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Human Tip60 (NuA4) Complex and Cancer

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1. Introduction

Recent publications implicate human Tip60 (NuA4) complex in colorectal and other cancers. Our lab and others discovered deregulations in the components of human Tip60 (NuA4) complex in advanced colon cancers, and the functional significance and the potential as a therapeutic target, has been investigated. Human Tip60 (NuA4) complex likely represents a fusion form of yeast NuA4 and SWR1 complexes, and the functions seem to be evolutionarily preserved. This notion has greatly contributed in understanding functions of human Tip60 (NuA4) complex. The Tip60 (NuA4) complex is a multiprotein complex with at least 16 subunits. It is thought to function in at least two ways; (a) as a chromatin remodeling factor, it controls chromatin structure and transcription through its Histone Acetyl Transferase (HAT) activity, and (b) it controls activities of other non-histone proteins, such as metabolic enzymes, through protein acetylation. Through the enzymatic activity and other interactions, Tip60 (NuA4) complex is involved in wide variety of cellular functions, including transcriptional activation, DNA repair, cell cycle progression, chromosome stability, stem cell maintenance and differentiation, and cell migration and invasion. This review will discuss functions of Tip60 (NuA4) complex, consequences of the defect in the subunit, its connection to human cancer, and its potential as a therapeutic target in clinic.

2. A chromatin remodeling factor with Histone Acetyl Transferase (HAT) activity, Tip60 (NuA4) complex

Readout of genomic information is regulated through multiple mechanisms. A major part of the regulatory role is played by chromatin remodeling factors; enzyme complexes that modify DNA or chromatin proteins. The modifications change local chromatin structure, thus change accessibility of transcription factors and availability of genomic information (Kouzarides 2007). In the case of Histones and major chromatin proteins, protein modifications occur in a variety of ways, including phosphorylation, acetylation, methylation, ubiquitylation, and ADP-ribosylation. These different types of modifications may functionally influence each other, creating possibilities of multiple layers of regulations, which have been referred as the "Histone code". Although the possibility has been pointed out, the multiple layers of regulations (the "Histone code") have not fully been deciphered yet.

Among the modifications, acetylation has a defined role: To change surface charge distribution of the target protein and change accessibility to DNA and/or to other proteins.

The histones are acetylated and deacetylated on lysine residues in the N-terminal tail. These acetylation/deacetylation reactions are catalyzed by two groups of enzymes, Histone Acetyl Transferase (HAT) and Histone DeACetylase (HDAC), respectively. Histones are not the only target for these enzymes. HATs and HDACs can acetylate/deacetylate non-histone proteins as well.

In this review, we will focus on a human multisubunit and multifunctional HAT complex, Tip60 (NuA4) (Nucleosomal Acetyltransferase of H4) complex. We will describe the complex and known functions from the standpoint of each subunit and discuss new insights relevant to cancer, especially in colon cancer. We will also discuss the possibility of targeting Tip60 (NuA4) subunits for therapeutic purposes.

3. Human Tip60 (NuA4) complex; Its components and functions

Human Tip60 (NuA4) complex is a multiprotein complex with at least 16 subunits, and it has HAT activity (Cai et al., 2003, Doyon et al., 2004). The subunit composition suggests that Human Tip60 (NuA4) complex is a fusion form of two yeast HAT complexes, NuA4 and SWR (Allard et al, 1999) (Table 1). As seen in Table1, these two yeast HAT complexes share four components (Eaf2, Arp4, Act1 and Yaf9), together they correspond to all human subunits. Supporting the fusion theory, the expression of a chimeric Eaf1-Swr1 protein provides a scaffold for the complex assembly and recreates a single human-like complex in yeast cells (Auger et al, 2008).

Historically speaking, yeast has been a superior model system to investigate functions of molecular and cellular machineries with its genetical tractability, its ease of experimental manipulations, feasibility for biochemistry and its short life cycle and time span for experiments. Several cellular functions of NuA4 and SWR complex were identified directly with yeast studies and later confirmed in human cultured cells. The known acetylation targets of yeast NuA4 *in vivo* are histone H4 (Mitchell et al., 2008) and the histone H2A variant Htz1 (Babiarz et al., 2006, Keogh et al., 2006, Mizuguchi et al., 2004). Yeast NuA4 complex also targets non-histone proteins, which are equally important to evaluate cellular functions of NuA4 complex. With yeast protein array, Lin et al. (2009) screened the target proteins. Among 5800 proteins screened for *in vitro* acetylation with NuA4 complex, 91 candidates were identified, 20 were selected for validation, and 13 were validated. The functions of validated proteins encompass metabolism, transcription, cell cycle, RNA processing, and stress response. The authors focused on Pck1, a key metabolic enzyme that regulates gluconeogenesis, and showed that Pck1 activity and glucose secretion is regulated through NuA4-mediated acetylation in yeast and in human hepatocellular carcinoma cells HepG2. Thus NuA4 is implicated in metabolism and energy generation through its non-histone targets.

The human TIP60 complex has at least three interrelated enzymatic activities: histone H4/H2A acetyltransferase, ATP-dependent H2AZ-H2B histone dimer exchange, and DNA helicase (Auger et al., 2008). Only a limited number of non-histone targets, including human Pck1, has been identified so far (Liu et al., 2009).

Knockdown and/or mutational studies have been performed to identify functions of the subunits of human Tip60 (NuA4) complex. The studies implicate following biological events to Tip60 (NuA4) complex, directly or indirectly.

- DNA repair
- Transcriptional regulation
- Chromatin structure alteration
- Interaction and/or regulation with factors relevant to tumorigenesis (e.g. c-myc, E1A, E2F1, p53, STAT3, NF-kappaB)
- Cell migration and invasion
- Mitosis
- Genomic instability
- Stem cell maintenance and differentiation

In addition, RNAi-based screening with nematode *C. elegans* implicated Tip60 (NuA4) complex in attenuation of *ras*-signaling involving development of vulva in the model. The *C. elegans* MLL (Mixed Lineage Leukaemia (MLL)) complex-like complex cooperates with the TIP60 (NuA4) complex to regulate the expression of a novel *ras*-signaling attenuator, AJM-1 (Fischer et al., 2010).

4. Functions of each subunit

In the following section we will discuss each of the subunits.

4.1 TRRAP/Tra1/*

(human protein/yeast protein in NuA4 complex/ yeast protein in Swr complex. Asterisk * if not applicable)

Human TRRAP (transformation/transcription domain-associated protein) has a FATC (FRAP, ATM, TRRAP C-terminal) domain and a kinase domain, and belongs to ATM/PI3K family. However, TRRAP does not appear to possess kinase activity, because the kinase domain in TRRAP lacks the conserved amino acids required for ATP binding and catalytic activity for phosphate transfer. For that reason, it is speculated that TRRAP has evolved as a specialized PIKK member to serve as an adaptor/scaffold for protein–protein interaction and multiprotein assemblies or as a platform for recruitment of different regulatory factors and complexes to chromatin (Murr et al 2007). The FATC domain in the C-terminus likely affects the protein stability in an oxidation/redox-dependent manner (Dames et al., 2005).
TRRAP is a common component of many HAT complexes (e.g. SAGA, PCAF and Tip60 (NuA4) complex). As such, targeting TRRAP will influence a broader range of biological events and pathways than targeting more specialized components in Tip60 (NuA4) complex.
TRRAP is one of the frequently mutated genes in melanoma. TRRAP harbored a recurrent mutation that clustered in one position (p. Ser722Phe) in 6 out of 167 affected individuals (~4%), although the effects of the mutation on the protein function is unclear (Wei et al., 2011). Expression profiling revealed that TRRAP is frequently both amplified and overexpressed in Pancreatic Ductal AdenoCarcinoma (PDAC), and the overexpression is associated with poor prognosis (Bashyam et al., 2005, Loukopoulos et al,2007). In brain tumor-initiating cell, knockdown of TRRAP significantly increased differentiation and decreased cell cycle progression, leading to overall inhibition of tumor formation. The result indicates a critical role for TRRAP in maintaining a tumorigenic, stem cell-like state (Wurdak et al., 2010). TRRAP is shown to regulate a major player in colon cancer, beta-catenin. TRRAP interacts with Skp1/SCF and mediates its recruitment to beta-catenin target promoter in chromatin. TRRAP deletion leads to a reduced level of beta-catenin

Human Tip60 (NuA4) complex subunits	Yeast NuA4 complex subunits	Yeast SWR1 complex subunits	Protein domain(s)	Yeast null phenotype	Inhibition (e.g. siRNA) in cultured cells	Knockout in mouse	Relationship to cancer (See text)
TRRAP (transformation/transcription domain-associated protein)	Tra1		ATM/PI3K family kinase, FATC domain	inviable	Mitotic defect with Mad1 and Mad2 misregulation	Embryonic lethal	High expression in mouse leukemogenic cell lines; co-factor for c-myc oncogenic transformation
hDomino p400/EP400	Eaf1 (HAS/SANT)	Swr1 (HAS/SWI2)	SWI2/SNF2 related, ATPase, Trico Peptide Repeat (TPR) domain	Viable; decreased growth, genome instability		Embryonic lethal	
Brd8 (Bromodomain 8)		Bdf1	Bromodomain	Viable; decreased growth, multidrug sensitivity, enhanced salt sensitivity by mitochondrial dysfunction	Enhanced spindle poison sensitivity	ND	Protein accumulated in rat colon cancer and human colon cancer cell lines
EPC1/EPC-like (Enhancer of Polycomb homolog)	Epl1			inviable			Locates in chromosomal breaking point in ATLL
Tip60 (TAT interactive protein)	Esa1			inviable		Embryonic lethal	Prostate cancer promotion; tumor suppressor candidate/ expression reduced in cancers
DMAP1 (DNA methyltransferase 1-associated protein 1)	Eaf2/swc4	Eaf2/swc4	a SWI3-ADA2-N-CoR-TF IIIB (SANT) domain	Inviable; G2/M arrest		lethal during preimplantation	Binds to DNA methyltransferase 1 (DNMT1), which is progressively upregulated in colon adenoma-carcinoma sequence
ING3 (Inhibitor of Growth Protein 3)	Yng2		PHD finger	Viable			Tumor suppressor candidate; Overexpression inhibits cell growth and promote apoptosis; allelic loss detected in head and neck cancers
YL-1 (Vacuolar protein sorting-associated protein 72 homolog)		Vps72		Viable; decreased fitness			
RuvBL1		Rvb1/Tip49A		inviable			Binds to beta-catenin
RuvBL2		Rvb2/Tip49B		inviable			
BAF53a	Arp4	Arp4	Actin-related	inviable			
Actin	Act1	Act1	actin	inviable			
MRG15	Eaf3			Viable; increased lifespan			
GAS41	Yaf9	Yaf9		Viable; Enhanced spindle poison sensitivity, multidrug sensitivity, decreased chromosome maintenance			
?	Eaf5			Viable			
MRGBP	Eaf7			Viable; decreased fitness			Overexpressed in human colon cancer
hEaf6	Eaf6			Viable			

Table 1. Subunits of Human Tip60 (NuA4); (columns from left) subunits of the yeast counterpart complexes NuA4 and SWR1; notable protein domains; yeast mutant phenotypes that implicate functions; inhibition in cultured cells and mice; and information relevant to cancer. ND: Not Determined. The order listed is following the size of the protein. Larger subunit is shown on top.

ubiquitination, lower degradation rate and accumulation of beta-catenin protein. Furthermore, recruitment of Skp1 to chromatin and ubiquitination of chromatin-bound beta-catenin are abolished upon TRRAP knock-down, leading to an abnormal retention of beta-catenin at the chromatin and concomitant hyperactivation of the canonical Wnt pathway (Finkbeiner et al., 2008). TRRAP is also involved in DNA damage repair. TRRAP depletion impairs both DNA-damage-induced histone H4 hyperacetylation and accumulation of repair molecules at sites of Double Strand Breaks (DSBs), resulting in defective homologous recombination (HR) repair, albeit with the presence of a functional ATM-dependent DNA-damage signaling cascade (Murr et al., 2006). TRRAP regulates expressions of many cancer-relevant genes, including mitotic checkpoint proteins Mad1 and Mad2 (Li et al., 2004) and mdm2 (Ard et al., 2002).

Consistent with the loss of mitotic checkpoint proteins essential for cellular survival, null mutation of Trrap (mouse homolog of human TRRAP) results in peri-implantation lethality due to a blocked proliferation of blastocysts. Loss of Trrap blocks cell proliferation because of an aberrant mitotic exit accompanied by cytokinesis failure and endoreduplication. Trrap-deficient cells failed to sustain mitotic arrest despite chromosome missegregation and disrupted spindles, and display compromised cdk1 activity. Thus, Trrap is essential for early development and required for the mitotic checkpoint, presumably through expression control of mad1 and mad2, and normal cell cycle progression (Herceg et al., 2001).

In yeast, deletion of TRRAP homolog Tra1 is also lethal. Tra1 is identified as a component of multiple yeast transcription regulator complexes, Ada-Spt, SAGA and NuA4 (Saleh et al., 1998; Grant et al., 1998; Allard et al., 1999). Tra1 directly interacts with the acidic transcriptional activators Gcn4, Hap4, and Gal4 (Brown et al., 2001). Tra1 is required for both the acetylation of Histone H4 surrounding the promoters and the transcription of Gcn4-dependent genes, suggesting that Tra1 may mediate the recruitment of NuA4 to certain promoters.

4.2 hDomino p400/Eaf1/Swr1

hDomino (also known as p400, EP400, E1A binding protein p400) is a DEXH-box class of RNA-dependent ATPase subunit in Tip60 (NuA4) complex, and can destabilize histone-DNA interactions in reconstituted nucleosomes in an ATP-dependent manner. hDomino also contains a highly conserved SANT (SWI3–ADA2–NcoR–TFIIIB) domain, a histone tail-binding module (Boyer et al. 2004). The protein is related to yeast Swi2/Snf2 (SWItch 2/Sucrose NonFermentable 2) and to Domino in fruit fly *Drosophila*. *Drosophila* Domino was isolated in search of immune system mutants devoid of circulating larval hemocytes from P-element insertion-based mutant library. Because of the very striking lymph gland phenotype that results in mutant larvae with two black dots visible on the anterior half, the authors named the mutation *domino* (Braun et al., 1997).

Through the Swi2/Snf2 domain, hDomino binds to adenovirus oncoprotein E1A. Mutational loss of E1A binding results in the loss of transformation, indicating that the binding plays a critical role in cellular transformation. hDomino also binds to c-myc with different protein components (Fuchs et al., 2001). In most human colorectal carcinoma, the ratio between Tip60 and p400 mRNAs is affected. Reversing the p400/Tip60 imbalance by Tip60 overexpression or the use of siRNAs resulted in increased apoptosis and decreased proliferation of colon-cancer-derived cells, suggesting that this ratio defect is important for cancer progression (Mattera et al., 2009).

In mice, p400 knockout results in embryonic lethality. Homozygous knockout mice died on embryonic day 11.5 (E11.5), and displayed an anemic appearance and slight deformity of the neural tube. Their results suggest that p400/mDomino plays a critical role in embryonic hematopoiesis by regulating the expression of developmentally essential genes such as those in the Hox gene cluster (Ueda et al., 2007). Tip60-p400 is necessary to maintain characteristic features of Embryonic Stem Cells (ESCs) (Fazzio et al., 2008). Through an RNAi screen in mouse ESCs of 1008 loci encoding chromatin protein, the authors identified 68 proteins that exhibit diverse phenotypes upon knockdown, including seven subunits of the Tip60-p400 complex, Trrap, Tip60, p400, DMAP1, RuvBL1, RuvBL2 and GAS41. Phenotypic analyses revealed that p400 localization to the promoters of both silent and active genes is dependent upon histone H3 lysine 4 trimethylation (H3K4me3). The Tip60-p400 knockdown gene expression profile is enriched for developmental regulators and significantly overlaps with that of the transcription factor Nanog. Depletion of Nanog reduces p400 binding to target promoters without affecting H3K4me3 levels. Together, these data indicate that Tip60-p400 integrates signals from Nanog and H3K4me3 to regulate gene expression in ESCs (Fazzio et al., 2008).

Yeast p400 homolog Eaf1 (Esa1-associated Factor 1, VID21) is the only subunit exclusively found in the NuA4 complex in biochemical preparation. Eaf1 is the platform on which four different functional modules of the other subunits are assembled into the native complex (Auger et al., 2008). Although eaf1 deletion strain is viable, the cells show genome instability and high incidences of sporulation defects and aneuploidy. The mutant is also highly sensitive to DNA damage-inducing stress such as X-ray (Auger et al., 2008; Hughes et al., 2000; Krogan et al., 2004).

4.3 Brd8/*/Bdf1

Human Brd8 was functionally identified as a Thyroid hormone receptor coactivator p120 (Monden et al., 1997; Yuan et al., 1998). Later, its role as a transcriptional coactivator with RXR/PPAR-gamma was also reported, establishing the role as a nuclear receptor coactivator (Monden et al., 1999). Human Brd8 has one or two Bromodomain(s), depending on the isoform. The Bromodomain is a domain that can bind to acetylated lysine, typically observed in histones, suggesting its role in regulating protein-protein interactions in histone-directed chromatin remodeling and gene transcription. (Zeng and Zhou, 2002; Mujtaba et al., 2007).

Brd8 was isolated through a HeLa cell-based expression cloning for genes that influence sensitivity to a microtubule inhibitor (Yamada and Gorbsky, 2006). Ectopic expression of Brd8 provides partial resistance to microtubule inhibitors and proteasome inhibitor, and knockdown sensitized cells to the drugs, suggesting Brd8 influences sensitivity to microtubule inhibitors and proteasome inhibitor (Yamada and Rao, 2008). Human Brd8 protein is overexpressed in human metastatic colorectal cancer cell lines. Brd8 is also overexpressed in advanced colon adenocarcinoma in rats induced with Dextran sulfate and azoxymethane (an inflammatory colon cancer model system). SiRNA-mediated Brd8 knockdown resulted in cell death in HCT116 and growth delay in DLD1, both are colorectal cancer cells (Yamada and Rao, 2008). With shRNA, an independent lab showed that inhibition of Brd8 resulted in growth inhibition (Yamaguchi et al., 2010), thus Brd8 is suspected to provide survival fitness and growth advantage. In our lab, transcriptome analysis showed little difference in the amount of Brd8 transcripts in colonic normal-looking

epithelial and cancer cells, yet the protein accumulates in cancer cells. The protein accumulation is enhanced with an addition of proteasome inhibitor in cultured human colon cancer cells, suggesting that a post translational, proteasome-dependent pathway is involved in the regulation (unpublished results).
Yeast homolog Bdf1p (Bromo Domain Factor 1) contains two bromodomains and is thought to correspond to a missing piece of TFIID (Matangkasombut et al., 2000). Bdf1 deletion in yeast is viable, but affects general transcription including small nuclear RNA, sporulation, mitochondrial function and stress-induced cell death (Lygerou et al., 1994; Liu et al, 2009). Overexpression of Bdf1 can suppress phenotypes and defects of yaf9 (human GAS41 homolog) deletion, indicating functional overlap between Bdf1 and Yaf9 (Bianchi et al., 2004).

4.4 Epc1/Epl1/*

In *Drosophila*, EPC1 (Enhancer of PolyComb 1) mutation was isolated as a mutation that enhances the effect of homeotic proteins Polycomb. Although homozygotic mutations of *E*pc1 in *Drosophila* are lethal in the embryo, heterozygous mutations do not by themselves result in a zygotic homeotic phenotype (Stankunas et al, 1998). Epc1 protein is a chromatin protein with no known enzymatic activity by itself.
EPC1 deregulation is observed in Adult T-cell leukemia/lymphoma (ATLL), a malignant tumor caused by latent human T-lymphotropic virus 1 (HTLV-1) infection. In acute-type ATLL, there is a common breakpoint cluster region at 10p11.2. The chromosomal breakpoints are localized within the enhancer of polycomb 1 (EPC1) gene locus (Nakahata et al., 2009).
In mice development, Epc1 is involved in skeletal muscle differentiation. The expression of *Epc1* mRNA is gradually decreased with aging from embryonic day 11.5 to postnatal week 8. Epc1 is highly expressed in skeletal muscles and heart ventricle in week 8 mice (Kee et al., 2007). Epc1 knockdown caused a decrease in the acetylation of histones associated with serum response element (SRE) of the skeletal alpha-actin promoter. The Epc1.SRF (Serum Response Factor) complex bound to the SRE, and the knockdown of Epc1 resulted in a decrease in SRF binding to the skeletal alpha-actin promoter. Epc1 recruited histone acetyltransferase activity, which was potentiated by cotransfection with p300 but abolished by siRNA-mediated p300 inhibition. Epc1 directly bound to p300 in myoblast cells. Epc1 heterozygous mice showed distortion of skeletal alpha-actin, and the isolated myoblasts from the mice had impaired muscle differentiation. These results suggest that Epc1 is required for skeletal muscle differentiation by recruiting both SRF and p300 to the SRE of muscle-specific gene promoters (Kim et al., 2009).
Deletion of Yeast homolog Epl1 (Enhancer of Polycomb Like 1) is inviable, causes cells to accumulate in G2/M and global loss of acetylated histones H4 and H2A (Boudreault et al., 2003).

4.5 Tip60/Esa1/*

TIP60 in humans and Esa1 in yeast are the catalytic (acetyltransferase) subunit of the NuA4 complex (Ikura et al., 2000; Smith et al., 1998) and play a central role in Tip60 (NuA4) complex function. MYC associates with TIP60 and recruits it to chromatin *in vivo* with four other components of the TIP60 complex: TRRAP, p400, RuvBL1 and RuvBL2 (Frank et al., 2003)

The Tip60 histone acetyltransferase has been recently shown to be underexpressed in many human cancers from various origins (Lleonart et al., 2006; Gorrini et al., 2007). Moreover, in a model of tumor induction mice, it has been shown to function as a haploinsufficient tumor suppressor, providing a causal link between Tip60 underexpression and tumorigenesis (Gorrini et al., 2007).
A down-regulation of the TIP60 gene was observed in 28 out of 46 (61%) specimens of primary gastric cancer (Sakuraba et al, 2011). As mentioned in p400, in colon cancer expression ratio of Tip60-p400 is altered, and it may be involved in tumor growth (Mattera et al., 2009).
In yeast the catalytic subunit Esa1 is the only HAT protein essential for viability and is responsible for the bulk of histone H4 and H2A acetylation in vivo (Doyon and Cote, 2004). *esa1* temperature sensitive (ts) mutants provoke a *RAD9*-dependent G2/M delay (Megee et al., 1995; Clarke et al., 1999). Yeast Esa1 mutation is inviable, and *esa1* conditional mutation serve to dissolve whole complex (Allard et al., 1999).

4.6 DMAP1/Eaf2/Eaf2

Human DMAP1 and its yeast homolog Eaf2 contain a highly conserved SANT (SWI3–ADA2–NcoR–TFIIIB) domain, a histone tail-binding module (Boyer et al. 2004). DMAP1 (DNA methyltransferase (DNMT)-1 associated protein 1) is a subunit of the TIP60-p400 complex that maintains embryonic stem (ES) cell pluripotency (Fazzio et al., 2008) and also a subunit of a complex containing the somatic form of DNA methyltransferase 1 (DNMT1s). The lack of DNMT1 in the purified TIP60-p400 complex indicates that DMAP1 interacts with DNMT1 in a distinct complex, thus DMAP1 functions in two distinct manner, as a Tip60 (NuA4) complex and with DNMT1 (Cai et al. 2003, Doyon et al., 2004). The non-catalytic amino terminus of DNMT1 binds to HDAC2 and can mediate transcriptional repression (Rountree et al, 2000). DNMT1 is essential for epidermal progenitor cell function and replenishing the tissue (Sen et al., 2010).
DMAP1 associated proteins (DNMT1,3A and 3B) were progressively upregulated in colorectal adenoma-carcinoma sequence (Schmidt et al., 2007). Since counteracting demethylase MBD2 amount remained unchanged, the authors suggested that epigenetic regulation in the adenoma-carcinoma sequence may be driven by increased methylating activity by DNMTs rather than suppressed demethylation.
In mice, DMAP1 homozygous knockout resulted in lethality during preimplantation (Mohan et al., 2010). Reduction of the expression of DMAP1 caused a loss of characteristic ES cell morphology and activation of genes associated with cell differentiation (Fazzio et al., 2008), and it is a likely cause of the embryonic lethal phenotype. Dmap1 knockdown in mouse embryonic fibroblasts (MEFs) lead to spontaneous double-strand breaks (DSBs), resulting in growth arrest because of p53-dependent cell cycle checkpoint activation (Negishi et al., 2009).
Yeast homolog Eaf2 (also known as SWC4) is a shared component of NuA4 and SWR1 complexes. Mutant yeasts are highly sensitive to DNA breaks induced by DNA-damaging agents, suggesting an essential role for these two proteins in DNA repair (Auger et al., 2008).

4.7 Ing3/Yng2/*

Human ING1 (Inhibitor of Growth 1) was identified as a tumor suppressor candidate, and subsequently the "Ing family" proteins (ING1-ING5) were investigated. Human Ing3 is a

47kd protein with a C-terminal plant homeodomain (PHD)-finger motif, common in proteins involved in chromatin remodeling and is a sequence-specific histone recognition protein module (Gunduz et al., 2002; Nagashima et al., 2003; Sanchez and Zhou, 2011). p47ING3 activates p53-transactivated promoters, including promoters of p21/waf1 and bax. Thus p47ING3 modulates p53-mediated transcription, cell cycle control, and apoptosis. Later, ING family proteins are identified as components of chromatin remodeling complexes; ING1 in mSin3A HDAC, ING2 in an HDAC complex similar to ING1, ING3 in Tip60 (NuA4) HAT complex, ING4 in HBO1 HAT, and ING5 fractionates with two distinct complexes containing HBO1 or nucleosomal H3-specific MOZ/MORF HATs. (Doyon et al., 2006).

Consistent with the proposed function as a tumor suppressor, a decrease of ING3 expression or LOH are observed in tumors. Decreased or no expression of ING3 mRNA was observed in 50% of primary head and neck squamous cell carcinomas (HNSCC) as compared with that of matched normal samples. About 63% of tongue and larynx tumors showed the decrease, and a tendency of higher mortality was observed in cases with decreased ING3 expression. It suggests that the ING3 gene functions as a tumor suppressor in a subset of HNSCC (Gunduz et al., 2002). Expression of ING3 is correlated with poor prognosis in HNSCC (Gunduz et al., 2008). Distorted ING3 expression has been found in several lymphoma-derived cell lines (Fadlelmola et al., 2008). Nuclear ING3 expression was reduced in melanomas in a Skp2-ubiquitin/proteasome pathway-dependent manner (Chen et al., 2010). This reduction was correlated with a poorer patient survival (Wang et al., 2007). Decreased ING3 expression is associated with melanoma progression and poor prognosis.

The yeast Saccharomyces cerevisiae has three homologs of ING family proteins. Homolog of human ING3 is Yng2 (Loewith et al., 2000). Yng2 is a plant homeodomain (PHD)-finger protein and a NuA4 complex subunit. Deletion of YNG2 results in several phenotypes, including an abnormal multibudded morphology, an inability to utilize nonfermentable carbon sources, heat shock sensitivity, slow growth, temperature sensitivity, and sensitivity to caffeine (Loeweth et al., 2000). Also notable was its requirement for normal progression through mitosis and meiosis. Some of the phenotypes were suppressed by HDAC inhibitor Tricostatin A, demonstrating that the phenotypes are based on defects in acetylation cycle (Choy et al., 2001). Yng2p is stabilized by the proteasome inhibitor MG-132, and is likely regulated through an ubiquitin-proteasome pathway (Lin et al., 2008).

4.8 YL-1/*/Vps72

Human YL-1 is a nuclear protein with an acidic region and a proline-rich region (Horikawa et al., 1995), and was identified as a component of Tip60 (NuA4) complex with biochemical purification and mass spectrometry. YL-1 is also a part of human counterpart of yeast SWR1 complex (Cai et al., 2005). Notably, mammalian SRCAP and *Drosophila* Tip60 complexes are associated with histone H2AZ or its fly counterpart H2AvD. These similarities suggest that YL-1 may serve as a binding module for histone H2AZ in metazoans, as does Swc2 in yeast (Wu et al., 2005).

In the Kirsten sarcoma virus–transformed NIH3T3 cells highly expressing the exogenous human YL-1 protein, the anchorage-independent growth (colony-forming ability in soft agar medium) was markedly suppressed. However, in contrast to the suppression of anchorage-independent growth, the forced expression of YL-1 did not affect the transformed phenotypes in adherent culture and tumorigenicity in nude mice. The data suggest that YL-

1 is involved in the transformation process, and once cells are transformed, additional YL-1 expression does not play additional role in tumor growth (Horikawa et al., 1995).
Yeast homolog VPS72 (Vascular Protein Sorting 72, also known as SWC2) is a histone variant H2AZ (Htz1p)-binding component of the SWR1 complex, which exchanges Htz1p for chromatin-bound histone H2A (Wu et al., 2005).

4.9 RuvBL1/*/Rvb1(Tip49A) and 4.10 RuvBL2/*/Rvb2(Tip49B)

RuvBL1 and RuvBL2 belong to the family of AAA+ ATPases (ATPases Associated with various cellular Activities). Ruvbl1 is also called Pontin, NMP238, ECP54, TAP54α, TIH1 or Tip49, while Ruvbl2 is also called Reptin, ECP51, TAP54α, TIH2 or Tip48. RuvBL1 and RuvBL2 bind each other and function as a hexameric helicase (Ikura et al., 2000; Shen et al., 2000). The names come from their homology with the bacterial RuvB helicase, which is involved in DNA recombination and repair. In bacteria, the ruvA-ruvB complex in the presence of ATP renatures cruciform structure in supercoiled DNA with palindromic sequence, indicating that it may promote strand exchange reactions in homologous recombination. RuvAB is a helicase that mediates the Holliday junction migration by localized denaturation and reannealing.
Human RuvBL1 and RuvBL2 are components of multiple multiprotein complexes, INO80, SRCAP, URI-1, R2TP and Tip60 (NuA4) complex. RuvBL1 and RuvBL2 were co-immunoprecipitated or affinity-purified with at least 48 proteins (Grigoletto et al., 2011).
Human RuvBL1 and RuvBL2 are overexpressed in a variety of cancers inculding colorectal (Carlson et al., 2003). Regulation of COX-2 transcription in a colon cancer cell line by Pontin52/TIP49a, (Lauscher et al.; 2007; Ki et al., 2007), gastric (Li et al., 2010), bladder (Sanchez-Carbayo et al., 2006), mesothelioma (Zhan et al., 2007), non-small cell lung cancer (Dehan et al., 2007), as well as in several types of acute (Andersson et al., 2007) or chronic leukemias (Haslinger et al., 2004), in multiple myeloma (Zhan et al., 2007) and high-grade lymphoma (Nishiu et al., 2002). In ovarian cancer cell lines, microcell-mediated chromosome transfer and expression microarray analysis identified nine genes associated with functional suppression of tumorogenicity; AIFM2, AKTIP, AXIN2, CASP5, FILIP1L, RBBP8, RGC32, RUVBL1 and STAG3. Two SNPs in RUVBL1 were associated with increased risk of serous ovarian cancer (Notaridou et al., 2011). The expression of an ATPase-deficient mutant form of RuvBL1/TIP49 substantially inhibited β-catenin-mediated neoplastic transformation of immortalized rat epithelial cells and anchorage-independent growth of human colon cancer cells with deregulated β-catenin (Feng et al., 2003).
Disruption of the yeast RuvBL1 (Kanemaki et al., 1999; Lim et al., 2000) or RuvBL2 genes (Lim et al., 2000) is lethal.

4.11 BAF53a (ACTL6a)/Arp4/Arp4

Human BAF53a (BRG1-associated factor 53a) is also known as ACTL6a (Actin-like 6a). As the name implies, the protein has a 36% identity and 50% similarity with the human beta-actin. BAF53 is a part of Tip60 (NuA4) complex (Cai et al., 2003, Doyon et al., 2004, 2006). In addition, BAF53a is also a part of other multiple multiprotein complexes, including INO80, SWI/SNF, and myc-containing nuclear cofactor complex (Park et al., 2002; Sung et al., 2001). For SWI/SNF-like protein complex, beta-actin and BAF53 are required for maximal ATPase activity of BRG1 and are also required with BRG1 for association of the complex with

chromatin/matrix (Zhao et al., 1998). Baf53 protein was also identified as a major binding target for HIV Tat protein through affinity chromatography coupled with mass spectrometry. The result suggests that Baf53 and Tip60 (NuA4) complex is a major target for HIV-1 proviral gene silencing and activation (Gautier et al., 2009).
In yeast, Arp4/Act3 was identified as a component of NuA4 complex with affinity-purification followed by mass spectrometry (Galarneau et al., 2000). *ARP4* gene is essential for growth in yeast (Harata et al., 1994). In temperature-sensitive *arp4* mutants, NuA4 complex disintegrated and lost its activity in restrictive temperature, demonstrating the critical role of Arp4 in the NuA4 complex (Galarneau et al., 2000). Upon DNA damage, Arp4 recognizes and interacts with histone H2A phosphorylated at serine 129. This action recruits NuA4 to regions of DNA double-strand breaks where histone H4 acetylation is required for DNA double-strand break repair (Bird et al., 2002; Downs et al., 2004).

4.12 Actin/Act1/Act1

A major cytoskeletal protein beta-actin is also a subunit of Tip60 (NuA4) complex (Cai et al., 2003; Doyon et al., 2004, 2006). As in BAF53a, Actin is also a subunit of other multiprotein complex. Inhibition of Actin with the Actin monomer sequestering natural product Latrunculin B blocks chromatin-dependent ATPase activation of the BAF complex, indicating that Actin is a functionally critical component of SWI/SNF complex (Zhao et al., 1998). As a major cytoskeletal component, beta-actin (Actb) gene is an essential gene, and its hypomorph is embryonic lethal in mice (Tondeleir et al., 2009).
In yeast, in addition to cytoskeletal roles, Act1 is shown to be a component of distinctive chromatin remodeling complexes including INO80, SWR and NuA4 (Shen et al., 2000; Krogan et al., 2003; Galarneau et al., 2000). Act1 deletion is lethal.

4.13 MRG15/Eaf3/*

MRG 15 (Morf-related genes (Mrg) on chromosomes 15 (Mrg15)) belongs to Morf family proteins. From cellular senescent study to identify single chromosomes from normal human cells that can inhibit growth of immortal human cells, an intronless transcription factor-like protein, mortality factor on chromosome 4 (*MORF4*) was identified. From structural homology, other family proteins including MRG15 and MRGX were identified and investigated. MRG15 has helix-loop-helix and leucine zipper domains, which are typically found in transcriptional regulators, and a chromodomain thought to be involved in protein-protein interaction in chromatin remodeling factors. MRG15 and -MRGX are expressed ubiquitously in all cells and tissues. Currently, MRG proteins, which have pro-growth activity, are hypothesized to antagonize growth inhibition activity by Morf4.
Mrg15 knockout mice are embryonic lethal, and mouse embryonic fibroblasts derived from Mrg15 null embryos proliferate poorly, enter senescence rapidly, and have impaired DNA repair compared to wild type mice (Tominaga et al., 2005). Mrg15 null embryonic neural stem and progenitor cells also have a decreased capacity for proliferation and differentiation (Garcia et al., 2007). Expression of the cyclin-dependent kinase inhibitor p21 is specifically up-regulated in Mrg15 deficient neural stem/progenitor cells (NSCs). Mrg15 deficient NSCs exhibit severe defects in DNA damage response following ionizing radiation (Chen et al., 2011).
So far, cancer association of Mrg15 has been poorly shown. No alterations or mutations were identified for MRG15/MORF4L1 in unclassified FA patients and Breast Cancer (BrCa)

familial cases. No significant associations between common MORF4L1 variants and BrCa risk for BRCA1 or BRCA2 mutation carriers were identified (Martrat et al., 2011).
Yeast Eaf3 is a shared component of the NuA4 complex and Rpd3 histone deacetylase complex. The loss of Eaf3 greatly alters the genomic profile of histone acetylation (Reid et al., 2004).

4.14 GAS41/Yaf9/Yaf9

GAS41 (Glioma Amplified Sequence 41) is a nuclear protein containing a C-terminal alpha-acidic activation domain and an N-terminal YEATS domain (Fischer et al., 1997). The YEATS domain family of proteins is well conserved from yeast to human, and functions as transcriptional regulators as a part of multiprotein complexes. GAS41 is associated with TFIIF via its YEATS domain. GAS41 is also a subunit of the human TIP60 and SCRAP complexes (Doyon et al., 2004; Cai et al., 2005). In addition, GAS41 physically interacts with transforming acidic coiled-coil 1(TACC1) protein, microtubule-associated colonic and hepatic tumor overexpressed (ch-TOG) protein and nuclear matrix (NuMA) protein (Lauffart et al., 2002; Harborth et al., 2000).
Yeast homolog Yaf9 encodes a protein of 226 residues, containing an N-terminal YEATS domain and a C-terminal predicted coiled-coil sequence (Le Masson et al., 2003). Deletion of Yaf9 shows pleiotropic effect, including sensitivity to a variety of drugs such as cadmium, cecium chrolide, cycloheximide, and microtubule inhibitor benomyl. The phenotype is associated with a change in transcriptome. The transcriptomic change can be suppressed by Bdf1 multicopy expression, suggesting functional overlapping between these two components (Bianchi et al., 2004). Since human Brd8 (Bdf1) was isolated from a screen that influenced sensitivity to microtubule inhibitors, it is tempting to speculate that Brd8-GAS41 (Bdf1-yaf9) may be an interface module to genes involved in sensitivity to microtubule inhibitors.

4.15 */Eaf5/*

Yeast Eaf5 (Esa1p-associated factor 5) is a component of yeast NuA4 complex (Nourani et al., 2001). Its direct human counterpart is unclear. Eaf5 protein forms subcomplex with Eaf7, and Eaf5 interacts with NuA4 complex (Mitchell et al., 2008). Eaf5 deletion strain is viable, and shows resistance to chemicals such as acetic acid and lactic acid (Kawahata et al., 2006).
Deletion strains of *eaf5* and *eaf7* display similarity in microarray transcriptional profiles (Krogan et al., 2006).

4.16 MRGBP/Eaf7/*

MRGBP (MRG Binding Protein) was identified as a NuA4 component with biochemical purification (Cai et al., 2003). MRGBP is also a component of the human INO80 complex (Jin et al., 2005). Crystal structure determination of the MRG domain indicated that MRGBP has structural similarity to DNA binding domains of the tyrosine site-specific recombinases XerD, lambda integrase, and Cre (Bowman et al., 2006).
In human colon cancer, MRGBP was upregulated in the majority of the cancers. Inhibition of MRGBP with shRNA in vitro resulted in an inhibition of cell growth (Yamaguchi et al., 2010). High levels of MRGBP expression were observed more frequently in human colonic carcinomas (45%) than adenomas (5%), linking its role to malignant properties of colorectal tumors (Yamaguchi et al., 2011).

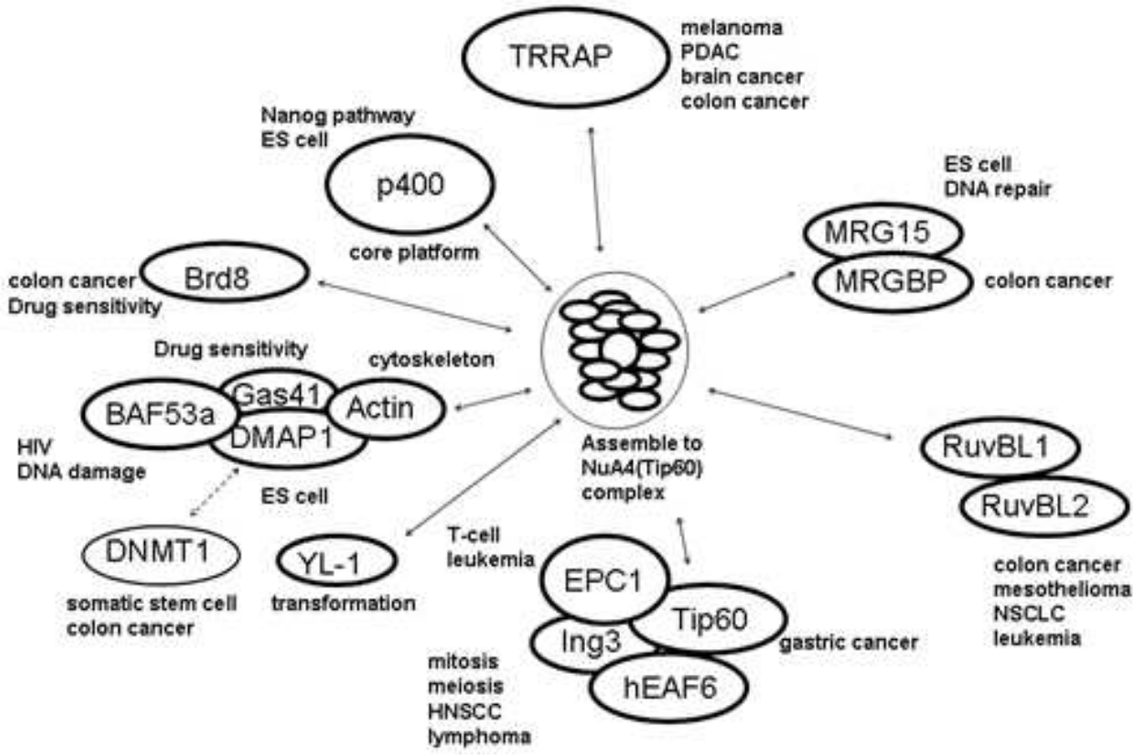

Fig. 1. Tip60 (NuA4) complex is assembled by combining subcomplexes and subunits. Each subunit of Tip60 (NuA4) complex is linked to different biological events, presumably because each subunit represents an interface to the proteins involved in the particular events. Inhibition of a subunit results in different phenotypes, which may provide intervention opportunities for cancer prevention and/or therapeutic purpose.
Abbreviations: PDAC (Pancreatic Ductal Adeno Carcinoma); ES cell (Embryonic Stem cell); NSCLC (Non Small Cell Lung Cancer); HNSCC (Head and Neck Small Cell Carcinoma).

4.17 hEaf6/Eaf6/*

Human Eaf6 was isolated as a component of Tip60 (NuA4) complex (Doyon et al., 2004). hEaf6 is also a component of HBO and/or MOZ/MORF HAT complex (Ullah et al., 2008; Saksouk et al., 2009).

5. Relevance to colon cancer

Among multiple subunits, Brd8, MRGBP, RuvBL1 and RuvBL2 show particularly strong connections to colon cancer. These subunits are overexpressed in colon cancer (Yamada and Rao, 2009; Yamaguchi et al.,2010, 2011; Carlson et al., 2003; Lauscher et al., 2007; Graudens et al., 2006; Ki et al., 2007). Brd8 plays a role in survival and/or drug resistance of cultured colon cancer cells. MRGBP also plays a role in survival of cultured colon cancer cells. RuvBL1 is an important cofactor in beta-catenin/TCF gene regulation, and expression of its dominant-negative form inhibited β-catenin-mediated neoplastic transformation of

immortalized rat epithelial cells and anchorage-independent growth of human colon cancer cells with deregulated β-catenin (Feng et al., 2003).
In addition, DMAP1 associated proteins (DNMT1,3A and 3B) were progressively upregulated in colorectal adenoma-carcinoma sequence (Schmidt et al., 2007). DNMT1 may play a role in colon cancer progression directly or indirectly.

6. Subunit-specific targeting strategy

As in above, deregulations in subunits of human Tip60 (NuA4) complex are common in various cancers, and the complex is gaining attention as a potential target for cancer therapy. However, concerns for targeting whole Tip60 (NuA4) complex are raised because the complex plays essential roles for cellular survival and targeting the core components of the complex would impair the essential functions, which may lead to general toxicity to both normal and cancer cells. Although many successful drugs in existence do target essential and ubiquitous cellular components (e.g. Taxol for microtubule, Velcade for proteasome), the concern needs to be addressed.
As a rebuttal, targeting of each component has been proposed. Although the Tip60 (NuA4) complex is thought to function as a complex, targeting each subunit does not necessarily show the same biological effect and phenotype empirically, suggesting unique roles of each subunit. This fact may be exploited for developing therapeutic strategy. Further investigation of the unique roles of each subunit would allow us to develop subunit-specific targeting strategies for therapeutic purpose.
Extrapolating from yeast and mice results, the following subunits of Tip60 (NuA4) complex are essential for cellular survival; TRRAP, p400, EPC1, Tip60, DMAP1, RuvBL1, RuvBL2, BAF53a and Actin. Inhibiting these subunits may require caution. Components whose inhibition may not directly or immediately kill cells are; Brd8, ING3, YL-1, MRG15, GAS41, MRGBP and hEaf6. Inhibition of these components may prove valuable as an adjuvant approach to improve other therapies such as chemo- and radio-therapies.
In some subunits and associating factors (Brd8, MRGBP, DNMT1), overexpression is correlated to stage advancement of colon cancer, thus drug-mediated inhibition seems intuitively appropriate. GAS41 and Brd8 may have a more prominent effect on cellular sensitivity to anti-microtubule drugs. It is possible that chemoresistance of colon cancer is at least in part provided by deregulation of these subunits, and drug-mediated inhibition of these subunits results in enhancement of the effect of these drugs.

7. Conclusion

Accumulating evidence supports that the Tip60 (NuA4) complex plays a role in various cancers including that in colon, and possibly in drug sensitivity/resistance of cells. Targeting the components may prove successful in preventing cancer and/or in killing or chemosensitizing cancer cells. Since the major hindrance to a colon cancer cure is its chemoresistance, chemosensitizing through modulation of the Tip60 (NuA4) complex component seems to be a novel and attractive strategy. However, thus far validation of Tip60 (NuA4) complex, or the subunit(s), as a therapeutic target is yet to be performed. Continuing investigation is required to translate current knowledge to clinical or translational studies. Strategies for targeting (e.g. siRNA, small molecule) should be explored.

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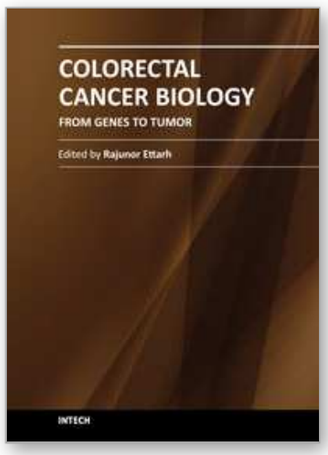

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Colorectal cancer is a common disease, affecting millions worldwide and represents a global health problem. Effective therapeutic solutions and control measures for the disease will come from the collective research efforts of clinicians and scientists worldwide. This book presents the current status of the strides being made to understand the fundamental scientific basis of colorectal cancer. It provides contributions from scientists, clinicians and investigators from 20 different countries. The four sections of this volume examine the evidence and data in relation to genes and various polymorphisms, tumor microenvironment and infections associated with colorectal cancer. An increasingly better appreciation of the complex inter-connected basic biology of colorectal cancer will translate into effective measures for management and treatment of the disease. Research scientists and investigators as well as clinicians searching for a good understanding of the disease will find this book useful.

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