MINIREVIEW

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 291, NO. 13, pp. 6714–6722, March 25, 2016

Role of Intrinsic Protein Disorder in the Function and Interactions of the Transcriptional Coactivators CREB-binding Protein (CBP) and p300*

Published, JBC Papers in Press, February 5, 2016, DOI 10.1074/jbc.R115.692020

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The transcriptional coactivators CREB-binding protein (CBP) and p300 undergo a particularly rich set of interactions with disordered and partly ordered partners, as a part of their ubiquitous role in facilitating transcription of genes. CBP and p300 contain a number of small structured domains that provide scaffolds for the interaction of disordered transactivation domains from a wide variety of partners, including p53, hypoxia-inducible factor 1α (HIF-1α), NF-κB, and STAT proteins, and are the targets for the interactions of disordered viral proteins that compete with cellular factors to disrupt signaling and subvert the cell cycle. The functional diversity of the CBP/p300 interactome provides an excellent example of the power of intrinsic disorder to facilitate the complexity of living systems.

Intrinsically disordered proteins (IDPs)[3] and protein regions (IDRs) are highly abundant in eukaryotic transcription factors (1, 2) and perform critical functions in regulation of the transcriptional machinery (3–5). The intrinsic lack of structure in IDPs and IDRs provides functional advantages that make them ideally suited to mediate transcriptional regulatory processes. These include (i) the presence of small recognition motifs that fold upon binding, (ii) the flexibility to interact with multiple targets, (iii) accessible sites for post-translational modification (enables IDPs to function as molecular switches and rheostats), (iv) efficient utilization of a small number of residues to mediate binding interactions, and (v) the ability to bind with high specificity but modest affinity (an important attribute that could facilitate spontaneous dissociation or displacement after signaling is complete) (5–11).

The present review focuses on the interactions of the transcriptional coactivator CREB-binding protein (CBP), and its paralog p300, to illustrate the diverse functions of protein disorder in the regulation of gene expression. CBP and p300 are central nodes in eukaryotic transcriptional regulatory networks (12). They interact with more than 400 transcription factors and other regulatory proteins (13), which must compete for binding to the limiting amounts of CBP/p300 present in the cell (14, 15). CBP and p300 regulate crosstalk and interference between numerous cellular signaling pathways, and are targeted by tumor viruses to hijack the cellular regulatory machinery.

CBP and p300 are large proteins that contain seven folded domains (Fig. 1). The regions outside these globular domains, containing more than 1400 amino acids (nearly 60% of the sequence), are predicted to be intrinsically disordered. In addition, the histone acetyltransferase domain (HAT) domain contains an ~60-residue, disordered, autoinhibitory loop that regulates acetyltransferase activity (16). The nuclear coactivator binding domain (NCBD, also called the IRF-3 binding domain, IBiD (17)) has the properties of a molten globule in its unbound state, but folds upon binding to its protein targets (18). The TAZ1, TAZ2, KIX, and NCBD domains form the interaction sites for intrinsically disordered activation domains of cellular transcription factors and other regulatory proteins and are also targeted by viral oncoproteins. Structures have been determined for all of the globular domains of CBP or p300, either free or bound to protein ligands. A graphic structural model for full-length CBP/p300 is shown in Fig. 1*B*.

Role of Disordered, Flexible Linkers in Promoter Recognition

CBP and p300 have been found at the promoters of more than 16,000 human genes (19). Smith *et al.* (20) suggested that CBP and p300 are "molecular interpreters that can parse and/or conjugate the regulatory words, phrases, and sentences of the genome." Their ability to perform this function derives from two attributes: promiscuous interactions with the disordered transactivation domains of hundreds of cellular transcription factors, and the presence of long, intrinsically disordered regions between the various CBP/p300 interaction domains. These attributes impart to CBP and p300 the flexibility to bind diverse arrays of transcription factors at promoters of variable architecture and with different spacing between binding sites, thereby "reading" the language encoded in these gene regulatory sequences (Fig. 2).

Although the overall "structure" of CBP/p300 is unknown, intrinsic flexibility is suggested by a recent cryo-EM analysis of a complex formed between DNA-bound estrogen receptor, the steroid receptor coactivator SRC-3, and full-length p300 (21). Free p300 is somewhat compacted, and there are changes in the overall conformation upon binding to estrogen receptor and SRC-3.

* This work was supported by Grants GM113251 (to H. J. D.) and CA096865 (to P. E. W.) from the National Institutes of Health. This is the fifth article in the Thematic Minireview series "Intrinsically Disordered Proteins." The authors declare that they have no conflicts of interest with the contents of this article. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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[3] The abbreviations used are: IDP, intrinsically disordered protein; IDR, intrinsically disordered region; CBP, CREB-binding protein; CREB, cAMP-response element-binding protein; NCBD, nuclear coactivator binding domain; IBiD, IRF-3 binding domain; KIX, KID-interacting domain; KID, kinase-inducible domain; HIF-1α, hypoxia-inducible factor 1α; MLL, mixed lineage leukemia protein; HPV, human papillomavirus; HAT, histone acetyltransferase; TAZ, transcriptional adapter zinc finger; C/EBP, CCAAT/enhancer-binding protein; pRb, retinoblastoma protein.

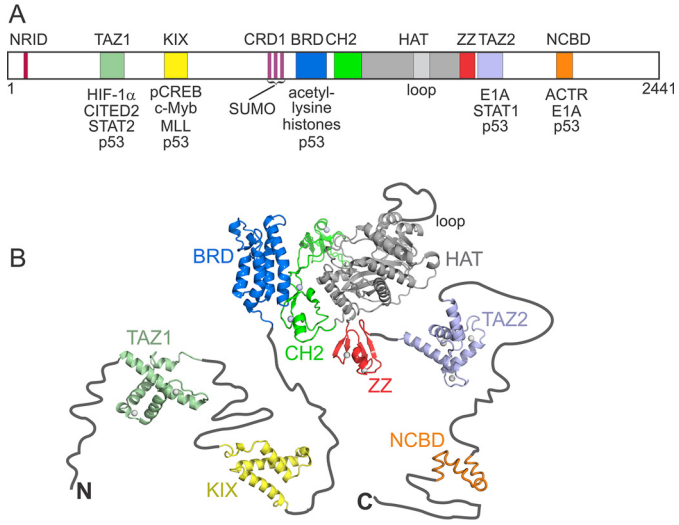

FIGURE 1. **Domain arrangement of CBP/p300.** *A*, schematic diagram of the domain structure of CBP showing binding sites of proteins that are mentioned in this review. *NRID*, nuclear receptor interaction domain (disordered in the free state); *TAZ1* and *TAZ2*, transcriptional adapter zinc binding motifs; *KIX*, partner of KID of CREB; *CRD1*, cyclin-dependent kinase inhibitor-reactive domain (disordered in the free state); *BRD*, bromodomain; *CH2*, cysteine-histidine-rich domain 2, incorporating a PHD domain and a RING finger domain (TAZ1 and ZZ-TAZ2 are sometimes termed CH1 and CH3 respectively); *HAT*, histone acetyltransferase domain, including a disordered regulatory loop; *ZZ*, dystrophin-like small zinc binding domain; *NCBD*, nuclear receptor coactivator binding domain, also called IBiD (molten globule in the free state). *Box sizes* correspond approximately to the lengths of the amino acid sequences belonging to each region. *B*, schematic representation of the overall structure of CBP/p300, incorporating the domain structures obtained by NMR for the CBP TAZ1 (24), KIX (4), ZZ (100), TAZ2 (23), and NCBD (18), as well as the x-ray crystal structure of the combined BRD, CH2, and HAT domains of p300 (62). *Gray spheres* in the TAZ1, CH2, ZZ, and TAZ2 structures represent Zn^{2+}. *SUMO*, small ubiquitin-like modifier; *pCREB*, phosphorylated CREB.

TAZ1 Interactions

The TAZ1 and TAZ2 (transcriptional adapter zinc finger (22)) domains share the same fold, a bundle of four helices (designated α_1–α_4) stabilized by three zinc atoms (23, 24). The TAZ domains are selective in their interactions and bind different subsets of intrinsically disordered regulatory motifs.

The TAZ1 domain mediates transcription of genes involved in regulation of the hypoxic response, the immune and inflammatory response, and cellular proliferation and survival. IDRs that bind with high affinity to TAZ1 tend to be relatively long, with multiple amphipathic regions that make extensive hydrophobic contacts in a deep binding groove (25). These contacts are complemented by electrostatic interactions between acidic residues in the ligand and positively charged side chains on the surface of TAZ1. Structures have been determined for the complexes of TAZ1 with the intrinsically disordered transactivation domains of hypoxia-inducible factor 1α (HIF-1α) (26, 27), CITED2 (28, 29), STAT2 (25), and NF-κB (30). Apart from a conserved LP(Q/E)L motif in HIF-1α and CITED2, there is no sequence conservation between these activation domains, all of which bind in the hydrophobic groove and wrap almost entirely around TAZ1. Although all four activation domains fold upon binding to form local elements of helical structure, there is little similarity in their locations on the TAZ1 surface (Fig. 3, *A* and *B*). The structure of the bound state is determined by the amino acid sequences of the amphipathic regions, the distribution of these regions in each IDR, and the physicochemical characteristics of their interactions with the TAZ1 hydrophobic groove and surrounding electrostatic charge. The lack of directionality in the binding pose of the different activation domains, as well as the fact that any given region of TAZ1 may bind different secondary structures, demonstrates the promiscuous nature of TAZ1 recognition.

Competition between transcription factors for binding to TAZ1 plays an important role in cellular regulation. For example, HIF-1α and CITED2 compete for binding to TAZ1 in a negative feedback circuit that attenuates the hypoxic response (28, 29, 31). Crosstalk between the HIF-1α and p53 pathways also occurs through competition for binding to TAZ1 (32).

TAZ2 Interactions

The TAZ2 domain binds promiscuously to IDRs from numerous cellular regulatory proteins. Unlike TAZ1, interactions with the TAZ2 domain are mostly localized to a hydrophobic binding surface at the interface of the α_1, α_2, and α_3 helices. This surface functions as a docking site for intrinsically disordered activation domains, which adopt helical structure upon binding to TAZ2 (Fig. 3*C*). The promiscuity of this binding site has resulted in some potentially misleading interactions in x-ray structures. In the crystal structure of free TAZ2, a C-terminal extension of the α_4 helix extends beyond the globular core and docks to the hydrophobic surface on a neighboring molecule in the crystal lattice, mimicking the interactions of TAZ2 with the amphipathic helices of regulatory IDRs (33). The long α_4 helix observed in the x-ray structure appears to be stabilized by lattice contacts. The helices formed by the isolated AD1 motif of the intrinsically disordered N-terminal activation domain of p53 and by the activation domain of transcription factor E2α bind to the same region of TAZ2, but in opposite orientations (34). The isolated AD2 motif of p53 binds in a partly helical conformation to a different region of the TAZ2 hydrophobic surface (35). The STAT1 activation domain utilizes a similar binding site but forms supplementary interactions on the surface formed by helices α_3 and α_4 of TAZ2 (25) (Fig. 3*C*). It is of note that STAT1 and the p53 AD2 share a common sequence motif (25) yet differ significantly in their interactions with TAZ2. The bipartite activation domain of C/EBP binds in a similar mode to STAT1, with helices docked to the primary α_1, α_2, α_3 surface and also to the secondary α_3, α_4 site (36). However, the longer of the two C/EBP helices is displaced relative to that of STAT1 (Fig. 3*C*); this displacement may well be an artifact of crystallization, because the C/EBP IDR was engineered into the α_4 helix of TAZ2 to promote crystallization and makes numerous contacts with neighboring molecules in the crystal lattice (36).

Numerous promoter-bound transcription factors activate transcription by recruiting CBP/p300 through interactions with TAZ2 (12). Binding to TAZ2 also brings the transcription factor close to the HAT domain, providing an additional level of regulation through acetylation-mediated mechanisms (37).

KIX Interactions

The CBP/p300 KIX domain is the primary interaction site for numerous cellular transcription factors that function in hematopoietic differentiation: CREB, c-Myb, MLL (mixed

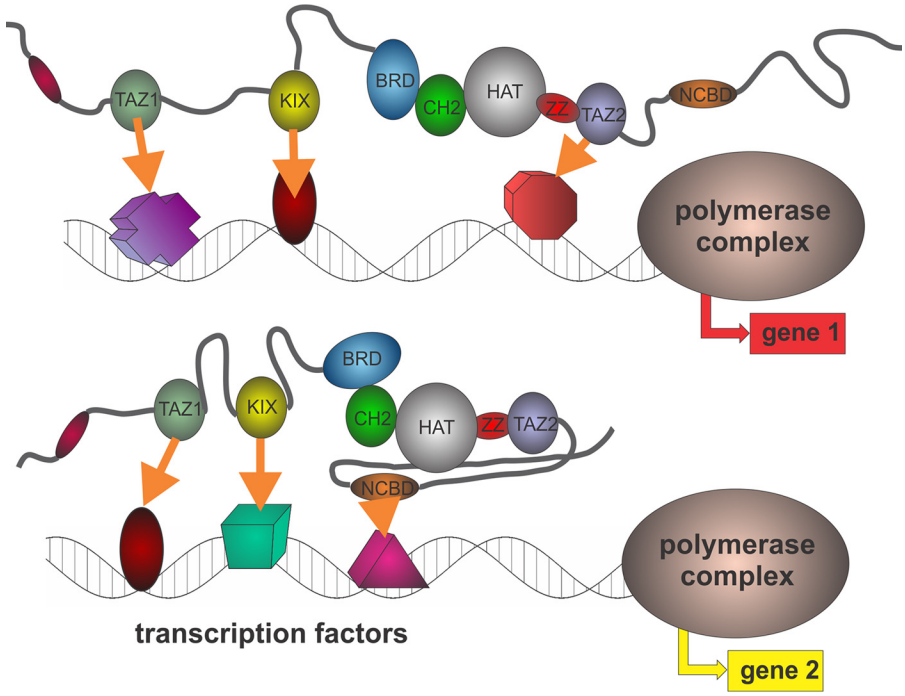

FIGURE 2. **Schematic representation of the interactions of CBP/p300 domains with arrays of different transcription factors assembled at promoters for transcription of different genes.** The ability of CBP and p300 to broker transcriptional coactivation at many different promoters is mediated both by the long disordered regions linking the structured interaction domains and by the promiscuous affinity of those domains for disordered transactivation domains of many gene-specific transcription factors.

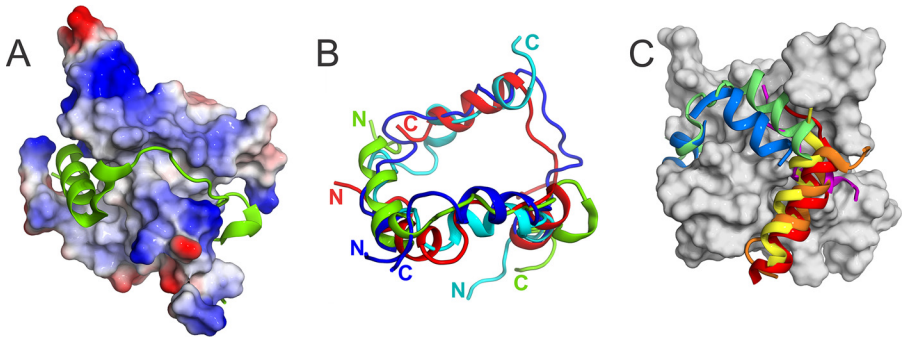

FIGURE 3. **TAZ domain structures.** *A*, surface representation of TAZ1, colored according to electrostatic potential (*blue*, positive; *red*, negative), in complex with the activation domain of CITED2 (*green ribbon*) (29). *B*, superposition of the structures of the activation domains of HIF-1α (26), CITED2 (29), STAT2 (25), and RelA (30). The structures are superimposed on a best fit of the TAZ1 domains, which are omitted for clarity. The portions of each partner protein are shown as follows: HIF-1α (Protein Data Bank (PDB) 1L8C; residues 776–826; *red*); CITED2 (1R8U; 220–260; *green*); STAT2 (2KA4; 788–838; *cyan*); and RelA (2LWW; 431–484; *blue*). The N and C termini of each construct are indicated. *C*, structures of IDRs bound to TAZ2. Superposition of the structures of TAZ2 in complex with STAT1 (PDB 2KA6 (25); residues 723–750; *green*); C/EBP (3T92 (36); 37–59; *blue*); p53 AD1 (2K8F (34); 14–29; *orange*); p53 AD2 (2MZD (35); 43–56; *magenta*); and ETAD1 (2MH0; 11–29; *red*) is shown. The *yellow ribbon* is derived from the x-ray crystal structure of free TAZ2 (3IO2 (33)), and shows the extended α_4 helix of a neighboring TAZ2 molecule (residues 1834–1819) in the crystal lattice. Structures were aligned on a best fit of the TAZ2 domains; the *gray surface* shows the TAZ2 structure from the STAT1 complex (PDB 2KA6 (25)).

lineage leukemia protein), c-Jun, E2A, and FOXO3, among many others. Some hematopoietic transcription factors compete for binding to the same surface of KIX (*e.g.* CREB and Myb (38, 39)) or bind synergistically to different surfaces of the KIX domain (*e.g.* MLL and Myb, MLL, and CREB (40, 41)). Because KIX is a central hub for interactions with hematopoietic transcription factors, it is likely to perform a key function in integrating and regulating crosstalk between different signaling pathways.

KIX is a small domain, comprising three α- and two 3_{10}-helices (4), that utilizes two distinct binding surfaces (Fig. 4). The intrinsically disordered activation domains of CREB and c-Myb fold into helical conformations and bind in a shallow hydrophobic groove in the α1-α3 surface of KIX (4, 42) (Fig. 4*A*). The kinase-inducible activation domain of CREB (KID), phosphorylated at Ser^{133} (pKID), forms a pair of orthogonal helices upon binding to KIX, with the C-terminal helix (α_B) dominating the binding interaction. c-Myb forms a slightly bent helix that binds in the same site as the pKIDα_B helix. The MLL activation domain binds in a helical conformation on the opposite face of KIX, in a hydrophobic groove formed by the α_2, α_3, and 3_{10} helices (43) (Fig. 4*B*). MLL and Myb, or MLL and pKID, can bind simultaneously and cooperatively to KIX to form a ternary complex, resulting in allosteric enhancement of the binding affinity (40, 41). Binding cooperativity has been attributed to stabilization and decrease in dynamics in local regions of the

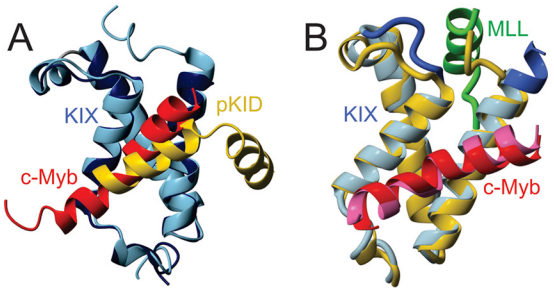

FIGURE 4. **KIX complexes.** *A*, superimposed structures of binary complexes of KIX with pKID (1KDX (4)) and c-Myb (1SB0 (42)). The backbone of KIX in complex with pKID (*yellow*) is colored *dark blue*, and the KIX backbone in complex with c-Myb (*red*) is colored *light blue*. *B*, superimposed structures of the KIX-c-Myb binary complex (KIX, *yellow*; c-Myb, *pink*; 1SB0 (42)) with the ternary complex KIX-c-Myb-MLL (KIX, *light blue*; c-Myb, *red*; MLL, *green*; 2AGH (43)). Allosteric changes in the ternary complex (a loop movement and the extension of the C-terminal helix) are shown in *dark blue*.

KIX structure upon binding of MLL (43–45), resulting in a decrease in the dissociation rates of both activation domains (46).

The complexes described in the preceding paragraph each involve interactions between KIX and an amphipathic binding motif ($\Phi XX\Phi\Phi$, where Φ is a bulky hydrophobic residue) located within an intrinsically disordered region of the transcriptional activation domain. The $\Phi XX\Phi\Phi$ motif interacts promiscuously with both the c-Myb/pKID and MLL binding surfaces of KIX; specificity is imparted by flanking residues (47). For example, although the pKID and c-Myb activation domains bind preferentially to their cognate high affinity site on the α1-α3 surface of KIX, both domains also bind with lower affinity to the MLL site (48); conversely, MLL binds tightly in its cognate site and weakly in the c-Myb site (49). Activation domains with bipartite interaction motifs can potentially bind simultaneously to both KIX sites. The disordered activation domain of FOXO3a, a transcription factor that regulates cell differentiation, survival, and apoptosis genes, contains two amphipathic interaction motifs (CR2 and CR3) that bind synergistically to KIX (50). The bipartite FOXO3a activation domain makes promiscuous multivalent interactions with KIX. The complex is heterogeneous, adopting two equally populated conformational states with helical structure in the CR2 and CR3 motifs. In one conformer, the CR2 helix binds in the c-Myb site and CR3 occupies the MLL site, whereas in the second conformer, CR2 is in the MLL site and CR3 occupies the c-Myb site. The bipartite N-terminal transactivation domain of p53 also forms a heterogeneous complex on binding to KIX (51). The AD1 and AD2 regions of p53, which contain $\Phi XX\Phi\Phi$ motifs that fold into helices on the surface of KIX, bind simultaneously and synergistically to the MLL and c-Myb sites, thereby enhancing the binding affinity. Similar to FOXO3a, the p53 AD1 and AD2 helices each interact with both the MLL and c-Myb binding surfaces. However, in contrast to FOXO3a, each of the p53 helices binds in each site in alternate conformations, which differ by an ~180° rotation of the helix axis (51). Some level of disorder is frequently retained in the interface between IDPs and their target proteins, a property that is referred to as "fuzziness" (52, 53).

NCBD Interactions

In the absence of binding partners, the NCBD, also known as the IBiD, has the properties of a molten globule, with substantial helical structure (18). Upon binding to its physiological partners, the NCBD folds to form a bundle of three helices that differ in their topological arrangements in complexes with intrinsically disordered targets, such as the p160 nuclear coactivators ACTR (coactivator for thyroid and retinoid receptors) and SRC-1 and the p53 activation domain (18, 54, 55), and in the complex with the stably folded interferon regulatory factor IRF-3 (56). Detailed NMR and computational studies suggest that in the unbound state, the NCBD is flexible and fluctuates over an ensemble of conformations that includes both the ACTR/SRC-1-bound conformation and the IRF-3-bound conformation (57–61). The inherent flexibility of the NCBD and its ability to sample a number of conformational states in the unbound state are likely of functional importance in allowing it to fold into different structures upon binding to different physiological targets.

The Bromodomain

CBP and p300 contain a bromodomain fused to a novel zinc binding domain that contains both RING and plant homeodomain (PHD) fingers (62, 63). In common with other bromodomains, the CBP/p300 bromodomain recognizes acetyl-lysine residues in histone tails and in transcription factor IDRs including those of p53 and CREB (64).

Mechanisms of Coupled Folding and Binding

CBP/p300 has been a paradigm for detailed studies, using NMR, stopped flow kinetics, and molecular simulations, of the mechanism by which intrinsically disordered proteins fold upon binding to their targets. NMR provides unique atomic resolution insights into the mechanisms by which intrinsically disordered proteins bind to a folded protein target. The addition of an IDP to an isotopically labeled ordered protein target allows rapid and accurate identification of the binding site on the target, using chemical shift mapping (65). Analysis of NMR relaxation dispersion profiles for the isotopically labeled IDP in the presence of unlabeled binding partner provides a comprehensive picture of the kinetics and mechanism of binding and folding (66, 67). Two extreme mechanisms can be envisaged: conformational selection and induced fit. In the conformational selection mechanism, the target protein "selects" a conformation that closely approximates that of the bound form from the ensemble of conformations populated by the unbound IDP; *i.e.* folding of the IDP occurs before binding. In the induced-fit mechanism, the IDP associates with its binding partner in a fully disordered or incorrectly folded state and folds in association with the target protein; *i.e.* folding after binding to the target. The binding of IDPs to the KIX domain provides examples of both of these types of interaction. However, it should be noted that IDP binding processes rarely occur by pure conformational selection or induced-fit mechanisms, and most interactions involve some combination of the two processes; it is to be expected that some structural rearrangement will be necessary even when a preformed structural motif in an IDP binds to its target.

Induced-fit Binding of pKID to KIX

In the unbound state, the α_B helix of pKID is fully unstructured, whereas the α_A helix spontaneously forms ~50% population of helix (68). Using NMR and ^{15}N relaxation dispersion measurements with ^{15}N-labeled pKID, Sugase *et al.* (66) showed that binding of pKID to KIX occurs by an induced-fit mechanism, forming an intermediate in which pKID is docked to the surface of KIX in a partly folded state. The α_A helix of pKID is fully folded in the intermediate state, whereas the α_B region is only partially structured in the intermediate and folds to form stable helical structure only after pKID has docked to the surface of KIX. The weak propensity of the α_B region of pKID to spontaneously fold into helix may impose a barrier to folding, such that stabilization of the α_B helix requires formation of favorable intermolecular interactions after docking to KIX (48). Molecular simulations were able to capture the principal features of the experimental binding and folding pathway, providing molecular level insights into the ensemble of intermediate states formed by the partially folded α_B helix (69, 70).

Elements of Conformational Selection: The c-Myb-KIX Complex

The c-Myb activation domain occupies the same binding site as the α_B helix of pKID, forming a long amphipathic helix with a distinct bend that positions the side chain of Leu^{302} in a deep hydrophobic pocket in the surface of KIX and effectively breaks the helix into N- and C-terminal halves (42, 43). The free c-Myb activation domain is dynamically disordered, fluctuating between helical and more extended conformational states. The N-terminal half spontaneously forms helical structure (~70% population) in aqueous solution, whereas the C-terminal region has a much weaker propensity to form helix in the absence of binding (48). Stopped-flow kinetics and NMR relaxation dispersion measurements show that the c-Myb activation domain binds to KIX in an extremely fast two-state process, without formation of observable intermediates (48, 71, 72). The N-terminal region, which has strong propensity for spontaneous helix formation, binds by the conformational selection mechanism, as evidenced by the correlation observed (48) between the population of helix in a series of mutants and the association rates reported by Giri *et al.* (73). In contrast, folding of the C-terminal region of the c-Myb peptide occurs after binding to KIX, by an induced-fit mechanism. Thus, the binding mechanism of c-Myb is complex and involves elements of both conformational selection and induced fit. A similar mechanism has been observed for binding of the intrinsically disordered ACTR to the NCBD of CBP; the N-terminal helix of ACTR folds rapidly and binding involves conformational selection (74), whereas other regions of ACTR fold by a slower, induced-fit process following the initial binding event (75).

The differences in the propensities of the disordered pKID and c-Myb activation domains to fold spontaneously into helical structure appear to be related to their functions and may be, at least in part, determinants of the folding rate and binding mechanism (48). CREB is an inducible transcriptional activator that must be phosphorylated at Ser^{133} in the KID to bind with high affinity to the KIX domain of CBP/p300 (76, 77). The high degree of disorder of the α_B region in the unbound state and its limited propensity to form helical structure are expected to facilitate binding, in an extended conformation, to the active site of protein kinase A (39). In turn, this imposes a barrier to folding of the α_B helix on association with KIX, such that development and stabilization of helical structure in the α_B region occur slowly, after the initial binding event (66). In contrast, c-Myb is a constitutive transcriptional activator. No post-translational modifications of the c-Myb activation domain are needed for interaction with KIX, and the strong propensity for spontaneous helix formation may be beneficial for promoting rapid, high affinity binding to CBP/p300 and other target proteins.

The KIX association mechanisms for the pKID and c-Myb peptides show significant differences, despite binding to an identical site on KIX. Clearly, the characteristics of the IDP itself, its sequence, charge, and population of transiently structured states in the conformational ensemble, play a role in determining the binding kinetics and mechanism. It seems likely that the coupled binding and folding processes of all but the simplest IDPs will occur by complex multi-step mechanisms, certainly for those IDPs that interact through more than one binding motif (78). In the case of pKID and c-Myb, it appears that the intrinsic secondary structure propensities of the IDP play an important part in determining the binding mechanism (48), but much experimental and theoretical work will be required before the principles governing folding and binding are sufficiently well defined that mechanisms can be predicted.

The Tumor Suppressor p53 as a Promiscuous Multivalent Regulator

The intrinsically disordered N-terminal transcriptional activation of p53 binds with varying affinities to four domains of CBP/p300 (TAZ1, TAZ2, KIX, and NCBD), raising the possibility of multivalent binding where each activation domain of the p53 tetramer interacts with a different domain of CBP/p300, thereby increasing the binding avidity (79, 80). The p53 activation domain is bipartite, with two amphipathic interaction motifs (termed AD1 and AD2) that can bind synergistically to a single target protein or bind simultaneously to two different targets to form a ternary complex. Binding to the CBP/p300 domains is dominated by interactions with AD2, whereas interactions with the p53 binding domain of the ubiquitin ligase Mdm2 are dominated by AD1. In unstressed cells, p53 can bind simultaneously to both Mdm2 and CBP/p300 to form a ternary complex that promotes polyubiquitination and degradation of p53 (80). Following genotoxic stress, multisite phosphorylation of the disordered p53 activation domain weakens binding to Mdm2 and enhances binding to CBP/p300, resulting in stabilization of p53, acetylation of the disordered C-terminal regulatory region, and transcriptional activation (80, 81). Phosphorylation at Thr^{18} functions as a simple switch to control binding to Mdm2. Binding to CBP/p300 is determined by the extent of phosphorylation, with successive phosphorylation events functioning as a rheostat to progressively enhance the binding affinity for the TAZ1, TAZ2, and KIX domains (82). The complex interplay of interactions between CBP/p300, Mdm2, and p53 is

made possible by the characteristics of the intrinsically disordered, bipartite activation domain of p53, which facilitates promiscuous interactions with binding partners and dynamically exposes serine and threonine residues for phosphorylation by stress response kinases.

Viral IDPs Compete with Cellular Proteins for CBP/p300 Binding

Intrinsically disordered proteins are highly abundant in viral proteomes (83) and are utilized by viruses to mimic cellular IDR motifs and as hubs or scaffolds to rewire cellular signaling networks (11, 84, 85). Given the role that CBP and p300 play in the regulation of critical cellular signaling and transcriptional networks, it is perhaps not surprising that they are targeted by numerous viral proteins (12, 86). These include oncoproteins encoded by DNA tumor viruses (adenovirus E1A, human papillomavirus E7, and simian virus SV40 large T antigen), Tax and HBZ (HTLV-1 b-zip factor) encoded by the human T-cell leukemia virus HTLV-1, and the Tat protein of HIV-1.

Adenovirus E1A mediates cell transformation by activating viral gene expression and deregulating the host cell cycle and forcing S-phase entry (87). E1A functions as an intrinsically disordered molecular hub that can bind to diverse cellular proteins and subvert the host cell regulatory machinery (88). E1A binds tightly to the TAZ2 domain of CBP/p300, with conserved region 1 (CR1) occupying the α_1, α_2, α_3 surface binding surface that is utilized by cellular IDRs (89). The N-terminal region of E1A makes additional, disordered ("fuzzy") contacts with the α_3, α_4 surface that increase the binding affinity (89, 90). E1A binds much more tightly to TAZ2 than do cellular transcription factors (*e.g.* E1A binds with $K_d \sim 2$ nM (90), whereas p53 activation domain binds with $K_d = 26$ nM (80) and STAT1 binds with $K_d \sim 50$ nM (25)), allowing it to compete efficiently for CBP/p300, hijack the transcriptional machinery, and inhibit p53-mediated cell cycle arrest.

The intrinsically disordered N-terminal half (residues 1-140) of E1A contains four binding motifs, which function synergistically in their interactions with cellular proteins (90). Interactions at these sites are allosteric and display either positive or negative cooperativity (90). The disorder in this region provides E1A with the flexibility to target multiple cellular proteins and organize them into higher order complexes (89, 90). In particular, E1A is able to recruit CBP/p300 and the retinoblastoma protein pRb into a ternary complex that promotes acetylation and degradation of pRb and loss of cell cycle control (89).

The human papillomavirus (HPV) E7 protein encoded by strains with a high risk of promoting cancerous transformation employs a mechanism similar to that used by E1A to deregulate the host cell cycle. The CR1 and CR2 regions of E7 are intrinsically disordered (91, 92), whereas CR3 is a zinc binding domain that mediates formation of a homodimer (93, 94). The disordered CR1 and CR2 regions of E7 from high risk HPV16 bind with high affinity to the TAZ2 domain of CBP (95). Although the TAZ2 binding site overlaps the binding site for pRb, the full-length E7 dimer functions as a scaffold to recruit TAZ2 and the pRb pocket domains into a ternary complex. By bringing the CBP/p300 HAT domain into proximity to pRb, the E7 dimer stimulates acetylation and subsequent degradation of pRb, and drives S phase entry and deregulation of the host cell cycle (95). In contrast, E7 from the low risk strain HPV6b binds TAZ2 with much lower affinity than high risk HPV16 E7. This would impair the ability of HPV6b to suppress p53-mediated transcriptional programs and disfavor formation of a ternary complex with CBP/p300 and pRb (95).

The HTLV-1 Tax and HBZ proteins, as well as the HIV-1 Tat protein, recruit CBP/p300 to viral promoters to activate transcription of viral genes. All three proteins utilize intrinsically disordered interaction motifs to bind to the MLL site on the KIX domain (96–98). Tax and HBZ compete with cellular transcription factors for binding to KIX, thereby interfering with CBP/p300-mediated transcriptional processes that regulate critical hematopoietic signaling pathways (98, 99). Infection by these viruses is frequently a precursor to diseases such as leukemia.

Conclusion

The central role of the transcriptional coactivators CBP and p300 in regulation and integration of eukaryotic transcriptional and signaling pathways is entirely dependent upon the existence and utilization of intrinsically disordered regions, both within the coactivators themselves and in the interaction domains of their partners. Disorder mediates the formation of both highly specific and promiscuous complexes, with dissociation constants that range from nanomolar to micromolar; these complexes can be dissociated either spontaneously or by competition with other partners. This facility is particularly important for signaling, where the activation of genes in response to extracellular signals must not only be turned on with high specificity, but must also be turned off when these gene products are no longer required. Disorder also allows sequences to interact with a number of different partners, promoting redundancy and efficiency in the utilization of cellular resources, as well as facilitating crosstalk between signaling pathways. The coactivators CBP and p300 provide a paradigmatic example of a system that employs both order and disorder to fulfill complex and multifarious functions.

References

1. Liu, J., Perumal, N. B., Oldfield, C. J., Su, E. W., Uversky, V. N., and Dunker, A. K. (2006) Intrinsic disorder in transcription factors. *Biochemistry* **45,** 6873–6888
2. Minezaki, Y., Homma, K., Kinjo, A. R., and Nishikawa, K. (2006) Human transcription factors contain a high fraction of intrinsically disordered regions essential for transcriptional regulation. *J. Mol. Biol.* **359,** 1137–1149
3. Sigler, P. B. (1988) Transcriptional activation: acid blobs and negative noodles. *Nature* **333,** 210–212
4. Radhakrishnan, I., Pérez-Alvarado, G. C., Parker, D., Dyson, H. J., Montminy, M. R., and Wright, P. E. (1997) Solution structure of the KIX domain of CBP bound to the transactivation domain of CREB: a model for activator:coactivator interactions. *Cell* **91,** 741–752
5. Wright, P. E., and Dyson, H. J. (1999) Intrinsically unstructured proteins: re-assessing the protein structure-function paradigm. *J. Mol. Biol.* **293,** 321–331
6. Kriwacki, R. W., Hengst, L., Tennant, L., Reed, S. I., and Wright, P. E. (1996) Structural studies of $p21^{Waf1/Cip1/Sdi1}$ in the free and Cdk2-bound state: conformational disorder mediates binding diversity. *Proc. Natl. Acad. Sci. U.S.A.* **93,** 11504–11509

7. Dyson, H. J., and Wright, P. E. (2005) Intrinsically unstructured proteins and their functions. *Nat. Rev. Mol. Cell Biol.* **6,** 197–208
8. Oldfield, C. J., Cheng, Y., Cortese, M. S., Romero, P., Uversky, V. N., and Dunker, A. K. (2005) Coupled folding and binding with α-helix-forming molecular recognition elements. *Biochemistry* **44,** 12454–12470
9. Tompa, P. (2005) The interplay between structure and function in intrinsically unstructured proteins. *FEBS Lett.* **579,** 3346–3354
10. Tompa, P., Davey, N. E., Gibson, T. J., and Babu, M. M. (2014) A million peptide motifs for the molecular biologist. *Mol. Cell* **55,** 161–169
11. Wright, P. E., and Dyson, H. J. (2015) Intrinsically disordered proteins in cellular signalling and regulation. *Nat. Rev. Mol. Cell Biol.* **16,** 18–29
12. Goodman, R. H., and Smolik, S. (2000) CBP/p300 in cell growth, transformation, and development. *Genes Dev.* **14,** 1553–1577
13. Bedford, D. C., Kasper, L. H., Fukuyama, T., and Brindle, P. K. (2010) Target gene context influences the transcriptional requirement for the KAT3 family of CBP and p300 histone acetyltransferases. *Epigenetics* **5,** 9–15
14. Kamei, Y., Xu, L., Heinzel, T., Torchia, J., Kurokawa, R., Gloss, B., Lin, S.-C., Heyman, R. A., Rose, D. W., Glass, C. K., and Rosenfeld, M. G. (1996) A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. *Cell* **85,** 403–414
15. Vo, N., and Goodman, R. H. (2001) CREB-binding protein and p300 in transcriptional regulation. *J. Biol. Chem.* **276,** 13505–13508
16. Thompson, P. R., Wang, D., Wang, L., Fulco, M., Pediconi, N., Zhang, D., An, W., Ge, Q., Roeder, R. G., Wong, J., Levrero, M., Sartorelli, V., Cotter, R. J., and Cole, P. A. (2004) Regulation of the p300 HAT domain via a novel activation loop. *Nat. Struct. Mol. Biol.* **11,** 308–315
17. Lin, C. H., Hare, B. J., Wagner, G., Harrison, S. C., Maniatis, T., and Fraenkel, E. (2001) A small domain of CBP/p300 binds diverse proteins. Solution structure and functional studies. *Mol. Cell* **8,** 581–590
18. Demarest, S. J., Martinez-Yamout, M., Chung, J., Chen, H., Xu, W., Dyson, H. J., Evans, R. M., and Wright, P. E. (2002) Mutual synergistic folding in recruitment of CBP/p300 by p160 nuclear receptor coactivators. *Nature* **415,** 549–553
19. Ramos, Y. F. M., Hestand, M. S., Verlaan, M., Krabbendam, E., Ariyurek, Y., van Galen, M., van Dam, H., van Ommen, G. J., den Dunnen, J. T., Zantema, A., and 't Hoen, P. A. C. (2010) Genome-wide assessment of differential roles for p300 and CBP in transcription regulation. *Nucleic Acids Res.* **38,** 5396–5408
20. Smith, J. L., Freebern, W. J., Collins, I., De Siervi, A., Montano, I., Haggerty, C. M., McNutt, M. C., Butscher, W. G., Dzekunova, I., Petersen, D. W., Kawasaki, E., Merchant, J. L., and Gardner, K. (2004) Kinetic profiles of p300 occupancy *in vivo* predict common features of promoter structure and coactivator recruitment. *Proc. Natl. Acad. Sci. U.S.A.* **101,** 11554–11559
21. Yi, P., Wang, Z., Feng, Q., Pintilie, G. D., Foulds, C. E., Lanz, R. B., Ludtke, S. J., Schmid, M. F., Chiu, W., and O'Malley, B. W. (2015) Structure of a biologically active estrogen receptor-coactivator complex on DNA. *Mol. Cell* **57,** 1047–1058
22. Ponting, C. P., Blake, D. J., Davies, K. E., Kendrick-Jones, J., and Winder, S. J. (1996) ZZ and TAZ: new putative zinc fingers in dystrophin and other proteins. *Trends Biochem. Sci.* **21,** 11–13
23. De Guzman, R. N., Liu, H. Y., Martinez-Yamout, M., Dyson, H. J., and Wright, P. E. (2000) Solution structure of the TAZ2 (CH3) domain of the transcriptional adaptor protein CBP. *J. Mol. Biol.* **303,** 243–253
24. De Guzman, R. N., Wojciak, J. M., Martinez-Yamout, M. A., Dyson, H. J., and Wright, P. E. (2005) CBP/p300 TAZ1 domain forms a structured scaffold for ligand binding. *Biochemistry* **44,** 490–497
25. Wojciak, J. M., Martinez-Yamout, M. A., Dyson, H. J., and Wright, P. E. (2009) Structural basis for recruitment of CBP/p300 coactivators by STAT1 and STAT2 transactivation domains. *EMBO J.* **28,** 948–958
26. Dames, S. A., Martinez-Yamout, M., De Guzman, R. N., Dyson, H. J., and Wright, P. E. (2002) Structural basis for Hif-1/CBP recognition in the cellular hypoxic response. *Proc. Natl. Acad. Sci. U.S.A.* **99,** 5271–5276
27. Freedman, S. J., Sun, Z. Y., Poy, F., Kung, A. L., Livingston, D. M., Wagner, G., and Eck, M. J. (2002) Structural basis for recruitment of CBP/p300 by hypoxia-inducible factor-1α. *Proc. Natl. Acad. Sci. U.S.A.* **99,** 5367–5372
28. Freedman, S. J., Sun, Z. Y., Kung, A. L., France, D. S., Wagner, G., and Eck, M. J. (2003) Structural basis for negative regulation of hypoxia-inducible factor-1α by CITED2. *Nat. Struct. Biol.* **10,** 504–512
29. De Guzman, R. N., Martinez-Yamout, M. A., Dyson, H. J., and Wright, P. E. (2004) Interaction of the TAZ1 domain of CREB-binding protein with the activation domain of CITED2: regulation by competition between intrinsically unstructured ligands for non-identical binding sites. *J. Biol. Chem.* **279,** 3042–3049
30. Mukherjee, S. P., Behar, M., Birnbaum, H. A., Hoffmann, A., Wright, P. E., and Ghosh, G. (2013) Analysis of the RelA:CBP/p300 interaction reveals its involvement in NF-kB-driven transcription. *PLoS Biol.* **11,** e1001647
31. Bhattacharya, S., Michels, C. L., Leung, M. K., Arany, Z. P., Kung, A. L., and Livingston, D. M. (1999) Functional role of p35srj, a novel p300/CBP binding protein, during transactivation by HIF-1. *Genes Dev.* **13,** 64–75
32. Schmid, T., Zhou, J., Köhl, R., and Brüne, B. (2004) p300 relieves p53-evoked transcriptional repression of hypoxia-inducible factor-1 (HIF-1). *Biochem. J.* **380,** 289–295
33. Miller, M., Dauter, Z., Cherry, S., Tropea, J. E., and Wlodawer, A. (2009) Structure of the Taz2 domain of p300: insights into ligand binding. *Acta Crystallogr. D Biol. Crystallogr.* **65,** 1301–1308
34. Feng, H., Jenkins, L. M. M., Durell, S. R., Hayashi, R., Mazur, S. J., Cherry, S., Tropea, J. E., Miller, M., Wlodawer, A., Appella, E., and Bai, Y. (2009) Structural basis for p300 Taz2-p53 TAD1 binding and modulation by phosphorylation. *Structure* **17,** 202–210
35. Miller Jenkins, L. M., Feng, H., Durell, S. R., Tagad, H. D., Mazur, S. J., Tropea, J. E., Bai, Y., and Appella, E. (2015) Characterization of the p300 Taz2–p53 TAD2 complex and comparison with the p300 Taz2–p53 TAD1 complex. *Biochemistry* **54,** 2001–2010
36. Bhaumik, P., Davis, J., Tropea, J. E., Cherry, S., Johnson, P. F., and Miller, M. (2014) Structural insights into interactions of C/EBP transcriptional activators with the Taz2 domain of p300. *Acta Crystallogr. D Biol. Crystallogr.* **70,** 1914–1921
37. Dancy, B. M., and Cole, P. A. (2015) Protein lysine acetylation by p300/CBP. *Chem. Rev.* **115,** 2419–2452
38. Parker, D., Rivera, M., Zor, T., Henrion-Caude, A., Radhakrishnan, I., Kumar, A., Shapiro, L. H., Wright, P. E., Montminy, M., and Brindle, P. K. (1999) Role of secondary structure in discrimination between constitutive and inducible activators. *Mol. Cell. Biol.* **19,** 5601–5607
39. Zor, T., Mayr, B. M., Dyson, H. J., Montminy, M. R., and Wright, P. E. (2002) Roles of phosphorylation and helix propensity in the binding of the KIX domain of CREB-binding protein by constitutive (c-Myb) and inducible (CREB) activators. *J. Biol. Chem.* **277,** 42241–42248
40. Ernst, P., Wang, J., Huang, M., Goodman, R. H., and Korsmeyer, S. J. (2001) MLL and CREB bind cooperatively to the nuclear coactivator CREB-binding protein. *Mol. Cell. Biol.* **21,** 2249–2258
41. Goto, N. K., Zor, T., Martinez-Yamout, M., Dyson, H. J., and Wright, P. E. (2002) Cooperativity in transcription factor binding to the coactivator CREB-binding protein (CBP): the mixed lineage leukemia protein (MLL) activation domain binds to an allosteric site on the Kix domain. *J. Biol. Chem.* **277,** 43168–43174
42. Zor, T., De Guzman, R. N., Dyson, H. J., and Wright, P. E. (2004) Solution structure of the KIX domain of CBP bound to the transactivation domain of c-Myb. *J. Mol. Biol.* **337,** 521–534
43. De Guzman, R. N., Goto, N. K., Dyson, H. J., and Wright, P. E. (2006) Structural basis for cooperative transcription factor binding to the CBP coactivator. *J. Mol. Biol.* **355,** 1005–1013
44. Law, S. M., Gagnon, J. K., Mapp, A. K., and Brooks, C. L., 3rd (2014) Prepaying the entropic cost for allosteric regulation in KIX. *Proc. Natl. Acad. Sci. U.S.A.* **111,** 12067–12072
45. Brüschweiler, S., Konrat, R., and Tollinger, M. (2013) Allosteric communication in the KIX domain proceeds through dynamic repacking of the hydrophobic core. *ACS Chem. Biol.* **8,** 1600–1610
46. Shammas, S. L., Travis, A. J., and Clarke, J. (2014) Allostery within a transcription coactivator is predominantly mediated through dissociation rate constants. *Proc. Natl. Acad. Sci. U.S.A.* **111,** 12055–12060
47. Denis, C. M., Chitayat, S., Plevin, M. J., Wang, F., Thompson, P., Liu, S., Spencer, H. L., Ikura, M., LeBrun, D. P., and Smith, S. P. (2012) Structural basis of CBP/p300 recruitment in leukemia induction by E2A-PBX1.

Blood **120,** 3968–3977
48. Arai, M., Sugase, K., Dyson, H. J., and Wright, P. E. (2015) Conformational propensities of intrinsically disordered proteins influence the mechanism of binding and folding. *Proc. Natl. Acad. Sci. U.S.A.* **112,** 9614–9619
49. Arai, M., Dyson, H. J., and Wright, P. E. (2010) Leu628 of the KIX domain of CBP is a key residue for the interaction with the MLL transactivation domain. *FEBS Lett.* **584,** 4500–4504
50. Wang, F., Marshall, C. B., Yamamoto, K., Li, G. Y., Gasmi-Seabrook, G. M., Okada, H., Mak, T. W., and Ikura, M. (2012) Structures of KIX domain of CBP in complex with two FOXO3a transactivation domains reveal promiscuity and plasticity in coactivator recruitment. *Proc. Natl. Acad. Sci. U.S.A.* **109,** 6078–6083
51. Lee, C. W., Arai, M., Martinez-Yamout, M. A., Dyson, H. J., and Wright, P. E. (2009) Mapping the interactions of the p53 transactivation domain with the KIX domain of CBP. *Biochemistry* **48,** 2115–2124
52. Tompa, P., and Fuxreiter, M. (2008) Fuzzy complexes: polymorphism and structural disorder in protein-protein interactions. *Trends Biochem. Sci.* **33,** 2–8
53. Fuxreiter, M. (2012) Fuzziness: linking regulation to protein dynamics. *Mol. Biosyst.* **8,** 168–177
54. Waters, L., Yue, B., Veverka, V., Renshaw, P., Bramham, J., Matsuda, S., Frenkiel, T., Kelly, G., Muskett, F., Carr, M., and Heery, D. M. (2006) Structural diversity in p160/CREB-binding protein coactivator complexes. *J. Biol. Chem.* **281,** 14787–14795
55. Lee, C. W., Martinez-Yamout, M. A., Dyson, H. J., and Wright, P. E. (2010) Structure of the p53 transactivation domain in complex with the nuclear receptor coactivator binding domain of CREB binding protein. *Biochemistry* **49,** 9964–9971
56. Qin, B. Y., Liu, C., Srinath, H., Lam, S. S., Correia, J. J., Derynck, R., and Lin, K. (2005) Crystal structure of IRF-3 in complex with CBP. *Structure* **13,** 1269–1277
57. Kjaergaard, M., Andersen, L., Nielsen, L. D., and Teilum, K. (2013) A folded excited state of ligand-free nuclear coactivator binding domain (NCBD) underlies plasticity in ligand recognition. *Biochemistry* **52,** 1686–1693
58. Naganathan, A. N., and Orozco, M. (2011) The native ensemble and folding of a protein molten-globule: functional consequence of downhill folding. *J. Am. Chem. Soc.* **133,** 12154–12161
59. Knott, M., and Best, R. B. (2012) A preformed binding interface in the unbound ensemble of an intrinsically disordered protein: evidence from molecular simulations. *PLoS Comput. Biol.* **8,** e1002605
60. Ebert, M. O., Bae, S. H., Dyson, H. J., and Wright, P. E. (2008) NMR relaxation study of the complex formed between CBP and the activation domain of the nuclear hormone receptor coactivator ACTR. *Biochemistry* **47,** 1299–1308
61. Zhang, W., Ganguly, D., and Chen, J. (2012) Residual structures, conformational fluctuations, and electrostatic interactions in the synergistic folding of two intrinsically disordered proteins. *PLoS Comput. Biol.* **8,** e1002353
62. Delvecchio, M., Gaucher, J., Aguilar-Gurrieri, C., Ortega, E., and Panne, D. (2013) Structure of the p300 catalytic core and implications for chromatin targeting and HAT regulation. *Nat. Struct. Mol. Biol.* **20,** 1040–1046
63. Plotnikov, A. N., Yang, S., Zhou, T. J., Rusinova, E., Frasca, A., and Zhou, M. M. (2014) Structural insights into acetylated-histone H4 recognition by the bromodomain-PHD finger module of human transcriptional coactivator CBP. *Structure* **22,** 353–360
64. Zeng, L., Zhang, Q., Gerona-Navarro, G., Moshkina, N., and Zhou, M. M. (2008) Structural basis of site-specific histone recognition by the bromodomains of human coactivators PCAF and CBP/p300. *Structure* **16,** 643–652
65. Arai, M., Ferreon, J. C., and Wright, P. E. (2012) Quantitative analysis of multisite protein-ligand interactions by NMR: binding of intrinsically disordered p53 transactivation subdomains with the TAZ2 domain of CBP. *J. Am. Chem. Soc.* **134,** 3792–3803
66. Sugase, K., Dyson, H. J., and Wright, P. E. (2007) Mechanism of coupled folding and binding of an intrinsically disordered protein. *Nature* **447,** 1021–1025
67. Demers, J. P., and Mittermaier, A. (2009) Binding mechanism of an SH3 domain studied by NMR and ITC. *J. Am. Chem. Soc.* **131,** 4355–4367
68. Radhakrishnan, I., Pérez-Alvarado, G. C., Dyson, H. J., and Wright, P. E. (1998) Conformational preferences in the Ser^{133}-phosphorylated and non-phosphorylated forms of the kinase inducible transactivation domain of CREB. *FEBS Lett.* **430,** 317–322
69. Turjanski, A. G., Gutkind, J. S., Best, R. B., and Hummer, G. (2008) Binding-induced folding of a natively unstructured transcription factor. *PLoS Comput. Biol.* **4,** e1000060
70. Ganguly, D., and Chen, J. (2011) Topology-based modeling of intrinsically disordered proteins: balancing intrinsic folding and intermolecular interactions. *Proteins* **79,** 1251–1266
71. Gianni, S., Morrone, A., Giri, R., and Brunori, M. (2012) A folding-after-binding mechanism describes the recognition between the transactivation domain of c-Myb and the KIX domain of the CREB-binding protein. *Biochem. Biophys. Res. Comm.* **428,** 205–209
72. Shammas, S. L., Travis, A. J., and Clarke, J. (2013) Remarkably fast coupled folding and binding of the intrinsically disordered transactivation domain of cMyb to CBP KIX. *J. Phys. Chem. B* **117,** 13346–13356
73. Giri, R., Morrone, A., Toto, A., Brunori, M., and Gianni, S. (2013) Structure of the transition state for the binding of c-Myb and KIX highlights an unexpected order for a disordered system. *Proc. Natl. Acad. Sci. U.S.A.* **110,** 14942–14947
74. Iešmantavičius, V., Dogan, J., Jemth, P., Teilum, K., and Kjaergaard, M. (2014) Helical propensity in an intrinsically disordered protein accelerates ligand binding. *Angew. Chem. Int. Ed. Engl.* **53,** 1548–1551
75. Dogan, J., Schmidt, T., Mu, X., Engström, Å., and Jemth, P. (2012) Fast association and slow transitions in the interaction between two intrinsically disordered protein domains. *J. Biol. Chem.* **287,** 34316–34324
76. Chrivia, J. C., Kwok, R. P., Lamb, N., Hagiwara, M., Montminy, M. R., and Goodman, R. H. (1993) Phosphorylated CREB binds specifically to nuclear protein CBP. *Nature* **365,** 855–859
77. Parker, D., Ferreri, K., Nakajima, T., LaMorte, V. J., Evans, R., Koerber, S. C., Hoeger, C., and Montminy, M. (1996) Phosphorylation of CREB at Ser-133 induces complex formation with CPB via a direct mechanism. *Mol. Cell. Biol.* **16,** 694–703
78. Dogan, J., Gianni, S., and Jemth, P. (2014) The binding mechanisms of intrinsically disordered proteins. *Phys. Chem. Chem. Phys.* **16,** 6323–6331
79. Teufel, D. P., Freund, S. M., Bycroft, M., and Fersht, A. R. (2007) Four domains of p300 each bind tightly to a sequence spanning both transactivation subdomains of p53. *Proc. Natl. Acad. Sci. U.S.A.* **104,** 7009–7014
80. Ferreon, J. C., Lee, C. W., Arai, M., Martinez-Yamout, M. A., Dyson, H. J., and Wright, P. E. (2009) Cooperative regulation of p53 by modulation of ternary complex formation with CBP/p300 and HDM2. *Proc. Natl. Acad. Sci. U.S.A.* **106,** 6591–6596
81. Teufel, D. P., Bycroft, M., and Fersht, A. R. (2009) Regulation by phosphorylation of the relative affinities of the N-terminal transactivation domains of p53 for p300 domains and Mdm2. *Oncogene* **28,** 2112–2118
82. Lee, C. W., Ferreon, J. C., Ferreon, A. C., Arai, M., and Wright, P. E. (2010) Graded enhancement of p53 binding to CREB-binding protein (CBP) by multisite phosphorylation. *Proc. Natl. Acad. Sci. U.S.A.* **107,** 19290–19295
83. Xue, B., Williams, R. W., Oldfield, C. J., Goh, G. K., Dunker, A. K., and Uversky, V. N. (2010) Viral disorder or disordered viruses: do viral proteins possess unique features? *Protein Pept. Lett.* **17,** 932–951
84. Davey, N. E., Travé, G., and Gibson, T. J. (2011) How viruses hijack cell regulation. *Trends Biochem. Sci.* **36,** 159–169
85. Hagai, T., Azia, A., Babu, M. M., and Andino, R. (2014) Use of host-like peptide motifs in viral proteins is a prevalent strategy in host-virus interactions. *Cell Rep.* **7,** 1729–1739
86. Hottiger, M. O., and Nabel, G. J. (2000) Viral replication and the coactivators p300 and CBP. *Trends Microbiol.* **8,** 560–565
87. White, E. (2001) Regulation of the cell cycle and apoptosis by the oncogenes of adenovirus. *Oncogene* **20,** 7836–7846
88. Pelka, P., Ablack, J. N. G., Fonseca, G. J., Yousef, A. F., and Mymryk, J. S. (2008) Intrinsic structural disorder in adenovirus E1A: a viral molecular

hub linking multiple diverse processes. *J. Virol.* **82,** 7252–7263
89. Ferreon, J. C., Martinez-Yamout, M. A., Dyson, H. J., and Wright, P. E. (2009) Structural basis for subversion of cellular control mechanisms by the adenoviral E1A oncoprotein. *Proc. Natl. Acad. Sci. U.S.A.* **106,** 13260–13265
90. Ferreon, A. C., Ferreon, J. C., Wright, P. E., and Deniz, A. A. (2013) Modulation of allostery by protein intrinsic disorder. *Nature* **498,** 390–394
91. García-Alai, M. M., Alonso, L. G., and de Prat-Gay, G. (2007) The N-terminal module of HPV16 E7 is an intrinsically disordered domain that confers conformational and recognition plasticity to the oncoprotein. *Biochemistry* **46,** 10405–10412
92. Calçada, E. O., Felli, I. C., Hošek, T., and Pierattelli, R. (2013) The heterogeneous structural behavior of E7 from HPV16 revealed by NMR spectroscopy. *Chembiochem* **14,** 1876–1882
93. Ohlenschläger, O., Seiboth, T., Zengerling, H., Briese, L., Marchanka, A., Ramachandran, R., Baum, M., Korbas, M., Meyer-Klaucke, W., Dürst, M., and Görlach, M. (2006) Solution structure of the partially folded high-risk human papilloma virus 45 oncoprotein E7. *Oncogene* **25,** 5953–5959
94. Liu, X., Clements, A., Zhao, K., and Marmorstein, R. (2006) Structure of the human papillomavirus E7 oncoprotein and its mechanism for inactivation of the retinoblastoma tumor suppressor. *J. Biol. Chem.* **281,** 578–586
95. Jansma, A. L., Martinez-Yamout, M. A., Liao, R., Sun, P., Dyson, H. J., and Wright, P. E. (2014) The high-risk HPV16 E7 oncoprotein mediates interaction between the transcriptional coactivator CBP and the retinoblastoma protein pRb. *J. Mol. Biol.* **426,** 4030–4048
96. Vendel, A. C., and Lumb, K. J. (2004) NMR mapping of the HIV-1 Tat interaction surface of the KIX domain of the human coactivator CBP. *Biochemistry* **43,** 904–908
97. Vendel, A. C., McBryant, S. J., and Lumb, K. J. (2003) KIX-mediated assembly of the CBP-CREB-HTLV-1 Tax coactivator-activator complex. *Biochemistry* **42,** 12481–12487
98. Cook, P. R., Polakowski, N., and Lemasson, I. (2011) HTLV-1 HBZ protein deregulates interactions between cellular factors and the KIX domain of p300/CBP. *J. Mol. Biol.* **409,** 384–398
99. Van Orden, K., Yan, J. P., Ulloa, A., and Nyborg, J. K. (1999) Binding of the human T-cell leukemia virus Tax protein to the coactivator CBP interferes with CBP-mediated transcriptional control. *Oncogene* **18,** 3766–3772
100. Legge, G. B., Martinez-Yamout, M. A., Hambly, D. M., Trinh, T., Lee, B. M., Dyson, H. J., and Wright, P. E. (2004) ZZ domain of CBP: an unusual zinc finger fold in a protein interaction module. *J. Mol. Biol.* **343,** 1081–1093