Molecular Therapy
Oncology
Review

Genetic dysregulation of EP300 in cancers in light of cancer epigenome control – targeting of p300-proficient and -deficient cancers

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Some cancer types including bladder, cervical, and uterine cancers are characterized by frequent mutations in EP300 that encode histone acetyltransferase p300. This enzyme can act both as a tumor suppressor and oncogene. In this review, we describe the role of p300 in cancer initiation and progression regarding EP300 aberrations that have been identified in TGCA Pan-Cancer Atlas studies and we also discuss possible anticancer strategies that target EP300 mutated cancers. Copy number alterations, truncating mutations, and abnormal EP300 transcriptions that affect p300 abundance and activity are associated with several pathological features such as tumor grading, metastases, and patient survival. Elevated EP300 correlates with a higher mRNA level of other epigenetic factors and chromatin remodeling enzymes that co-operate with p300 in creating permissive conditions for malignant transformation, tumor growth and metastases. The status of EP300 expression can be considered as a prognostic marker for anticancer immunotherapy efficacy, as EP300 mutations are followed by an increased expression of PDL-1.HAT activators such as CTB or YF2 can be applied for p300-deficient patients, whereas the natural and synthetic inhibitors of p300 activity, as well as dual HAT/bromodomain inhibitors and the PROTAC degradation of p300, may serve as strategies in the fight against p300-fueled cancers.

INTRODUCTION

Cancer is considered a complex disease, being a multistep process associated with the accumulation of genetic alterations. However, it is now widely accepted that non-genetic factors also contribute to cancer development and progression,[1] represented by *inter alia* epigenetic mechanisms that alter gene expression patterns without changing the DNA sequence. Epigenetic changes can be divided into three main categories: the modification of nucleic acids (such as DNA methylation), post-translational modifications (PTMs) of histone tails, and the alteration of gene expression by non-coding RNAs (e.g., microRNAs [miRNAs] and long non-coding RNAs [lncRNAs]).[2] The first two groups represent the covalent modifications of nucleotides and amino acid residues, usually working together to integrate regulatory inputs and leading to coordinated alteration in chromatin structure and function. This defines the cell transcriptomes at the earliest step of RNA synthesis. The existence of many combinations of modifications that are either more likely to occur together, or mutually exclusive, suggest a functional crosstalk between some epigenetic marks. This can occur between modified DNA and histones, distinct modifications on the same histone tail, on neighboring histones within the same nucleosome, or on neighboring nucleosomes in a chromatin domain. Well-described modifications include acetylation, methylation, phosphorylation, ADP ribosylation, ubiquitination, citrullination, and SUMOylation,[3] which regulate the nucleosome structure and dynamics by directly altering histone-histone or DNA-histone interactions and by recruiting chromatin remodeling enzymes resulting in positive and negative feedback loops.[4,5] Various histone modifications that are altered by aberrantly expressed modifier enzymes contribute to tumor development, progression, and metastasis. Among them, altered histone acetylation is most frequently referred to.[6] This modification usually marks active transcription, as it neutralizes the positive charge on the histone lysine residues, thereby facilitating nucleosome disassembly and increases the chromatin accessibility for RNA polymerase and transcription factors, initiating or enhancing ongoing transcription.[4,7] Histone tail acetylation level is dynamically adjusted in different physiological conditions, with the required balance being controlled by the action of two enzyme families: histone acetyl transferases (HATs) and histone deacetylases (HDACs). HATs catalyze the transfer of an acetyl group from acetyl-CoA molecules to the lysine ε-amino groups in the N-terminal tails of histones, whereas the HDACs remove the acetyl groups, thus working as repressors of gene expression.[8] H3/H4 acetylation is mediated by other PTMs, such as active chromatin methylation marks—H3K4me3 and H3K4me1—which do not alter the histone charge but recruit HATs and other chromatin modifiers to specific chromatin sites[5,9,10]; and, vice versa, H3K27ac in the promoter region may lead to H3K4me3 enrichment and transcriptional activation.[11] Active and repressive chromatin marks are summarized in Figure 1.

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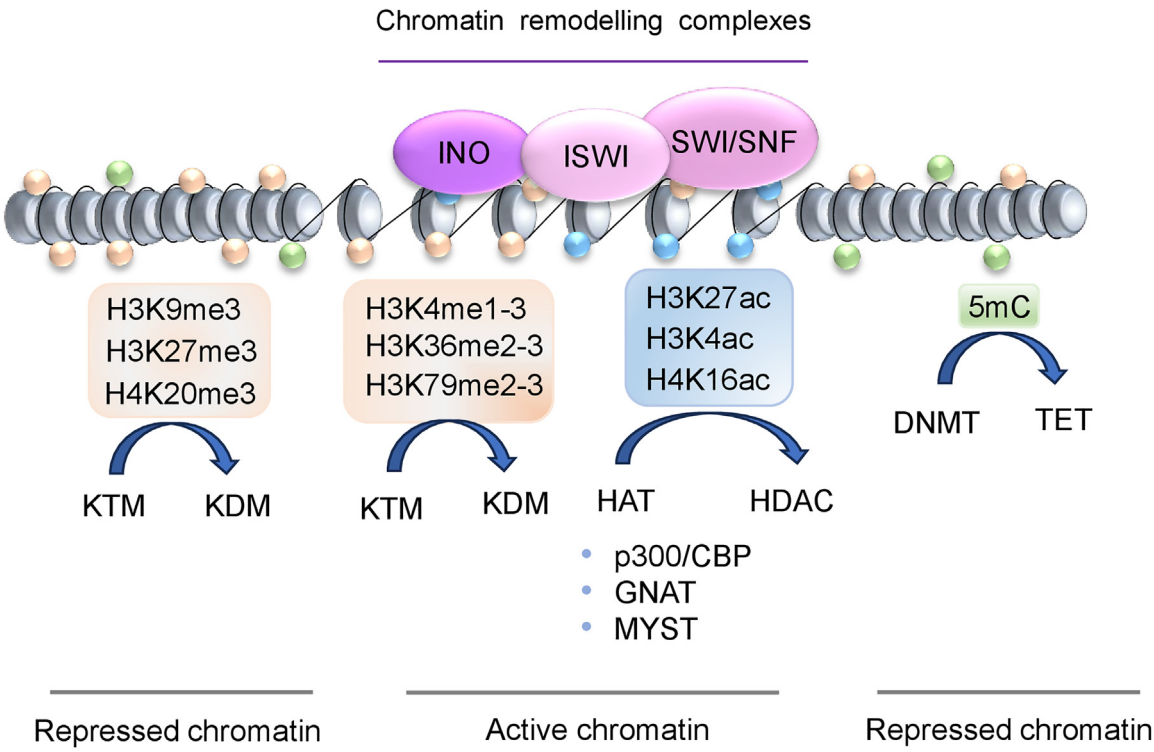

Figure 1. Coordinated insertion and deletion of post-translational modifications shape chromatin structure to allow transcription of cancer-promoting genes or to repress tumor suppressors

Histone acetylation by histone acetyltransferases (p300/CBP, GNAT, MYST) and deacetylation by the HDAC family of deacetylases cooperates with other histone and DNA-modifying enzymes. Histone methylation, which refers to the addition of either one, two, or three methyl groups by histone lysine methyltransferases (KMTs) or protein arginine N-methyltransferases (PRMTs), can both facilitate and repress transcription.[12,13] KMT make use of S-5′-adenosyl-L-methionine (SAM) as a methyl donor to transfer of methyl groups to lysine's residues on histone H3 and H4 tails, whereas histone lysine demethylases (KDMs) remove the methylation marks.[13] H3K4me1, H3K4me2, H3K4me3, H3K36me2, and H3K36me3 are associated with a transcription-permissive environment, whereas H3K9me3, H3K27me3, and H4K20me3 are considered as repressive marks.[14] As well as histone tail deacetylation, DNA methylation, which is strictly connected with HDAC activity, is mostly referred as a repressive mark present predominantly on CpG dinucleotides that prevents transcriptional activation of genic regions, which are meant to be silenced in a cell-type specific manner.[15] DNA methylation is catalyzed by the DNA methyltransferase (DNMT) family, including DNMT1, DNMT3A, and DNMT3B, which utilize SAM as a methyl donor to form 5-methycytosine (5mC). Conversely, the 10-11 translocation (TET) family enzymes mediate DNA demethylation in an indirect manner through the oxidization of 5-methylcytosine.[16] Histone lysine acetylation has been reported to recruit SWI/SNF chromatin remodelers that change the nucleosome structure.[4,17] Several chromatin remodelers belonging to CHD and ISWI are known to read methylation marks and participate in the regulation of gene expression via PHD fingers.[18,19]

Mammalian HATs, which are also named lysine acetyltransferases (KATs) because of their capacity to acetylate non-histone proteins, are grouped into three main families based on their structural homology and substrate binding: Gcn5-related N-acetyltransferases (GNAT), p300 and CREB-binding proteins (p300/CBP), and the MYST-family histone acetyltransferases.[20,21] These families share a conserved central core region that contributes to the acetyl-CoA binding (KAT) domain but differ in the N- and C-terminal region flanking the core, which is responsible for substrate specificity. HDACs are often components of large protein complexes and are recruited to DNA methylation by methyl DNA-binding proteins.[8]

In addition to the direct effects on nucleosome structures, lysine acetylation has been reported to act as an epigenetic mark specifically recognized by bromodomain-containing transcription factors. These proteins recruit chromatin remodelers that change the nucleosome structure.[4] These essential epigenetic regulators utilize ATP hydrolysis to mobilize nucleosomes, thereby linking the chromatin structure with gene transcription. According to the homology in the catalytic ATPases and associated subunits, ATP-dependent chromatin-remodeling complexes can be divided into four subfamilies: switch/sucrose non-fermentable (SWI/SNF), imitation switch (ISWI), chromodomain helicase DNA-binding (CHD), and inositol 80 (INO80).[17]

Genomic studies have clearly implicated the dysregulation of chromatin modifiers for numerous cancer types and the recurrent mutations that occur in these enzyme genes. Intriguingly, the functionality of certain chromatin modifiers was elevated in some and declined in other cancers, therefore suggesting a dual role in malignancies.[22] HATs may function as tumor suppressors, helping cells to control cellular proliferation and cell cycles, or act as oncogenes, activating malignant proteins via an abnormal acetylation.[23] The

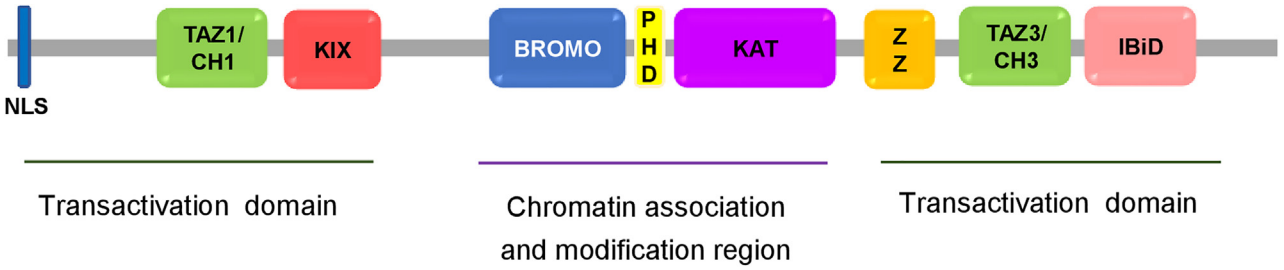

Figure 2. Schematic structure of p300 protein including its functional and structural domains and their localization

acetyltransferase E1A-binding protein P300 (EP300; also known as P300 or KAT2B) is one of the most frequently altered HATs in cancers, with altered expression in some tumors,[24–27] but somatic mutations in *EP300* have been also identified in multiple cancers,[28,29] This enzyme modifies histones within proximal and distal gene regulatory elements and its activity is closely linked to excessive H3K27 acetylation at the enhancer loci, which is massively deregulated in various cancer types.[29] P300 is closely related to CREB-binding protein (CREBBP, also known as CBP or KAT2A),[30] and increased acetylation levels caused specifically by CBP/p300 promotes cancer metastasis, immune evasion, and drug resistance.[31]

In this review, we present a comprehensive analysis of p300 dysregulation in cancer but focus in detail on the expression changes of this gene. Publicly available datasets allowed us to describe an abundance of EP300 alterations (mutations, copy number alterations, and expression changes) in various types of cancer and correlate the expression of EP300 with survival rate and clinicopathological features such as histological subtypes, tumor stages, and metastases. The relationship between p300 and the expression of other genes involved in gene expression regulation is reviewed and the expression status of p300 as prognostic mark and therapeutic target for anticancer approaches is discussed.

p300 structure and function

Transcriptional co-activator protein p300 is ubiquitously expressed in all mammals and other multicellular organisms. In humans, the *EP300* gene is located in chromosome 22 at the 22q13 locus. The gene is comprised of 31 coding exons, which span approximately 90 kb giving the product of the 300 kDa protein.[32] Several protein-interacting domains of this large multidomain protein flank the central chromatin association and modification region. These consist of the KAT acetyltransferase activity domain and the bromodomain, as well as the RING and PHD, which regulate KAT domain activity in an acetylation-dependent manner. Due to the presence of both the KAT and bromodomain, this protein can act as both a "writer" and a "reader" of lysine acetylation.[33] Additional fragments, include the cysteine-histidine-rich region 1 (CH1), encompassing the transcriptional adapter zinc finger 1 (TAZ1) domain, the KIX domain, another cysteine-histidine-rich region (CH3) containing the transcriptional adapter zinc finger 2 (TAZ2) domain, a ZZ-type zinc finger domain, and the nuclear receptor co-activator binding domain, also known as the interferon-binding domain (Figure 2). These TADs mediate the interactions with other DNA-binding transcription factors including other coactivators.[34] A new line of evidence suggests that TAZ2 inhibits the HAT activity by modulating p300 autoacetylation and that this autoinhibition is alleviated when TAZ2 binds to transcription factors, leading to an active acetylation of p300 substrates.[35]

P300 and its homolog CBP share high sequence identity in several structured regions. Sequence alignments of these two enzymes revealed an ∼90% homology in the KAT domain, and an ∼93% homology in the bromodomain. However, the homology is substantially lower outside of these highly conserved domains. Accumulating evidence suggests that the two acetyltransferases have unique roles in cells. CBP and p300 acetylate multiple lysines on histone H3 and histone H4, but the functional difference between the two enzymes lies in their specificity and selectivity for the acetylated residues, and is dependent on whether histone or acetyl-CoA is limiting.[36] In mice, heterozygous inactivation of p300 leads to more severe abnormalities in heart, lung, and small intestine formation than inactivation of CBP.

Although P300/CBP belongs to the family of histone acetyltransferases, its enzymatic activity is not just limited to histones, but also regulates transcription through remodeling other chromatin-associated proteins and upstream signaling mediators, thereby playing an important role in cell proliferation and differentiation. P300 has been shown to acetylate all the acetylation sites of histones H2A and H2B, and K14, K18, K27, and K56 from H3, and K5 and K8 from H4 *in vitro*.[34] In addition, this KAT interacts with a wide spectrum of transcription factors including protooncogenes (MYC,[37] MYB,[38] and GATA-3[39]), tumor suppressors (p53,[40,41] HBP1,[42] HIPK2,[43] and FOXO3[44,45] and other transcription factors, which may affect cancerogenesis and cancer progression (E2F1,[46,47] PARP1,[48] HIF1,[49] STAT-3,[50] and HSPA5).[51] p300 acts as a coactivator for nuclear receptors such as the androgen receptor (AR)[52] and estrogen receptor, facilitating the growth of hormone-dependent cancers.[53]

EP300 mutations in cancers

Analysis of 32 TGCA Pan-Cancer Atlas studies (10,967 samples) using the cBioPortal for Cancer Genomics[54,55] revealed *EP300* mutations with the approximate ratio of 10% in all cancer samples tested (1,083 samples). It increased to 23.2% in melanomas and genitourinary cancers (Figure 3A). Point mutations (37% of altered samples)

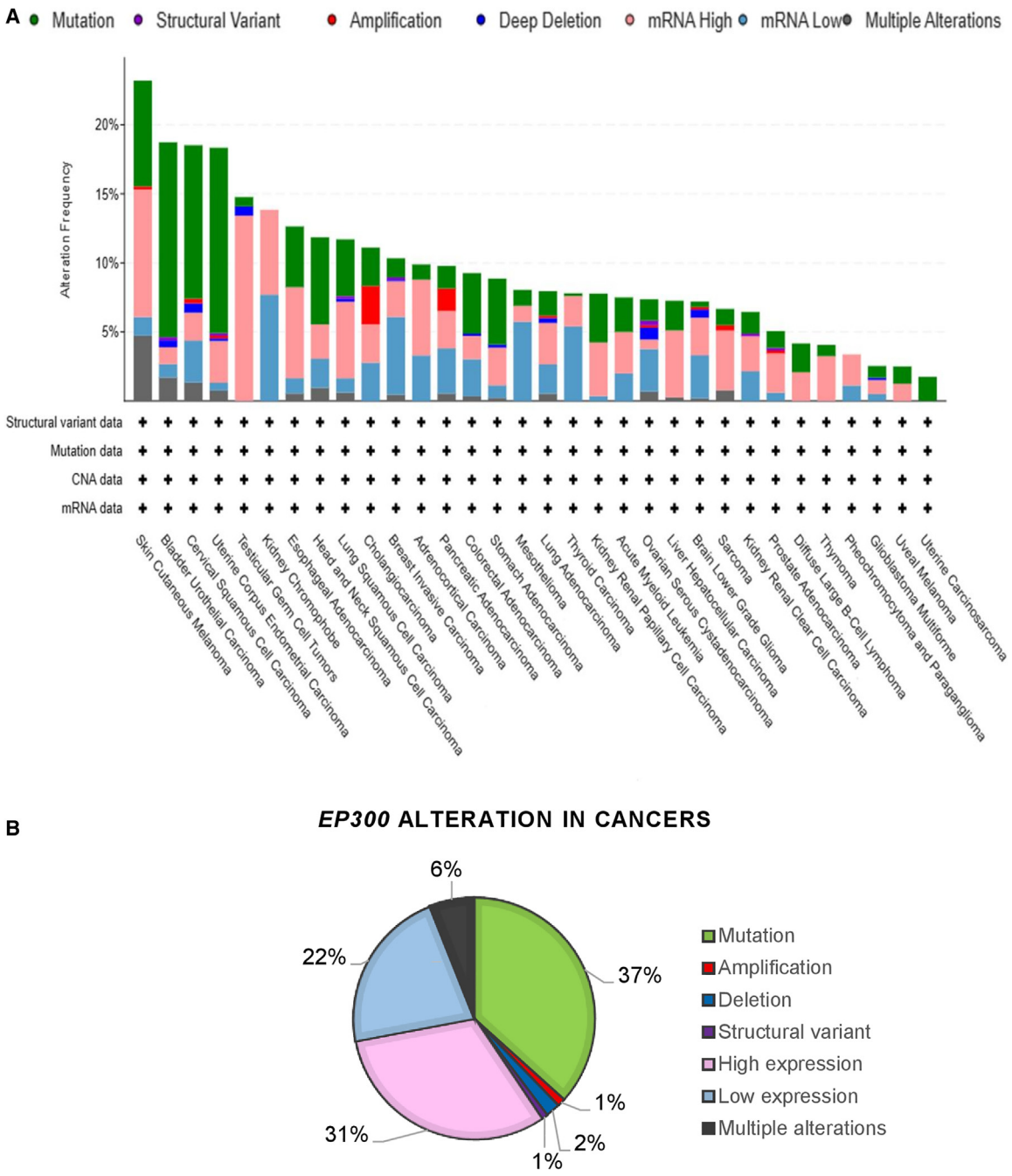

Figure 3. EP300 alterations in cancers

(A) *EP300* changes across cancer types and (B) quantitative summary of *EP300* changes in cancers was generated in cBioPortal based on the TCGA Pan-Cancer dataset.

and changes in gene expression without genetic alterations (high expression 31% and low expression 22%) represented the most frequently occurring cases (Figure 3B).

Missense and truncating mutations occur most often among the somatic mutations and account for approximately 93% of all detected changes (Figure 4A). The majority of observed missense alterations that are spread along *EP300* gene are assigned to passenger-type mutations (Figure 4B). These changes in cancer genomes are not considered significant in the initiation or progression of cancer since the selective growth advantage has not been observed.[56] On the contrary, the driver mutations that provide a cancer cell with beneficial

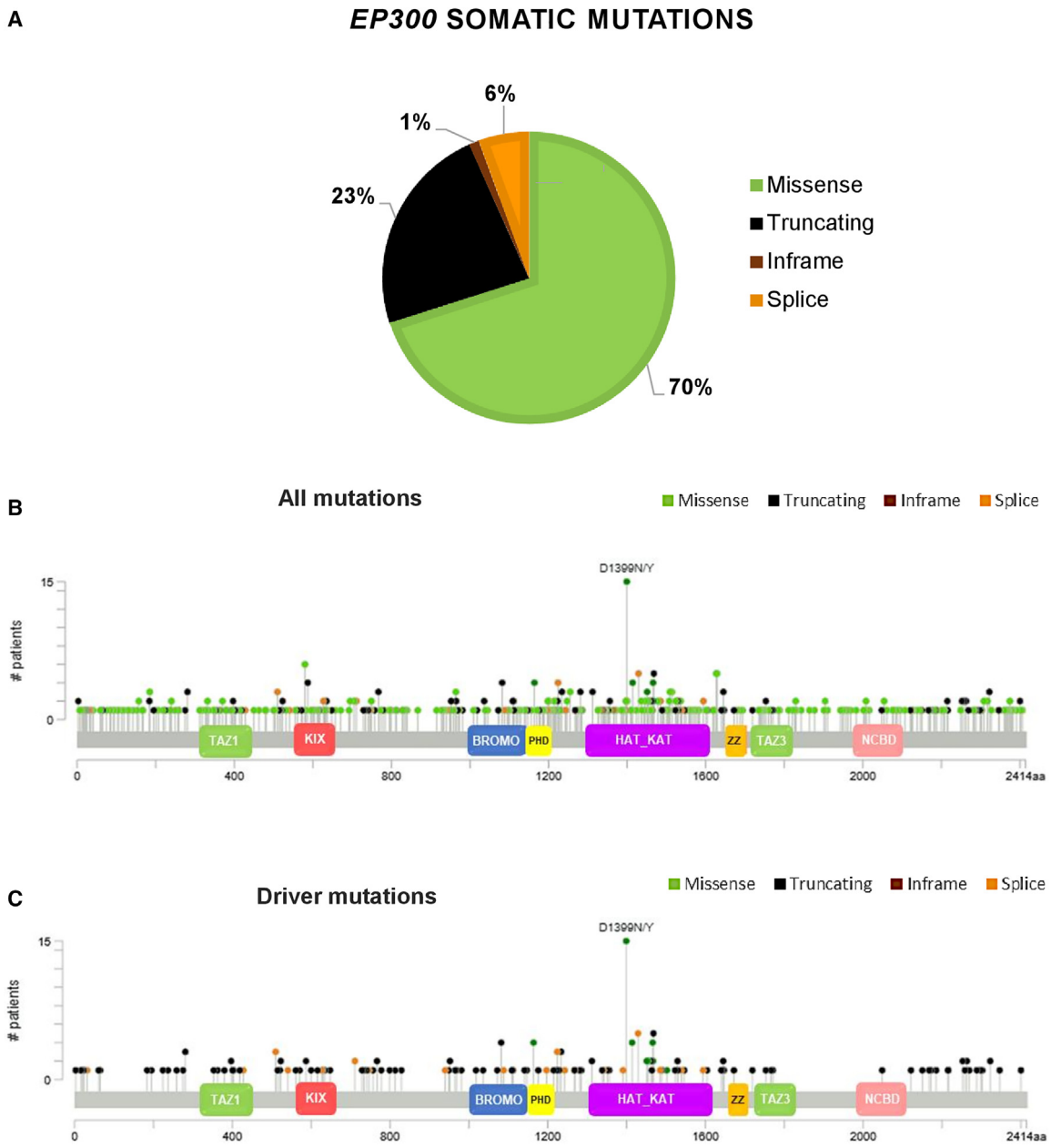

Figure 4. EP300 somatic mutations in cancers

(A) Frequency of EP300 somatic mutations in cancers, (B) localization of all somatic mutations in EP300 gene, and (C) localization of driver mutations in EP300 structure; (B) and (C) were generated in cBioPortal based on the TCGA Pan-Cancer dataset.

adaptative features, were mainly identified in the catalytic domain and bromodomain/PHD region (Figure 4C). Among them, the most frequent substitution D1399N/Y changed the conformation of histone acetyltransferase KAT domain in the p300 protein, thereby abolishing its autoacetylation activity that is essential for proper protein functioning.[57] Other mutations in the KAT domain (Y1414C/D, H1451L, and P1502L) similarly disrupted the acetyltransferase function.[58,59] Deletions within the PHD finger that regulates p300 catalytic activity, reduced the p300 efficacy in acetylating histones, but surprisingly retained the capability of the enzyme to acetylate non-histone proteins such as p53.[33] Protein-truncating variants led to a shortening or complete protein loss of p300.[60] However, truncated variants with an intact catalytic domain can still maintain their function. It has been shown that the TAZ2 domain cooperates with other HAT neighboring domains to maintain the HAT active site in a closed state. Truncating TAZ2 induces a conformational change

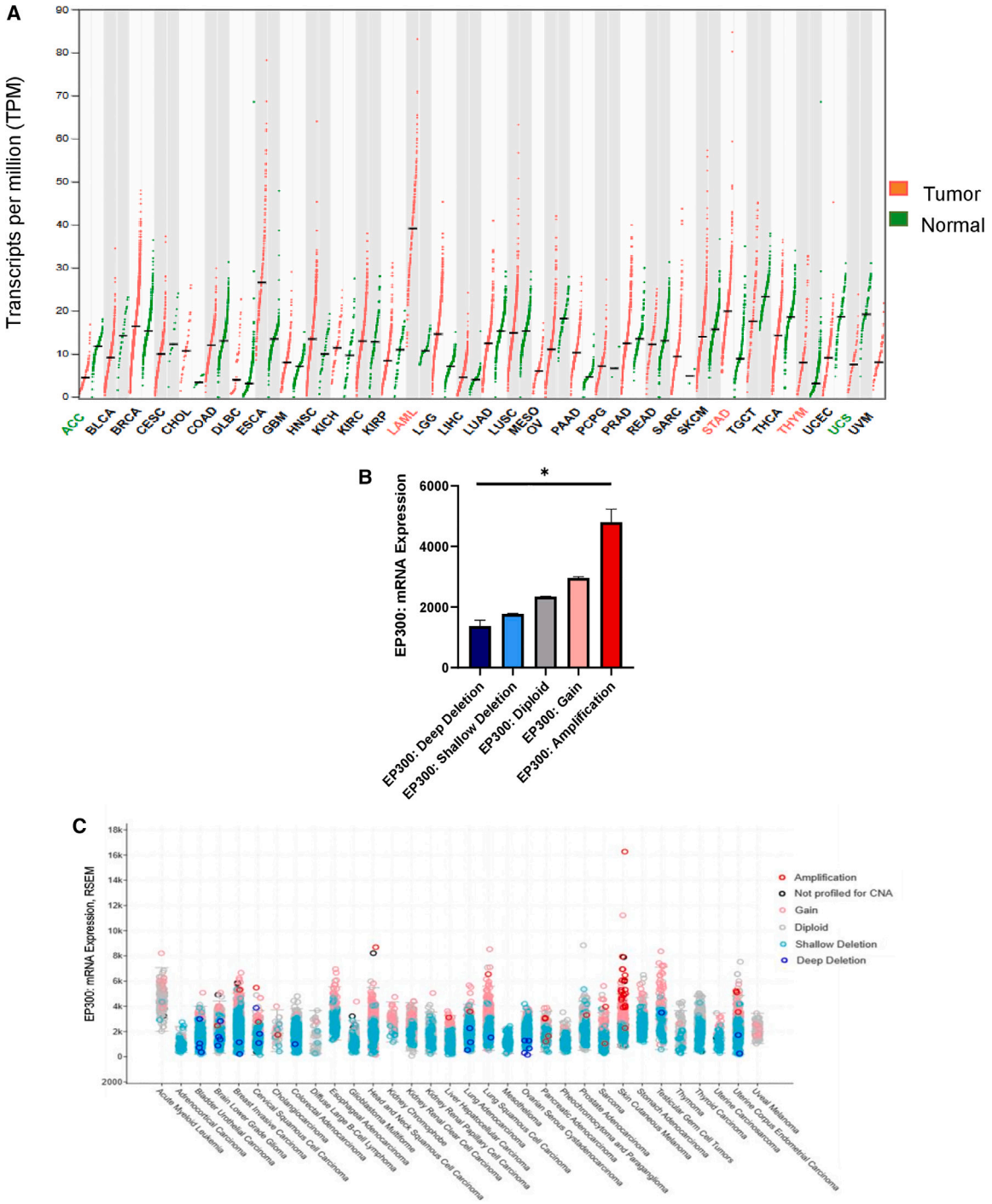

Figure 5. EP300 expression in cancers

(A) Comparison of *EP300* expression in cancers and normal tissues. ACC, adrenocortical cancer; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower-grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin

(legend continued on next page)

that opens the active site for substrate acetylation and confers an over-activation of p300.[35] Interestingly, *EP300* mutations may co-exist with mutations in *CBP*. In the 32 studies analyzed, 329 cancer patients were characterized by simultaneous alteration in these two genes. Similarly to *EP300*, the mutations in CBP occurred most frequently in the KAT domain.

COPY NUMBER ALTERATION AND EXPRESSION CHANGES OF EP300 IN CANCERS CLINICAL OUTCOMES, PROGNOSES, AND FEATURES

To compare the transcription status of *EP300* and to identify the possible expression changes of *EP300* in cancer, we compared selected features between the tumor and normal samples from the TCGA and GTEx databases using GEPIA 2.[61] As shown in Figure 5A, the mRNA level of EP300 varied in numerous normal and cancerous tissues. Among all the cancers that were considered, thymoma, stomach adenocarcinoma, and acute myeloid leukemia were characterized by a substantial increase in expression of EP300, whereas a decline was found in uterine carcinosarcoma and adenoid cystic carcinoma. The yield of the EP300 transcript can be determined by the rate of RNA synthesis, but also by the alteration of gene copy numbers that were shown to affect the expression level of some specific genes in cancers, hence promoting the development and progression of the disease. The results of pan-cancer studies provided evidence for strong correlation and a positive linear influence of the copy number on the expression of the majority of genes considered.[62] However, it was also noted that, due to transcriptional adaptive mechanisms, changes in the gene copy number at the genome level did not always translate proportionally into altered gene expression levels.[63] The causative interdependence between mRNA (mRNA expression *Z* scores relative to normal samples) and the copy number of EP300 was also found in TGCA Pan-Cancer Atlas studies (10,967 samples) (Figures 5B and 5C), and suggest that genetic variation generated a direct effect on the gene transcriptional level.

The increase in the expression and copy number of EP300 is associated with several clinicopathological features that specify tumor stages and prognosis such as grading, metastases, and patient survival in some cancer types. Cancer grading is used to predict the clinical behavior of malignancies and establish appropriate therapies.[64] The grade score (numerical: G1–G4) increases with decreasing cellular differentiation: G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; and G4, undifferentiated/anaplastic.[65] The degree of resemblance between the tumor and its tissue of origin is assessed based on morphological criteria. A high degree of differentiation meaning that the neoplasia is morphologically similar to the native organ and forms neoplastic organoid structures, whereas tumors in low stages of differentiation gradually lose the capacity for structural organization and start to display reduced cohesiveness. The term anaplasia signifies tumor morphology where all similarity with the origin has been lost.[66] Malignant neoplasms range from well differentiated to undifferentiated. In general, increasingly undifferentiated tumors are usually more aggressive.[67] Evaluation of the EP300 expression at different stages of tumor dedifferentiation shows that expression increases in the tumor cells that are not fully differentiated but decreases in undifferentiated tumors (Figure 6A). Since EP300 regulates various key physiological functions, including cell proliferation, differentiation, and somatic cell reprogramming, higher EP300 abundance and intracellular overall activity may facilitate tumor initiation and progression at an early stage.[30] P300 acetylates pluripotency-related transcription factors and enhances their transcription activity, thus promoting stemness acquisition. In cancer, EP300 was considered as an oncogene capable of supporting tumor growth and metastatic potential and facilitating cancer stemness.[68] Deficiency of EP300 abolished the cancer stem cell phenotype by reducing tumor sphere formation *in vitro* and in a xenograft mouse model *in vivo*,[69] meaning a higher activity of p300 may promote the initial malignant transformation. However, in line with the observed reinstatement of p300 levels in high-grade tumors, the decline of EP300 directly suppresses GATA6 expression, which interferes with the GATA6-regulated differentiation program and leads to a phenotypic transition from the classical subtype to the dedifferentiated basal-like/squamous subtype of pancreatic cancer.[70] Although a late decrease in p300 expression may look surprising, accumulating mutations and chromosome aberrations are likely to lead to the inactivation of numerous genes, including *EP300* and p300-fueled epigenetic reprogramming and the adaptation of cancer cells may be dispensable in advanced, high-grade tumors. One line of evidence suggests that strongly elevated miRNA targets mRNA of EP300 in advanced cancers.[71]

Another internationally accepted criterion for cancer staging, the tumor-node-metastasis (TNM) system, includes tumor size and local growth (T), the extent of lymph node metastases (N), and the occurrence of distant metastases (M).[64] T is used to describe the size of the primary tumor and invasion into adjacent tissues. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. N describes the regional lymph node involvement of the tumor. Lymph nodes function as biological filters with fluid from body tissues being absorbed into lymphatic capillaries and flowing to the lymph nodes. N0 indicates zero regional nodal spread, while N1–N3 indicates some degree of nodal spread, with a progressively distal spread from N1 to N3. M identifies the presence of distant metastases of the primary tumor. Metastasis is when the tumor spreads beyond the regional lymph nodes. A tumor is classified as M0 if there are no distant metastases present, whereas M1 is assigned to distant metastases.[72] The increase in tumor size did not result in any considerable change in EP300 expression (Figure 6B). This is in line with previously published

cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THYM, thymoma; THCA, thyroid carcinoma; UCS, uterine carcinosarcoma; UCEC, uterine corpus endometrial carcinoma; UVM, uveal melanoma. (B) Association of *EP300* expression with copy number alterations in cancers. (C) Expression of *EP300* across cancer types, generated in cBioPortal based on TCGA Pan-Cancer datasets. The comparison in (A) was generated using GEPIA 2. (B) TCGA-Pan Cancer datasets available in cBioPortal was analyzed using GraphPad Prism 8.

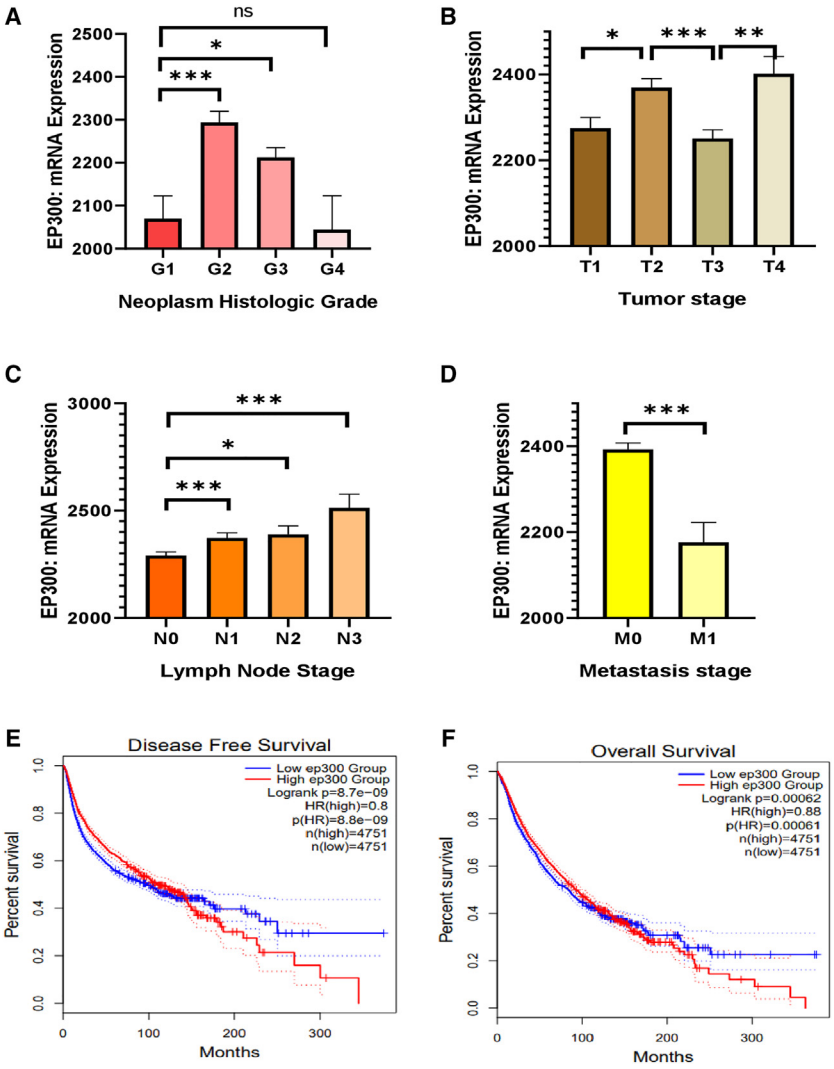

Figure 6. Association of *EP300* expression with clinical parameters and outcomes

The link between EP300 expression and tumor histologic grade is shown in (A), with tumor stage in (B), lymph node stage in (C), and metastasis stage in (D). The disease-free survival and overall patient survival in relation to EP300 expression is shown in (E) and (F), respectively. TCGA-Pan Cancer datasets available in cBioPortal were analyzed using GraphPad Prism 8 (A–D), and generated using GEPIA 2 (E and F).

observations where no significant correlation was detected between p300 expression and age, sex, tumor location, or depth of invasion.[73] However, the mRNA level of EP300 does correlate with the number of lymph node metastases (Figure 6C). In colorectal cancer, the p300 abundance in tumors was significantly associated with histological grade and lymph node involvement.[73] The enhanced migration potential was previously reported in the breast cancer cell line HS578T-overexpressing EP300, where extensive protein acetylation led to upregulation of mesenchymal markers and increased invasion, anchorage-independent growth, and drug resistance.[71] In an esophageal cancer study, increased p300 expression correlated to a higher histologic grade, T category, and N category.[26] Although a high expression of EP300 appears to promote a change in tumor phenotype and increase tumor invasiveness into lymph nodes, the opposite relationship has been observed for the formation of distant metastases, as metastatic tumors were characterized by lower p300 expression (Figure 6D). Lymph nodes and distant metastases can arise from independent subclones of the primary tumor, with lymph node metastases exhibiting different genetic profiles compared with primary colorectal cancer and distant metastases.[74,75] This suggests that tumor subclones, characterized by low p300 status, are more prone to form distant metastases, whereas high p300 cancer cells invade local lymph nodes. This also agrees with the observed interdependence between p300 expression and tumor grades, since high-grade, undifferentiated cells with lower p300 levels are likely to spread further to distal parts of the body. Moreover, the study comparing highly metastatic pancreatic ductal adenocarcinomas with liver metastases, nonmetastatic, or marginally metastatic cells, provided evidence for the elevated expression of miRNA targeting mRNA of EP300 in a highly metastatic group that was also associated with substantial decline of p300.[71]

Despite the fact that low expression of acetyltransferase appears to promote the formation of distant metastases, higher expression of this protein also led to a poorer disease-free survival (Figure 6E) and overall survival rate of cancer patients (Figure 6F). Some studies documented the beneficial effect of high p300 expression, and were limited to non-small cell lung cancer, melanoma,[76] and glioblastoma.[77] More literature data showed that high expression of p300 is associated with poor overall survival in hepatocellular carcinoma, esophageal squamous cell carcinoma, nasopharyngeal cancer, breast cancer, cutaneous squamous cell carcinoma, and small cell lung cancer,[76] as well as non-small cell lung cancer.[78] A similar result was observed in disease-free survival. High expression of the considered gene correlates with poor prognosis in breast cancer, cutaneous squamous cell carcinoma,[76] esophageal squamous cell carcinoma,[26] and non-small cell lung cancer.[78] The missing piece of information in the diagnosis stage, treatment scheme, or its lack in each of the above studies can be crucial when linking *EP300* expression with patient outcomes and survival.

EP300 IRREGULARITIES IN CANCER

Pro-oncogenic role of *EP300* overexpression

Despite the well-described examples of the tumor-suppressive role of p300, the histone acetyltransferase can also foster cancer progression,

as suggested by the enhanced EP300 expression in early, low-differentiated tumors and in lymph node metastases.

p300 may function as a coactivator of the Myc oncogene and facilitate the initiation of cancerogenesis. Myc-dependent transcription is stimulated in a HAT domain-dependent manner at the Myc target gene promoters.[37] p300 was shown to be an essential coactivator and context-dependent corepressor in the intrinsic transforming ability of c-Myb. The interaction between c-Myb and p300 is essential for the transforming and leukemogenic capabilities of AML1-ETO and MLL fusion oncoproteins, which are products of two of the most frequently occurring chromosomal translocations in human acute myeloid leukemia.[38] Furthermore, p300 binds and acetylates GATA-3, a master regulator of the growth and proliferation of T cells, with possibly GATA-3 acetylation being required for optimal transcriptional regulation of the target genes in T cell neoplasms.[39]

In addition to oncogenes, p300 regulates the activity of nuclear receptors that are involved in cancer cell proliferation. P300 acts as a component of the estrogen receptor (ER) transcriptional complex with its acetyltransferase activity being crucial for ER signaling. Within the complex, HAT directly acetylates ER to enhance the receptor binding to DNA and its transactivation, thereby stimulating mitotic divisions of ER+ breast cancer cells.[53] Interestingly, the histone acetyltransferase activity of p300 supports the expansion of ER-independent triple-negative breast cancer via a functional interaction with the AR. Treatment of triple-negative breast cancer cells[79,80] as well as prostate cancer cells[80,81] with CBP/EP300 inhibitors, downregulates the expression of an AR-dependent genes so these compounds can be considered as drugs to treat ER–/AR+ cancers.

The overexpression of EP300 leads to upregulation of mesenchymal markers and increases the migration, invasion, anchorage-independent growth, and drug resistance in breast cancer cells.[71] Cell proliferation, colony formation, migration, and invasion depend on p300 activity in esophageal squamous carcinoma and the transcription of genes associated with angiogenesis, hypoxia, and epithelial-to-mesenchymal transition substantially decreases upon EP300 knockdown in these cells.[25] In addition, p300 promotes the acetylation of pluripotency-related transcription factors such as *OCT4*, *SOX2*, and *KLF4* and changes their transcription activity, thus regulating the acquisition of stemness markers and features in induced pluripotent stem cells.[68]

A growing body of experimental evidence indicates that cancer drug resistance can be conditioned by p300 activity. For example, the clonogenic potential of docetaxel-resistant prostate cancer cells, their migration, and invasion are fueled by p300, the abundance of which is substantially elevated in the drug-resistant phenotype.[82] The promoter sequences of ATP binding cassette (ABC) transporters, which are overexpressed in cisplatin-resistant breast and lung cancer cell lines, are characterized by a considerable enrichment of p300-catalyzed acetylation of nucleosomes conferring an augmented efflux of anticancer drugs.[83] Cisplatin-induced DNA damage activates the p53-mediated recruitment of p300 to *ABC* gene promoters that are not repressed by the CoREST complex.[84] p300 plays an important role in DNA repair since it is recruited to the sites of DNA breaks, where it facilitates DNA repair and enhances transcription of some DNA repair proteins. Although p300 does not contribute to DNA repair itself, it serves as a cofactor and binding module for multiple proteins that are involved in DNA repair pathways such as PCNA, KU70, and KU80.[85] In triple-negative breast cancer cells, it serves as transcription cofactor of *NEIL3* and *LIG1*, which play an indispensable role in base excision repair.[86] In pancreatic cancer cells it was reported as an anti-apoptotic agent upon gemcitabine-induced DNA damage. p300 targeting by either siRNA or a small-molecule p300 inhibitor enhanced the cytotoxicity of gemcitabine.[85]

Low expression and inactivating mutations in cancer initiation and progression

Deficiency of p300 activity has been weakly linked to genomic instability, the fundamental basis for the initiation and progression of almost all human cancers. Instability usually arises when DNA repair genes and mitotic checkpoint genes, as well as non-classic-caretaker genes such as *TP53* and *ATM*, which are crucial in the DNA damage response, undergo inactivation. Some oncogenes can induce DNA replication fork collapse with an accompanying catastrophe for DNA replication, DNA double-strand breaks, accelerated mutations, and chromosome aberration.[87] Inactivating the mutations in *EP300* causes chronic DNA replication stress, resulting in persistent genomic instability. Aberrant DNA replication in EP300-mutated cells is characterized by increased replisome pausing and nucleolytic degradation of nascently synthesized DNA at stalled forks due to a prominent defect in fork stabilization and protection. This in turn results in the accumulation of single-stranded DNA gaps at the collapsed replication forks.[88] *EP300*-mutated cancers had significantly higher microsatellite instability and tumor mutational burden (TMB), representing the number of mutations per megabase harbored by tumor cells in each neoplasm. High TMB values in *EP300*-mutant-type cancers indicate a potential response to immunotherapy caused by significantly higher programmed death-ligand 1 (PD-L1) expression.[28,89] Moreover, EP300 was co-mutated with DNA mismatch repair genes.[28]

p300 is considered as a tumor-suppressive gene that acts through the promotion of the functions of tumor suppressors such as p53, HBP1, FOXO, and HIPK2. The first of these proteins, transcription factor p53, becomes phosphorylated, released from Mdm2 inhibitory protein, and interacts with p300 in response to DNA damage.[41] p300 is required for full p53 transactivation as well as the downstream p53 effects of growth arrest and/or apoptosis.[90] As with other transcription factors involved in controlling pro-apoptotic genes, p53 is phosphorylated by nuclear serine/threonine kinase HIPK2 upon DNA damage. p300-mediated acetylation of HIPK2 increases the enzyme stability and enhances its tumor-suppressor function.[43] HBP1 activates or represses the expression of some specific genes during cell growth and differentiation. p300-mediated acetylation of HBP1is essential for its transactivation on the p16 promoter and activation

of the cyclin-dependent kinase inhibitor.[42] Decreased acetylation of tumor-suppressor FOXO upon p300 deficiency promotes cell growth and increases the cancer cell resistance to cisplatin.[44] In addition, p300 deletion activates prooncogenic signals such as mitogen-activated protein (MAP) kinase, Janus kinase/signal transducer, and the activator of transcription (STAT) pathways. In chimeric mice, loss of p300 leads to upregulation of NOTCH1, BMI1, MYC, CCNE, and SKP2 oncogenes, as well as the development of thymic lymphoma and histiocytic sarcomas.[31]

p300-depleted cells have aggressive cancer phenotypes that are characterized by loss of cell-cell adhesion, defects in cell-matrix adhesion and increased migration.[91] The deficiency of p300 upregulates the expression of genes associated with adhesion, cytoskeletal remodeling, stemness, apoptosis, and metastasis.[92] The cell responds to EP300 downregulation by acquiring a phenotype that is characteristic of it undergoing epithelial-to-mesenchymal transition (EMT), including enhanced cell motility and invasion, ability to proliferate after anticancer treatment as a consequence of drug resistance, and activation of the EMT regulatory pathway.[93]

Some cancer types lacking p300 became more resistant to anticancer drugs such as paclitaxel,[92] doxorubicin[93,94] and cisplatin.[44] One study documented the development of multidrug resistance (MDR) as a consequence of p300 downregulation.[95] Overexpression of some ABC proteins contributes to MDR considerably, since these membrane transporters are responsible for the efflux of diverse drugs from cancer cells and therefore decreasing intracellular drug concentration and drug toxicity.[96] However, the abovementioned p300-deficient MDR phenotype was drug-transporter independent as P-glycoprotein remained low and cells ineffectively effused a fluorescent derivative of paclitaxel. In this case, lesser activation of apoptosis, caspase-9, and caspase-3/-7 activities were observed, leading to apoptosis evasion.[95]

Relationship of EP300 and other epigenetic regulators in cancer

The expression of *EP300* crosstalk with other epigenetics factors has been studied according to data deposited in TGCA Pan-Cancer Atlas (pan-cancer analysis of whole genomes (ICGC/TCGA, Nature 2020). As shown in Figure 7, a high mRNA level of *EP300* is accompanied by high transcript level of other histone acetyltransferases, histone lysine methyltransferases, histone demethylases, RNA methyltransferases, and SWI/SNF subunits, and by repression of HDACs, histone arginine methyltransferases, and DNA methyltransferases.

Interplay between expression of *EP300*, histone acetylases, and deacetylases

High mRNA level of *EP300 is* accompanied by a high expression of other histone acetyltransferases such as *KAT2B*, *KAT5*, *KAT6A*, *KAT6B*, and *KAT7*, and by the repression of opposing acting HDACs: *HDAC2*, *HDAC4*, *HDAC8*, and *HDAC11* (Figure 7A). This suggests that cancer cells with a high abundance of p300, CBP, and other acetyltransferases are generally susceptible to an elevated status of histone acetylation, while simultaneously having reduced mechanisms to prevent acetylation-driven gene overexpression.

The studies documented co-operation between various acetyltransferases that may act together. For example, NuA4 synergizes locally with the SAGA complex, and is capable of histone acetylation due to the occurrence of a GCN5 subunit with acetyltransferase activity during DSB repair.[97] In contrast, HDAC1 and p300 compete for histone binding since these two opposing acting enzymes can directly interact with the overlapping regions of the histone H3 tail. Moreover, p300 can acetylate HDAC1 and attenuate its deacetylase activity.[98] Therefore, a hyperactive EP300 likely reduces nuclear HDAC activity in cancer cells.[99]

In human gastric cancer cell lines, crosstalk of 4 epigenetic modification types including H3K4me1, H3K4me3, H3K27ac, and m6A were observed, with co-regulation of about 360 protein-coding genes. Nearly 50% of dysregulated genes in tested cancer cell lines were simultaneously regulated by more than one modification type and characterized by a high expression of multiple histone modification writers (SETD1B, KMT2A, and CREBBP) and the low expression of histone modification erasers (KDM1A, KDM1B, HDAC1, and HDAC2). This epigenetic-modification-dysregulated cluster had poor survival, stromal activation, and immune suppression.[100]

Importantly, the low expression of *EP300* is followed by low expression of its homolog: *CBP*. Therefore, the compensation mechanism by CBP seems unlikely in the majority of the considered p300-deficient cancers.

In summary, the positive correlation between transcription of EP300 and other acetyltransferases with simultaneous opposite interconnection with some HDACs indicates the existence of two cancer types in terms of their favored protein acetylation status.

Relationship between expression of *EP300* and histone methylation status

Interestingly, both histone methylases, such as *KMT2A*, *KMT2D*, and *KMT2E*, and demethylases, such as *KDM2A*, *KDM3B*, *KDM5A*, and *KDM6A*, show a positive correlation with a high EP300 expression in TGCA Pan-Cancer Atlas study (Figure 7B). These enzymes of opposite functions form a regulatory loop that controls gene expression. Acetylation of histones H3 and H4 coexists frequently with trimethylation of H3K4 at the promoter and TSS of transcriptionally active genes, as H3K4me3 promotes downstream H3/H4 acetylation by the recruitment of HATs. H3K4me3 readers have been identified in many HAT complexes. For example, SGF29, a component of the SAGA HAT complex, contains a Tudor domain that binds H3K4me3. SGF29 deletion causes the loss of H3K9ac and disassembly of the SAGA complex at target sites.[5] In contrast, acetylation of H3K27 at the promoter region of *IL1RN* and *GRM2* genes leads to H3K4me3 enrichment around TSS and transcriptional activation. Blocking the reading of H3K27ac by BRD proteins abolished H3K27ac-induced H3K4me3 and downstream gene activation.[11] H3K4me1, another mark of active transcription, also demonstrated the relationship with acetylation

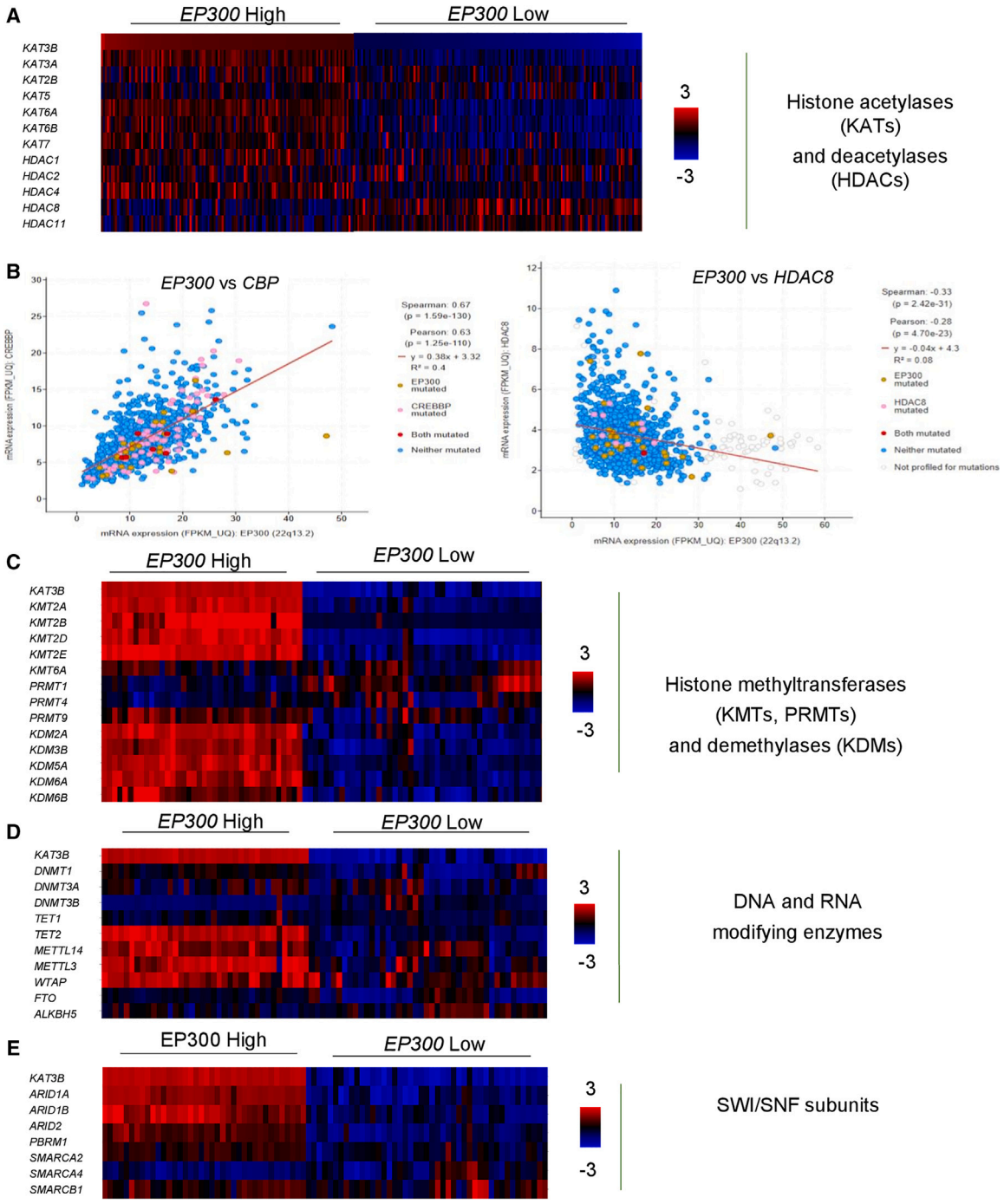

Figure 7. Co-expression of *EP300* with other epigenetic factors

Heatmap presents overexpressed and downregulated *KAT3B* (*EP300*) samples and co-expression of *EP300* with (A) other acetyltransferases (*KATs*) and (B) deacetylases (*HDACs*), histone methyltransferases (KMTs, PRMTs) (C), and demethylases (KDMs) (D), DNA and RNA methyltransferases and demethylases (E), and some SWI/SNF subunits in various tumor samples. (B) Exemplary dot-plot correlation graph with expression of *EP300* and *KAT6A*, and between *EP300* and *HDAC8*. The underlying data were derived from all TGCA Pan-Cancer Atlas (Pan-cancer analysis of whole-genome (ICGC/TCGA, Nature 2020) samples.

marks. However, the relationship between these two modifications is unequal. The loss of H3K4me1 reduced H3K27ac, but H3K27ac reduction did not affect H3K4me1.[10] UTX (KDM6A) and MLL4 (KMT2B) form a feedforward regulatory loop that drives simultaneous H3K4 mono-methylation and H3K27ac on enhancers and super-enhancers to generate an active enhancer landscape. p300 forms an epigenetic protein complex with the H3K27 demethylase UTX and the H3K4 methyltransferase MLL4. MLL4-dependent H3K4 mono-methylation further augments the CBP/p300-dependent H3K27ac and transcriptional activation.[31] Like H3K4me3 and H3K4me1, H3K36me3 is linked to regulation of histone acetylation. H3K36me3 recruits HDACs to the sites of active transcription. Moreover, H3K4me3 has been found to be promoter associated before transcription initiation and H3K4me3-dependent co-targeting of p300/CBP and HDACs may facilitate the dynamic turnover of histone acetylation. It is suggested that H3K4me3 and histone hyperacetylation at gene promoters may regulate transcriptional initiation from the TSS, whereas H3K36me2/3-mediated deacetylation is required to prevent initiation from aberrant sites within the gene body.[5] Histone lysine acetylation and arginine methylation can also act cooperatively to localize and activate other methyltransferases. Pre-acetylation of H3K18 and H3K23 by CBP/EP300 triggers recruitment of arginine methyltransferase PRMT4 (CARM1), which methylates H3R17, thereby activating estrogen-responsive genes.[22,101]

The cooperation between modifications may increase the effectiveness of the recruitment of specific factors. For example, PHF8 specifically binds to H3K4me3 via its PHD finger, and this interaction is stronger when H3K9 and H3K14 are also acetylated on the same tail of H3.[102] Several reports have demonstrated that H3K9me3 and H3K27me3 modifications are mutually exclusive. H3K27me3 inserted by the KMT6A-containing PRC2 complex is associated with gene repression, while H3K27ac is associated with gene activation and active enhancers. The removal of H3K27ac by the HDAC1/2-containing NURD complex, facilitates the recruitment of the PRC2 complex and accumulation of H3K27me3 at promoters leading to gene repression. Methylation of H3K27me3 by KMT6A causes extrusion of p300 and CBP from chromatin, thereby preventing the accumulation of H3K27ac at enhancers and gene activation.[5]

Histone acetyltransferase EP300 and the histone demethylases KDM5A, KDM6A, and KDM6B, which can be jointly elevated in some cancer types, cooperate with KLF4 in transcriptional activation of POU5F1.[103] POU5F1 has been identified as one of the most important cancer stem cells markers and participates in stemness maintenance in cancer cells as well as correlating with clinicopathological features and poor prognosis for various tumors.[104]

Concluding, the high EP300 transcription in the subset of cancer patients is mostly associated with high transcription of methyltransferases (KMTs) and demethylases (KDMs) listed in Figure 7C, which insert transcription promoting marks and remove repressive modifications, respectively. The discrepancy in this very general statement is evident for PRMT1 and PRMT4, which are considered as transcription-promoting enzymes, but their activity toward non-histone substrates must be also taken into account while predicting their functional interaction with p300.

The relationship between expression of *EP300* and enzymes, which covalently modify DNA and RNA

The alteration in the mRNA level of *EP300* in cancers are associated with up- and downregulation of enzymes that are involved in covalent modifications of DNA and RNA (Figure 7D). Cancers that overexpress *EP300* are characterized by a low level of DNA (cytosine-5)-methyltransferase 3β (DNMT3), which is considered as *de novo* methyltransferase, as well as by overexpression of TET2, which catalyzes the conversion of the modified DNA base methylcytosine to 5-hydroxymethylcytosine, methyltransferase-like 3 and 14 (MTTL3, MTTL14), and pre-MRNA-splicing regulator WTAP. Although inactivating CREBBP/EP300 mutations were associated with hypermethylation in the literature,[105] transcription of DNMT1 DNMT3A/B remains mostly low in the studied group. It has been documented that overexpression of DNMTs in cancers, which cause hypermethylation of numerous genes such as hMLH1, p16, p53, CDH1, CEACAM6, CST6, ESR1, LCN2, and SCNN1A, also cause the activation of oncogene OCT4 through the IL-6/STAT3 pathway.[106] However, DNMT3B can act as a tumor suppressor in lymphomas, so a relatively low expression of DNMT3B and other DNA methyl transferases can support p300-dependent gene transcription in EP300-overexpressing tumors since many gene promoters are potential targets for DNMT3B activity. CpG methylation prevents the transcription-promoting methylations of H3K4, usually followed by nucleosome acetylation, because of the physical interference between DNMT3L, DNMT3A/B, and KDM1A/B, which compete for the N-terminal tail of histone H3.[107] Furthermore, methyl CpG binding protein 2 (MECP2) binds methylated DNA, recruits the H3K9me3 methyltransferase SUV3-9,[5] and interacts with Sin3A, which brings HDAC to the histone of methylated DNA, thereby repressing gene transcription and antagonizing the transcription activating role of p300.[108]

DNA demethylases TET1 and TET2 have different functions and are characterized by a distinct expression pattern in relation to *EP300*. TET1 regulates the 5mC levels at the promoters and transcription start sites, whereas TET2 demethylates CpG islands, gene bodies and cell-type-specific enhancers, particularly for highly expressed genes.[109] The similar expression pattern of *TET2* and *EP300* can be related to their functional relationship. p300 is involved in recruiting TET2 to chromatin through direct protein-protein interactions.[110] In breast cancer cells, TET2 facilitated the proper recruitment of ERα to active enhancers,[111] which are then dynamically activated through a p300/CBP-catalyzed acetylation that promotes the recruitment of TFIID and RNAPII at enhancers and enhancer-regulated genes.[112]

The observed positive correlation between the mRNA level of RNA methyltransferases and *EP300* can be explained by the fact that the H3K27 acetylation of *METTL3* promoter regulates transcription of this methyltransferase.[113] Such an interdependence in transcription control by p300 may also apply to other N^6-adenosine-methyltransferases. However, in normal cells m6A destabilizes the EP300/CBP

transcript, thereby suggesting that METLL activity may protect cells from p300/CBP overexpression.[114] The loss of the m6A reader protein YTHDF2 leads to the stabilization of the histone demethylase KDM6B transcript, increasing KDM6B abundance and declining the transcription repressive mark H3K27me3. Similarly, the methyltransferases METTL3 and METTL14 reduce the repressive histone mark H3K9me2 by a recruitment of KDM3B, which is mediated by the m6a reader protein YTHDC1. In various normal and cancer cell lines, the mRNA expression of *SETD2*, the histone methyltransferase of H3K36, positively correlated with the expression of the m6A writers METTL3, METTL14, and WTAP. Knockdown of SETD2 or overexpression of the histone demethylase KDM4A drastically decreased global m6A levels, as well as genes such as *MYC*. METTL14 acts as a key player that recognizes and binds H3K36me3, linking m6A deposition with H3K36me3, which marks transcriptionally active regions.[114] METTL3 was remarkably elevated in gastric cancer tissues, where it promoted cell proliferation via the SNHG3/miR-186-5p/cyclinD2 axis.[115] Similarly, p300- and WDR5-dependent transcription of *MLL3* facilitated the malignant progression of cervical cancer by the regulation of TXNDC5 expression.[116]

In summary, *EP300*-overexpressing cancers are characterized by gene expression-promoting profile, which starts with lowered level of DNMT3B and increased TET2, which likely cause hypomethylation of the subset of gene promoters, thereby promoting transcription permissive environment. Furthermore, m6A writers such as METTL3, METTL14, and WTAP play a role in the efficiency of mRNA splicing and RNA processing.

Co-expression of *EP300* and genes encoding subunits of SWI/SNF complex

Histone acetylation by p300 and its consequent impact on the gene transcription is mediated by the above-described histone, DNA modifying enzymes, and transcription factors, and by the bromodomain proteins, which adapt the chromatin structure to make DNA more or less accessible to transcription machinery. H3K27ac depletion by p300/cbp inhibition at both enhancers and promoters causes a clear reciprocal loss of multiple bromodomain-containing proteins including BRD2, BRD4, BRG1, and BRM from chromatin and transcriptional suppression of dependent genes.[117] The expression of *EP300* positively correlates with SWI/SNF chromatin remodeling complex subunits such as *ARID1A*, *ARID2*, *PBRM1*, *SMARCA2* (BRM), and *SMARCB1*, but is associated with a low *SMARCA4* transcription (Figure 7D). The SWI/SNF complex subunits recruits p300 to distal enhancers, rather than promoters, inducing H3K27 acetylation and enhancer-associated gene transcription.[31] In co-operation with BRD4 and BRG1, CBP/p300 plays an important role in inducing H3K27ac and the transcription of pluripotency genes, such as OCT4 and NANOG.[31] In addition, BRG1-dependent SWI/SNF was shown to enable the EP300-dependent transcription of proliferation and DNA repair genes from their E2F/CpG-driven promoters in breast cancer cells. BRG1/SWI/SNF-EP300 complexes, accompanied by poly-ADP-ribose polymerase 1 (PARP1), was present at highly acetylated promoters of genes such as *CDK4*, *LIG1*, or *NEIL3*, which are responsible for cancer cell growth and the removal of DNA damage.[86] Therefore, the lack of direct correlation between the transcription of *EP300* and *SMARCA4* in EP300-overexpressing cells may look surprising, but the high degree of overlap between BRG1 and BRM, which are mostly associated with active regulatory regions of the genome, may suggest that the two siblings replace each other at certain conditions.[118] However, there is no direct evidence to support this hypothesis. *SMARCA4* is frequently mutated, truncated, and epigenetically silenced in various cancers, which become transcriptionally dependent on BRM, and BRG1 loss or decline is associated with a poor prognosis.[119] Hence, the advantage of BRG1 silencing, which can act as tumor suppressor in *EP300*-overexpressing cells, can surpass the benefits of BRG1-p300 cooperation on chromatin that can be compensated by BRM.[86,120] Suppression of SWI/SNF subunits in *EP300* repressed cancers may further limit unwanted gene transcription when the role of p300 is taken over by other acetyltransferases.[121] The suppression of *SMARCA4* in *EP300*-overexpressing cancers is even more surprising in light of the weak but positive correlation between *EP300* and *PBRM1* expression. Product of the latter gene contains six tandem bromodomains, which are specialized in recognizing acetyl-lysine residues, thereby making *PBRM1* product an important reader of H3K14ac and a universal epigenetic marker of actively transcribing genes.[122] Importantly, PBRM1 marks only BRG1-dependent PBAF sub-complexes of SWI/SNF, so the functional impact of simultaneous p300 and PBRM1 elevation with the likely deficiency of crucial PBAF subunit—BRG1 remains unknown.

The colorectal cancer study suggests that inhibition of histone deacetylation leads to increased *ARID1A* expression in LS180, HT29, and SW742 cells,[123] thereby linking elevated co-occurrence of *ARID1A* and *EP300*. ARID1A may function as a tumor suppressor through transcriptional downregulation of cancer stemness gene *ALDH1A1*, which is associated with reduced histone H3K27 acetylation in cholangiocarcinoma cells.[124] Another SWI/SNF gene—*ARID2*—that is co-expressed with *EP300* is known to inhibit metastasis of hepatocellular carcinoma cells by recruiting *DNMT1* to the promoter of genes, which belong to the Snail family. Elevated DNA methylation leads to suppression of Snail transcription.[125] Therefore, low *ARID2* mRNA level may link p300 declined cancers with their predisposition to metastasis as demonstrated in Figure 6D.

Concluding, expression of ARID domain-containing proteins such as *ARID1A/B* and *ARID2* positively correlates with expression of EP300 in the subset of analyzed cancer samples, and to possibly facilitate P300-dependent gene transcription. SWI/SNF-driven chromatin remodeling most likely involves BRM in EP300-overexpressing cancers since expression of another ATPase of this complex—BRG1 is relatively low.

EP300 changes as a prognostic mark and therapeutic target

Pan-cancer studies demonstrate the link between the expression of *EP300* and improved cancer patient survival. However, the data indicate that both high and low expression of *EP300* may be associated with poor prognosis. High expression of p300 was followed by poor

overall survival in hepatocellular carcinoma, esophageal squamous cell carcinoma, nasopharyngeal cancer, breast cancer, cutaneous squamous cell carcinoma, and small cell lung cancer,[76] as well as non-small cell lung cancer.[78] Overexpression of *EP300* was associated with improved survival in non-small cell lung cancer, melanoma,[76] and glioblastoma.[77] In addition, it is indicated that both low and high expressions contribute to tumor invasiveness and resistance to chemotherapy. Therefore, personalized therapy seems to be a reasonable therapeutic approach in patients with dysregulated *EP300*. P300 status can be considered as an indicator for the use of EP300 inhibitors, HAT activators, or immunotherapy in anticancer therapy.

p300 declined cancers

The development of immune checkpoint inhibitor (ICI) therapy has opened a new era of anticancer therapy, with durable responses and significant survival benefits observed in many cancers.[126] The FDA has successfully approved three different categories of ICIs: PD-1 inhibitors (Nivolumab, Pembrolizumab, and Cemiplimab), PDL-1 inhibitors (Atezolimumab, Durvalumab, and Avelumab), and a CTLA-4 inhibitor (Ipilimumab).[127] However, a big group of patients do benefit from this approach to combat cancer. Consequently, increasing attention is being paid to the identification and development of predictive biomarkers of response to immune therapy. Tumor mutational burden, variations in DNA damage response pathways, neoantigen load (the number of mutations actually targeted by T cells), and PD-L1 expression[126] are listed among the most characteristic and promising features to discriminate patients for immune therapies. The ability of cytotoxic T cells and natural killer cells in the elimination of tumor cells and the tumor mutation burden as well as PD-L1 expression, was significantly higher in *EP300*-mutated than in *EP300*-wild-type cancers. These features indicated a favorable response to ICIs. Thus, the lack of *EP300* could be a predictive biomarker for a patient's response to immunotherapy.[28] Recent studies suggest that inactivating mutations in SWI/SNF, particularly subunits of in PBAF complex (*PBRM1*, *ARID2*, and *BRD7*) increase patient sensitivity to ICIs. Loss of function of SWI/SNF increased chromatin accessibility to transcription activators in IFN-γ-inducible genes in tumor cells, and subsequently increased production of chemokines, thereby leading to more effective recruitment of effector T cells to tumors.[126]

In cancers characterized by the low expression of *EP300*, where activity of the enzyme is detrimental for cancer cell survival or proliferation, HAT activators and immunotherapy can be applied as a monotherapy or in combination with other drugs to improve the treatment outcome. To date, several p300 activators have been developed. These can be represented by CTB (cholera toxin B subunit) that induces acetylation of p53 by increasing the expression of p300 and consequently triggers cell death in a culture of breast cancer MCF-7 cells, while being well tolerated by normal lung MRC-5 fibroblasts.[128] YF2, a P300 and CBP HAT activator, has selective cytotoxicity in the *EP300*-mutated, diffuse large B cell lymphoma cell lines and induces acetylation of H3K14 and H3K27 as well as p53 *in vitro* and *in vivo*.[129] Moreover, YF2 upregulated the expression of several MHC class I-II genes resulting in the activation of numerous immune regulatory signaling pathways, allowing for the synergic effect of YF2 and PD-L1 inhibitors.[130] The question whether p300 activators can be more potent in cancers characterized by the loss or decline of two and more acetyltransferases remains open, but the simultaneously low expression of p300 and other KAT family members provides a solid ground for such a hypothesis. Alike HAT activators, HDAC inhibitors are documented to attenuate tumor progression and improve immunotherapy. Inhibition of HDACs increases the immunogenicity of cancer cells by upregulating the expression of numerous compounds including components of the antigen-processing and presentation machinery, co-stimulatory molecules, stress-induced ligands, and death-inducing receptors, while simultaneously downregulating the expression of checkpoint ligands by tumor cells. The immune response is further enhanced by activation of the adaptive and innate host immune cells, which recognize and eliminate cancer cells.[131] Some treatment schemes involving HDAC inhibitors combined with immune therapy have already demonstrated promising efficacy in various phases of pre-clinical and clinical trials.

EP300 overexpressed cancers

Patients diagnosed with cancers fueled by elevated p300 activity can possibly benefit from p300/CBP inhibitors. Several natural compounds block acetyltransferase activity of p300. These include garcinol, anacardic acidcurcumin,[132] curcumin,[133] and carnosol.[134] Garcinol and anacardic acidcurcumin significantly reduce the invasive phenotype of rhabdomyosarcoma cells by inhibiting their growth rate, viability, and clonogenic ability. These compounds cause cell-cycle arrest in the G2/M phase and induce apoptosis.[132] Garcinol prevents esophageal cancer metastasis *in vitro* and *in vivo*, suggesting its therapeutic potential for metastatic tumors.[135] Carnosol suppressed tumor growth and metastasis of breast cancer xenografts as well as strongly induced apoptosis in melanoma cells.[136,137] A-485, C646, B026, L002, DCH36_06, CPI-1612, and PU141 represent small-molecule, synthetic inhibitors of CBP/p300 catalytic activity. These agents reduce the growth of cancers, including hormonal-responsive cancers, by inducing cell death, disturbing metabolic reprogramming of cancer cells and sensitizing cells to chemotherapy and immunotherapy.[53,85,138–148] P300 inhibitor A-485 was suggested as possible effective anticancer treatment in *ARID1A*-mutated endometrial epithelium, where p300-dependent acetylation of super-enhancers promoted endometrial invasion in the absence of functional ARID1A. However, in ARID1A-proficient cancers inhibition of p300 may support ARID1A-based repression of genes responsible for migration such as *SERPINE1*.[121] Identification of the bromodomain in the structure of p300 and CBP led to development of another group of inhibitors that interfere with acetyltransferase interaction with chromatin. Cell membrane-permeable compounds such as I-CBP112, SGC-CBP30, CPI-637, PF-CBP1, Y08197, GNE-781, and CCS1477 induce apoptosis, reduce growth and metastatic potential of cancers,[149,150] growth of hormone-responsive cancers,[79–81,147,151] sensitize cancer cells to immunotherapy,[152] chemotherapy,[149,150,153] and reverse drug-resistant phenotypes.[83] From the last synthetic group of CBP/p300 inhibitors, which simultaneously target the

bromodomain and the catalytic activity of acetyltransferases, NEO2734, NEO1132, and XP-524, there emerges promising anticancer approaches. NEO2734 substantially limits the proliferation of multiple cell lines. Although the cellular response and transcriptional changes in various lymphomas treated with NEO2734 were similar to either bromodomain and extra-terminal domain (BET) or CBP/EP300 inhibitors, the magnitude of NEO2734 was substantially higher.[154] NEO2734 and NEO1132 eliminated leukemic stem/progenitor cells in patient samples.[155] The dual BET/EP300 inhibitor XP-524 has a pronounced single-agent efficacy *in vitro*, *ex vivo*, *in vivo*, and in human pancreatic cancers. XP-524 *in vivo* led to extensive reprogramming of the pancreatic tumor microenvironment, sensitized murine carcinoma to ICIs and further extended survival, and in so doing provided evidence that the combined therapy XP-524 and immune checkpoint can be beneficial for at least some cancer patients.[156]

Although the lack of specificity of p300 inhibitors is often considered as weak point, the simultaneous targeting of two or more acetyltransferases, which are overexpressed together with p300, may potentiate the effect of single p300 inhibition. The pan-inhibitor PU139, which blocks acetyltransferase activity of Gcn5, p300/CBP-associated factor (PCAF), CREB (cAMP response element-binding) protein (CBP), and p300, triggers caspase-independent cell death in cell culture, blocks growth of SK-N-SH neuroblastoma xenografts in mice and synergizes the cytotoxic effects with doxorubicin *in vivo*.[138] L002 reduces activity of p300, GCN5 (KAT2A), and PCAF (KAT2B), but their IC_{50} varies from 1.98 to 34 μM and 35 μM, respectively.[157] Similarly, CBP/p300 bromodomain inhibitors interfere with the functioning of some BET family members, particularly with BRD4, which often associates with p300-containg and transcription-promoting complexes at the gene promoters and enhancers.[158] Therefore, an attempt to make use of p300 inhibitors for multi-KAT targeting likely requires far higher doses of these compounds, hence their adverse effects or toxicity may act as limiting factors.

Another approach with the target of declining p300 activity in cancer cells is the degradation of p300. The proteolysis-targeting chimera (PROTAC) compound termed "JQAD1" selectively targets EP300 for degradation. Cell treatment with JQAD1 causes loss of H3K27 acetylation and rapid neuroblastoma apoptosis, while showing a very limited toxicity to untransformed cells.[159] Another p300 degrader—dCBP-1—is exceptionally potent in killing multiple myeloma cells and can abolish the activity of the enhancer that drives MYC oncogene expression.[160] The genetic background as well as co-existed alteration in the expression and activity of other chromatin remodeling enzymes were not taken into consideration while testing anticancer efficacy of p300 degraders.

The new mode of synthetic lethality, which involves targeting p300 activity, can be taken into consideration in cancers that are fueled by p300 in the *SMARCA4*-mutated genotypes. The beneficial impact of BRG1 deficiency, widely described in primary tumors, for malignant transition, cancer growth, and metastases may result from BRG1-mediated silencing of genes by the REST complex, which interacts with acetylated chromatin at the BRG1 binding sites in a fashion dependent on BRG1 bromodomain.[161] If BRG1-REST-repressed genes emerge crucial for cancer well-being, then inhibition of histone acetylation by p300 or pan-acetyltransferase inhibitors may mirror the activity of mutated *SMARCA4*. Furthermore, simultaneous inhibition of p300/CBP and KDM6A was proposed as effective anticancer strategy since these two enzymes co-operate in activating oncogenic transcription.[117] KDM6A, which is frequently overexpressed in parallel to p300, prevents suppression of oncogenes by antagonizing PRC2-mediated methylation of H3K27me1/2/3 in the absence of p300 activity. Interestingly, overexpression of p300 and KDM6A correlates negatively with the mRNA level of various HDAC family members, and this observation seems to be of crucial importance for the success of the suggested anticancer strategy involving prolonged inhibition of p300 and KDM6A. The loss of NCoR/SMRT complexes, which comprise HDAC3 as a catalytically active subunit, overcomes p300/CBP inhibition, and can possibly substantially limit beneficial effects of ip300- or ip300/iKDM6A-based anticancer therapies.[117]

SUMMARY

EP300 is frequently dysregulated in cancers. Some cancers are characterized by high expression and activity of EP300, which can serve as an indicator for the implementation of antagonizing or activating drugs in anticancer therapies. Despite extensive efforts and the development of many structurally different compounds capable of modulating p300 activity and expression, none have been accepted by the FDA for the treatment of malignancies. Immunotherapy and HAT activators seem promising for the treatment of cancers with *EP300* deleterious mutation and downregulation, but also require further investigation and testing in clinical trials. The observed interdependence between the expression of *EP300* and other chromatin remodeling enzymes and their documented functional crosstalk should be a prompt for considering the use of pan-acetyltransferase inhibitors and pan-bromodomain inhibitors in *EP300*-overexpressing cancers. Some of the above referred examples indicate likely limitation in the beneficial outcomes of p300 targeting in anticancer strategies, which result from mutations in other epigenetic factors. Although numerous options for up- and downregulation of p300 activity is currently available, the proper choice must be imposed by careful analysis of patient-specific genotype and co-existed mutations, which define the repertoire of chromatin and DNA remodeling enzymes capable of fine-tuning p300 role in cancer progression.

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Conceptualization, K.G. and A.R.; writing – original draft, K.G.; writing – review & editing, A.R.; formal analysis, K.G.; supervision, A.R.; funding acquisition, A.R.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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