An obligatory step in the activation of Signal Transducers and Activators of Transcription (STATs) by cytokines is their docking to specific receptors via phosphorylating kinases. However, this model does not address whether STATs pre-associate with their corresponding receptor or exist free in the cytoplasm before receptor activation. In this report, we demonstrate that pre-association of STAT1 with the receptor is required for type I interferon (IFN) signaling. Interestingly, the interaction between the human type I IFN receptor and STAT1 is not direct but mediated by the adapter protein receptor for activated protein kinase C (RACK1). Disruption of the IFNα receptor-RACK1 interaction abrogates not only IFNα-induced tyrosine phosphorylation of STAT1 but also activation of STAT2, indicating that RACK1 plays a central role in early signaling through the Jak-STAT pathway. These findings demonstrate the involvement of RACK1 in STAT1 activation and raise the possibility that other STATs may pre-associate with cytokine receptors through similar adapter-STAT-mediated interactions.

Cytokines and interferons (IFNs) bind to receptors of the cytokine receptor superfamily (1–3), resulting in the activation of kinases of the Jak family and transcription factors designated STATs or Signal Transducers and Activators of Transcription (4–7). The Jak-STAT pathway has evolved as the paradigm of cytokine and IFN signaling (4–7). Although STAT can be activated by different cytokines (i.e. STAT1 is activated by IFNα, IFNγ, IL6, leukemia inhibitory factor, IL10, etc.), studies with knockout mice clearly indicated that their function is well restricted to precise systems. For example, STAT1 is only required for the physiological functions of IFNα and IFNγ (reviewed in Ref. 7).

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† ‡ Researches at the laboratories of both authors contributed equally to this article.
¶ To whom correspondence should be addressed: Dept. of Pharmacology, University of Illinois, Chicago, Illinois 60612.
© The abbreviations used are: IFN, interferon; STAT, Signal Transducer and Activator of Transcription; IL, interleukin; IFNα, IFNβ, IFNγ, receptor; RACK1, receptor for activated protein kinase C; IFNαRβL, long form of the β subunit of the IFNαR; GST, glutathione S-transferase; hu, human; StIP, STAT3-Interacting Protein.

STATs are recruited to distinct phosphotyrosines within the receptor complex and then are phosphorylated, probably by Jaks, on the highly conserved C-terminal tyrosines (i.e. tyrosine 701 of Stat1), allowing the SH2 domain of one STAT to interact with the phosphorylated tyrosine on another STAT to form homo- or heterodimers. STAT dimers translocate to the nucleus, where they bind specific DNA elements to activate or inhibit transcription of specific genes (reviewed in Refs. 5 and 8).

One distinctive feature in the type I IFN system is that STAT2 is pre-associated with IFNαRβL chain (9, 10). Activation of STAT2 in response to type I IFNs (IFNα, β, or ω) requires the presence of this constitutive site and one or more of the five proximal tyrosines of the βL chain (9). However, the mechanism for STAT1 activation by type I IFNs has not been elucidated. It is known that activation of STAT1 requires the previous activation of STAT2 (11), but it has not been determined whether receptor tyrosines are also required for activation. This is in clear contrast to the activation of STAT1 by IFNγ, which requires docking of STAT1 to a phosphorylated tyrosine on the α chain of the receptor (12).

We have recently reported (13) that RACK1, originally described as a Receptor for Activated C Kinase β (14–16), constitutively interacts with the β long subunit of the type I IFN receptor (IFNαRβL/IFNAR2). RACK1 has a molecular mass of 36,000 daltons and is composed of 7 WD repeats that resemble the structure of the β subunit of G proteins (Gβ) (17, 18). RACK1 also interacts with protein kinase C β, σ19, and integrins (20), PDE4D5 (21), and the β common subunit of the granulocyte/macrophage colony-stimulating factor/IL3/IL5 receptors (22).

We report here that RACK1 constitutively interacts with non-phosphorylated STAT1 and functions as an adaptor between this factor and the long form of the β subunit of the IFNαR (IFNαRβL). No interaction between RACK1 and other STAT factors was detected. The interaction between IFNαRβL and RACK1 is critical for normal STAT activation and IFN signaling. This is supported by the finding that mutations in the RACK1 binding site of IFNαRβL, which includes the Box 2 motif, impaired IFNα-induced tyrosine phosphorylation of STAT1 and STAT2 and the development of the antiviral state.

MATERIALS AND METHODS

Cell Lines, Reagents, and Antiviral Assays—U-266 and Daudi cells were grown in RPMI (Life Technologies, Inc.) supplemented with 10% (v/v) fetal bovine serum. Human IFNα2 (specific activity, 2 × 10^8 units/mg) was a gift of Ronald Bordens (Schering-Plough). The anti-phosphotyrosine antibody 4G10 was purchased from Upstate Biotechnologies Inc., and the anti-RACK-1, anti-STAT1, -STAT2, -STAT5, and -Jak1 monoclonal antibodies were purchased from Transduction Labo-
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Rectories, Inc. Polyclonal antibodies against STAT3, STAT4, STAT5, and STAT6 were kindly provided by Drs. Evan Parganas and James Ihle (St. Jude Children’s Research Hospital, Memphis, TN). The anti-Stat1 and -Stat2 sera were kindly provided by Dr. A. Larner (Cleveland Clinic, Cleveland, OH). Antiviral assays were performed as previously described (23, 24).

**Immunoprecipitation and Immunoblotting**—U-266 or Daudi cells (1 × 10⁶ cells) were treated as indicated and then lysed in lysis buffer (20 mM Tris-HCl, pH 6.6 containing 1% Nonidet P-40, 50 mM NaCl, 1 mM EDTA, 2.5% glycerol (v/v), 1 mM sodium fluoride, 1.0 mM sodium orthovanadate, 1.0 mM phenylmethylsulfonyl fluoride, 0.5 μg/ml leupeptin, and 5.0 μg/ml trypsin inhibitor) for 30 min at 4°C. Immunoprecipitations were performed as previously described (9). Proteins were transferred to polyvinylidene difluoride membranes, immunoblotted with the indicated antibodies, and developed using a chemiluminescent detection method (Pierce).

**GST Fusion Proteins and Mammalian Expression Constructs**—The different GST fusion proteins encoding different regions of the cytoplasmic domain of IFNαR1βL have been described previously (25). For mapping of the RACK1 binding site of IFNαR1βL, a combination of two or three alanine mutations per construct was introduced in the GSTβL300–375 that contains the minimum region that binds RACK1. GST fusion expression constructs with mutations of the RACK1 site were made by polymerase chain reaction using the Quickchange kit (Stratagene). All mutations were confirmed by sequencing. A GST fusion protein encoding the full-length RACK1 (GST-RACK1) was produced by polymerase chain reaction and subcloned into the pGEX-KG vector. GST fusion proteins were produced in BL-21 cells as described previously (25). Pull-down experiments and immunoblotting were performed using the same procedure described above for immunoprecipitations.

**Study of the Adaptor Function of RACK1 Using a Wheat Germ in Vitro Translation**—The STAT1 and RACK1 were produced by a T7 wheat germ in vitro transcription/translation kit (Promega) following the manufacturer’s procedure. [35S]Met/homone-labeled STAT1 and RACK1 proteins alone or in combination were incubated with GST-βL overnight, washed, and analyzed by SDS-polyacrylamide gel electrophoresis as described for immunoprecipitations.

**Expression of IFNαR1βL Constructs in Mammalian Cells**—Mammalian expression constructs with mutations of the RACK1 site of IFNαR1βL (amino acids 302, 304, and 305) were made by polymerase chain reaction using the Quickchange kit (Stratagene). All mutations were confirmed by sequencing. Constructs were subcloned into the pCMV-Tag2 vector. GST fusion proteins were produced in BL-21 cells as described previously (25). Pull-down experiments and immunoblotting were performed using the same procedure described above for immunoprecipitations.

**RESULTS**

**RACK1 Specifically Associates with STAT1**—It has been suggested that proteins containing WD repeats may serve as scaffold or adaptor proteins (27). Because RACK1 interacts with a region of IFNαR1βL (amino acids 300–346) (13) that is required for activation of STATs and the antiviral response (25), we hypothesized that RACK1 could recruit STAT1 to the receptor complex. We first performed coimmunoprecipitation experiments using an anti-RACK1 monoclonal antibody to test for an interaction between RACK1 and STAT1. Fig. 1A shows that the anti-RACK1 antibody coimmunoprecipitated STAT1 (upper panel, lane 6) but not STAT3 (lower panel, lane 6) or STAT2 (data not shown) present in unstimulated U266 cell lysates. This interaction is specific, because it cannot be detected in the absence of an IgG control (Fig. 1A, lane 5). The anti-STAT1 and -STAT2 antibodies also coprecipitated STAT3 and STAT1, respectively, as previously reported (28). However, the strong signal for STAT3 detected in anti-STAT1 immunoprecipitates (Fig. 1A, lower panel, lane 2) may correspond in part to incomplete stripping of the membrane after STAT1 immunoblotting. This result strongly suggests that STAT1 specifically interacts with RACK1. It should be noticed, however, that we have not consistently been able to coimmunoprecipitate RACK1 using anti-STAT1 antibodies. One possible explanation is that both antibodies recognize epitopes close to the C-terminal part of the protein, where the RACK1 binding site may be located, and therefore disrupt the interaction.

To further characterize the RACK1-STAT1 interactions, a GST fusion protein that encoded the full-length RACK1 protein was used to determine whether other STAT proteins bind RACK1. Fig. 1B shows that GST-RACK1, but not GST alone, binds to STAT1. However, GST-RACK1 failed to bind STAT2, -3, -4, -5, or -6 (Fig. 1, C–F), confirming that the interaction between RACK1 and STAT1 is specific. Interestingly, GST-βL also bound STAT1 present in cell lysates (Fig. 1B). This result differs from our previous observation using STAT1 produced in wheat germ in vitro translation systems, in which no interaction between IFNαR1βL and STAT1 was detected (9). One possible explanation is that a protein such as RACK1 present in cell lysates, but absent in the wheat germ in vitro translation system, may serve as an adapter between IFNαR1βL and STAT1 (see below).

**RACK1 Functions as an Adaptor between STAT1 and the IFNαR**—We reasoned that if RACK1 links STAT1 to IFNαR1βL, deletions or mutations in IFNαR1βL that decrease RACK1 binding should also decrease the association of STAT1 with the receptor. To test this hypothesis, we performed pull-down experiments using GST fusion proteins containing different regions of the cytoplasmic domain of IFNαR1βL. Fig. 2A, top panel shows that GST fusion proteins encoding the entire cytoplasmic domain (lane 7, GSTβL-wt) and proteins truncated at amino acids 462, 375, and 346 (lanes 5–3), but not at amino acids 265–299 (lane 2), were also able to interact with STAT1. Similarly, a GST fusion protein encoding amino acids 300–515 (Fig. 2A, lane 6, GSTβL300–515) and therefore lacking the first 35 amino acids of the cytoplasmic domain (265–299) also interacts with STAT1. The same GST-βL fusion proteins that bound STAT1 also interacted with RACK1 (Fig. 2A, lower panel). This result indicates that the minimal interaction domain for STAT1 corresponds to amino acids 300–346 of IFNαR1βL and is identical to the RACK1 binding site (Fig. 2A, lower panel and Ref. 13).
We next performed an alanine scan of this region to further define the RACK1 and STAT1 binding sites. Although no individual mutation completely abolished RACK1 or STAT1 binding to GST-βL, some mutations produced a decrease in binding of STAT1 to IFNαRβL that paralleled the decrease in binding of RACK1 to this receptor chain (Fig. 2B). The most intense reduction in binding was observed when amino acids within the region 302–305 and 314–327 of IFNαRβL (Fig. 2B, lanes 2 and 6–8) were mutated to alanine. The overlapping in RACK1 and STAT1 binding sites strongly supports the concept that RACK1 functions as an adaptor between IFNαRβL and STAT1.

Although the interaction between IFNαRβL and STAT1 is detected in cellular lysates (Figs. 1B and 2A), the association between these proteins is not observed when STAT1 is produced in wheat germ lysates (9). A possible explanation for this is that RACK1 functions as an adaptor between IFNαRβL and STAT1 and that the wheat germ homolog of RACK1 fails to interact with IFNαRβL, STAT1, or both. Therefore, we assessed the ability of GST-βL to bind STAT1 produced alone or together with RACK1 using a wheat germ in vitro translation system. Fig. 2C shows that GST-βL interacts with RACK1 but not STAT1 when these proteins are produced separately (Fig. 2C, lanes 2 and 6). However, when RACK1 and STAT1 are in vitro translated together GST-βL pulls down STAT1 (Fig. 2C, lane 10). Thus, IFNαRβL and STAT1 interact only when RACK1 is present, strongly suggesting that RACK1 functions as an adaptor between IFNαRβL and STAT1.

RACK1 Interacts Specifically with the Non-phosphorylated Form of STAT1—Although the experiments presented above demonstrate that the non-activated forms of IFNαRβL, RACK1, and STAT1 form a complex, they do not address whether RACK1 interacts with the phosphorylated form of STAT1. This is an important issue because once STAT1 is phosphorylated it must detach from the receptor to form a DNA-binding complex in association with STAT2 and p48. To address this issue, STAT1 phosphorylation was induced by treating U-266 cells with IFNα for 15 min. Then, we assessed the ability of GST-RACK1 and/or GST-IFNαRβL to associate with tyrosine-phosphorylated STAT1, as determined by immunoblotting with the anti-phosphotyrosine antibody 4G10. Immunoprecipitations with an anti-STAT1 serum or GST alone were used as positive and negative controls, respectively. The resultant precipitates were divided in equal parts, resolved in separate gels, and immunoblotted using either anti-phosphotyrosine or anti-STAT1 antibodies. Fig. 3A shows that neither GST-βL nor GST-RACK1 can precipitate the tyrosine-phosphorylated fraction of STAT1 after IFNα treatment (lower panel, lanes 6 and 7), but both bind non-phosphorylated STAT1 in control cells (upper panel, lanes 2 and 3) as well as the non-phosphorylated fraction after IFNα treatment (upper panel, lanes 6 and 7). As expected, the anti-STAT1 antibody precipitates the phosphorylated and non-phosphorylated forms of STAT1 (Fig. 3A, lanes 4 and 8). Identical results were obtained in similar experiments in which the same membrane was first immunoblotted with anti-phosphotyrosine and then anti-STAT1 antibodies and the converse (data not shown). These results demonstrate that RACK1 interacts only with the non-phosphorylated form of STAT1 and support the concept that STAT1 dissociates from the IFNαRβL-RACK1 complex after becoming phosphorylated to form a DNA-binding complex. This was further demonstrated by the finding that 20 min after IFNα treatment almost all STAT1 was localized to the nucleus (Fig. 3B, panel f), whereas RACK1 fluorescence increased and remained in the cytoplasm (panel e). In untreated cells, RACK1 is detected in the cytoplasm, as previously reported (13), whereas STAT1 was present in both cytoplasm and nucleus (Fig. 3B, panels c and d, respectively). The specificity of the immunofluorescence procedure is demonstrated by the complete lack of signal when normal rabbit serum and anti-IgM were used as negative controls for STAT1 and RACK1 (Fig. 3B, panels a and b, respectively).
The Interaction between RACK1 and IFNαRβL Is Critical for Activation of STAT1, STAT2, and the Antiviral Response—To further determine the importance of the interaction between IFNαRβL, RACK1, and STAT1 in IFNα signaling, we expressed the human IFNαRβL chain with mutations of the RACK1 binding site in mouse L-929 cells. Several stable clones expressing the mutant IFNαRβL chain (designated abLΔR1) were selected by fluorescence-activated cell sorter analysis (Fig. 4). We next tested whether disruption of the interaction between the receptor and RACK1 would prevent the activation of STAT1. Human IFNα2 induced significantly lower levels of STAT1 phosphorylation in cells expressing mutations of the RACK1 binding site (Fig. 5A, lanes 3 and 7), demonstrating that the STAT pathway was functional when activated through the endogenous mouse receptor. The decrease in tyrosine phosphorylation of STAT1 and STAT2 in response to huIFNα treatment was not due to a defect in kinase activation, because tyrosine phosphorylation of Jak1 was normal (Fig. 5A, lower panel).

We next studied whether huIFNα2 was able to elicit an antiviral response in cells expressing a mutation of the RACK1 binding site of IFNαRβL (Fig. 5B, abLΔR1, clones 21 and 24). Fig. 5B shows that huIFNα2 induced significantly lower levels of protection against encephalomyocarditis virus than did murine IFNα4, which activates the endogenous murine receptor, in two independent clones expressing mutations of the RACK1 binding site.

Control

| IgM (red) | NR (green) |
|-----------|------------|
| a, c, and d | a and b |

Non-immune IgM and normal rabbit serum (NR) were used as negative controls (a and b). Translocation of STAT1 was achieved by treatment with huIFNα for 20 min (e and f). Nuclear staining is indicated (arrows).
site. The level of protection detected was also lower than that induced by huIFNα2 in cells expressing the wild type receptor. These results demonstrate that recruitment of RACK1 to the IFNαR complex is critical for the activation of STAT1 and STAT2 and for the induction of an antiviral state.

**DISCUSSION**

The results presented in this study demonstrate that the adaptor protein RACK1 links STAT1 to the human type I IFN receptor. The interaction between the receptor and RACK1 is required for activation of STAT1 and the induction of an antiviral state by huIFNα. The RACK1-mediated interaction between STAT1 and IFNαRβL and the direct association of STAT2 with the distal part of the same chain (9, 10) demonstrate that activation of the STAT pathway by type I IFNs requires the pre-association of STAT factors with the receptor.

These findings raise the question whether a model in which STATs pre-associate with cytokine receptors through adaptor proteins containing a WD motif also applies to other cytokine systems. It has been recently reported that the WD motif-containing proteins containing a WD motif also applies to other cytokine STATs pre-associate with cytokine receptors through adaptor proteins containing a WD motif (solid line). It is tempting to speculate that StIP and RACK1 are members of a novel family of proteins involved in Jak-STAT signaling. The concept that other STAT-specific adaptors may exist is also supported by reports indicating that activation of STAT5 by growth hormone occurs in the presence of growth hormone receptors devoid of all tyrosines.

The alternative to a general model in which all STATs are pre-associated with cytokine receptors is that the only system that requires such pre-association is the type I IFN pathway. In this scenario, the recruitment of STAT1 through RACK1 may reflect a more stringent regulation of STAT activation due to the need for phosphorylation of a specific tyrosine on the receptor for STAT1 activation. Unfortunately, we have not been able to address the latter question, because activation of STAT1 is dependent on the previous activation of STAT2 (11). However, addition of single tyrosines to IFNα chain is critical for STAT1 phosphorylation (12, 32), tyrosine phosphorylation of the IFNα receptor, where phosphorylation of tyrosine 440 of the α chain is critical for STAT1 phosphorylation (12, 32), tyrosine phosphorylation of the IFNαR is not critical for STAT1 activation.

Our data also suggest that once STAT1 is tyrosine-phosphorylated, it can dissociate from RACK1 and the receptor complex. This is supported by the finding that RACK1 interacts only with the inactive (non-phosphorylated) form of STAT1 and that soon after type I IFN stimulation STAT1 is almost exclusively detected in the nucleus, whereas RACK1 remains in the cytoplasm. These data suggest that RACK1 should not be part of the ISGF3 or γ-activated factor complex and does not translocate to the nucleus. This and our previous finding that RACK1 is not tyrosine-phosphorylated (13) further support the concept that RACK1 is an adaptor or scaffold protein important in targeting specific signaling components such as STAT1 to the appropriate subcellular compartment for their activation.

It should be pointed out that the region of IFNαRβL that
interacts with RACK1 appears to overlap, at least in part, with the Box 2 domain. It has been proposed that this motif could play a role in the activation of Jak1 by the IL2Rγ chain (33). Our results suggest that the interaction between RACK1 and the Box 2 motif could be important for the recruitment of specific signaling proteins such as STAT1 and/or for providing the appropriate receptor configuration that allows Jak1 to activate signaling components such as STATs. Unfortunately, the high levels of endogenous RACK1 make it extremely difficult to assess whether the impaired tyrosine phosphorylation of STAT1 and STAT2 observed when RACK1 cannot interact with the receptor is due only to the failure to recruit STAT1 or to the fact that RACK1 may also recruit other signaling proteins. Either mechanism may explain the finding that RACK1 is also required for efficient phosphorylation of STAT2. Thus, the biological significance of RACK1 could go beyond the recruitment of STAT1. This is also suggested by the finding that the Box 2 motif is important in signaling by cytokine receptors in which STAT1 is not required for biological activity.

Finally, it should be pointed out that RACK1, as well as the β-subunit of G-proteins, binds pleckstrin homology domains, the SH2 domain of src, and protein kinase C β, raising the possibility that these or other proteins with similar motifs may be recruited by RACK1 to cytokine receptors. We are currently addressing the possibility that RACK1 recruits ubiquitously expressed proteins activated by type I IFNs such as insulin receptor substrate-phosphatidylinositol 3-kinase, Akt, and Fyn (34–36)2 to the receptor.

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The WD Motif-containing Protein Receptor for Activated Protein Kinase C (RACK1) Is Required for Recruitment and Activation of Signal Transducer and Activator of Transcription 1 through the Type I Interferon Receptor

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