Supplementary Table S1. Summary of structural statistics[a], Related to Figures 2, 3, 4, 6 and Table 1.

	BRD3 ET	IN TP - BRD3 ET	IN CTD -BRD3 ET	NSD3$_{(148-184)}$ - BRD3 ET
Conformationally-restricting restraints[b]				
NOE based distance restraints				
Total	1277	1533	1996	1609
Intra-residue ($i = i$)	305	418	411	366
Sequential ($\|i-j\| = 1$)	446	461	532	568
Medium range ($1 < \|i-j\| < 5$)	370	392	218	366
Long range ($\|i-j\| \geq 5$)	156	262	835	309
Dihedral angle restraints	122	166	212	138
Hydrogen bond restraints	38	22	56	52
Total no. of conformationally-restraining restraints	1437	1721	2264	1799
No. of restraints per residue	16.3	16.0	15.3	14.3
No. of long-range restraints per residue	1.8	2.5	5.9	2.5
Residual restraint violation statistics[b]				
Average no. of distance violations per structure[c]				
0.1–0.2 Å	22.3	6.7	1.2	13.2
0.2–0.5 Å	12.9	1.6 (0.45 Å)[c]	0	5.1
> 0.5 Å	0.45 (0.7Å)	0 (0.35 Å)	0 (0.14 Å)	0.1 (0.57 Å)
Average no. of dihedral angle violations per structure[c]				
1–10°	9.9	8.25	10.15	4.8
>10°	0 (8.0°)	0 (7.0°)	0.35 (11.9°)	0 (5.8°)
Model quality statistics [b]			IN SH3 / ETBM - ET	
RMSD backbone atoms	0.5 Å	0.6 Å	0.5 Å / 1.1 Å	0.6 Å
RMSD heavy atoms	1.0 Å	1.1 Å	0.8 Å / 1.6 Å	1.1 Å
RMSD bond angles	1.20°	1.10°	1.20°	1.20°
RMSD bond lengths	0.019 Å	0.018 Å	0.019 Å	0.018 Å
MolProbity Ramachandran statistics[b,d]				
Most favored regions (%)	98.1%	97.8%	93.1%	95.4%
Allowed regions (%)	1.5%	2.2%	5.1%	4.5%
Generously allowed regions (%)	0.4%	0.0%	1.8%	0.1%
Global quality scores (Raw/*Z*-score)[b]				
Verify3D	0.16 / -4.82	0.18 / -4.49	0.18 / -4.49	0.39 / -1.12
ProsaII	0.68 / 0.12	0.57 / -0.33	0.47 / -0.74	0.63 / -0.08
Procheck (phi-psi)[d]	0.03 / 0.43	-0.03 / 0.20	-0.43 / -1.38	-0.24 / -0.63
Procheck (all)[d]	-0.24 / -1.42	-0.12 / -0.71	-0.56 / -3.31	-0.24 / -1.42
MolProbity clash score	9.4/-0.09	6.07 / 0.48	7.21 / 0.29	5.76 / 0.54
RPF scores[e]				
Recall/precision	0.91 / 0.88	0.89 / 0.78	0.92 / 0.94	0.97 / 0.80
F-measure/DP-score	0.89 / 0.78	0.84 / 0.71	0.93 / 0.76	0.89 / 0.89

[a]Structural statistics computed for the ensemble of 20 deposited structures. [b]Calculated using PSVS 1.5 (Bhattacharya et al., 2007). Average distance violations were calculated using the sum over r^{-6}. [c]Largest violation is show in parenthesis. [d]Based on ordered residue ranges [S(phi) + S(psi) > 1.8]. [e]RPF-DP scores reflecting the goodness-of-fit of the final ensemble of structures (including disordered residues) to the NOESY data and resonance assignments (Huang et al., 2012).

Supplementary Table S2 . Key intermolecular interactions between peptides and BRD3 ET in complexes[a], Related to Figure 7.

Intermolecular interactions	BRD3 ET- TP	BRD3 ET- $NSD3_{148-184}$
Hydrogen bond pairs	Gly589(O), Trp390(NE1); Ile614(O), Leu403(N); Ile614(N), Leu403(O); Glu615(OE2), Ser395(O); Ile616(O), Ile401(N); Ile616(N), Ile401(O); Phe618(N), Leu399(O); Glu619(OE2), Asn397(ND2);	Asp612(O), Lys159(N); Ile614(O), Ile157(N), Ile614(N), Ile157(O); Ile616(N), Leu155(O); Ile616(O), Leu155(N); Phe618(N), Ile153(O); Glu619(N), Ile153(O); Glu619(OE1), Ile153(N);
Salt bridges	Asp612(OD1), Arg405(NH2); Glu613(OE1), Arg402(NH1); Glu615(OE2), Arg402(NH2); Asp617(OD2), Lys400(NZ);	Glu613(OE2), Lys156(NZ); Glu615(OE2), Lys154(NZ); Asp617(OD2), Lys154(NZ);
Residues of ET forming Hydrophobic interactions	Ile584, Leu592, Val595, Val596, Ile599, Ile614, Ile616, Phe618, Leu621	Ile584, Leu592, Val595, Val596, Ile599, Ile614, Ile616, Phe618, Leu621
Residues of Peptide forming Hydrophobic interactions	Trp390, Val392, Ile401, Leu403	Ile153, Leu155, Ile157, Phe168

[a]The H-bond and salt bridges were identified using the default settings in CHIMERA (Petterson et. al 2004) and distance measurements using PyMOL with donor-acceptor distances $\leq$ 3.2 A^o and $\leq$ 4.0 A respectively. Hydrophobic interactions were identified using PyMOL (The PyMOL Molecular Graphics System, Version 2.0 Schrodinger, LLC.).

Supplementary Table S3. Buried surface analysis for interfaces of BRD ET complexes[a], Related to Figure 7.

	TP : BRD3-ET	**$NSD3_{148-184}$: BRD3-ET**	**JMJD6 : BRD3-ET** PDB ID: 6BNH	**$NSD3_{152-163}$: BRD4-ET-** PDB ID: 2NCZ
Complex	7081	9317	6677	6442
ET	6178	6035	6377	5949
Peptide	2539	4891	1900	1931
Buried surface	1635	1609	1560	1439

[a]Solvent accessibility determined in units of $Å^2$ using the program *GETAREA/PyMol* (Fraczkiewicz and Braun, 1998)

Supplementary Table S4: List of Oligonucleotides, Related to STAR Methods.

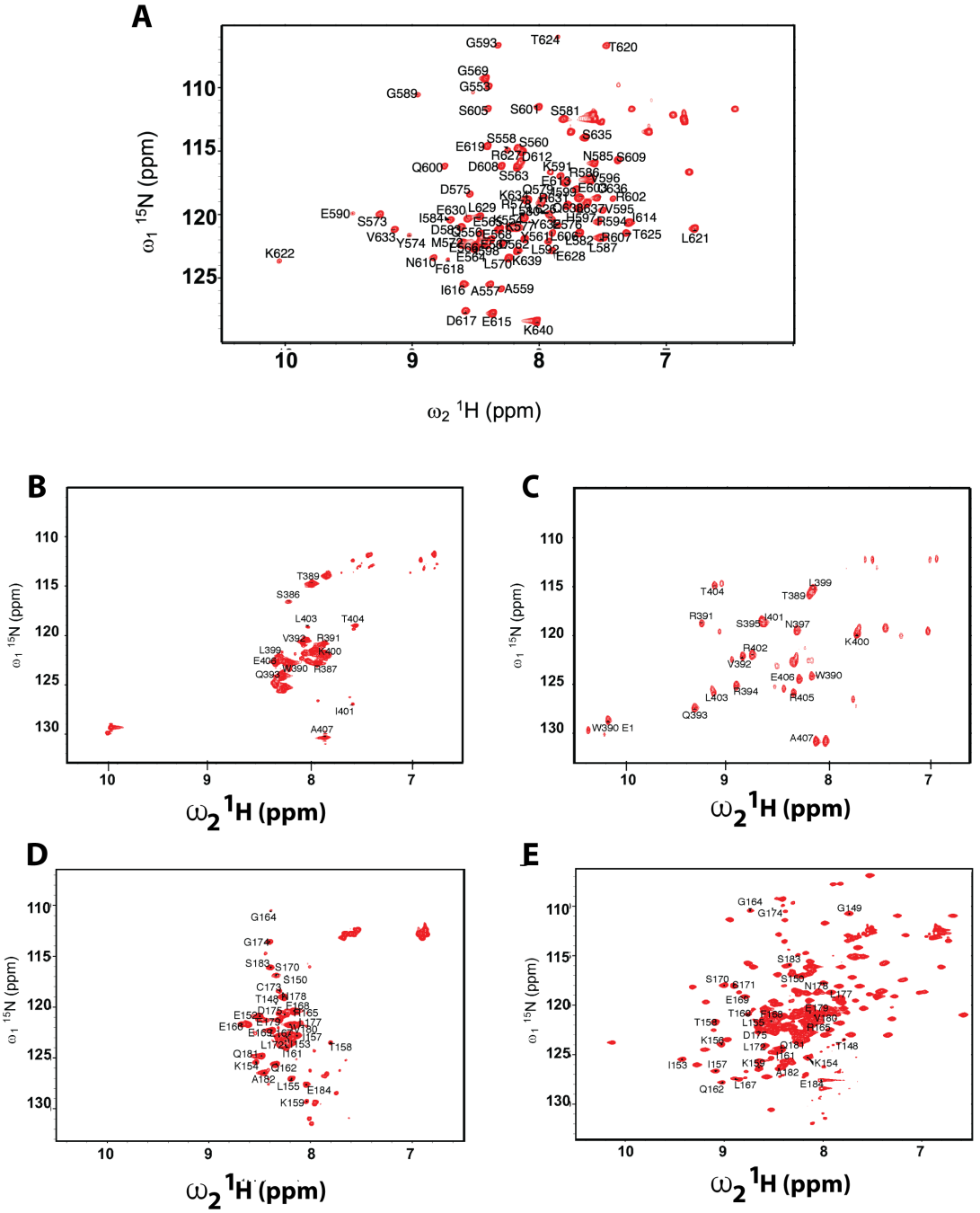
Construct	Oligonucleotide
MLV $IN_{386-407}$ (IN CTD TP) duplex DNA for cloning into pGV358 vector	5′TATGAGCCGCCTGACCTGGCGCGTGCAGCGCAGCCAGAACCCGCTGA AAATTCGCCTGACCCGCGAAGCGTGCATCACGGGAGATGCA 3′
	5′CTAGTGCATCTCCCGTGATGCACGCTTCGCGGGTCAGGCGAATTTTC AGCGGGTTCTGGCTGCGCTGCACGCGCCAGGTCAGGCGGCTCA 3′
Gene block synthesized for $NSD3_{100-263}$	5′GGAATTCCATATGTTCGGTGCTGTTCGTAACTTCTCTCCGACCGACT ACTACCACTCTGAAATCCCGAACACCCGTCCGCACGAAATCCTGGAAAA ACCGTCTCCGCCGCAGCCGCCGCCGCCGCCGTCTGTTCCGCAGACCGTT ATCCCGAAAAAAACCGGTTCTCCGGAAATCAAACTGAAAATCACCAAAA CCATCCAGAACGGTCGTGAACTGTTCGAATCTTCTCTGTGCGGTGACCT GCTGAACGAAGTTCAGGCTTCTGAACACACCAAATCTAAACACGAATCT CGTAAAGAAAAACGTAAAAAATCTAACAAACACGACTCTTCTCGTTCTG AAGAACGTAAATCTCACAAAATCCCGAAACTGGAACCGGAAGAACAGAA CCGTCCGAACGAACGTGTTGACACCGTTTCTGAAAAACCGCGTGAAGAA CCGGTTCTGAAAGAAGAAGCTCCGGTTCAGCCGATCCTGTCTTCTGTTC CGACCACCGAAGTTTCTTATTGCATTACCGGCGATGCACTAGTCC 3′
$NSD3_{100-263}$ amplification for cloning into pSUMO vector	5′CCGGAATTCTTCGGTGCTGTTCGTAACTTCTCTCCG 3′
	5′CCATGAAGCTTTTAAGAAACTTCGGTGGTCGGAACAGAAGAC 3′
$NSD3_{142-166}$ duplex DNA for cloning into pSUMO vector	5′AATTCACCGTTATCCCGAAAAAAACCGGTTCTCCGGAAATCAAACTG AAAATCACCAAAACCATCCAGAACGGTCGTGAATAA 3′
	5′AGCTTTATTCACGACCGTTCTGGATGGTTTTGGTGATTTTCAGTTTG ATTTCCGGAGAACCGGTTTTTTTCGGGATAACGGTG 3′
$NSD3_{148-184}$ amplification for cloning into pSUMO vector	5′CCGGAATTCACCGGTTCTCCGGAAATCAAACTG 3′
	5′CCATGAAGCTTTTATTCAGAAGCCTGAACTTCGTTCAGCAG 3′
Gene block synthesized for $LANA_{1108-1141}$ for cloning into pGV358 vector	5′GGGAATTCCATATGAATAAAGATACCTCCAAAAAAGTGCAGATGGCG CGTCTGGCGTGGGAAGCGTCCCATCCGCTGGCGGGCAATCTGCAGTCCT CCATTGTGAAATTTAAAAAATGCATTACCGGCGATGCACTAGTCC 3′
$JMJD6_{1-336}$ amplification for cloning into pSUMO vector	5′CCGGAATTCATGAACCACAAGAGCAAGAAGCGC 3′
	5′CCATGAAGCTTTCATGTGGACTCCTGAAGGTCAACC 3′

Supplementary Table S5: NMR samples and data used for resonance assignments, structure determination, and nuclear relaxation measurements, Related to STAR Methods.

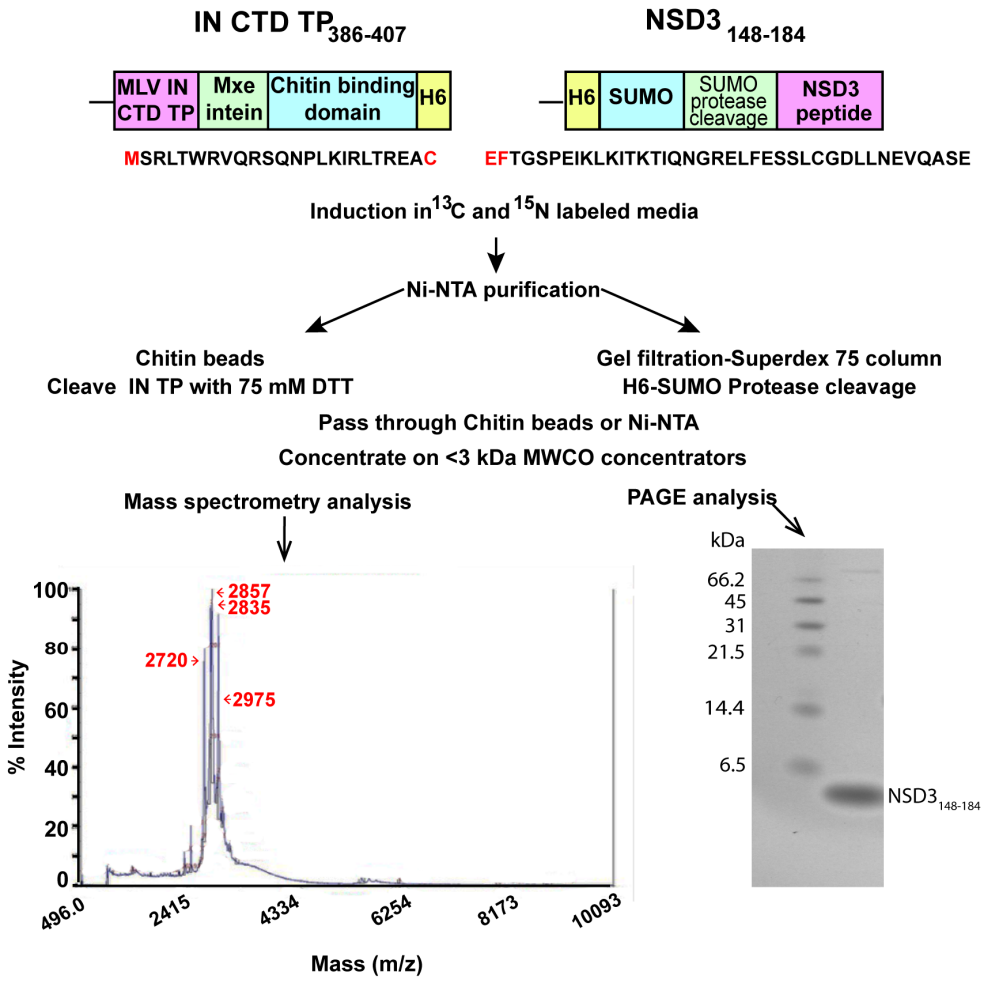
Sample	Volume (μL)	pH	NMR Tube Diameter (mm) / Probe	Field Strength	NMR Experiments
^{13}C ^{15}N BRD3 ET	275	7.0	4 / 5-mm CRP TXI	800 MHz	2D ^{15}N-^{1}H HSQC, 2D HNOE, 2D 13C-1H HSQC, 3D HNCO, 3D HNCA, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D hCCH-TOCSY, 3D ^{13}C-aromatic NOESY, 3D ^{13}C,^{15}N simNOESY
^{13}C ^{15}N MLV IN TP	350	7.0	5 / 5-mm CRP TXI	800 MHz	2D ^{15}N-^{1}H HSQC, 2D HNOE, 2D ^{13}C-^{1}H HSQC, 2D ^{15}N-^{1}H TROSY, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D HNCA, 3D hCCH-TOCSY, 3D ^{13}C,^{15}N simNOESY
^{13}C ^{15}N MLV IN TP + ^{unlabeled} BRD3 ET complex	275	7.0	4 / 5-mm CRP TXI	800 MHz	2D ^{15}N-^{1}H HSQC, 2D HNOE, 2D ^{13}C-^{1}H HSQC, 3D HNCO, 3D HNCA, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D hCCH-TOCSY, 3D ^{13}C X-filtered NOESY, 3D ^{13}C,^{15}N simNOESY
^{13}C ^{15}N BRD3 ET + ^{unlabeled} MLV IN TP complex	275	7.0	4 / 5-mm CRP TXI	800 MHz	2D ^{15}N-^{1}H HSQC, 2D HNOE, 2D ^{13}C-^{1}H HSQC, 3D HNCO, 3D HNCA, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D hCCH-TOCSY, 3D ^{13}C X-filtered NOESY, 3D ^{13}C,^{15}N simNOESY
^{13}C ^{15}N BRD3 ET-^{13}C ^{15}N MLV IN TP complex	275	7.0	4 / 5-mm CRP TXI	800 MHz	2D ^{15}N-^{1}H HSQC, 2D ^{13}C-^{1}H HSQC, 3D HNCO, 3D HNCA, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D hCCH-TOCSY, 3D ^{13}C-aromatic NOESY, 3D ^{13}C,^{15}N simNOESY
^{13}C ^{15}N BRD3 ET-MLV IN CTD complex	275	7.0	3 / 5-mm CRP TXI	800 MHz	2D ^{15}N-^{1}H HSQC, 2D ^{15}N-^{1}H TROSY, 2D ^{13}C-^{1}H HSQC, 3D HNCO, 3D HNCA, 3D HNcoCA, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D HNHA, 3D HCCH-COSY, 3D hCCH-TOCSY, 3D ^{13}C-aromatic NOESY, 3D ^{13}C,^{15}N simNOESY
^{15}N BRD3 ET-MLV IN CTD complex	275	7.2	3 / 5-mm TCI	600 MHz	2D T1_relax, 2D T2_relax, 2D HNOE
^{13}C ^{15}N $NSD3_{148-184}$	40	7.0	1.7 / 5-mm TCI	600 MHz	2D ^{15}N-^{1}H HSQC, 2D ^{13}C-^{1}H HSQC, 2D HNOE, 3D HNCO, 3D HNCA, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D hCCH-TOCSY, 3D ^{13}C,^{15}N simNOESY
^{13}C ^{15}N BRD3 ET-^{unlabeled} $NSD3_{148-184}$	40	7.0	1.7 / 5-mm CRP TXI	800 MHz	2D ^{15}N-^{1}H HSQC, 2D ^{13}C-^{1}H HSQC, 2D HNOE, 3D HNCO, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D hCCH-TOCSY, 3D ^{13}C,^{15}N simNOESY, 3D ^{13}C-aromatic NOESY, 3D ^{13}C X-filtered NOESY
^{13}C ^{15}N BRD3 ET-^{13}C ^{15}N $NSD3_{148-184}$	275	7.0	3 / 5-mm TCI	600 MHz	2D ^{15}N-^{1}H HSQC, 2D ^{13}C-^{1}H HSQC, 2D HNOE, 3D HNCO, 3D HNCA, 3D HNCACB, 3D CBCAcoNH, 3D HBHAcoNH, 3D hCCH-TOCSY, 3D ^{13}C,^{15}N simNOESY, 3D ^{13}C-aromatic NOESY

Solution NMR structures were determined using uniformly labeled samples of ^{13}C, ^{15}N-BRD3 ET at ~ 0.5 mM protein concentration, in buffers containing 20 mM sodium phosphate, 100 mM NaCl, 2 mM 2-mercaptoenthanol at pH 7.0 (or for one sample pH 7.2). The complexes of BRD3 ET were prepared by adding the TP, MLV IN-CTD or NSD3148-184 to ET . 1D ^{15}N T_1 and T_2 relaxation data acquired and analyzed to confirm the complex formation under the buffer conditions. These free induction decay (FID) data have been deposited in the BioMagResDatabase.

Supplementary Fig. S1. [^{15}N-^{1}H]-HSQC spectrum, Related to Figures 2, 3 and 6. (A) [^{15}N-^{1}H]-HSQC of BRD3 ET domain. 2D [^{15}N,^{1}H]-HSQC spectrum of ^{13}C,^{15}N BRD3 ET acquired at 25^{o}C using 45 μL of 0.5 mM sample at pH 7.0 and 600 Hz Bruker Avance NMR spectrometer equipped with a 1.7-mm micro cryoprobe. Backbone amide ^{15}N, $^{1}H^{N}$ resonance assignments are labeled in black. (B and C). Perturbations for the ^{15}N,^{13}C -enriched TP without and with ET domain. (B) [^{15}N-^{1}H]-HSQC spectrum of unbound ^{15}N labeled MLV IN CTD TP. (C) [^{15}N-^{1}H]-HSQC spectrum of ^{15}N labeled MLV IN CTD TP bound to unlabeled BRD3 ET domain. Assignments of some resonances of TP are indicated. (D and E) Perturbations for the ^{15}N,^{13}C -enriched $NSD3_{148-184}$ without and with ET domain. (D) 2D ^{15}N-^{1}H HSQC spectrum of ^{13}C, ^{15}N-$NSD3_{148-184}$. (E) ^{13}C, ^{15}N-$NSD3_{148-184}$-^{13}C, ^{15}N-BRD3 ET complex. Assignments of some resonances of $NSD3_{148-184}$ are indicated.



Supplementary Fig. S2. Peptide purification schematic, Related to Figures 3 and 6. Isotopically enriched peptides for NMR analyses were initially expressed as fusion proteins in *E.coli*, to facilitate cost effective rapid structure determination. The schematic of the IN CTD $TP_{386-407}$ chitin binding domain (CBD) fusion protein (left) and the $NSD3_{148-184}$-SUMO fusion protein (right) are illustrated at the top. Position of the His_6 tag (H6) is indicated. The sequences of the peptides are indicated below each construct; amino-acid residues indicated in red are not encoded by the peptides of interest. For MLV CTD IN $TP_{386-407}$, the C-terminal fusion of an intein-based self-cleavage system to express the peptide as a fusion protein encoded a non-native methionine at the N-terminus to initiate translation (right). The terminal Pro-408 was omitted, since prolines are incompatible with the intein self-cleavage system. Excluding the terminal proline did not affect the stability and binding efficiency of the TP construct. Purification of the peptides follow parallel protocols. On-column self-cleavage of the intein-CBD-6xHis under highly reducing conditions (Mitchell and Lorsch, 2015) following by affinity purification resulted in a greater than 90% pure, tagless peptide as assessed by mass spectrometry. Exemplary mass spectrometry of the $TP_{386-407}$ is shown on the left. The predicted molecular mass of the labeled peptide containing the N-terminal Met is 2830. Species smaller migrating at 2720 could result from loss of the terminal Met. Products larger at 2975 Da could result from incomplete removal of the DTT adduct after cleavage of the CBD. Using this purification strategy, we obtained highly-purified isotopically-enriched IN CTD TP with a yield of ~1.5 mgs per 1.5 liter culture. The schematic of the $NSD3_{148-184}$-SUMO fusion protein is shown on the right. Parallel purification involved Nickel NTA affinity column purification, S75 size exclusion chromatography, enzymatic cleavage by the SUMO-protease, and concentration. Exemplary Coomassie staining of the purified NSD3 peptide is shown on the bottom right. Molecular weight standards are as indicated.



Supplementary Fig. S3. **Alignment of gammaretroviral IN linker regions (top) and NSD3 (bottom) proteins, Related to Figures 4, 5 and 7.** Alignments were performed using Clustal Omega (1.2.4) (Madeira et al., 2019, Sievers et al., 2011, Sievers and Higgins, 2018). Gammaretroviruses analyzed include: P10273- Feline leukemia virus, Q83379- Rat Leukemia virus, MH450110.1- Xenotropic murine leukemia virus (MLV) isolate AKR6, O39735- Friend murine leukemia virus, O41250- Rauscher murine leukemia virus, P08361- Cas-Br-E MLV, ABU54793.1- Amphotropic MLV 4070A, P03355- Moloney murine leukemia virus, P10272- Baboon endogenous virus, Q8J4V8- PERV-A, P21414- GaLV, and Q9TTC1- KoRV. M-MLV Δ5 and Δ 20 were isolated as described (Loyola et al., 2019). NSD3 protein sequences analyzed include: F1QV68- NSD3 (zebrafish), A0A1L8H2H2- NSD3 (xenopus), E1BNH7- NSD3 (bovine), F6WYL3- NSD3 (horse), Q9BZ95-NSD3 (human), H2R3Q8- NSD3 (chimpanzee), A0A286ZK72- NSD3 (pig), E2QUJ0-NSD3 (dog), M3WJ59-NSD3 (cat), Q6P2L6- NSD3 (mouse), and D3ZK47- NSD3 (rat). Consensus sequences notations are: (*) fully conserved residue, (:) conservation between groups of strongly similar properties, and (.) conservation between groups of weakly similar properties (Gonnet et al., 1992). IN-TP and NSD3 peptide used in these studies are indicated in bold. Pro are highlighted in yellow. Conserved Trp for MLV-IN and Phe for NSD3 that form the cap to the hydrophobic network are highlighted in cyan. Position and conservation of the two beta-strands (B) of MLV IN and NSD3 interacting with the ET domain are indicated in red.

Gammaretrovirus

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                                          BBB       BBBB
FeLVA (Feline)        KAAGPTTNQDLSDSPSSDDPSRWKVQRTQNPLKIRLSRGT-     412
RaLV (Rat)            KAARPEETADHN-----IAPQTWKAQRTQNPLKLRFSRCCS     414
XMLV (Xenotropic)     KAATTP----------PAGAAWKVQRSQNPLKIRLTRGAP     405
MLV  (Friend)         KAADTKIE--P------PSESTWRVQRSQNPLKIRLTRGTS     408
MLV (Rauscher)        KAADTRIE--P------PSESTWRVQRSQNPLKIRLTRGTS     408
MLV (CasBrE)          KAATTSP----------ARTAWKVQRSQNPLKIRLSREPS     405
MLV (Ampho/4070A)     KAADTESG--PS-----S-GRTWRVQRSQNPLKIRLTRGSP     408
MLV  (Moloney)        KAADPGGG--PS------SRLTWRVQRSQNPLKIRLTREAP     408
MLV Δ5 (Moloney)      KAADPGGG--LC-----GRKLTWRVQRSQNPLKIRLTREAP     409
MLV Δ20 (Moloney)     KAADPG----------RKLTWRVQRSQNPLKIRLTREAP     404
BaEV (Baboon)         KAAPGTPGP--------TSSGTWRLRRSEDPLKIRLSRT--     392
PERVA (Porcine)       KPAPP-----------PDSGWKAEKTENPLKLRLHRVVP     400
GaLV  (Gibbon Ape)    KPAPPS----------APDESWELEKTDHPLKLRIRRRRD     373
KoRVA (Koala)         KPAPPG----------APDESWELEKTDHPLKLRVRRRRN     373
Consensus             * *                 *. .:::.**:*. *
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NSD3

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NSD3zebrafish         VLPPPPPLLLPSSPPLLSPQESTISNPIGQPVNTIITTTP      221
NSD3xenopus           PEPTSPPNLLQA-----------------PPSST-TTPQ      148
NSD3bovine            PQPPPP----------------------PPSVPQTVIP      146
NSD3Horse             PQPPP-----------------------PPSVPQTVIP      145
NDS3human             PQPPP-----------------------PPSVPQTVIP      145
NSD3chimpanzee        PQPPP-----------------------PPSVPQTVIP      145
NSD3pig               PQPPP-----------------------PPSVPQTVIP      145
NSD3dog               PQLPP-----------------------PPSVPQTVIP      145
NSD3cat               PQPPP-----------------------PPSVPQTVIP      145
NSD3mouse             PQPPP-----------------------PPSVPQTVIP      145
NSD3rat               PQPPPPPLLPPP----------------PPPVPQTVIP      146
Consensus                                         *     *.

                            BBBB          BBB
NSD3zebrafish         KKTSSPEIKLKIIKTYQNGRELFESSLCGDLLQEFQAGEDSR  263
NSD3xenopus           KKTGSPEIKLRITKTIQNGREMFESSLCGDLLHEFQASEMTR  190
NSD3bovine            KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHTK  188
NSD3horse             KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHTK  187
NDS3human             KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHTK  187
NSD3chimpanzee        KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHTK  187
NSD3pig               KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHTK  187
NSD3dog               KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHTK  187
NSD3cat               KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHTK  187
NSD3mouse             KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHTK  187
NSD3rat               KKTGSPEIKLKITKTIQNGRELFESSLCGDLLNEVQASEHLK  188
Consensus             ***.*******:* ** *****:**********:*.**.* ::
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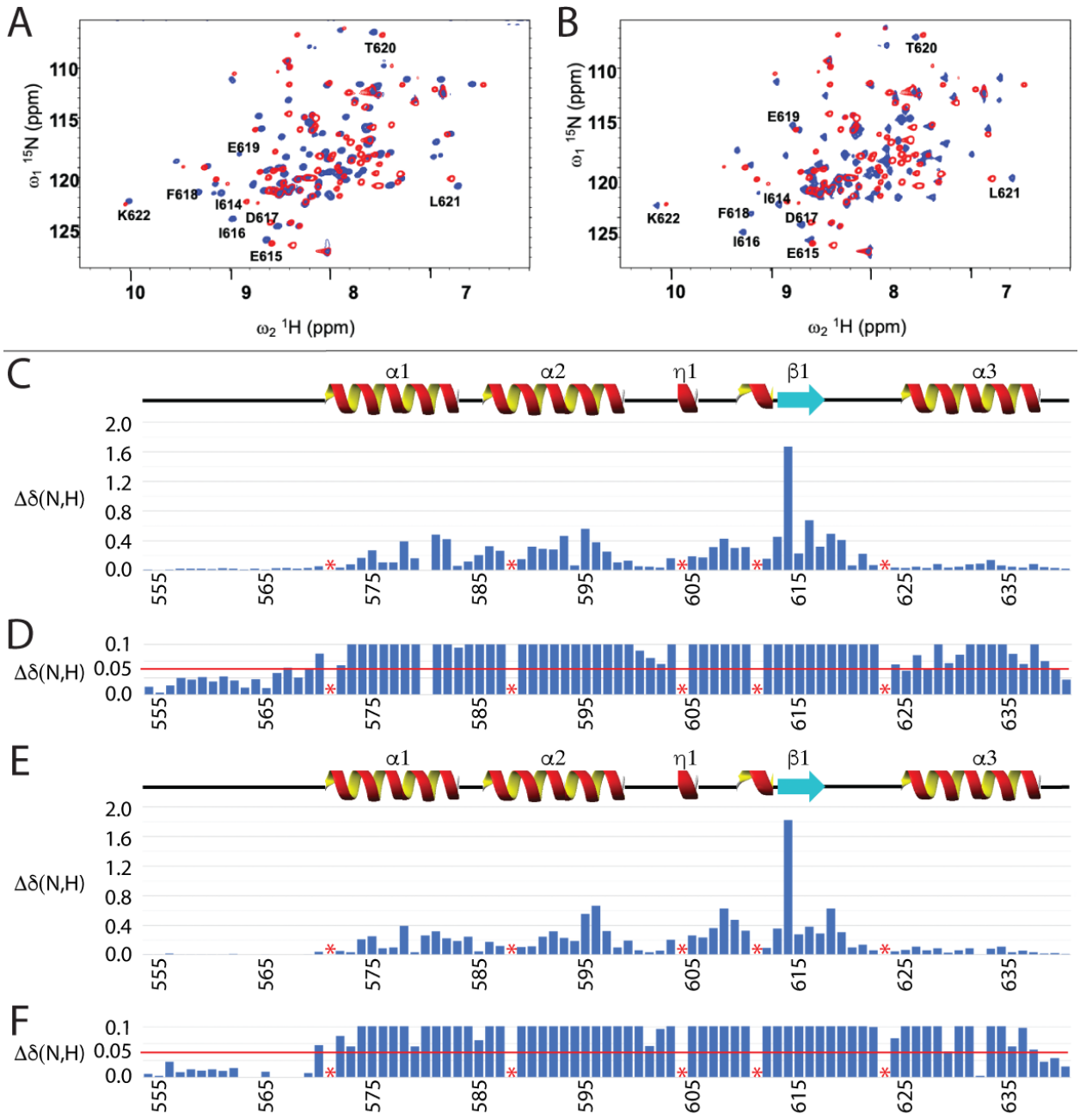
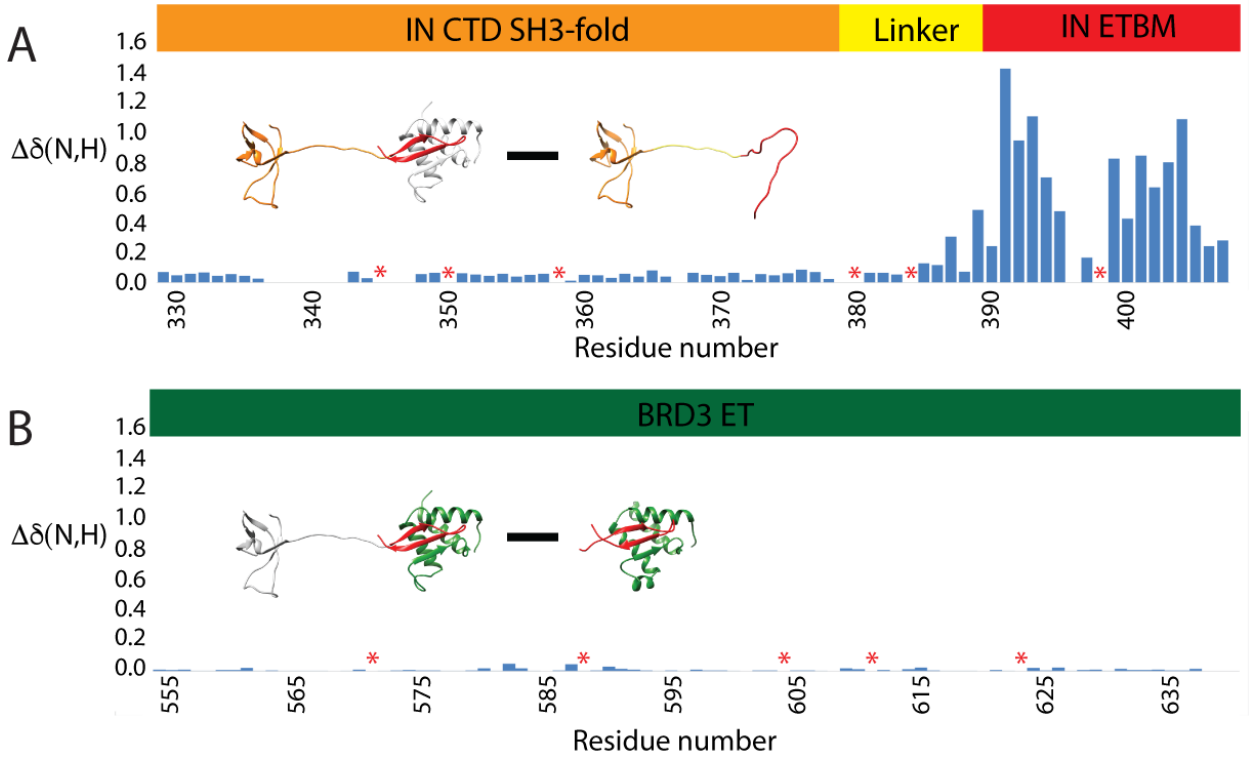
Supplementary Fig. S4. Comparison of chemical shift perturbations of BRD3 ET induced by IN TP and NSD3, Related to Figures 3 and 6. Panels A and B: HSQC of the BRD3 ET (blue) in the presence of unlabeled IN TP (panel A, red) and NSD3 (panel B, red). Chemical shift perturbations of BRD3 ET domain relative to the bound (C, D) TP and (E, F) $NSD3_{148-184}$ calculated using $\Delta\delta(N,H) = ((\delta N/6)^2+(\delta H)^2)^{0.5}$ and plotted as a function of BRD3 ET sequence. Panels D and F show an expansion of the data in Panels C and E, demonstrating that most residues have $\Delta\delta(N,H)$ greater than 0.05 ppm (horizontal red lines), a typical cutoff value for unperturbed chemical shift changes on complex formation (Ma et al., 2016). Amino-acid residue positions marked with a red * correspond to Pro. Assignments of some resonances of ET are indicated. Secondary structure of BRD3 ET is shown schematically in panels C and E.



Supplementary Fig. S5. Comparison of chemical shift perturbations of backbone amides, Related to Figures 2, 3, 4 and 5. (A) Chemical shift perturbations of MLV IN CTD, in complex with BRD3 ET minus chemical shifts of apo MLV IN CTD. (B) Chemical shift perturbations of BRD3 ET, in complex with MLV IN CTD : BRD3 ET minus chemical shifts of MLV IN TP : BRD3 ET. Inset of the ribbon diagrams in color indicate the amide $^{15}N,^{1}H$ resonances being compared while the rest is shown in gray. Residue numbers of the IN CTD and BRD3 ET domain are indicated in each panel (bottom) along with the schematic of the domains (top). Residues indicated by a red * correspond to Pro.



Supplementary Fig. S6. Comparison of chemical shift perturbations of BRD3 ET induced by LANA and JMJD6, Related to Figures 2 and 3. (A) Constructs of LANA and JMJD6. Chemical shift perturbations of BRD3 ET domain relative to the bound (B) LANA and (C) JMJD6 calculated using $\Delta\delta(N,H)= ((\delta_N/6)^2+(\delta_H)^2)^{0.5}$ and plotted as a function of BRD3 ET sequence. Amino-acid residue positions marked with a red * correspond to Pro. The residues that were not assigned in the spectrum due to ambiguity of the assignment or missing cross peaks in the complex are included with $\Delta\delta(N,H)=0$. (D) and (E) are the perturbations mapped onto the 3D structure of BRD3 ET and IN TP (IN TP is not displayed for ease of visualization) indicating the major interactions of the peptides are in the region of $_{613}$EIEID$_{617}$ in both the complexes in addition to those shown.