

Structure of the Quaternary Complex of Interleukin-2 with Its α , β , and γ_c Receptors

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Interleukin-2 (IL-2) is an immunoregulatory cytokine that acts through a quaternary receptor signaling complex containing alpha (IL-2R α), beta (IL-2R β), and common gamma chain (γ_c) receptors. In the structure of the quaternary ectodomain complex as visualized at a resolution of 2.3 angstroms, the binding of IL-2R α to IL-2 stabilizes a secondary binding site for presentation to IL-2R β . γ_c is then recruited to the composite surface formed by the IL-2/IL-2R β complex. Consistent with its role as a shared receptor for IL-4, IL-7, IL-9, IL-15, and IL-21, γ_c forms degenerate contacts with IL-2. The structure of γ_c provides a rationale for loss-of-function mutations found in patients with X-linked severe combined immunodeficiency diseases (X-SCID). This complex structure provides a framework for other γ_c -dependent cytokine-receptor interactions and for the engineering of improved IL-2 therapeutics.

The cytokine IL-2 is mainly produced by antigen-activated T cells and promotes the proliferation, differentiation, and survival of mature T and B cells as well as the cytolytic activity of natural killer (NK) cells in the innate immune defense (1, 2). IL-2 is used therapeutically as an immune adjuvant in certain types of lymphoproliferative diseases and cancers, and IL-2 antagonists can prevent organ transplant rejection (3, 4). However, severe dose-limiting toxicity has limited its effectiveness in the clinic. These deleterious side effects are mediated through different combinations of IL-2 receptors, which suggests that structure-based engineering of receptor-selective variants could have clinical benefit (5).

IL-2 exerts its pleiotropic activities through binding to different receptor complexes, depending on which of the components are expressed on the cell surface: the alpha chain (IL-2R α), beta chain (IL-2R β), and common cytokine receptor gamma chain (γ_c) (6–10). Isolated IL-2R α has been termed the “low-affinity” IL-2 receptor (binding affinity $K_d \approx 10$ nM) and is not involved in signal transduction (11). A complex of IL-2R β and γ_c binds with intermediate affinity ($K_d \approx 1$ nM) and is the receptor form on NK cells, macrophages, and resting T cells (2), although IL-2R β alone has very low affinity ($K_d \approx 100$ nM) and γ_c alone has no detectable binding affinity for IL-2 (12). The association of IL-2R β and γ_c in the presence of IL-2 is necessary and sufficient for effective signal transduction through

the heterodimerization of their cytoplasmic domains and subsequent kinase activation of multiple signaling pathways (13, 14). A complex with three subunits—IL-2R α , IL-2R β , and γ_c —binds with high affinity ($K_d \approx 10$ pM) and is the receptor form on activated T cells (10). The high-affinity receptor complex mediates most biological effects of IL-2 in vivo (2).

Whereas IL-2R α is a specific receptor for IL-2, IL-2R β is also a component of the IL-15 receptor and γ_c is shared by cytokines IL-4, IL-7, IL-9, IL-15, and IL-21 (15). Mutations in γ_c can abolish the activity of all γ_c -dependent cytokines and result in X-linked severe combined immunodeficiency diseases (X-SCID), in which the T and NK cells are absent or profoundly reduced in number (16). Because the six γ_c -dependent cytokines have low sequence homology, structural information will be helpful to delineate shared versus ligand-specific binding determinants that could be exploited therapeutically. Previously, we reported the structure of the binary complex of IL-2 with IL-2R α (17). We now present the crystal structure, at 2.3 Å resolution, of the quaternary complex of IL-2 with the extracellular domains of receptors IL-2R α , IL-2R β , and γ_c .

Overall structure. Because of the heterogeneity of the fully glycosylated proteins expressed from insect cells, we crystallized a glycan-minimized quaternary complex, which had five potential Asn-linked glycosylation sites mutated (18). This material behaved identically to the fully glycosylated proteins and yielded crystals that diffracted to 2.3 Å resolution (18).

The quaternary complex is composed of one copy each of IL-2, IL-2R α , IL-2R β , and γ_c (Fig. 1A). The orientation of IL-2R α explains the necessity for the long connecting

peptide, disordered in the structure, between the IL-2R α globular head and the transmembrane segment. This allows the IL-2R α binding domain to extend away from the cell surface and reach the dorsally located binding site on IL-2 (Fig. 1B). The bases of the receptors IL-2R β and γ_c , both class I-type cytokine receptors, converge to form a Y shape and IL-2 binds in the fork (Fig. 1, A and B). Formation of the quaternary complex is mediated by four binding sites—IL-2/IL-2R α , IL-2/IL-2R β , IL-2/ γ_c , and IL-2R β / γ_c —burying a total of 5700 Å² of surface area (fig. S1). The IL-2/IL-2R α and IL-2/IL-2R β contacts are independent, whereas IL-2 and IL-2R β form a composite interface with γ_c , reflecting the cooperative nature of complex assembly.

IL-2R α has been shown to deviate from typical cytokine receptor structure and mode of interaction with IL-2 (17). It is composed of two domain-swapped “sushi” modules, essentially miniature β -sheet sandwich domains. IL-2R β and γ_c are prototypical members of the class I cytokine receptor superfamily (19). Both are composed of N- and C-terminal fibronectin-III domains (D1 and D2, respectively), which are characterized by a β -sandwich sheet consisting of seven antiparallel strands arranged in a three-on-four topology. In IL-2R β , the D1 and D2 domains are connected by a helical linker and are bent at $\sim 90^\circ$, whereas in γ_c the D1 and D2 domains are bent at $\sim 120^\circ$ (Fig. 1A). Both IL-2R β and γ_c contain the two disulfide bonds in the N-terminal domain (D1) and a “WSXWS” motif (20) in the C-terminal domain (D2) that are characteristic of class I cytokine receptors (19). However, a third disulfide bond in the γ_c D2 domain is unusual because of its central position in the interface with IL-2 and its role in enabling degenerate cytokine recognition (Cys¹⁶⁰ to Cys²⁰⁹) (discussed below).

IL-2/IL-2R α . In the “low-affinity” complex, the atomic interactions between IL-2 and IL-2R α , now visualized at 2.3 Å, are unchanged from the binary complex at 2.8 Å (17). The binding interface between IL-2 and IL-2R α in the quaternary complex is composed of helices A' and B' and part of the AB loop in IL-2 and strands G, C, and D in the D1 domain and strand A in the D2 domain in IL-2R α (table S2A). The two prominent hydrophobic ridges around residues Phe⁴² and Tyr⁴⁵ of IL-2 insert into grooves between the IL-2R α beta strands. Superposition of the two IL-2R α structures in the binary and quaternary complexes shows a significant shift in the D2 domain of IL-2R α (~ 2 Å), which is most likely a result of crystal packing and reflects some flexibility in the D1-D2 junction.

IL-15 is the only other cytokine that uses an atypical sushi-domain alpha receptor (IL-

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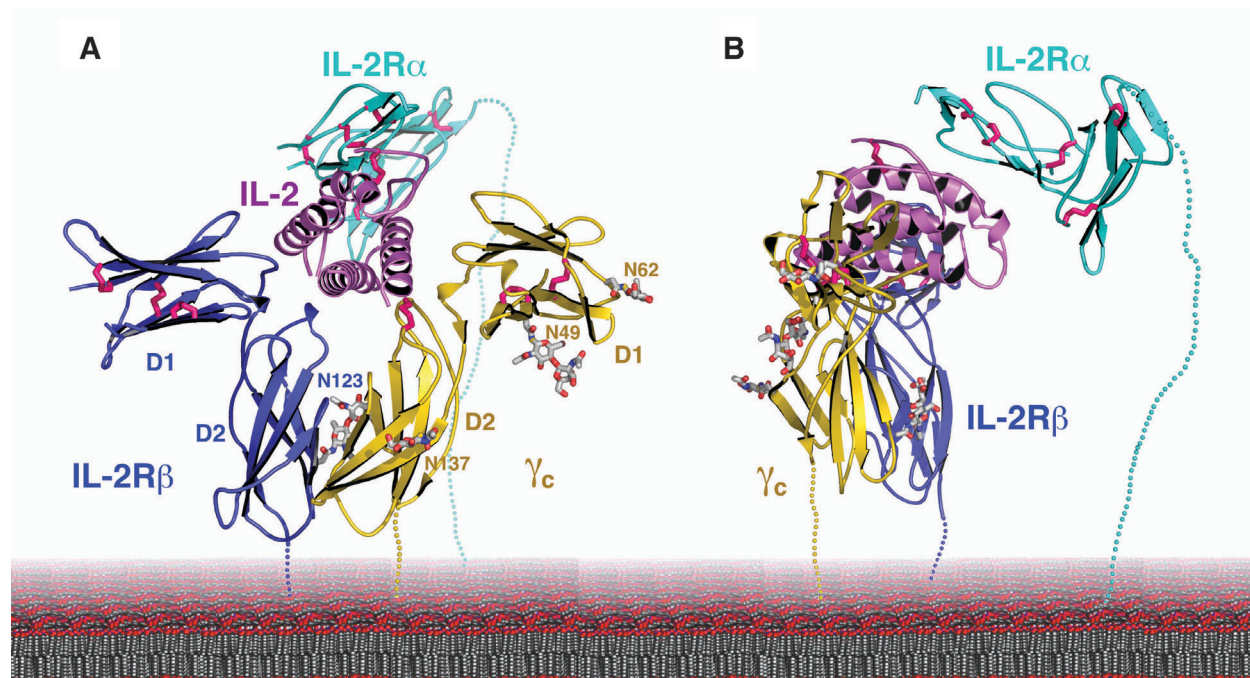


Fig. 1. Structure of the human IL-2/R $\alpha\beta\gamma$ quaternary signaling complex. (A and B) Ribbon diagram of the complex structure shown in two views related by a $\sim 90^\circ$ rotation about the vertical axis. IL-2 is shown in violet, and the receptors are shown in cyan (IL-2R α), blue (IL-2R β), and gold (γ_c). The observed N-linked carbohydrates at

Asn¹²³ of IL-2R β and at Asn⁴⁹, Asn⁶², and Asn¹³⁷ of γ_c are shown in gray (20). Disulfide bonds are shown in red. The disordered peptides connecting the C terminus of the receptors to the cell membrane are shown as dotted lines in their respective colors. The program PyMol (43) was used to make all figures.

15R α), which is expressed primarily on NK cells (21). However, IL-15R α is only a single sushi domain analogous to the IL-2R α D1 domain (22, 23). By analogy with IL-2, the IL-15/IL-15R α complex likely forms first, followed by binding to IL-2R β and γ_c to form the quaternary signaling complex.

IL-2R α does not appear to make any contact with either IL-2R β or γ_c . This is rather surprising, given that the IL-2/IL-2R α complex binds with much higher affinity to IL-2R β ($K_d \approx 30$ pM) than does IL-2 binding to IL-2R β alone ($K_d \approx 100$ nM) (12, 24) and the on-rate of IL-2 for IL-2R β is faster in the presence of IL-2R α by a factor of 3 to 20 (11, 25). We see no evidence of a composite receptor binding surface for IL-2, so what is the basis of the cooperativity? One possibility would be simple entropy reduction, wherein IL-2R α captures and concentrates free IL-2 at the cell surface for presentation to IL-2R β and γ_c . Another possibility would be an IL-2R α -induced conformational change in IL-2 that stabilizes the formation of the ternary complex.

To address the latter mechanism, we compared IL-2 structures in the quaternary complex, binary complex, and unbound states. The root mean square deviations for C α atoms in the helical core between the different IL-2 molecules indicate nearly identical structures, ranging from 0.29 Å to 0.57 Å. One notable exception is at the beginning of helix C of IL-2, where, in the

binary and quaternary complexes, several turns of helix C are slightly unwound and translated forward by ~ 1.0 Å toward IL-2R β (Fig. 2A). This local conformational adjustment moves IL-2 residue Asn⁸⁸ into hydrogen-bonding distance to IL-2R β residue Arg⁴² (Fig. 2B). This movement possibly “primes” the next step in complex assembly by forming a more complementary IL-2R β binding site. Consistent with this, mutation of Asn⁸⁸ in IL-2 ablates binding to IL-2R β (5). IL-2R α may stabilize a favorable IL-2R β -binding conformation of IL-2 helix C, reducing a conformational entropy penalty that would be incurred during binding to IL-2R β . This priming of a “quiescent” IL-2R β binding site in IL-2 by IL-2R α could effectively increase the on-rate for the IL-2 interaction with IL-2R β , as has been observed.

IL-2/IL-2R β . The interface between IL-2 and IL-2R β buries ~ 1350 Å² formed by residues from helices A and C in IL-2 and residues from loops CC'1, EF1, BC2, and FG2 in IL-2R β (table S2B). The interface is highly polar, with eight hydrogen bonds directly between IL-2 and IL-2R β residues. Strikingly, there are seven water molecules buried in the interface that bridge interactions between IL-2 and IL-2R β by forming bonds with protein atoms (Fig. 3A) (table S2B). Solvent exchange with the layer of water molecules between IL-2R β and IL-2 could explain the fast on- and off-rates and the weak affinity of the IL-2/IL-2R β binary complex.

Two residues of IL-2 that have been shown by mutagenesis to be critical for IL-2R β binding, Asp²⁰ and Asn⁸⁸, are involved in hydrogen bonding networks to both water molecules and side chains on IL-2R β (Fig. 3A). The side chains of IL-2R β residues His¹³³ and Tyr¹³⁴ insert into a complementary cavity in IL-2 to form hydrogen and ionic bonds with Asp²⁰ of IL-2 (Fig. 3B).

IL-2R β is also used by IL-15 to form a quaternary complex along with IL-15R α and γ_c (15). IL-15 has limited sequence identity (19%) with IL-2, so its contact with IL-2R β is probably through a unique set of interactions. The bridging water molecules may contribute to the ability of IL-2R β to cross-react by accommodating the different IL-15 residues through remodeling of the intervening solvent layer.

IL-2/ γ_c . Neither IL-2 nor IL-2R β alone have measurable affinities for γ_c (12). Therefore, two very weak interactions, IL-2/ γ_c and IL-2R β / γ_c , combine to produce an intermediate-affinity IL-2/IL-2R β / γ_c complex. In the quaternary complex structure, the interaction surface of the IL-2/R $\alpha\beta$ complex with γ_c is composed of two interfaces: a small one between IL-2 and γ_c , and a larger one between IL-2R β and γ_c .

The IL-2/ γ_c interface buries ~ 970 Å² of surface area and is the smallest of the four protein-protein interfaces in the complex. The γ_c binding surface is striking in its absence of extended side chain-specific interactions with

Fig. 2. IL-2R α binding results in local conformational changes within IL-2 helix C. (A) Backbone superposition of IL-2 structures in quaternary complex (violet), binary complex (orange) (PDB 1Z92) (17), and three unbound states: PDB 1M4C (green), 1M47 (dark green), and 3INK (gray) (44, 45). (B) IL-2 residue Asn⁸⁸ in helix C forms a hydrogen bond with Arg⁴² from IL-2R β in quaternary and binary complexes as a result of closer proximity induced by IL-2R α binding.

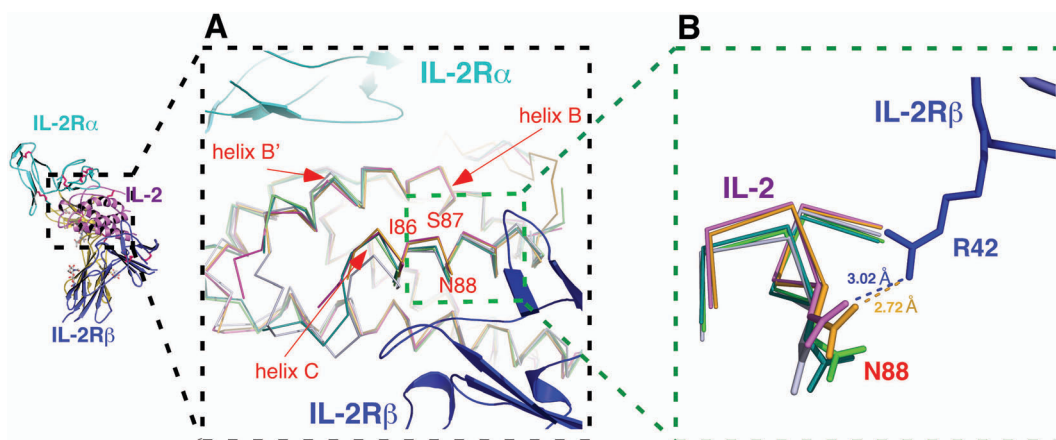
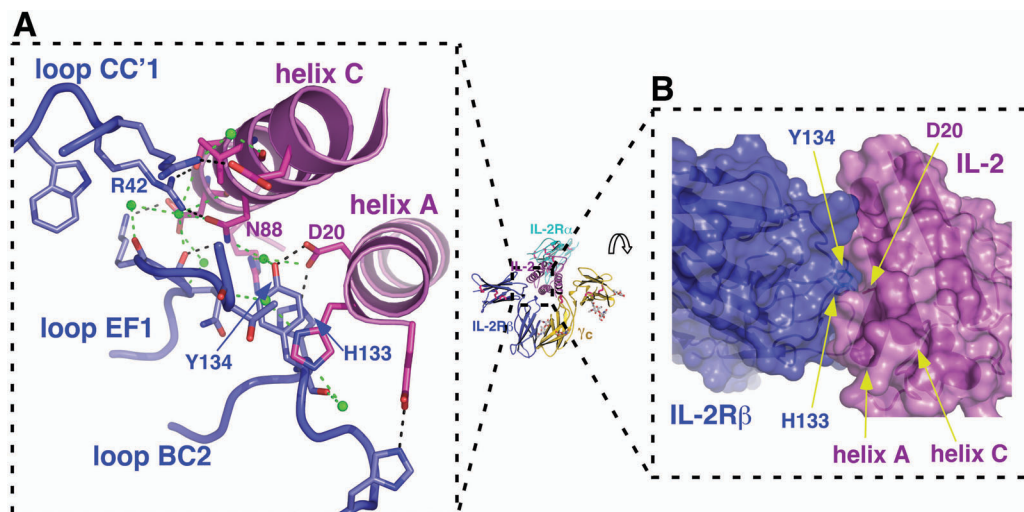


Fig. 3. A polar interface and hydration layer between IL-2 and IL-2R β . (A) All interactions between IL-2 and IL-2R β . The buried water molecules in the interface are shown as green spheres. The hydrogen bonds between IL-2 and IL-2R β are in black; those between water molecules and protein atoms are in green. (B) Close-up view of the shape complementarity in the interface, as viewed from above.



IL-2 and in the preponderance of main-chain contacts. Although there are several apparent “hotspots,” the γ_c binding surface is remarkable in its flatness and almost tangential contact with IL-2 (Fig. 4A). The γ_c structure contains an unusual disulfide bond in the heart of the interface with IL-2 that connects loops FG2 with BC2 and supports the conformations of Ser²⁰⁷ to Pro²¹¹ that form direct contacts with IL-2 (Fig. 4A). The disulfide also contributes to the apparent rigidity of the cytokine-binding surface, which is surprising given that one prevailing assumption for receptor cross-reactivity is structural plasticity (26). The γ_c binding surface does not appear to contain mobile structural elements, although we do not have a structure of the unliganded receptor for comparison.

The overall interface involves residues from helices A and D in IL-2 and residues from loops CC'1, EF1, BC2, FG2, and the linker between strands G1 and A2 in γ_c (table S2C). In contrast to the broad array of specific polar interactions between IL-2 and IL-2R β , small contact patches dominate the IL-2/ γ_c interface. The first one is composed of residue Tyr¹⁰³ from γ_c and residues Ser¹²⁷

and Ser¹³⁰ from IL-2. The Tyr¹⁰³ aromatic ring packs flat against the side chains of Ser¹²⁷ and Ser¹³⁰ in IL-2 (Fig. 4, A and B). The second is around residue Gln¹²⁶ in IL-2, which has been shown by mutagenesis to be a critical energetic hotspot. Similar to Tyr¹⁰³, the side chain of Gln¹²⁶ is almost parallel to the surface formed by main-chain atoms of residues Pro²⁰⁷ to Ser²¹¹ in γ_c , and this orientation is further fixed by two hydrogen bonds with the receptor, to Pro²⁰⁷ O and Ser²¹¹ OG (Fig. 4A). A single bridged water molecule in the IL-2/ γ_c interface forms hydrogen bonds with Gln¹²⁶ of IL-2 and with Gln¹²⁷ and Asn¹²⁸ of γ_c , respectively (table S2C).

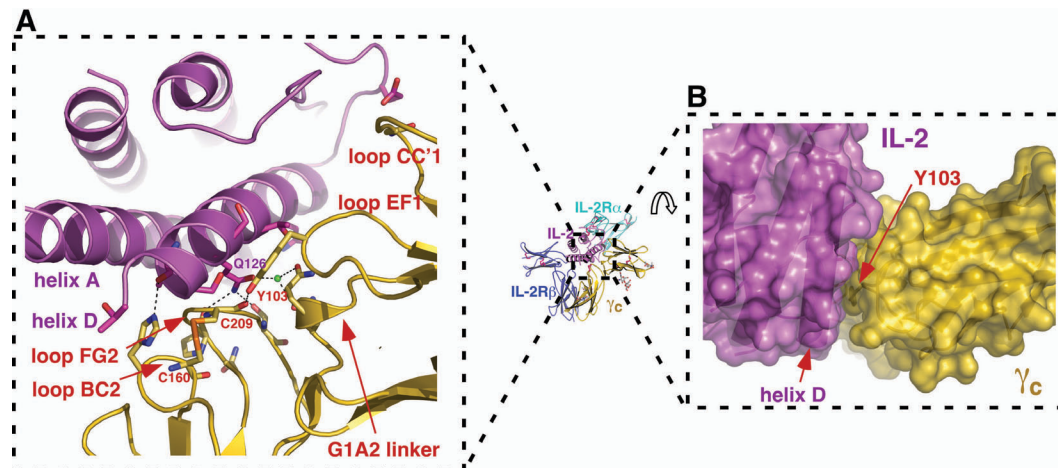
Previous mutagenesis studies have found that two of the flat γ_c patches we see in the structure that are involved in binding IL-2—residue Tyr¹⁰³ and residues from Leu²⁰⁸ to Ser²¹¹ in γ_c —are also important for binding IL-4, IL-7, IL-15, and IL-21 (27–29). There is also evidence that γ_c binding sites for different cytokines overlap but are not identical (30). We propose that these two patches form the central degenerate recognition surfaces that participate in binding all cytokines in the γ_c -dependent family by using

their flat surfaces, and that the peripheral polar interactions modulate specificity for individual cytokines.

IL-2R β / γ_c . The second part of the composite interface between IL-2/R β and γ_c is formed by extensive interactions between the D2 domains of IL-2R β and γ_c , burying more than 1750 Å² of surface area (Fig. 5A). The D2 domains from IL-2R β and γ_c are related by almost exact two-fold symmetry, and the interface is formed by 21 residues from IL-2R β and 19 residues from γ_c from strands C2, C'2, and E2 and loop C'E2 (table S2D). The interface is highly polar, with a peripheral ring of 17 hydrogen bonds surrounding a hydrophobic stripe in the center dominated by Trp¹⁶⁶ from IL-2R β and Tyr¹⁶⁷ from γ_c (Fig. 5B) (table S2D).

The D2-D2 interaction between IL-2R β and γ_c is the largest buried surface seen so far in cytokine-receptor complexes, and it underscores the role of receptor-receptor contact in the cooperative assembly of the quaternary complex. Although it is surprising that IL-2R β and γ_c have no measurable affinity toward one another given this extensive contact surface, a lack of interaction would prevent the receptors from heterodi-

Fig. 4. Interactions between γ_c and IL-2. (A) Contacting residues in the IL-2/ γ_c interface. (B) Surface representation of the relative contact patch around Tyr¹⁰³ from γ_c as viewed from above.



merizing and signaling in the absence of cytokine. Given the structural observations of a small IL-2/ γ_c interface and a large and tightly packed IL-2R β / γ_c interface, we suggest that the receptor-receptor (i.e., D2-D2) contact may serve as an important energetic determinant. If so, the role of the cytokine would be to stabilize complex formation by guiding a perfect geometrical alignment of the numerous interatomic contacts (hydrogen bonds, van der Waals contacts, etc.) in the D2-D2 interface. In this respect, considering the relatively flat and chemically inert IL-2/ γ_c interface, it may be that specificity is largely provided by receptor-receptor contact with IL-2R β rather than cytokine.

This model can in part be rationalized by the “shared” function of γ_c . γ_c is expressed on most immune cell types, but the tissue and cytokine specificity are regulated by the coordinate expression of different α receptors (or, in the case of IL-2, the β receptor). Given the lack of sequence homology between γ_c -dependent cytokines, the capacity of γ_c to discriminate among (and to cross-react with) these ligands would be more easily achieved by spreading the energetics of the interaction over the combined ~ 2600 Å² of surface area presented by the IL-2/IL-2R β composite surface, rather than focusing it all on the small portion of this surface contributed by cytokine alone (~ 970 Å²). By comparison, in the structures of more ligand-specific cytokine receptors such as human growth hormone receptor (hGHbp) and erythropoietin receptor (epoR) complexed with their ligands, there is much less receptor-receptor contact (~ 900 Å² for hGHbp, no contact for epoR) (31, 32).

X-SCID mutations. X-linked severe combined immunodeficiency (SCID) is a syndrome of profoundly impaired cellular and humoral immunity caused by mutations in the gene encoding the common gamma chain (33). The mutated gene results in faulty signaling through several cytokine receptors;

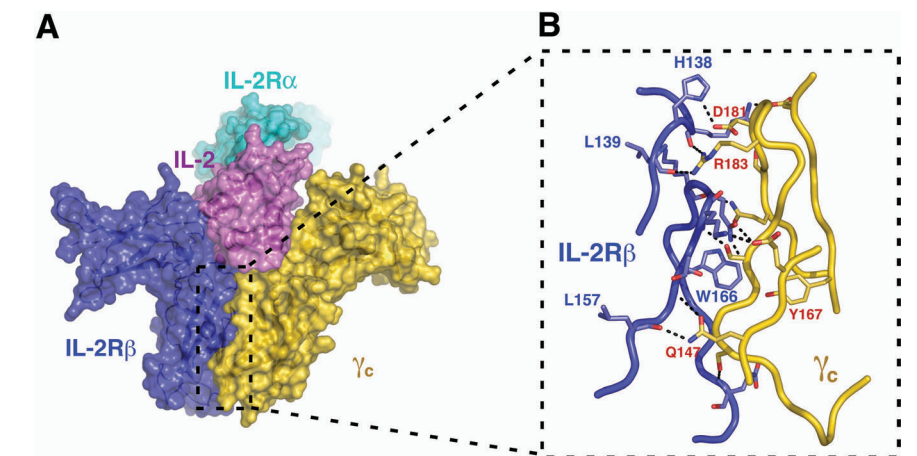


Fig. 5. Extensive receptor-receptor contact between IL-2R β and γ_c . (A) Surface representation of the quaternary complex shows the shape complementarity in the IL-2R β / γ_c interface. (B) Hydrogen-bonding interactions between IL-2R β and γ_c .

thus, T, B, and NK cells can be affected by a single mutation. We mapped extracellular γ_c mutations that have been found in X-SCID patients in which γ_c is expressed but is not competent for activation by any of the γ_c cytokines. Many mutations appear to concentrate near the γ_c cytokine-binding site, and several of these—Y103N, Y103C, L208P, C209R, C209Y, G210R, G210V, and C160R (20, 33)—map to the γ_c binding interface with IL-2 (Fig. 6A). Mutation of Cys²⁰⁹ or Cys¹⁶⁰, which participate in the disulfide bond in the γ_c cytokine-binding surface, would be particularly destabilizing. The interface mutations would effectively ablate cytokine recognition by γ_c , but it seems likely that the receptor would still appear to be competent to signal if heterodimerized. Although the database X-SCID mutations map to all other parts of the γ_c structure, none of the X-SCID mutations map to the IL-2R β / γ_c interface, possibly implying a structural necessity for this area to be preserved in the expressed receptor (Fig. 6B).

Degenerate cytokine recognition by γ_c . The γ_c -dependent cytokines have,

on average, 19% sequence identity to one another, with most of the homology concentrated inside the helical cores. Although we currently know the structures of only IL-2 and IL-4 in the γ_c -dependent cytokine family, we sought to identify conserved residues that might serve as a recognition code for γ_c binding throughout the family. Sequence alignment between IL-2 and other γ_c -dependent cytokines (fig. S3) indicates that residue Gln¹²⁶, which plays a key structural role in IL-2 interactions with γ_c , is conserved in IL-2, IL-9, IL-15, and IL-21, whereas IL-4 and IL-7 have Arg¹²¹ and Lys¹³⁹ in this position, respectively. Superposition of the IL-4/IL-4R α complex (34) with the IL-2 quaternary complex indicates that Arg¹²¹ may play a structural role similar to that of Gln¹²⁶ in IL-2 in contacting γ_c . Although position 126 in helix D may serve as a common contact point with γ_c , there are not obvious constellations of conserved residues that allow us to dock the different cytokines with γ_c . It appears that each cytokine uses distinct structural solutions for γ_c recognition.

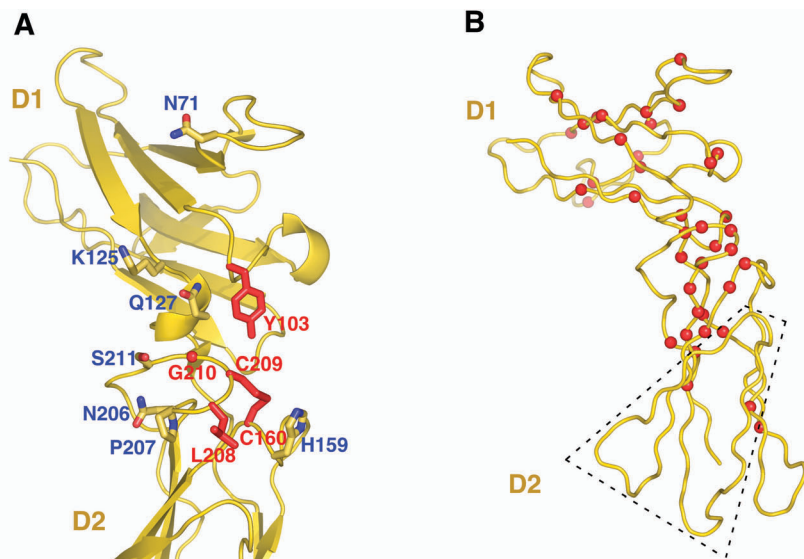


Fig. 6. Mapping known X-SCID mutations in the structure of γ_c . (A) Five missense mutations that are located in the γ_c cytokine-binding epitope, and make contact with IL-2 in the structure, are shown as red sticks. (B) Distribution of all missense mutations in the X-SCID mutation database (<http://genome.nhgri.nih.gov/scid>) in γ_c . The γ_c area participating in the D2-D2 interaction with IL-2R β is free of mutations and is indicated within the dashed line.

Cytokine recognition by shared receptors. The flat and apparently rigid surface in the common binding epitope of γ_c suggests that it uses somewhat chemically inert complementary surfaces to interact with divergent cytokine residues. Although this contrasts with notions of receptor promiscuity through binding site flexibility (26), it parallels structural results for gp130, the shared cytokine receptor for long-chain cytokines (35), in complex with three different cytokines: LIF, viral IL-6, and human IL-6 (36–38). In the gp130 system, thermodynamic compensation between rigid surfaces, rather than conformational change, enables cross-reactivity with a broad range of chemically diverse cytokine surfaces (35). We predict, on the basis of direct thermodynamic measurements of the quaternary complex assembly (12), that γ_c also uses such a mechanism for cross-reactivity. Such a large range of energetic compensation appears to be a property of binding sites found in shared receptors, which are tuned for degenerate recognition through a mechanism that bypasses the entropic penalty for conformational change (39).

Therapeutic implications. A recombinant human IL-2 (rIL-2) analog (Aldesleukin, Proleukin, Chiron Inc., Emeryville, CA) is currently licensed in the United States for the treatment of metastatic melanoma and renal cell carcinoma and is undergoing clinical trials for patients with HIV/AIDS (40, 41). Treatment of cancer patients with rIL-2 results in robust responses but is associated with life-threatening toxicity, which limits its use (40). The antitumor efficacy of rIL-2 therapy has been shown to be mediated by

the high-affinity quaternary complex containing IL-2R $\alpha\beta\gamma$ expressed on T cells, whereas the toxic side effects are mediated through the IL-2R $\beta\gamma$ form of the receptor on NK cells (42). This hypothesis suggests that it might be possible to dissociate efficacy and toxicity by generating an IL-2 variant with selectivity for the IL-2R $\alpha\beta\gamma$ receptor complex, versus the IL-2R $\beta\gamma$ complex of NK cells (5). Proof-of-concept was demonstrated with an IL-2 variant bearing an Asn⁸⁸ → Arg mutation that conferred a factor of 3000 selectivity increase for the IL-2R $\alpha\beta\gamma$ complex by crippling the interaction between IL-2 and IL-2R β (5).

In the structure we see that Asn⁸⁸ is the side chain brought into hydrogen-bonding distance to IL-2R β by the structural perturbation of helix C in response to IL-2R α binding, and is involved in an extensive hydrogen-bonding network (Fig. 3A). Such an energetically critical residue may not be the most desirable choice for generating a receptor-selective IL-2, because it may not be necessary to completely ablate binding to the IL-2R $\beta\gamma$ receptors. Rather, weakening the IL-2R β interaction, or even contact with γ_c , while maintaining near wild-type affinity for the IL-2R $\alpha\beta\gamma$ complex appears tenable through structure-guided engineering. It is our hope that this quaternary complex structure can be used to design IL-2 variants that will allow its powerful clinical potential to be more fully realized.

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20. Single-letter abbreviations for amino acid residues: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; Y, Tyr.
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46. We thank N. Goriatheva for expert technical assistance; K. Smith, T. Springer, and W. Leonard for helpful discussions; and the Advanced Light Source (UC-Berkeley) and Stanford Synchrotron Radiation Laboratory for synchrotron beamtime. Supported by the Keck Foundation, HHMI, and NIH grant AI51321. Coordinates and structure factors have been deposited in the Protein Data Bank with accession number 2B5I.

Supporting Online Material

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References

25 July 2005; accepted 14 October 2005
10.1126/science.1117893