IL-2-induced gene expression of protein-tyrosine phosphatase LC-PTP requires acidic and serine-rich regions within IL-2 receptor β chain

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Abstract A protein-tyrosine phosphatase LC-PTP is preferentially expressed in hematopoietic cells and is an early response gene in lymphokine stimulated cells. Here, we found the LC-PTP mRNA induction by IL-2 was markedly inhibited by several tyrosine kinase inhibitors. The induction required both the acidic and serine-rich regions of the IL-2 receptor β chain (IL-2Rβ) in mouse IL-3-dependent pro-B BAF-B03 transfectants. This is strikingly different from the induction of c-*myc* gene expression, which requires the serine-rich region alone. In addition, overexpression of activated-Lck or -Raf kinases resulted in augmented LC-PTP mRNA expression in myeloid cell line 32D transfectants. Considering the previous findings that the acidic region of the IL-2Rβ is responsible for association with Lck and activation of Raf kinase, IL-2-induced expression of LC-PTP mRNA may be primarily transduced through a Lck-Raf mediated signaling pathway.

Key words: Protein-tyrosine phosphatase; LC-PTP; IL-2; Signal transduction

1. Introduction

Many growth factor receptors possess an intrinsic protein tyrosine kinase (PTK) region [1] or a region(s) responsible for coupling with a non-receptor PTK, such as those of the Src family. For example, $p56^{lck}$associates with CD4/CD8 in T-cells, $p59^{fyn}$ with the T-cell receptor complex, and $p56^{lyn}$ with the B-cell antigen receptor [2–4]. Proliferation of T-cells is triggered by the interaction of IL-2 with IL-2 receptor (IL-2R) which consists of three distinct subunits, IL-2Rα, IL-2Rβ, and IL-2Rγ [5]. Structure–function analysis of the IL-2Rβ chain (IL-2Rβ) has revealed that at least two distinct cytoplasmic regions are involved in IL-2-induced cellular signaling [6]. A 'serine- rich' region within the cytoplasmic domain of IL-2Rβ is crucial for IL-2-induced mitotic signaling and leads to the induction of c-*myc* gene, whereas an 'acidic' region is responsible for its physical association with $p56^{lck}$ and leads to the induction of c-*fos*/c-*jun* genes [7].

Protein-tyrosine phosphatases (PTPs) may also be involved in IL-2-signaling by removing phosphates from the phosphotyrosyl groups on target proteins. For the most part, however, the role of PTPs in cytokine signal transduction still remains enigmatic. Recently, we and others cloned a cDNA encoding a non-receptor LC-PTP (also called by HePTP) [8–10] which is preferentially expressed in T-cells. We have previously shown that LC-PTP gene has 11 exons [11] and is classified as an early response gene in that LC-PTP mRNA induction by lymphokines does not require new protein synthesis [12]. The expression pattern of LC-PTP gene leads us to investigate the possible signaling pathway leading to its expression. We report here that the induction of LC-PTP mRNA expression was inhibited by PTK inhibitors. The induction requires both the cytoplasmic serine-rich and acidic regions of the IL-2Rβ. In addition, we show that the overexpression of the constitutively active form of Lck or Raf kinase results in the augmented expression of LC-PTP mRNA, suggesting the involvement of the Lck/Raf mediated signaling in the LC-PTP mRNA induction.

2. Materials and methods

2.1. Reagents and cell culture

Murine pro-B cell BAF-B03 and myeloid 32D transfectants were IL-3-dependent, and were maintained in RPMI-1640 medium (Gibco, Grand Island, NY) with 10% fetal calf serum (FCS) and 10% WEHI-3B conditioned medium (as a source of murine IL-3). BAF-B03-derived transfectants, which express the wild type of IL-2Rβ (F7), mutant IL-2Rβ lacking the acidic region (A15), or mutant IL-2Rβ lacking the serine-rich region (S25) were established as described previously [6]. For factor-deprivation experiments, cells were washed twice, and resuspended in a medium without the factor for 18–24 h. Following 400 U/ml of IL-2 (kindly provided by Shionogi Chemical Pharmacy, Japan) or IL-3 stimulation, RNA expression levels were analyzed by Northern blot analysis. To evaluate the effects of various inhibitors, 1 μM KN-62 (Seikagaku Co.); a Ca^{2+}/CaM kinase II inhibitor [13], 30 μM H-89 (Seikagaku Co.); a cAMP-dependent protein kinase inhibitor [14], 100 μM tyrphostin ST638 (kindly provided by Kanebuchi Chemical Co., Japan) and 100 μM genistein; protein tyrosine kinase specific inhibitors [15,16], 2.5 nM FK506 (kindly provided by Fujisawa Chemical Co.); a serine/threonine phosphatase PP2B inhibitor [17], and 10 mg/ml of cycloheximide (Sigma); a protein synthesis inhibitor were added into the culture 0.5 h before IL-2 stimulation.

2.2. Northern blot analysis

Total RNAs were extracted from BAF-B03 and 32D transfectants by the guanidium/CsCl procedure. Ten μg of the total RNAs were separated by 1% agarose formaldehyde gel electrophoresis and were

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Abbreviations: PTK, protein-tyrosine kinase; PTP, protein-tyrosine phosphatase; LC-PTP, leukocyte PTP; IL-2, interleukin-2.

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transferred onto nitrocellulose filters. The filters were hybridized with ^{32}P-labeled cDNA fragments as probes; the 0.6-kb 5′ region of the human LC-PTP cDNA clone [8], and the 2.2-kb human full-length c-*myc* cDNA [18]. The hybridization and washing condition were performed as described previously [8]. The intensities of the respective bands were assessed by the Bio-Imaging Analyzer (Fuji Photo Film Co., model BAS-2000).

2.3. Western blot analysis

Preparation of anti-LC-PTP polyclonal antibody is described previously [12]. BAF-B03 cells expressing the IL-2Rβ, F7 cells were washed with cold phosphate-buffered saline (PBS) and lysed in 100 μl of a buffer containing 100 mM NaCl, 2 mM EDTA, 10 mM sodium orthovanadate, 1 mM PMSF, 1% NP-40 and 50 mM Tris (pH 7.2). The protein concentrations of the lysates were analyzed by the Protein Assay kit (BioRad) and each lysate was subjected to SDS-PAGE, followed by electrophoretical transfer onto Immobilon (Millipore). The blots were incubated with blocking buffer containing 3% BSA, 10 mM Tris (pH 8.2), 140 mM NaCl, and 0.01% NaN_3. Then, they were incubated with 2 μg/ml of anti-LC-PTP antibody for 2 h in washing solution (150 mM NaCl, 10 mM Tris (pH 7.5) and 0.01% Tween 20) with 2% FCS, and washed several times in washing solution, following by an additional 1 h of incubation with peroxidase-conjugated anti-rabbit IgG antibody (Amersham). The blots were developed by a standard ECL method.

3. Results

3.1. IL-2 upregulates LC-PTP mRNA and its protein levels in F7 cells

F7 cells are an IL-2Rβ-expressing transfectant of the murine IL-3-dependent pro-B cell clone BAF-B03, which expresses endogenous mouse IL-2Rα and IL-2Rγ chains at relatively high levels, but normally lack IL-2Rβ and thus fail to respond to IL-2. The F7 transfectant expressing the human IL-2Rβ (wild-type) binds IL-2 with high affinity and proliferates in response to IL-2 [6]. Although LC-PTP mRNA was not induced by IL-2 stimulation in BAF-B03 (data not shown), the induction was clearly seen in F7 clone (Fig. 1A). The induction was detectable within 3 h and peaked at 9 h after IL-2 stimulation, revealing a similar kinetics of LC-PTP mRNA induction to IL-2-stimulated human T-cell line ILT-Mat, as described previously [12]. We performed Western blot analysis to determine whether the IL-2-induced increases in LC-PTP mRNA levels in F7 cells were associated with increases in the level of LC-PTP protein. The polyclonal antibody to LC-PTP protein that we previously generated [12], recognized a major band with molecular mass of 40-kDa, and the intensity of the major band was increased by approximately 2-fold in F7 cells at 12 h after IL-2 stimulation (Fig. 1B), indicating that LC-PTP mRNA induction leads to elevations in LC-PTP protein levels.

3.2. Two functional domains of IL-2Rβ are required for LC-PTP mRNA induction

To identify the region(s) of IL-2Rβ responsible for the LC-PTP mRNA induction, we employed two BAF-B03-derived transfectants expressing the respective mutant IL-2Rβ. A15 cells express IL-2Rβ lacking the acidic region and S25 cells express IL-2Rβ lacking the serine-rich region [6]. IL-2 stimulation of both clones failed to induce LC-PTP mRNA expression,

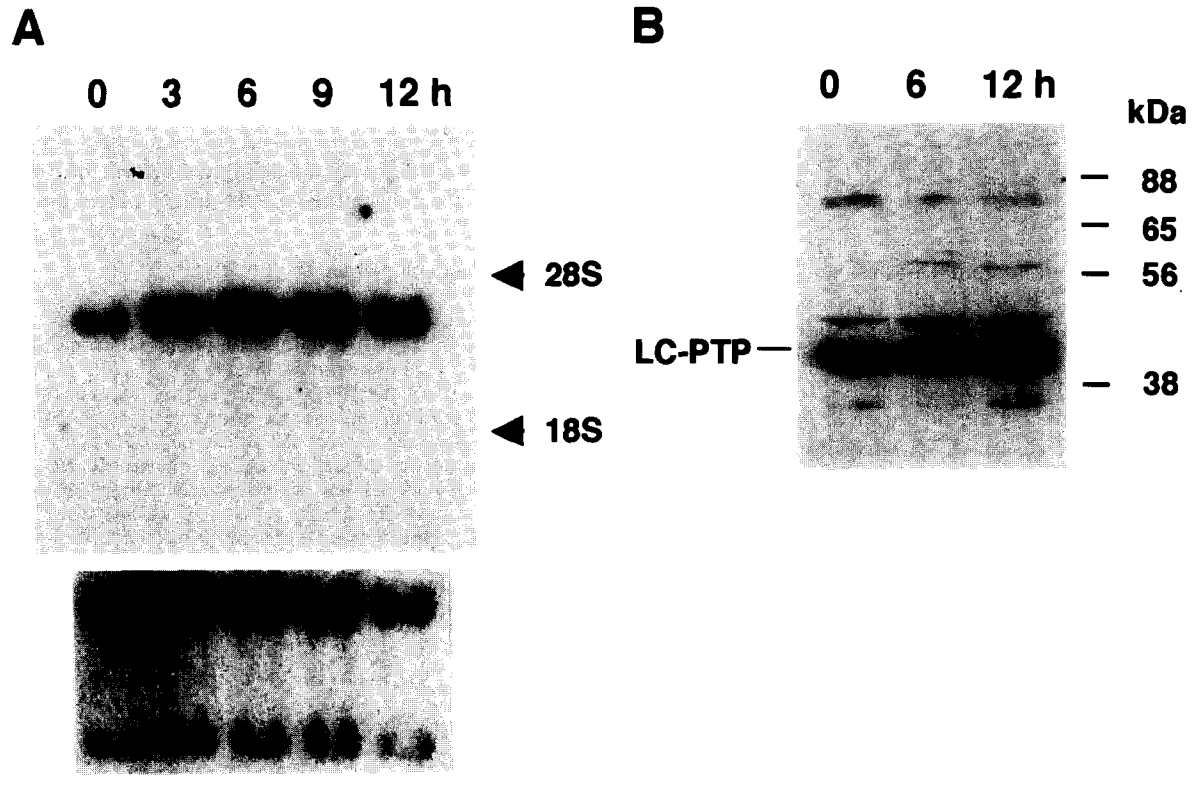

Fig. 1. Time course of LC-PTP mRNA induction and LC-PTP protein by IL-2 in BAF-B03 F7 transfectants. (A) BAF-B03 transfectants (F7) were treated with IL-2 (400 U/ml) and total RNA was extracted from the cells at the indicated times. Northern blot analysis was performed by hybridizing with a ^{32}P-labeled LC-PTP probe. The positions of ribosomal RNAs, which are shown for relative amounts of total RNA loaded and their quality, are indicated to the right of the blot. (B) Cell lysates from control and IL-2-treated F7 cells (6 h and 24 h) were normalized for the amount (75 μg/lane) of protein, and fractionated by 10% SDS-gel electrophoresis. LC-PTP protein was subsequently detected by immunoblotting with a polyclonal anti-LC-PTP antibody (2 μg/ml).

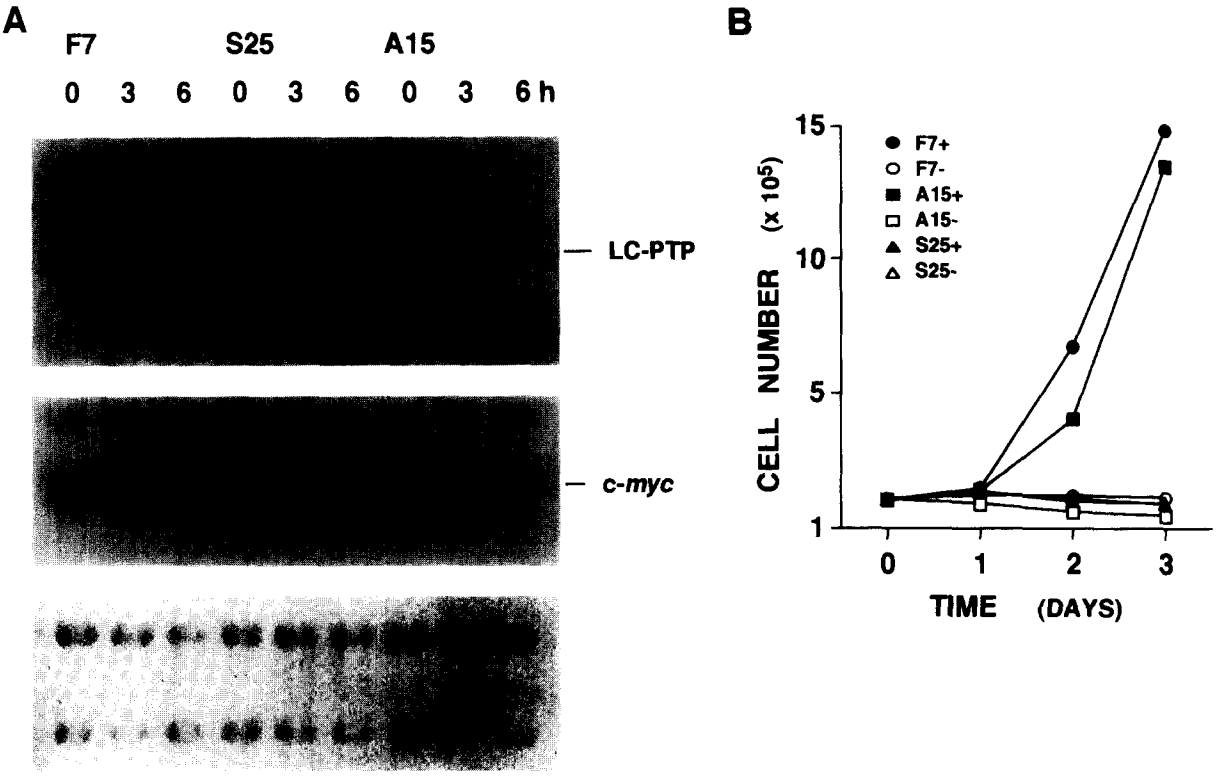

Fig. 2. LC-PTP mRNA induction and cellular proliferation by IL-2 in BAF-B03 transfectants. (A) BAF-B03 transfectants (F7, A15, and S25) were treated with IL-2, and their LC-PTP mRNA and c-*myc* mRNA expressions were analyzed by Northern blots. Ribosomal RNAs are shown for relative amounts of total RNA loaded and their quality. (B) F7, A15 and S25 transfectants grown in control medium (open) or in medium containing IL-2 (closed) were counted every day. The mean number of the cells from three independent experiments was plotted against the number of days. Standard error values are indicated.

whereas stimulation of A15 cells induced c-*myc* gene expression (Fig. 2A). These findings therefore, indicate that the induction of LC-PTP mRNA requires both the acidic and serine-rich regions of the IL-2Rβ. When the BAF-B03 transfectants were exposed to IL-2, A15 and F7 cells exhibited good proliferative response, while S25 cells did not respond at all. The cellular growth curve of A15 cells was similar to that of F7 cells, but the increase of cell numbers in A15 cells was slightly delayed (Fig. 2B).

3.3. *IL-2-induced LC-PTP gene expression requires tyrosine phosphorylation*

In order to explore the signaling pathways involved in the IL-2-mediated LC-PTP mRNA induction, F7 cells were deprived of IL-3 for 24 h, exposed to various pharmacological reagents for 0.5 h and then stimulated by IL-2. Consistent with our previous observations [12], the IL-2-mediated induction of LC-PTP mRNA was not blocked by the addition of CHX (Fig. 3), indicating that protein synthesis is not necessarily required. The induction of LC-PTP expression by IL-2 was inhibited almost completely by the tyrosine kinase inhibitors ST638 and genistein, but was not affected by other protein kinase inhibitors including KN-62 and H-89, or by the PP2B inhibitor FK506 (Fig. 3). These data suggest that tyrosine phosphorylation is required for LC-PTP gene expression in IL-2-stimulated F7 cells. In addition, these pharmacological reagents produced similar effects on c-*myc* gene expression, although the effects of ST638 showed different sensitivity to ST638 (Fig. 3).

3.4. *IL-3-induced LC-PTP gene expression also requires tyrosine phosphorylation*

To examine whether the signaling pathways involved in LC-PTP gene expression utilizes a common pathway shared by IL-2 and IL-3, we analyzed LC-PTP mRNA expression in F7 cells after IL-3 stimulation. LC-PTP gene expression was clearly induced at 3 h after IL-3 stimulation (Fig. 4). We also examined the effects of the tyrosine kinase inhibitors, ST638 and genistein. As seen when IL-2 was employed, IL-3-induced LC-PTP mRNA expression also required activation of tyrosine kinase(s), since the induction was completely inhibited by these tyrosine kinase inhibitors (Fig. 4).

3.5. *Augmented expression of LC-PTP mRNA in Lck- and Raf-transfected 32D cells*

Previously, it has been shown that the IL-3-dependent myeloid progenitor cell clone 32D.3 cells proliferate in response to IL-2 when the IL-2Rβ was introduced into the cells by gene transfer methods, implying that 32D cells utilized similar intracellular signaling machinery to IL-2-dependent T-cells and IL-3-dependent BAF-B03 cells. We already established 32D transfectants, which express constitutively active forms of Lck or Raf kinases [19,20]. In order to clarify the involvement of these kinases in LC-PTP mRNA induction, the relative steady-state levels of LC-PTP mRNA was analyzed in these transfectants following deprivation of IL-3 for 24 h. As shown in Fig. 5, 2-fold and 3-fold higher levels of LC-PTP mRNA were observed in the Lck-transfectants and in the Raf-transfectants,

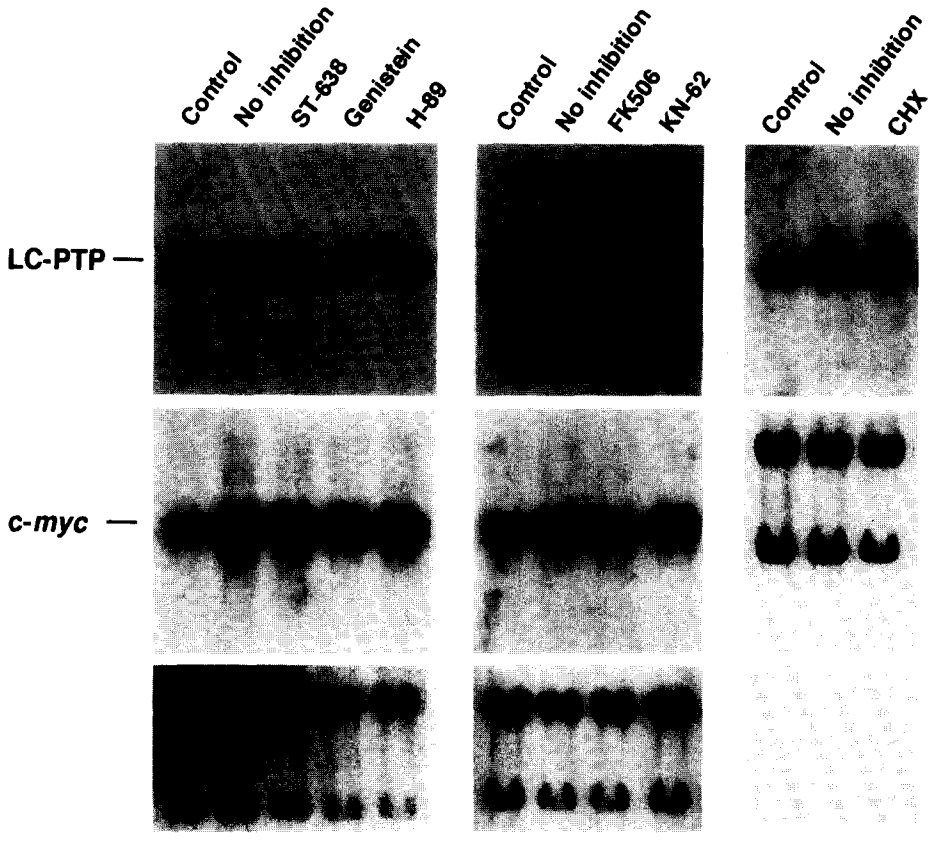

Fig. 3. Effects of various reagents on induction of LC-PTP mRNA in BAF-B03 (F7) cells. F7 cells were treated with the indicated reagents 0.5 h prior to the stimulation of IL-2 (400 U/ml) for 3 h. RNAs were extracted from the cells which received no treatment as a negative control (Control) and the cells stimulated with IL-2 alone as a positive control (No inhibition). Northern blot analyses were performed with 10 μg of total RNA/lane which was hybridized with a ^{32}P-labeled LC-PTP or c-*myc* probe. The ribosomal RNAs are shown for relative amounts of total RNA loaded and their quality.

respectively, compared to Neo-control cells. Similar results were obtained in the transfectants without deprivation of IL-3.

4. Discussion

LC-PTP is one of the early-response gene products that is produced in IL-2-stimulated lymphoid cells. In this study, we demonstrated that expression of the LC-PTP gene and its product was increased upon IL-2 stimulation of an IL-3-dependent BAF-B03 transfectant, F7, in which a functional IL-2R was reconstituted by introduction of the IL-2Rβ (Fig. 1). The kinetics of the IL-2-induced LC-PTP gene expression was increased within 3 h after the stimulation, peaked at 9 h and continued for at least 12 h. Since LC-PTP was also induced by stimulation of F7 cells with IL-3 (Fig. 4), expression of this phosphatase LC-PTP was assumed to be mediated by a common intracellular signaling pathway that is shared by IL-2 and IL-3.

Two distinct functional subdomains have been identified within the cytoplasmic domain of the β subunits of IL-2R. The membrane proximal, the serine-rich region of IL-2Rβ is essential for activation of JAK-family PTKs [21] and Src-family Syk [22] as well as for c-*myc* gene induction. On the other hand, the membrane distal, the acidic region of IL-2Rβ is crucial for activation of Src-family PTKs and for c-*fos* and c-*jun* gene induction [23]. To determine the functional subdomain of the IL-2Rβ involved in the LC-PTP gene induction, we examined the LC-PTP gene induction in two BAF-B03 transfectants expressing mutant IL-2Rβs. S25 and A15 cells express IL-2Rβ lacking the serine-rich and the acidic regions, respectively. Stimulation of S25 cells with IL-2 failed to induce the expression of both c-*myc* and LC-PTP genes. Though c-*myc* gene expression was induced in A15 cells, LC-PTP gene was not induced (Fig. 2A). Thus, LC-PTP gene expression appears to be mediated by both the serine-rich and acidic regions of the IL-2Rβ, which is distinct from c-*myc* gene expression.

In order to probe the intracellular signaling pathways through which LC-PTP expression is regulated, the possible involvement of PTK-dependent, cAMP-dependent, and calcium/calmodulin-dependent mechanisms were examined by using various pharmacological inhibitors. In the presence of tyrosine kinase inhibitors such as ST638 and genistein, IL-2-stimulated increases in LC-PTP mRNA elevation was almost completely abolished. In contrast, LC-PTP expression was not affected by KN-62, H-89, or FK506, suggesting involvements of the calcium/calmodulin-dependent protein kinase II, cAMP-dependent protein kinase, and calcium/calmodulin-dependent protein phosphatase PP2B are marginal, if any (Fig. 3). Thus IL-2-induced LC-PTP gene expression presumably required the activation of some tyrosine kinase(s) or an imbalance in the dephosphorylation of protein on tyrosine by a phosphatase.

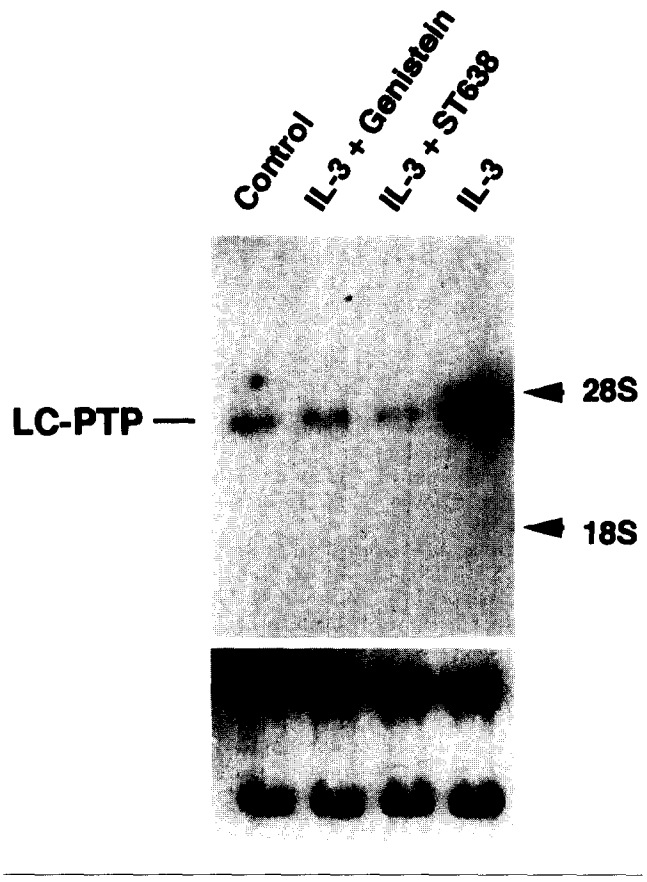

Fig. 4. LC-PTP mRNA induction by IL-3. After 24 h deprival of IL-3, F7 cells were treated with the indicated reagents 0.5 h prior to the addition of 10% WEHI-3B cells containing murine IL-3 and total RNA was extracted from the cells at 3 h incubation. RNA was also extracted from the cells which received nothing as a negative control (Control) and the cells stimulated with IL-3 alone as a positive control (IL-3). Northern blot analyses (10 μg of total RNA/lane) were performed with hybridizing to a ^{32}P-labeled LC-PTP probe. The ribosomal RNAs are shown for relative amounts of total RNA loaded and their quality.

Activation of Src-family PTKs, such as Lck, Fyn, and Lyn occurs during IL-2 and IL-3 signaling [24–26]. As a downstream signaling molecule of the PTKs, an SH_2-containing adapter protein SHC becomes tyrosine phosphorylated, then recruiting GRB2/SOS complexes to the plasma membrane, which has a GDP/GTP exchange activity for small G-protein RAS. The GTP-bound form of p21-Ras can then physically interact with the serine/threonine kinase Raf-1, which in turn activates the mitogen-activated protein (MAP) kinase cascade, following by c-*fos* gene induction. Since IL-2-induced c-*fos* gene expression also requires both the serine-rich and acidic regions of the IL-2Rβ, the Lck-mediated signaling pathway rather than the JAK pathway may be involved in the regulation of LC-PTP gene expression. Consistent with this hypothesis, overexpressions of activated-Lck or Raf-1 kinases in 32D cells resulted in the higher levels of LC-PTP mRNA accumulation than in 32D cells transfected with a control vector (Fig. 5). These results imply that IL-2-induced LC-PTP gene expression might be mediated through the signaling pathway that involves Lck, Ras and Raf-1.

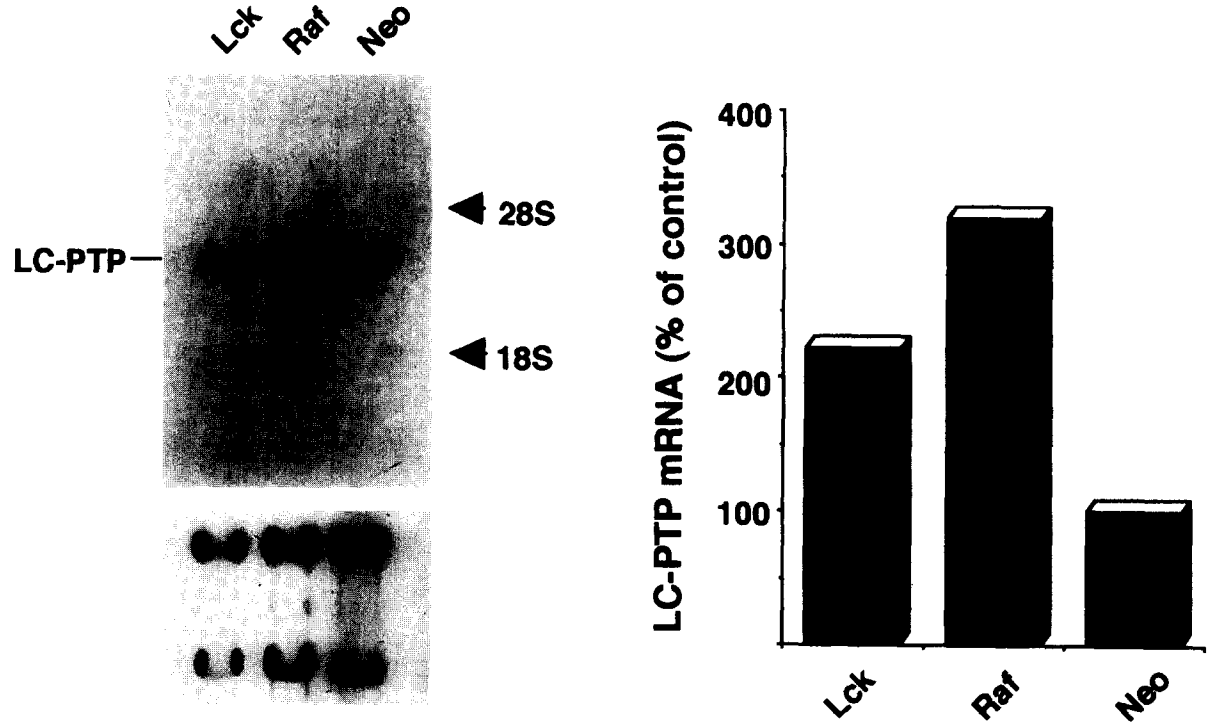

Fig. 5. High levels of LC-PTP mRNA expression in 32D transfectants with overexpression of mutant LCK or mutant RAF. 32D cells transfected with mutant *lck* cDNA (Lck), mutant *raf* cDNA (Raf), or vector alone (Neo) were deprived of IL-3 for 24 h, and total RNA was extracted from the cells. 10 μg of total RNA were subjected to electrophoresis and transferred to nitrocellulose filters, followed by hybridization to a ^{32}P-labeled LC-PTP probe. Ribosomal RNAs visualized by ethidium bromide are shown in bottom. Similar results were obtained in the transfectants without IL-3 starvation. The LC-PTP mRNA expressions normalized for their RNA amount analyzed by densitometry are measured by Bio-Imaging Analyzer, and their relative levels are shown in the right of the data.

Although the functional consequence of LC-PTP expression in IL-2 signaling remains to be determined, our data indicates the possible involvement in IL-2 signaling. It has been shown that Lck-mediated signaling has a crucial role in cell-mediated cytotoxic function of T-cells [27], and activation of Src-family PTKs in lymphoid cells or myeloid cells. It is possible therefore that LC-PTP may participate in the regulation of these cellular responses which have been functionally linked to Src-family kinases in lymphokine-dependent hematolymphoid cells. In addition, it has recently been demonstrated that $p56^{lck}$ PTK is involved in IL-2-induced cell proliferation [28]. As shown in Fig. 2B and in our previous report [7], the rate of cell growth is slightly delayed in A15 cells in comparison with F7 cells. This may be reflected by the disruption of $p56^{lck}$ activation, which shuts off the LC-PTP mRNA induction. Thus, the increase of LC-PTP expression may also be involved in IL-2-induced cell proliferation.

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