is important to note that activation of either Lck or Fyn does not block lymphoid differentiation, as it is seen in *csk*-null cells (141, 233). This finding indicates that Csk, in addition to its generalized functions related to the inhibition of Src-family PTKs, may have specific functions in lymphoid cells that are mediated by other targets of Csk.

In contrast, matk-null mice are viable, exhibiting no significant abnormalities (234). Furthermore, kinase activity of Src-family PTKs remains unchanged in bone marrow cells of matk-null mice (234). This finding indicates a high degree of redundancy between Csk and Matk and points to the difference in their functions. These differences have also been observed in other experimental systems. For instance, Csk, but not Matk, is capable of inhibiting antigen-induced signaling in T cells (235), whereas Matk, but not Csk, can bind to TrkA, a nerve growth factor receptor PTK, and upregulate neurite outgrowth of PC12 cells (236).

In contrast to the Src-family PTKs, the kinase activity of Csk-family PTKs is not regulated by tyrosine phosphorylation, consistent with the lack of the respective phosphorylation sites. It appears, instead, that Csk is activated as a result of phosphorylation of its Ser-364 by cAMP-dependent protein kinase (PKA) (237). The cAMP-induced activation of Csk may be a key mechanism for the immune cell suppression caused by cAMP (238-244). Furthermore, the Csk activation loop itself contains a few putative serine and threonine phosphorylation sites, but there is no evidence of their phosphorylation.

The lack of the C-terminal negative regulatory tyrosine in Csk-family PTKs rules out the inhibitory intramolecular interaction of the phosphorylated form of this tyrosine with the SH2 domain. In contrast, it appears that the intramolecular interaction between the catalytic domain and the SH3 domain of Csk is important for efficient catalysis (245).

Although intermolecular interactions regulating the activity of Csk-family PTKs are less studied than those

regulating Src-family PTKs, it has been shown that the transmembrane protein PAG/Cbp, which is constitutively phosphorylated on tyrosine, binds to the SH2 domain of Csk in T cells. PAG/Cbp is localized to the lipid rafts and thus anchors Csk to these membrane domains, where Csk may phosphorylate and, hence, inhibit Src-family PTKs. TCR stimulation induces transient dephosphorylation of PAG/Cbp and dissociation of Csk. Gradually, Csk re-associates with PAG/Cbp and returns to the lipid rafts, thus abrogating the activity of Src-family PTKs (246, 247).

3.3. Syk

The Syk family has two members, Syk and Zap-70. Syk is expressed ubiquitously, including all types of hematopoietic cells, fibroblasts, epithelial and endothelial cells, hepatocytes, and neurons, whereas Zap has been found exclusively in T and NK cells (reviewed in (248-250)).

The common structure of Syk and Zap includes the two SH2 domains located in tandem in its N-terminal half, which are followed by a catalytic domain. Syk-family PTKs possess no fatty-acid modification sites, which are characteristic for Src-family PTKs, and are, as a result, predominantly cytosolic proteins. However, their localization is dramatically affected by cell stimulation. The tandem SH2 domains of Syk-family PTKs demonstrate an extremely high degree of affinity to doubly phosphorylated ITAMs, which dramatically exceeds that of single SH2 domains, including the SH2 domains of Syk and Zap, to single phosphotyrosine residues (251-253). Therefore, phosphorylation of ITAMs by Src-family PTK, which represents one of the initial signaling events for multiple receptors (see above), generates an excellent binding platform for Syk-family PTKs. As a result of this binding, cytosolic molecules of Zap and Syk become translocated to the cytoplasmic tails of MIRRs in the close proximity of the membrane (254-258). This event is critical in signal transduction involving Syk-family PTKs, since its disruption inhibits further signaling (259-261).

Upon recruitment, Syk-family PTKs phosphorylate multiple downstream targets (262-275). Two major mechanisms appear to activate Syk-family PTKs upon their recruitment to ITAM-containing receptors. First, phosphorylation of both Syk and Zap by Src-family PTKs can activate them (276-280). Several lines of evidence indicate that this mechanism is more important for Zap than for Syk, since Syk can be activated and function in a Src-family PTK-independent manner (281-284). This difference is likely to be due to the ability of Syk to phosphorylate ITAMs under certain experimental conditions (284), which is apparently lacked by Zap. The substantially higher intrinsic enzymatic activity of Syk as compared to Zap (285) may also contribute to its relative independence of Src-family PTKs.

In contrast, the second mechanism of activation of Syk-family PTKs is specific for Syk, which, unlike Zap, can be directly activated by binding to a doubly phosphorylated ITAM (284, 286-289). This binding causes conformational changes in Syk similar to those seen in this PTK in activated cells (288). This specific feature of Syk may, at least in part, be caused by the higher conformational flexibility and structural independence of the SH2 domains of Syk as compared to those of Zap (290), which is likely to result in a higher flexibility of Syk binding to various phosphorylated motifs and a less stringent dependence of this binding on the double phosphorylation of ITAMs. The differential ability of Zap and Syk to bind to doubly phosphorylated ITAMs is also related to the structure of their linker region between the tandem SH2 domains and the kinase domain, which is frequently referred to as interdomain B. The prevalent splice form of Syk contains a 23-amino acid insert in this region, which is not found in Zap or a less abundant splice form of Syk, SykB (291). The presence of this insert clearly correlates with a higher ability to bind to phosphorylated ITAMs and to transduce signals from ITAM-bearing receptors (292), although mechanisms mediating the effects of this insert remain unclear.

The described differences between Syk and Zap are likely to be linked to their distinct biological functions. First, Zap is regulated more stringently than Syk is. Whereas binding of Zap to ITAMs and its activation are strictly dependent on prior stimulation of Src-family PTKs in response to receptor ligation, Syk appears to be able to phosphorylate ITAMs and induce signal transduction in the absence of help from Src-family PTK (see above). Therefore, the functions of Syk show some similarities to those of Src-family PTKs. Indeed, Syk, but not Zap, can reconstitute T-cell signaling disrupted by the absence of Lck (293). Likewise, Syk can mediate T-cell signaling in the absence of TCR ligation, whereas Zap requires TCR ligation to induce signaling (294).

Furthermore, Zap appears to be exclusively a lymphoid kinase, whereas Syk is expressed ubiquitously and the list of its functions outside the lymphoid and even hematopoietic tissue is constantly expanding (250). An interesting example of a non-hematopoietic function of Syk is provided by its participation as a tumor suppressing protein in the development of breast cancer (295).

The results of studies using targeted disruption of *zap* and *syk* genes are consistent with the findings described above. Mice lacking Zap show a deficiency localized specifically to the T-cell lineage, they have no mature T cells (296, 297). NK cells, which also express Zap in wild-type animals, are not affected by Zap deficiency (296). In contrast, disruption of *syk* induces multiple defects, including severe hemorrhaging, that result in embryonic lethality (298, 299). In addition to this, Syk deficiency impairs development of various hematopoietic cells, including B cells (298-300). This effect of Syk deficiency on B-cell development is consistent with the critical role of Syk in BCR-induced signaling (75, 257, 259, 276, 301).

Although Syk can mediate TCR-induced signaling in multiple experimental systems (see above), and its forced overexpression can rescue T-cell development in Zap-negative animals (302), it is not essential for T-cell development (reviewed in (303)). The lack of effect of Syk on T-cell

maturation is likely due to a dramatic decrease in its level early in T-cell development (304).

The kinase activity of Syk-family PTKs, like that of Src-family PTKs, is regulated by their tyrosine phosphorylation. However, unlike Src-family PTKs, Zap and Syk have a large number of tyrosine phosphorylation sites that affect the functions of these PTKs in various ways.

The primary autophosphorylation sites of Zap appear to be the three residues located in the interdomain B, tyrosines 292, 315 and 319 (human sequences are used for numbering residues in Zap and Syk) (305, 306), corresponding to tyrosines 323, 348 and 352 of human Syk, which are also autophosphorylated (307, 308). Furthermore, these sites in Syk can be phosphorylated by Lyn, a Src-family PTK (308). Phosphorylation of the interdomain B sites is not essential for kinase activity of either Zap or Syk (267, 309, 310), playing instead an important regulatory role.

Cells expressing Y292F mutant Zap or the analogous Y323F Syk demonstrate hyperactive signal transduction and biological responses to TCR, BCR and FcepsilonRI receptor ligation (308, 311-314). Therefore, Tyr-292 of Zap/Tyr-323 of Syk is a major negative regulatory site. The mechanism of this negative regulation, is unlikely to be related to a decrease in the intrinsic enzymatic activity of these PTKs (311) and appears to involve binding of a negative regulator of PTKs, c-Cbl, to this site (315-317). For Syk, this negative effect of c-Cbl has been shown to be dependent on the E3 ubiquitin-protein ligase activity of c-Cbl and mediated by ubiquitylation of the activated form of Syk followed by its proteosomal degradation (316, 327, 328). This mechanism might also be involved in the c-Cbl-dependent inhibition of Zap, although this possibility has not been shown directly.

In contrast, phosphorylation of Tyr-319 has a positive effect on Zap-mediated signaling. First, it appears to mediate interactions of Zap with Lck (306, 318, 319) and PLC-gamma1 (319). Furthermore, this site is essential for tyrosine phosphorylation of Zap-specific substrates and multiple downstream signaling events mediated by Zap (306, 318-320).

The role of Tyr-315 of Zap is not very clear. One report argues that this residue might be involved in the interactions of Zap with Vav and in tyrosine phosphorylation of Zap-specific substrates (320), but this has not been seen in the other studies (306, 321).

Consistent with the role of Tyr-319 and Tyr-315, phosphorylation of tyrosines 352 and 348 in the linker region of Syk is not required for the activity of this PTK, but is essential for its binding to PLC-gamma1 its ability to phosphorylate PLC-gamma1 *in vivo* (267).

Tyrosines 492 and 493 of Zap are major sites of its phosphorylation by Lck (305). The Y493F mutation does not affect basal activity of Zap, but abrogates its ability to be activated by Lck (this activation is approximately 10-fold for wild-type Zap) and to induce antigen receptor-mediated signaling and biological responses in lymphocytes (277, 278, 312). In contrast, the Y492F mutation increases basal activity of Zap (277) and its ability to induce antigen receptor-mediated signaling and responses (312). Hence, Tyr-492 and -493 play in the activation of Zap a negative and a positive regulatory role, respectively.

In contrast to phosphorylation of tyrosines 492 and 493 of Zap by Lck, the corresponding tyrosines 525 and 526 of Syk are autophosphorylated (307, 308). Although consequences of phosphorylation of Tyr-525 and -526 of Syk are less studied than those for Tyr-492 and -493 of Zap, it appears that their phosphorylation is unlikely to significantly affect the intrinsic kinase activity of Syk (267, 322, 323). Despite the lack of this effect, the autophosphorylation sites of Syk are required for Syk-mediated signal transduction and biological responses (259, 267, 322-324). The essential role of Tyr-525/Tyr-526 phosphorylation may be due to binding of proteins that propagate Syk-mediated signaling, for example, Lck (324).

C-terminal tyrosines 629, 630 and 631 of Syk have been shown to be autophosphorylated (307, 308). Mutation of these tyrosines or of those corresponding to them in Zap (Tyr-597 and –598) resulted in the gain-of-function phenotypes of Syk and Zap, as demonstrated by tyrosine phosphorylation of potential targets *in vivo*, elevated intracellular calcium mobilization and promoter activation (325). These results implicate the C-terminal tyrosine residues of Syk and Zap as important negative regulatory sites. Phosphorylation of these residues, like that of the majority of other tyrosine residues of Syk and Zap, does not affect the intrinsic enzymatic activity of these PTKs, but reduces their ability to transmit signals.

With the exception of Tyr-292 of Zap/Tyr-323 of Syk, the mechanisms mediating effects of negative regulatory tyrosines of Zap and Syk remain unclear. However, one may speculate that some of them play their role by interacting intramolecularly with the SH2 domains of the same molecule. Indeed, the deletion of both SH2 domains moderately increases enzymatic activity of Zap *in vitro* and increases its tyrosine phosphorylation *in vivo* (309). The deletion of both SH2 domains also abolishes a lag phase of kinase activity detectable with the full-length Zap (326). However, the addition of recombinant SH2 domains to the truncated Zap lacking SH2 domains restored the lag phase. In contrast, this lag phase can be abolished by the addition of a diphosphorylated ITAM peptide (326).

3.4. Tec

The Tec family of PTKs has five members, all of which are present in human and mouse genomes. Tec-family PTKs have similar domain structures consisting typically of the N-terminal pleckstrin-homology domain (PH) followed by a Tec-homology domain (TH), which is sometimes subdivided into the cystein-rich, Zn^{2+}-binding Btk motif and a proline-rich motif. The PH and TH domains are followed by SH3, SH2 and kinase domains.

Two Tec-family kinases are exceptions from this typical structure. First, TH and SH3 domains of Bmx are significantly modified, so they are sometimes referred to as TH-like and SH3-like domains (329, 330). Second, Txk lacks both PH and TH (331-334), but has, instead, a unique cystein string motif, which can be palmitoylated (335).

Whereas Bmx and Tec are expressed in multiple tissues and cell types, both hematopoietic and non-hematopoietic, other Tec-family kinases show primarily hematopoietic distribution. Itk is expressed mainly in T and NK cells. Btk is expressed in B lymphocytes and cells of erythromyeloid lineage. Txk is expressed primarily in T and mast cells (reviewed in (330, 336)).
Tec-family PTKs typically lack an acylation site and are, therefore, localized in the cytosol in the absence of stimulation (330, 336). However, they can re-localize to the membrane following cell stimulation, because cell stimulation typically causes activation of PI-3' kinase, producing phosphoinositides containing a phosphate in the position 3 of their inositol ring, to which a PH domain binds with very high affinity (337-341). Such membrane localization is highly transient, since these phosphorylated lipids are short-lived. Indeed, Btk becomes constitutively membrane-localized when PTEN, a lipid phosphatase dephosphorylating PI-3' kinase products, is defective (342, 343).

Txk, which has an unusual structure, also shows the unusual subcellular distribution. The cystein string-containing palmitoylated form of Txk is membrane-localized. The alternative initiation form of Txk, which does not have the cystein string, is localized in the nucleus (335). Recently, Btk has also been found in the nucleus. Nuclear translocation of Btk is facilitated by the loss of PH or SH3 domains (344). Similarly, Itk has been found to localize to the nucleus, and this localization is upregulated by TCR ligation (345). It is unclear whether other Tec-family PTKs can translocate to the nucleus in a similar manner. It is however apparent that PH, TH, SH3 and SH2 domains of Tec-family PTKs may regulate their functional interactions with multiple proteins (reviewed in (330, 336)).

Tec-family PTKs participate in multiple signaling pathways. They have been shown to become activated in response to MIRR ligation (346-349) and to mediate MIRR-induced signaling that involves adaptor proteins BLNK and SLP-76, PLC-gamma, Ca^{2+} mobilization and Ca^{2+}-induced events (350-362). Itk and Tec are also activated by the ligation of CD28, an important T-cell co-receptor molecule (363, 364). This activation leads to multiple downstream effects, which are specific for individual PTKs. These effects include activation of PLC-gamma, Ca^{2+} mobilization, and activation of IL-2 and IL-4 promoters (355, 364-367). Tec-family PTKs have also been shown to become activated through various cytokine receptors (368-371), G protein-coupled receptors (372, 373) and integrins (373, 374).

In addition to the triggering of Ca^{2+}-mediated signaling in response to MIRR ligation, which appears to be studied in most detail, Tec-family PTKs mediate signaling that leads to the activation of NF-kappaB (375-377), the Akt kinase (378), Stat transcription factors (379-382), Rho-family GTPases (372, 383) and integrins (384).
The important role of Tec-family PTKs in signaling is supported by the phenotype of deletion and loss-of-function mutants. It should be noted that the lack of functional Btk causes a severe human disease, X-linked agammaglobulinemia (XLA) (385, 386). Patients with XLA essentially lack B cells and immunoglobulins. The targeted disruption of Btk in mice is consistent with these findings, leading to a decrease in the number of B cells and the levels of immunoglobulins, although the phenotype of *btk*-null mice is substantially milder than that of XLA (387). Inactivation of the *tec* gene does not generate a distinct phenotype, but the double *btk*/*tec*-null mutation results in a more severe B-cell phenotype than the single *btk* knock-out, which is still milder than the XLA phenotype (388). Inactivation of the *itk* gene in mice results in a mild T-cell phenotype characterized by a decrease in the numbers of mature T cells and their lower responsiveness to TCR-mediated stimulation (389). This phenotype is exacerbated when *txk* is also inactivated (390). The *bmx* knock-out mice do not demonstrate an overt phenotype (391).

The functions of Tec-family PTKs are regulated by several very distinct mechanisms, including their tyrosine phosphorylation. It has been shown that intramolecular interactions between an SH3 domain and a proline-rich region are likely to yield an inactive conformation in Itk (392). Furthermore, interactions between these domains of Tec-family PTKs may lead to dimerization of these kinases (393, 394), which may also play a negative regulatory role. It is possible that the two proline-rich motifs of the proline-rich regions are differentially involved in intra- and inter-molecular interactions with SH3 domains (395). Consistent with these findings, a deletion of SH3 constitutively activates Tec (396). It is thought that these inhibitory interactions are disrupted, when the PH domain of Tec-family PTKs binds to phosphoinositides, G-proteins, or other PH ligands. Furthermore, the association of PH domains of Tec-family PTKs to phosphoinositides or G-proteins results in the membrane translocation of these kinases, which appears to be another critical event in their physiological activation. Indeed, PI-3' kinase has been shown to be a critical upstream regulator of Tec-family PTKs in multiple systems (362, 371, 397-400). In agreement with these findings, the constitutive production of PH-binding lipid products of PI-3' kinase in PTEN-deficient cells (343), as well as the modification of Tec-family PTKs with a membrane-interactive site (401, 402), activates Tec-family PTKs and facilitates signaling mediated by them. In addition, the adaptor protein Lat and Zap, a PTK that phosphorylates Lat in T cells, have been shown to be essential for the activation of Itk in T cells (273, 274). Binding of the SH2 domain of Itk to tyrosine phosphorylated Lat appears to mediate the effect of Lat on Itk activation (274). Similarly, BLNK appears to mediate activation of Btk by Syk (275).

The membrane translocation of Tec-family PTKs facilitates phosphorylation of the activation loop tyrosine residue in these kinases, this tyrosine is homologous to Tyr-419 of human Src (Tyr-551 and -517 in human Btk and Itk, respectively), and its phosphorylation activates Tec-family PTKs (349, 403-407). This activation results in autophosphorylation of Tyr-223 (numbering for Btk) within the SH3 domain, which disrupts the inhibitory interactions between the SH3 domain and the TH domain proline-rich region, thus further enhancing protein phosphorylation by Tec-family PTKs (408).

3.5. Jak

The Jak (or Janus) family of PTKs has four members, all of which are present in human and mouse genomes. Jak-family PTKs differ markedly from other PTKs by the presence of two kinase domains, which are both located in the C-terminal half on the molecule. Only the C-terminal-most domain is functional, the other one thus being a pseudokinase domain (reviewed in (409, 410)). The N-terminal region of Jak-family PTKs contains several highly conserved sequence stretches, which were originally termed JH domains (reviewed in (409)). It has been shown recently that some of these sequences represent the FERM (see Section 3.6) and SH2 domains of Jak-family PTKs.

Jak-family PTKs lack an acylation site and, hence, are localized in the cytosol in the absence of stimulation. However, these PTKs are bound to multiple membrane receptors in the absence of stimulation and, in many cases, additionally recruited to these receptors following their ligation ((411-419), reviewed in (409, 410)). This binding is mediated by the N-terminal region of Jak PTKs (420-425). The interactions of Jak-family PTKs and membrane receptors play a crucial role in the biological function of these PTKs, which mediate signaling induced by most interleukins, all interferons, and multiple other cytokines and colony-stimulating factors, as well as by some growth factors and hormones. Tyk2, Jak1 and Jak2 mediate signaling through a wide variety of receptors, whereas the involvement of Jak3 is more specific, it is involved in signaling induced by IL-2, IL-4, IL-7, IL-15 and G-CSF ((411-416, 426-428, 429 9486, 430-444), reviewed in (409, 410)).

The specificity of the involvement of Jak-family PTKs in receptor-mediated signaling is also reflected in their expression pattern. Tyk2, Jak1 and Jak2 are expressed ubiquitously, whereas Jak3 is expressed primarily, although not exclusively, in hematopoietic cells (reviewed in (409, 410)).

The involvement of Jak-family PTKs in receptor-mediated signaling is due to their binding to the corresponding receptors and their further recruitment to these receptors following ligation of the latter. The recruitment of Jak-family PTKs to the corresponding receptors appears to result in their tyrosine phosphorylation and activation, which results, in turn, in specific tyrosine phosphorylation of these receptors that generates docking sites for Stat-family transcription factors and other SH2-containing proteins ((411-416, 427, 429 9486, 430-442, 444), reviewed in (409, 410)). Stat-family proteins become phosphorylated on tyrosine following their binding to the receptors, form homo- or heterodimers mediated by phosphotyrosine-SH2 interactions, relocate to the nucleus and activate transcription controlled by the corresponding DNA elements (reviewed in (445-447)). Although Jak-family PTKs are, to a certain degree, capable of phosphorylating Stat's, it appears that Stat's are tyrosine-phosphorylated primarily by Src-family PTKs (105, 448), whereas the major role of Jak-family PTKs appears to be the generation of docking sites for Stat's and, possibly, Src-family PTKs on the corresponding receptors.

The crucial role of Jak-family PTKs in cell signaling is supported by the phenotype of the Jak-negative mice. The targeted disruption of Jak1 or Jak2 is lethal (449-451). Jak3-deficient mice are viable, but immunodeficient, exhibiting profound defects of lymphoid cell development (452-454). These defects drive, in turn, hyperexpansion of myeloid lineage (455). Furthermore, mutations in Jak3 that disrupt normal Jak3-mediated signaling have been found in several patients with autosomal severe combined immunodeficiency (425, 456).

The functions of Jak-family PTKs are regulated by several distinct mechanisms. Receptor-mediated activation of a Jak-family PTK is induced by tyrosine phosphorylation of its activation loop as a result of its auto(trans)phosphorylation or phosphorylation by other PTKs that may or may not belong to the Jak family. Two adjacent tyrosine residues become phosphorylated in the activated loop of several Jak-family PTKs. Phosphorylation of these tyrosines, especially that of the more N-terminally located one, appears to be required for a ligand-induced increase in the activity of Jak-family PTKs (457-459).

The tyrosine phosphorylation-mediated activation of Jak-family PTKs is negatively regulated by several protein-tyrosine phosphatases, such as SHP-1 and -2, SH-PTP1, SHPeC, and TC-PTP (460-466). Interactions of Jak-family PTKs with these phosphatases may be mediated by their direct binding independent of SH2 or phosphotyrosines or by the recruitment of these phosphatases to the corresponding receptors phosphorylated on tyrosine by Jak-family PTKs. The latter mechanism may represent a negative feedback loop that rapidly dampens an increase in Jak-family PTK activity.

Furthermore, Jak-family PTKs appear to be negatively regulated by proteosome-mediated degradation in a manner similar to that of Src- and Syk-family PTKs (467, 468). However, this regulatory mechanism is less studied for Jak-family PTKs than for those of Src and Syk families.

Another negative feedback loop that regulates Jak-mediated signaling appears to be specific for these signaling pathways. Jak-mediated activation of Stat's induces expression of multiple genes, including those encoding for small SH2-containing proteins referred to as COCS, CIS, SIS or JAB (reviewed in (409, 469, 470)). Different proteins of this family negatively regulate Jak-

mediated signaling by various mechanisms, including binding to the tyrosine phosphorylated receptors that blocks recruitment of signaling molecules to these receptors and binding to the phosphorylated activation loop of Jak-family PTKs that directly inhibit their catalytic activity.

3.6. Fak

The Fak family of PTKs has two members, both of which are present in human and mouse genomes. Fak, the prototypical family member, is expressed ubiquitously, whereas the second PTK of this family, referred to as Pyk2, Cak-beta, Cadtk, Raftk, or Fak2, is primarily expressed in brain and, to a lower extent, in liver, lung, kidney and hematopoietic cells (471-478).

The catalytic domain of Fak-family PTKs is flanked with extensive N- and C-terminal sequences. The N-terminal region of Fak-family PTKs contains the FERM domain, which is also present in talin and other cytoskeletal proteins and is capable of mediating interactions of these proteins with transmembrane receptors. It is possible that the FERM domain of Fak mediates the interactions of Fak with integrins and/or receptor PTKs (479-482). The C-terminal region of Fak-family PTKs also possesses a region implicated to focal adhesion targeting of Fak (FAT domain) (483-485). It is possible that the FAT-dependent targeting of Fak to focal adhesions is mediated, at least partially, by paxillin (483, 486, 487). Talin was also proposed as a mediator of this targeting (488). Finally, the C-terminal region of Fak-family PTKs contains two SH3-binding sites. These sites mediate binding of Fak and Pyk2 to several proteins, including Cas, which is likely to be important for their functions (489-492). Interestingly, two alternatively spliced isoforms of Pyk2 specific for either hematopoietic cells or the brain have been described that differ by the presence of an insert between the SH3-binding sites (493, 494).

Although both Fak and Pyk2 contain the FERM and FAT domains and in spite of the fact that Fak and Pyk2 bind to several identical proteins, their subcellular localization is different. Whereas Fak can localize to focal adhesions, the localization of Pyk2 is diffuse. This is unlikely to be a reflection of the intrinsic inability of the corresponding Pyk2 domains to interact with focal adhesions (488, 493, 495, 496), but might be caused by the specific cytoplasmic interactions of Pyk2. Some results also argue that the ability of Pyk2 to reorganize the cytoskeleton is inhibited *in vivo* by Fak (497).

The differences in subcellular localization of Fak and Pyk2 correspond to the differences in their functions. Fak is activated following integrin stimulation through a mechanism requiring the focal adhesion targeting of Fak and apparently involving Rho as an upstream signaling element (reviewed in (498, 499)). Activation of Fak appears to trigger multiple signaling pathways, including the MAP kinase cascade (reviewed in (498-500)). The major biological function of Fak signaling is likely to be the regulation of disassembly of focal adhesions (501-503). It is possible that this effect of Fak is due to the Fak-dependent inhibition of Rho GTPase (503). Furthermore, it has been well documented that Fak plays a critical role in cell migration (reviewed in (498, 499)). These functions are naturally linked, since the focal adhesion turnover is essential for cell migration. Other possible functions of Fak include positive regulation of cell cycle (504) and survival (505-507).

Unlike Fak, Pyk2 can be activated in a Ca^{2+}-dependent fashion by multiple stimuli that elevate the intracellular level of free Ca^{2+}, as well as by some stress signals. Activation of Pyk2 results in triggering several signaling pathways, including the MAP kinase cascade. The ability of Pyk2 to respond to Ca^{2+} facilitates its function as a link between heterotrimeric G protein-coupled receptors and downstream signaling pathways, such as the MAP kinase cascade (reviewed in (508, 509)) and the I-kappaB/NF-kappaB system (510). Furthermore, in some cases Pyk2 may act opposite to Fak, as it happens in the regulation of cell cycle progression, which is promoted by Fak, but inhibited by Pyk2 (511). Biological functions of Pyk2 remain to be characterized further. Considering that Pyk2 is most abundantly expressed in the brain, its recently described roles in neuronal differentiation (512) and the development of long-term potentiation in neurons (513) appear to be important.

In spite of these differences, Pyk2 and Fak phosphorylate a common set of proteins including tensin, paxillin, and Cas (495), and their functions appear to be redundant to some extent. Thus, tyrosine phosphorylation of Pyk2 was enhanced by integrin stimulation in Fak-deficient cells (514, 515). Furthermore, Pyk2 enhanced adhesion-stimulated activation of Erk in Fak-deficient cells (515). Finally, although wild-type Pyk2 did not restore normal migration of Fak-deficient cells (496, 515), an engineered form of Pyk2 capable of binding to focal contacts could reconstitute it fully (496).

Fak-deficiency is embryonic-lethal in mice (501) due to profound developmental abnormalities similar to those caused by the lack of fibronectin (516). Cells obtained from Fak-deficient mouse embryos demonstrated a significant decrease in motility (501, 517). In contrast, Pyk2-null mice are viable, although B-cell development in these mice is defective (518)

The regulation of Fak functional activity is primarily mediated by tyrosine phosphorylation. It appears that the tyrosine residue of Fak phosphorylated upon integrin stimulation is its major autophosphorylation site, Tyr-397 (120, 125, 519, 520). This tyrosine is located outside the kinase domain and is, in its phosphorylated form, a docking site for the SH2 domains of several proteins, including Src-family PTKs (125, 521-523). Upon binding to Fak, Src-family PTKs phosphorylate tyrosines 576 and 577 inside the activation loop of the catalytic domain of Fak, thus enhancing the kinase activity of Fak to its maximal level (520). In addition, several other sites of tyrosine phosphorylation have been identified (Tyr-407, -861, -925) (520, 524, 525). These phosphotyrosines are likely to act as docking sites for Fak-binding proteins. Thus, phosphorylated Tyr-925 has been shown to bind to

Grb2 (524, 525). Sites corresponding to four of the identified sites are also phosphorylated in Pyk2, whereas Tyr-407 and -861 sites appear to be unique for Fak (526). Furthermore, Pyk2 appears to be phosphorylated on tyrosines other than the four currently identified sites (527). Finally, four serine phosphorylation sites have been mapped to the C-terminal domain of Fak. Some of these sites are hyperphosphorylated during mitosis, and this hyperphosphorylation correlates with a decrease in Fak activity (528).

The events that triggers activation of Pyk2 are very different from those of Fak, Pyk2 is positively regulated by Ca^{2+} and, therefore, activated by a variety of stimuli that elevate the intracellular level of free Ca^{2+} (reviewed in (509)). It should be noted that in spite of the ability of Pyk2 to respond to Ca^{2+}, its activation requires the intact actin cytoskeleton (reviewed in (509)). This connection may be due to the ability of Rho to regulate Pyk2 in an F-actin-dependent fashion (529).

Multiple protein tyrosine phosphatases, including Shp-2 and PTP1B, may be involved in the negative regulatation of Fak. Furthermore, PTEN, a phosphatase better known for its lipid dephosphorylation activity, has been implicated in the negative regulation of Fak (reviewed in (499)). Protein tyrosine phosphatases are likely to be involved in the regulation of Pyk2, as well (530, 531). Negative regulation of both Fak and Pyk2 may also be mediated by the FIP200 protein, which can bind to these PTKs and inhibit their catalytic activity *in vitro* (532).

Finally, negative regulation of Fak and Pyk2 may be mediated by an unusual mechanism based on the autonomous expression of their C-terminal domains, referred to as Frnk and Prnk (Fak- and Pyk2-related non-kinases) (493, 533). Frnk is a translation product of the specific mRNA that is transcribed from the alternate promoter located inside the genes encoding for Fak (534). The effects of Frnk and Prnk in several experimental systems (493, 535-537) suggest that they may function as natural inhibitors of the corresponding PTKs.

3.7. Abl

The Abl family of PTKs consists of two members, Abl and Arg, both of which are present in human and mouse genomes and are expressed ubiquitously with the highest levels detected in the thymus, spleen and testes for Abl and in the brain for Arg (538-545).

The structure of Abl, a prototypical member of the Abl family, is similar to that of Src-family PTKs within its N-terminal region, which includes one SH3, one SH2, and one tyrosine kinase domain. Unlike Src-family PTKs, Abl has no C-terminal negative regulatory site, but instead possesses a large C-terminal region containing multiple functional sites. Immediately following the kinase domain is a proline-rich region followed by a DNA-binding domain. The most C-terminal portion of Abl is an actin-binding domain. The C-terminal region contains three nuclear localization signals (NLS) and one nuclear export signal (NES) (reviewed in (546-548)). Arg demonstrates a high sequence similarity to Abl within the N-terminal region encompassing SH3, SH2 and kinase domains (over 90%), but only moderate within the C-terminal region (29% overall), with 56% in the last 60 amino acids (540). Some critical elements of structure, such as the SH3-binding sites and the actin-binding domain, are conserved in Arg (549, 550). Furthermore, both Abl and Arg genes contain two alternative 5' exons, generating two variant proteins referred to as 1a and 1b. The latter contains an N-myristoylation site similar to that in Src-family PTKs, which enables it to localize to the membrane (reviewed in (548, 551)).

Localization of Abl is complex and is regulated by multiple elements of its structure. The majority of cell types demonstrate predominant localization of Abl to the nucleus with a significant amount of it present also in the cytoplasm, where much of Abl is bound to the membranes and actin filaments. In hematopoietic cells and neurons Abl is predominantly cytoplasmic. Arg appears to be exclusively cytoplasmic ((544, 552-555), reviewed in (547, 548, 551)). Nuclear localization of Abl is controlled by its NLS and NES sites (556, 557). Membrane localization of Abl is dependent on a myristoylation site (558, 559), whereas Abl association with the actin cytoskeleton is mediated primarily by its actin-binding domain (560, 561). The cytoplasmic localization of Arg is similar to that of Abl. First, the splice isoform 1b of Arg possesses the N-myristoylation site (555). Second, Abl and Arg have been shown to co-localize with each other and with the actin filaments (544). The subcellular localization of Abl appears to be dynamic. Thus, Abl demonstrates transient re-localization from the nucleus to focal adhesions upon re-attachment of suspended fibroblasts (562).

The characteristic subcellular localization pattern of Abl argues that it may be involved in the regulation of cellular processes associated with the nucleus (reviewed in (547)). Thus, Abl has been implicated in transcription based on its ability to phosphorylate the C-terminal domain of RNA polymerase II (563, 564) and to interact with several proteins known to regulate transcription, such as p53 (565). Furthermore, several studies have argued that Abl participates in the signaling pathway, which is induced by DNA damage and regulates DNA recombination and repair (566-569). Furthermore, it has also been proposed that Abl is involved in the cell cycle through its ability to negatively regulate the G1/S transition (556, 565, 570-574). Finally, Abl may be involved in the regulation of apoptosis. The evidence has been presented to support both a pro-apoptotic (573-575) and anti-apoptotic role (576) for Abl. It is not clear whether Arg plays any role in the nucleus, because it appears to localize to the cytoplasm. However, it has been shown that Arg, like Abl, can phosphorylate the C-terminal domain of RNA polymerase II (577).

In the cytoplasm, the majority of Abl is associated with the actin cytoskeleton through its C-terminal actin-binding domain (560, 561). Furthermore, re-attachment of trypsinized fibroblasts causes transient activation of Abl and its translocation to focal adhesions (562), as well as its binding to paxillin, which is a substrate

of Abl and a major component of focal adhesions (578). These findings argue that Abl is involved in the cytoskeleton regulation. This involvement may be mediated by the adaptor protein Crk, whose protein-binding activity is negatively regulated by Abl (579), it has been shown that Abl disrupts interactions of Crk with paxillin and Cas and, as a consequence, affects cell adhesion and migration (580, 581). Another possible target of Abl involved in the regulation of cytoskeleton rearrangements and cellular morphogenesis is delta-catenin, a potent substrate of Abl (582). The effects of Abl on the cytoskeleton and morphogenesis appear to be induced not only by integrins, but also by various receptor PTKs (580, 583, 584). The last of these studies indicated considerable similarities between the interactions of Abl and Arg with Eph receptor PTKs. Although little is known about the functions of Arg as compared to Abl, these results, as well as those obtained using cells lacking Abl and Arg (see below), suggest that some functions of these PTKs overlap.

Finally, it should be noted that all deregulated oncogenic forms of Abl, such as v-Abl and Bcr-Abl, causing cell transformation in experimental and real pathological situations, are cytoplasmic (reviewed in (551)). These findings further support the importance of cytoplasmic c-Abl for cell activation and argue that its functions are unlikely to be restricted to the cytoskeletal regulation.

Targeted disruptions of Abl-family PTK genes confirmed their biological importance and outlined their specific biological functions. The loss of Abl is lethal, and many *abl*-null mice show thymic and splenic atrophy and T- and B-cell lymphopenia (542). Furthermore, mice homozygous for the mutant form of Abl lacking the C-terminal region demonstrate a very similar phenotype, including the increased perinatal mortality and abnormal spleen and B-cell development (585). (This study provides evidence not only for the importance of Abl, but also argues that the C-terminal region is essential for the biological functions of Abl.) In contrast, *arg*-null mice developed normally, but exhibited multiple behavioral abnormalities (544). Deficiency in both Arg and Abl resulted in embryonic lethality, which was associated with profound alterations of the actin cytoskeleton in *arg*/*abl*-null cells (544).

The model of Abl-family regulation is based on Abl, a prototypical family member, since little is known about the regulation of Arg. A characteristic feature of Abl regulation is that *in vivo* its wild-type form is not tyrosine-phosphorylated and induces no tyrosine phosphorylation of other proteins under non-stimulated conditions (558, 586, 587). This tight regulation appears to be mediated by the SH3 domain of Abl, since mutations affecting this domain resulted in an increase in Abl kinase activity *in vivo* and its transformation potential (558, 586-588). It is not entirely clear whether the Abl SH3 domain down-regulates the activity of Abl because of intermolecular interactions with SH3-binding inhibitor proteins acting in *trans*, or because of intramolecular interactions of this domain with SH3-binding sites of Abl. The lack of a difference in *in vitro* kinase activities between wild-type c-Abl and deregulated oncogenic forms of Abl reported in several studies (558, 587, 588) argued in favor of the intermolecular mechanism. Several Abl-binding proteins, such as 3BP1, 3BP2, Aap1, Abi-1, Abi-2, and Pag, have been implicated in the regulation of Abl activity, but their roles in this phenomenon remain to be elucidated ((589-594), reviewed in (548)).

The recent findings indicating significant differences in kinase activity *in vitro* between wild-type Abl and its constitutively active forms (595, 596) argued that the Abl SH3 domain can inhibit Abl kinase activity through an intramolecular interaction. Further studies argued that this interaction is likely to be mediated by the proline-rich linker region of Abl located between its SH2 and kinase domains (597).

Tyrosine phosphorylation of Abl, like that of other PTKs, appears to play an important role in its enzymatic activation. Autophosphorylation of Abl on tyrosine 412 in the activation loop significantly increases its kinase activity (595). Some role in Abl activation, albeit a weaker one than that of Tyr-412, is played by Tyr-245 located inside the linker region between the SH2 and kinase domains (595). The autophosphorylation of Abl is concentration-dependent (595) indicating its intermolecular nature, when Abl molecules phosphorylate each other. The phosphorylation of the positive-regulatory Tyr-412 can be achieved not only by Abl itself, but also by heterologous PTKs, such as Src (583).

3.8. Fes

The Fes family of PTKs has two members, Fes (also referred to as Fps) and Fer, which are present in both human and mouse genomes. The members of this family are highly homologous and consist of an N-terminal FCH domain followed by three coiled-coil regions, an SH2 domain in the central part of the protein, and a kinase domain in the C-terminal region (reviewed in (598, 599)). Fes is highly expressed in cells of the myeloid lineage, but also in endothelial, epithelial and neuronal cells (600-604). Fer is expressed ubiquitously (605).

Fes-family PTKs lack any membrane-attachment sites and are localized primarily to the cytosolic fraction (604, 606, 607). Furthermore, it has been shown that a substantial fraction of Fes is localized to the *trans*-Golgi vesicular network (604, 607). Binding of Fes to cytoskeletal components, including Cas, has also been shown (608), suggesting that Fes may be associated with the cytoskeletal structures. The FCH domain of Fes-family PTKs is capable of binding to tubulin (reviewed in (599)), thus further arguing in favor of the possible cytoskletal localization of Fes-family PTKs. Nuclear localization of Fes and Fer was also reported (609, 610), but this observation could be an artifact related to their perinuclear localization to the *trans*-Golgi network.

Multiple retroviral oncogenes contain Fes and Fer sequences, and activated forms of Fes and Fer can mediate cellular transformation (reviewed in (598, 599)). These

findings argued that Fes-family PTKs may play an important role in cell physiology. Indeed, physical interactions of Fes with multiple cytokine receptors and its ligand-induced activation through these receptors, including those for IL-3, IL-4 and GM-CSF, has been shown (611-616). Although these findings would be consistent with an important role of Fes in hematopoietic cell development, mice targeted with either a kinase-inactivating mutation or a null mutation in *fes* developed normally, demonstrating no significant defects (617-619), thus arguing against the essential role of Fes in hematopoiesis. However, the targeted mutation of *fes*, resulting in production of the truncated Fes lacking both SH2 and kinase domains, results in hyperproliferation of early myeloid cell and causes embryonic lethality correlating with multiple developmental defects, the most striking being cardiovascular abnormalities, which is consistent with the endothelial expression of Fes (620). Furthermore, regardless of whether or not the role of Fes in hematopoiesis and overall development is essential, it appears to be involved in the regulation of inflammatory response (619).

Ligation of PDGF receptor causes tyrosine phosphorylation of Fer and its association with PDGF receptor in fibroblasts followed by Fer-dependent tyrosine phosphorylation of cortactin, which is known to inhibit the actin crosslinking activity of this protein (621-623). Furthermore, the involvement of Fer in the regulation of adherens junctions and focal adhesions during neurite outgrowth (624, 625) and fibroblast adhesion (626) has been demonstrated. These biological functions of Fer appear to be mediated by its effect on the N-cadherin/catenin/Cas system. In spite of the apparent involvement of Fer in growth-factor signaling and cell adhesion and migration, mice expressing a targeted kinase-inactivating mutation in *fer* developed normally (621, 627). However, the studies with mutant mice indicate that Fer, like Fes, may be involved in the regulation of inflammatory response (627).

Recent results obtained using mice carrying targeted inactivating mutations in both *fes* and *fer* further supported that these PTKs may play an important role in the regulation of inflammation by upregulating expression of IL-10, an immunosuppressive cytokine, while not being essential for viability (599). These double-mutant mice also demonstrated defects in migration of mast cells, supporting the results obtained with *fer*-mutant mice (628).

Like most other PTKs, Fes-family PTKs have a conserved tyrosine in the activation loop (Tyr-713 or –715 in Fes and Fer, respectively), which serves as their autophosphorylation site (599, 629-633). The lack of autophosphorylation at Tyr-713 inhibits Fes dramatically (630). Another autophosphorylation site has been mapped in the kinase domain of Fes (Tyr-811) (632). It is likely that the N-terminal region of Fer possesses an additional tyrosine phosphorylation site (634). Tyrosine phosphorylation of Fes-family PTKs is likely to be mediated not only by their autophosphorylation, which is intermolecular (632), but by other PTKs as well. Thus, it has been shown that the level of tyrosine phosphorylation of inactivated Fer is increased in response to PDGF receptor ligation (621).

The role of tyrosine phosphorylation sites, other than Tyr-713/715, in the regulation of Fes-family PTKs is unclear. At least, the negative regulation of kinase activity of these PTKs by tyrosine phosphorylation, similar to that observed in Src-family PTKs, appears unlikely. In contrast, the Fes SH2 domain appears to be essential for kinase activity of Fes *in vitro* and *in vivo* (630, 635). Therefore, interactions of the SH2 domains of Fes-family PTKs with their kinase domains may stabilize the active kinase structure.

Autophosphorylation of Fes occurs in *trans* (632) and, therefore, should be affected by oligomerization. Indeed, both Fes and Fer are capable of forming oligomers through the interactions of their coiled-coil domains (621, 622, 636, 637). The effect of these interactions on Fes and Fer may be different, since mutations in their coiled-coil domains activated Fes (637), but did not affect autophosphorylation of Fer (621). However, the importance of these interactions is supported by the finding that the truncated form of Fes possessing only the FCH and coiled-coil (in contrast to its kinase-inactive form - see above), causes embryonic lethality in mice (620). It is possible that this fragment of Fes disrupts oligomerization of endogenous Fer, thus functioning as a dominant-inhibitory protein. It is clear, however, that the effects of coiled-coil domains may not be restricted to the oligomerization of Fes-family PTK and may play other roles, such as mediating interactions of these PTKs with other coiled-coil proteins.

3.9. Frk

The Frk family of PTKs has three members, Frk, Brk, and Srm. Frk and Brk have been cloned independently from human, mouse and rat cells by several laboratories, and therefore multiple names for these PTKs are used, Frk is also known as Rak, Bsk, Iyk, and Gtk (638-642), whereas Brk is also known as PTK6 and Sik (643-645). Srm was cloned and studied only in mice (646), but its ortholog is present in the human genome, as well. Frk-family PTKs are highly homologous to Src-family PTKs, even more so than are Csk-family PTKs (1). The domain structure of Frk-family is very similar to that of Src-family PTKs, consisting of a highly divergent N-terminal sequence followed by an SH3 domain, an SH2 domain, and a tyrosine kinase domain.

Unlike Src-family PTKs, most Frk-family PTKs lack the N-myristoylation site. The only exception from this rule is rodent Frk, which retains the glycine residue in position 2 and, as a consequence, is myristoylated and localized to the membrane (642). Due to the lack of an N-myristoylation site, Frk-family PTKs (with the exception of rodent Frk) are not targeted to the membrane. In contrast, Frk is localized to the nucleus (639). Recently, nuclear localization has also been reported for Brk (647).

The divergence between the Src and Frk families of PTKs is not restricted to the lack of the N-myristoylation

site. The structural analysis of *brk* gene demonstrated that its exon-intron structure is different from that of other genes encoding for non-receptor PTKs, including Src-family PTKs (648, 649).

Expression of Frk has been detected in the epithelium of small intestine, in liver, kidney, lung, skeletal muscle and, to a very low extent, in mammary epithelium during the estrus cycle and early pregnancy, but never in brain, heart, testis or hematopoietic cells (638-642). Epithelial expression of Frk is dramatically upregulated in tumors, such as hepatocellular, breast and colon carcinomas (638, 641). It has also been found in B and T lymphomas in spite of its absence from normal hematopoietic cells (638). Brk has been found in skin, liver, and the intestinal tract, but not in spleen, kidney, liver, testis, lung, muscle or brain (644, 645, 650, 651). Brk is highly expressed in breast carcinomas, but not in normal breast tissue (644, 651, 652). It is also expressed in some melanomas (643). Therefore, Frk and Brk are expressed specifically in the epithelial cells, primarily those of the intestinal tract, and their expression is dramatically upregulated in epithelial tumors. In contrast, Srm is expressed ubiquitously, although most abundantly, in lung, liver, spleen, kidney and testis (646).

It has been shown that Frk binds to Rb, a cell cycle regulator protein (653). Furthermore, a mutant of Frk lacking putative negative regulatory tyrosine residues inhibits proliferation of fibroblasts and epithelial cells (654, 655). Frk has also been shown to promote neurite outgrowth in PC12 cells through the Crk/C3G/Rap1 pathway (656). These findings hinted that Frk might be involved in the regulation of cell differentiation. However, Frk-deficient mice demonstrated no morphological abnormalities in epithelial tissues, no related metabolic or developmental changes, and no increase in the incidence of spontaneous tumors (657). The only phenotypic change detected in these mice was a slight decrease in the level of circulating thyroid T3 hormone.

Brk has been shown to phosphorylate Sam68, negatively regulating its RNA-binding activity (647). Brk has also been shown to induce transformation of fibroblasts and to sensitize mammary epithelial cells to EGF (658). The latter is likely mediated by the functional interactions of Brk with ErbB3, which enhance EGF signaling via PI-3' kinase/Akt pathway (659).

Functions of Srm are even less clear than those of other Frk-family PTKs. Srm-deficient mice appear to be normal, they demonstrate normal fertility and the lack of abnormalities in the tissues expressing Srm at a high level (646). Overall, the functions of Frk-family PTKs remain to be understood.

An analysis of mouse Brk using mutagenesis, mass-spectrometry and enzyme kinetics indicated that Brk is capable of autophosphorylation, which significantly upregulates its kinase activity (660). This study mapped the autophosphorylation site of Brk to Tyr-342, a conserved tyrosine residue inside the activation loop. Based on this study, one may speculate that this autophosphorylation is a general mechanism of activation for Frk-family PTKs.

Frk and Brk, although not Srm, possess tyrosine residues near their C termini, which might mediate negative regulation of these PTKs in a Src-like fashion. Several studies argue in favor of this hypothesis. First, mouse Frk with both putative negative-regulatory tyrosines mutated to phenylalanines (Y497F/Y504F) inhibits cell proliferation and activates hormone production by pancreatic cells, whereas wild-type Frk shows no effect in these experimental systems (654, 655). Furthermore, the corresponding Y447F mutant of mouse Brk demonstrated the increased kinase activity when overexpressed in epithelial cells (647, 660). The activity of Y447F Brk toward a peptide substrate exceeded that of autophosphorylated wild-type Brk and was independent of autophosphorylation (660). These findings argue that the negative regulation of Brk by tyrosine phosphorylation of its C-terminal tyrosine residue is similar to that of Src-family PTKs. It remains to be determined how this tyrosine becomes phosphorylated in Brk, since it is phosphorylated neither by Brk itself nor by Csk, playing this role for Src-family PTKs (660). However, the role of the C-terminal tyrosines in the regulation of Frk-family PTKs clearly requires further analysis, since the Y447F mutation of Brk has also been shown to decrease the transformation potential of this PTK in fibroblasts (658).

3.10. Ack

Ack family of PTKs consists of two members, Ack and Tnk1 (661, 662), both of which are present in human and mouse genomes. Two forms of Ack, Ack1 and Ack2, have been described (661, 663). A catalytic kinase domain is positioned C-terminally in Ack PTKs and is closely followed by an SH3 domain. In Ack, the SH3 domain is immediately followed by the CRIB domain, a sequence capable of specific GTP-dependent binding to Cdc42, but not other Rho-family GTPase (661, 663). Homology of Tnk1 with Ack ends immediately after the SH3 domain, so Tnk1 does not possess a CRIB domain (662). Finally, Ack has an arrestin-like clathrin-binding region, which immediately follows the CRIB domain (664).

Ack isoforms are expressed highly in the brain and skeletal muscle and, to a low extent, in lung, liver, and pancreas (663). Tnk1 is highly expressed in early, immature progenitor hematopoietic cells, especially in fetal blood, and less in other hematopoietic cells, intestine, colon, testis, ovary, fetal tissues, but not in lung, liver, kidney or brain (662, 665).

The ability of Ack to bind to active Cdc42, a small GTPase involved in the cytoskeletal rearrangements, implicates Ack in the cytoskeleton-mediated events. Indeed, cell adhesion has been shown to modulate the activity of Ack. In most cases, attachment activates Ack (663, 666, 667), but the activation in response to removal of ECM has also been reported (668). The adhesion-induced stimulation of Ack is caused by beta-1 integrins, but is not specific for fibronectin (666, 667). It is likely that this type of Ack stimulation is mediated by activated Cdc42

(663). Furthermore, Ack is activated by stress, growth and nerve impulse signals (663, 669-671). The activation of Ack through EGF receptor depends on the binding of Ack to Grb2 and Shc, adaptor proteins known to be involved in the growth receptor-mediated signaling (669, 672). The activation of Ack through acetylcholine receptors depends on the Rho-family GTPases (probably Cdc42) and Fyn (671).

Signaling through Ack appears to regulate various cytoskeleton-mediated events (667, 672-674). These effects are likely to be mediated by the Ack-dependent phosphorylation of Dbl, a guanine nucleotide exchange factor (GEF) specific for Rho-family GTPases, which causes activation of Dbl and, consequently, Rho-family GTPases (675).

The effect of Ack on the cytoskeleton and its responsiveness to the nerve impulse argue that this PTK may be involved in the axon guidance. This hypothesis is supported by the recent results indicating that Drosophila Ack phosphorylates the DSH3PX1 adaptor protein inside its SH3 domain, thus turning off binding of DSH3PX1 to WASP and inducing the binding of DSH3PX1 to the SH2 domain of Dock (Drosophila Nck), an adaptor protein known to be important for axon guidance (676).
However, the cytoskeleton is not the sole target of Ack, since this PTK has been shown to activate Ras *in vivo* (670), whereas its dominant-inhibitory form has been shown to block Ras-dependent cell transformation (673). The effect of Ack on Ras appears to be mediated by Ack-dependent tyrosine phosphorylation and activation of Ras-GRF1, a protein regulating the activity of Ras (670). Therefore, the mechanisms of the effects of Ack on the cytoskleton and cell growth are, at least to some extent, similar.

Finally, Ack appears to bind to clathrin through an arrestin-like clathrin-binding site (664, 677). When Ack is overexpresed, it increases the amount of clathrin in the fraction of clathrin-coated vesicles, induces re-distribution of clathrin and inhibits endocytosis (664, 677). However, when Ack was expressed at more physiological levels, no co-localization of Ack with clathrin or clathrin re-distribution was observed, making the significance of Ack/clathrin interactions unclear (664).

Very little is known about the biological functions of Tnk1, which does not posses a CRIB domain. Tnk1 appears to be constitutively active, is enriched in the membrane (although is also present in the cytosol), and is associated with PLC-gamma *via* its proline-rich region and PLC-gamma SH3 (665).

Little is known about the regulation of Ack-family PTKs. Since they are capable of autophosphorylation (663, 665, 675), their activity may be regulated by autophosphorylation, as it has been shown for other PTKs. Furthermore, Fyn appears to activate Ack in response to acetylcholine receptor stimulation (671), thus indicating that Ack may be regulated by heterologous tyrosine phosphorylation.

It has been shown that Ack is activated *in vivo* by activated Cdc42 (663). Although it is possible that this activation is caused by direct binding of Ack to activated Cdc42 (661, 663), which has been shown to induce substantial changes in the conformation of both Cdc42 and Ack (678, 679), the functional significance of the CRIB-mediated interactions between Ack and Cdc42 remains unclear. For example, Drosophila Ack appears to be essential for the developmental events that are controlled by Drosophila Cdc42, although this PTK possesses no CRIB domain and is incapable of binding to Drosophila Cdc42 (680).

Finally, regulation of Ack-family PTKs by SH3-containing and/or SH3-interacting proteins similar to that discussed for Src- and Abl-family PTKs is also possible, because both Ack and Tnk1 possess SH3 domains and proline-rich motifs. Indeed, Ack and Tnk1 have been shown to interact with SH3 domains of multiple proteins, including Nck, Grb2 and Src (Ack) (664, 669, 672) and PLC-gamma (Tnk1) (665). However, the role of these interactions in the regulation of Ack-family PTK activity remains to be established.

4. CONCLUDING REMARKS

In recent years, several vertebrate and invertebrate genomes, including the human genome, have been fully sequenced, providing us with the final (or nearly final) version of the list of existing PTKs (1, 4). In light of these discoveries, it appears that the era when identification of novel PTKs by cloning was a major direction of research in this area, is finally over. However, the genomic information, although important, is insufficient for determining biological functions and regulatory mechanisms of the known PTKs, and therefore, the research in this area is unlikely to subside any time soon.

An important finding made by the sequencing of human and mouse genomes is that the number of non-receptor PTKs in mammals is rather small. Thirty-plus non-receptor PTKs mediate all biological functions that are dependent on this class of protein kinases. Moreover, only a fraction of these PTKs are typically expressed in an individual cell or a specific tissue. However, the number of molecular events in the cells and the resulting biological responses that are dependent on non-receptor PTKs is vast. These phenomena are very diverse, highly specific and finely regulated. How can this complexity be mediated by a very limited number of non-receptor PTKs involved? It is likely that the answer to this question lies not in the differential specificity of non-receptor PTKs, albeit considerable, but primarily in the multitude of the interactions of non-receptor PTKs with multiple non-kinase proteins that can modify the effects of these PTKs and regulate their functions in the cell.

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