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Review

Cellular functions of TIP60

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Abstract

TIP60 was originally identified as a cellular acetyltransferase protein that interacts with HIV-1 Tat. As a consequence, the role of TIP60 in transcriptional regulation has been investigated intensively. Recent data suggest that TIP60 has more divergent functions than originally thought and roles for TIP60 in many processes, such as cellular signalling, DNA damage repair, cell cycle and checkpoint control and apoptosis are emerging. TIP60 is a tightly regulated transcriptional coregulator, acting in a large multiprotein complex for a range of transcription factors including androgen receptor, Myc, STAT3, NF- κ B, E2F1 and p53. This usually involves recruitment of TIP60 acetyltransferase activities to chromatin. Additionally, in response to DNA double strand breaks, TIP60 is recruited to DNA lesions where it participates both in the initial as well as the final stages of repair. Here, we describe how TIP60 is a multifunctional enzyme involved in multiple nuclear transactions.

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Keywords: TIP60; MYST; Acetylation; Transcription; Coregulator

Contents

1. Introduction	00
2. HTATIP gene	00
3. Acetyltransferase activity	00
4. TIP60 complex	00
5. Cytoplasmic TIP60	00
6. Involvement in transcription	00
6.1. Nuclear receptor coactivation and involvement in prostate cancer	00
6.2. Involvement of TIP60 in myc signalling	00
6.3. TIP60 and amyloid- β precursor protein signalling	00

Abbreviations: AICD, amyloid precursor protein intracellular domain; AR, androgen receptor; ATM, Ataxia Telangiectasia Mutated; BAF53, 53 kDa BRG-1/human BRM-associated factor; Esa1, essential Sas family acetyltransferase 1; HAT, histone acetyltransferase; HDAC, histone deacetylase; HIV-1, human immunodeficiency virus type 1; ING3, inhibitor of growth 3; IL-1 β , interleukin 1 β ; Mdm2, mouse double minute 2; Myc, myelocytomatosis oncogene c; MYST, MOZ-Ybf2/Sas3-Sas2-TIP60; NR, nuclear receptor; NuA4, nucleosome acetyltransferase of H4 complex; PHD, plant homeodomain; RuvBL1/2, RuvB-like protein 1/2; SWR1, Swi2 ATPase domain related 1 complex; STAT3, signal transducer and activator of transcription 3; TIP60, Tat-interactive protein 60 kDa; TRRAP, transformation/transcription domain associated protein

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6.4. Involvement of TIP60 in NF- κ B signalling	00
6.5. Involvement of TIP60 in E2F transcription	00
6.6. Involvement of TIP60 in other transcriptional processes	00
6.7. TIP60 as a corepressor of transcription	00
7. Regulation of TIP60 protein	00
8. Involvement of TIP60 in the p53 pathway	00
9. Role of TIP60 in apoptosis	00
10. TIP60 and DNA double strand break response	00
11. TIP60 involvement in the mitotic checkpoint	00
12. Concluding remarks	00
Acknowledgements	00
References	00

1. Introduction

Acetyltransferases are enzymes that catalyse the transfer of acetyl groups from acetyl coenzyme A to either the α -amino group of N-terminal amino acids or the ϵ -amino group of internal lysine residues. N-terminal acetylation occurs during translation in the majority of eukaryotic proteins. Lysine acetylation is a post-translational modification that affects many protein functions, including DNA binding, protein–protein interactions, enzymatic activity and stability (Polevoda & Sherman, 2002). A multitude of proteins are modified by lysine acetylation, including histones, high mobility group (HMG) proteins, transcription factors and nuclear import factors (Polevoda & Sherman, 2002). The best characterised examples of lysine-acetylated proteins are histones. Histone acetylation regulates chromatin accessibility and in combination with other post-translational modifications, creates a multisite modification code (histone code), which is recognised by transcriptional proteins in order to regulate transcription (Strahl & Allis, 2000; Turner, 2002).

Lysine acetyltransferases fall into several categories, one of which is the MYST family, named after its founding members: MOZ, Ybf2/Sas3, Sas2 and TIP60. MYST family members function in a broad range of biological processes, such as gene regulation, dosage compensation, DNA damage repair and tumorigenesis (Utley & Cote, 2003). Although MYST proteins seem to have diverse cellular roles, all family members are characterised by the highly conserved MYST acetyltransferase domain and most MYST enzymes exist as the catalytic subunits of multiprotein complexes.

TIP60, one of the best characterised MYST proteins, is a human homologue with relevance to human pathology. This review will summarise what is known about Tat-interactive protein 60 kDa (TIP60), focusing on its involvement in transcription and DNA damage response.

2. HTATIP gene

TIP60 was originally isolated as a HIV-1 Tat interactive protein (Kamine, Elangovan, Subramanian, Coleman, & Chinnadurai, 1996). The HTATIP gene encoding TIP60 is located at 11q13.1 and consists of 14 exons. Alternative splicing results in the expression of at least three splice variants, TIP60 isoform 1, TIP60 isoform 2 (TIP60 α) and TIP60 isoform 3 (TIP60 β , PLA2 interacting protein, PLIP). The best characterised splice variant is isoform 2. Isoform 1 arises from translation of intron 1 and encodes for a novel protein with potentially distinct functions (Legube & Trouche, 2003). Isoform 3 (TIP60 β) results from the exclusion of exon 5 that encodes a proline-rich region (Ran & Pereira-Smith, 2000) and appears to have similar properties as TIP60 α (Sheridan et al., 2001). TIP60 isoforms are expressed at relatively low levels in a broad variety of tissues and cells and exhibit cell type specific functions (Hlubek et al., 2001). HTATIP homologues have been identified in various organisms, including *G. gallus*, *M. musculus* and *D. melanogaster*, which encode proteins that share considerable homology with human TIP60 (57–99%) (McAllister, Merlo, & Lough, 2002).

TIP60 isoform 2 (TIP60 α) encodes a 513 amino acid protein (58 kDa), which contains an N-terminal chromodomain and a C-terminal conserved MYST domain (Fig. 1). Chromodomains are present in many chromatin regulatory proteins and are thought to mediate interactions with methylated histone lysines or RNA molecules, although in the case of TIP60 the chromodomain may have yet unidentified functions (Akhtar, Zink, & Becker, 2000; Utley & Cote, 2003). The MYST domain is the catalytic domain and contains a short sequence (residues 335–404, ‘conserved HAT domain’), which binds to acetyl coenzyme A and the substrate (Section 3) and which is structurally conserved within other acetyltransferase families. The MYST domain also

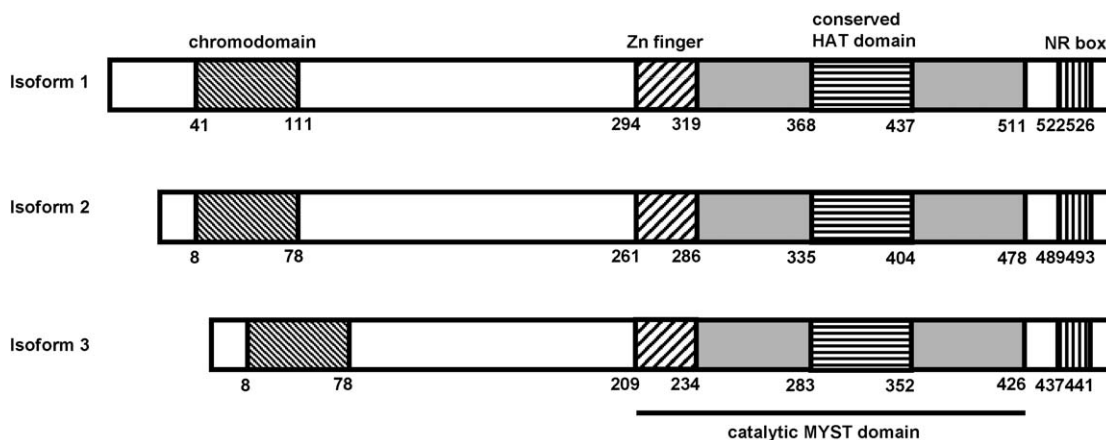


Fig. 1. Schematic diagram of TIP60 protein domains. Isoform 2 (Accession Number: NP_006379) is the best characterised TIP60 isoform. Isoform 1 (Accession Number: NP_874369) encodes additional 33 amino acids at the N-terminus, while isoform 3 (Accession Number: NP_874398) results from the exclusion of 52 amino acids between the chromodomain and the MYST domain.

contains a Cys-Cys-His-Cys zinc finger, which is essential for acetyltransferase activity and is required for protein–protein interactions (Nordentoft & Jorgensen, 2003; Xiao, Chung, Kao, & Yang, 2003). At the extreme C-terminus of TIP60 α lies a short nuclear receptor (NR)-interaction box (Gaughan, Brady, Cook, Neal, & Robson, 2001). As most of the published data have utilised TIP60 α , ‘TIP60’ will denote TIP60 α , unless otherwise stated.

3. Acetyltransferase activity

Shortly after its discovery it became evident that TIP60 possesses histone acetyltransferase (HAT) activity. Recombinant TIP60 acetylates core histones H2A (Lys5), H3 (Lys14) and H4 (Lys5, Lys8, Lys12 and Lys16) *in vitro*; Kimura & Horikoshi, 1998; Yamamoto & Horikoshi, 1997). When in a stable multiprotein complex, TIP60 can also modify *in vitro* histones assembled into nucleosomes; in this case, TIP60 selectively targets nucleosomal H2A and H4 (Ikura et al., 2000). Recent evidence from *D. melanogaster* indicates that TIP60 can also acetylate modified histone variants, such as phospho-H2Av at Lys5 (Kusch et al., 2004).

Apart from histones, cellular TIP60 can acetylate transcription factors, such as androgen receptor (AR), upstream binding transcription factor (UBF), myelocytomatosis oncogene c (c-Myc) (Gaughan, Logan, Cook, Neal, & Robson, 2002; Halkidou, Logan, Cook, Neal, & Robson, 2004; Patel et al., 2004) and the kinase Ataxia Telangiectasia mutated (ATM) (Sun, Jiang, Chen, Fernandes, & Price, 2005).

The catalytic mechanism of lysine acetylation by a MYST enzyme has been studied in detail *in vitro* in the

case of the TIP60 orthologue in *Saccharomyces cerevisiae*, essential Sas family acetyltransferase 1 (Esa1). The catalytic core of MYST proteins adopts a similar structural fold to that of other lysine acetyltransferases, such as the general-control-non-depressible-5-related *N*-acetyltransferases (GNAT) family, in which a conserved Glu residue (Glu403 in *H. sapiens*, Accession Number: NP_006379) functions to deprotonate the substrate Lys residue (Yan, Barlev, Haley, Berger, & Marmorstein, 2000). However, MYST proteins catalyse the transfer of the acetyl group to the substrate Lys via a distinct ‘ping-pong’ mechanism, whereby a conserved Cys residue of the MYST enzyme (Cys369 in *H. sapiens*) forms an enzyme-acetyl intermediate which is in turn targeted by the deprotonated substrate Lys residue by nucleophilic attack to form acetylated Lys (Yan, Harper, Speicher, & Marmorstein, 2002).

In vitro studies of lysine site specificity of TIP60 in histones suggest that there is no apparent ‘consensus’ motif for substrate recognition by TIP60. Although TIP60 preferentially acetylates histone lysines that are preceded by Gly or Ala residues, there exist similar sequences that are not targeted by TIP60 (Kimura & Horikoshi, 1998).

4. TIP60 complex

Depending on the cellular process in which it participates, TIP60 forms distinct transient complexes with the appropriate binding partners. However, the majority of cellular TIP60 exists in a stable nuclear multiprotein complex (Table 1) that consists of at least 18 subunits and performs most transcriptional and DNA damage-related TIP60 functions.

Table 1

Components of TIP60 complex in *H. sapiens* (*H.s.*) and homologous complexes from *D. melanogaster* (*D.m.*) and *S. cerevisiae* (*S.c.*) (NuA4)

<i>H.s.</i> complex	<i>D.m.</i> complex	<i>S.c.</i> complex	Function
TIP60	dTIP60	Esa1	Acetyltransferase
TRRAP	dTra1	Tra1	PIKK domain, component of Hat complexes
Actin	Act87E	Act1	ATPase, cytoskeleton
BAF53a	BAP55	Arp4	Actin related, DNA repair
p400/Domino	Domino	Eaf1/Swr1 ^a	SWI2/SNF2-like ATPase
RuvBL1	dPontin	Rvb1 ^a	Helicase/ATPase?
RuvBL2	dReptin	Rvb2 ^a	Helicase/ATPase?
Mrg15	dMrg15	Eaf3	Chromo domain, senescence
MrgX		Eaf3	Chromo domain, senescence
MrgBP	dMrgBP	Eaf7	
Epc1	E(Pc)	Epl1	Transcription control, silencing
Epc-like protein			Transcription regulation
ING3	dIng3	Yng2	PHD finger domain, growth inhibitor, apoptosis
Brd8/TRCp120	dBrd8	Bdf1 ^a	Bromo domain, TR coactivator
YL-1	dYL-1	Vps72 ^a	Chromatin remodelling
DMAP	dDMAP1	Eaf2	SANT domain, DNA replication
Gas41	dGas41	Yaf9	YEATS domain, cell viability
FLJ11730	dEaf6	Eaf6	
(H2A.X/H2A.Z)	H2Av	H2A/H2A.Z ^a	Histones
(H2B)	H2B	H2B ^a	Histones

The presence of H2A.X/H2A.Z and H2B has not yet been confirmed in the human complex.

^a Denotes subunits of the distinct SWR1 complex in yeast. PIKK domain: phosphatidylinositol kinase-related kinase, chromo: chromatin organisation modifier, PHD: plant homeodomain, SANT: SWI3-Ada2-NCOR-TFIIB domain, YEATS: YNK7-ENL-AF9-TFIIF small subunit domain, TR: thyroid receptor (Doyon & Cote, 2004; Kusch et al., 2004).

Central to the TIP60 stable complex is the scaffold protein transformation/transcription domain-associated protein (TRRAP) (Ikura et al., 2000), which is present in other acetyltransferase complexes, e.g. p300/CBP associated factor complex (PCAF) (Carrozza, Utley, Workman, & Cote, 2003). Another essential component of the complex is p400/Domino, an ATPase that has chromatin remodelling activity (Ikura et al., 2000). BAF53 (53 kDa BRG-1/human BRM-associated factor) and actin are also present in the TIP60 complex (Ikura et al., 2000). BAF53 contains an actin-related domain that may have histone chaperone activity. The yeast orthologue of BAF53 is responsible for recruiting chromatin modifying complexes to damaged DNA. The putative helicases RuvBL1 and RuvBL2, related to the bacterial DNA repair RuvB protein, are also subunits of the complex. The TIP60 complex has helicase activity, which, however, is not attributable to RuvBL1/2 (Ikura et al., 2000). The complex contains inhibitor of growth 3 (ING3), which comprises plant homeodomain (PHD) fingers, domains that are commonly found in chromatin modifying complexes (Doyon, Selleck, Lane, Tan, & Cote, 2004). ING3 is also involved in DNA damage-responsive p53 transcription, supporting a role of TIP60 in DNA damage signalling and apoptosis (see Sections 8 and 9). The TIP60 complex contains

two further chromodomain-containing protein, mortality factor 4 related gene 15 (Mrg15) and mortality factor 4 related gene X (MrgX). These proteins, as well as glioma amplified sequence 41 (Gas41) are involved in regulation of cell proliferation, viability and senescence. The novel protein Mrg-binding protein (MrgBP) is also a subunit of the complex (Cai et al., 2003). In addition, the bromo-protein bromodomain containing protein 8/thyroid receptor coactivator protein 120 kDa (Brd8/TRCp120) is present in the complex, which is homologous to yeast chromatin remodelling proteins that bind modified histones (Cai et al., 2003; Doyon et al., 2004). This complex also contains the DNA replication protein DNA methyltransferase associated protein 1 (DMAP1) that has SWI3-Ada2-NCOR-TFIIB (SANT) domains that bind to histone tails (Cai et al., 2003; Doyon et al., 2004). Other components of the complex are enhancer of polycomb 1 (EPC1) and EPC1-like (Cai et al., 2003), which are involved in transcription and in the case of the homologous *D. melanogaster* complex, histones H2A.v and H2B (Kusch et al., 2004). The complexes of TIP60 α and TIP60 β are identical (Doyon et al., 2004).

Similar TIP60 complexes have been identified in other organisms, such as *D. melanogaster* and possibly *C. elegans* (Ceol & Horvitz, 2004; Kusch et al.,

2004). The TIP60 complex could be the metazoan functional equivalent of two distinct complexes in budding yeast, one harbouring HAT activity (NuA4) and another involved in ATP-dependent chromatin remodelling (SWR1) (Doyon & Cote, 2004). Supporting this hypothesis, the human complex shares components with the SNF2-related chromatin remodelling complex SRCAP (Cai et al., 2005; Doyon et al., 2004).

The yeast complex NuA4 is essential for viability (Clarke, Lowell, Jacobson, & Pillus, 1999), however, this has not been tested in the case of *D. melanogaster* or *C. elegans*.

5. Cytoplasmic TIP60

Both TIP60 α and TIP60 β are predominantly nuclear proteins involved in nuclear processes (Cao & Sudhof, 2001; Gavaravarapu & Kamine, 2000; Ran & Pereira-Smith, 2000; Yamamoto & Horikoshi, 1997). However, in some cases TIP60 has been found to localise in the cytoplasm in association with internalised membrane receptors thus regulating downstream kinase pathways or gene expression. For example, TIP60 is involved in interleukin-9 (IL-9) signalling, a cytokine promoting proliferation, growth regulation and inhibition of apoptosis. TIP60 interacts with interleukin-9 receptor (IL-9R) as well as its downstream transcription factor signal transducer and activator of transcription 3 (STAT3) in the cytoplasm (Sliva, Zhu, Tsai, Kamine, & Yang, 1999; Xiao et al., 2003). IL-9 stimulation then targets the STAT3–TIP60 complex into the nucleus, where TIP60 is believed to recruit HDAC7 to STAT3-regulated promoters and thus repress transcription. TIP60 and HDAC7 also interact with the C-terminus of internalised endothelin receptor A (ETA) in the perinuclear compartment in response to endothelin 1 (ET-1), a vasoconstrictive peptide that controls gene expression, differentiation and secretion. This interaction with ETA results in stimulation of downstream signalling pathways, such as mitogen activated protein kinase (MAPK) (Lee, Chun, & Kandror, 2001).

Although TIP60 can be found in the cytoplasm, the mechanisms governing its nuclear-cytoplasmic shuttling are largely unknown. One might speculate that TIP60 translocation is dependent on specific binding of unidentified partners and that it is regulated by various intra- or extracellular stimuli including cytokines and hormones (Section 6.1) (Halkidou et al., 2003; Sliva et al., 1999). The mechanism by which the nuclear multiprotein TIP60 complex is assembled is also unclear, although it has been suggested that the high molecular weight TRRAP protein, present in acetyltransferase complexes includ-

ing the TIP60 complex, may act as a molecular scaffold, thereby assisting in protein–protein complexing.

6. Involvement in transcription

6.1. Nuclear receptor coactivation and involvement in prostate cancer

Soon after its discovery, TIP60 was found to be involved in nuclear receptor (NR) signalling and to be a NR-coregulator. TIP60 binds to the ligand binding domain of AR and other NRs via a single NR-box that comprises the Leu-X-X-Leu-Leu motif near the TIP60 C-terminus and thus coregulates NR mediated gene expression (Brady et al., 1999; Gaughan et al., 2001). TIP60 predominantly coactivates NR transactivation of genes, although there have been reports of TIP60-dependent NR corepression (Sharma, Zarnegar, Li, Lim, & Sun, 2000). AR can be acetylated by TIP60 and this acetylation event is essential for TIP60-dependent AR coactivation. TIP60 forms a ternary complex with histone deacetylase 1 (HDAC1) and AR on AR-regulated promoters and competes with HDAC1 potentially by inducing changes in AR acetylation status (Gaughan et al., 2002).

The fact that TIP60 is involved in AR signalling suggests that it may be important for prostate cancer development. AR signalling is central to normal prostate development and carcinogenesis. Tumour growth is initially androgen dependent and the most common treatment is androgen ablation, sometimes accompanied by prostatectomy or radiotherapy. However, many patients fail this therapy and die of recurrent ‘androgen-independent prostate cancer’ (AIPC) (reviewed in (Feldman & Feldman, 2001)). AIPC is a lethal form of the disease and at present, no effective treatment is available. Little is known about the molecular mechanisms that underlie cancer initiation/progression and AIPC development. AIPC could arise when more AR is produced by gene amplification or AR has increased sensitivity to low residual levels of testosterone or cells increase the metabolism of testosterone into more potent androgens. Alternatively, non-androgenic steroid molecules that are normally present in the circulation may activate AR. This may result from AR mutations or modulation of AR coregulatory proteins. In addition, AR could be activated hormone-independently by kinase pathways, such as downstream cascades of growth factors. Also, parallel pathways may circumvent AR signalling completely, thus obviating the need for AR for cell proliferation. Finally, androgen independent cells that were present during early stages of prostate develop-

ment could be clonally selected during androgen ablation and lead to androgen independent tumours (Feldman & Feldman, 2001).

Interestingly, TIP60 localisation and protein levels appear to be hormone dependent. In normal prostate tissue, in the presence of interleukin 1 β (IL-1 β), TIP60 antagonises the pro-metastatic Wnt/ β -catenin dependent signalling. In metastatic prostate cancer cells, this function of TIP60 is lost (Kim et al., 2005), expression of TIP60 protein is decreased and TIP60 localisation is more diffuse (Halkidou et al., 2003). Surprisingly, upon androgen ablation, TIP60 stabilises and accumulates in the nucleus as shown in prostatic cancer cell lines grown in steroid depleted media, human prostate cancer xenografts and in AIPC biopsies (Halkidou et al., 2003). This led to the hypothesis that in androgen ablated cells TIP60 could be activating AR in a ligand-independent manner and suggests a putative role of TIP60 in the molecular pathway leading to the development of AIPC via AR dysregulation.

6.2. Involvement of TIP60 in myc signalling

The Myc family of transcription factors plays a direct role in G1/S progression by regulating genes required for growth and DNA replication as well as apoptosis and is among the most frequently disrupted networks in cancer. The TRRAP–TIP60 complex acts as a dual cofactor for Myc transcription factors: TIP60 can directly acetylate and stabilise c-Myc (Patel et al., 2004), but in addition, TIP60 can be recruited to Myc-dependent promoters and enhance Myc transactivation efficiency independently of Myc acetylation (Frank et al., 2003). Viral proteins, such as HTLV-1 p30^{II} utilise TIP60 coactivation to regulate c-Myc function partly through interactions with the TIP60 complex (Lang & Hearing, 2003).

6.3. TIP60 and amyloid- β precursor protein signalling

Amyloid- β precursor protein (APP) is a ubiquitous transmembrane protein involved in the pathophysiology of Alzheimer's disease. APP is processed by successive proteolytic cleavage carried out by specific secretases, which generate amyloid- β peptides that aggregate to form plaques in patients with Alzheimer's disease as well as small cytoplasmic peptides, such as the APP intracellular domain (AICD), which is involved in transcriptional regulation.

AICD forms a complex with TIP60, the transcriptional protein Fe65, the nuclear assembly factor SET and 14-3-3 γ (Cao & Sudhof, 2001, 2004; Sumioka et al.,

2005; Telese et al., 2005). This complex stimulates histone acetylation (Kim et al., 2004) and coactivates gene promoters which are linked to apoptosis and neurotoxicity (Kinoshita, Whelan, Berezovska, & Hyman, 2002). However, recent evidence have cast doubt on the exact role of TIP60 in this complex as, in some cases TIP60 appears to be redundant or even acts as a Fe65 corepressor (Sumioka et al., 2005; Yang Cool, Martin, & Hu, 2006). One example of an AICD/Fe65 regulated promoter is the IL-1 β /NF κ B regulated tetraspanin (*KAI1*) gene promoter, where the AICD/Fe65 complex acts by antagonising complexes containing HDAC activity, such as nuclear corepressor (NCoR) complexes (Baek et al., 2002). The AICD/Fe65 complex also appears to regulate the APP and HTATIP genes, thereby establishing a positive feedback loop. AICD also forms separate complexes with TIP60 and the adaptor protein JNK-interacting protein 1b (Jip1b) (von Rotz et al., 2004).

In a similar manner to AICD, TIP60/Fe65 forms transcription-regulatory complexes with the cytoplasmic fractions of other transmembrane proteins that are processed by proteolytic cleavage, such as the low density lipoprotein receptor related protein (LRP) and the amyloid- β precursor like proteins 1, 2 (APLP1/2) (Kinoshita, Shah, Tangredi, Strickland, & Hyman, 2003; Li & Sudhof, 2004).

6.4. Involvement of TIP60 in NF- κ B signalling

The transcription factor nuclear factor kappa light chain gene enhancer in B cells (NF- κ B) is a homo- or heterodimeric transcription factor that consists of members of the Rel family (Rel-A/p65, REL-B, c-Rel, p50 and p52) and controls processes, such as immunity, inflammation, proliferation and apoptosis. TIP60 acts as a coactivator of certain NF- κ B-regulated genes via distinct mechanisms. As mentioned above, the *KAI1* promoter is repressed by a corepressor complex in unstimulated cells. This corepressor contains subunits, such as NCoR, HDAC3 and TAK1 binding protein 2 (TAB2) (Baek et al., 2002). In response to cytokines, such as IL-1 β , the NCoR complex is phosphorylated and exported from the nucleus, thus allowing a TIP60 coactivating complex to bind and derepress the *KAI1* promoter. This TIP60 complex contains TRRAP and is recruited to p50 complexes bound to the promoter via interactions with the NF- κ B adaptor protein B-cell leukaemia/lymphoma 3 (Bcl3). Alternatively, overexpressed TIP60, Fe65 and AICD can directly displace NCoR and activate transcription of *KAI1* even in the absence of extracellular stimulus (Baek et al., 2002; Dechend et al., 1999; Kim et al., 2005).

6.5. Involvement of TIP60 in E2F transcription

Cell cycle progression in higher eukaryotes is tightly regulated by the E2F family of transcription factors, which consists of three ‘activating’ factors, E2F1/2/3 and two ‘repressive’ factors E2F4/5. E2F factors are tightly regulated by interactions with the repressive ‘pocket proteins’, such as Retinoblastoma protein (Rb). Phosphorylation of pocket proteins by cyclin dependent kinase 2 (cdk2) complexes leads to derepression of E2F1-3 and cell cycle progression. Once activated, E2F1-3 factors bind to the promoters of their target genes, in which chromatin is acetylated at H3 and H4. TIP60 complexes containing TRRAP, RuvBL1/2 and p400 are recruited to target gene promoters by E2F1 and are responsible for the H4 acetylation observed in several E2F responsive genes, such as the pocket protein p107, proliferating cell nuclear antigen (PCNA), minichromosome maintenance 3/4 (MCM3 and MCM4) (Taibert et al., 2004). In addition, E2F, in cooperation with the transcription factors specificity protein 1/3 (Sp1 and Sp3), recruits TIP60 to the MYCN promoter (Kramps, Strieder, Sapetschnig, Suske, & Lutz, 2004).

6.6. Involvement of TIP60 in other transcriptional processes

TIP60 was originally discovered as a gene that coactivates transcription of the Tat protein of human immunodeficiency virus 1 (HIV 1) (Kamine et al., 1996). TIP60 has subsequently been reported to coregulate several other transcription factors. UBF is a ribosomal specific transcription factor that interacts with and becomes acetylated and coactivated by TIP60 within the nucleolus at sites of active rDNA transcription (Halkidou et al., 2004). Jade-1 is a PHD finger containing protein involved in renal cancer exhibiting heterologous transcriptional activity when fused to the DNA binding domain of Gal4. TIP60 interacts with Jade-1 and is believed to be responsible for Jade-1-dependent H4 acetylation (Panchenko, Zhou, & Cohen, 2004). TIP60 is also reported to coactivate transactivation of the serum response factor (SRF) gene by the T-Box 2,5 (Tbx2 and Tbx5) transcription factors in cardiac cells (Barron et al., 2005).

6.7. TIP60 as a corepressor of transcription

In the majority of cases, TIP60 was reported to coactivate gene expression. However, the presence of TIP60 does not always correlate with transcriptional coactivation. It is not unexpected that TIP60 alterna-

tively activates expression of certain genes and concurrently represses the expression of others, as this would support a selective gene-specific coregulatory role of TIP60 in transcription (Fig. 2). TIP60 usually induces gene repression via recruitment of other complexes, for example, deacetylases. Examples of transcription factors corepressed by TIP60 include cAMP response element binding protein (CREB) and STAT3 (Gavaravarapu & Kamine, 2000; Xiao et al., 2003). CREB is a transcriptional activator stimulated by hormone and growth factor dependent phosphorylation by protein kinase A (PKA). TIP60 corepresses CREB by direct binding to CREB and repressing CREB stimulation by PKA (Gavaravarapu & Kamine, 2000). As mentioned in Section 4, STAT3 activity is modulated by a TIP60/HDAC7 complex (Xiao et al., 2003). Furthermore, TIP60 represses gene expression by cooperating with transcriptional repressors. Zinc finger E box (ZEB) binding protein is a repressor that associates with TIP60 and whose repressor activity is stimulated by TIP60 in certain cell types (Hlubek et al., 2001). Translocation E26 transforming-specific leukaemia (TEL) gene is a tumour suppressor and transcriptional repressor disrupted by a number of chromosomal translocations in haematological malignancies. TIP60 directly interacts with TEL and corepresses TEL-dependent genes, possibly by stimulating the interaction of TEL with corepressor complexes, such as Switch independent 3 (Sin3) and Silencing Mediator for Retinoid and Thyroid Receptor (SMRT)/NCoR (Nordentoft & Jorgensen, 2003).

7. Regulation of TIP60 protein

Based on the data presented above, it is apparent that TIP60 is an important cofactor of several nuclear as well as cytoplasmic processes. This implies that TIP60 expression, stability, activity and localisation should be tightly regulated in the cell by various modes.

So far, regulation of TIP60 by protein binding and post-translational modifications has been documented. Complex formation modifies TIP60 function and acetyltransferase activity and only in the context of the nuclear complex described above is TIP60 able to modify nucleosomal histones (Ikura et al., 2000). In addition, association with Tat reduces TIP60 acetyltransferase activity in a process that is believed to be utilised by the viral protein Tat to hinder expression of cellular genes (Creaven et al., 1999).

TIP60 is an unstable protein with a short half-life of 30–190 min, depending on cell type (Legube et al., 2002), (VS, unpublished data). In the absence of stimuli, low protein levels in the cell are maintained via proteo-

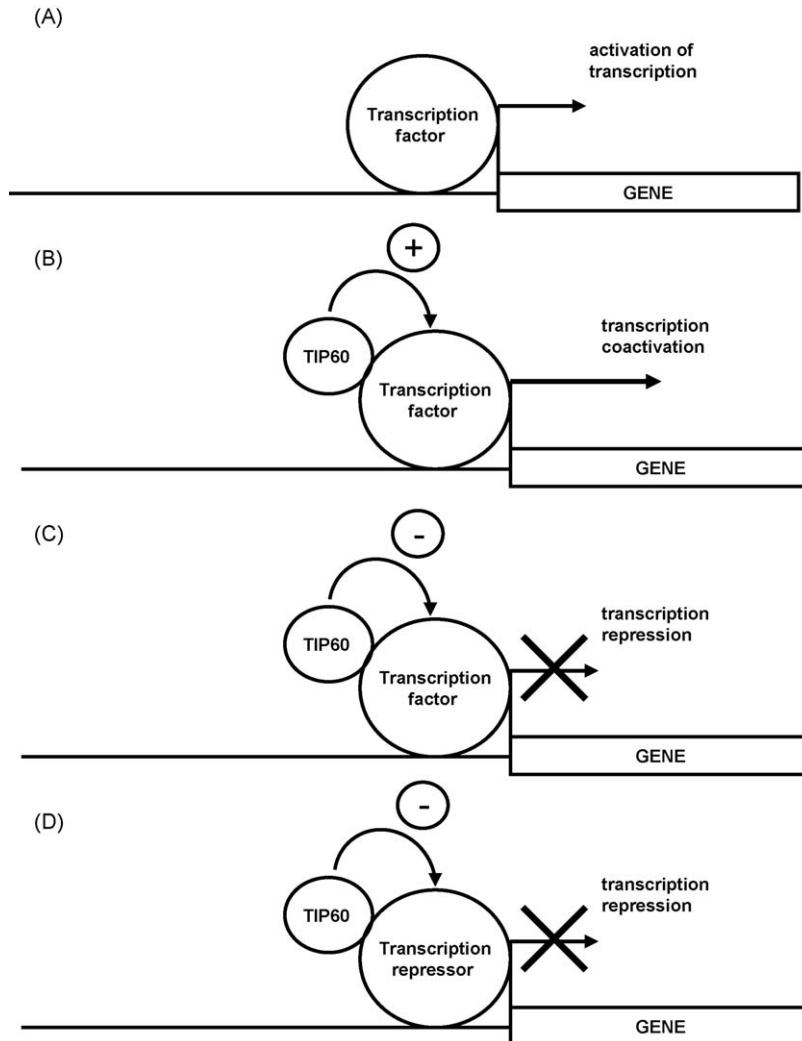


Fig. 2. Simplified model of TIP60 involvement in gene transcription. In the majority of cases, transcription factors have a basal transactivation activity (A), which is enhanced by TIP60 (B), which acts as a coactivator. However, TIP60 can also repress gene transcription by selectively repressing transcription factors (C) or assisting transcriptional activators (D). This dual role of TIP60 allows the cell to pleiotropically affect the activation of distinct genes by regulation of a single coregulator. At this point, it is not clear if TIP60 needs to be modified by a posttranslational modification or other type of regulation in order to have a coactivating or corepressive role.

somal degradation. TIP60 is targeted for degradation by mono- and polyubiquitination by mouse double minute 2 (Mdm2) (Legube et al., 2002), a Mdm2-linked, Tat-dependent, p300-associated E4 ubiquitin ligase (Col et al., 2005) and possibly p53 induced protein with ring H2 domain (PIRH2) (IRL, unpublished data). DNA damaging signals, such as UV inhibit Mdm2-driven ubiquitination and TIP60 levels rapidly stabilise in order to participate in the DNA damage response (Legube et al., 2002).

One efficient mode of protein regulation is phosphorylation and TIP60 was recently found to be phosphorylated at Ser86 and Ser90 when the human protein is

overexpressed and purified from insect cells (Lemercier et al., 2003). Ser90 lies within a cyclinB/cell division cycle 2 (cdc2) consensus motif and TIP60 becomes phosphorylated by cdc2 in vitro. Consistent with this, phosphorylated TIP60 accumulates at the G2/M transition and cdc2 inhibition interferes with this increased phosphorylation. Ser86 and Ser90 are conserved in metazoan TIP60 homologues (*M. musculus*, *D. melanogaster*) but are not present in Esa1p (*S. cerevisiae*).

Finally, TIP60 is modified by p300/CREB binding protein (CBP) acetyltransferases; this acetylation occurs in the zinc finger at Lys268 and Lys282, but its effect on TIP60 function is currently unknown (Col et al., 2005).

8. Involvement of TIP60 in the p53 pathway

Indications that TIP60 is involved in the p53 pathway initially arose from the fact that TIP60 and p53 share some functional similarities: both proteins are regulated by the human homologue of Mdm2 which catalyses their ubiquitylation and proteosomal degradation, levels of both proteins accumulate after DNA damage and both share binding partners, such as PIRH2 (Logan, Sapountzi, Gaughan, Neal, & Robson, 2004). The TIP60 complex also contains the tumour suppressor ING3, a component of the p53 pathway (Cai et al., 2003; Doyon et al., 2004; Nourani et al., 2001).

Accordingly, a large-scale inhibitory RNA (RNAi) screen identified TIP60 as a component of the p53 pathway, essential for the p53-dependent G1/S arrest in response to DNA damage in human cells (Berns et al., 2004). Moreover, the TIP60 transcriptional complex was able to upregulate p53-responsive genes, including p21, growth arrest and DNA damage inducible gene 45 (GADD45) and MDM2 and the acetyltransferase activity of TIP60 was required for p53 coactivation in response to DNA damage (Doyon et al., 2004). ING3 is possibly involved in TIP60 coactivation of p53 (Doyon et al., 2004).

In the absence of a stress stimulus, TIP60 was shown to regulate p53 stability by interfering with Mdm2-mediated p53 degradation, thus maintaining a basal pool of p53 ready to respond to DNA damage (Legube et al., 2004). PIRH2 is a p53 responsive gene that polyubiquitylates p53 and is believed to participate in the negative feedback loop that controls p53 stability (Leng et al., 2003). PIRH2 also interacts with TIP60, which in turn protects PIRH2 from ubiquitylation-dependent proteosomal degradation (Logan et al., 2004). It is not yet clear how the association of TIP60 and PIRH2 affects p53 regulation but it is plausible that TIP60 controls p53 function via distinct and possibly opposing mechanisms.

9. Role of TIP60 in apoptosis

TIP60 is believed to be involved in the initiation of apoptotic pathways. The acetyltransferase activity of TIP60 is essential for sensing DNA damage and triggering apoptosis while cells expressing HAT-deficient TIP60 exhibit severe defects in apoptosis after γ -irradiation (Ikura et al., 2000). The exact mechanism of this effect is unclear, but is possibly dependent on p53. Components of the TIP60 complex, such as the proapoptotic protein ING3 are considered in part responsible for the involvement of TIP60 in apoptotic signalling (Cai et al., 2003; Doyon et al., 2004).

Additionally, TIP60 β potentiates cytosolic phospholipase A₂ (cPLA₂)-dependent apoptosis by binding nuclear cPLA₂ in response to serum deprivation (Sheridan et al., 2001). AICD-induced apoptosis of neuroglioma cells is also dependent on the acetyltransferase activity of TIP60 (Kinoshita et al., 2002).

This involvement of TIP60 in apoptotic signalling is targeted by viral proteins. The viral transactivator HIV-1 Tat interferes with cellular acetylation signalling mediated by TIP60 by inhibiting its catalytic activity as well as reducing TIP60 stability. Consequently, Tat impairs the cellular apoptotic response thus optimising Tat function (Col et al., 2005; Creaven et al., 1999).

10. TIP60 and DNA double strand break response

Eukaryotic genomes are packaged in chromatin; therefore an efficient DNA damage response requires changes in chromatin architecture. Accumulating data confirm that acetyltransferases play an important role in DNA damage response.

Cells expressing catalytically inactive TIP60 accumulate double strand DNA breaks, indicating that TIP60 is crucial for damage repair (Ikura et al., 2000). The TIP60 complex is capable of binding structural DNA intermediates involved in DNA repair and replication. This fact and the presence in the TIP60 complex of proteins involved in DNA damage signalling, such as RuvBL1/2, BAF53 and ING3 support this hypothesis. Indeed, accumulating evidence implies that TIP60 is involved in double strand break response via at least four mechanisms. First, TIP60 is involved in p53 activation and gene transactivation in response to damaging agents, as mentioned in Section 9.

Secondly, TIP60 forms a distinct stable complex with the DNA damage sensor protein ATM and in response to damage activates ATM by direct acetylation (Fig. 3) (Sun et al., 2005). ATM normally exists in an inactive dimeric form and upon DNA damage ATM is autophosphorylated and converted to an active, monomeric form that signals the existence of DNA lesions to downstream mediators. One well characterised target of ATM is the histone variant H2AX, which becomes phosphorylated in the C-terminus almost immediately after DNA damaging stimuli, such as ionising radiation (the phosphorylated form is termed γ H2AX) and acts as a landmark for DNA repair enzymes. Acetylation by TIP60 is required for efficient ATM autophosphorylation and upregulation of ATM kinase activity. The catalytic activity of TIP60 is stimulated in response to DNA damage, but does not appear to be regulated by ATM, which leads to the spec-

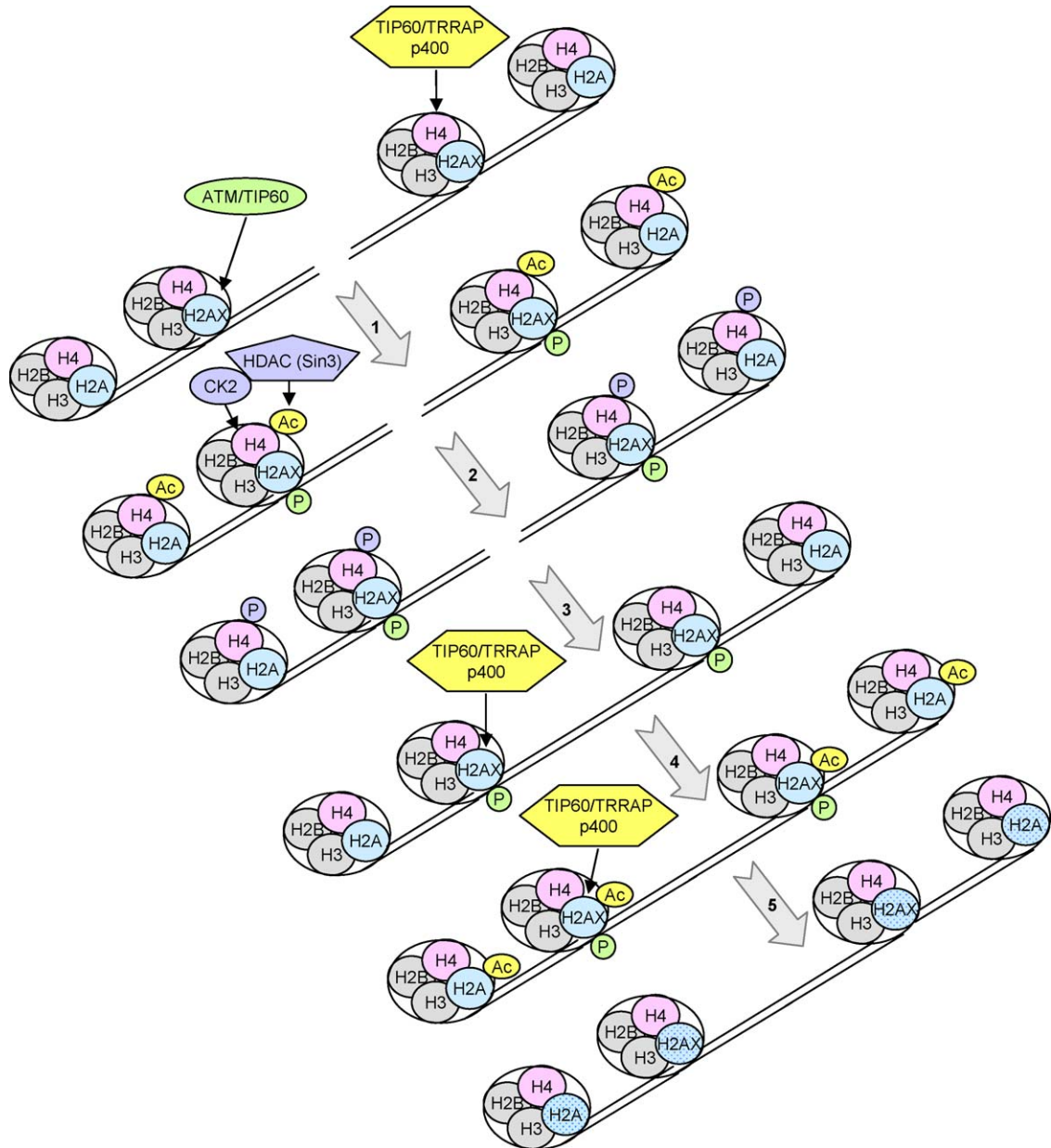


Fig. 3. Proposed mechanism of TIP60 involvement in chromatin changes during DNA double strand break repair. Step 1: Shortly after the induction of double strand breaks, TIP60 acts in the initial sensing of DNA lesions in complex with ATM and promotes phosphorylation of H2AX. The TRRAP/TIP60 complex also acetylates H4, thus ‘opening’ chromatin so that the DNA repair machinery gains access to the damaged area. Step 2: HDAC complexes coupled with kinase activities remove the TIP60-induced acetylation for DNA repair to be completed. Step 3: DNA repair takes place. Step 4: The TIP60 complex specifically targets γ H2AX. Step 5: Components of TIP60 complex (p400) catalyse the exchange of acetylated γ H2AX with an unmodified histone molecule, thus ‘switching off’ the signal of damaged DNA.

ulation that TIP60 functions upstream of ATM, sensing DNA damage-caused chromatin changes and signalling them to ATM. TIP60 is not the only MYST acetyltransferase that influences the function of ATM; human males absent on the first (hMOF) also interacts with ATM and has been proposed to transduce chromatin struc-

tural alterations to ATM after DNA damage (Gupta et al., 2005).

Thirdly, TIP60 participates in DNA damage responses via acetylation of H4 (Fig. 3). Experiments in *S. cerevisiae* showed that DNA breaks and subsequent repair by homologous recombination (HR) and

non-homologous end joining (NHEJ) recruit the HAT complex of the yeast orthologue Esa1 (NuA4 complex) to the vicinity of damage and induce a transient increase in Esa1-driven H4 acetylation (Tamburini & Tyler, 2005). This acetylation is thought to ‘open up’ the chromatin structure to facilitate the accessibility of the DNA repair machinery. Subsequent recruitment of a reduced potassium dependency 3 (Rpd3)/Sin3 deacetylase complex abolishes H4 acetylation (Jazayeri, McAinsh, & Jackson, 2004). This complex is coupled to casein kinase 2 (CK2), which phosphorylates H4 at Ser1 thus inhibiting NuA4 from re-acetylating Lys16 of H4 (Utley, Lacoste, Jobin-Robitaille, Allard, & Cote, 2005). H4 Lys16 deacetylation is required for correct repair and is believed to assist stabilisation and juxtaposition the broken DNA ends (Jazayeri et al., 2004). The requirement of TIP60–TRRAP complex for the DNA damage-induced H4 hyperacetylation and homologous recombination has been recently confirmed in mammalian cells (Murr et al., 2006).

Finally, studies performed in *D. melanogaster* suggest that the drosophila TIP60 (dTIP60) complex is responsible for selective histone variant exchange at DNA damage sites (Fig. 3) (Kusch et al., 2004). H2Av is thought to be the homologue of H2AX and H2AZ in *D. melanogaster* and becomes rapidly phosphorylated after DNA damage. dTIP60 selectively acetylates phosphorylated H2Av in a nucleosomal context shortly after the damaging stimulus. The p400/Domino subunit of dTIP60 complex is an ATPase that is thought to catalyse selective exchange of acetylated phosphoH2Av with unmodified H2Av present in the dTIP60 complex. These findings suggest that TIP60 has a physiological role in acetylation-mediated phosphoH2Av removal at sites of DNA lesions after DNA repair. This is structurally homologous to the human counterpart and it is expected to have a similar function. As *D. melanogaster* H2Av is the homologue of both *H. sapiens* H2AX and H2AZ, it is possible that the human TIP60 complex exchanges acetylated γ H2AX with ‘fresh’ H2AZ.

In *S. cerevisiae*, Esa1 acts in an analogous manner (Downs et al., 2004). In response to DNA lesions, H2A becomes phosphorylated by the ATM homologues telomere maintenance 1/mitosis entry checkpoint 1 (Tel1/Mec1) in a similar way as H2AX in mammals. NuA4 is recruited to the vicinity of DNA lesions, via direct interaction of the BAF53-like subunit actin related protein 4 (Arp4) with phosphorylated H2A. H2A is an Esa1p substrate under normal conditions; however, it has not yet been tested whether H2A acety-

lation increases after DNA damage. After docking to the proximal regions of DNA breaks, NuA4 promotes recruitment of the chromatin remodelling complexes INO80 and SWR1 (Downs et al., 2004). In higher eukaryotes, NuA4 and SWR1/INO80 are believed to be incorporated into a single acetyltransferase complex. It is plausible that SWR1 and INO80 assist NuA4 in phosphoH2A exchange in a similar mechanism as in *D. melanogaster* as they contain homologues of TIP60 (Esa1) and p400/domino (Eaf1, Swr1) (Doyon et al., 2004) and the SWR1 complex is required for the exchange of H2A with the homologue of H2A.Z under normal conditions in yeast (Kobor et al., 2004; Mizuguchi et al., 2004).

11. TIP60 involvement in the mitotic checkpoint

Downregulation of TIP60 leads to deregulation of cell cycle checkpoints after ionising radiation (Berns et al., 2004). Moreover, TIP60 is involved in the maintenance of genomic stability by participating in the regulation of the mitotic checkpoint. The mitotic checkpoint prevents onset of anaphase in cases of incorrect chromosome segregation during cell division by blocking anaphase promoting complex (APC). Mitotic arrest deficient 1/2 (Mad1 and Mad2) proteins are key components of the mitotic checkpoint and their expression is tightly regulated by TRRAP containing acetyltransferase complexes, including the one containing TIP60 (Li, Cuenin, Murr, Wang, & Herceg, 2004).

12. Concluding remarks

TIP60 is a protein with multiple roles, affecting the functions of a diverse variety of targets, including transcriptional regulators, cell cycle and checkpoint machinery and DNA repair regulators. It does so using its acetyltransferase activity but also by directed protein–protein interactions and sequestration of binding partners to specific compartments.

Future research should focus on understanding how this multifaceted protein is regulated to gain insight into the exact mechanism of function, particularly as it has been shown to have both positive and negative effects on the same pathways. This is especially important as it is involved not only in normal cellular processes but also in pathological conditions including viral infection, neurodegenerative disease and cancer. Its involvement in multiple pathways that are deregulated in cancer, such as those of steroid receptors, Myc, E2F, p53 and DNA damage response could make it an attractive therapeutic target.

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