Interleukin-22 (IL-22) Activates the JAK/STAT, ERK, JNK, and p38 MAP Kinase Pathways in a Rat Hepatoma Cell Line

PATHWAYS THAT ARE SHARED WITH AND DISTINCT FROM IL-10*

IL-221 was originally described as an IL-9-induced gene and was called IL-TIF for IL-10-related T cell-derived inducible factor (1). This cytokine shows 22% amino acid identity with IL-10 and belongs to a family of cytokines with limited homology to IL-10, namely IL-10, IL-22, mda-7/IL-24, IL-19, IL-20, and AK155/IL-26 (2–4). As discovered thus far, IL-22 activities include up-regulation of acute-phase reactants in the liver and hepatoma cells (1) as well as induction of pancreatitis-associated protein (PAP1) in pancreatic acinar cells (5), suggesting a role for this cytokine in inflammatory processes. IL-22 also induces STAT activation in several cell lines such as mesangial cells, lung and intestinal epithelial cells, melanomas, and hepatomas (1, 6).

IL-22 binds at the cell surface to a receptor complex composed of two chains belonging to the class II cytokine receptor family: IL-22R1 and Tyk2 but not JAK2, as well as phosphorylation of STAT1, STAT3, and STAT5 on tyrosine residues, extending the similarities between IL-22 and IL-10. However our results unraveled some differences between IL-22 and IL-10 signaling. Using antibodies specific for the phosphorylated form of MEK1/2, ERK1/2, p90RSK, JNK, and p38 kinase, we showed that IL-22 activates the three major MAPK pathways. IL-22 also induced serine phosphorylation of STAT3 on Ser727. This effect, which is not shared with IL-10, was only marginally affected by MEK1/2 inhibitors, indicating that other pathways might be involved. Finally, by overexpressing a STAT3 S727A mutant, we showed that serine phosphorylation is required to achieve maximum transactivation of a STAT responsive promoter upon IL-22 stimulation.

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In this report, we show that binding of IL-22 to its surface receptor on rat hepatoma cell line H4IIE induced the rapid activation of JAK1 and Tyk2, leading to phosphorylation of STAT1, STAT3, and STAT5. IL-22 also activated the three major MAPK pathways: MEK-ERK-RSK, the JNK/SAPK, and the p38 kinase pathways. In addition, IL-22 induced phosphorylation of STAT3 on a serine residue. This further STAT modification was necessary for maximum transactivation and depended only marginally on the ERK pathway.

**Experimental Procedures**

*Cell Culture, Reagents, and Cytokines—H4IIE rat hepatoma cells (from Dr. J.-P. Thissen, University of Louvain, Belgium) were grown in Iscove-Dulbecco’s medium supplemented with 10% fetal calf serum, 0.55 mM l-arginine, 0.24 mM l-asparagine, and 1.25 mM l-glutamine. HEK293-EBNA human embryonic kidney cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum. 2C4, U4C, (generously provided by Dr. Ian Kerr, Imperial Cancer Research Fund, London, UK) and γA (generously provided by Dr. George Stark, Cleveland Clinic Research Institute, Cleveland, OH) fibrosarcoma cells (18, 19) were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum and with 400 μg/ml geneticin (Invitrogen). Recombinant mouse IL-22 was produced either...*
in Escherichia coli as described previously (6, 20) or by transient transfection of HEK293 cells using the LipofectAMINE method (Invitrogen). Recombinant human IL-10 was purchased from Peprotech Inc. (Rocky Hill, NJ). Recombinant mouse IFN-γ was provided by Dr. W. Fiers (University of Gent, Belgium). Cytokines were added to the cultures at the University of Gent concentration: 200 units/ml for rIL-22, 1% for IL-22-containing HEK293 supernatant, 10 ng/ml for IL-10, and 250 units/ml for IFN-γ.

Western Blots and Inhibitor Treatment—H4IIE cells were seeded in 6-well plates (Nunc, Rochester, NY) at 5 x 10^{5} cells/well 1 day before stimulation. The next day, cells were stimulated with new medium containing or not containing IL-22. When indicated, cells were preincubated for 1 h with 50 μM PD98059 (Cell Signaling, Beverly, MA) or 10 μM U0126 (Cell Signaling) MEK inhibitors. After various periods of time, cells were lysed in 500 μl of Laemmli buffer (Bio-Rad) and boiled for 3 min before being loading on pre-cast Novex (Carlsvad, CA) SDS-polyacrylamide gels (8 or 14%) and transferred electrophoretically to nitrocellulose membranes (Hybond C; Amersham Biosciences). Membranes were then blocked in 5% nonfat dry milk, washed, and probed using antibodies specific for phosphorylated Tyk2, STAT1–Y701, STAT3 S727A, or anti-JAK2 antibodies as a control.

Immunoprecipitation—Thirty million H4IIE cells were stimulated with mIL-22 (1% HEK293 cell supernatant), IFN-γ (250 units/ml), or control medium for 5 min, washed, and resuspended in 1 ml of lysis buffer (1% Nonidet P-40, 0.1% deoxycholate, 0.1% SDS, 50 mM Tris, pH 8, 150 mM sodium chloride, 1 mM EDTA, 1 mM sodium vanadate, 1 mM sodium fluoride, and inhibitor mixture (Roche Molecular Biochemicals). Lysates were homogenized by five passages through a 20-gauge needle, incubated for 45 min on ice, and centrifuged (14,000 g). 2.5 μg of anti-JAK1 or anti-JAK2 polyclonal antibody (Upstate Biotechnology, Lake Placid, NY) were added to the supernatant and incubated overnight at 4 °C. Lysates were then incubated with protein A-agarose for 2 h. Beads were washed, resuspended in Laemmli buffer (25 μl), and boiled. Proteins were separated in an 8% SDS-PAGE (Novex, Carlsbad, CA) or 14% SDS-PAGE (University of Gent, Belgium). Cytokines were added to the cultures at 10 ng/ml for IL-10, and 250 units/ml for IL-22. When indicated, cells were preincubated 1 h with 50 μM PD98059 or 10 μM U0126 MEK inhibitors. Luciferase assays were performed using the dual luciferase reporter assay kit (Promega). The same protocol was used for transient transfection of 2C4, U4C, and γ2A fibrosarcoma cells with 500 ng of hIL-22R cDNA, 40 ng of pIK5-JAK1, pRK5-JAK2, or empty vector, 100 ng of pGRR5, and 10 ng of pRL-TK.

RESULTS
IL-22 Induces Phosphorylation of STAT1, STAT3, and STAT5 in Rat Hepatoma Cells—In previous reports, we and others (1, 6–8) showed that IL-22 induced STAT1, STAT3,
and STAT5 phosphorylation in a variety of cell lines including H4IIE. To further study the kinetics of STATs phosphorylation, we stimulated H4IIE cells with IL-22 for various periods of time. Within 5 min, IL-22 induced tyrosine phosphorylation of STAT1, STAT3, and STAT5 (Fig. 1A). This phosphorylation was transient, decreasing to barely detectable levels for STAT1 and STAT5 after 30 min. However, phosphorylated STAT3 could still be detected at least 1 h after IL-22 stimulation (data not shown). To confirm that IL-22-induced STAT phosphorylation correlated with transcriptional activation, we used luciferase assays with pGRR5-luc reporter plasmid. The pGRR5-luc construct is regulated by five copies of a STAT-binding sequence recognizing at least STAT1, STAT3, and STAT5. As shown in Fig. 1B, when H4IIE cells were electroporated with pGRR5-luc, IL-22 stimulation induced a 35-fold increase in luciferase activity.

**IL-22 Activates JAK1 and Tyk2**—As JAK kinases are known to be responsible for STAT phosphorylation in response to cytokines, we next investigated which JAK kinase is activated by IL-22. H4IIE rat hepatoma cells were stimulated with control medium or IL-22, and a Western blot analysis was performed with an anti-phospho-Tyk2 antibody, while the membranes were then reprobed with anti-JAK1 or anti-JAK2 antibody. Similar results were obtained when H4IIE cells were stimulated with E. coli-derived IL-22 (data not shown). C, 400,000 2C4 parental, U4C JAK1-deficient, or γ2A JAK2-deficient cells were seeded in 12-well plates. The next day, cells were transfected with a vector coding for IL-22R together with pGRR5-luc and pRL-TK reporter plasmids and, when mentioned, with a vector coding for JAK1 or JAK2 cDNA. Cells were stimulated with IL-22 (2000 units/ml) or with control medium for 4 h before a luciferase assay was performed.
phosphorylation of Tyk2 and JAK1 but not of JAK2. As a control for JAK2 immunoprecipitation, H4IIE cells were stimulated with IFN-γ/H9253, which is known to activate this JAK family member as well as JAK1 (25). To further assess the functional role of JAK1 in IL-22 signaling, we transfected JAK1-deficient U4C cells with the IL-22R cDNA together with pGRR5-luc reporter plasmid. As shown in Fig. 2C, IL-22 failed to induce a luciferase activity in U4C cells unless these cells were transfected with JAK1 cDNA. By contrast, parental cells (2C4) or JAK2-deficient cells (H9253/2A) were both able to respond to IL-22.

IL-22 Activates MAPK Pathways — We next analyzed the ability of IL-22 to activate the MAP kinase pathways. As shown in Fig. 3A, IL-22 induced a sustained phosphorylation of ERK1/2. Two MEK inhibitors, PD98059 and U0126, totally blocked this phosphorylation, suggesting that ERK1/2 phosphorylation results from MEK activation. In line with this result, IL-22 induced the phosphorylation of MEK1/2 (Fig. 3B). p90RSK, a well known substrate of ERK, was also phosphorylated in response to IL-22. To confirm the functional activation of this pathway, we electroporated H4IIE cells with the pSRE-luc reporter plasmid regulated by the serum-responsive element from the c-fos promoter. As shown in Fig. 4, IL-22 stimulation induced a 2.25-fold increase in luciferase activity, which was completely abolished when cells were preincubated with any of the MEK inhibitors. In contrast with IL-22, IL-10 does not induce phosphorylation of ERK. 5.10^5 H4IIE cells stably transfected with IL-10Ra were seeded in 6-well plates 1 day before stimulation with IL-10 (10 ng/ml) or mIL-22 (2000 units/ml) for 10, 20, 30, or 40 min or with control medium for 40 min. Total lysates were analyzed by Western blot with an anti-phospho-ERK1/2 antibody. The membranes were then reprobed with an anti-β-actin antibody. Similar results were obtained by stimulating H4IIE cells with 1% IL-22-containing 293-EBNA cell supernatant (data not shown).
did not activate the ERK MAPK pathway in H4IIE cells transfected with IL-10Rα cDNA (Fig. 5). In addition to this MEK-ERK-RSK cascade, IL-22 also induced a delayed phosphorylation of JNK/SAPK and p38 MAP kinases, detectable after 30–40 min (Fig. 3B).

**IL-22 Induces STAT3 Serine Phosphorylation by a MAPK-independent Mechanism**—In addition to tyrosine phosphorylation, STAT3 can be phosphorylated on a serine residue in response to cytokines such as IL-6 (22). In our system, IL-22 stimulation of H4IIE cells induced rapid serine phosphorylation of STAT3. Although MAPKs have often been described as mediating STAT3 Ser phosphorylation (22, 26, 27), preincubation of H4IIE cells with MEK inhibitors only slightly delayed but did not inhibit this effect (Fig. 6, A and B).

**IL-22-induced STAT3 Serine Phosphorylation Is Necessary for Maximal Transactivation**—To test the functional significance of STAT3 serine phosphorylation, we transfected H4IIE cells with the pGRR5-luc and pRL-TK reporter plasmids together with a plasmid encoding wild-type or a mutated form of STAT3, in which the serine 727 is mutated into alanine, thus preventing phosphorylation (28). As shown in Fig. 7, mutation of Ser727 of STAT3 reduced luciferase induction from an 8-fold to a 4-fold increase upon IL-22 stimulation, strongly suggesting that STAT3 serine phosphorylation is required to achieve maximal transactivation.

To further support this hypothesis, we studied the effect of this STAT3 S727A mutant on IL-10-induced transactivation because IL-10 has never been described to phosphorylate STAT3 on a serine residue. HEK293 cells were transiently transfected with a plasmid encoding either IL-22R or IL-10R cDNA together with a plasmid encoding the wild-type or S727A mutated form of STAT3, pGR85-luc, and pRL-TK reporter vectors. As shown in Fig. 8A, IL-22 stimulation of IL-22R-transfected HEK293 cells induced a 6.5-fold increase in luciferase activity. Co-transfection of the STAT3 S727A mutant reduced this induction to 4-fold. By contrast, co-transfection of the STAT3 S727A mutant in cells expressing IL-10R had no effect on IL-10-induced transactivation (Fig. 8A). In line with this result, IL-22, but not IL-10, induced STAT3 serine phosphorylation in these cells, whereas both cytokines induced tyrosine phosphorylation of STAT3 (Fig. 8B).

**DISCUSSION**

IL-22, a new cytokine that is structurally related to IL-10, was originally identified as an IL-9-induced gene and shown to up-regulate the acute phase response in the liver (1, 6). In
Membranes were then reprobed with an antibody for STAT3 (pS727). Cells were stimulated with IL-22 (2000 units/ml), IL-10 (10 ng/ml), or control medium for 24 h (Fig. 8A). Simultaneously, cells were transfected with IL-22 (2000 units/ml), IL-10 (10 ng/ml), or control medium for 15 min before lysis. Total lysates were analyzed by Western blot using antibodies detecting either the serine- or tyrosine-phosphorylated form of STAT3 (B). Membranes were then reprobed with an anti-β-actin antibody.

Both cytokines induce the phosphorylation of the same STAT factors (12–14). However, our results unravel some of the differences between IL-22 and IL-10 signaling. First, IL-22 induces the activation of the ERK, JNK, and p38 MAPK pathways that are not activated by IL-10 (2). Secondly, IL-22, but not IL-10, induces serine phosphorylation of STAT3. Thus, despite the structural relationship between IL-22 and IL-10, these cytokines activate overlapping but not identical signaling pathways.

IL-22 activity and signaling pathways are reminiscent of those of IL-6 on hepatocytes. Indeed, IL-22 has been shown to induce acute phase proteins in the liver (6), an effect that has been described to be regulated by IL-6 mainly through STAT3 activation (30–32). Although the IL-6 receptor complex is less related to the IL-22 receptor than the IL-10 receptor complex, IL-6 binding also leads to JAK1 activation and the subsequent phosphorylation of STAT3, STAT1, and STAT5 (33). Moreover, IL-6 also activates the MAPK pathways (34, 35). A synergistic effect between the JAK/STAT and MAPK pathways has been proposed to regulate acute phase protein expression in response to IL-6 (36). Our results suggest that such a synergy can also take place in the regulation of the acute phase response by IL-22.

Accumulating data have stressed the importance of STAT regulation by serine phosphorylation. In this report, we have shown that STAT3 Ser727 phosphorylation is induced upon IL-22 stimulation and is required for maximal transcriptional activation. Similar results were previously reported for IL-6 (22). By contrast, IL-10 signaling does not involve STAT3 Ser727 phosphorylation, indicating that this process is not shared by all STAT3-activating cytokines.

In the case of IL-6, STAT3 serine phosphorylation results from the sequential activation of a Vav-Rac-1-SEK-1-MKK4-PKCδ cascade (22, 37). However, we failed to show any IL-22-induced PKCδ activation (data not shown). STAT3 serine phosphorylation can also be mediated by MAPKs such as ERK (38), MEKK1 (39), JNK (27), or p38 kinase (40). Interestingly, IL-22-induced STAT3 serine phosphorylation was only slightly delayed but not inhibited by MEK inhibitors PD98059 and U0126, suggesting that this effect could result from several cooperating signaling pathways. This hypothesis is further supported by a recent report showing that both H7 (a PKC inhibitor) and PD98059 inhibitors were required to block STAT3 serine phosphorylation induced by high IL-6 concentrations (41). However, we have failed thus far to identify the kinases responsible for IL-22-induced STAT3 serine phosphorylation by combining signaling pathway inhibitors (data not shown).

This report is the first description of signal transduction by one of the recently described IL-10-related cytokines (IL-22, IL-19, IL-20, mda-7/IL-24, AK155/IL-26; reviewed in Refs. 3 and 4). Our data show both similarities (JAK1, Tyk2, and JAK2, and that JAK1 is absolutely required for IL-22 signaling. However, when we failed to show any IL-22-induced PKCδ activation (data not shown). STAT3 Ser727 phosphorylation is induced upon IL-22 stimulation and is required for maximal transcriptional activation. Similar results were previously reported for IL-6 (22). By contrast, IL-10 signaling does not involve STAT3 Ser727 phosphorylation, indicating that this process is not shared by all STAT3-activating cytokines.

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