Trends in Cell Biology 2007, 17(4): 187-192.

Control of transcription by Pontin and Reptin

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Abstract

Pontin and Reptin are two closely related members of the AAA+ family of DNA helicases. They play roles in diverse cellular processes, including the response to DNA double-strand breaks and the control of gene expression. The two proteins share residence in different multi-protein complexes, such as the Tip60-, Ino80-, SRCAP- and Uri1-complexes in animals which are (directly or indirectly) involved in transcriptional regulation, but they also function independently from each other. Both Reptin and Pontin repress certain transcriptional targets of Myc, but only Reptin is required for the repression of specific β-Catenin and nuclear factor-κB targets. Here, I review recent studies that have addressed the mechanisms of transcriptional control by Pontin and Reptin.

Main text

RuvB-like helicases with many different roles

Most eukaryotes contain two proteins that are closely related to the bacterial DNA helicase RuvB, a member of the AAA+ family of helicases (***A***TPases ***a***ssociated with diverse cellular ***a***ctivities; reviewed in 1): Pontin, also called Pontin52, Ruvbl1, Rvb1, Tip49, Tip49a, NMP238, ECP54, TAP54α (in metazoans), RVB1, TIP48, TIP49A, TIH1 (in the yeast *Saccharomyces cerevisiae*), and Reptin, also called Reptin52, Ruvbl2, Tip48, Tip49b, ECP51, TAP54β, CGI-46 (in metazoans), RVB2, TIP49, TIP49B, TIH2 (in *S. cerevisiae*). In the remainder of this text, I will refer to these proteins as Pontin and Reptin, respectively. Bacterial RuvB catalyzes the branch migration at Holliday junctions, which occurs during homologous recombination or during the repair of stalled replication forks (reviewed by 2, 3). Similar functions may also be fulfilled by eukaryotic Pontin and Reptin (as indicated for example by the association of Pontin with the human replication protein RPA3; 4). However, these proteins have attracted most attention for their association with microtubular structures (not discussed here, but see 5-8), for their role in the maturation of small nucleolar RNAs (snoRNAs; not discussed here, but see 9-12), and above all for their involvement in DNA damage response and transcriptional control in which both Pontin and Reptin play essential roles. This review summarizes recent publications that address these latter roles of Pontin and Reptin.

Structure of Pontin and Reptin

The structure of human Pontin has recently been solved to 2.2 A resolution (13). Pontin consists of three distinct domains (Fig. 1A). Domains 1 and 3 are involved in ATP binding and hydrolysis, and they are also found in bacterial RuvB and other AAA+ helicases. In contrast to these other helicases, however, Pontin contains an insertion of 170 amino acids between the so-called Walker A and Walker B motifs that are located in domain 1 and serve to bind ATP and Mg^{2+}. This Pontin-specific "domain 2" shows similarity to the ssDNA binding domain of the replication factor RPA. Indeed, both full length Pontin and the isolated domain 2 were shown to bind *in vitro* to ssDNA, as well as to dsDNA and to RNA (13). Like bacterial RuvB and other AAA+ helicases (2), Pontin monomers assemble to form a hexameric ring (see Fig. 1B, C). The central channel of this structure is 18 A wide – large enough to fit ssDNA but too small for a DNA double helix, suggesting that such hexamers might only operate on ssDNA (13).

The structure of Reptin has not yet been determined, but mixed Pontin:Reptin oligomers were analysed by electron microscopy (14). They form a dodecamer consisting of two differently shaped,

juxtaposed hexamers, both of which look different than Pontin hexamers; these dodecamers contain a 26 A wide central channel, which would be wide enough to accommodate dsDNA (14). While the dodecamers are made up of equimolar amounts of Pontin and Reptin, it is not clear whether one of the hexamers contains exclusively Reptin and the other Pontin (in which case Reptin would assume a different conformation from Pontin), or whether both contain equimolar mixtures of Pontin and Reptin (in which case different conformations for Pontin:Reptin hexamers would exist). The comparison of the X-ray and electron microscopic structures suggests that the interaction with Reptin affects the conformation of Pontin (and possibly *vice versa*). Such effects are consistent with the observation that mixed preparations of Pontin and Reptin display a solid ATPase activity, whereas either protein alone (either as a mono- or oligomer) is almost inactive (4, 13-15; but see 16). In this context it is also worth noting that Pontin and Reptin have non-redundant functions in all systems analysed so far.

Pontin and Reptin, and chromatin remodeling complexes

Two converging lines of research have firmly established a role for Pontin and Reptin in the control of transcription. First, both proteins were found to interact physically with different sequence-specific transcription factors; the functional consequences of these interactions will be discussed in a later section. Second, Pontin and Reptin were revealed to be integral subunits of different chromatin modifying complexes: the Ino80 complex in yeast and animals (17-21), the Swr1 complex in yeast (22-24) and the corresponding SRCAP complex in animals (21, 25, 26), as well as Tip60 complexes in animals (15, 25, 27-29). Central to the first two complexes are the ATP-dependent helicases Ino80 and Swr1 (called SRCAP in vertebrates), whereas the latter complex is built around the Tip60 histone acetyltransferase (HAT), a member of the MYST (**M**OZ, **Y**bf2/Sas3, **S**as2, **T**ip60) family of HATs. In addition, these complexes typically contain 11 to 16 proteins (depending on species and purification scheme), including Pontin, Reptin, Actin and different actin-related proteins (Fig. 2). Of note, yeast has a HAT complex called NuA4 that shares several subunits with the metazoan Tip60 complex, but lacks Pontin, Reptin and several other core components. Based on a comparison of these subunits, it has been hypothesized that metazoan Tip60 complexes correspond to a fusion of yeast Ino80- or Swr1-complexes with NuA4 (30). Indeed, the functions ascribed to the different complexes would be consistent with such a proposal.

One of these functions clearly resides in the control of gene expression. Ino80 is recruited to at least two yeast promoters, and either activates or represses a large number of genes, presumably by mobilizing nucleosomes and altering the accessibility of the underlying DNA to the transcription machinery (19, 20). As expected, Reptin is required for the correct expression of many of the same genes (20); other studies showed a significant overlap between the genes controlled by Pontin and those controlled by Reptin (18, 31-33). This demonstrates that Reptin and Pontin play a role in activation and repression and suggests that they function in the same complex (but see also the section on gene repression below). However, neither Pontin nor Reptin are physically located at the promoters bound by Ino80, suggesting that they are not integral structural components of the Ino80 complex (20). Instead, they might function as (essential) assembly factors that only transiently associate with the remainder of the complex. Consistent with this hypothesis, Pontin and Reptin are less abundant in normal yeast cells (about 1900 and 500 hexamers, respectively) than Ino80 or Swr1 (6300 and 700 molecules, respectively) – or the proteins associating with Pontin and Reptin in their other functions with snoRNAs and microtubules (34).

The Swr1 complex also affects gene expression, albeit by a different route. This complex is required for the deposition of the variant histone Htz1 (also known as H2A.Z) in euchromatic sequences located next to the heterochromatin found at yeast telomeres, at silent mating loci, or in rDNA. In the absence of Htz1, heterochromatin spreads into the euchromatin and silences the expression of the genes situated in this region, and an overlapping set of genes is also repressed upon deletion of Swr1 (22-24). A role in transcription has also been demonstrated for the mammalian Tip60 complex and its yeast analog NuA4: components of this complex can be found at different promoters (reviewed by 30), and in some instances they have also been demonstrated to be

functionally important for gene expression, e.g. for the activation of transcriptional targets of p53 (35-37). Thus, by belonging to these different complexes, both Pontin and Reptin play a role in the activation or repression of specific genes. In addition to controlling transcription, these different complexes also play a role in the cellular response to DNA double strand breaks, suggesting that Pontin and Reptin also have a transcription-independent role in the response to DNA damage (15, 29, 38-40).

Another complex containing both Pontin and Reptin was purified from vertebrate cells and called Uri1 complex (41). Besides Pontin and Reptin, this complex contains components of the E3-ubiquitin ligase SCF^{Skp2}, Rbp5 (a protein previously shown to associate with RNA Polymerases I, II, and III), and several prefoldin-related proteins, amongst which is the name-giving subunit Uri1 (also known as Rmp) - but none of the chromatin-remodeling enzymes mentioned above (Fig. 2). The Uri1 complex functions downstream of Tor (target-of-rapamycin) to mediate the repression of Tor-repressed genes, and hence it plays a role in the cellular response to extracellular nutrient levels. Yeast Uri1 plays a similar role, and it does so by repressing the translation of the transcription factor Gcn4. Thus, the Uri1 complex contributes indirectly to the control of gene expression, but it might also affect transcription more directly since at least Uri1 physically interacts with RNA polymerase II as well as with components of the Paf complex in human cells, which controls different steps of transcription (42). Uri1 is also important for the maintenance of genomic integrity, as loss of *uri1* results in an increased number of double-strand breaks in the nematode *C.elegans* (43). These different observations provide an additional link between the transcription and the repair of double-strand breaks and the activity of Pontin and Reptin - although their exact roles within the Uri1 complex still need to be elucidated.

Transcriptional repression by Reptin (and Pontin)

Independently from the experiments described above, Pontin and Reptin were also identified by virtue of their physical interaction with the transcription-associated protein β-Catenin (44, 45), and with the transcription factors TBP (32, 45-47), Myc (48), E2F1 (only Pontin; 49) and ATF2 (only Reptin; 50). Subsequently, Pontin and/or Reptin were shown to bind to the promoters of transcriptional targets of c-Myc (51, 52), E2F1 (52) and NFκB (53), often along with components of the Tip60 complex. These data are consistent with a transcriptional role for Pontin and Reptin in animals, and several recent reports provide direct proof for such a role.

c-Myc represses targets such as the $p21^{CIP1}$ gene by binding and inhibiting the transcription factor Miz1, which would normally activate expression of $p21^{CIP1}$ (reviewed by 54). A recent report now shows that co-expression of wildtype forms of either Pontin or Reptin (but not mutant proteins unable to interact with Myc) potentiates Myc's ability to repress a $p21^{CIP1}$ reporter construct in vertebrate tissue culture cells, and further, that Myc, Pontin, Reptin and Miz1 interact genetically in *Xenopus* embryos (55). These data indicate that the inhibition of Miz1 (and hence repression of $p21^{CIP1}$) is mediated by a complex containing Myc, Pontin and Reptin (55). A similar conclusion was drawn from a separate study in *Drosophila* (33). In this organism, Myc also shows a strong genetic interaction with Pontin (and a weaker one with Reptin), although a comparison of the transcriptional targets of Myc on one side and Pontin or Reptin on the other side revealed a very limited overlap. However, a small number of genes require Myc and Pontin (and possibly also Reptin) for their repression in cultured cells and *in vivo*, and the promoter of one of these genes, *mfas*, is indeed bound by both Pontin and Myc. These data also suggest that a complex of Myc and Pontin (probably also containing Reptin) represses genes like *mfas*, although in this case it is not known whether the repression involves the inhibition of an activator such as Miz1 (33). Neither the *Xenopus* nor the *Drosophila* study addresses the enzymatic basis of the repression mechanism, nor the possible involvement of other Tip60 complex components. Given the documented interaction between Myc and several other proteins of the Tip60 complex (56, 57), it is possible that Myc recruits the entire complex which then (somehow) silences the gene thus targeted.

The situation is different in the case of the repressed β-Catenin and NFκB targets. Bauer and coworkers first showed that overexpressed Pontin weakly activates a β-Catenin dependent reporter

in cultured cells, whereas Reptin represses the same construct. The observed genetic interactions between the Wingless (Wg)/β-Catenin signalling pathway and Pontin or Reptin were also consistent with opposing effects of Pontin and Reptin on Wg-signalling (44, 58). Such data are difficult to reconcile with a function of Pontin and Reptin as part of the same chromatin remodelling complex. Instead, the recent analysis of two β-Catenin targets during pituitary development in the mouse suggests that Reptin might act in complex with the co-repressor TLE1 (Groucho in *Drosophila*) and the histone deacetylases HDAC1 and 2 (59). Reptin and also TLE1, β-Catenin, and HDACs were found to localize to the promoters of the β-Catenin targets *hesx1* and *pit1* at a time of development when their expression was silenced. Tissue culture experiments with a reporter derived from the *hesx1* gene further showed that Reptin and β-Catenin are both required for this repression. The possible role of Pontin or of other Tip60 complex components was not investigated in this study, nor was the functional relevance of the HDACs demonstrated.

However, these points were addressed in the analysis of the NFκB target KAI1, another gene that is repressed by Reptin (53). The tetraspanin protein KAI1 was identified by Kim et al. (53) as a suppressor of tumor metastasis. Normal cells, but also non-metastatic transformed cells, can be induced to express KAI1 by incubation with IL-1β. By contrast, transformed metastatic cells do not express KAI1 (but ectopic expression of KAI1 in these latter cells markedly reduces their potential for forming metastases in a mouse *in vivo*). The IL-1β induced expression changes are accompanied by the differential recruitment of transcriptional co-factors to the KAI1 promoter. In all situations, NFκB p50 is bound to the promoter; in uninduced cells, p50 is accompanied by the co-repressors N-CoR and TAB2, and also the histone deacetylase HDAC3. IL-1β treatment triggers the loss of these co-factors. In non-metastatic cells, they are replaced by Pontin and Tip60, and the promoter region becomes acetylated on histones H3 and H4. Tip60 is required both for the acetylation and for the subsequent induction of KAI1 expression, but surprisingly, Pontin is dispensable for both processes (although in a different context, inhibition of Pontin by expression of a dominant-negative mutant was able to reduce both histone acetylation and target gene expression; 60). In metastatic cells, however, instead of Pontin and Tip60, Reptin and β-Catenin are recruited to the KAI1 promoter, and they are both needed for its efficient repression; this repression further requires the activity of HDAC1, which is brought to the promoter through physical interaction with Reptin (53).

So far, so good – but why do metastatic and non-metastatic cells recruit different co-factors to the KAI1 promoter? Kim and colleagues propose two answers to this question. First, metastatic cells contain relatively lower levels of Tip60 and higher levels of β-Catenin (53). Second, metastatic cells contain higher levels of the small ubiquitin-like modifier (SUMO)-conjugating enzyme Ubc9, that attaches SUMO to lysine 456 of Reptin, and lower levels of the SUMO-processing enzymes SENP1 and SUSP1, that physically bind to Reptin and cleave SUMO off (61). As a consequence, a larger fraction of Reptin is sumoylated in metastatic cells, and Kim *et al.* showed that sumoylation stimulated the repressive potential of Reptin by promoting the nuclear localization of Reptin and by increasing its interaction with the histone deacetylase HDAC1 (61). In addition, the presence of sumoylated Reptin on the KAI1 promoter (achieved experimentally by the forced expression of an artificial SUMO-Reptin fusion protein) prevents the recruitment of Tip60, whereas binding of a SUMO-free mutant of Reptin (an NLS-tagged Reptin carrying a lysine 456 to arginine mutation) to the KAI1 promoter allows recruitment of Tip60 and activation of KAI1 expression (61). Some aspects of the sumoylation or Reptin are still puzzling, however. For example, less than 5% of the total wildtype Reptin pool is sumoylated, yet more than one third is nuclear – how does non-sumyolated Reptin reach the nucleus, and why does it not compete with sumoylated Reptin for binding to the KAI1 promoter, and hence promote activation of this promoter? How does sumoylation affect the subcellular location of Reptin? How does it affect its interaction with Tip60? Clearly, there is room for more analysis of Reptin's post-translational modifications.

An additional means of modulating the transcriptional activity of Pontin/Reptin was revealed with the identification of the interacting protein Hint1 (histidine triad nucleotide-binding protein 1; also

known as protein kinase C inhibitor 1, protein kinase C interacting protein 1, adenosine 5′-monophosphoramidase) (62). Hint1 interacts with the same domain in Pontin and Reptin that also serves for multimerization between the two helicases. Therefore, binding to Hint1 disrupts formation of Pontin-Pontin, Reptin-Reptin and Pontin-Reptin complexes, but does not interfere with the association of Pontin or Reptin with β-Catenin. Thereby, Hint1 reduces the ability of Pontin to activate reporter constructs or endogenous targets such as *axin2* and *cyclin D2*. Hint1 is also required for the expression of *p53* and its target *bax*, although it is not clear whether these effects also involve Pontin, Reptin and the Tip60 complex (63). However, the observation that Hint1 acts as a haplo-insufficient tumor suppressor (64, 65) raises the possibility that it is an important modulator of the activity of the β-Catenin:Pontin axis.

Taken together, the studies described in this section suggest a model whereby Reptin (at least in some instances in combination with β-Catenin) gets recruited to promoters, and brings along a histone deacetylase which deacetylases histones and thereby converts the chromatin to a more repressive state. The repressive potential of Reptin may also be controlled by sumoylation (which, among other things, enhances the interaction with the histone deacetylase). In this mode, Reptin does not seem to function as part of the chromatin remodeling complexes described earlier (which contain equimolar amounts of Pontin and Reptin), because, at least in the situations where this has been investigated, Reptin is not accompanied by Pontin (or Tip60). Thus, Reptin might act as part of a novel complex, dealing specifically with repression of transcription. This repressive complex could be related to the "Polycomb Repressive Complex 1" (PRC1), which contains several members of the Polycomb group of repressors and has a role in maintaining certain genes in a transcriptionally silent state. Reptin and HDAC (but neither Pontin nor Tip60) were shown to co-purify with *Drosophila* PRC1 (66); furthermore, *reptin* interacts genetically with Polycomb-group genes belonging to the PRC1, and *reptin* mutants share some properties with *PRC1* mutants (67). However, Reptin and HDAC are only present at sub-stochiometric amounts in the purified PRC1 and do not correspond to core PRC1 components, and the genetic interaction of *reptin* with the PRC1 can also be explained if Reptin functions as part of the Tip60 complex (67). It is more likely therefore, that this repressive Reptin complex still awaits identification.

Concluding remarks and future perspectives

This review is limited to transcription-associated activities of Pontin and Reptin, but it already illustrates the multitude of identities these proteins can take on. Is there any unifying theme under these functions of Pontin and Reptin – or do they contribute different activities to the different complexes they belong to? The latter seems likely, since their enzymatic activity is essential for the survival of yeast (and hence for some functions of Pontin and Reptin), but not for their role within the Ino80 complex (20). Hence the question arises, how do Pontin and Reptin influence the activity of the different complexes listed above, and what is their substrate - ssDNA or chromatin-bound dsDNA? How can the same protein contribute to gene repression on one promoter and to activation on a different one? Do they always act as hexamers, or are some functions performed by homo- or hetero-dimers? What is the biochemical difference between these two proteins that are so similar in primary sequence – why does Reptin function as a repressor in some situations where Pontin activates gene expression? Clearly, we still know very little about these two helicases. Given the promiscous nature of these proteins, above all it will be necessary to identify their partners in crime for each particular process we are interested in – be it the activation of a specific gene or the repression of another one. The study of Pontin and Reptin function is not likely to be over soon.

Acknowledgements

Many thanks to Pedro Matias and Nuno Micaelo for the diagrams of Pontin, and to Denise Aragnol and to two anonymous reviewers for comments on the manuscript. Research in the author's group is supported by the Schweizerische Nationalfonds and the Universität Zürich.

Figure legends

Figure 1. Structure of Pontin. **A,** Ribbon diagram of the Pontin monomer bound to ADP. The domains are colored in yellow (domain 1), green (domain 2) and red (domain 3), and the Walker A and B domains are shown in black and blue, respectively. The ADP molecule is shown in space-filling mode, where each atom is represented by a sphere with a diameter twice its conventional van der Waals radius. Carbon, nitrogen, oxygen and phosphorus atoms are coloured gray, blue, red and green, respectively [prepared by Pedro Matias using DINO]. **B**, Ribbon diagram of the Pontin hexamer (*side view*). Adjacent monomers are coloured light cyan and light gold. The bound ADP molecules and the front "gold" monomer are depicted according to the same conventions as in panel A to reveal the domain structure [prepared by Pedro Matias using DINO]. **C**, Cartoon diagram of the Pontin hexamer (*top view*). Each chain is colored in rainbow fashion, from N-terminal (red) to C-terminal (blue) [prepared by Nuno Micaelo using PYMOL].

Figure 2. Components of transcription-associated complexes mentioned in the text that also contain Pontin and Reptin. The compositions of metazoan versions of the indicated complexes are shown (human Ino80: 21; human SRCAP: 26; *Drosophila* Tip60: 29; human Uri1: 41, 42; human β-Catenin: 53). Note, however, that different authors have published slightly differing versions of these complexes. Also, it is unknown whether all of the Uri1-associated proteins reside in the same complex as Pontin and Reptin. The name-giving subunits of the different complexes are marked in red; within the Uri1 group, the SCF- and PAF-subcomplexes are also labeled.

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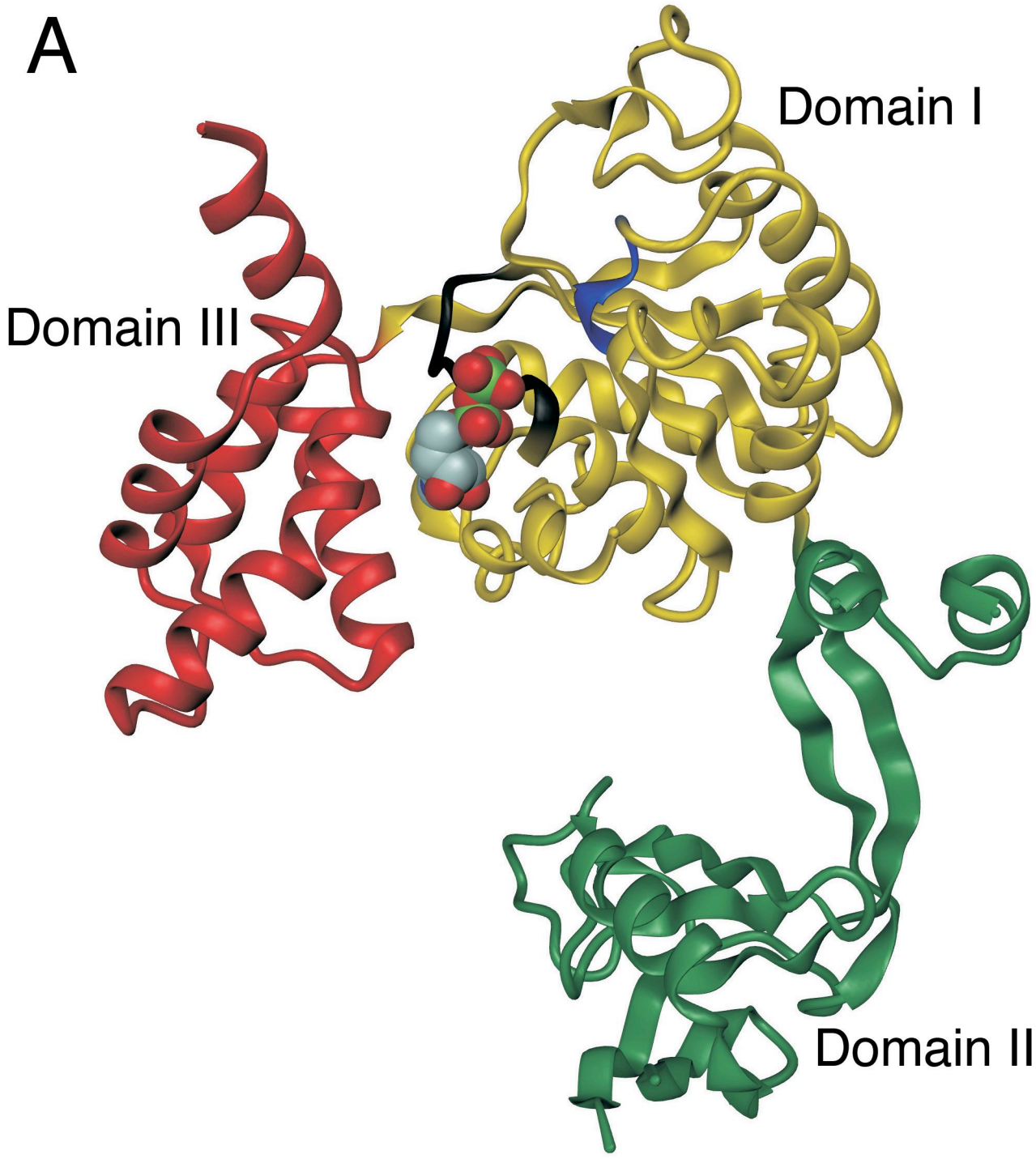
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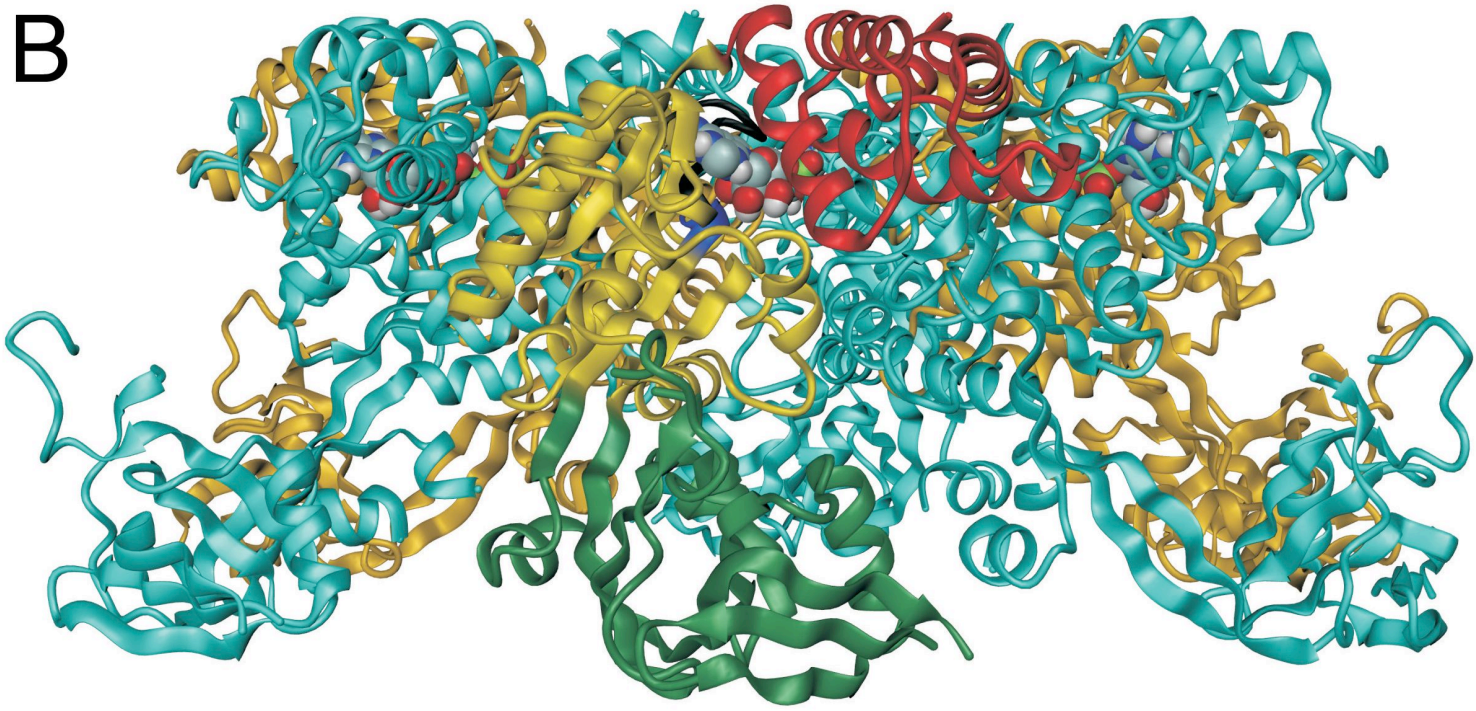
Domain I
Domain III
Domain II

B



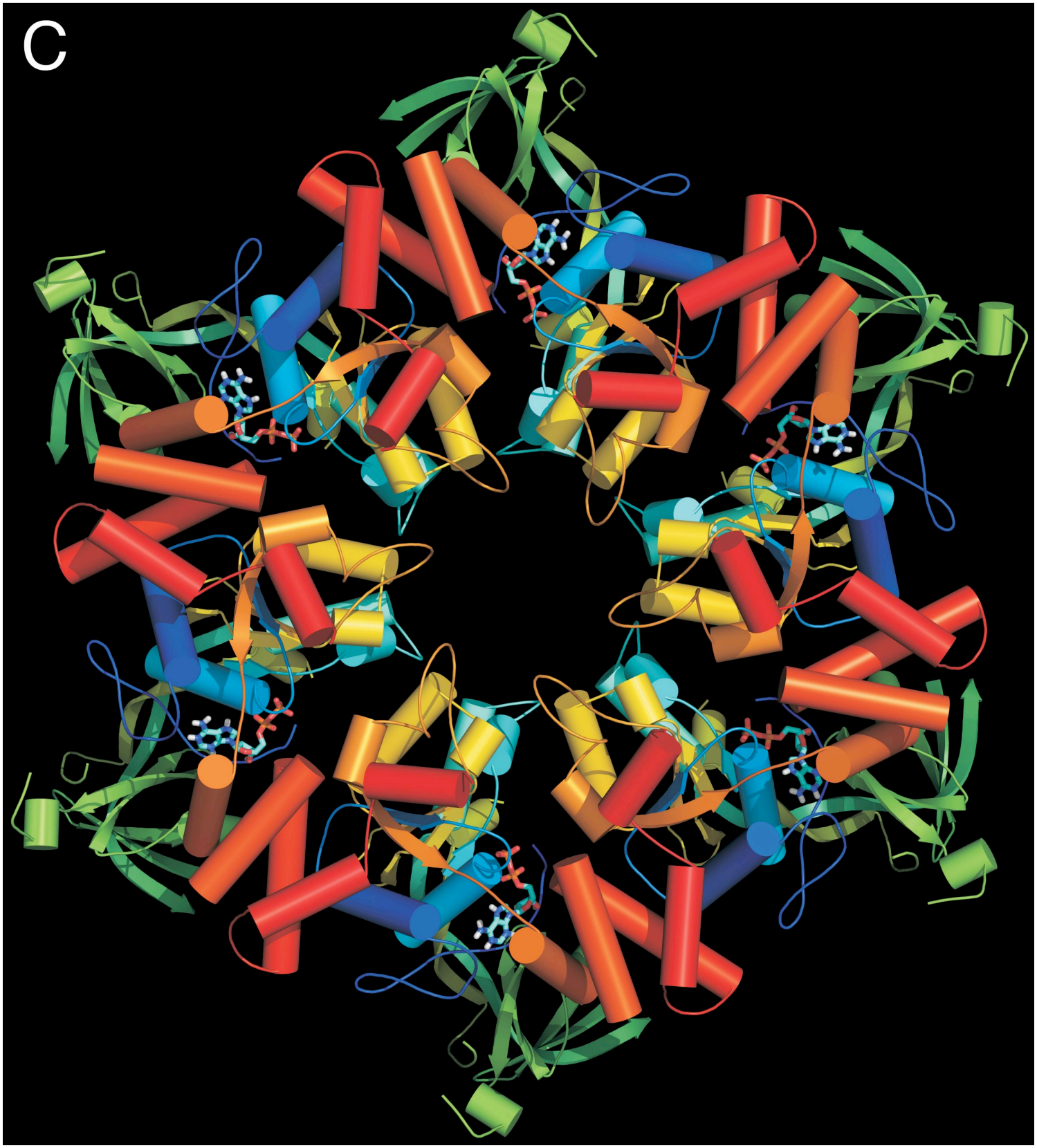
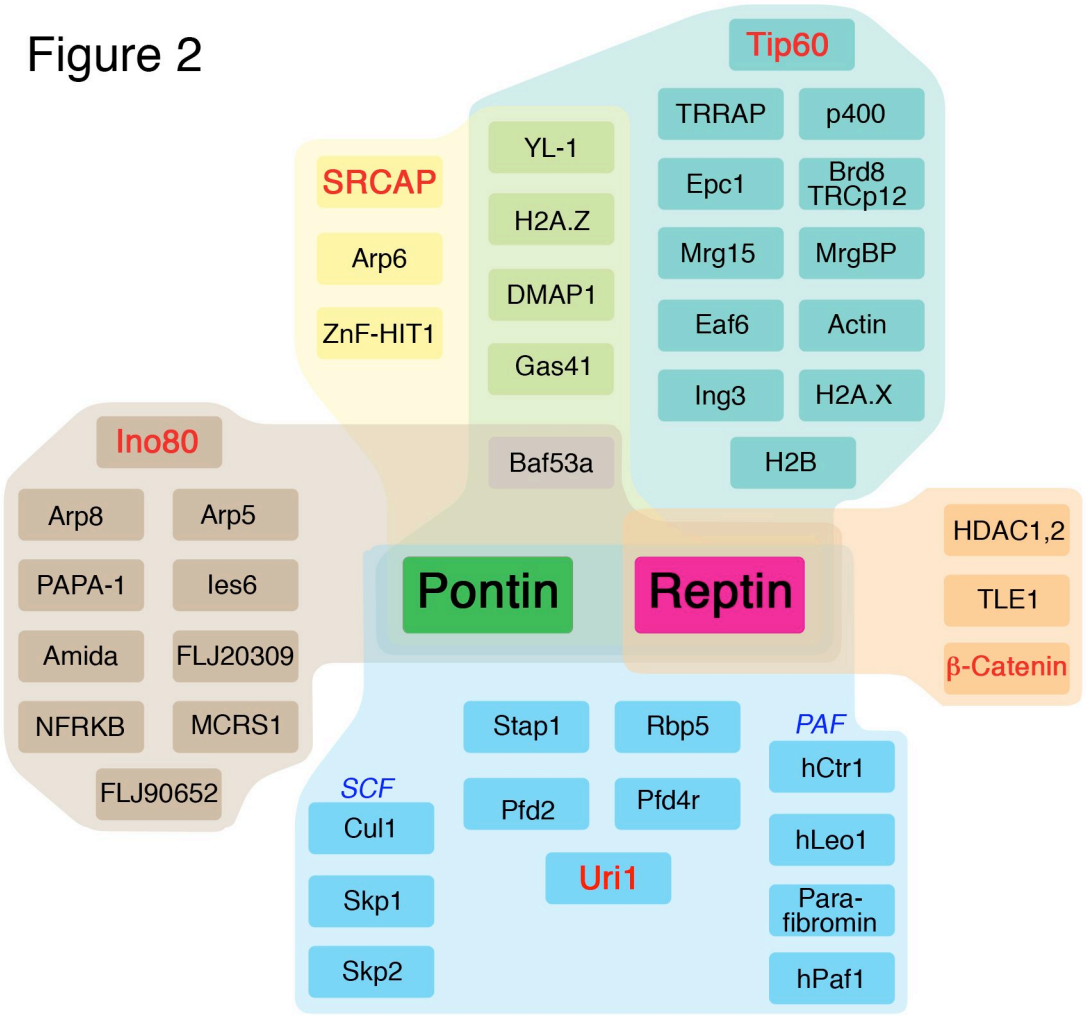

C

Figure 2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Actin
Ing3
H2A.X
H2B
SRCAP
Arp6
ZnF-HIT1
YL-1
H2A.Z
DMAP1
Gas41
Baf53a
Ino80
Arp8
Arp5
PAPA-1
Ies6
Amida
FLJ20309
NFRKB
MCRS1
FLJ90652
Pontin
Reptin
HDAC1,2
TLE1
β-Catenin
Stap1
Rbp5
PAF
hCtr1
SCF
Pfd2
Pfd4r
hLeo1
Cul1
Uri1
Skp1
Para-
fibromin
Skp2
hPaf1