C-terminal binding proteins: emerging roles in cell survival and tumorigenesis

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Within a cell, the levels and activity of multiple pro- and anti-apoptotic molecules act in concert to regulate commitment to apoptosis. Whilst the balance between survival and death can be tipped by the effects of single molecules, cellular apoptosis control pathways very often incorporate key transcription factors that co-ordinately regulate the expression of multiple apoptosis control genes. C-terminal binding proteins (CtBPs), which were originally identified through their binding to the Adenovirus E1A oncoprotein, have been described as such transcriptional regulators of the apoptosis program. Specifically, CtBPs function as transcriptional co-repressors, and have been demonstrated to promote cell survival by suppressing the expression of several pro-apoptotic genes. In this review we summarise the evidence supporting a key role for CtBP proteins in cell survival. We also describe the known mechanisms of transcriptional control by CtBPs, and review the multiplicity of intracellular signaling and transcriptional control pathways with which they are known to be involved. Finally we consider these findings in the context of additional known roles of CtBP molecules, and the potential implications that this combined knowledge may have for our comprehension of diseases of cell survival, notably cancer.

Discovery of CtBPs: cellular binding partners of transforming viral oncoproteins

Isolation of the cellular binding partners of the viral transforming oncoproteins has, historically, proven to be a fruitful approach for the identification of key cellular regulators of proliferation and survival. E1A proteins of type 2/5 adenoviruses, in particular, associate with multiple cellular proteins in order to reprogram cellular growth, survival and differentiation pathways to facilitate viral gene expression and replication.[1,2] E1A proteins are encoded by two exons; the first exon, which contains conserved regions that bind to the cellular proteins Rb and p300/CBP, is sufficient for E1A to co-operate with activated *ras* in baby rat kidney (BRK) cell co-transformation assays.[3,4] E1A truncation mutants lacking exon 2 are markedly more effective than wild type E1A in these assays, although intriguingly, the loss of these C-terminal sequences renders E1A unable to cooperate with Adenovirus E1B in transformation assays, or immortalize BRK cells in the absence of a co-operating oncogene.[3,5-7]

The region in exon 2 that conferred these effects was subsequently mapped to a 14 amino acid sequence in the C-terminus of the protein. CtBPs were identified as the cellular proteins that interact with a PxDLS peptide consensus within this sequence.[8-10] Further viral oncoproteins, EBNA3A and EBNA3C, also contain variants of this sequence and bind CtBPs, and EBNA3C requires CtBP-binding for co-transformation with mutant *ras.*[11,12] Reports identifying the presence of a functional CtBP-binding consensus sequence in the *Drosophila* transcriptional repressors, Hairy, Knirps and Snail,[13-15] were the first of many that have defined a normal cellular function of CtBPs as transcriptional co-repressors of DNA-binding transcription factors.[16,17]

CtBP structure and function

Gene and protein structure

In *Drosophila* there is a single *dCtbp* gene, whereas humans and mice have two CtBP-encoding genes, *Ctbp1 and Ctbp2*. In humans these map to chromosomes 4p16 and 10q26.13 respectively, the chromosomal location that was initially assigned.to CtBP2[10] having been one of a number of *Ctbp* pseudogenes. Transcripts from both *Ctbp1 and Ctbp2* are widely expressed in both adult tissue, and during development.[10,18-20] *Ctbp1* is expressed in a greater number of tissues and often at greater levels than *Ctbp2*.[18,20] Interestingly, *Ctbp2* expression patterns differ between human and mouse.[10] In retinal cells, use of an alternative, tissue-specific promoter in the first intron of the *Ctbp2* gene leads to the production of mRNA encoding the synaptic ribbon protein RIBEYE, which consists of a large, unique N-terminal domain fused to all but the N-terminal 20 amino acids of CtBP2.[21,22] Similarly, the protein originally identified as CtBP3/BARS in the rat,[23] and which is also expressed in human cells,[24] lacks the first 13 a.a. of CtBP1 and almost certainly represents an alternatively spliced transcript of the *Ctbp1* gene. For the purposes of this review, functions so far ascribed solely to CtBP3/BARS will be considered as potential characteristics of all CtBP proteins, whilst the specialised role of RIBEYE will not be discussed further.

The proteins encoded by *Ctbp1* and *Ctbp2* share 78% amino acid identity and 83% similarity.[10] They appear to function interchangeably, although evidence is emerging from analysis of mouse models and various post-translational modifications that their activity is differentially regulated.[19,25] CtBPs are characterized by a significant degree of homology between their central domain and NAD^+-dependent dehydrogenase enzymes (Figure 1). However, whilst CtBPs possess weak *in vitro* dehydrogenase activity, the significance of this remains unclear.[26,27] This

domain does however have an important role as a dimerization site, allowing the formation of homo- and hetero-dimers between CtBP1 and CtBP2.[20,26,28] Critically, dimerization is stimulated by the occupation of a dinucleotide-binding site within the domain,[26,27,29] the preferred ligand of which being NADH, which binds to the site with >100 fold higher affinity than NAD^+.[30,31]

The three-dimensional structure of CtBPs comprises a single globular domain formed by its N- and C-terminal regions, linked to the core dimerization domain through two flexible hinges.[26,28] Within this globular domain, the CtBP N-terminus contains a PxDLS peptide binding cleft, and the C-terminus has been proposed to play a regulatory role.[28,32] Notably, the conformational changes induced upon NADH binding are propagated to the N-terminus, and promote binding to E1A and other PxDLS containing proteins.[26,28] Importantly, a CtBP dimer has the potential to form the core of a complex containing two PxDLS-containing proteins.

CtBP functions in the nucleus and cytoplasm

Two distinct functions have been assigned to CtBP proteins – a nuclear role in the regulation of transcription, and a distinct function, thus far only directly ascribed to the CtBP3/BARS isoform, in regulating Golgi membrane maintenance. The role in transcription was first indicated by studies on E1A that showed when exon 1 of E1A is fused to a sequence-specific DNA-binding domain it activated transcription, and this activation is inhibited by the presence, in *cis*, of the CtBP-binding region of exon 2.[33] Subsequent fusion of CtBP itself to a DNA-binding domain provided direct evidence that CtBPs repress transcription.[15,34,35] A large number of DNA-binding transcriptional repressors have now been shown to recruit CtBPs, the majority, but not all,[36] containing a consensus PxDLS sequence[16,17,37]. The best characterized of these are the Snail,

Slug, and ZEB/δEF1 factors, which together recruit CtBPs to repress the expression of epithelial-specific genes in mesenchymal cells.[13,18,38-42] These, and other CtBP-recruiting factors with potential roles in the control of apoptosis, are discussed in more detail in subsequent sections.

CtBPs employ a number of mechanisms to regulate gene transcription, as summarized in Figure 2. The most extensively characterized mechanism whereby it acts as a transcriptional co-repressor is by the recruitment of a co-repressor complex, which includes class I histone deacetylases (HDACs) and histone methyltransferases (HMTs), and resulting in the co-ordinated modification of chromatin into a repressed state.[43] CtBPs can also recruit class II HDACs,[44] as well as repress transcription without HDAC involvement.[35,45] An additional mechanism whereby CtBPs appear to act as a co-repressor is by promoting the recruitment of Polycomb proteins to DNA.[20,46] These repress transcription through several mechanisms, including by compacting chromatin.[47] Finally, recent research has also determined that CtBPs interact with histone acetyltransferase (HAT) co-activators such as p300, CBP and pCAF and prevents their interaction with chromatin.[48]

Independently of its role in regulating transcription, CtBP (in the form of CtBP3/BARS) was cloned as a protein involved in the disassembly of the Golgi complex.[23] CtBP3/BARS is able to induce the breakdown of tubular Golgi networks.[49] It is responsible for driving the fission of Golgi membranes during mitosis and also plays a role in endocytic and exocytic pathways.[50-52] The distinct nuclear and cytoplasmic functions of CtBPs may be defined by the conformational shift induced by occupation of the dinucleotide binding site, with NADH driving CtBPs towards a nuclear function, and acyl-CoA, which also binds CtBPs, promoting the monomeric,

cytoplasmic form.[28,52] Ultimately, it will require the use of specific CtBP mutants to dissect the relative contributions of these distinct functions of CtBPs in cell proliferation and survival.

CtBP functional knockouts reveal key roles for CtBPs in differentiation, cell cycle progression and the suppression of apoptosis

Before considering the multiplicity of signaling pathways and transcription control networks that CtBPs are involved in, it is useful to review the effects of experimentally abrogating CtBP expression or function on the phenotype of the organism or the individual cell. Homozygous inactivation of the *dCtbp* gene in *Drosophila* is lethal, with embryos displaying severe defects in segmentation, consistent with a role for dCtBP in the function of Hairy, Knirps and Snail transcriptional repressors.[13-15] In *Xenopus* embryos, injection of mRNA encoding an xCtBP fusion protein designed to activate, rather than repress, transcription, resulted in similarly dramatic defects such as loss of head and/or eyes and a shortened anterior-posterior axis.[53] In murine development, homozygous deletion of *Ctbp1* results in mice which develop normally, but are smaller than heterozygotes.[19] *Ctbp2*$^{-/-}$ embryos exhibited multiple defects, including axial truncations and abnormal heart and brain development, and embryonic lethality occurred due to defects in extra-embryonic vascularization. Crosses between *Ctbp1*$^{+/-}$ and *Ctbp2*$^{+/-}$ revealed further developmental defects, with *Ctbp1*$^{-/-}$/*Ctbp2*$^{-/-}$ embryos showing the most severe phenotype.

Murine embryonic fibroblasts (MEFs) from *Ctbp1*$^{-/-}$/*Ctbp2*$^{-/-}$ embryos have been established, and immortalised with SV40 large T antigen. They have defects in CtBP-sensitive gene transcription,

but normal Golgi apparatus.[19] They are, however, hypersensitive to apoptosis in response to diverse stimuli including loss of cell-cell contact (anoikis), genotoxic chemotherapeutics, staurosporine, and Fas ligand.[54] Validated micro-array analysis showed two classes of genes to be constitutively up-regulated in these *Ctbp* null cells, and suppressed, by CtBP1 re-expression: those encoding epithelial-specific proteins including E-cadherin and several keratins, and pro-apoptotic proteins including PERP, PTEN, insulin-like growth factor binding proteins, Bax, Noxa and Id-1.[54] Together with separate evidence that siRNA-mediated CtBP 'knockdown' in human tumor cell lines is sufficient to induce apoptosis in the absence of any additional stress,[55] these data confirm previous indirect evidence from studies on E1A,[39] that CtBPs function as global repressors of the pro-apoptotic program.

The above studies attributed the effects of CtBP ablation on cellular phenotype to the transcriptional function of CtBPs. Interestingly, another group has independently knocked down CtBP expression in rat cell lines. Rather than apoptosis, they observed G_2 arrest, which they demonstrated to be consistent with the disruption of Golgi architecture.[50,52] Further clarification is undoubtedly warranted.

CtBP regulates multiple transcription factor networks with roles in tumorigenesis and survival

Whilst the precise mechanisms that link CtBPs to the suppression of pro-apoptotic gene expression programs remain essentially undefined, molecular studies have identified physical and functional involvement of CtBPs with numerous cellular transcription factors. Some of these

interactions that are likely to have particular relevance to cell survival pathways and tumorigenesis are reviewed in the following sections and summarized in Figure 3.

Repression of the epithelial phenotype

Negative regulation of the expression of epithelial-specific genes, and particularly those encoding E-cadherin, desmoglein-2, plakoglobin and various keratins, is perhaps the most well-characterized function of CtBP proteins. E-cadherin is a calcium-dependent membrane protein required for the formation of adherens junctions, which are essential for cell adhesion and intercellular interactions[56]. It interacts with the actin cytoskeleton via catenins to mediate cellular integrity, polarity and morphogenesis.[41,57,58] Loss of E-cadherin expression in epithelial cells is associated with an event referred to as epithelial-mesenchymal transformation (EMT). EMT is a major mechanism of vertebrate embryological tissue remodeling, which involves a switch in expression of epithelial- to mesenchymal cell specific genes, resulting in a characteristic motile, migratory mesenchymal phenotype.[59] EMT and loss of E-cadherin expression is also associated with disease progression, increased malignancy and poor prognosis in many epithelial tumors, including those of the colon, stomach, lung, bladder, oesophagus, prostate and breast.[60-66] Along with increased invasive properties, one of the key outcomes of EMT is a marked reduction in a cell's susceptibility to pro-apototic stimuli such as loss of cell-cell contact, growth factor withdrawal, and TNF-α.[39,67]

Activation of transcription from the *E-cadherin* promoter is driven by ubiquitously expressed, and constitutively active transcription factors. Its lack of expression in cells of mesenchymal origin is due primarily to the interaction of Snail, Slug and ZEB/δEF1 transcriptional repressors

to E-box elements within their promoters.[41,68] These repressors all contain PxDLS motifs which are required, at least in part, for their repressor activity.[15,18,42,69] Their expression and activity is regulated throughout development, and is important during carcinogenesis. Snail expression, for example, is predictive of poor prognosis in breast and hepatocellular carcinoma.[70-73] CtBPs can associate with the *E-cadherin* promoter in cells with a non-epithelial phenotype,[43] and down-regulation of CtBP activity, either by the C-terminus of E1A, or *Ctbp* gene disruption, results in changes in histone modifications at the *E-cadherin* promoter, and de-repression of *E-cadherin* transcription.[39,43,54] Interestingly, the protein pinin/DRS, which is known to promote the epithelial phenotype, binds CtBPs and relieves its repression of the *E-cadherin* promoter.[74]

One model that has been proposed, but not yet experimentally tested, is that the repression of pro-apoptotic genes by CtBPs may be an indirect consequence of EMT. Another factor to consider is the recruitment of CtBPs by Snail, Slug or ZEB/δEF1 to the promoters of other genes, such as *BRCA2*.[42] It will be of interest to establish whether CtBPs directly associate with the promoters of pro-apoptotic genes, as well as determining the effects of inhibiting CtBP expression in epithelial cells where these repressors are not expressed.

Wnt signaling

Some of the developemental defects observed following loss of CtBP function are suggestive of defects in the Wnt signaling pathway.[53] Binding of Wnt to its cell surface receptors results in the accumulation of free cytoplasmic β-catenin followed by its translocation to the nucleus, where it acts as a co-activator for TCF family transcription factors.[75] Constitutive activation of this pathway occurs in multiple human cancers, notably colorectal carcinoma where it is associated

with suppression of apoptosis.[76] In *Xenopus,* xCtBP was found to bind, and act as a co-repressor for xTCF-3, which functions as a transcriptional repressor in the absence of Wnt pathway activation.[53] In mammalian cells, CtBPs do not interact with TCFs, but rather bind the product of the *Adenomatous polyposis coli (APC)* gene.[77] This results in CtBP-mediated suppression of Wnt signaling by sequestering complexes of APC and β-catenin away from TCF transcription factors. In this context, therefore, CtBPs actually appear to play a role in promoting apoptosis and tumor suppression.

Transforming Growth Factor- β (TGF-β) signaling pathways

A common chromosomal translocation of a number of myeloid malignancies, including acute myeloid leukaemia, chronic myelogenous leukemia and myelodysplastic syndromes, results in the production of a fusion protein with AML1 and Evi-1, driven by the AML1 promoter.[78] Under normal conditions, Evi-1 is barely detectable in bone marrow and peripheral blood; however over-expression of AML1/Evi-1 is associated with transformation of haematopoietic stem cells. Evi-1 is a transcriptional repressor, and a negative regulator of (TGF-ß) signaling. Evi-1 acts on TGF-ß-mediated regulation of cellular proliferation and differentiation by repressing the TGF-β activated transcription factor, Smad3. Effective inhibition of TGF-β signaling and promotion of cellular transformation by both AML1/Evi-1 and Evi-1, is dependent upon their recruitment of CtBPs, through a PxDLS motif.[78-82]

TGF-β has a complex role in regulating apoptotic pathways, and can activate either pro- or anti-apoptotic pathways, depending on cell type.[83] Whilst the interaction with Evi-1 is consistent with an anti-apoptotic role for CtBPs,[84] CtBPs also interact with several other key components of

TGF-β signaling pathways that may also control cell survival. TGIF interacts with a TGF-β activated Smad complex to repress Smad-mediated transcription, this repression involves the recruitment of CtBPs by a PxDLS motif in TGIF.[85] The importance of the TGIF-CtBP interaction in human development is demonstrated by an inherited point mutation in the PxDLS motif in TGIF, which results in defects in craniofacial development.[85] CtBPs also interact with the inhibitory Smad, Smad6, which contributes to the repression of *Id-1* gene transcription.[86] *Id-1* is up-regulated in *Ctbp1*^{-/-}*Ctbp2*^{-/-} MEFs,[54] and can either induce or suppress apoptosis, depending on the cellular context.[87,88] CtBPs are also recruited to Smads indirectly through ZEB/δEF1 proteins, particularly ZEB-2, repressing TGB-β induced transcription.[89]

Growth factor receptor, and nuclear hormone receptor signaling

Ets protein family members are key transcriptional activating factors that transmit signals from growth factor-induced ras-signaling pathways to changes in gene expression, for example through their binding to the serum response element (SRE) on the c-fos promoter. Net is a somewhat atypical Ets family member in that, under certain conditions, it can also function as a transcriptional repressor. Criqui-Filipe *et al* [32] demonstrated that Net contains a CtBP binding site, and in the absence of serum growth factors it recruits CtBPs to actively repress transcription from SRE-dependent promoters.

Ligand-activated nuclear hormone receptors play a key role in regulating cell proliferation, differentiation, and survival in diverse tissue types. Typically, ligand binding to its receptor results in the recruitment of transcriptional co-activators to induce target gene expression. RIP140 is unusual in this respect, as it is recruited to most activated nuclear hormone receptors,

but acts as a transcriptional repressor. It appears to be essential for suppressing nuclear hormone receptor-induced transcription in certain tissues, to allow key processes such as ovulation and adipogenesis.[90] Recruitment of CtBPs by RIP140, which is regulated by acetylation of a lysine residue adjacent to the PxDLS sequence on RIP140,[36] plays an important role in the repressor activity of RIP140.[36,91]

C-terminal binding protein interacting protein (CtIP)

CtIP was originally identified as a PxDLS-containing binding partner for CtBP.[92] It is a large, 125 kDa nuclear protein that plays a complex role in transcriptional repression, cell cycle control and DNA damage responses. CtIP acts as a molecular bridge to recruit CtBPs to at least two known transcriptional repressors: the G_1 checkpoint regulator, Rb,[45] and the haemo-lymphoid factor, Ikaros.[93] In both cases, the CtBP-CtIP complex is thought to co-operate with these factors to co-repress target gene transcription. Mice with heterozygous inactivation of the *Ctip* gene show increased incidence of multiple tumor types, particularly large lymphomas. This is consistent with a tumor suppressor role for the protein, although the wild-type *Ctip* allele is not lost in the cancers.[94] However, homozygous *Ctip* gene inactivation results in lethality very early in mouse embryogenesis, with cells arresting prior to S phase, and also showing elevated levels of cell death. Experiments on cell lines showed this G_1 arrest to be Rb-dependent, and associated with elevated levels of the cyclin dependent kinase inhibitor, p21[WAF1].[94]

Potentially some of these effects of CtIP loss may be accounted for by its interaction with the BRCT domains of the BRCA1 protein.[95,96] BRCA1 is a well characterized tumor-suppressor protein that plays a central role in DNA damage response.[97,98] It has been reported that BRCA1

recruits the CtIP-CtBP complex to repress transcription of BRCA1 target genes such as *gadd45* and *WAF-1*, and that this association is disrupted following DNA damage,[99,100] although some of these findings have subsequently been disputed.[101,102] BRCA1–CtIP complex formation is critical for the DNA damage-induced G_2/M checkpoint, though the role of CtBPs in this is undetermined.[103]

Regulation of p53-dependent pro-apoptotic genes

P53 is a stress-activated transcription factor that plays a central role in the regulation of cell proliferation, and the induction of apoptosis.[104] Many of the genes up-regulated in *Ctbp1^{-/-}Ctbp2^{-/-}* MEFs are known transcriptional targets of the pro-apoptotic transcription factor p53, however CtBPs could repress their transcription independently of p53 function.[54] It seems likely that one consequence of repression of a distinct subset of p53-target genes by CtBPs would be to either dampen, or otherwise modify the cellular response to p53 activation.

CtBPs also directly suppress p53-dependent transcription through its interaction with the Hdm2 oncoprotein.[105] Hdm2 is the major cellular regulator of p53 protein function, inhibiting the interaction of p53 with transcriptional co-activators, and driving its export from the cytoplasm and degradation by the proteosome.[106] Hdm2 also recruits CtBPs to p53, repressing p53-dependent promoters such as *bax*.[105] This provides an additional mechanism whereby CtBPs suppress apoptosis in cells that retain a functional p53 stress-response pathway.

Regulation of CtBP function by stress and survival signaling pathways

In addition to interacting with the known components of signaling pathways described above, it is becoming clear that the activity of CtBPs themselves are regulated by post-translational modification and protein-protein interactions in response to a range of intracellular signals. In some cases, the associated changes in CtBP activity have a direct effect on cell survival.

Before the *Ctbp* genes were even cloned, their protein products were known to be phosphorylated in a cell-cycle dependent manner,[8] however the enzymes responsible, and the effect on CtBP function has yet to be clarified. Phosphorylation of CtBP does, however, play a key role in the induction of apoptosis in response to UV-irradiation activated stress-signaling. High doses of UV activate homoedomain interacting protein kinase 2 (HIPK2), an enzyme which has a known role in pro-apoptotic signaling through its phosphorylation and activation of p53.[107-109] HIPK2 phosphorylates CtBP1 at serine 422 (the site is conserved in CtBP2), which results in the targeting of CtBP1 for ubiquitin-dependent degradation by the proteosome.[55,110] The subsequent decrease in CtBP protein levels is sufficient to trigger apoptosis in p53 null cells, and either siRNA 'knockdown' of HIPK2, or over-expression of a serine 422 mutant of CtBP1 incapable of being phosphorylated, inhibits UV-induced apoptosis.

CtBPs are also regulated at the level of their subcellular distribution, with nuclear localization being required for transcriptional repressor activity. In most cell types examined, CtBP1 and CtBP2 are predominantly detectable in the nucleus. To some extent, this nuclear localization is a consequence of recruitment by PxDLS-containing transcription factors such as Net.[32] CtBP1 is also regulated at this level through two mutually exclusive modifications. SUMOylation at lysine

428 following interaction with the SUMO E3 ligases Pc2, PIAS1, or PIASxβ promotes nuclear localization of CtBP1, whereas interactions of its C-terminal PDZ domain with neuronal nitric oxide synthase (nNOS), and potentially other proteins, promotes cytoplasmic localization.[25,111,112] It is not yet clear whether CtBP2 localization and activity is similarly regulated, as the critical SUMOylation consensus site is not conserved, even though CtBP2 is also SUMOylated by Pc2.[112] Regulation of these interactions in response to cellular signaling has yet to be established. Signaling pathways downstream of growth factor tyrosine kinase receptors do, however, regulate CtBP subcellular localization. The kinase Pak1, which is activated by multiple growth factors including Heregulin and epidermal growth factor, phosphorylates CtBP1 at serine 158. This results in a transient exclusion of CtBP1 from the nucleus following growth factor stimulation.[113] This serine is conserved in CtBP2, but it is not yet known whether CtBP2 is similarly regulated. This effect is intriguing, given that these factors are associated with cell survival, rather than the induction of apoptosis, and suggest that transient exclusion of CtBPs from the nucleus may be required for certain responses to growth factor stimulation, and does not, in itself, induce apoptosis.

Probably the most interesting mechanism of regulation of CtBPs is the conformational change induced by occupancy of the dinucleotide binding site. NADH binding to CtBPs promotes both its dimerization and interaction with PxDLS-containing transcriptional repressors, and consequently promotes its ability to repress transcription from a set of target promoters.[29,31,44] Conversely, the NADH unbound form preferentially binds to Hdm2, which represses p53-dependent transcription,[105] and also to p300/CBP, with potentially broad ranging effects on p300-dependent gene transcription.[48] Levels of intracellular NADH show dramatic changes at

birth, in response to ethanol, cellular hypoxia, and in metabolic disease such as diabetes. Potentially, CtBPs may regulate broad-ranging changes in gene expression patterns in response to these alterations in cellular metabolism.

Future perspectives

CtBPs are clearly involved in numerous transcriptional regulatory programs and intracellular signaling pathways that regulate cell proliferation, differentiation and survival. Given that loss of CtBP expression induces either apoptosis or G_2 arrest, one might predict that cellular levels of CtBPs might be elevated in diseases of dysregulated proliferation and survival, such as cancer. However the pleiotrophic nature of CtBPs activities may complicate its role in carcinogenesis. Indeed, in one of the few published studies of CtBP protein expression in human primary cancers, CtBP1 levels were markedly reduced in malignant melanomas, compared to primary melanocytes.[114] This was found to be consistent with a role for CtBPs in suppressing the expression of MIA, a protein associated with malignant progression in this tumor type,[114,115] and highlights the need for further studies into CtBP expression patterns in other tumor types.

In contrast, microarray analysis of follicular thyroid carcinomas found a mean 3.6 fold increase in *Ctbp2* mRNA levels in a defined subset of these tumors.[116] Unfortunately, the commercial qPCR assay used to validate these findings recognises the unique exon 1 found in the *ribeye* transcript, and therefore the role of CtBP2 in these tumors remains to be confirmed. CtBPs are, however, ubiquitously expressed, and are detectable in the majority of cancer cell lines that have been examined. The finding that cells derived from *Ctbp1*^{-/-}*Ctbp2*^{-/-} embryos proliferate normally, whereas siRNA-mediated knockdown of CtBPs in cancer cell lines can induce

apoptosis, could have a number of explanations, one of which is that some of genetic changes associated with cellular transformation render cells more dependent on the suppression of pro-apoptotic genes by CtBPs. This would be entirely consistent with the original observations that full length E1A is required for cellular immortalization, whereas exon 2, which functions at least in part by preventing the interaction of CtBPs with cellular PxDLS containing transcription factors,[117] suppresses transformation in the presence of mutant *ras*.

In summary, CtBPs are clearly key regulators of both gene transcription and organelle assembly. They have been implicated in the context of a striking number of transcriptional regulatory networks, and intracellular signaling pathways. They play an essential pro-survival role in tumour-derived cells, though, intriguingly the mechanism basis of this critical function remains to be clarified. Further studies will undoubtedly shed light on these multifaceted molecules.

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Fig 1
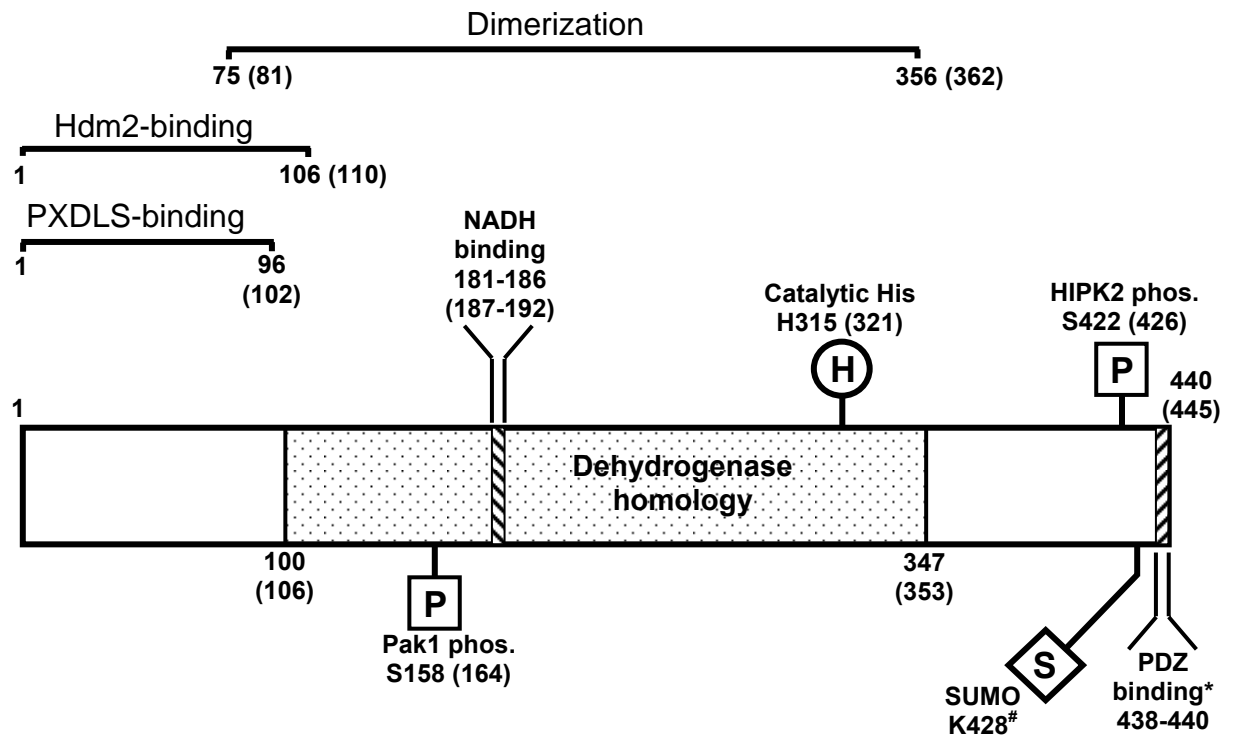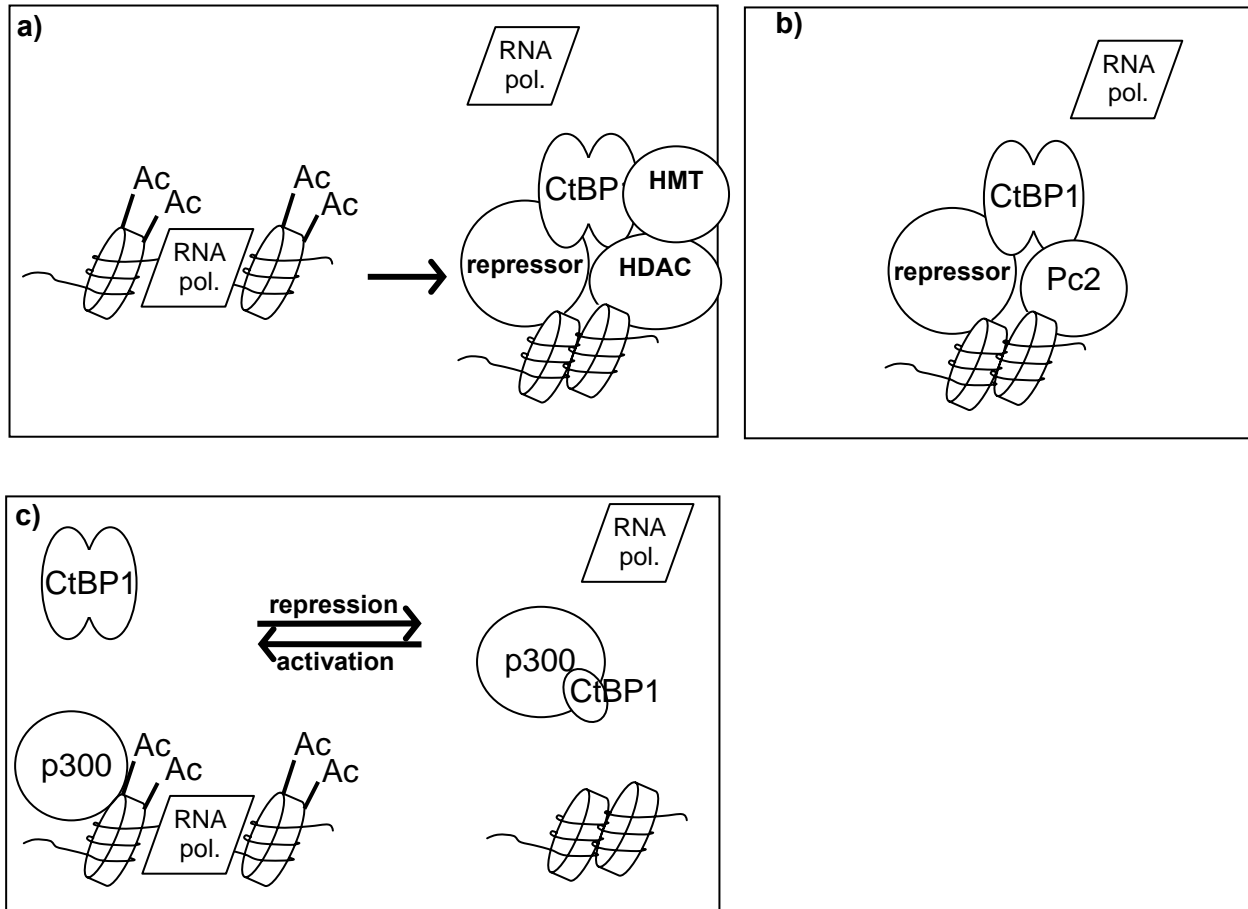

Fig 2

Fig 3