The Receptor Interaction Region of Tyk2 Contains a Motif Required for Its Nuclear Localization*

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Janus kinases have so far been viewed as enzymatic intermediates that couple a variety of cell surface receptors to downstream substrates with diverse effector functions. Tyk2 is a member of this family that is involved in the interferon-α/β and interleukin-12 signaling pathways via its specific interaction with the IFNAR1 and the β receptor subunits. Here, we have analyzed the subcellular distribution of the wild-type Tyk2 protein and of several mutants expressed in Tyk2-deficient human cells. Direct GFP-associated fluorescence and immunostaining showed a diffuse localization of Tyk2 throughout the cell, including the nuclear compartment. The nuclear localization of Tyk2 requires a nuclear localization signal-like motif rich in arginine residues that maps within the region mediating interaction with cytokine receptors. To address the question of the role of the Tyk2 nuclear pool in interferon-α/β-induced biological effects, cells expressing a membrane-targeted form of Tyk2-green fluorescent protein were analyzed for their interferon-α responses. Our studies demonstrate that Tyk2 can reside in the nucleus independently of receptor binding and that the nuclear pool is dispensable for the transcriptional and anti-vesicular stomatitis virus responses induced by interferon-α.

In vertebrates the Janus or JAK1 proteins form a family of four tyrosine kinases (Tyk2, JAK1, JAK2, JAK3) that function in membrane-proximal signaling events initiated by a variety of extracellular factors binding to cell surface receptors. Notably, receptors that bind helical-bundled cytokines rely primarily on JAK kinases to activate and integrate signaling circuits (1, 2). In such receptor complexes JAK proteins are specifically targeted to the cytoplasmic regions of transmembrane receptor subunits and are brought together through ligand-induced clustering and conformational changes of the subunits (3, 4). Catalytic activation of the JAK occur via their reciprocal trans-

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The abbreviations used are: JAK, Janus kinase; IFN, interferon; IL, interleukin; STAT, signal transducer and activator of transcription; NLS, nuclear localization signal; HAT, hypoxanthine/aminopterin/thymidine; GFP, green fluorescent protein; FERM, band 4.1-erzin-radixin-moesin (ERM); mAb, monoclonal antibody; aa, amino acid(s).
a role of the nuclear Tyk2 pool in these cytokine-induced biological activities.

EXPERIMENTAL PROCEDURES

Cell Culture—Human fibrosarcoma 11,1 (U1A) cells and derived clones expressing Tyk2 mutated forms N, 1–384, Δ1–287, Δ1–51, ΔJH4, and T (1–518J) were described in Gauzzi et al. (17) and Richter et al. (18). Cells were grown in Dulbecco's modified Eagle's medium containing 10% fetal calf serum and 250 μg/ml hygromycin. Stable and transient transfections were performed by calcium phosphate and selection was in G418 (450 μg/ml) (17). Cell survival in hypoxanthine/aminopterin/thymidine (HAT) medium or in 6-thioguanine-containing medium was assayed by seeding 6 × 10^4 cells in 6-well plates in the presence of 1 μl to 1 μl IFN-α2 (recombinant IFN-α2, provided by D. Gewert). After 5 days, cells were fixed and stained. To obtain cells expressing the IL-12R, 11,1 cells were transfected with pSRα-J1, and single puromycin-resistant colonies were isolated and screened for surface β1 expression by fluorescence-activated cell sorter analysis. A β1-expressing clone was then co-transfected with either pEF-BOS-β2 and pRc-Tyk2 to obtain clone Sββ2T2 or with pEF-BOS-β2 and pRcCMVneo to obtain clone Sββ4. Surface β1 and β2 expression was monitored by staining cells with 5 μg/ml purified rat anti-huIL-12Rβ1 mAb (2B10) (19) and with 10 μg/ml of rat anti-huIL-12Rβ2 mAb (2B6) (20). Both antibodies and recombinant IL-12 were provided by U. Gubler (Hoffman-La Roche Ltd.). Cells were incubated with 10 μg/ml biotinylated polyclonal anti-rat IgG Ab and subsequently with streptavidin-phycocyanin (Jackson Immuno Research Laboratories, West Grove, PA).

Plasmid Constructs—For construction of Tyk2-GFP, a BssHI-XhoI fragment that spanned Tyk2 from aa 1025 to 1187 and contained at the 3' end a KpnI site was amplified and swapped into pBS-Tyk2. From this construct, the 3.9-kilobase HindIII-KpnI fragment containing Tyk2 cDNA was cloned in-phase into pEGFP-N3 vector (CLONTECH). Construction of mutants R220K, N384, N, 1–384, mutant 1–51, and mutant Δ1–287 was monitored by staining cells with 5 μg/ml purified rat anti-huIL-12Rβ1 mAb (2B10) (19) and with 10 μg/ml of rat anti-huIL-12Rβ2 mAb (2B6) (20). Both antibodies and recombinant IL-12 were provided by U. Gubler (Hoffman-La Roche Ltd.). Cells were incubated with 10 μg/ml biotinylated polyclonal anti-rat IgG Ab and subsequently with streptavidin-phycocyanin (Jackson Immuno Research Laboratories, West Grove, PA).

Protein Analysis—The amino-terminal region directs Tyk2 into the nucleus—The subcellular distribution of the Tyk2 was investigated in human HT-1080 fibrosarcoma cells by indirect immunofluorescence using a high affinity mAb directed to an epitope within the amino-terminal portion of the protein. A weak specific staining appeared distributed in both the cytoplasmic and the nuclear compartments in wild-type cells as compared with Tyk2-deficient 11,1 cells (data not shown). To improve the rather weak signal, immunostaining experiments were performed on an 11,1-derived clone stably reconstituted with wild-type Tyk2 expressed at a 5-fold higher level with respect to the endogenous protein (21). Staining in these cells appeared in denser regions of the cell surface, diffuse in the cytoplasm, and it was clearly detected in the nucleus (Fig. 1A, top left panel). The same distribution was obtained upon using the mAb p5D4 directed to the vesicular stomatitis virus epitope fused at the carboxyl terminus of the protein (data not shown). These results suggested that Tyk2 could reside within the nuclear compartment. No detectable change in the localization profile was observed upon stimulation of the cells with IFN-α. Given the mass of the protein (134 kDa), its nuclear import may represent an active process relying on a discrete region(s) of the protein. To narrow down the region contributing to nuclear import, we analyzed the localization of truncated Tyk2 mutants stably

A | IF | GFP  
---|---|---
WT | stable | transient | transient  
N | transient | transient | transient  
I–384 | transient | transient | transient  
Δ1–287 | transient | transient | transient  
Δ1–51 | transient | transient | transient  
ΔJH4 | transient | transient | transient  
T(1–518J) | transient | transient | transient

FIG. 1. Nuclear localization of Tyk2 mutant forms. A, left panels, the subcellular localization of wild-type (WT) Tyk2, mutant N (aa 1–591), mutant 1–384, and mutant Δ1–287 was monitored in representative neo^6^ transfectants by indirect immunofluorescence (IF) using the anti-Tyk2 mAb, T10–2. Middle panels, wild-type and mutant forms were similarly analyzed after transient expression in 11,1 cells. Right panels, wild-type Tyk2 and the Δ1–287 mutant, both fused to GFP, were transiently transfected in 11,1 cells and localized by direct fluorescence microscopy. B, mutant Δ1–51, mutant ΔJH4 lacking aa 385–496, and the chimera T1–518J containing an 1–518 of Tyk2 fused to JAK1 were transiently transfected into 11,1 cells, and localization was assessed by indirect immunofluorescence microscopy.

RESULTS

The Amino-terminal Region Directs Tyk2 into the Nucleus—The subcellular distribution of the Tyk2 was investigated in human HT-1080 fibrosarcoma cells by indirect immunofluorescence using a high affinity mAb directed to an epitope within the amino-terminal portion of the protein. A weak specific staining appeared distributed in both the cytoplasmic and the nuclear compartments in wild-type cells as compared with Tyk2-deficient 11,1 cells (data not shown). To improve the rather weak signal, immunostaining experiments were performed on an 11,1-derived clone stably reconstituted with wild-type Tyk2 expressed at a 5-fold higher level with respect to the endogenous protein (21). Staining in these cells appeared in denser regions of the cell surface, diffuse in the cytoplasm, and it was clearly detected in the nucleus (Fig. 1A, top left panel). The same distribution was obtained upon using the mAb p5D4 directed to the vesicular stomatitis virus epitope fused at the carboxyl terminus of the protein (data not shown). These results suggested that Tyk2 could reside within the nuclear compartment. No detectable change in the localization profile was observed upon stimulation of the cells with IFN-α. Given the mass of the protein (134 kDa), its nuclear import may represent an active process relying on a discrete region(s) of the protein. To narrow down the region contributing to nuclear import, we analyzed the localization of truncated Tyk2 mutants stably
expressed in 11.1 cells. The functional characterization of these mutant proteins has been previously reported (17, 23). The 70-kDa N protein lacks the two kinase domains and encompasses the amino-terminal region of Tyk2. Its overall distribution resembled that of the full-length protein, with nuclear staining slightly more intense and clear nucleolar exclusion (Fig. 1A). A 42-kDa mutant form encompassing residues 1–384 was exclusively nuclear (Fig. 1A, left panel), suggesting that an active process of nuclear import overcomes the passive diffusion of this small protein across the nuclear pore. The Δ1–287 mutant is an amino-terminal truncated version of Tyk2 spanning residues 288–1128. Its distribution profile was strikingly different, being cytoplasmic and perinuclear (Fig. 1A, middle panel). Similar staining profiles were obtained from the analysis of 11.1 cells transiently transfected with the three constructs (Fig. 1A, middle panels).

To substantiate these findings and rule out possible localization artifacts due to the immunostaining procedure, we fused GFP at the carboxyl terminus of Tyk2. To assess the functionality of Tyk2-GFP, the construct was stably expressed in 11.1 cells, which are unresponsive to IFN-α due to Tyk2 deficiency. Since these cells contain an integrated IFN-inducible gpt construct, rescuing of the IFN-α response can be assessed by their ability to survive in HAT or 6-thioguanine when supplemented with the cytokine (24). Clones expressing Tyk2-GFP were as responsive to IFN-α as cells expressing wild-type Tyk2 (data not shown). Thus, the addition of the GFP moiety did not alter the function of Tyk2. As shown in Fig. 1A (right panel), Tyk2-GFP was found in the nucleus with the exclusion from nucleoli. On the other hand, the truncated Δ1–287 mutant fused to GFP was totally excluded from the nucleus (Fig. 1A, right panel). These results demonstrated that Tyk2 is distributed in all cellular compartments, including the nucleus, and the presence of the 287 amino-terminal residues is required for nuclear import.

Nuclear Localization of Tyk2 Requires an Arginine-rich Motif in the N Region—Classical nuclear NLS motifs are short sequences with positively charged residues grouped in a single or a bipartite cluster (25, 26). To identify a potential NLS in Tyk2, we scanned the first 287 residues and found an arginine-rich stretch within the JH6 box. Alignment of the four JAK proteins showed a conservation of basic residues in this region that was less evident in JAK1 (Fig. 2A). To prove that this motif was required for the nuclear translocation of Tyk2, it was disrupted by point mutations or by a small deletion (Fig. 2B). In mutant designated R220–221/AA, adjacent Arg-220 and -221 were changed to Ala, in mutant R231–233-235/AAA, Arg-231, -233, and -235 were changed to Ala, and in the Δ219–240 mutant 22 aa spanning the potential NLS were deleted. After transient expression in 11.1 cells, these mutants showed distinct subcellular distributions (Fig. 2C). Although the R220–221/AA mutant was distributed as the wild-type protein, the R231-R233-R235/AAA mutant was significantly less nuclear. The Δ219–240 mutant was totally excluded from the nucleus. These data demonstrate that this motif plays a critical role in the nuclear localization of Tyk2.

To determine whether the NLS-like motif can function as a genuine nuclear-targeting element, the 22-amino acid motif(aa 219–240) was moved from its natural location to the carboxyl terminus of Tyk2, and localization was assessed. Nuclear staining was not restored. Likewise, when the same motif was fused to the amino terminus of the GFP protein (wt22-GFP), no appreciable change in distribution was observed as compared with the diffusing GFP (data not shown). Therefore, the 22-amino acid motif per se did not act as a NLS when removed from its natural context.

The NLS-like Motif Is Part of the IFNAR1 Interaction Domain of Tyk2—Since the triple alanine substitution or the deletion of aa 219–240 partially or totally impaired the ability of Tyk2 to accumulate in the nucleus, we asked the question of whether these changes affected the functionality of Tyk2 in the IFN-α-signaling pathway. To this aim, using the HAT/6-thio-guanine survival test (24) we compared the IFN-α sensitivity of three clones expressing the R231–233-235/AAA mutant with that of wild-type cells. Two R231–233-235/AAA-expressing...
clones (clones 10 and 20) displayed a 10-fold reduced IFN-α2 sensitivity as compared with control cells, whereas a third clone (clone 2) was fully sensitive. Interestingly, quantification of the exogenous protein expressed in each clone revealed a 2–3-fold higher level in clone 2 with respect to the others. Thus, higher protein levels appeared to compensate for the partial impairment of this mutated protein. Conversely, cells expressing the Δ219–240 protein were IFN-unresponsive and indistinguishable from Tyk2-deficient 11,1 cells. These data, summarized in Table I, demonstrated a partial loss of function of the weakly nuclear R231–233-235/AAA mutant and a complete loss of function of the Δ219–240 protein.

We had previously shown that Tyk2 sustains the level of expression of the IFN-α receptor chain IFNAR1 in human fibrosarcoma cells (17, 18). Hence, we tested whether the Δ219–240 mutant protein was still able to perform this chaperone-like function. For this, we monitored by immunoblot the expression level of IFNAR1 in these stable transfectants. As shown in Fig. 3A, the IFNAR1 level in a representative clone differed from Tyk2-deficient 11,1 cells. This finding demonstrates that Tyk2 deleted of the NLS-like motif had lost its ability to interact with IFNAR1.

Deletion of the NLS Motif Impairs Tyk2 Interaction with the IL-12R β1 Chain—Tyk2 has been shown to be activated by IL-12 and to interact with the β1 component of the IL-12 receptor (27, 28). We therefore asked whether the deletion of the NLS-like motif impairs Tyk2 activation by IL-12. Since the IL-12 receptor is restricted to specific hematopoietic cell types (29), we engineered its expression in our cellular system. We derived from 11,1 cells a clone expressing IL-12Rβ2-positive clone (SββT23) that expresses at the cell surface the components of the IL-12R, the β1 and the β2 chains (Fig. 4A). To assess correct function of the ectopic receptor complex in these cells, we measured Tyk2 phosphorylation after treatment with IL-12. As predicted, in SββT23 cells, Tyk2 was activated not only by IFN-α but also by IL-12 (Fig. 4B). The more robust phosphorylation seen upon IL-12 treatment is likely to reflect the overexpression of IL-12 receptors with respect to the level of endogenous IFN-α receptors. Interestingly, in the absence of added cytokine, Tyk2 was basal phosphorylation in SββT23 cells but not in the control WT cells (Fig. 4B, compare lanes 1 and 4), most likely as a consequence of its constitutive association with the IL-12R β1 chain. Having shown that reconstituted IL-12 receptors are functional, we asked whether the Δ219–240 mutant could be activated in response to IL-12. For this, we used Sββ4 cells, also expressing the IL-12R subunits (Fig. 4A) but lacking Tyk2. Sββ4 and 11,1 cells were transiently transfected with either the wild-type Tyk2 or the Δ219–240 mutant, and phosphorylation was monitored. Wild-type Tyk2 was more basal phosphorylated in Sββ4 cells as compared with 11,1 cells (Fig. 4C, lanes 1 and 5) as a result of its association with the IL-12 receptors. This was not the case with the Δ219–240 mutant (Fig. 4C, lanes 3 and 7). Furthermore, IL-12 treatment induced hyperphosphorylation of wild-type Tyk2, whereas the phosphorylation level of Δ219–240 remained unchanged, indicating that the Δ219–240 mutant failed to be activated in response to IL-12.

The results described above showed that deletion of the NLS-like motif in Tyk2 not only impaired its nuclear localization but also prevented its interaction with cytokine receptor

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**TABLE I**

| Cell line | IFN-α2 for 50% cell survival |
|-----------|-----------------------------|
|           | HAT | 6TG |
| 11,1      | 2500 | <5  |
| Wild type | 50  | <5  |
| R220–221/AA | 50 | <5  |
| R231–233–235/AAA cl.2 | 50 | <5  |
| R231–233–235/AAA cl.10, cl.20 | 500 | <50 |
| Δ219–240 | 2500 | 0   |
| Wild type-GFP | 50 | <5  |
| mbTyk2-GFP | 50 | <5  |
chains. To determine whether these two apparently unrelated properties, nuclear localization and receptor interaction, could be functionally dissociated, we tested whether other mutations within the receptor binding region of Tyk2 similarly affected subcellular localization. For this, the localization of three Tyk2 mutants that retain an intact NLS-like motif but lack the structural determinant for IFNAR1 binding was monitored. Mutant Δ1–51 lacks residues 1–51, mutant ΔJH4 lacks the JH4 homology box, and mutant T (1–518) contains the amino-terminal 518 residues of Tyk2 (JH7 to JH4) fused to the carboxyl-terminal portion of JAK1 (17, 18). Immunofluorescence staining revealed the presence of all three mutant proteins in both the cytoplasmic and nuclear compartments (Fig. 1B), demonstrating that the integrity of the receptor binding domain is not required for nuclear import. These results, summarized in Table II, suggest that the subcellular localization of Tyk2 is receptor-independent.

A Membrane-localized Form of Tyk2 Is Functional—A key question is whether the nuclear Tyk2 pool plays a role toward IFN-α/β-induced biological effects. To circumvent the problem of the positional and functional overlapping of the NLS-like motif and the receptor binding domain, a membrane-anchored form of Tyk2-GFP was generated by fusing to its amino terminus residues 1–16 of human Lck, a member of the Src family of tyrosine kinases. This sequence promotes membrane binding by allowing myristoylation and palmitoylation (30). The subcellular localization of this protein (mbTyk2-GFP) was monitored both by direct GFP visualization and immunostaining. In transiently or stably transfected cells expressing mbTyk2-GFP, the fluorescence heavily decorated the plasma membrane (Fig. 5). Confocal microscopy confirmed the absence of nuclear fluorescence (data not shown). The ability of the modified protein to sustain the IFNAR1 receptor in stable transfectants was analyzed by immunoblot and by fluorescence-activated cell sorter. Immunoblot analysis of one representative clone is shown in Fig. 3B. The level of IFNAR1 in mbTyk2-GFP-expressing cells was ~50% of the level present in Tyk2-GFP-expressing cells. These transfectants were monitored for their transcriptional response to IFN-α by testing their dose-dependent survival in HAT-containing medium. No appreciable difference in the IFN sensitivity (1 µM–1 nM range) was detected. A more complex biological effect of IFN-α, i.e. its ability to induce in sensitive cells a state of resistance to viral infection, was measured in the two clones. The mbTyk2-GFP-expressing cells and the WT-GFP control cells were comparably sensitive to IFN when challenged with the vesicular stomatitis virus; 50% antiviral protection was obtained after treatment with 5–15 µM IFN-α.

**Table II** Localization of Tyk2 mutants and level of IFNAR1

| NeoR clone | Nuclear staining | IFNAR1 |
|------------|------------------|--------|
| Wild type  | +                | +      |
| N          | +                | +      |
| 1–384      | +                | -      |
| Δ 1–51     | +                | -      |
| Δ JH4      | +                | -      |
| T (1–518)  | +                | -      |
| Δ 1–287    | -                | -      |
| Δ 219–240  | -                | -      |

**FIG. 5.** Membrane localization of Tyk2 fused to aa 1–16 of human Lck. Left panel, 11.1 cells were transfected with Tyk2-GFP (WT-GFP) or the form containing at its amino terminus aa 1–16 of Lck (mbTyk2-GFP). Localization of each protein was monitored in a representative neoR clone by indirect immunofluorescence (IF) using the anti-Tyk2 mAb. Right panel, the same constructs were transiently transfected in 11.1 cells and analyzed by direct fluorescence microscopy.

We have addressed the question of the role of nuclear Tyk2 by studying the function of a membrane-bound form of the protein modified by amino-terminal myristoylation and palmitoylation. Given the properties of the Lck-derived motif, the mbTyk2 protein should be directed to discrete microdomains of the plasma membrane, the lipid rafts (37). Accordingly, this modification did not appear to greatly affect the ability of the kinase to associate with the IFN-α/β receptor, which at least in part is localized in caveolin-rich membrane domains (38). The full rescuing capacity of the mbTyk2 protein excludes a role of this kinase in the nuclear import mechanism of the activated STAT proteins (32–36). The possibility that nuclear Tyk2 intervenes in the dephosphorylation of nuclear STAT, for example by activating a nuclear tyrosine phosphatase (39), was tested by comparing the duration of STAT1 and STAT2 phosphorylation in wild-type and mbTyk2-expressing cells upon long term IFN-α treatment. STAT dephosphorylation occurred...
with similar kinetics in both cell types (data not shown), ruling out a role of nuclear Tyk2 in STAT inactivation.

A number of cytokines and cytokine receptors, including the IFN families, have been found in the nuclear compartment of a variety of cell types (14, 15, 40–44). These findings have no clear biological significance yet, but they raise the possibility that JAK proteins could reach the nucleus when complexed to receptors. This is unlikely, since it was found through the study of mutant forms that nuclear localization of Tyk2 did not require the integrity of the receptor binding domain (Table II). Our data support a model where the enzyme can reside in the nucleus independently of its association to cytokine receptors. Little is known of the post-activation fate of JAK proteins. Our data support a model where the enzyme can reside in the nucleus independently of its association to cytokine receptors. Little is known of the post-activation fate of JAK proteins. The possibility that the fraction of Tyk2 that is not involved in the mitogen-activated protein kinase cascade (48).

This mechanism has been described for a number of proteins with tyrosine phosphorylation cascades involving JAK activity (52). Some of these represent culmination of cytolytic events, as is the case for the translocated STATs, but it will be important to establish whether tyrosine phosphorylation cascades involving JAK kinases can occur within the nucleus.

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