Tyrosine Phosphorylation of the vav Proto-oncogene Product Links FceRI to the Rac1-JNK Pathway*

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Stimulation of high affinity IgE Fc receptors (FceRI) in basophils and mast cells activates the tyrosine kinases Lyn and Syk and causes the tyrosine phosphorylation of phospholipase C-γ, resulting in the Ca^{2+} and protein kinase C-dependent secretion of inflammatory mediators. Concomitantly, FceRI stimulation initiates a number of signaling events resulting in the activation of mitogen-activated protein kinase (MAPK) and c-Jun NH2-terminal kinase (JNK), which, in turn, regulate nuclear responses, including cytokine gene expression. To dissect the signaling pathway(s) linking FceRI to MAPK and JNK, we reconstructed their respective biochemical routes by expression of a chimera interleukin-2 receptor α subunit (Tac)-FceRI γ chain (Tacy) in COS-7 cells. Cross-linking of Tacy did not affect MAPK in COS-7 cells, but when coexpressed with the tyrosine kinase Syk, Tacy stimulation potently induced Syk and Shc tyrosine phosphorylation and MAPK activation. In contrast, Tacy did not signal JNK activation, even when coexpressed with Syk. Ectopic expression of a hematopoietic-specific guanine nucleotide exchange factor (GEF), Vav, reconstituted the Tacy-induced, Syk- and Rac1-dependent JNK activation; and tyrosine-phosphorylation of Vav by Syk stimulated its GEF activity for Rac1. Thus, these data strongly suggest that Vav plays a critical role linking FceRI and Syk to the Rac1-JNK pathway. Furthermore, these findings define a novel signal transduction pathway involving a multimeric cell surface receptor acting on a cytosolic tyrosine kinase, which, in turn, phosphorylates a GEF, thereby regulating its activity toward a small GTP-binding protein and promoting the activation of a kinase cascade.

Activation of high affinity IgE Fc receptors (FceRI) in basophils and mast cells induces the rapid release of histamine and other inflammatory mediators from secretory granules, and initiates a cascade of signal transduction events leading to enhanced production and secretion of various biologically active cytokines (1). One of the earliest events induced upon FceRI aggregation is the activation of the nonreceptor tyrosine kinases Lyn and Syk, and the tyrosine phosphorylation of cytoplasmic molecules, including phospholipase C-γ (2). Phosphorylated phospholipase C-γ hydrolyses phosphatidylinositol 4,5-bisphosphate and liberates inositol 1,4,5-trisphosphate and diacylglycerol, which mobilizes Ca^{2+} from intracellular and extracellular sources and activates protein kinase C (3), respectively. Whereas these second-messenger generating systems appear to be sufficient for the FceRI-mediated secretory response (4), whereas signals initiated by FceRI aggregation at the plasma membrane are transmitted to the nucleus thereby controlling cytokine gene expression is much less understood.

Recently, it has been shown that stimulation of FceRI in mast cell lines, such as RBL-2H3 cells, leads to the activation of members of the mitogen-activated protein kinase (MAPK) superfamily of serine-threonine kinases. The function of these enzymes is to convert extracellular stimuli to intracellular signals which, in turn, participate in gene expression regulation. In particular, engagement of FceRI receptors in mast cell lines has been shown to result in the activation of MAPK and JNK (5, 6). In this regard, recent available evidence suggests that engagement of FceRI with antigen leads to the increased tyrosine phosphorylation of Shc and the association of Shc with Grb2, thus resulting in the recruitment of SOS and the stimulation of the Ras-MAPK pathway. Furthermore, Shc phosphorylation and MAPK activation was shown to be diminished upon overexpression of a dominant negative mutant of Syk, thus suggesting a central role for this kinase in the biochemical route communicating FceRI to MAPK (5). In contrast, how FceRI stimulation activates JNK is still unknown.

In this study, we thought to dissect the signaling pathway(s) linking FceRI to MAPK and JNK by reconstructing their respective biochemical routes upon ectopic expression of signaling molecules in COS-7 cells. Using this experimental approach, we provide evidence that whereas Syk and Shc connect FceRI to the Ras-MAPK pathway, signaling from FceRI to JNK involves the tyrosine phosphorylation by Syk of a hematopoietic specific guanine-nucleotide exchange factor, Vav, the exchange of GDP for GTP-bound to Rac1, and the consequent stimulation of a kinase cascade leading to JNK activation.

MATERIALS AND METHODS

RBL-2H3 Cell Stimulation—RBL-2H3 cells were grown in DMEM supplemented with 10% fetal bovine serum (FBS). Before cross-linking of IgE, cells were incubated overnight in DMEM containing 0.1% FBS. Sensitization with anti-trinitrophenyl (TNP) IgE ascites fluid (1:5,000) at 37 °C for 2 h and cross-linking with 0.1 μg/ml diisopropylfluorophosphorylated phosphatidylcholine (Avanti Polar Lipids, Inc.) was performed at 37 °C for 2 h. Sensitized cells (0.1 μg/ml) were washed and cultured overnight.

COS-7 Cell Transfection and Stimulation—Expression plasmids (1 μg/plate) were transfected into subconfluent COS-7 cells by the DEAE-dextran technique (8), adjusting the total amount of DNA to 5 μg/plate with vector DNA (pcDNA3, Invitrogen) when necessary. Forty-eight hours later, transfected cells were collected and washed three times with DMEM containing 0.1% FBS.

The abbreviations used are: MAPK, mitogen-activated protein kinase; JNK, c-Jun NH2-terminal kinase; BTL, rat basophilic leukemia; DMEM, Dulbecco's modified Eagle's medium; FBS, fetal calf serum; TNP, trinitrophenyl; DNP, dinitrophenyl; GEF, guanine nucleotide exchange factor.

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RESULTS AND DISCUSSION

To begin dissecting the signaling pathway(s) linking FceRI to MAPK and JNK, we initially studied the temporal relationship between MAPK and JNK activation in RBL-2H3 cells. As expected, engagement of FceRI by addition of dinitrophenyl (DNP) coupled to human serum albumin to anti-TNP IgG primed RBL-2H3 cells potently activated MAPK and JNK, however, each followed a distinct temporal pattern (Fig. 1, A and B). These data suggested that MAPK and JNK might be activated by different signaling pathways. For MAPK, FceRI cross-linking is known to activate the nonreceptor tyrosine kinase Syk, and it has been suggested recently that Syk phosphorylates the adapter protein Shc, thereby stimulating the Ras-MAPK pathway through Grb2 and Sos (10). Consistent with that, we observed that in RBL-2H3 cells FceRI activation leads to the rapid tyrosine phosphorylation of Syk and the adapter protein Shc, following a time course similar to that of MAPK stimulation (Fig. 1, C and D).

FceRI is a multimeric receptor containing a single α and β subunit and a homodimer of γ subunits (11). Both β and γ chains exhibit a structural motif termed ITAM, for immunoreceptor tyrosine-based activation motif (12), which participate in the recruitment of cytoplasmic tyrosine kinases and in the consequent tyrosine phosphorylation of their downstream targets (1). Studies with chimeric molecules containing the extracellular and transmembrane domains of the interleukin-2 receptor α subunit (Tac) fused to the cytosolic domain of β (Tacβ) and γ (Tacγ) chains of FceRI have helped simplify the analysis of early signaling events provoked by FceRI activation (13). When expressed in RBL-2H3 cells, cross-linking of the Tac chimera is sufficient to mimic the majority of the biochemical and biological responses triggered by FceRI stimulation. In contrast, cross-linking of Tacβ does not appear to elicit signaling responses (13). Therefore, to investigate whether activation of Tacγ is sufficient to activate Syk, both were expressed in COS-7 cells, which lack endogenous FceRI or Syk (see below). TransfectedTacγ was efficiently expressed, as judged by immunofluorescence labeling techniques (data not shown). Cross-linking of Tacγ chimeras with biotinylated anti-Tac antibodies followed by streptavidin induced the rapid tyrosine phosphorylation of a coexpressed epitope-tagged Syk (Fig. 2A). When coexpressed with an epitope-tagged form of Shc, cross-linking of Tacγ induced only a limited increase in Shc tyrosine phosphorylation (Fig. 2B). However, when Syk was coexpressed, Tacγ engagement provoked a rapid and substantial increase in Shc tyrosine phosphorylation (Fig. 2B). Parallelizing Shc phosphorylation, cross-linking of Tacγ induced a very poor MAPK response, but when coexpressed with Syk, Tacγ potently elevated the phosphorylating activity of MAPK to an extent comparable with that elicited in response to EGF (Fig. 2C). Taken together, these results support a central role for the γ subunit of FceRI and Syk in signaling from IgE receptors to the MAPK pathway. Surprisingly, however, cross-linking of Tacγ chimeras did not result in JNK activation, even when coexpressed with Syk. As a control, EGF effectively elevated JNK activity under identical experimental conditions (Fig. 2C). Collectively, these data established that coexpression of Tacγ and Syk in COS-7 cells is sufficient to reconstitute the MAPK response to FceRI stimulation, while suggesting that additional molecules not endogenously expressed in COS-7 cells were necessary to link FceRI to JNK.

Whereas Ras controls the activation of MAPK, we and others have recently observed that two members of the Rho family of small GTP-binding proteins, Rac1 and Cdc42, regulate JNK activity (8). Although most molecules connecting Syk to Ras, including Shc, Grb2, and Sos, are ubiquitously expressed, guanine nucleotide exchange factors (GEFs) for Rho, Rac1, and Cdc42 exhibit a very restricted cell type and tissue distribution (14). Thus, we hypothesized that COS-7 cells might lack an endogenous Rho family GTPase, and we tested this by transfecting COS-7 cells with an expression vector for pcDNA3 Myr-Syk. Following coexpression of Tacγ and Syk in signaling from IgE receptors to the MAPK pathway, cells were maintained in serum-free medium containing 125 g/mI of aprotinin, 25 g/ml leupeptin, and 25 g/ml sodium orthovanadate, 1 mM phenylmethylsulfonyl fluoride, 250 mM NaCl, and resuspended in 1 M KH2PO4, 5mM EDTA (pH 8.0). Bound nucleotides were released by heating and fractionated using polyethyleneimine thin layer chromatography plates (J. T. Baker).
product (Vav) (Fig. 3A), which is preferentially expressed in cells of the hematopoietic lineage. Moreover, Vav exhibits structural motifs frequently found in GEFs for small GTP-binding proteins of the Ras and Rho families (14), and we have shown recently that truncated, oncogenically active forms of Vav (Onco-Vav), can potently activate JNK, but not MAPK, acting on a Rac-1-dependent signaling pathway (15). These results prompted us to explore the possibility that wild-type Vav serves as a link between FceRI and the Rac-1-JNK pathway.

Expression of Vav alone (15) or together with the Tacy chimeras failed to induce JNK activation (Fig. 3B), and cross-linking of Tacy failed to induce Vav tyrosine phosphorylation when coexpressed in COS-7 cells (Fig. 3B). However, when Tacy, Syk and Vav were each simultaneously coexpressed in these cells, Tacy aggregation resulted in enhanced Vav tyrosine phosphorylation and a remarkable activation of JNK. These data together with results obtained in RBL-2H3 cells demonstrate the importance of Vav in signaling from FceRI/Syk to JNK.

We next asked whether recruitment of Syk to the plasma membrane upon aggregation of FceRI or cross-linking of Tacy chimeric molecules is the determining step initiating activity of Syk downstream signaling pathways. To that end, we examined the ability of a membrane-targeted form of Syk to bypass the requirement of Tacy engagement for signaling to the MAPK and JNK pathway. A chimeric protein containing the NH₂-terminal myristoylation signal of Src fused to Syk (Myr-Syk), localized to the plasma membrane when expressed in COS-7 cells, rather than exhibiting the typical cytosolic location of wild-type Syk (Ref. 16 and data not shown). Furthermore, this membrane-targeted form of Syk was heavily tyrosine-phosphorylated (Fig. 3C), and its expression was sufficient to elevate the activity of a cotransfected epitope-tagged MAPK (Fig. 3D).

FIG. 3. Phosphorylation of Vav in RBL-2H3 cells and COS-7 cells. A. RBL-2H3 cells were left unstimulated (0 min) or treated with IgE + DNP. Cells were lysed, and Vav was immunoprecipitated with antisera to Vav and analyzed by immunoblotting with antibodies to phosphotyrosine (Anti-pTyr) or anti-Vav. B. Expression of wild-type Vav or mutants thereof in COS-7 cells transfected with pcDNA3-HA-Vav, pcDNA3-Tacy + pcDNA3 Syk + Vav, or pcDNA3-Tacy + pcDNA3 Syk + Vav. C. Localization of Myr-Syk in COS-7 cells. Total cellular extracts were immunoprecipitated with antisera to Src (anti-Myr) and immunoblotted with antibodies to phosphotyrosine (Anti-pTyr) or antisera to Vav. D, activation of MAPK and JNK by overexpression of Myr-Syk. COS-7 cells were transfected with pcDNA3 expression vector carrying cDNAs for pcDNA3 or pcDNA3-HA-Shc, and pcDNA3 Syk or pcDNA3 HA-Syk, as indicated. Cells were transfected with pcDNA3 Tac and pcDNA3 HA-Syk, or pcDNA3-Tacy + pcDNA3 Syk, or pcDNA3 Syk alone (vector), as indicated. Cell lysates were immunoprecipitated with antibodies to HA and analyzed by immunoblotting with antibodies to phosphotyrosine or to HA. Total cell lysates were immunoprecipitated with antibodies to HA and analyzed by immunoblotting with antibodies to phosphotyrosine (Anti-pTyr) and antiserum to Syk. B. COS-7 cells were transfected with pcDNA3 Tacy, pcDNA3 HA Shc, and pcDNA3 Syk or pcDNA3 alone (vector), as indicated. Cell lysates were immunoprecipitated with antibodies to HA and analyzed by immunoblotting with antibodies to phosphotyrosine or to HA. Total cell lysates were immunoprecipitated with antiserum to Syk. C. COS-7 cells were transfected with pcDNA3-HA-MAPK or pcDNA3-HA-JNK for, respectively, MAPK and JNK assays, together with pcDNA3 alone, pcDNA3 Tacy, or pcDNA3 Tacy + pcDNA3 Syk, as indicated. COS-7 cells were left unstimulated (0 min) or treated with IgE + DNP or anti-Tac. MAPK and JNK activity was assayed in cellular lysates. These experiments were repeated five times with similar results.
the levels of 32P-labeled GDP bound to these small GTPases. We took advantage of a recently described technique that uses radiolabeled GDP containing medium to evaluate their nucleotide exchange activity on bacterially expressed Rac1 when analyzed in vivo. In this regard, the high intrinsic GTPase activity of Rho, Rac1, and Cdc42 upon overexpression of Myr-Syk and Vav in COS-7 cells. C, effects of dominant negative mutants of Rac, Ras, RhoA, and Cdc42 on JNK activation induced by cross-linking of Tac in Syk and Vav transfectants. COS-7 cells were transfected with pcDNA3-HA-JNK together with pcDNA3 alone or dominant negative mutants of Ras, Rac1, RhoA, and Cdc42, as indicated. COS-7 cells were left unstimulated (0 min) or treated with antibodies to Tac (15 min). COS-7 cells were lysed, and JNK assays were performed as described (11). Data represent the average ± S.E. of three independent experiments, expressed as fold increase in JNK activity with respect to vector transfected cells (vector).

brane, no other FcεRI-associated kinases are required to signal to MAPK or to activate JNK in a Vav-dependent manner.

We have reported recently that JNK activation by Onco-Vav can be blocked by expression of a dominant negative mutant of Rac-1, N17 Rac-1 (15), thereby inferring that Onco-Vav acts as a GEF for Rac-1. In view of those results and our present data, we next asked whether expression of Vav proteins could promote guanine nucleotide exchange on Rac1 in vivo. In this regard, the high intrinsic GTPase activity of Rho, Rac1, and Cdc42 has prevented the detection in living cells of their corresponding GTP-bound forms (17). Thus, for these experiments we took advantage of a recently described technique that uses the levels of 32P-labeled GDP bound to these small GTPases after a brief exposure to 32Porthophosphate-containing medium as an approach to evaluate their nucleotide exchange in vivo. Initially, we expressed in COS-7 cells AU5-epitope-tagged Hs-Ras, RhoA, Rac1, and Cdc42 (18, 19), together with empty expression vector (control), a membrane-targeted form of the catalytic domain of Sos (Myr-Sos) (8), or Onco-Vav (Fig. 4A). All tagged small GTP-binding proteins were efficiently expressed, as judged by Western blotting with the anti-epitope antibody. Furthermore, when transfected cells were starved and then cultured for a short period of time in the presence of 32Porthophosphate, each small GTPase incorporated labeled GDP, as determined by thin layer chromatography analysis of anti-AU5 immunoprecipitates. Under these experimental conditions, no labeled nucleotides were observed in mock-transfected cells (not shown), and Myr-Sos consistently enhanced 2–3-fold the level of radioactive GDP bound to Ras, without displaying any demonstrable effect on the other small GTP-binding proteins (Fig. 4A, left panel). As a control, we used the standard, more prolonged incubation with [32P]orthophosphate containing medium. Under those conditions, Myr-Sos induced a dramatic increase in GTP-bound Ras (Fig. 4A, right panel). In contrast, under either incubation time expression of Onco-Vav did not affect Ras, but increased the level of labeled GDP bound to Rac1 more than 8-fold (Fig. 4A). Collectively, these results indicate that Onco-Vav can promote guanine nucleotide exchange in vivo on Rac1.

Under identical experimental condition, neither wild-type Vav nor Myr-Syk induced nucleotide exchange on Rac1 (Fig. 4B), which was consistent with the failure of each one alone to induce JNK activity (see above). However, when Myr-Syk was coexpressed with Vav, we observed a dramatic increase in the incorporation of labeled GDP into Rac1. These two observations, 1) potent JNK activation provoked by coexpression of Myr-Syk together with Vav or upon cross-linking of Tac when coexpressed with Syk and Vav and 2) Syk’s ability to effectively tyrosine-phosphorylate Vav in vivo, strongly suggest that Syk-induced tyrosine phosphorylation of Vav increases its GEF toward Rac1, leading to JNK activation. Consistent with this conclusion, JNK stimulation induced by Tac cross-linking in Tacγ, Syk-, and Vav-transfected COS-7 cells was blocked by the dominant negative mutant of Rac1, N17 rac1 (Fig. 4C). Moreover, we have recently observed that tyrosine phosphorylation of purified Vav protein dramatically enhances its GEF activity on bacterially expressed Rac1 when analyzed in vitro (19), further supporting the emerging notion that Vav behaves as a tyrosine phosphorylation-dependent GEF for Rac1.

A number of GEFs for small GTP-binding proteins of the Rho family have been identified by virtue of their transforming potential in murine fibroblasts (20). Nevertheless, the normal function of these GEFs, as well as the molecular mechanisms controlling their enzymatic activity in their natural setting, is still unknown. In this regard, our findings provide solid evidence that whereas Onco-Vav is constitutively active, wild-type Vav only promotes guanine nucleotide exchange in Rac1 upon activation of an upstream tyrosine kinase, Syk, and that Vav function(s) in this setting are controlled by tyrosine phosphorylation. Thus, these findings define a novel signal transduc-
tion pathway involving a cell surface receptor activating a nonreceptor tyrosine kinase, which, in turn, phosphorylates a GEF in tyrosine residues, thereby regulating its activity toward a small GTP-binding protein and promoting the activation of a kinase cascade. A schematic representation of such a likely biochemical route, including, sequentially, FcεRI, Syk, Vav, Rac1, and its downstream target, JNK, as well as the pathway connecting Syk to MAPK is depicted in Fig. 5.

Our present findings might also have important implications regarding the functioning of other multimeric antigen receptors. As discussed above, in mast cells accumulating evidence demonstrates that the $\gamma$ subunit of FcεRI signals Syk activation. The FcεRI $\gamma$ chain is functionally analogous to the $\zeta$ chain of the antigen T cell receptor, and whereas FcεRI $\gamma$ subunits recruit Syk, the T cell receptor $\zeta$ subunits interact with Zap70 (21, 22). Furthermore, T cell receptor and B cell receptor activation both lead to Vav tyrosine phosphorylation (23, 24) and JNK activation (25). Based upon our results, it is predictable that Vav plays a common role in basophils, mast cells, T cells, and B cells, linking multimeric antigen receptors and their associated downstream nonreceptor tyrosine kinases to the Rac1-JNK signaling pathway.

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REFERENCES
1. Scharenberg, A. M. & Kinet, J. P. (1995) Chem. Immunol. 61, 72–87
2. Eisenman, E. & Bolen, J. B. (1992) Nature 355, 78–80
3. Ozawa, K., Yamada, K., Kazanietz, M. G., Blumberg, P. M. & Beaven, M. A. (1993) J. Biol. Chem. 268, 1749–1756
4. Jabril-Cuenod, B., Zhang, C., Scharenberg, A. M., Paolini, R., Numerof, R., Beaven, M. A. & Kinet, J. P. (1996) J. Biol. Chem. 271, 16268–16272
5. Hirasawa, N., Andrew, S., Yamamura, H., Beaven, M. A. & Kinet, J. P. (1995) J. Biol. Chem. 270, 10960–10967
6. Ishizuka, T., Oshiba, A., Sakata, N., Terada, N., Johnson, G. L. & Gelfand, E. W. (1996) J. Biol. Chem. 271, 12762–12766
7. Benhamou, M., Gutkind, J. S., Robbins, K. C. & Siraganian, R. P. (1990) Proc. Natl. Acad. Sci. U. S. A. 87, 5327–5330
8. Coso, O. A., Chiariello, M., Yu, J. C., Teramoto, H., Crespo, P., Xu, N., Miki, T. & Gutkind, J. S. (1995) Cell 81, 1137–1146
9. Fazioli, F., Minichiello, L., Matsoska, E., Wong, W. T. & Di Fiore, P. P. (1993) Mol. Cell. Biol. 13, 5814–5828
10. Jabril-Cuenod, B., Zhang, C., Scharenberg, A. M., Paolini, R., Robert, N., Beaven, M. A. & Kinet, J. P. (1996) J. Biol. Chem. 271, 16268–16272
11. Ravetch, J. V. & Kinet, J. P. (1991) Annu. Rev. Immunol. 9, 457–492
12. Weiss, A. & Littman, D. R. (1994) Cell 76, 263–274
13. Letourneur, F. & Klausner, R. D. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 8905–8909
14. Hart, M. J., Eva, A., Zangrilli, D., Aaronson, S. A., Evans, T., Cerione, R. A. & Zheng, Y. (1994) J. Biol. Chem. 269, 62–65
15. Crespo, P., Bustelo, X. R., Aaronson, D. S., Coso, O. A., Lopez-Barahona, M., Barbacid, M. & Gutkind, J. S. (1996) Oncogene 13, 455–466
16. Taniguchi, T., Kobayashi, T., Kondo, J., Takahashi, K., Nakamura, H., Suzuki, J., Nagai, K., Yamada, T., Nakamura, S. & Yamamura, H. (1991) J. Biol. Chem. 266, 15790–15796
17. Laudanna, C., Campbell, J. J. & Butcher, E. C. (1996) Science 271, 981–983
18. Teramoto, H., Coso, O. A., Miyata, H., Iigishi, T., Miki, T. & Gutkind, J. S. (1996) J. Biol. Chem. 271, 27225–27228
19. Crespo, P., Schuebel, K. E., Ostrom, A. A., Gutkind, J. S. & Bustelo, X. R. (1997) Nature 385, 169–172
20. Boguski, M. S. & McCormick, F. (1993) Nature 366, 643–654
21. Chan, A. C., Iwashima, M., Turck, C. W. & Weiss, A. (1992) Cell 71, 649–662
22. Iwashima, M., Irving, B. A., van Oers, N. S., Chan, A. C. & Weiss, A. (1994) Science 263, 1136–1139
23. Bustelo, X. R. & Barbacid, M. (1992) Nature 356, 68–71
24. Margolis, B. (1992) Nature 356, 71–74
25. Su, B., Jacinto, E., Hibi, M., Kallunki, T., Karin, M. & Ben-Neriah, Y. (1994) Cell 77, 727–736
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