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YEATS2: a novel cancer epigenetic reader and potential therapeutic target

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Abstract

YEATS2, an evolutionarily conserved reader of histone acylation marks (H3K27ac, H3K27cr, H3K27bz), functions as a central oncogenic driver in diverse cancers, including non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), and hepatocellular carcinoma (HCC). Its structurally plastic YEATS domain bridges acyl-CoA metabolism to chromatin remodeling, amplifying transcription of survival genes such as *MYC*, *BCL2*, and *PD-L1*. YEATS2 orchestrates malignancy-specific programs—sustaining ribosome biogenesis in NSCLC through ATAC complex recruitment, enhancing NF-κB-dependent immune evasion in PDAC, and activating PI3K/AKT-driven metabolic rewiring in HCC. Structural studies demonstrate a unique aromatic cage architecture that selectively engages diverse acylated histones. Although pyrazolopyridine-based inhibitors targeting the YEATS domain show preclinical efficacy, developing isoform-selective agents remains challenging. Clinically, YEATS2 overexpression correlates with therapy resistance and may synergize with immune checkpoint blockade. This review integrates mechanistic insights into the role of YEATS2 in epigenetic regulation, evaluates its therapeutic potential, and proposes future directions: elucidating full-length complex topologies, mapping synthetic lethal interactors, and optimizing selective inhibitors. Disrupting YEATS2-mediated epigenetic adaptation presents novel opportunities for precision cancer therapy.

Keywords Epigenetic reader, YEATS2, Histone acylation marks, Immune checkpoint blockade, Precision cancer therapy

Introduction

The term "epigenetics," first coined by Conrad H. Waddington in 1942, describes heritable changes in gene expression independent of DNA sequence alterations [1, 2]. These changes are mediated through covalent DNA modifications and histone post-translational modifications (PTMs), which remodel chromatin architecture to regulate DNA accessibility and transcriptional activity [3–5]. While genetic mutations disrupt DNA sequences, epigenetic dysregulation reprograms gene expression profiles to drive tumorigenesis [6]. Early studies linked cancer to DNA methylation and histone modifications [7], with epigenomic alterations now recognized as central to malignant traits such as self-renewal, differentiation arrest, and metastatic potential [8]. Key

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regulators—including DNA methylation, histone PTMs, non-coding RNAs, and chromatin remodelers—exhibit heightened precision in cancer cells, enabling oncogenic adaptation [2, 9]. Their spatiotemporal accuracy underpins clinical utility: epigenetic marks serve as biomarkers for cancer screening and surveillance [10, 11].

Epigenetic crosstalk in cancer involves dynamic interplay between DNA methylation and histone modifications. DNA Methyltransferases (DNMTs) and Ten-Eleven Translocation (TET) enzymes mediate CpG island methylation, silencing tumor suppressors like *CDKN2A* and *BRCA1*, which is therapeutically targeted by hypomethylating agents (e.g., azacitidine) [12, 13]. Conversely, histone PTMs modulate chromatin states via "writer," "eraser," and "reader" proteins. While cytosine methylation and histone modifications are often studied independently, emerging evidence reveals their functional interdependence: DNMT3A recruitment requires H3K36me2 recognition [14], while TET2 activity is associated with histone acetylation [15]. Among epigenetic readers, the YEATS family has emerged as critical interpreters of histone acylation marks. Named for its founding members (Yaf9, ENL, AF9, Taf14, Sas5) [16, 17], this family includes four human proteins (ENL/YEATS1, YEATS2, AF9/YEATS3, GAS41/YEATS4) that share 88% YEATS domain homology but diverge functionally [18, 19].

YEATS2, initially identified as KIAA1197 [20, 21], is a scaffolding subunit of the Acetylation Domain Associated (ADA) Two Acetyl-CoA-containing (ATAC) histone acetyltransferase complex, regulating transcription and stress responses [21–23]. Its oncogenic role spans cancers such as non-small cell lung cancer (NSCLC), where it binds H3K27ac and H3K27cr to activate survival genes [23–25]. Notably, YEATS2 uniquely recognizes histone benzoylation (H3K27bz) via a "tip sensor" structural motif [26], positioning it as a multifunctional metabolic sensor. However, key questions remain: (1) How does YEATS2 discriminate between acylated marks (e.g., acetylation vs. benzoylation) in tumor-specific contexts? (2) What non-histone substrates mediate its protumorigenic signaling? (3) Can small-molecule inhibitors selectively target the YEATS domain without off-tumor effects? (4) How does metabolic flux (e.g., acetyl-CoA levels) modulate its epigenetic activity? This review synthesizes advances in YEATS2 biology to address these gaps and evaluate its therapeutic potential.

YEATS2 drives tumorigenesis via pathway-specific mechanisms in selected cancers

YEATS2 has emerged as a pivotal epigenetic regulator in cancer, exhibiting striking tissue-specific functions shaped by its dual capacity to decode histone acylation marks and recruit malignancy-specific transcriptional cofactors. Structural studies reveal its aromatic cage dynamically accommodates acetyl, crotonyl, and benzoyl groups [23, 26, 27], functioning as a nutrient-sensitive bridge between metabolic states and chromatin remodeling. Clinically, YEATS2 overexpression—observed in > 20 cancer types—correlates with advanced staging, therapy resistance, and poor survival [The Cancer Genome Atlas (TCGA) Pan-Cancer Atlas Pan-Cancer Atlas] [27, 28]. Amplification of its 8q21.3 locus further underscores oncogenic relevance. This section delineates the context-dependent interactions of YEATS2 with chromatin modifiers and transcriptional machinery across malignancies (Table 1; Fig. 1).

Non-small cell lung cancer (NSCLC): YEATS2/ATAC complex and ribosomal gene addiction

NSCLC constitutes ~ 85% of lung cancers and remains a leading cause of cancer mortality due to frequent recurrence and limited therapeutic options for advanced disease [29]. Although EGFR/ALK inhibitors and immunotherapies improve outcomes, epigenetic plasticity-driven resistance necessitates novel targets [30, 31]. Accumulating evidence identifies YEATS2 as a master epigenetic regulator in NSCLC, where elevated expression predicts poor prognosis [27]. Mechanistically, YEATS2 recruits the ATAC complex to H3K9ac-enriched promoters of ribosomal genes (e.g., *RPS6*, *RPL7*), leveraging General Control Non-depressible 5 (GCN5) / CREB-binding protein-associated factor (PCAF)-mediated acetylation to amplify transcriptional activation and fuel.

ribosome biogenesis [27] (Table 1; Fig. 1). This epigenetic rewiring directly links histone acetylation readouts to NSCLC progression, with YEATS2 depletion suppressing tumor growth through ribosomal pathway downregulation [27].

Table 1 YEATS2 in major cancer types and targeted pathways/genes

Cancer	Target gene	Key Pathways/Mechanisms	Functional Role of YEATS2	References
NSCLC	*MYC*, *RPS6*, *RPL7*	ATAC complex recruitment, H3K9ac deposition	Drives ribosomal gene addiction; essential for growth	[27]
PDAC	*BCL2*, *XIAP*, *PD-L1*	TAK1/NF-κB stabilization, PD-L1 regulation; HIF1α-TWIST1/EMT axis	Promotes survival, Chemoresistance, immune evasion; Mediates hypoxia-induced metastasis	[32, 33, 39]
HCC	*AKT1*, *MYC*, *CCND1*	PI3K-AKT activation, AKT stabilization; p53/p21	Enhances metabolic reprogramming and therapy resistance; independent prognostic marker	[28, 35, 49]

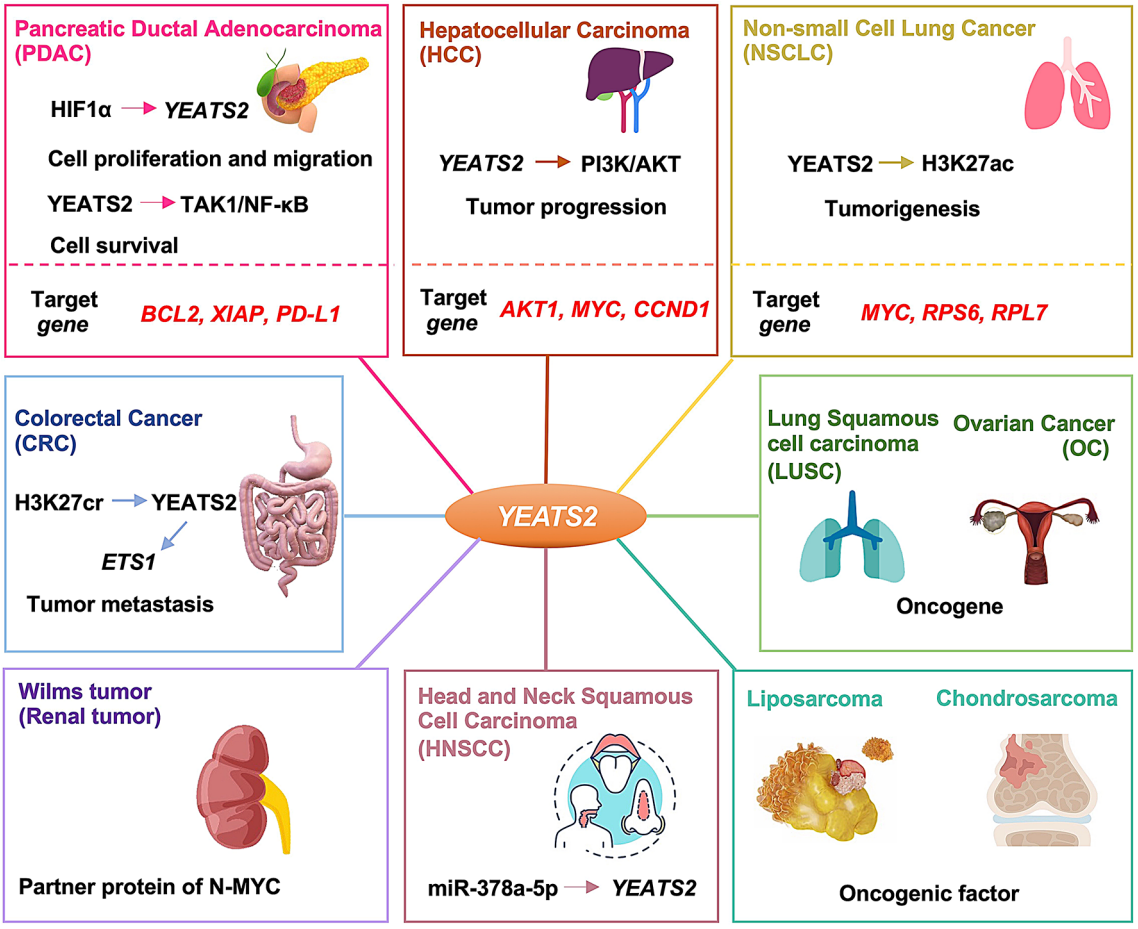

Fig. 1 YEATS2 Drives Tumorigenesis via Context-Dependent Target Genes and Pathways [19, 27, 32–35]. YEATS2 has been shown to orchestrate malignancy-specific transcriptional programs by decoding distinct histone acylation marks (H3K27ac/cr) and recruiting tissue-specific coactivators. In NSCLC, it has been observed to recruit the ATAC complex to deposit H3K9ac at ribosomal gene promoters (*RPS6/RPL7*), thereby sustaining ribosome biogenesis. Furthermore, analysis of PDAC models reveals that YEATS2 stabilizes TAK1, thereby constitutively activating NF-κB, which in turn drives anti-apoptotic (*BCL2/XIAP*) and immunosuppressive (*PD-L1*) gene expression. In the context of HCC progression, the PI3K/AKT pathway is implicated in metabolic rewiring, while MYC amplification occurs via H3K27ac-dependent promoter activation. Cross-cancer analyses identify common oncogenic nodes (*MYC*, *AKT*) and unique microenvironmental regulators (HIF1α in PDAC hypoxia; miR-378a-5p in HNSCC). In CRC, YEATS2 responds to elevated levels of Kcr, thereby activating *ETS1* and promoting cancer metastasis. The acronyms used in this text are PDAC (pancreatic ductal adenocarcinoma cells), HCC (hepatocellular carcinoma), NSCLC (non-small cell lung cancer), CRC (colorectal cancer), LUSC (lung squamous cell carcinoma), OC (ovarian cancer), and HNSCC (head and neck squamous cell carcinoma). NF-κB, Nuclear factor kappa-B; Kac, Lysine acetylation; Kcr, Lysine crotonylation. The graphic framework is adapted from Ji et al., 2023 [19], Mi et al., [27], Zeng et al., [32], Sheng et al., [33], Liao et al., [34], and Liu et al., [35]

Pancreatic ductal adenocarcinoma (PDAC): YEATS2/TAK1/NF-κB axis

PDAC, accounting for over 90% of pancreatic malignancies, exhibits aggressive clinical behavior marked by early metastasis and chemoresistance, contributing to a dismal 5-year survival rate of 5–8% [36]. Emerging evidence implicates epigenetic dysregulation—particularly aberrant histone acylation signaling—in driving PDAC progression and therapeutic resistance [37, 38]. Mechanistically, YEATS2 stabilizes TGF-β-activated kinase 1 (TAK1) through N-terminal interaction, shielding it from proteasomal degradation to sustain constitutive nuclear factor kappa-B (NF-κB) activation [33] (Table 1). This axis promotes transcription of anti-apoptotic genes (*BCL2*, *XIAP*) and immune checkpoint ligands (*PD-L1*) [39], establishing YEATS2 as a molecular linchpin in PDAC survival (Fig. 1). Notably, the traditional Chinese medicine Cinobufacini—derived from dried toad skin—induces PDAC cell cycle arrest by targeting the YEATS2/TAK1/NF-κB pathway [40]. While preclinical studies validate Cinobufacini's anti-tumor efficacy [41–44], its direct binding targets remain undefined. Furthermore, hypoxia-induced YEATS2 expression via hypoxia-inducible factor 1-alpha (HIF1α) enhances pancreatic cancer cell proliferation and migration under low oxygen conditions [32], suggesting microenvironmental regulation of its oncogenic activity.

Hepatocellular carcinoma (HCC): YEATS2/PI3K-AKT metabolic reprogramming

HCC, the predominant form of liver cancer, is characterized by high mortality rates due to late diagnosis and limited efficacy of systemic therapies [45]. Metabolic-epigenetic crosstalk increasingly underpins HCC pathogenesis [46, 47], with YEATS2 emerging as a key oncogenic driver. Early bioinformatics studies proposed *YEATS2* as a metabolic suppressor in hepatocytes [48], while subsequent work revealed its conflicting role in tumor progression. Liu et al. demonstrated that YEATS2 overexpression remodels the extracellular matrix via Phosphoinositide 3-kinase/Protein kinase B (PI3K/AKT) activation, directly promoting HCC invasion [35] (Table 1; Fig. 1). Notably, YEATS2 amplifies *MYC* transcription by depositing H3K27ac at its promoter, forming a feedforward loop that accelerates tumor growth [28]. Functional studies further elucidate YEATS2 dual mechanisms: its knockdown induces DNA damage with concomitant γ-H2A.X upregulation and *p53/p21* pathway activation [49]. Through the c-Myc/miR-93-5p axis, YEATS2 depletion enhances *p21* expression, driving HCC cell senescence [49]. Clinically, Du et al. established that elevated YEATS2 expression correlates with advanced TNM staging, vascular invasion, and reduced overall survival in HCC patients [28], consolidating its prognostic significance in this malignancy.

Other types of cancer: intertwined cancer signaling pathways of YEATS2

Beyond its established roles in common malignancies, YEATS2 exhibits oncogenic functions across diverse tumor types (Table 1; Fig. 1). Bioinformatics analyses identify YEATS2 amplification as a potential driver in liposarcoma and chondrosarcoma [50, 51], while clinical studies link its epigenetic activity to smoking-associated methylation changes [52] and cancer progression [53, 54].

In Wilms tumor—a pediatric kidney cancer—YEATS2 interacts with N-MYC, with expression levels tightly correlated to *MYCN* amplification [55]. This interaction holds clinical relevance given the preclinical efficacy of MYC-targeting agents [56, 57], suggesting therapeutic potential in disrupting the YEATS2-N-MYC complex. Pan-cancer relevance of YEATS2 is further evidenced by its amplification in lung squamous cell carcinoma (LUSC), ovarian cancer (OV), and head/neck squamous carcinomas (HNSCC), where genetic deletion suppresses tumorigenic phenotypes [27]. Mechanistically, miR-378a-5p-mediated YEATS2 suppression inhibits HNSCC proliferation and metastasis while promoting apoptosis [58]. Additionally, H3K27cr-driven YEATS2 recruitment to the *ETS1* promoter activates transcriptional programs underlying colorectal cancer (CRC) metastasis [34]. While these studies collectively establish YEATS2 as a ubiquitous oncogene (Fig. 1), the precise molecular determinants of its context-dependent regulation remain poorly defined.

Functional interpretation of histone modifications by YEATS2

Epigenetic dysregulation serves as a pivotal driver of tumorigenesis, with the erroneous decoding of histone modifications acting as an early oncogenic trigger across diverse malignancies [59, 60]. Among epigenetic readers, YEATS domains have emerged as versatile sensors of histone acylation marks (Table 2). While AF9/YEATS3 and ENL/YEATS1 exhibit rigid substrate selectivity—preferentially binding H3K9ac or H3K18ac through confined aromatic cages—YEATS2 displays remarkable structural plasticity that enables recognition of diverse modifications including acetyl (Kac), crotonyl (Kcr), and benzoyl (Kbz) groups [26, 61, 62]. This functional divergence is rooted in distinct structural architectures: AF9/ENL recruit transcriptional elongation complexes [e.g., super elongation complex (SEC)] via stable interfaces, whereas YEATS2 primarily orchestrates promoter-centric acetylation through dynamic interactions with the ATAC complex [27, 63].

Central to the adaptability of YEATS2 is its flexible aromatic cage (Y262/W282), which expands to accommodate bulkier acyl moieties—a stark contrast to the rigid pockets of other family members. Structural analyses reveal three distinct recognition modes: (1) The compact acetyl group of Kac nests within the hydrophobic cage through Y262/W282 interactions (PDB:5XNV) [27]; (2) The extended crotonyl chain of Kcr adopts a hook-like conformation, forming van der Waals contacts with F281/L259 (PDB:5IQL) [23]; (3) The bulky benzoyl group of Kbz penetrates deeper into the pocket, stabilized by π-π stacking with W282 and a unique "tip-sensor" motif (S264) (PDB:6LSD) [26] (Fig. 2). Notably,

Table 2 The indexes of YEATS2 for reading histone acetylation (ac), crotonylation (cr), and benzoylation (bz)

Histone PTMs	Core residues	Target gene	Cancer	Binding affinity K_D (μM)	Reference
H3K27ac	Y262 W282	Ribosomal protein genes	NSCLC	50.0	[27]
H3K27cr	Y262 W282	*EST1*	CRC	27.5	[23, 34]
H3K27bz	Y262 W282	Unknown	Unknown	21.6	[26]

Note: NSCLC, non-small cell lung cancer; K, Lysine; ac, acetylation; cr, crotonylation; bz, benzoylation; Y, tyrosine; W, tryptophan

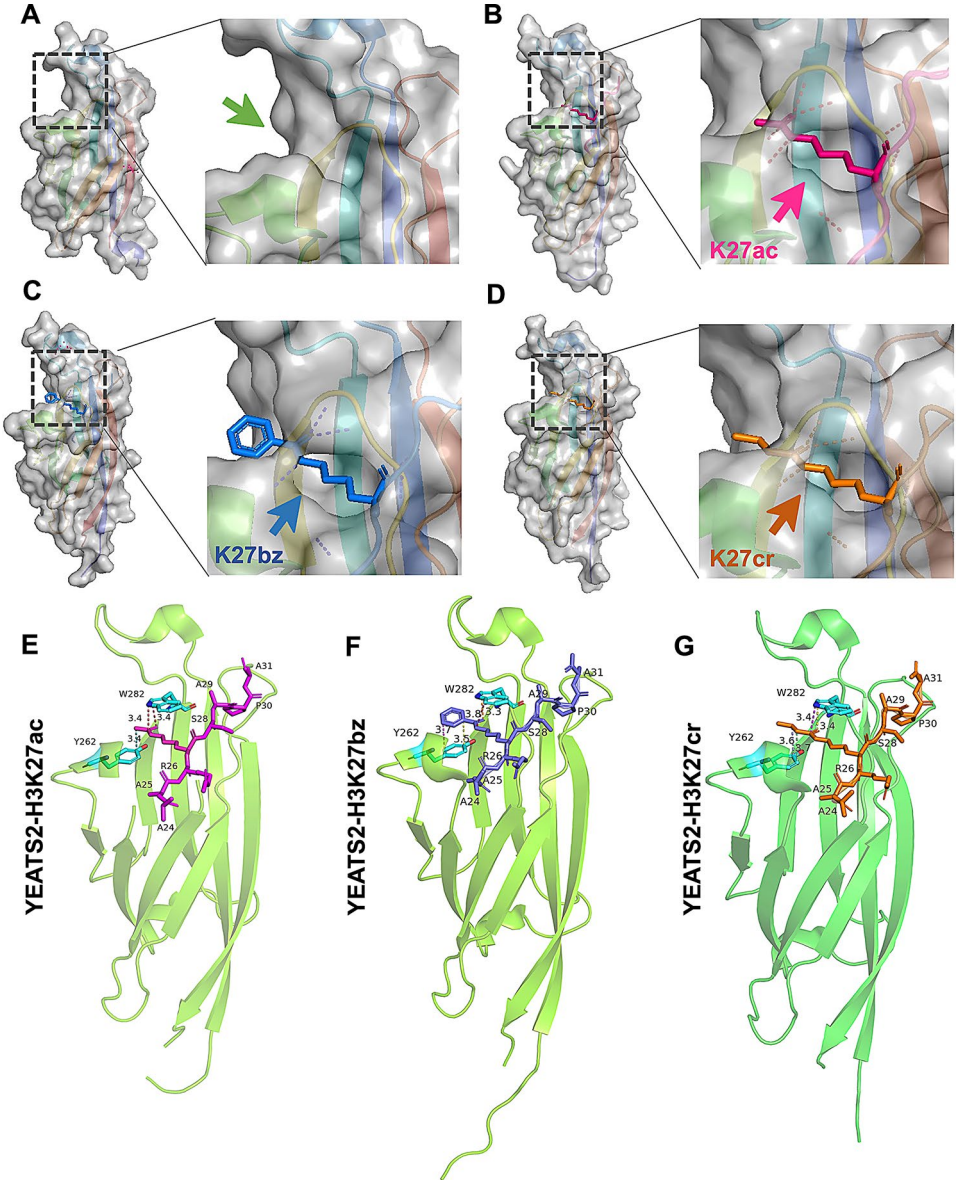

Fig. 2 Structural Basis of YEATS2 Recognition for Histone Acylation Marks. (**A**-**D**) Overall architecture of the YEATS domain (PDB: 7EIE) featuring a β-sheet core (color) and residue surface (gray). The aromatic cage (Y262/W282) accommodates diverse acyl groups, including Kac, Kbz, and Kcr. The H3K27ac, H3K27Kbz, and H3K27Kcr regions are represented by pink, blue, and orange, respectively. The data presented here show the YEATS domain of YEATS2 and its complex bound to Kac (PDB: 5XNV), Kbz (PDB: 6LSD) and Kcr (PDB: 5IQL). (**E**-**F**) Shared interactions include π-π stacking with Y262 and hydrophobic contacts with W282. The acetyl moiety nests within the hydrophobic pocket via Y262/W282 interactions, stabilized by S261 hydrogen bonding. The benzoyl group engages W282 through π-π stacking, with the "tip-sensor" S264 stabilizing the benzene ring. The crotonyl chain adopts a hook-like conformation, forming van der Waals contacts with F281/L259. Structural alignment (RMSD < 1.2 Å) highlights sidechain plasticity rather than global rearrangements during acyl group adaptation. The structure framework is adapted from Mi et al., [27], Ren et al., [26], and Zhao et al., [23]. H3, Histone H3; K, Lysine; ac, Acetylation; cr, Crotonylation; bz, Benzoylation

backbone superimposition of K27ac/cr/bz-bound complexes demonstrates minimal conformational changes (RMSD < 1.2Å), suggesting sidechain rearrangements rather than global structural shifts enable this chemical adaptability (Fig. 2B-D) [23, 26, 27].

This structural plasticity positions YEATS2 as a metabolic integrator, translating acyl-CoA fluctuations into chromatin remodeling—a mechanism diverging from the canonical transcriptional roles of AF9/ENL. The precise coordination between dynamic recognition modes of YEATS2 and oncogenic reprogramming remains a critical area for future investigation, particularly in malignancy-specific contexts where acyl-CoA abundance varies dramatically.

YEATS2 and histone lysine acetylation (Kac)

Lysine acetylation (Kac)—an early-characterized histone modification—orchestrates chromatin dynamics by modulating DNA accessibility [64, 65]. Acetyl-CoA-dependent histone acetylation, mediated by histone acetyltransferases (HATs) such as GCN5/PCAF within the ATAC complex [21], establishes transcriptional competence at specific loci. Mounting evidence positions.

H3K27ac as a central epigenetic mediator in malignancies, with its dysregulation driving subtype-specific transcriptional programs in PDAC models [38, 66–68]. YEATS2 emerges as a critical H3K27ac reader in NSCLC, where its recognition of this mark recruits the ATAC complex to deposit H3K9ac at ribosomal gene promoters (Fig. 2B and E) [27]. Genetic or pharmacological disruption of this pathway impairs GCN5/PCAF-mediated acetylation, silencing pro-survival ribosomal transcripts essential for tumor growth [27, 69, 70]. Structural studies reveal a conserved mechanism: aromatic residues in the YEATS2 domain form a serine/threonine-lined sandwich cage that encapsulates acetylated lysine, a feature shared across YEATS family members [27, 63, 71, 72]. However, functional divergence exists—unlike GAS41, which binds H3K23acK27ac diacetylation via its dimeric C-terminal coiled-coil domain [73], the substrate specificity of YEATS2 remains confined to single acyl marks. Determining whether YEATS2 exhibits latent diacetylation recognition capacity could uncover novel chromatin-regulatory mechanisms in cancer.

YEATS2 and histone lysine benzoylation (Kbz)

Histone Kbz—a recently identified acylation mark—regulates chromatin remodeling and transcriptional activation [74, 75]. Mass spectrometry analyses have mapped 22 Kbz sites across human, murine, and Drosophila systems [74], with yeast studies revealing 27 conserved modification sites [76]. This evolutionarily conserved modification targets all core histones, predominantly localizing to amino-terminal tails—a distinct pattern distinguishing it from other lysine acylations [5]. YEATS2 has emerged as the first in vitro reader of Kbz through its 'tip sensor' binding pocket, exhibiting marked selectivity for this modification [26]. Structural studies of the YEATS2-H3K27bz complex reveal precise recognition: the benzoyl group inserts between Y262 and W282 residues, stabilized by π-π stacking interactions (Fig. 2C and F) [26]. Unlike AF9 and ENL, which bind H3K9/H3K27 acylations via the ARKS motif [23, 62, 71], YEATS2 exclusively recognizes H3K27 modifications, highlighting its unique substrate specificity. Despite these advances, critical questions persist: Does YEATS2 engage Kbz in vivo, particularly in malignant contexts? Is this interaction conserved across species? A proposed model suggests that Kbz recognition recruits the GCN5-containing ATAC complex to modified promoters, driving transcriptional reprogramming—a hypothesis awaiting experimental validation.

YEATS2 and histone lysine crotonylation (Kcr)

Histone Kcr was first characterized as an epigenetic hallmark of active sex chromosome-associated genes in postmeiotic germ cells [77]. Subsequent studies revealed its broader tumor-suppressive role—reducing Kcr levels reprograms tumor immunity and suppresses malignant progression [78]. YEATS2 selectively recognizes H3K27cr through structural adaptations distinct from bromodomains: its elongated binding channel accommodates bulkier acyl groups, while the aromatic cage formed by Y262/W282 engages Kcr via π-arene stacking (Fig. 2D and G) [23, 60, 79]. Hydrogen bonding between the Kcr amide group and S261/W282 residues further stabilizes this interaction [23]. Notably, while H3K27cr typically associates with transcriptional repression (e.g., GAS41-mediated *p21* silencing in colorectal cancer [80]), YEATS2-driven H3K27ac deposition paradoxically activates oncogenic pathways. This duality is exemplified by LINC00887, which recruits YEATS2 to enhance GCN5-dependent H3K27cr levels and drive colorectal cancer metastasis by enhancing *ETS1* expression [34]. Clinically, elevated H2BK12cr in peripheral blood mononuclear cells shows promise as a non-invasive biomarker for early colorectal cancer detection [81]. These findings position YEATS2-Kcr interplay as a mechanistically rich target for epigenetic therapy development.

Small-molecule tools to study the YEATS domain

Tumor heterogeneity and the dynamic reversibility of epigenetic modifications drive therapeutic resistance while offering opportunities for novel anticancer strategies. Epigenetic therapies aim to restore physiological DNA methylation and histone PTM patterns disrupted in malignancies [82]. Targeting epigenetic readers—particularly YEATS domain-containing proteins implicated in oncogenesis [16]—represents a promising approach [83–85]. However, their selective inhibition remains challenging due to structural homology across family members and gene-specific regulatory roles [86].

Current efforts focus on disrupting YEATS domain-histone acylation interactions. Chen et al. developed phage-displayed noncanonical amino acids (ncAAs) mimicking epigenetic marks to identify selective inhibitors [87], though the lack of Chromatin Immunoprecipitation (ChIP)-grade antibodies for YEATS proteins hampers target validation. While broad-spectrum inhibitors like SGC-iMLLT (targeting AF9/ENL with minimal YEATS2 affinity [18]) and SR-0813 (leukemia-specific probe [88]) show preclinical efficacy, their optimization for in vivo use remains ongoing. For instance, the

pharmacokinetics of SGC-iMLLT were improved via benzimidazole-to-pyrrolidine pyridine substitutions [83]. Notably, YEATS2-specific inhibitors remain elusive, though pyrazolopyridine derivatives (compounds 3b/4d) exhibit sub-micromolar potency [89]. Parallel strategies include amino thiophene-based GAS41 inhibitors (e.g., compound 11) [85] and virtual screening of benzimidazolones [89]. These methodologies, though not directly targeting YEATS2, provide frameworks for developing isoform-selective agents.

Outlook and perspective

YEATS2 and histone modifications

Histones undergo diverse PTMs, among which lysine acylations exhibit remarkable structural heterogeneity [90]. These PTMs dynamically reshape chromatin architecture to regulate DNA-templated processes without altering genetic sequences [91–93]. Notably, aberrant acetylation and methylation patterns dominate cancer epigenomes, correlating strongly with metastatic progression [94, 95]. YEATS2 plays a pivotal role in interpreting histone acylation signals. In NSCLC, it binds H3K27ac to recruit the ATAC complex, facilitating H3K9ac deposition and transcriptional activation of pro-tumorigenic genes [27]. Similarly, GAS41—a YEATS family member—engages H3K27ac and H3K14ac to promote histone 2 A variant Z (H2A.Z) incorporation in NSCLC chromatin [96, 97], revealing a conserved mechanism linking histone acetylation readouts to nucleosome remodeling (Fig. 3A).

Two critical questions remain unresolved: (1) How does YEATS2 discriminate between structurally similar acyl marks (e.g., H3K27ac vs. H3K27bz) in tumor-specific contexts? Although conformational flexibility of its YEATS domain may contribute, context-specific cofactors remain unidentified. (2) How do fluctuations in acyl-CoA metabolites (e.g., acetyl-CoA) within nutrient-rich tumor microenvironments modulate YEATS2 activity? Addressing these gaps is essential for understanding its metabolic-epigenetic crosstalk in malignancy.

YEATS2 links cellular metabolism and gene expression

Metastasis remains a major contributor to cancer mortality, driven not only by genetic mutations but also by epigenetic plasticity that enables rapid adaptation to microenvironmental stresses [98]. Termed "epigenetic drivers," these dynamic modifications—particularly aberrant DNA and histone PTMs—rival genetic alterations in prevalence and directly fuel tumor heterogeneity [99–101]. Reprogramming chromatin states through these changes establishes stable malignant phenotypes, allowing cells to bypass growth control mechanisms. This plasticity mirrors Conrad Waddington's epigenetic landscape theory, where spatiotemporal epigenetic patterns dictate cell fate during development [102].

Central to this process is the bidirectional crosstalk between metabolism and epigenetics [103, 104]. YEATS2 exemplifies this link: localized hyperacetylation at loci like MYC relaxes chromatin to amplify oncogene transcription, sustaining proliferation across cancers [16, 24]. Its overexpression may arise as both a consequence

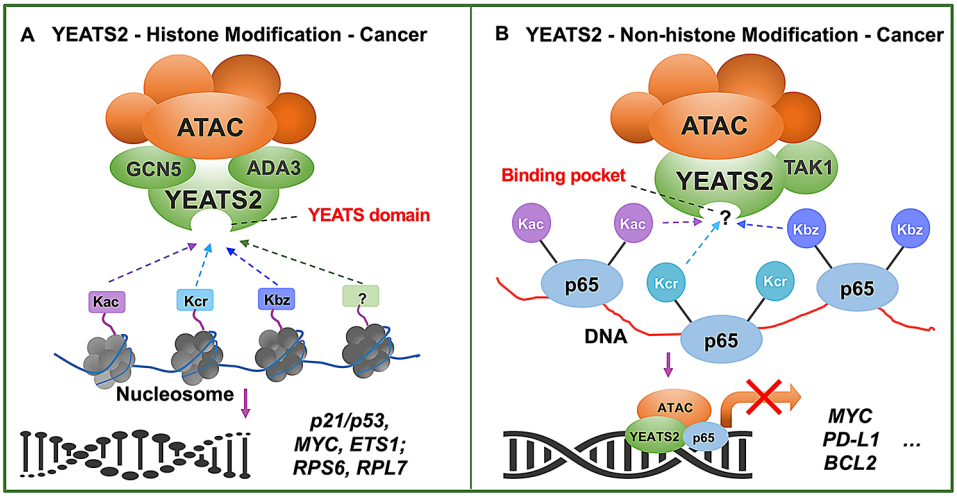

Fig. 3 Dual Mechanisms of YEATS2 in Cancer Epigenetics. (**A**) Histone-dependent regulation: YEATS2 binds nucleosomal H3K27ac/cr/bz via its aromatic cage, recruiting the ATAC complex (GCN5/PCAF) to deposit H3K9ac at promoters of oncogenes (*MYC*, *ETS1*, or *p21/p53)* and ribosomal genes (*RPS6* and *RPL7*). (**B**) Non-histone cross-talk: YEATS2 recognizes acylated p65 (NF-κB) to sustain PD-L1 transcription. This dual functionality positions YEATS2 as a metabolic-epigenetic integrator, linking acetyl-CoA abundance to immune evasion and therapy resistance. ATAC, ADA Two A-Containing Complex; ADA3, Alteration/Deficiency in Activation 3; BCL2, B-cell lymphoma 2; GCN5, General Control non-depressible 5; ETS1, E26 transformation-specific 1; PD-L1, Programmed Death Ligand-1; TAK1, Transforming growth factor-beta-activated kinase 1; K, Lysine; ac, Acetylation; cr, Crotonylation; bz, Benzoylation. The graphic framework is adapted from Mi et al., [27], Ren et al., [26], Zhao et al., [23], Sheng et al., [33], Zhou et al., [39], and Wang et al., [21]

of oncogenic signaling (e.g., HIF1α-driven hypoxia responses [32]) and a primary epigenetic regulator [33]. By integrating metabolic cues (e.g., acetyl-CoA levels) with transcriptional output, YEATS2 emerges as a nodal coordinator of malignant adaptation. Deciphering its context-dependent regulatory logic—whether as signal transducer or epigenetic orchestrator—holds promise for novel therapeutic targeting.

YEATS2 and immune-related pathways

YEATS2 modulates immune evasion through NF-κB pathway activation—a central regulator of PD-L1 expression [33, 39, 40]. In pancreatic ductal adenocarcinoma (PDAC), YEATS2 stabilizes TAK1 to activate NF-κB, thereby promoting PD-L1 upregulation and tumor cell survival [33, 39]. Biochemical analyses confirm its direct interaction with the NF-κB subunit p65, facilitating nuclear translocation in PDAC cells [33]. ChIP-seq studies further demonstrate YEATS2 co-localization with p65 at promoters of pro-survival genes (*BCL2*, *XIAP*, *CCL2*), where it recruits the ATAC complex to deposit H3K9ac and sustain transcriptionally active chromatin states [33, 39] (Fig. 3A).

The acetylation status of p65 critically influences immune escape mechanisms. Palmitate-enriched microenvironments enhance p65 acetylation to drive metastasis [105–109], whereas its deacetylation correlates with PD-L1 expression in pancreatic and breast cancers [39, 110]. YEATS2 exacerbates this immune suppression by elevating PD-L1 levels, evidenced by its knockdown reducing PD-L1 in PDAC models [33, 39]. Intriguingly, as a reader of non-histone acylations [111], YEATS2 may stabilize NF-κB complexes by recognizing p65 acetylation marks (e.g., K310)—a mechanism parallel to Bromodomain-containing Protein 4 (BRD4) regulation of acetylated transcription factors [112, 113] (Fig. 3B). However, critical gaps persist: the structural basis of YEATS2-p65 interaction remains undefined, and its broader role in regulating acylated non-histone oncoproteins warrants systematic investigation.

Epigenetic synergy with immunotherapy

YEATS2 has emerged as a key modulator of tumor immunogenicity, particularly under hypoxic conditions where HIF1α-mediated upregulation fosters immunosuppressive microenvironments through PD-L1 induction and checkpoint activation [32, 114, 115]. Although inhibitors targeting other epigenetic readers (e.g., BET/HDAC proteins) enhance the efficacy of immune checkpoint inhibitors (ICIs) by remodeling immune gene expression [116, 117], YEATS2-targeted agents.

remain underdeveloped. The reversible nature of epigenetic modifications—unlike genetic mutations—provides unique therapeutic opportunities [6]. Combining epigenetic modulators with ICIs could leverage chromatin plasticity to overcome resistance, as demonstrated by HIF1α pathway targeting that reverses PD-1 blockade resistance [118–122]. Given the hypoxia-inducible expression of YEATS2 [32], its inhibition may similarly potentiate immunotherapy responses.

The role of YEATS2 in stabilizing oncogenic chromatin states positions it for rational combination therapies. Co-administration with HDAC inhibitors (e.g., panobinostat) counteracts compensatory BRD4 recruitment, synergistically suppressing NSCLC growth in *vivo* [27, 123, 124]. Dual targeting of YEATS2 and BET proteins disrupts MYC/BCL2 transcriptional networks while reducing off-target toxicity [89, 125]. Clinically, YEATS2 overexpression correlates with poor prognosis in NSCLC (hazard ratio (HR) = 2.4), PDAC (HR = 1.8), and HCC, and predicts BET inhibitor resistance in lymphoma models [125]. Compared to pan-epigenetic inhibitors, YEATS2-selective agents like pyrazolopyridines exhibit enhanced specificity by selectively silencing oncogenic promoters [89], with preclinical studies demonstrating PD-L1 reduction in PDAC [33]. Current efforts focus on optimizing small-molecule inhibitors (e.g., compound 14a) and developing proteolysis targeting chimera (PROTAC) degraders linking YEATS2 binders to E3 ligases (e.g., VHL). While no clinical trials directly target YEATS2, insights from ongoing ENL/AF9 trials (NCT04817007) may inform future therapeutic strategies.

Development of chemical tools for YEATS2

YEATS2 remains an underexplored epigenetic reader in oncology, primarily due to its structural complexity. This knowledge gap arises from technical challenges, including the protein's large size (> 1,000 residues), complicating full-length recombinant production for biochemical studies. The versatility of YEATS domain in recognizing diverse acylation marks—from acetylation (Kac) to bulkier modifications—contrasts with other family members' narrower substrate preferences [126, 127]. Current inhibitors lack selectivity against homologous YEATS proteins (e.g., ENL, GAS41), confounding functional interpretation. Structural studies reveal a "tip sensor" mechanism where binding pocket residues distinguish acylation types, while adjacent regions mediate histone sequence specificity [26], enabling context-dependent substrate engagement. The scarcity of isoform-selective chemical probes has forced reliance on genetic approaches, leaving direct pharmacological consequences of YEATS2 inhibition poorly defined [23, 26, 27, 89]. To address these limitations, two strategic priorities emerge: (1) Developing covalent probes (e.g., photoaffinity labels) to map the interactome of YEATS2 in live cells; (2) Optimizing pyrazolopyridine derivatives for in vivo stability and immune checkpoint inhibitor compatibility. Such innovations will

Table 3 Research roadmap for YEATS2

Focus Area	Key Goals	Tools/Methods
Structural Biology	Resolve YEATS2 complexes with acylated histones	Cryo-EM, X-ray crystallography
Chemical Probes	Develop isoform-selective inhibitors/degraders	PROTACs, photoaffinity labeling
Functional Genomics	Map YEATS2 dependencies in tumor subtypes	CRISPR-Cas9 screens, spatial transcriptomics
Translational Studies	Validate YEATS2 as a biomarker/therapeutic target	Patient-Derived Xenograft (PDX) models, clinical cohort analyses

ultimately illuminate how YEATS2 coordinates chromatin remodeling through context-specific acylation decoding in malignancies.

Future directions

Three critical gaps hinder therapeutic exploitation of YEATS2 in cancer: (1) Its immunomodulatory roles remain undefined. While YEATS2/NF-κB activation drives PD-L1 expression in preclinical models [33, 39, 40], whether its inhibition synergizes with anti-PD-1/PD-L1 therapies requires validation. Hypoxia-induced YEATS2 may amplify HIF1α-mediated immunosuppression [32], suggesting combinatorial approaches to reverse PD-L1-driven T-cell exhaustion. (2) Crosstalk with other epigenetic regulators lacks systematic study. Despite evidence linking YEATS2 to BET protein networks, its broader roles in therapy resistance (e.g., sorafenib-refractory HCC [35]) and immune exclusion remain unexplored. (3) Clinical validation lags. While The Cancer Genome Atlas (TCGA) analyses associate *YEATS2* overexpression with poor prognosis, its utility as a pan-cancer biomarker demands multicenter validation. Technological priorities include: single-cell/spatial transcriptomics to map context-dependent functions across tumor niches; CRISPR screens to identify synthetic lethal partners in resistant cancers; and Cleavage Under Targets and Tagmentation (CUT&Tag) and Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq)" in patient-derived organoids to resolve treatment-induced chromatin dynamics. Finally, optimizing pyrazolopyridine inhibitors for in vivo stability and ICI co-delivery remains paramount to bridge preclinical promise with clinical translation. Table 3 list the research roadmap for YEATS2 in the future detection.

Conclusion

YEATS2 has emerged as a pivotal epigenetic nexus bridging metabolic signaling, chromatin dynamics, and oncogenic transcription. Its YEATS domain uniquely deciphers heterogeneous histone acylations (acetyl/crotonyl/benzoyl) through a conformationally flexible aromatic cage, allowing adaptation to nutrient-replete tumor microenvironments. Context-dependent functions—from sustaining NSCLC ribosome biogenesis to orchestrating PDAC immune evasion—position it as a multifunctional scaffold in cancer progression. Therapeutically, YEATS2 presents both promise and complexity. While pyrazolopyridine inhibitors validate its acetyl-lysine pocket as druggable [89], isoform selectivity challenges persist. Three priorities demand attention: (1) Structural resolution of full-length YEATS2 complexes (e.g., ATAC/NF-κB) to inform covalent inhibitor design; (2) Multi-omics integration (single-cell CRISPR, spatial profiling) to identify synthetic lethal partners in resistant cancers; (3) Clinical validation of YEATS2 as a biomarker for epigenetic therapy resistance and PROTAC development. Notably, YEATS2 inhibition may potentiate HDAC/BET inhibitors by disrupting compensatory transcriptional circuits. However, its dual roles in gene activation (via ATAC) and repression (via Polycomb crosstalk [128]) necessitate context-guided targeting. With advancing chemical tools and multi-omics datasets, YEATS2 is poised to transition from mechanistic novelty to actionable node in precision oncology.

Abbreviations

ADA	Acetylation domain associated
ADA3	Alteration/Deficiency in activation 3
AF9	ALL1-fused gene from chromosome 9 protein
ALL1	Acute lymphoblastic leukemia 1
ATAC	ADA Two Acetyl-CoA-containing
BCL2	B-cell lymphoma 2
BRD4	Bromodomain-containing Protein 4
ChIP	Chromatin Immunoprecipitation
CUT&Tag	Cleavage Under Targets and Tagmentation
DNMTs	DNA Methyltransferases
EMT	Epithelial-Mesenchymal Transition
ENL	Eleven-nineteen leukemia
ETS1	E26 transformation-specific 1
GAS41	Glioma amplified sequence 41
GCN5	General Control Non-depressible 5
HAT	Histone acetyltransferase
H2A.Z	Histone 2 A variant Z
HCC	Hepatocellular carcinoma
HIF1α	Hypoxia-Inducible Factor 1-alpha
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Hazard Ratio
ICIs	Immune Checkpoint Inhibitors
Kac	Lysine Acetylation
Kbz	Lysine Benzoylation
Kcr	Lysine Crotonylation
LUSC	Lung Squamous Cell Carcinoma
ncAAs	Noncanonical Amino Acids
NF-κB	Nuclear Factor Kappa B
N-MYC	Neuroblastoma MYC
NSCLC	Non-Small Cell Lung Cancer
OC	Ovarian cancer
PCAF	P300/CREB-binding Protein-associated Factor
PD-1	Programmed Death-1
PDAC	Pancreatic Ductal Adenocarcinoma
PD-L1	Programmed Death Ligand-1
PI3K/AKT	Phosphoinositide 3-Kinase/Protein Kinase B
PROTAC	Proteolysis Targeting Chimera
PTMs	Post-Translational Modifications
RMSD	Root-Mean-Square Deviation
Sas5	Something About Silencing 5
SEC	Super Elongation Complex

SGC-iMLLT	Structural Genomics Consortium inhibitor of Mixed-Lineage Leukemia Translocation
Taf14	TATA-binding Protein Associated Factor 14
TAK1	Transforming Growth Factor Beta-Activated Kinase 1
TCGA	The Cancer Genome Atlas
TET	Ten-Eleven Translocation
XIAP	X-linked Inhibitor of Apoptosis Protein
Yaf9	Yeast Associated Factor 9
YEATS	Yaf9, ENL, AF9, Taf14, and Sas5

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Author contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

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