Role of the Interleukin (IL)-28 Receptor Tyrosine Residues for Antiviral and Antiproliferative Activity of IL-29/Interferon-α1

SIMILARITIES WITH TYPE I INTERFERON SIGNALING

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Interferon (IFN)-α1, -α2, and -α3 are the latest members of the class II cytokine family and were shown to have antiviral activity. Their receptor is composed of two chains, interleukin-28R/likely interleukin or cytokine receptor 2 (IL-28R/LICR2) and IL-10Rβ, and mediates the tyrosine phosphorylation of STAT1, STAT2, STAT3, and STAT5. Here, we show that activation of this receptor by IFN-α1 can also inhibit cell proliferation and induce STAT4 phosphorylation, further extending functional similarities with type I IFNs. We used IL-28R/LICR2-mutated receptors to identify the tyrosines required for STAT activation, as well as antiproliferative and antiviral activities. We found that IFN-α1-induced STAT2 tyrosine phosphorylation is mediated through tyrosines 434 and 517 of the receptor, which showed some similarities with tyrosines from type I IFN receptors involved in STAT2 activation. These two tyrosines were also responsible for antiviral and antiproliferative activities of IFN-α1. By contrast, STAT4 phosphorylation (and to some extent STAT3 activation) was independent from IL-28R/LICR2 tyrosine residues. Taken together, these observations extend the functional similarities between IFN-αs and type I IFNs and shed some new light on the mechanisms of activation of STAT2 and STAT4 by these cytokines.

The interleukin-28 receptor (IL-28R, also named LICR2 and CRF2–12) is a member of the class II cytokine receptor family

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The interleukin-28 receptor (IL-28R, also named LICR2 and CRF2–12) is a member of the class II cytokine receptor family (CRF2) (1–3), which includes receptors for type I and type II IFNs (IFNAR1, IFNAR2, IFNγR1, and IFNγR2), tissue factor, and receptors for IL-10-related cytokines: IL-10Ra, IL-22R, CRF2–9, IL-10Rβ/CRF2–4, IL-20Ra/CRF2–8, IL-20Rβ/CRF2–11, and IL-28β/CRF2–12 (4–7). Here, we introduced point mutations into the cytoplasmic domain of IL-28R/LICR2 to determine which tyrosines are required for STAT activation, as well as antiproliferative and antiviral activities. We found that IFN-α1-induced STAT2 tyrosine phosphorylation is mediated through tyrosines 434 and 517 of the receptor, which showed some similarities with tyrosines from type I IFN receptors involved in STAT2 activation. These two tyrosines were also responsible for antiviral and antiproliferative activities of IFN-α1. By contrast, STAT4 phosphorylation (and to some extent STAT3 activation) was independent from IL-28R/LICR2 tyrosine residues. Taken together, these observations extend the functional similarities between IFN-αs and type I IFNs and shed some new light on the mechanisms of activation of STAT2 and STAT4 by these cytokines.

EXPERIMENTAL PROCEDURES

Cell Culture and Cytokines—BW5147 T lymphoma cells 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. Recombinant human IFN-α1 was produced in Escherichia coli as described previously (2) or by transfecting transfection of HEK293 cells with expression vectors using the LipofectAMINE method (Invitrogen). IFN-α1 was cloned into the pEF-SFP vector as described previously (2). Based on the growth inhibition assay with LICR2-expressing BW5147 cells described below, typical HEK293 supernatants contained 60,000 units/ml IFN-α1. Mouse IFN-β was produced by transfection of pcDNA3-IFNβ (10) into HEK293 cells.

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k; IFN-α1, interferon regulatory factor-7; LICR2, likely interleukin or cytokine receptor 2; FACS, fluorescence-activated cell sorter.
Plasmid Constructions, Stable Transfections, and Analysis of Transfected Cells—The construct encoding the complete IL-28R/LICR2 receptor in fusion to a signal peptide and a hemagglutinin A epitope was generated as follows. The sequence encoding the mature form of IL-28R/LICR2 (starting from glutamine 16) was amplified by PCR using mutated primers with SfiI and NotI sites, which allowed the direct cloning into pBPyssplay (Invitrogen) just after the signal peptide and the sequence coding for the hemagglutinin A epitope present in this expression vector. For stable expression in BW5147 cells, the cDNA was subcloned into the pEF-BoSpro expression vector under the control of the EF-1 (elongation factor 1) promoter (14). Mutagenesis was performed by changing tyrosine into phenylalanine residues using the GeneEditor in vitro Site-Directed Mutagenesis System (Promega, Madison, WI). Constructs obtained were sequenced using the DYEnamic ET Dye Terminator Kit (Amersham Biosciences).

For stable transfections, 5 × 10^6 BW5147 cells were electroporated (270 V, 74 μF, 1500 microfarads) with 50 μg of sterile DNA in 800 μl of complete medium and selected using puromycin (1.6 μg/ml; Sigma, Bornem, Belgium). Cells expressing the receptor constructs were selected by fluorecence-activated cell sorter (FACS) analysis with a biotinylated anti-hemagglutinin antibody (Invitrogen) or with a mouse polyclonal anti-LICR2 antibody, followed by phycoerythrin-conjugated streptavidin (BD Biosciences) or fluorescein isothiocyanate-conjugated goat anti-mouse antibody, respectively (BD Biosciences). To produce anti-LICR2 polyclonal antibodies, P815 mastocytoma cells were transfected with the human LICR2 cDNA (1) cloned into the pE8-BO5 plasmid, before injection into DBA/2 mice. After rejection of the tumors, the sera of these mice had high titers of neutralizing anti-LICR2 antibodies, and the spleens were used to generate LICR2-specific monoclonal antibodies. At least three independent BW5147 cell clones expressing LICR2 constructs were used in each experimental setting for all transfectants. BW5147 cells express the endogenous IL-10Rβ as illustrated by the fact that they respond to IL-10 upon transfection with the IL-10Rα cDNA or with a chimeric receptor consisting of the extracellular domain of IL-10Rα and the cytoplasmic domain of IL-28R/LICR2 (1). To check that the absence of IFN-α response in some of our transfectants was not due to the loss of expression of IL-10Rβ, real-time reverse transcriptase-PCR for the endogenous IL-10Rβ mRNA was performed with the bulk transfected cell line for each receptor mutant (data not shown).

**Western Blots**—BW5147 stable transfectants were stimulated with control medium or medium containing IFN-α or IFN-β. After 15 min or different periods of time, cells were lysed in 250 μl of Laemmli buffer (Bio-Rad) and boiled for 3 min before loading on 8% precast SDS-PAGE polyacrylamide gels (Invitrogen) and electrophoretic transfer to nitrocellulose membranes (Hybond-C; Amersham Biosciences). Membranes were then blocked in 5% nonfat dry milk, washed, and probed using antibodies specific for phosphorylated STAT2-Y689 (Upstate Biotechnology, Lake Placid, NY), STAT1-Y701, STAT3-Y705, STAT4-Y694, STAT5-Y694 (Cell Signaling, Beverly, MA). Blots were re-probed with anti-actin antibodies (Sigma, Bornem, Belgium) or anti-STAT3 monoclonal antibodies (Transduction Laboratories, Lexington, KY), as a control. A monoclonal antibody recognizing the coding sequence of the murine IRF-7 gene was amplified by PCR and inserted upstream from a luciferase gene controlled by the elongation factor 1 (EF-1) promoter (14). Mutagenesis was performed by Site-Directed Mutagenesis System (Promega, Madison, WI).

**BWLICR2 Cell Proliferation Assay**—BW5147 cells were seeded in 24-well plates at 75,000 cells/well in 500 μl medium. Cells were primed with IFN-β (0.05% of HEK293 supernatant) or IFN-α (12 or 2.4 units/ml) for 24 h and were then infected with 4 × 10^5 plaque-forming units per well of Mengo virus produced from the pMC24 cDNA clone (16). 24 h later, 400 μl of infected cells were collected into FACS tubes. 0.4% of paraformaldehyde and propidium iodide (125 μg/ml, final concentration) were added to the cells. Percentages of cells stained with propidium iodide were immediately counted by FACS analysis.

**RESULTS**

**Tyr^343 and Tyr^517 of IL-28R Are Required for Antiviral and Antiproliferative Activities of IFN-α**—To better characterize the signaling pathway and function of IFN-α, we stably transfected BW5147 cells with the full-length IL-28R/LICR2 cDNA. The stimulation of these cells by IFN-α leads to a dose-dependent inhibition of proliferation (Fig. 1). Each tyrosine of IL-28R/LICR2 (Tyr^343, Tyr 406, and Tyr 517) was mutated into phenylalanine, and the resulting mutant cDNAs were stably transfected in BW5147 cells. Comparable levels of expression were found for each mutated receptor, indicating that the cytoplasmic tyrosine residues are not required for cell surface expression (Fig. 2). Mutation of these tyrosines individually did not affect either the antiproliferative activity of IFN-α. However, when both tyrosines 343 and 517 were mutated to phenylalanine, the antiproliferative activity of IFN-α was completely abolished (Fig. 2). We also studied the influence of tyrosine mutations on the antiviral activity of IFN-α, by infecting the BW5147 transfectant cells by Mengo virus. In line with our observation for inhibition of proliferation, the antiviral activity was lost when both tyrosines 343 and 517 were mutated into phenylalanine (Fig. 3).

**Tyrosine Residues Involved in STAT2 Phosphorylation**—Since STAT2 phosphorylation is considered as a key mediator of antiviral function, we analyzed STAT2 activation in these transfectants using a luciferase assay and Western blot. To
with all mutants except those where both Tyr343 and Tyr517 are redundant at high IFN-α concentrations. A significant activation of IRF-7 promoter was observed when Tyr343 or Tyr406, as well as in the double mutant for these two tyrosines. In contrast, when Tyr517 was mutated into phenylalanine the induction was decreased by 50% suggesting a predominant role for this tyrosine. STAT-1 and -5 phosphorylation was present in all the transfectants, except for the tyrosine-less triple mutant where we could not observe full IFN-α response under suboptimal conditions.

Role of IL-28R/LICR2 Tyrosine Residues in Activation of STAT1, -3, and -5—The pGRR5 reporter construct contains the luciferase gene under the control of five copies of STAT-1, -3, and -5, which are all activated by IL-28R/LICR2 (1). As shown in Fig. 6, IFN-α induced an 8-fold induction of luciferase activity in BW5147 expressing the wild type receptor. This induction was conserved in single mutants involving either Tyr343 or Tyr406, as well as in the double mutant for these two tyrosines. In contrast, when Tyr517 was mutated into phenylalanine the induction was decreased by 50% suggesting a predominant role for this tyrosine. STAT4 phosphorylation appeared to decrease significantly in the Tyr517 mutant suggesting a predominant role of this tyrosine for STAT1 phosphorylation and being

functionally assess STAT2 activation, we took advantage of a luciferase reporter gene cloned downstream from the IRF-7 promoter, which responds to STAT1/STAT2 dimers (17). This construct was transiently transfected in BWLICR2 transfectant cells before stimulation with different concentrations of IFN-α. At relatively high IFN-α concentrations (>50 units/ml), a significant activation of IRF-7 promoter was observed with all mutants except those where both Tyr343 and Tyr517 were mutated (Fig. 4A). The same observation was made when IRF-7 expression was analyzed by reverse transcriptase-PCR (Fig. 4B), and when STAT2 activation was monitored by Western blot with anti-phospho-STAT2 antibodies (Fig. 5), indicating that these 2 tyrosine residues are redundantly involved in STAT2 activation. At lower concentration (7 units/ml), IFN-α still activated the IRF-7 promoter (about 3-fold induction), but this effect was abrogated by mutation of either Tyr343 or Tyr517 separately (Fig. 4A). This indicates that although these 2 residues appeared to be redundant at high IFN-α concentrations, both are required
IFN-λs mediate their activities through a heterodimeric receptor composed of a specific chain, IL-28R/LICR2, and the IL-10Rβ chain, which is shared with other cytokines such as IL-10, IL-22, and IL-26 (2–5, 19). Based on previous reports concerning IL-10 and IL-22, the role of IL-10Rβ in signaling is limited to the recruitment of the Tyk2 tyrosine kinase (20). For both IL-10 and IL-22, downstream signaling events, such as activation of STAT factors, are not dependent on IL-10Rβ but rather on IL-10Rα and IL-22R, which have a longer cytoplasmic domain, including phosphorylatable tyrosine residues (20, 21). In this paper, to gain further insight into the mechanisms underlying the biological activities of IFN-λ, we studied the consequences of mutating tyrosine residues of the IL-28R/LICR2 cytoplasmic domain on growth inhibition and protection against virus infection.

Our results show that both activities were lost when both tyrosine 343 and 517 of IL-28R/LICR2 were mutated to phenylalanine, indicating that each of them could mediate these effects. Interestingly, this correlated with activation of STAT2, suggesting that this transcription factor is responsible for the antiviral and antiproliferative effects. This is in agreement with the role of STAT2 in type I IFNs activity as these cytokines have no antiviral activity in STAT2-deficient mice (22) and as dominant negative STAT-2 variants interfere with growth inhibition by type I IFNs in melanoma cells (23).

In response to type I IFNs, one tyrosine of IFNAR1 and 2 tyrosines of IFNAR2 seem to play a major role in STAT2 recruitment and activation (11, 12). Interestingly, the sequence of IL-28R/LICR2 surrounding Tyr343 (YIEPFS) shows some similarities with that surrounding Tyr466 of IFNAR1 (YVFFPS). For IFNAR1, a valine residue in position +1 and serine residue in position +5 were shown to be involved in the binding of the STAT2 SH2 domain (24). The IL-28R/LICR2 also shows a hydrophobic amino acid in position +1 and a serine residue in position +5. The second tyrosine involved in STAT2 activation by IFN-λ, Tyr517, is located at the C-terminal end of the receptor (YMARstop), very similar to Tyr512 of IFNAR2 (YMRstop), which is also implicated in STAT2 phosphorylation. Taken together, these observations point to two putative consensus sequences for STAT2 recruitment, YΦXXPS, where Φ should be hydrophobic, and YXXRstop.

In this paper, we also show that STAT4 is activated by IFN-λ through IL-28R/LICR2. Interestingly, STAT4 can also be activated by type I IFNs and some reports suggested that this event was dependent on STAT2 activation (25), although this conclusion has been challenged more recently (18). For IFN-λ, STAT4 phosphorylation was not affected by the mutations that abolish STAT2 activation, indicating that STAT4 is activated by a STAT2-independent mechanism. Moreover, STAT4 was still activated by a tyrosine-less IL-28R/LICR2, contrasting with the activation of this factor by IL-12, which involved a YLPNSD motif of the IL-12Rβ2 chain (26). Thus, STAT4 activation by IFN-λ might result from a third mechanism of recruitment and activation that deserves further investigation. Interestingly, for type I IFNs, STAT1 is also supposed to be recruited to the IFNAR receptor complex through STAT2 (27), whereas for IFN-λ, STAT1 activation did not correlate with STAT2 activation and could still be detected, although significantly decreased, with a IL-28R/LICR2 receptor that lacked any tyrosine (Fig. 7). The same observation was made for STAT3, whose activation was barely affected by the mutations of all 3 tyrosine residues of IL-28R/LICR2, in line with activation of STAT3 by the type I IFN receptor (28). Taken together, these observations indicate that neither STAT4, STAT1, nor STAT3 activation, even together, are sufficient to mediate the

in line with the reporter gene experiments. Surprisingly, we still observed STAT1 phosphorylation with the tyrosine-less IL-28R/LICR2. STAT3 phosphorylation looked similar in all mutants except for a slight diminution in the triple mutant. Taken together, these observations point to a mechanism that only partly depends on tyrosine residues from IL-28R/LICR2 for STAT1 and -3 phosphorylation. Concerning STAT5 phosphorylation, a significant decrease was obtained with the double mutant for Tyr343 and Tyr517, and STAT5 activation was completely lost with the triple mutant suggesting a tyrosine-dependent mechanism for STAT-5 in contrast to STAT1, -3, and -4, whose activation can occur independently from IL-28R/LICR2 cytoplasmic tyrosines.

**DISCUSSION**
antiproliferative and antiviral activities of IFN-\(\lambda\).

In contrast with the antiproliferative activity of IFN-\(\lambda\) described here, Sheppard and colleagues (3) reported that this cytokine failed to inhibit the proliferation of the Daudi cell line, suggesting that IFN-\(\lambda\) might recapitulate only parts of the effects of type I IFNs. We confirmed that type I IFNs, but not IFN-\(\lambda\), can inhibit Daudi cells proliferation (data not shown). However, the expression of the IL-28R/LICR2 receptor at the surface of these cells appeared to be rather low, as it could not be detected by FACS analysis using anti-LICR2 antibodies (data not shown). In addition, IFN-\(\lambda\) could induce phosphorylation of STAT1 and STAT2 in Daudi cells but not to the same extent as for type I interferon, although a significant IRF-7 promoter induction could still be detected (data not shown).

### FIG. 5. STAT4 phosphorylation is independent from LICR2 tyrosine residues.

5\(\times\)10^5 BWLICR2 stable transfectants were stimulated with 600 units/ml IFN-\(\lambda\) or with control medium for 15 min. Total lysates were analyzed by Western blot with an antibody directed against tyrosine-phosphorylated STAT4. The membranes were then reprobed with an anti-STAT2 phosphorylated antibody. To check for equal loading, the blot was further reprobed with anti-\(\beta\) actin antibodies (data not shown). Similar results were obtained by stimulating 2 different clones of transfected cells. No phosphorylation of STAT2 or STAT4 was observed in parental, nontransfected, BW5147 cells (data not shown). Similar results were obtained when STAT2 phosphorylation was studied after 10, 25, or 50 min of stimulation (data not shown).

### FIG. 6. Functional analysis of IFN-\(\lambda\)-induced STAT-1, -3, and -5 induction by IFN-\(\lambda\) with the pGRR5 construct.

10^7 BWLICR2 stable transfectants were transiently transfected with the pGRR5-luc plasmid, which contains the FcRRI gene-derived STAT-binding site. Cells were stimulated with 600 units/ml IFN-\(\lambda\) or with control medium for 3 h before a luciferase assay was performed. The results correspond to the mean ± S.D. of the data obtained with one bulk transfectant cell line and three independent clones.

| BW YYY | BW FYY | BW YFY | BW YYF |
|--------|--------|--------|--------|
| uns    | IFN-\(\lambda\) | IFN-\(\beta\) | uns    |

### FIG. 7. STAT-1, -3, and -5 phosphorylation by IL-28R/LICR2 mutants.

5\(\times\)10^5 BWLICR2 stable transfectants were stimulated with 600 units/ml IFN-\(\lambda\) or control medium for 10 min. Total lysates were analyzed by Western blot with antibodies directed against tyrosine phosphorylated STAT-1, -3, or -5. The membranes were then reprobed with an anti-STAT3 antibody. This analysis was performed for the seven IL-28R/LICR2 mutants, but only the most informative ones are shown. Similar results were observed in three different experiments with at least one bulk transfectant cell line and two independent clones for each mutant receptor (data not shown). Similar results were also shown after 25 and 50 min of stimulation (data not shown).
These similarities between the effects of IFN-λ and those of IFNβ raise the hypothesis that, besides IL-10Rβ, one subunit of the type I IFN receptor might associate with IL-28R/LICR2 and be involved in the IFN-λ response. However, we failed to obtain any experimental evidence supporting this hypothesis. When a chimeric receptor consisting of the extracellular domain of IL-10Rα and the cytoplasmic domain of IL-28R/LICR2 was expressed in BW5147 cells, IL-10 induced the same response as IFN-λ with BW5147 cells expressing the full-length receptor (1), ruling out the possibility that IFNAR1 or IFNAR2 are recruited by the ligand to the receptor complex. Experiments (1), ruling out the possibility that IFNAR1 or IFNAR2 are recruiting by the ligand to the receptor complex. Experiments (1), ruling out the possibility that IFNAR1 or IFNAR2 are

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