Stimulation of Src Family Protein-tyrosine Kinases as a Proximal and Mandatory Step for SYK Kinase-dependent Phospholipase Cγ2 Activation in Lymphoma B Cells Exposed to Low Energy Electromagnetic Fields

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Here, we present evidence that exposure of DT40 lymphoma B cells to low energy electromagnetic field (EMF) results in a tyrosine kinase-dependent activation of phospholipase Cγ2 (PLC-γ2) leading to increased inositol phospholipid turnover. B cells rendered PLC-γ2-deficient by targeted disruption of the PLC-γ2 gene as well as PLC-γ2-deficient cells reconstituted with Src homology domain 2 (SH2) domain mutant PLC-γ2 did not show any increase in inositol-1,4,5-trisphosphate levels after EMF exposure, providing direct evidence that PLC-γ2 is responsible for EMF-induced stimulation of inositol phospholipid turnover, and its SH2 domains are essential for this function. B cells rendered SYK-deficient by targeted disruption of the syk gene did not show PLC-γ2 activation in response to EMF exposure. The C-terminal SH2 domain of SYK kinase is essential for its ability to activate PLC-γ2. SYK-deficient cells reconstituted with a C-terminal SH2 domain mutant syk gene failed to elicit increased inositol phospholipid turnover after EMF exposure, whereas SYK-deficient cells reconstituted with an N-terminal SH2 domain mutant syk gene showed a normal EMF response. LYN kinase is essential for the initiation of this biochemical signaling cascade. Lymphoma B cells rendered LYN-deficient through targeted disruption of the lyn gene did not elicit enhanced inositol phospholipid turnover after EMF exposure. Inhibition of the wild-type (but not a kinase domain mutant) mouse fyn gene into LYN-deficient B cells restored their EMF responsiveness. B cells reconstituted with a SH2 domain mutant fyn gene showed a normal EMF response, whereas no increase in inositol phospholipid turnover in response to EMF was noticed in LYN-deficient cells reconstituted with a SH2 domain mutant fyn gene. Taken together, these results indicate that EMF-induced PLC-γ2 activation is mediated by LYN-regulated stimulation of SYK, which acts downstream of LYN kinase and upstream of PLC-γ2.

A number of epidemiologic studies suggested the possibility that electromagnetic field (EMF)1 radiation from residually proximate power lines, household electrical wiring, and appliance usage may contribute to the risk of childhood acute lymphoblastic leukemia (1–5). A recent study by Linet et al. (6) showed that living in homes characterized by high measured time-weighted average magnetic field levels or by the highest wire-code category does not increase the risk of acute lymphoblastic leukemia in children. However, concerns regarding other forms of EMF exposure remain. Since no directly genotoxic effects are exerted by EMF, it is thought that EMF may participate in leukemogenesis of childhood acute lymphoblastic leukemia by influencing their proliferation, survival, and/or differentiation programs (6–9).

The Src protooncogene family protein-tyrosine kinase (PTK) LYN plays a pivotal role in ligand-induced signal transduction events in B-lineage lymphoid cells (10–17). In a recent study, we discovered that exposure of B-lineage lymphoid cells to low energy EMF stimulates LYN as well as its downstream substrate SYK (18). These results prompted the hypothesis that a delicate growth regulatory balance might be altered in B-lineage lymphoid cells by EMF-induced activation of a biochemical signaling cascade intimately linked to LYN kinase. The purpose of the present study was to further characterize this signaling cascade using an EMF-responsive lymphoma B cell model and targeted disruption of the genes for known or suspected participants such as LYN, SYK, and PLC-γ2 by homologous recombination knockout.

EXPERIMENTAL PROCEDURES

Cell Lines—The establishment and characterization of wild-type and LYN-deficient, SYK-deficient, PLC-γ2-deficient clones of DT40 chicken lymphoma B cells were previously reported (19–23). Cells were maintained in suspension cultures at 37 °C, 5% CO₂, and 3% O₂ in a humidified incubator. The culture medium was RPMI 1640 (Life Technologies, Inc.), supplemented with 10% fetal calf serum, 2.5% chicken serum, 10 mM L-glutamine, and 50 μM 2-mercaptoethanol.

Western Blot Analysis of Protein Expression and Immune Complex Kinase Assays—The expression levels of wild-type and mutant enzyme proteins in the various cell lines were measured by Western blot analysis using appropriate monoclonal antibodies, as described previously (24). In brief, cells (5 × 10⁶ cells/sample) were lysed in 150 μL of SDS lysis buffer (50 mM Tris-HCl, pH 6.8, 2% SDS, 10% glycerol, 100 μM sodium orthovanadate, 25 mM dithiothreitol) and boiled for 5 min. The

1 The abbreviations used are: EMF, electromagnetic field; PTK, protein-tyrosine kinase; PLC-γ2, phospholipase C-γ2; SH2, Src homology domain 2; Ins-1,4,5-P₃, inositol-1,4,5-trisphosphate; ITAM, immunoreceptor tyrosine-based activation motif.
DNA was sheared by several passages through a 28-gauge needle, and 40-μl amounts of the whole cell lysate protein samples in SDS-reducing sample buffer were fractionated on reducing SDS-polyacrylamide gels by overnight electrophoresis at 4 mA. The proteins were transferred to a 0.45-μm Immobilon polyvinyldiene difluoride membrane (Millipore Corp., Bedford, MA) for 1 h at 130 mA using a semidy transfer apparatus ( Hoefer Scientific Instruments, San Francisco, CA). The polyvinyldene difluoride membranes were incubated for 1 h at room temperature in blocking solution (10 mM Tris-HCl, pH 7.5, 100 mM NaCl, 5% bovine serum albumin), washed in rinsing buffer, and incubated for 1 h with the appropriate primary antibody (i.e. polyclonal rabbit anti-FYN serum at 1:2,000 final dilution, monoclonal 4D10 IgG2a anti-SYK antibody from Santa Cruz Biotechnology, Inc. at 10 ng/ml final concentration, or polyclonal rabbit anti-PLC-γ2 serum at 1:1,000 final dilution mixed with monoclonal 4D10 IgG2a anti-SYK antibody) (for comparison of SYK protein levels in the lanes as an internal control) from Santa Cruz Biotechnology, Inc. at 10 ng/ml final concentration) in blocking solution followed by three 10-min washes in rinsing buffer. For detection of the target enzyme proteins, horseradish peroxidase-conjugated sheep anti-mouse/rabbit IgG (Signal Transduction Laboratories; 1:2500 dilution, 45-min incubation) and the ECL chemiluminescence detection system (Amersham Life Sciences) were used according to the manufacturer’s recommendations. The membranes immunoblotted with anti-FYN or anti-SYK antibodies were stripped and reblotted with the mouse monoclonal anti-actin antibody (Sigma, catalog no. A-4700; 1:50,000 final dilution) to compare the protein levels in the individual lanes. In other experiments, wild-type and mutant SYK proteins were immunoprecipitated, and in vitro immune complex kinase assays were performed, as described previously (25, 26).

EMF Exposure—A homogenous vertical magnetic field was set up by using a Merritt’s coil-based in vitro low frequency EMF exposure system (18). Merritt’s four square coil system is known to produce a large volume of uniform magnetic field. The applied vertical sinusoidal 60-Hz field was 0.1 mT (1 Gauss). The current needed to obtain 1 Gauss was 0.7 A. The magnetic field was parallel to the coil axis and was uniform near the axis and the center of the coil system. Cells were maintained at all times in a low AC (8 mG) environment except during a single centrifugation step. This was achieved by using a 2-pole motor tissue incubator (CEDCO model IRE 93) with low AC fields for routine cell culture and by defining the lowest field regions within the incubator. Exponentially growing cells (5 × 10⁶ cells/ml in serum-free α-minimum essential medium in 1.5-ml capacity microcentrifuge tubes) were exposed to 1-Gauss, 60-Hz EMF by placing the tubes at the center of the four-coil field generator, which was contained in an incubator with shielding sheets of metal alloy at the bottom of the chambers. Control tubes were simultaneously placed inside a duplicate incubator without the exposure apparatus. To measure the fields in the incubators, the laminar flow hood, centrifuge, and nearby areas, a gaussmeter (MAG model 25, Magnetic Sciences International) was used. EMF strength was constantly monitored with the gaussmeter and adjusted manually if needed. In all experiments, the cells were activated before the placement of the cells, to avoid fluctuations of the EMF during activation of the apparatus. The coils were turned off only after the cells were taken out of the exposure system. Ice-cold perchloric acid (20%) was added after EMF exposure to the cell suspensions to stop further response. The test tubes were kept on ice for 20 min and then sedimented at 2,000 × g for 15 min at 4 °C. The supernatant was collected, the pH was neutralized to 7.5 with ice-cold 10 mM KOH, and the solution was centrifuged again. The supernatant was collected and stored at −20 °C for subsequent measurement of inositol-1,4,5-trisphosphate (Ins-1,4,5-P₃) levels.

Analysis of Stimulation of Inositol Phospholipid Turnover—Ins-1,4,5-P₃ levels were measured by using a 4-α-mylo-[3H]Ins-1,4,5-P₃ assay system purchased from Amersham Corp., as reported elsewhere (26–29). This highly sensitive assay is based on the competition between nonradioabeled Ins-1,4,5-P₃ in the cellular extracts and a fixed quantity of a high specific activity [3H]Ins-1,4,5-P₃ tracer for a limited number of binding sites on an Ins-1,4,5-P₃-specific and sensitive bovine adrenal binding protein (26–29). In some experiments, cells were preincubated for 1 h at 37 °C with the PTK inhibitor genistein (ICN Biomedicals, Costa Mesa, CA) at 100 μg/mL (370 μM) or for 24 h at 37 °C with the PTK inhibitor herbimycin A (Sigma) at 7 μM/μl (12 μM), as previously reported (26–29). In some experiments, cells were stimulated with 3 μg/ml anti-chicken IgM monoclonal antibody M4 at 37 °C for the indicated periods of time in the figures.

**FIG. 1.** EMF-induced activation of inositol phospholipid turnover in DT40 lymphoma B cells. Cells (5 × 10⁵/ml) were exposed to 1-Gauss low frequency EMF at 60 Hz (diamonds). N = number of independent experiments, each performed in duplicate for each time point. The control cells (CON, squares) were sham-treated, under identical conditions except for exposure to the EMF. At the times indicated, the cells were lysed with ice-cold 20% perchloric acid and were then assayed for Ins-1,4,5-P₃ levels using a radioligand competition assay (see “Experimental Procedures”). Prior to EMF exposure, some cells were also treated with 100 μg/mL genistein (GEN) for 1 h (triangles), or 7 μg/ml herbimycin A (HERB) for 24 h (crosses). Positive controls were stimulated with 3 μg/mL monoclonal antibody M4 directed against IgM (adjM) for the times indicated (circles). A, wild-type (WT) DT40 cells. B, PLC-γ2-deficient (PLC-γ2) cells constructed through targeted disruption of the PLC-γ2 gene. C, PLC-γ2-deficient cells reconstituted with a PLC-γ2 gene with mutant C-terminal and N-terminal SH2 domains (mSH₂). Results are expressed as the mean picomolar amounts of Ins-1,4,5-P₃ per 10⁶ cells. Inset of C shows the anti-PLC-γ2 Western blot analysis of the WT cells, PLC-γ2 cells, and PLC-γ2 cells reconstituted with mSH₂ PLC-γ2, which employed the ECL chemiluminescence detection system. An anti-SYK antibody was included in the primary antibody solution to compare the SYK protein amounts in the individual samples as an internal control (see “Experimental Procedures”). Whereas SYK protein was expressed at comparable levels in all three cell lines, PLC-γ2 protein was not detected in PLC-γ2 cells, and the expression level of the mutant protein was higher than the expression of the wild-type PLC-γ2 protein.
RESULTS AND DISCUSSION

Activation of PLC-\(\gamma\)-2 in DT40 Lymphoma B Cells Exposed to Low Energy EMF—The catalytic activity of PLC-\(\gamma\)-2 is regulated through tyrosine phosphorylation by receptor- and non-receptor-type PTKs, and biochemical signals that trigger tyrosine-specific protein phosphorylation have been shown to precede the activation of PLC-\(\gamma\)-2 and stimulation of inositol phospholipid turnover in many experimental systems (10, 12–17, 26). Therefore, we examined the effects of EMF on inositol phospholipid turnover in DT40 lymphoma B cells using a highly specific and quantitative \(\alpha\)-myo-[\(3^3\)]H]Ins-1,4,5-P\(_3\) assay system. Exposure of DT40 cells to EMF stimulated a rapid and biphasic increase in the production of Ins-1,4,5-P\(_3\) leading to markedly elevated Ins-1,4,5-P\(_3\) levels at 1 min after the start of EMF exposure, which were 9.9-fold higher than the Ins-1,4,5-P\(_3\) levels in the sham-treated controls (21.8 ± 9 pmol/10\(^6\) cells versus 2.2 ± 0.6 pmol/10\(^6\) cells, p < 0.05). Thereafter, the level of Ins-1,4,5-P\(_3\) rapidly declined but at 5 min it was still higher than the baseline (Fig. 1A). The magnitude and kinetics of EMF-induced Ins-1,4,5-P\(_3\) response were similar to those of the Ins-1,4,5-P\(_3\) response triggered by engagement of the B cell antigen receptor with an anti-IgM monoclonal antibody (Fig. 1A). These experiments provided evidence that the biochemical signal triggered in DT40 lymphoma B cells by low energy EMF is intimately linked to signal transduction pathways that stimulate inositol phospholipid turnover, producing Ins-1,4,5-P\(_3\) as a second messenger. The PTK inhibitors herbimycin A and genistein attenuated the EMF-induced Ins-1,4,5-P\(_3\) signal (Fig. 1A), providing strong evidence that tyrosine phosphorylation is a requisite step in the EMF-triggered stimulation of inositol phospholipid turnover in lymphoma B cells. In contrast to wild-type DT40 cells, DT40 cells rendered PLC-\(\gamma\)-2-deficient by targeted disruption of the PLC-\(\gamma\)-2 gene did not show any increase in Ins-1,4,5-P\(_3\) levels after EMF exposure (Fig. 1B), confirming that PLC-\(\gamma\)-2 is required for EMF-induced stimulation of inositol phospholipid turnover.

Since the SH2 domains of PLC-\(\gamma\)-2 are essential in activation of PLC-\(\gamma\)-2 during the B cell antigen receptor-linked signaling cascade, we examined the effect of SH2 domain mutations on EMF-induced Ins-1,4,5-P\(_3\) production. As shown in Fig. 1C, PLC-\(\gamma\)-2-deficient DT40 cells reconstituted with a SH2 domain mutant PLC-\(\gamma\)-2 failed to elicit an Ins-1,4,5-P\(_3\) response upon EMF exposure. The inset of Fig. 1C depicts an immunoblot confirming the absence of PLC-\(\gamma\)-2 protein in PLC-\(\gamma\)-2- cells and abundant expression of the mutant protein in PLC-\(\gamma\)-2-deficient cells reconstituted with SH2 domain mutant PLC-\(\gamma\)-2. All three cell lines express comparable amounts of SYK kinase protein. The relative amount of mutant PLC-\(\gamma\)-2 in the reconstituted cell line is greater than the amount of wild-type PLC-\(\gamma\)-2 in the parent cell line. Thus, the absence of the Ins-1,4,5-P\(_3\) signal in the reconstituted cell line is not caused by expression of less PLC-\(\gamma\)-2 protein. Since SH2 domains mediate intermolecular interactions by binding to phosphotyrosine containing sequences, these results indicate that recruitment of PLC-\(\gamma\)-2 via its SH2 domains to inductibly tyrosine-phosphorylated proteins or associated PTK such as SYK is a prerequisite for EMF-induced activation of PLC-\(\gamma\)-2.

Since the tyrosine kinase SYK is required for antigen-receptor mediated activation of PLC-\(\gamma\)-2 (10, 20), we next examined the role of SYK in EMF-induced activation of PLC-\(\gamma\)-2. EMF exposure did not induce an Ins-1,4,5-P\(_3\) signal in SYK-deficient DT40 cells (Fig. 2A), providing experimental evidence that the tyrosine kinase SYK, which is required for antigen receptor-mediated activation of PLC-\(\gamma\)-2 and consequent production of Ins-1,4,5-P\(_3\), is also required for EMF-induced activation of PLC-\(\gamma\)-2. SYK-deficient cells reconstituted with a C-terminal SH2 domain mutant syk gene also failed to elicit increased inositol phospholipid turnover after EMF exposure (Fig. 2B), whereas SYK-deficient cells reconstituted with an N-terminal SH2 domain mutant syk gene showed a significant EMF response (Fig. 2C). Whereas no SYK protein or associated kinase activity could be detected in SYK-deficient cells, the amount of...
FIG. 3. EMF-induced activation of inositol phospholipid turnover in LYN-deficient DT40 lymphoma B cells. Cells (5 × 10⁶/ml) were exposed to EMF (diamonds) or sham-treated controls (CON, squares), and then assayed for Ins-1,4,5-P³ as described in Fig. 1. A, LYN-deficient (LYN−) mutant DT40 cells. B, LYN-deficient DT40 cells reconstituted with a wild-type fyn gene. C, LYN-deficient mutants reconstituted with a fyn gene containing a mutation in the SH2 domain. D, LYN-deficient DT40 cells reconstituted with a fyn gene containing a kinase domain mutation (K−). E, LYN-deficient mutants reconstituted with a fyn gene containing a mutation in the SH3 domain. In A–E, the results are expressed as the mean pmol amounts of Ins-1,4,5-P³ per 1 × 10⁶ cells. Data points represent the mean and S.E. of the Ins 1,4,5-P³ values obtained from independent experiments. N = number of independent experiments each performed with duplicate measurements for each time point. F, anti-FYN and anti-actin Western blot analyses were performed using the ECL chemiluminescence detection system to compare the relative wild-type or mutant FYN protein levels in the individual cell lines, as described under “Experimental Procedures.” FYN protein was detected only in FYN-reconstituted cell lines, since the wild-type DT40 cells express high levels of LYN but not any FYN (18, 19).

mutant SYK protein (Fig. 2D) and associated kinase activity (Fig. 2E) in the SYK-deficient cell line reconstituted with the C-terminal SH2 domain mutant syk gene were actually higher than the amount and associated kinase activity of the wild-type SYK protein in the parent cell line. Therefore, the absence of an EMF-induced Ins-1,4,5-P³ signal in this cell line indicates that the C-terminal SH2 domain of SYK is required for the EMF-induced Ins-1,4,5-P³ signal. Since both SYK-SH2 domain mutant cell lines expressed similar amounts of the respective mutant SYK proteins and associated kinase activity (Fig. 2, D and E), the absence of the Ins-1,4,5-P³ signal in the mutant cell line reconstituted with the C-terminal SH2 domain-mutant form of SYK cannot be explained by lower levels or less kinase activity of the mutant SYK protein in that cell line. Our results indicate that only the C-terminal SH2 domain of SYK is required for the EMF-induced Ins-1,4,5-P³ signal. The magnitude and kinetics of the Ins-1,4,5-P³ signal in the SYK-deficient DT40 cells reconstituted with the N-terminal SH2 domain-mutant form of SYK were different than those in wild-type DT40 cells. The reasons for these differences, which may be due to the relatively higher levels of kinase active SYK protein expression in the reconstituted cells (Fig. 2, D and E), remain unknown. We also noticed that the differences in SYK activity between the SH2-domain mutant versus wild-type DT40 cells were greater than predicted from the apparent SYK protein levels. The reasons for these observations are unknown but may relate to the inability of SH2 domain mutant SYK to interact with an as yet unidentified inhibitor associated with the SYK SH2 domain. Role of LYN Kinase and Its Downstream Substrate SYK in Activation of PLC-γ2 in DT40 Lymphoma B Cells Exposed to Low Energy EMF—Because LYN kinase is required for the antigen receptor-induced PLC-γ2 activation in DT40 cells and functions upstream of SYK (10), we next examined the role of LYN kinase in EMF-induced inositol phospholipid turnover. Targeted disruption of the lyn gene abolished the EMF-induced Ins-1,4,5-P³ signal (Fig. 3A). Introduction of the wild-type (Fig. 3B) or an SH2 domain mutant (Fig. 3C) but not a kinase domain mutant fyn gene (Fig. 3D) or an SH3 domain mutant fyn gene (Fig. 3E) into LYN-deficient cells restored the EMF responsiveness, even though LYN-deficient cells reconstituted with these genes expressed similar amounts of FYN protein (Fig. 3F). Thus, the kinase and SH3 domains of FYN are required for its ability to restore the EMF responsiveness in LYN-deficient cells. However, the Ins-1,4,5-P³ signal in FYN(WT)-reconstituted cells was monophasic with a single peak at 45 s (Fig. 3B), whereas the Ins-1,4,5-P³ signal in the parent cell line was biphasic with one early peak at 15 s and a second peak at 1 min (Fig. 1A). Furthermore, the magnitude of the Ins-1,4,5-P³ signal was larger in wild-type FYN-reconstituted cells as compared with wild-type DT40 cells as reported (18) and in all cell lines tested here. However, when we exposed wild-type fyn gene to EMF, a biphasic Ins-1,4,5-P³ signal was not observed (Fig. 3F). Therefore, reactivation of LYN-deficient cells with a wild-type fyn gene demonstrates that LYN kinase interacts with FYN, which may be due to the apparent similarity of the Ins-1,4,5-P³ signal in the parent cell line. While these results provide conclusive evidence that the SH2 domain of FYN is not required for the EMF-induced Ins-1,4,5-P³ signal, they also demonstrate that, despite the apparent similarity of the Ins-1,4,5-P³ signal between the SH2 domain mutants, the differences in activity of the SH2 domain mutants may indicate that the SH2 domain may play a role in the signaling pathway activated by EMF exposure and stimulation with an anti-IgM antibody, significant differences must exist between EMF-induced signaling events and signaling events induced by engagement of the B cell antigen receptor for which the SH2 domain of Src family PTK play a pivotal role. In summary, we examined the molecular mechanism of enhanced inositol phospholipid turnover in lymphoma B cells exposed to low energy EMF. Our findings are consistent with a...
sequential activation model, according to which EMF exposure first leads to activation of Src family PTK. Src family PTK interact with and phosphorylate as yet unidentified immunoreceptor tyrosine-based activation motifs (ITAMs), leading to recruitment of SYK tyrosine kinase as well as PLC-γ2 via their SH2 domains to phosphorylated ITAMs. However, we have no evidence that Src family PTK interact with an ITAM motif in EMF-stimulated cells, as proposed in this model. Subsequently, SYK may be activated by Src family PTK and phosphorylate PLC-γ2, leading to PLC-γ2 activation. Activation of PLC-γ2 results in increased inositol phospholipid turnover, production of Ins-1,4,5-P3 and protein kinase C activation. This study further supports the hypothesis that a delicate growth regulatory balance in B-lineage lymphoid cells might be altered by EMF exposure. The mechanism by which exposure of lymphoma B cells to low energy EMF triggers activation of Src family PTK remains to be deciphered.

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J. Biol. Chem. 1998, 273:4035-4039.
doi: 10.1074/jbc.273.7.4035

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