The interleukin-2 receptor α chain (IL-2Rα) is potentially induced by cytokines that include IL-2 itself. This induction leads to the formation of high affinity IL-2 receptors when IL-2Rα is co-expressed with the β (IL-2Rβ) and γ (γc) chains of this receptor. We investigated the signaling pathways mediating IL-2-induced IL-2R mRNA expression using 32D myeloid progenitor cells stably transfected with either wild type IL-2Rβ or mutants of IL-2Rβ containing tyrosine to phenylalanine substitutions. Of the six cytoplasmic tyrosines in IL-2Rβ, we have found that only the two tyrosines that mediate Stat5 activation (Tyr-392 and Tyr-510) contribute to IL-2-induced IL-2Rα gene expression, and that either tyrosine alone is sufficient for this process. Interestingly, the IL-7 receptor contains a tyrosine (Tyr-429)-based sequence resembling the motifs encompassing Tyr-392 and Tyr-510 of IL-2Rβ. Further paralleling the IL-2 system, IL-7 could activate Stat5 and drive expression of IL-2Rα mRNA in 32D cells transfected with the human IL-7R. However, IL-3 could not induce IL-2Rα mRNA in 32D cells, despite its ability to activate Stat5 via the endogenous IL-3 receptor. Moreover, the combination of IL-3 and IL-2 could not “rescue” IL-2Rα mRNA expression in cells containing an IL-2Rβ mutant with phenylalanine substitutions at Tyr-392 and Tyr-510. These data suggest that Tyr-392 and Tyr-510 couple to an additional signaling pathway beyond STAT protein activation in IL-2-mediated induction of the IL-2Rα gene.

Interleukin-2 (IL-2) is a pivotal cytokine that influences various arms of the immune system, including T cells, B cells, natural killer cells, and monocytes (1–4). Three classes of IL-2 receptors are known to exist: low affinity receptors contain the α chain, intermediate affinity receptors contain the β and γ chains, and high affinity receptors contain all three chains (2–4). Interestingly, the β chain is also a component of the IL-15 receptor, whereas the γ chain is a common chain (γc) shared by the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15 (2–5). Mutations in γc form the genetic basis of X-linked severe combined immunodeficiency, a disease state affecting both cellular and humoral immunity (5, 6).

In lymphocytes, IL-2Rβ and γc are constitutively expressed, while IL-2Rα is only expressed following activation by a variety of stimuli that include IL-2 itself (1, 7, 8). When induced, IL-2Rα complexes with β and γ chains to convert intermediate affinity to high affinity receptors (2–4). Although the intermediate and high affinity receptors are both functional (8–11), the induction of IL-2Rα is essential for normal immune function as evidenced by the autoimmune, inflammatory bowel disease, and premature death occurring in IL-2Rα knockout mice (12). The regulation of IL-2Rα expression is tightly controlled at the level of transcription, relying on the interaction of positive regulatory elements with multiple transcription factors that include Stat5, Elf-1, HMG-I(Y), and NF-κB (Refs. 13 and 14 and references therein).

While many of the regulatory proteins and binding sequences influencing expression of the IL-2Rα gene have been defined, the more proximal events leading from IL-2 binding to IL-2Rα gene transcription are less clear. Previous work with the tyrosine kinase inhibitor herbimycin A has demonstrated the importance of tyrosine phosphorylation in IL-2-signaling (15). Among the proteins tyrosine-phosphorylated in response to IL-2 is IL-2Rβ itself (16–19). This receptor chain contains six cytoplasmic tyrosines (Fig. 1), at least some of which can serve as phosphotyrosine docking sites for signaling proteins containing SH2 and PTB domains (20, 21).

Examination of signaling via mutant IL-2Rβ chains containing different tyrosine to phenylalanine substitutions therefore represents a method for mapping proximal events induced by IL-2 and has previously been used to investigate key functions such as proliferation (22–24). This analysis has demonstrated that tyrosine 338 (Tyr-338) mediates phosphorylation of the adaptor protein She (22, 25) (involved in ras activation), while Tyr-392 and Tyr-510 can independently direct activation of Stat5 (22–23, 26–28). To elucidate the role of these or other pathways in IL-2-induced expression of the IL-2Rα gene, we have examined multiple combinations of these tyrosine to phenylalanine substitutions in IL-2Rβ. These experiments show that IL-2Rβ mutants possessing Tyr-392 or Tyr-510 alone can augment expression of the IL-2Rα gene, whereas no IL-2Rα induction occurs when both Tyr-392 and Tyr-510 are mutated. Although previous studies link these tyrosines to Stat5 activation, our data suggest that Stat5 activation is not sufficient for IL-2Rα induction and that the same tyrosines may couple to additional signaling pathways(s).

**MATERIALS AND METHODS**

Reagents and Antibodies—Expression of IL-2Rβ was assessed using a polyclonal antiserum to IL-2Rβ (ErdA antiserum, Ref. 9) or 4G10 monoclonal antibody to phosphotyrosine (Upstate Biotechnology, Inc.).
as above. The existence of multiple murine IL-2R constructs was used for other IL-2R constructs.

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A. Northern blot of 32D cells transfected with the indicated constructs. Cells were washed in acidified RPMI 1640 to strip the cell surface of growth factors and subsequently treated with 5% WEHI-CM (as a source of IL-3) or 2 nM IL-2 for 16–18 h. At least two high expressing IL-2Rα clones were assayed for each construct. Although some differences in the expression of the glyceroldehyde-3-phosphate dehydrogenase (G3PDH) control were observed, the degree of variation is not sufficient to explain the differences in IL-2Rα mRNA levels. B. Northern blot of 32D cells transfected with either βFFFFF (lanes 1, 2, 5, 6), βFFFFYF (lanes 3 and 4) or βFFFFFY (lanes 7 and 8) and stimulated as above. The existence of multiple murine IL-2Rα transcripts is consistent with previously published results (31, 34).

Vectors and in Vitro Mutagenesis—Human IL-2Rβ was mutated using the altered sites in vitro mutagenesis system (Promega) and oligonucleotides designed to change tyrosine (TAC) to phenylalanine (TTC), as described previously (22). Following sequence confirmation (Sequenase, U. S. Biochemical Corp.), mutant constructs were subcloned into the vector pME18S in which expression is driven by the SR promoter (29). The human IL-7R cDNA has been described (30).

Cell Culture and Transfections—32D cells were grown in RPMI 1640 supplemented with 10% fetal bovine serum, 10−5 M 2-mercaptoethanol, 5% WEHI-3B conditioned medium (WEHI-CM) as a source of IL-3, 2 mM glutamine, and 100 units/ml each of penicillin and streptomycin. The transfectants expressing wild type and most of the mutant IL-2Rβ constructs were described previously (22). Additional transfectants were generated by electroporating cells (5 × 107 cells/600 μl) with linearized plasmids consisting of IL-2Rβ constructs and pCDNA3neo (InVitrogen) using a gene pulser (Bio-Rad; 300 V, 960 microfarads; time constant was approximately 30 ms). After 24 h, cells were aliquoted into 24-well plates and selected in 1 mg/ml G418 (Life Technologies, Inc.) for 2–3 weeks. Resistant clones were analyzed for IL-2Rβ expression by flow cytometry with fluorescein isothiocyanate-conjugated anti-IL-2Rβ monoclonal antibody (Endogen) or a control IgG2a (Becton Dickinson) on a FACSsort FST (Becton Dickinson). In some cases, Western blotting with Erα antiserum to IL-2Rβ was used to further evaluate receptor expression. IL-7R transfectants were established in a similar fashion.

Cytokine induction, RNA preparation, and Northern blot analysis—32D transfectants grown to a density of 2–6 × 105 cells/ml were washed three times in acidified RPMI to strip any growth factors bound to the cell surface. Cells were then incubated for 16–18 h in medium containing either IL-3 (5% WEHI-CM), IL-2 (2 nM), IL-2 plus IL-3, or IL-7 (5 nM) plus IL-3 or IL-7 (5 nM) plus IL-3, and RNA was prepared using TRIzol reagent (Life Technologies, Inc.) according to the established protocol. 30 μg of total RNA from each sample were run overnight in a 1% agarose formaldehyde gel and transferred to nylon membranes (Amersham Hybond). Equivalent loading and expression of RNA, blots were also hybridized with a 1-kilobase pair murine IL-2Rα cDNA fragment (31) was labeled with Life Technologies, Inc.’s random primer labeling kit and used to probe the blots. As an additional control for loading and expression of RNA, blots were also hybridized with a 1-kilobase pair murine glyceroldehyde-3-phosphate dehydrogenase cDNA fragment. All hybridizations were carried out for 20 h at 43 °C. Following multiple washes with SDS/SSPE-based solutions, blots were autoradiographed for 48–72 h at −70 °C.

Electrophoretic Mobility Shift Assays (EMSAs) and DNA affinity purification—EMSAs were performed as described previously (22). Wild type or transfected 32D cells (~5 × 105/ml) were washed and then depleted of growth factor for 4 h in phosphate-buffered saline or RPMI 1640 medium lacking serum and cytokines. Cells were then incubated at 37 °C for 20–30 min in RPMI, 10% fetal bovine serum medium with
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RESULTS

IL-2Rβ Tyr-392 or Tyr-510 Is Required for IL-2-induced IL-2Rα mRNA Expression—32D cells lack IL-2Rβ and are IL-3-dependent, but they can proliferate in response to IL-2 after IL-2Rβ is transfected and expressed (22, 34). To assess the potential contribution of different IL-2Rβ tyrosines in the signaling pathway(s) for IL-2-mediated IL-2Rα mRNA induction, we therefore examined 32D cells transfected with wild type IL-2Rβ, while IL-2 could induce IL-2Rα mRNA in the same cell line (Fig. 2A, lanes 3–4). The Northern blot analysis presented in Fig. 2A further demonstrated that IL-2 could potently induce IL-2Rα mRNA in all transfecants expressing IL-2Rβ chains retaining the terminal two tyrosines (Tyr-392, Tyr-510) (lanes 4, 8, and 10). Simultaneous mutation of Tyr-392 and Tyr-510 completely blocked the induction of IL-2Rα mRNA (compare βYYYYYY and βYYYYFF, lanes 3–4 versus 11–12), indicating that at least one of these tyrosines is required for IL-2-mediated IL-2Rα gene expression. Further analysis revealed that either Tyr-392 or Tyr-510 alone is sufficient for this process (Fig. 2B), analogous to the functional overlap of Tyr-392 and Tyr-510 in mediating IL-2-induced proliferation (22). Of note, the fact that either of these tyrosines can mediate IL-2Rα gene expression, but Tyr-338 cannot, indicates that IL-2Rα induction is not absolutely required for proliferation (which can occur at suboptimal levels with Tyr-338 alone (22)) and further supports observations that pathways linked to Tyr-338 are not functionally equivalent to signals directed from Tyr-392 and Tyr-510 (22).

Consistent with the functional redundancy of Tyr-392 and Tyr-510, previous work has shown that both Tyr-392 and Tyr-510 can independently mediate IL-2-induced Stat5 activation in 32D cells transfected with appropriate IL-2Rβ constructs (22). Since each of these tyrosines shares a motif similar to that surrounding Tyr-429 of the IL-7 receptor (26) (Fig. 3A), we speculated that IL-7 could trigger IL-2Rα gene expression in...
32D cells transfected with the IL-7 receptor. This hypothesis seemed plausible given the expression of IL-2Rα in double negative thymocytes normally exposed to IL-7 in vivo. Indeed, IL-7 induced both Stat5 activation (Fig. 3B) and IL-2Rα mRNA expression (Fig. 3C) in 32D-IL-7R transfectants.

**Stat5 Induction Alone Is Not Sufficient to Induce IL-2Rα mRNA in 32D Cells**—Collectively, these results suggested an important role for Stat5 activation in the induction of IL-2Rα mRNA. Hence, the inability of IL-3 (which also can activate Stat5 (35, 36)) to augment expression of IL-2Rα mRNA (Fig. 2A) was surprising, particularly since IL-2 and IL-3 induced indistinguishable STAT complexes in IL-2Rβ-transfected 32D cells when performing EMSAs with a probe comprised of the murine IL-2Rα GAS motifs. As shown in Fig. 4, the complexes resulting from IL-2 or IL-3 treatment (lanes 2 and 3) supershifted with anti-Stat5 antisera (lanes 5 and 6), but not with anti-Stat3 (lanes 8 and 9). Similar results were obtained using the FcγRII GAS site as a probe (data not shown). Because the anti-Stat5 antisera used in these experiments recognizes two closely related proteins termed Stat5a and Stat5b, we performed additional supershift experiments with Stat5a- and Stat5b-specific antisera to exclude the possibility that IL-2 and IL-3 differed in their induction of these proteins. In fact, this analysis demonstrated that both cytokines could independently activate Stat5a and Stat5b in 32D cells transfected with wild type IL-2Rβ (Fig. 5A). DNA affinity purification of STAT proteins with an oligonucleotide probe containing a trimer of the β-casein GAS motif confirmed these results (Fig. 5B). Overall, these data indicate that Stat3 is not required for IL-2-induced IL-2Rα expression in 32D cells and that Stat5a/Stat5b activation alone is not sufficient to mediate IL-2Rα mRNA induction, supporting a role for additional cooperating signal(s). Of note, the fact that IL-2 and IL-3 (which normally exert effects on different cell types) differ in their capacity to induce IL-2Rα gene expression **within the same cell line** indicates that such cooperating signals depend on the receptor system rather than cell lineage alone.

**IL-3 Is Unable to Rescue IL-2Rα Gene Induction in 32D-βYYYYFF Cells**—Given the possibility that IL-2Rα gene expression requires the coupling of Stat5 activation with other IL-2-derived signals, we examined the ability of IL-3 to complement IL-2 and rescue expression of the IL-2Rα gene in 32D cells transfected with βYYYYFF. Surprisingly, however, the combination of IL-2 and IL-3 did not induce IL-2Rα mRNA in cells transfected with βYYYYFF (Fig. 6A, lanes 3–5), despite the activation of STAT complexes indistinguishable from those induced by IL-2 in cells containing βYYYYY (Fig. 6B, lanes 4–6 versus 9–11). This experiment demonstrates that the four proximal tyrosines as well as the nonphosphorylated regions of IL-2Rβ cannot provide signals sufficient to cooperate with IL-3-mediated Stat5 activation in directing expression of IL-2Rα mRNA. These data therefore suggest that the additional factor(s) involved in IL-2-mediated IL-2Rα gene induction may also be linked functionally to Tyr-392 and Tyr-510.

**DISCUSSION**

Using IL-2Rβ constructs containing various combinations of tyrosine to phenylalanine substitutions, we have demonstrated that in the context of full-length IL-2Rβ either Tyr-392 or Tyr-510 is sufficient to direct IL-2-mediated induction of the IL-2Rα gene. Based on these results, at least four different models potentially explain the proximal events in IL-2Rα gene induction following binding of IL-2 to its receptor. In the first model, STATs are activated after docking at phosphorylated Tyr-392 or Tyr-510 and by themselves are sufficient for IL-2Rα gene induction (Fig. 7A). However, the failure of IL-3 to promote IL-2Rα gene expression in 32D transfectants minimizes this possibility, as the same STAT proteins are activated by IL-2 and IL-3 (Figs. 4 and 5).

The remaining models therefore assume that STAT protein
activation is not the sole pathway triggered by IL-2 in the induction of IL-2Rα mRNA. For example, the second model (Fig. 7B) portrays a direct interaction between an undefined “X” factor and Tyr-392 or Tyr-510, without the need for concomitant STAT activation. However, this paradigm is unlikely given the existence of consensus STAT binding sequences in the upstream region of the human and murine IL-2Rα promoters and the inability of IL-2 to induce IL-2Rα promoter activity when these binding sequences are mutated (14, 32). Incorporating these facts, the third model (Fig. 7C) depicts the interaction of STAT proteins activated at Tyr-392 or Tyr-510 with an unknown factor X bound to a different portion of IL-2Rβ. In this scheme, the requirement for these signaling molecules to functionally collaborate in cis accounts for the inability of IL-3 to rescue IL-2Rα gene induction when providing activated STATs in trans. Finally, the fourth model (Fig. 7D) links Tyr-392 and Tyr-510 to the activation of both STAT proteins and an additional signaling molecule (factor X). This scheme effectively couples both Tyr-392 and Tyr-510 to two separate pathways that cooperate in IL-2Rα gene induction. In turn, the “non-STAT” pathway may influence activation of other transcription factors required for IL-2Rα mRNA expression, consistent with the complex regulation of this gene (13, 14, 32).

Although we favor the final model, the identity of the putative additional signaling molecule for IL-2-induced IL-2Rα gene expression is unknown. Examination of the IL-7 receptor system may provide some insights in view of its functional overlap with IL-2Rβ. For example, in addition to Stat5 activation (26), Tyr-429 of the IL-7R has been implicated in the activation of PI 3-kinase (37). Along these lines, one published report proposed a direct interaction between Tyr-392 of IL-2Rβ and PI 3-kinase based on phosphopeptide competition experiments (38). Yet, because the same analysis failed to demonstrate any interaction between PI 3-kinase and Tyr-510 of IL-2Rβ (38), PI 3-kinase is unlikely to represent the missing molecule depicted in Fig. 7D that must be capable of interacting with Tyr-510 as well as Tyr-392. Further comparison of the IL-7 and IL-2 receptor systems reveals that both receptors employ Jak1 and Jak3. In contrast, IL-3 signaling involves Jak2. However, the use of Jak2 instead of Jak1 and Jak3 does not fully explain the inability of IL-3 to induce the IL-2Rα gene, as erythropoietin also activates Jak2 but can induce IL-2Rα mRNA in 32D cells transfected with the murine erythropoietin receptor (data not shown).

In conclusion, we have demonstrated that Tyr-392 and Tyr-510 play vital but redundant roles in IL-2Rα gene induction. Although more work is required to clarify the proximal events that culminate in IL-2-mediated expression of this gene, the evidence supports the existence of additional signaling molecule(s)/pathway(s) linked to Tyr-392 and Tyr-510. Defining the
missing element(s) may reveal yet another IL-2-mediated signaling pathway and provide insight to critical processes regulating the immune response.

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