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29. The structure factor of a helix with a repeat of u units in t turns, axially spanning distance c, is

$$F\left(R,\Psi,\frac{l}{c}\right) = \sum_{n=-\infty}^{\infty} G_{n,l}(R)e^{in(\Psi+\pi/2)} \quad (1)$$

$$G_{n,l}(R) = \sum_{j=1}^{N} f_j J_n(2\pi R r_j) e^{i}\left(\frac{2\pi l z_j}{c} - n\phi_j\right) \quad (2)$$

where R, Ψ, and l/c are the reciprocal space cylindrical coordinates and r_j, ϕ_j, and z_j are the real space cylindrical coordinates of the jth of N atoms, and G is the part independent of Ψ. The permitted Bessel function of order n on layer line l is from the helix selection rule $l = tn + um$, where m is an integer [A. Klug, F. H. C. Crick, H. W. Wyckoff, *Acta Crystallogr.* **11**, 199 (1958)]. For each pair of atoms from two protein subunits SU_0 and SU_1 and two O–P–O groups P_0 and P_1, radius r and diffraction factors f are constant, so we define $G_0 = fJ_n(2\pi Rr)$. For the structural unit containing two protein subunits SU_0 $(r,0,0)$ and SU_1 (r,ϕ_{SU},z_{SU}) and two nucleotides P_0 $(r,0,0)$ and P_1 $(r,\phi_{SU}-\pi,z_{SU})$

$$G = G_{DNA} + G_{SU} \quad (3)$$

$$G_{DNA} = G_{0,DNA} + G_{0,DNA}e^{i}\left[\frac{2\pi l z_{SU}}{c} - n(\phi_{SU} - \pi)\right]$$

$$= G_{0,DNA}\left[1 + (-1)^n e^{i}\left(\frac{2\pi l z_{SU}}{c} - n\phi_{SU}\right)\right] \quad (4)$$

$$G_{SU} = G_{0,SU} + G_{0,SU}e^{i}\left(\frac{2\pi l z_{SU}}{c} - n\phi_{SU}\right)$$

$$= G_{0,SU}\left[1 + e^{i}\left(\frac{2\pi l z_{SU}}{c} - n\phi_{SU}\right)\right] \quad (5)$$

The correct selection rule for Pf1 virus at low temperature is $l = 26n + 71m$, where there are 71 asymmetric subunits containing two protein subunits each, yet there are still 71 individual subunits in 13 turns. For DNA, when n is an even number, the diffraction of the O–P–O groups appears as if from a helix of O–P–O groups following the protein symmetry exactly; when n is an odd number, the diffraction appears to be from two such helices, thus revealing the existence of two strands.
30. It seems that even if the selection rule $l = 26n + 71m$ had been applied in the transform for an asymmetric unit containing two nucleotides and two protein subunits, not much more information would have been extracted from the diffraction patterns. Therefore, $l = 13n + 71m$ appears to be a good approximation applied to solve the structure that significantly simplified data processing while maintaining acceptable accuracy.
31. The maximum entropy calculation in the transform starts with a "flat" distribution of density (maximal entropy). It then rearranges the density according to the information from the diffraction patterns filtered through the selection rule. If the constraints obtained are not sufficient, it simply preserves much of the starting "flat" distribution.
32. L. Pauling, R. B. Corey, and H. R. Branson [*Proc. Natl. Acad. Sci. U.S.A.* **37**, 205 (1951)] predicted such secondary structure with $\{\phi,\Psi\} = \{-74°,-4°\}$; in a survey, D. J. Barlow and J. M. Thornton [*J. Mol. Biol.* **201**, 601 (1988)] found the average $\{\phi,\Psi\}$ to be $\{-71°,-18°\}$; on the basis of then available structural data, J. S. Richardson and D. C. Richardson [in *Prediction of Protein Structure and the Principles of Protein Conformation*, G. D. Fasman, Ed. (Plenum, New York, 1989), pp. 1–98] defined a 3_{10} helix as having $\{\phi,\Psi\}$ about $\{-70°,-5°\}$ and concluded that glycines terminate an α helix at a high frequency and favor a 3_{10} helix. We assigned $\{\phi,\Psi\}$ values on the basis of these values for a 3_{10} helix. For an α helix, the set of $\{\phi,\Psi\}$ angles is assigned as $\{-65°,-40°\}$.
33. We only used the radial positions of the labels because the axial and azimuthal positions currently available are uncertain, as a consequence of difficulties in backbone tracing (*20*).
34. Abbreviations for the amino acid residues are A, Ala; D, Asp; E, Glu; G, Gly; I, Ile; K, Lys; L, Leu; M, Met; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; and Y, Tyr.
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Specific Interaction of Type I Receptors of the TGF-β Family with the Immunophilin FKBP-12

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Transforming growth factor–β (TGF-β) family members bind to receptors that consist of heteromeric serine-threonine kinase subunits (type I and type II). In a yeast genetic screen, the immunophilin FKBP-12, a target of the macrolides FK506 and rapamycin, interacted with the type I receptor for TGF-β and with other type I receptors. Deletion, point mutation, and co-immunoprecipitation studies further demonstrated the specificity of the interaction. Excess FK506 competed with type I receptors for binding to FKBP-12, which suggests that these receptors share or overlap the macrolide binding site on FKBP-12, and therefore they may represent its natural ligand. The specific interaction between the type I receptors and FKBP-12 suggests that FKBP-12 may play a role in type I receptor–mediated signaling.

Transforming growth factor–β elicits its effects by binding to a heteromeric complex of type I and type II receptors (*1–3*). Four transmembrane serine-threonine kinases—R1, R2, R3, and R4—have been cloned (*4–11*). These are the type I receptors for members of the TGF-β family. R4 is the functional type I receptor for TGF-β (*7, 12*), and R1 and R3 both can bind activin and TGF-β when expressed with the appropriate type II receptors (*5, 6, 10, 13*). R1 mRNA is specifically localized in the mesenchyme surrounding the Müllerian duct during embryonic Müllerian duct regression, which suggests that it is a candidate type I receptor for Müllerian inhibiting substance (*4*).

To study type I receptor–mediated signaling, we used a variant of the yeast two-hybrid system (*14–16*) to identify proteins that interact with the cytoplasmic domain of R1 (R1C). The entire cytoplasmic domain of R1 was fused with the DNA binding domain of LexA to serve as the "bait" (*17*). Because R1 is expressed in heart tissue (*4*), a yeast expression complementary DNA (cDNA) library from neonatal rat heart was used for screening. Seventy-six cDNAs were isolated (*14*), partially sequenced, and grouped. The largest family, consisting of 47 cDNAs of about 1.5 kb,

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was almost identical to the DNA sequences of genes encoding mouse and human FKBP-12. The predicted amino acid sequence encoded by the cDNA differs from that of mouse FKBP-12 only at P10S and S79P (*18*); thus, the cDNA encodes the rat homolog of FKBP-12 (GenBank accession number U09386). A second family consisted of 10 cDNAs that did not have the first 6 to 15 base pairs of the coding region of the gene encoding rat FKBP-12.

The specificity of the interaction between R1C and FKBP-12 was tested with several unrelated molecules, all of which failed to interact with FKBP-12 (Fig. 1A). When the cytoplasmic domains of R3 and R4 were tested, positive interactions were detected (Fig. 1B); however, the cytoplasmic domains of the TGF-β type II receptor (tRIIC) and of the activin type II receptor (aRIIC) failed to interact (Fig. 1B). Because FKBP-12 interacted with all of the type I receptors tested but failed to interact with the type II receptors used here, FKBP-12 may be a common binding protein of the type I receptors. When we quantified interactions between different type I receptor cytoplasmic domains and FKBP-12 by measuring the β-galactosidase activities of the transformants, the strongest interaction was found between R1C and FKBP-12 (*19*).

Because a point mutation of Lys^{230} to Arg (*18*) within the adenosine triphosphate binding site of R4 completely abolishes its ability to transduce TGF-β–induced signals (*12*), we tested the binding of R4C K230R to FKBP-12 (*20*). The strength of the interaction was weakened (Fig. 1B), and when β-galactosidase activity was quantified, we observed a decrease to one-twentieth its original value (*19*).

We made a number of constructs encoding various domains of R1C (Fig. 1C) (*21*) that directed synthesis of the encoded fusion proteins. None interacted with FKBP-12

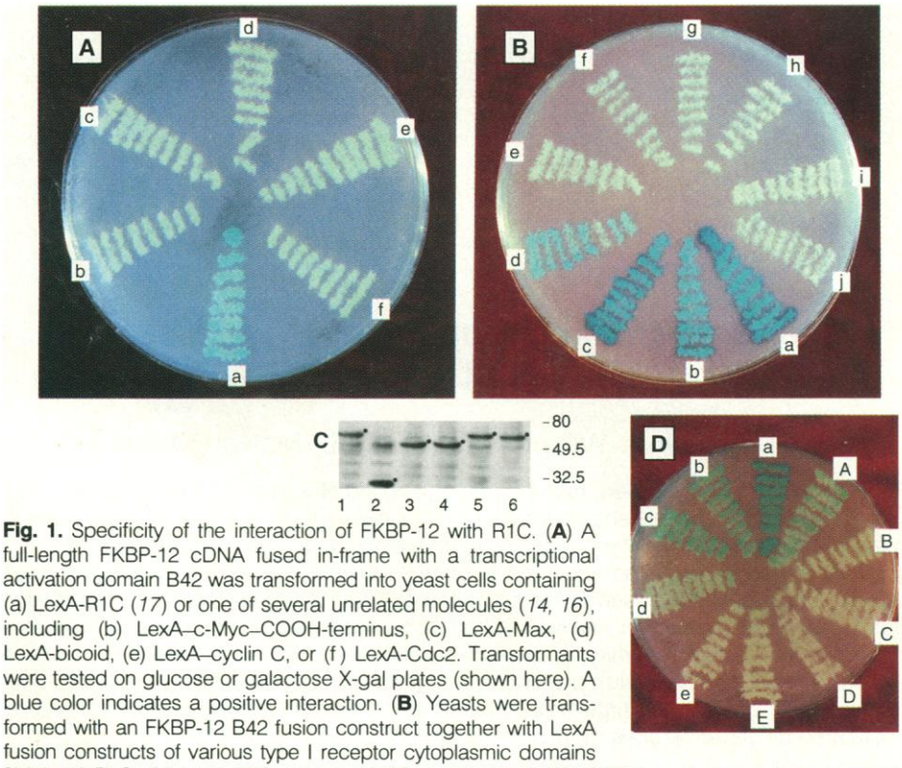

Fig. 1. Specificity of the interaction of FKBP-12 with R1C. (**A**) A full-length FKBP-12 cDNA fused in-frame with a transcriptional activation domain B42 was transformed into yeast cells containing (a) LexA-R1C (*17*) or one of several unrelated molecules (*14, 16*), including (b) LexA–c-Myc–COOH-terminus, (c) LexA-Max, (d) LexA-bicoid, (e) LexA–cyclin C, or (f) LexA-Cdc2. Transformants were tested on glucose or galactose X-gal plates (shown here). A blue color indicates a positive interaction. (**B**) Yeasts were transformed with an FKBP-12 B42 fusion construct together with LexA fusion constructs of various type I receptor cytoplasmic domains [(a) LexA-R1C; (b) LexA-R3C; (c) LexA-R4C; or (d) LexA-R4CK230R] or of various type II receptor cytoplasmic domains [(e) LexA-tRIIC (cytoplasmic domain of the TGF-β type II receptor) or (f) LexA-aRIIC (cytoplasmic domain of the activin type II receptor)]. Various subdomains of R1C were fused with LexA (*21*) to generate (g) LexA-R1C-JM; (h) LexA-R1C–K-T; (i) LexA-R1C-K; or (j) LexA-R1C–JM-K and were tested as described in (A). Abbreviations are as in (C). (**C**) A protein immunoblot with antiserum to LexA shows the expression of the LexA fusion proteins of R1C (residues 147 to 509); JM (residues 147 to 209) (the juxtamembrane domain); K-T (residues 210 to 509) (R1C with the juxtamembrane domain deleted); K (residues 210 to 485) (the R1C kinase domain with the last eight amino acids deleted from domain XI); JM-K (residues 147 to 485) (R1C with a 24–amino acid deletion from the COOH-terminus); and R4C (residues 147 to 501) (lanes 1 to 6, respectively). The numbers indicate the number of the amino acids from the start codon. Each dot points to the corresponding protein made in yeast. (**D**) Weakened interaction of truncated FKBP-12 with the cytoplasmic domains of the type I receptors. Yeasts transformed with constructs LexA-R1C (a), LexA-R3C (b), LexA-R4C (c), LexA-R4C K230R (d), and LexA-tRIIC (e) were retransformed with a B42 fusion construct of full-length FKBP-12 (lowercase letters) or FKBP-12Δ5 (uppercase letters), which lacks the first five amino acids from the NH_2-terminus. The transformants were tested on glucose or galactose X-gal plates.

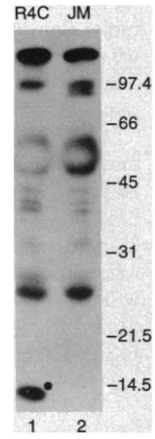

Fig. 2. Interaction of LexA-R4C with FKBP-12 in vitro. Single colonies of LexA-R4C or LexA-R1C-JM yeast transformants were grown in glucose medium lacking uradine and histidine. Cell lysates were prepared (*23*), incubated with rabbit preimmune serum coupled to protein A–Sepharose beads to preclean, and then incubated with antiserum to LexA (15 μl) coupled to protein A–Sepharose beads overnight at 4°C with shaking. The protein A–Sepharose beads were collected by centrifugation, washed four times with phosphate-buffered saline (PBS), resuspended in PBS, and then incubated with lysate of wild-type mink lung cells as a source of FKBP-12 (200 μl) (prepared from 10^6 cells in the same lysis buffer used for yeast extracts) for 4 hours at 4°C, with shaking. The beads were collected, washed four times with PBS, resuspended in concentrated (×2) sample buffer for SDS–polyacrylamide gel electrophoresis, and boiled for 10 min. Supernatants were loaded onto a 15% polyacrylamide gel. Fusion proteins were detected after electrophoresis by protein immunoblotting with antiserum to LexA (*19*). Immunoblotting with human antiserum to FKBP-12 was performed to detect FKBP-12 co-immunoprecipitated with LexA-R4C (lane 1) or LexA-R1C-JM (lane 2). Molecular size markers are shown on the right in kilodaltons. The dotted band represents the co-precipitated FKBP-12.

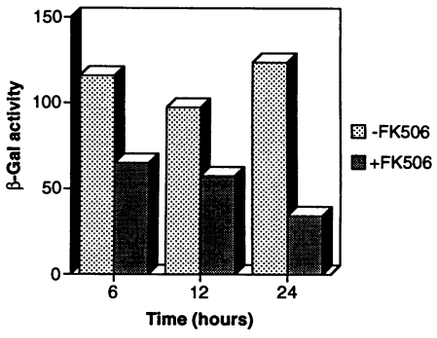

Fig. 3. Competition of FK506 and R4C for binding to FKBP-12. Single colonies of LexA-R4C–FKBP-12B42 transformants were picked and grown overnight in 5 ml of glucose medium lacking uradine, histidine, and tryptophan. Cells were collected by centrifugation, washed, and resuspended in galactose medium lacking uradine, histidine, and tryptophan in the presence (+) or absence (−) of FK506 (1 μM). Cells were collected after 6, 12, or 24 hours, and β-galactosidase (β-Gal) activities were measured. The average β-galactosidase activity for the FK506-treated group ($n = 4$) was 53.9 ± 5.4, whereas the mean for the untreated group ($n = 4$) was 111.7 ± 5.5 (SEM); ($P < 0.0003$ by the unpaired t test).

(Fig. 1B), which indicates that an intact R1C may be necessary for FKBP-12 binding. We also tested FKBP-12Δ5 (a clone of FKBP-12 lacking the first five amino acids) for interaction with a panel of type I receptor molecules (Fig. 1D), all of which showed weakened interaction with FKBP-12Δ5. Thus, an intact NH_2-terminus of FKBP-12 is required for optimal interaction.

Co-immunoprecipitation was used to confirm the specific interaction between FKBP-12 and R4C in vitro. We used fusion proteins of LexA-R4C or LexA-R1C-JM (the juxtamembrane domain of the R1C) (Fig. 1C, lane 2) made in yeast and lysates of mink lung cells, which are a rich source of FKBP-12 as confirmed by protein immunoblotting (*19*). FKBP-12 was coprecipitated with LexA-R4C but not with LexA-R1C-JM (Fig. 2).

Two immunosuppressant drugs, FK506 and rapamycin, bind to the same site on FKBP-12 (*22*). We therefore investigated whether the type I receptors and the drugs share the same binding site on FKBP-12. If the binding sites are the same or partially overlap, drug binding to FKBP-12 would compete with the cytoplasmic domain of the type I receptors. This would result in a decrease of the β-galactosidase activity in the yeast transformants. We added FK506 to a liquid culture of the yeast transformants at two concentrations that did not affect yeast growth. FK506 effectively competed with R4C for FKBP-12 binding at a concentration of 1 μM (Fig. 3), but not at 100 nM. When cyclosporin was used at various concentrations in the same assay, no competition was observed. To further confirm that the type I receptors and the drugs share the same binding site on FKBP-12, we tested in the two-hybrid system a mutant FKBP-12 (D37G) (*18*), which was shown to be defective in binding to FK506 and rapamycin. It failed to interact with the type I receptors (*19*).

Our results suggest that FKBP-12 interacts with type I receptors in a specific manner. A K230R mutation on R4, which abolishes R4 signaling activity (*12*), decreased binding of R4C to FKBP-12, as did a D37G mutation on FKBP-12, which suggests that the interaction may be functionally important. In mammalian cells, ligand binding may promote the type I receptors to bind FKBP-12; alternatively, it may stabilize a preexisting type I receptor–FKBP-12 complex. Although the function of FKBP-12 in the type I receptor–mediated signaling pathway needs to be clarified in TGF-β–responsive cell lines, our data indicate that the binding sites on FKBP-12 for R4C and FK506 may be shared or overlap, which suggests that the type I receptor may be a natural ligand for FKBP-12. Because the competition of FK506 for R4C to bind FKBP-12 can be easily monitored, this yeast system provides a potential screen for other candidate immunosuppressant drugs. If these interactions are confirmed to occur in mammalian cells, rapamycin and FK506 may prove useful in analyzing the downstream actions of TGF-β family ligands.

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17. R1C (residues 147 to 509) was amplified with the polymerase chain reaction (PCR) with Eco RI and Bam HI attached at the 5′ and 3′ ends, respectively, and subsequently inserted into the Eco RI and Bam HI sites of the multicloning region of PEG202 (*14*), with the LexA DNA binding domain fused 5′ to R1C.
18. Abbreviations for the amino acid residues are: D, Asp; G, Gly; K, Lys; P, Pro; R, Arg; and S, Ser. Mutations are indicated as follows: $Lys^{230} \rightarrow$ Arg, K230R.
19. T. Wang, P. K. Donahoe, A. S. Zervos, unpublished results.
20. The entire R4C (residues 147 to 501) was amplified by PCR and then subcloned into the Eco RI and Xho I sites of PEG202.
21. The constructs were generated by PCR and subcloned as described for LexA-R1C (*17*), except for the LexA-aRIIC construct. DNA sequencing and protein immunoblotting confirmed the expression of the fusion proteins.
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24. The neonatal rat heart cDNA library was from A. Green (Beth Israel Hospital, Boston). An R4 K230R pCMV6 plasmid was provided by X.-F. Wang. The LexA-aRIIC construct was from R. Perlman and R. A. Weinberg (Whitehead Institute). We thank T. Haqq for technical assistance; R. Brent for encouragement, support, and valuable suggestions; T. E. Starzl and W. W. He for helpful discussions; A. Green for the rat neonatal cDNA library; and X.-F. Wang, R. Perlman, R. A. Weinberg, and B. Bierer for materials critical for this study. We particularly thank S. Schreiber for supplying FK506 and antibody to FKBP-12; B. Gladstone for the FKBP-12 mutant; R. Finley, P. Baciu, M. Kozlowski, A. Vincent, P. Busto, H. Y. Lin, and J. Schnitzer for technical advice; and R. Brent, P. Goetink, S. Schreiber, J. Avruch, L. Perkins, D. MacLaughlin, and J. Teixeira for comments on the manuscript. Supported by a National Institute of Child Health and Human Development (NICHD) Reproductive Sciences Training Grant (P-32 HD07396) (T.W.) and by grant CA17393 from the National Cancer Institute and by P30 Reproductive Sciences grant (P-30 HD28138) from NICHD (P.K.D.). A.S.Z. was funded under an agreement between Massachusetts General Hospital and Shiseido.

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Reactivation of Hippocampal Ensemble Memories During Sleep

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Simultaneous recordings were made from large ensembles of hippocampal "place cells" in three rats during spatial behavioral tasks and in slow-wave sleep preceding and following these behaviors. Cells that fired together when the animal occupied particular locations in the environment exhibited an increased tendency to fire together during subsequent sleep, in comparison to sleep episodes preceding the behavioral tasks. Cells that were inactive during behavior, or that were active but had non-overlapping spatial firing, did not show this increase. This effect, which declined gradually during each post-behavior sleep session, may result from synaptic modification during waking experience. Information acquired during active behavior is thus re-expressed in hippocampal circuits during sleep, as postulated by some theories of memory consolidation.

The selective strengthening of interactions among small sets of neurons engaged in the encoding of specific external events has been a foundation of modern theories of neural information storage. Yet, despite indirect evidence that changes in synaptic efficacy may be the basis of learning within the hippocampus (*1, 2*), there has been no demonstration of changes in functional interaction among hippocampal cells specific to the representation of a given experience (*3*). Recent experiments with parallel recording methods, however, have revealed rapid changes in neuronal ensemble codes for space within the hippocampus during exposure to a novel environment (*4*). Also, Pavlides and Winson (*5*) previously demonstrated an increase in

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