International Journal of Biological Macromolecules 311 (2025) 143948

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac

Review

ATAD2 bromodomain in cancer therapy: current status and future perspectives

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ARTICLE INFO

Keywords:
ATAD2 bromodomain
cancer
Oncogene
Cell cycle
DNA replication
Hormone signalling

ABSTRACT

ATPase family AAA domain-containing protein 2, or ATAD2, is a novel carcinogen, essential for cancer development, chromatin remodeling, and transcriptional control. It contains a bromodomain, which binds to acetylated histones to control gene expression. It also impacts pathways that regulate the cell cycle, DNA replication, and hormone signalling. ATAD2 is overexpressed in several malignancies, including colorectal, lung, ovarian, and breast cancers, and cancer metastasis. Investigations into the function of ATAD2 in oncogenesis and its interactions may offer fresh approaches to creating cancer treatment plans. Although preclinical research is very encouraging, many unresolved aspects regarding therapeutic development remain, including toxicity being explored concurrently. Investigations into the function of ATAD2 in oncogenesis may offer fresh approaches to developing chemotherapy strategies. Most of ATAD2's molecular mechanisms behind carcinogenesis and functions are discussed here. Additionally, we included progress, including potential monoclonal antibodies, RNA-based therapies, and small chemical inhibitors, in the review. Therefore, we guarantee this study will provide researchers with new opportunities and directions for cancer therapeutics.

List of abbreviations

AAA + ATPases Associated with diverse cellular Activities.
ADCs Antibody-Drug Conjugates
AKT Protein Kinase B
APC Adenomatous Polyposis Coli
ATAD2 ATPase family AAA domain-containing protein 2
B-MYB B-Myeloblastosis Oncogene
BC Breast cancer
BET Bromodomain and extra-terminal motif
BRD Bromodomain
CBP CREB-Binding Protein
CDK Cyclin-Dependent Kinase
CENPE Centromere-associated protein E
CRC Colorectal cancer
CSC Cancer stem cell
DDR DNA Damage Response
DEGs Differentially Expressed Genes
EMT Epithelial-to-Mesenchymal Transition
ER Estrogen receptor
ESCC Esophageal squamous cell carcinoma
FDA Food and Drug Administration

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https://doi.org/10.1016/j.ijbiomac.2025.143948
Received 9 March 2025; Received in revised form 22 April 2025; Accepted 3 May 2025
Available online 5 May 2025

GSK GlaxoSmithKline
HAT Histone acetyltransferase
HCC Hepatocellular carcinoma
HDAC Histone Deacetylase
HIF1α Hypoxia-Inducible Factor 1-alpha
KAc Lysine Acetylation
LUAD Lung Adenocarcinoma
MDR Multidrug Resistance
MMR Mismatch Repair
MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
NGS Next-Generation Sequencing
NSD2 Nuclear receptor SET domain-containing protein 2
OSCC Oral Squamous Cell Carcinoma
PARP Poly (ADP-ribose) Polymerase
PI3K Phosphoinositide 3-Kinase
PTM Post-Translational Modification
RB Retinoblastoma
RCC Renal Cell Carcinoma
RNAi RNA Interference
siRNA Small Interfering RNA
TME Tumor Microenvironment
VEGF Vascular Endothelial Growth Factor
WNT Wingless/Integrated (Wnt) Signalling Pathway

1. Introduction

Tumorigenesis is a multi-step process that leads to unregulated cell proliferation by activating oncogenes and reducing tumor suppressors. It is caused by defects in several genes connected to cancer. Understanding cancer biology requires examining molecular complexity at the transcriptome, proteome, metabolomic, epigenomic, and genomic levels. [1]. Cancer epigenetics shows that changes in gene expression that do not alter the DNA sequence can significantly affect cancer. Encircled by 146 base pairs of DNA nucleotides, the chromatin comprises a histone octamer (H3-H4)2 tetramer and two H2A-H2B dimers. The term "epigenetic" describes heritable modifications in gene activity. Histone post-translational modification (PTM) is one epigenetic element that modifies chromatin structure and function, including lysine residues. [2]. The altered histone residue facilitates the contact by connecting directly to the host's ligand-binding pocket and other linkages via the surrounding histone sequence. A disease state can be modified by mutations that alter the expression or function of an epigenetic protein. It might be possible to marginally change the course of a disease by targeting epigenetic proteins. An epigenetic reader domain uniquely recognizes ε-*N*-acetylated lysine residues (Kac) called a bromodomain (BRD) [3]. The left-handed bundle of four α-helices (Z, A, B and C) makes up the BRD's conserved structure, and the ZA and BC loops form a hydrophobic Kac binding pocket. Asparagine in the BC loop and a conserved tyrosine in the ZA loop are essential for Kac recognition because they create hydrogen bonds with the acetyl group. Ligand interactions frequently entail a conserved cluster of five water molecules at the base of the pocket, as shown in Fig. 1. The 61 unique BRDs that comprise the 46 human proteome proteins are organized into eight families based on structure and sequence homology. BET BRDs (Bromodomain and Extra-Terminal motif), a subclade of family II, have been studied the most; families I, VI, and VIII have comprehensive structural characterizations [4].

BET proteins are essential for the control of genes. BRD2 facilitates cell cycle progression, and BRD3 binds acetylated GATA1 to control erythroid genes. BRD4 binds with P-TEFb to increase RNA polymerase II elongation and regulates c-Myc in cancer [5].

1.1. Bromodomain role in cancer

Bromodomains are essential for controlling the production of genes like H3k9ac, H4k5ac, and H3k14ac because they can identify and attach

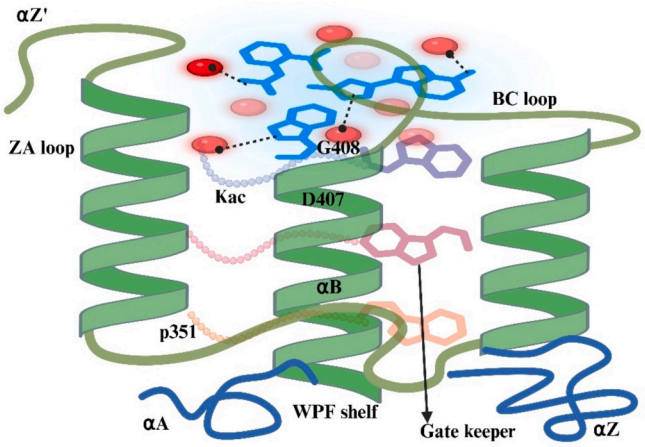

Fig. 1. Structural representation of the ATAD2 bromodomain and functional regions.

to acetylated lysine residues inside histone proteins. This binding influences gene expression by promoting chromatin opening and attracting other transcriptional factors. These proteins alter significant physiological processes, including cell cycle progression, oncogenic signalling pathways, DNA repair, and apoptosis. Additionally, bromodomains change the structure of chromatin to either promote or inhibit the transcription of genes in chromatin remodeling complexes. BRD4 can attach to super-enhancers during oncogenesis, which regulate the production of MYC and BCL2 oncogenes. Further, linking the proteins like ATAD2 and BRD2 with bromodomains promotes higher cell proliferation. [6,7].

1.2. ATAD2

ATPase family AAA domain-containing 2 is a chromatin regulator with a molecular weight of 158.5 kDa, which is composed of 28 exons and 1390 amino acids. ATAD2, a conserved oncoprotein, is a potential cancer biomarker and therapeutic target. It has an important function in DNA replication, chromatin dynamics, and gene transcription, which causes carcinogenesis in various malignancies. ATAD2A (also called ATAD2) and ATAD2B are the two paralogs of human ATAD2, with ATAD2A receiving the majority of research attention [8]. The protein is composed of four domains: the C-terminal domain (CTD), the N-terminal acidic domain (NTD), and the bipartite AAA+ ATPase domain (AAA-D1 and AAA-D2). By modifying histone acetylation, chromatin remodeling, and transcription factor recruitment, ATAD2 regulates transcription [9].

1.3. Functions of ATAD2 in transcription, replication and cell cycle regulation

ATAD2 uses ATP hydrolysis to restructure chromatin. Research finds that Yta7, an ATAD2 homolog in *Saccharomyces cerevisiae,* released by HTA1, binds to RNA polymerase II, phosphorylated by CK2 and CDK1, and initiates the transcription of histone genes [10]. ATAD2 interacts with histone (H4) at lysine (K5 and K12) during the initial phase of DNA replication. Its bromodomain binds directly to diacetylated lysine to promote replication-coupled nucleosome recombination. ATAD2 is primarily involved in heterochromatin replication, where its expression increases and localizes to heterochromatin sites [11]. In pancreatic cancer, inhibiting ATAD2 increases sensitivity to gemcitabine and radiotherapy by intensifying DNA damage and down-regulating DNA repair proteins, highlighting its critical role in DNA damage response (DDR) [12]. ATAD2 has a crucial role in chromatin remodeling, via histone acetylation, enhancing chromatin accessibility and promoting

gene expression. The AAA+ ATPase domain aids in eliminating nucleosomes, whereas its BRD-ATAD2 domain targets acetylated histones. By affecting chromatin structural changes, ATAD2 promotes tumor growth. These changes in turn enhance melanoma by making chromatin more accessible and changing chromatin linkages, which in turn promotes hepatocellular carcinoma [13] .

ATAD2 has a crucial role in regulating the malignant cell cycle. The Rb pathway is linked to its overexpression in several cancers, and its suppression results in G1/S cell cycle arrest. Important proteins involved in this pathway, such as CDKs and cyclin D1, are regulated by ATAD2 and are necessary for the G1 to S phase transition. Together with MYC, it acetylated E2F-related histones and activated genes essential for cell cycle progression. Furthermore, ATAD2 controls B-MYB, another important protein linked to the development of cancerous cells. ATAD2 affects many signalling pathways, which promote oncogenic development [14]. Additionally, ATAD2 plays a role in endocrine signalling, which promotes the growth of prostate and breast cancer. ATAD2 increases the expression of target genes controlled by estrogen receptors, including cyclin D1 and c-Myc. By helping the ERα–CBP complex associate with chromosomal sites, ATAD2 improves transcriptional regulation and histone modifications. Moreover, kinesin-related genes that are essential for the growth and survival of breast cancer cells are modulated by ATAD2 [15]. ATAD2 promotes androgen-induced gene expression by interacting with Cyclin D3 and IGF1R, and promotes the growth of prostate cancer as depicted in Fig. 2 [8].

Especially in cancer, the intricacy of ATAD2 action across several signalling pathways makes it extremely difficult to design safe and efficient treatments. Its function is not restricted to a single path but encompasses many biological functions, such as DNA replication, chromatin remodeling, and cell cycle progression. Its blockage may be detrimental to healthy proliferating cells. Additionally, ATAD2 has a role in carcinogenesis by affecting critical pathways linked to cancer, including the Wnt/β-catenin signalling cascades, PI3K/Akt/mTOR, and MAPK/ERK. Drug resistance, tumor growth, and stem-like cancer characteristics are all known to be mediated by these similar mechanisms. The inability to isolate ATAD2 as a pure therapeutic target without running the risk of off-target effects that could impair vital cellular processes in healthy tissues is made more difficult by its cross-pathway functioning. Furthermore, ATAD2 lacks clear binding sites for conventional small-molecule inhibitors, just as “undruggable” oncogenes like MYC, RAS, and mutant p53 that were previously described. It is in the nucleus and interacts with chromatin, making it challenging to target selectively and inaccessible to antibody-based treatments. Additionally, as seen with BET inhibitors employed against MYC, compensatory mechanisms in cancer cells may circumvent ATAD2 inhibition, decreasing therapeutic efficiency and perhaps resulting in adaptive resistance. Although each has its own set of biological and technical challenges, precision strategies like contextual inhibitors that only affect ATAD2 under oncogenic conditions (e.g., hypoxia or high MYC expression), targeted protein degradation (e.g., PROTACs), or epigenetic reprogramming may offer encouraging avenues for advancement [16].

1.4. ATAD2 in cancer therapy

Numerous cellular pathways are impacted by ATAD2, which is crucial for cancer development. Although oncogenesis results from transcriptional factors that amplify or dysregulate it, mitogenic signalling typically regulates ATAD2 levels. Studies on the genome have linked splicing and mutational events in lung, ovarian, and liver cancers to ATAD2 expression [17]. The image shows how ATAD2 facilitates carcinogenesis by changing the expression of certain genes in healthy cells, which causes those cells to develop into malignant cells. Through the activation of oncogenic pathways involving c-MYC, E2F1, Rb, PI3K, AKT, and mTOR, it promotes proliferation and advances the cell cycle from the G0 to G1/S phase (Fig. 3) [18]. Recent research indicates that ATAD2 is crucial in integrating metabolic reprogramming and epigenetic instability, two critical aspects of cancer. ATAD2 promotes metabolic alterations that support tumor growth and survival by controlling the PI3K/AKT signalling pathway and influencing significant glycolytic mediators such as GLUT1 and HK2. Due to its dual role, ATAD2 stimulates gene expression programs and metabolic modifications that allow cancer cells to multiply in hypoxic and nutrient-stressed conditions. The clinical significance of ATAD2 as a complex chromatin regulator and driver of oncogenic resilience is strengthened by this perspective, which calls for further study using precision oncology tools [19].

By altering the expression of specific genes in healthy cells, ATAD2 promotes carcinogenesis by causing those cells to differentiate into malignant cells (Fig. 3). It stimulates proliferation and moves the cell cycle from the G0 to G1/S phase by activating oncogenic pathways involving c-MYC, E2F1, Rb, PI3K, AKT, and mTOR. ATAD2 further encourages the epithelial-to-mesenchymal transition (EMT), which increases cancer cells' invasiveness and metastatic potential, by downregulating E-cadherin and upregulating transcription factors such as Snail and Slug. Furthermore, ATAD2 keeps cancer cells from dying and increases their chances of surviving by inhibiting tumor suppressors

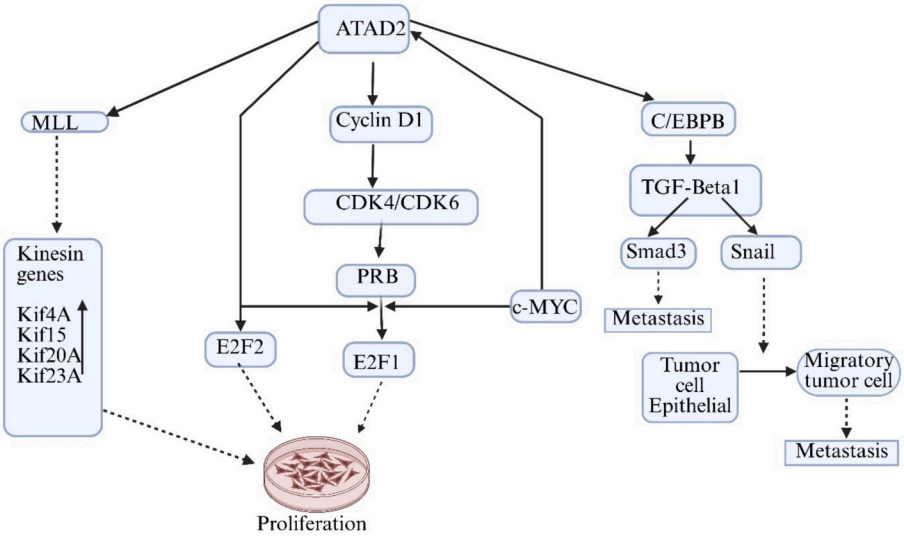

Fig. 2. ATAD2 function.

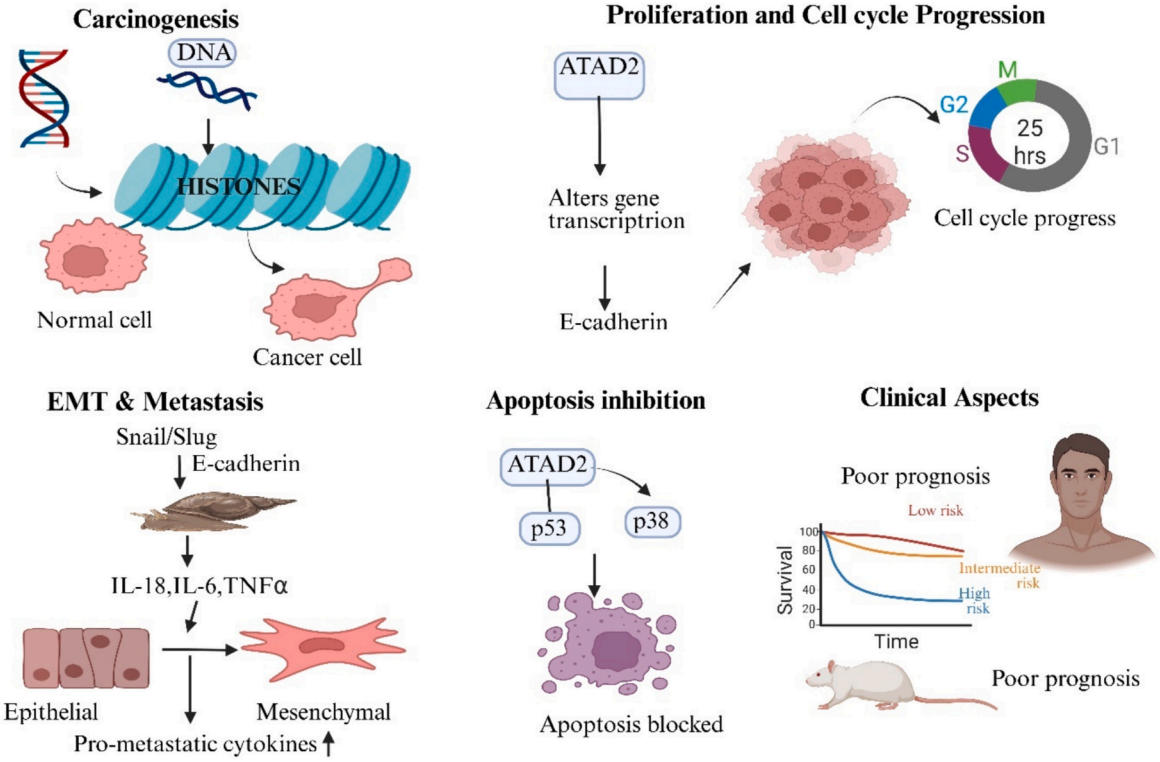

Fig. 3. Role of ATAD2 in cancer.

including p53 and p38. Maintaining the growth of cancer requires this anti-apoptotic activity. The clinical component of the image highlights the predictive importance of ATAD2 expression, showing that greater levels are associated with poorer cancer patient survival outcomes. By interacting with proto-oncogenes such ACTR, AIB1, SRC-3, EZH2, E2Fs, and MYC, as well as by activating pathways like Hedgehog in conjunction with MYC, ATAD2 leads to aggressive cancer phenotypes. Consequently, ATAD2 is a major molecular driver of tumor biology and a possible therapeutic target.

2. Structure and characteristics of ATAD2 bromodomain

A bipartite AAA+ ATPase domain (AAA-D1 and AAA-D2), a bromodomain (BRD-ATAD2), an N-terminal acidic domain (NTD), and a C-terminal domain (CTD) make up ATAD2's structure. Drugs can target the AAA-ATAD2 and BRD-ATAD2 domains, the most conserved domains for cancer treatment. The conserved domains of human and mouse ATAD2 are shared by similar proteins such as lex-1 in *Caenorhabditis elegans*, Yta7 in *Saccharomyces cerevisiae*, and Abo1 in *Schizosaccharomyces pombe* [12]. The AAA-ATAD2 domain is close to ATAD2's N-terminal domain (NTD). The preserved Walker A and B motifs, sensor regions 1 and 2, and an arginine finger are features of AAA-ATAD2. This domain involves the following processes: ATP binding, hydrolysis, oligomerization, protein folding, DNA repair, ion transport, and protein degradation. ATP/ADP binds at the AAA-D1 interface, as illustrated in Fig. 4, whereas AAA-D2 is catalytically inactive due to the absence of Walker motifs [20].

The bromodomain chromatin reader is a left-handed bundle structure consisting of a four-helix bundle with ZA (αZ-αA) and BC (αB-αC) loops. As a result, a hydrophobic pocket is formed that interacts with acetylated lysine to regulate target gene transcription. The bromodomain contains a folded structure called the "BRD fold" or lysine acetylation (KAc) binding pocket. Histone interactions are intimately linked to Asn1064 and other KAc pocket residues.

The biological function and ATAD2 binding to ligands are predicted

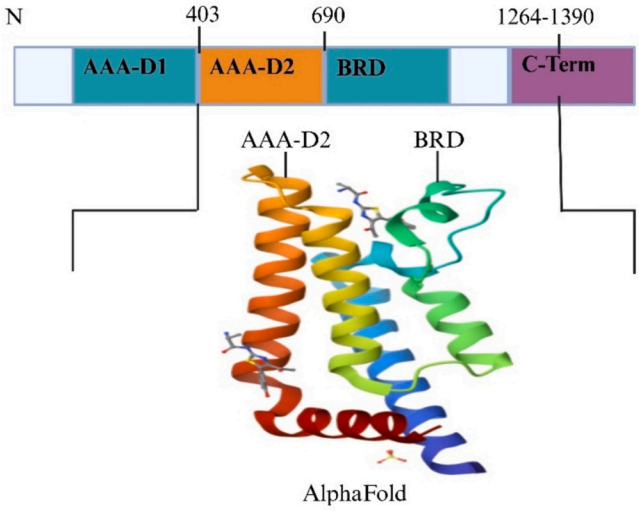

Fig. 4. Domain Architecture and Structural Features of ATAD2 in Humans.

by the structural flexibility of the KAc pocket. Moreover, the bromodomain is shared by a C-terminal domain (CTD) region that follows ATAD2-like proteins [9].

2.1. Binding specificity and mechanism of action

The C-terminal region of ATAD2 contains a single bromodomain, in contrast to other multi-bromodomain proteins such as BRD4 or CBP/p300. H3K14ac and H4K5ac are the main acetylated histone tails that the ATAD2 bromodomain can interact. ATAD2s binding pocket is distinct from other bromodomains in terms of form and electrostatic characteristics, it has specificity for acetylated proteins and histones. ATAD2 is implicated in the remodeling of chromatin through acetylated

histones and attracts additional chromatin-modifying proteins [14]. ATAD2 may be a target for therapy because of its carcinogenic role. Inhibitors that target the ATAD2 bromodomain are being studied to prevent ATAD2 from interacting with acetylated histones [21].

2.2. Analysing different bromodomains

Bromodomains (BRDs) comprise 110 amino acids and can recognize acetylated lysine residues, particularly those on histones. These domains are "readers" of epigenetic markers, linking histone acetylation to chromatin regulation and gene expression. BRD proteins fall into nine groups:

1. Histone acetyltransferases (9 members) [22]
2. Histone methyltransferases (2 members) [23]
3. Chromatin remodeling factors (11 members) [24]
4. AAA ATPase proteins (2 members) [20]
5. BET family transcriptional coactivators (4 members) [25]
6. E3 SUMO/ubiquitin ligases (4 members) [26]
7. SP family proteins of PML nuclear bodies (4 members) [27]
8. Transcriptional co-repressors (2 members) [28]
9. WD-repeat proteins (3 members) [29]

BRD-containing proteins are widely expressed in different organs and play various catalytic and scaffolding roles. The four α-helices (αZ, αA, αB, and αC), which form a conserved domain, are joined by ZA and BC loops, which offer binding specificity [30]. BRD4 has two bromodomains (BD1 and BD2) capable of recognizing acetylated histones, including H4K5ac and H4K12ac. Furthermore, BRD4 can interact with additional transcription factors due to its longer C-terminal domain than ATAD2. BET inhibitors, such JQ1 and I-BET762, are BRD4 inhibitors that effectively prevent cancer cell growth, especially in hematologic malignancies [31].

Members of the BRD2/3/4 Family can act as scaffolds for transcriptional complexes because of their tandem bromodomains and extra-terminal (ET) domain. Particularly in cell cycle control and inflammation, BRD2/3/4 plays a role in transcriptional elongation and chromatin stability. Inflammation and neurological diseases are also involved, and their therapeutic possibilities extend beyond oncology. The BRD2/3/4 Family's extra-terminal (ET) domain and tandem bromodomains allow them to function as scaffolds for transcriptional complexes. Beyond cancer, its therapeutic potential extends to neurological disorders and inflammation [32] . Larger multi-domain proteins with intrinsic histone acetyltransferase (HAT) activity and transcriptional coactivation function incorporate CBP/p300 bromodomains. Many transcriptional complexes employ them as scaffolds, such as p53, HIF-1α, and NFκB [33].

3. Role of ATAD2 in cancer

Small-cell oesophageal carcinoma (SCEC) and oesophageal squamous cell carcinoma (ESCC) are associated with advanced cancer stages when ATAD2 is overexpressed. It operates through the Hedgehog signalling pathway in ESCC, causing the C/EBPβ/TGF-β1/Smad3/Snail axis to initiate the epithelial-mesenchymal transition (EMT) and metastasis [33]. In gastric cancer, HIF1α regulates ATAD2 expression under hypoxic conditions, which promotes the cell cycle via the pRb-E2F1 pathway. Since ATAD2 is also linked to paclitaxel resistance, it might be a biomarker for chemoresistance. ATAD2, which is overexpressed in hepatocellular carcinoma (HCC), promotes the growth of liver cancer via the miR-520a/E2F2 pathway and suppresses migration by downregulating endoplasmic reticulum oxidoreductase 1 (ERO1L) and Ras-GTPase-activating protein-SH3-domain-binding protein 2 (G3BP2). It also promotes the Hedgehog pathway and β-catenin signalling, which contribute to the development and stemness of HCC [34,35]. ATAD2 enhances hepatocellular carcinoma (HCC) via miR-520a/E2F2 pathway and downregulates endoplasmic reticulum oxidoreductase 1 (ERO1L) and Ras-GTPase-activating protein-SH3-domain-binding protein 2 (G3BP2). Additionally, it stimulates β-catenin signalling and the Hedgehog pathway for HCC development [36].

Deletion of ATAD2 in pancreatic cancer decreases cell migration and increases gemcitabine sensitivity. By deactivating the AKT pathway, preventing migration and proliferation, and triggering apoptosis, miR-217 downregulates ATAD2, indicating that it may be a potential target for future treatments [37]. ATAD2 overexpression in colorectal cancer (CRC) promotes cell proliferation via the pRb-E2F1 pathway and stabilizes the TRIM25 E3 ligase, enhancing CRC progression. It also regulates the miR-126-5p/ATAD2 axis, promoting angiogenesis and paclitaxel resistance, and is linked to poor prognosis [38,39]. Through the miR-302/ATAD2 axis, ATAD2 overexpression is linked to the development of ovarian cancer [40,41]. MYC expression and 8q24 amplification are associated with ATAD2 in endometrial carcinoma of the uterine corpus (UCEC). It promotes the proliferation of cancer cells through the B-MYB, E2F, and KIF genes [42,43]. Overexpression of ATAD2 in prostate cancer promotes the synthesis of NSD2 and raises androgen receptor (AR) activation, which aids in angiogenesis, tumor development, and survival [44]. MiR-372 regulates ATAD2, influencing renal cancer cell (RCC), metastasis. RCC, is tightly linked to von Hippel-Lindau (VHL) gene alterations that stabilize the hypoxia-inducible proteins HIF-1α and HIF-1β. Other genes that are often changed in clear cell RCC include PBRM1, the histone deubiquitinate BAP1, lysine demethylase KDM5C, the tumor suppressor PTEN, and the histone methyltransferase SETD2 [45].

The overexpression of ATAD2 in lung adenocarcinoma (LUAD) stimulates glucose metabolism through the AKT-GLUT1/HK2 pathway and tumor development through the PI3K/AKT pathway [46]. Through the pRb/E2F/MYC pathways, ATAD2, which is overexpressed in breast cancer as a result of 8q24 amplification, promotes proliferation and survival [47]. ATAD2 is also involved in various cancers, such as oral squamous cell carcinoma (OSCC), glioblastoma (GBM), nasopharyngeal carcinoma (NPC), and retinoblastoma (RB). It regulates key processes such as EMT, angiogenesis, and stem cell properties. It is a potential biomarker and therapeutic target across different malignancies [48].

3.1. Overexpression in tumorigenesis

The ATAD2 expressions were increased in oral squamous cell carcinoma (OSCC) and tongue squamous cell carcinoma (TSCC). Higher ATAD2 expression was associated with a decreased survival rate in patients with OSCC. Additionally, the levels of ATAD2 protein in OSCC were strongly correlated with the expression of B7-H4, PD-L1, CMTM6, Slug, and ALDH1. Among the OSCC cell lines (Tca8113, Cal27, SCC4, SCC9), Cal27 had the greatest ATAD2 expression. Various siRNA sequences (ATAD2-Homo-507, ATAD2-Homo-1121, and ATAD2-Homo-2072) were used to knock down ATAD2 in Cal27 cells, resulting in a longer G1 phase and a shorter G2 phase. These findings showed that *in vitro* inhibition of ATAD2 results in apoptosis and prevents the OSCC cell cycle at the G1 phase [49]. Similarly, ATAD2 is significantly overexpressed in endometrial cancer, especially in severe forms. The activation of translational markers connected to B-MYB (MYBL2) is related to ATAD2 overexpression. It increases invasiveness, cell division, and other malignant characteristics, suggesting that ATAD2 interacts with the B-MYB pathway to initiate and spread endometrial cancer [42].

Renal cell carcinoma (RCC) tumor specimens exhibit a marked overexpression of ATAD2, which is linked to the alteration of c-Myc. This oncogenic protein improves the transcriptional regulation of glycolytic genes and enhances glycolytic activity in RCC cells. This aligns with the Warburg effect, demonstrating that cancer cells preferentially employ glycolysis to generate energy even in aerobic conditions. However, some RCC cell lines have significantly higher ATAD2 levels, accelerating their growth rates [50]. Recent research shows that by upregulating the production of CENPE (centromere protein E), ovarian tumor tissues had higher levels of ATAD2 than non-malignant tissues.

Additionally, in patient samples, increased expression of ATAD2 is a prognostic marker for recurrence and metastatic dissemination. Since a decrease in ATAD2 causes a decrease in CENPE, which in turn causes cell-cycle arrest and enhanced apoptosis in ovarian cancer cells, this implies a strong correlation between ATAD2 and CENPE [51–53]. Numerous cancer forms, such as endometrial, colorectal, and breast carcinomas, overexpress ATAD2. Increased cellular proliferation and the potential for metastasis are linked to its overexpression. Research indicates that ATAD2 is required for the main carcinogens required for cell cycle progression, including E2F1 and c-Myc. Through its interactions with transcription factors and involvement in chromatin remodeling, ATAD2 promotes the expression of genes that aid in the growth of tumors. ATAD2 inhibition enhances apoptosis and decreases tumor formation by disrupting these pathways [54].

3.2. ATAD2-regulated molecular pathways in cancer cells

3.2.1. Rb/E2F-cMyc pathway

The retinoblastoma tumor suppressor (RB), a powerful regulator of cellular proliferation, is crucial for determining the prognosis of various cancer types. In the G1 phase of the cell cycle, it regulates cell division. Studies reveal a close relationship between ATAD2, the Rb pathway, and cell-cycle proteins that facilitate cancer progression. During the G1/S phase, ATAD2 is quite active during the G2/M phase; however, it becomes less active. Studies in Rb-deficient mouse cells have found multiple E2F binding sites on the ATAD2 promoter, with E2F1, E2F2, and E2F3 playing key roles in activating ATAD2. The Rb/E2F pathway directly targets ATAD2, which binds E2Fs to control genes like cyclin A2, cyclin E1, cdk2, cdc6, and MCM7, which are necessary for cell-cycle progression. During late mitosis, ATAD2 binds to chromatin to attract E2F and the HCF-MLL complex, increasing histone modifications (such H3K4me3) and turning on genes that respond to E2F [42,55–58].

3.2.2. Hormone signalling

Cellular functions are regulated by steroid hormones, including androgen and estrogen, via their receptors. In breast cancer, the estrogen receptor (ERα) is coactivated by ATAD2, which is upregulated by estrogen (E2). to recruit CBP, a histone acetyltransferase, at the promoters of ERα target genes like cyclin D1 and cMyc, it causes the G1/S transition and proliferation. Furthermore, ATAD2 stimulates the production of kinesins, including Kif4A and Kif15, which aid survival and division of breast cancer cells vulnerable to tamoxifen resistance [59]. ATAD2 expression is elevated in prostate cancer cells that are androgen-sensitive as well as androgen-independent. Because ATAD2 overexpresses androgen receptor (AR)-regulated genes (including IGF1R, IRS-2, SGK1, survivin, cyclin A2, and cyclin D3), prostate cancer cells multiply and survive when this occurs. Androgen is a coactivator that increases AR-driven transcription by recruiting ATAD2 to AR-targeted gene promoters. ChIP-seq results also showed that AR and E2F1 interaction at its promoter mediates ATAD2 expression. These results demonstrate the crucial function of ATAD2 as a coactivator in androgen-mediated tumor formation, which may have consequences for prostate tumors [60].

3.2.3. p53 and p38-MAPK apoptotic signalling

Apoptosis, a feature of cancer, is prevented by ATAD2 by blocking p53- and p38-MAPK-mediated pathways. ATAD2 depletion causes apoptotic markers in several cancers, including caspase-3 and cleaved PARP. In hepatocellular carcinoma, ATAD2 suppression increases pro-apoptotic proteins (including Bax, Bad, and Puma) and phosphorylated p38 while decreasing anti-apoptotic Bcl-xL, causing both wild-type and mutant p53 cells to undergo apoptosis. Experimentally, ATAD2 binds MKK3/6 to prevent p38 activation. Its blockage causes apoptosis and promotes MKK3/6-mediated p38 activation. Consequently, ATAD2 is necessary for apoptosis evasion via the p53-Bcl-2 and p38 pathways, depending on the p53 status [61].

3.2.4. PI3K/AKT signalling and glycometabolism

The PI3K/AKT pathway, which controls important cancer characteristics like metabolism and survival, is linked to ATAD2. ATAD2 knockdown decreases pro-survival gene expression and AKT phosphorylation in lung, colorectal, and breast malignancies. In lung cancer, enhanced GLUT1 and HK2 levels and increased glucose absorption are correlated with high ATAD2 expression. By increasing the expression of GLUT1 and HK2, ATAD2 facilitates AKT-driven glucose metabolism; this effect is reversed upon ATAD2 inhibition. These results show that ATAD2 controls cancer metabolism and survival via the AKT pathway, even though it is still unclear how ATAD2 directly interacts with AKT signalling components [62,63].

3.2.5. Hedgehog signalling

Tumorigenesis is associated with aberrant activation of the Hedgehog (HH) pathway, which involves proteins such as SHH, SMO, and GLI. Furthermore, it functions as a Myc cofactor to activate the Myc target gene Miz1, which regulates HH signalling. The HH pathway protein expression is decreased when ATAD2 is silenced, indicating a feedback loop between ATAD2 and HH signalling. By controlling HH components, ATAD2 seems to act upstream of the HH pathway, encouraging the migration, invasion, and growth of cancer cells [64–66].

3.2.6. HIF1α-driven hypoxia signalling

The HIF1 complex attaches to the HIF1α binding site (HBS) in the ATAD2 promoter, translocate into the nucleus, and binds with HIF1β. Increased ATAD2 expression encourages stomach cancer cells to proliferate and migrate [34].

3.2.7. TGF-β1 pathway

ATAD2 has been identified to strongly control the TGF-β1 signalling pathway, particularly in relation to cancer development. Research indicates that ATAD2 may function as a coactivator for SMAD transcription factors, the primary effectors of TGF-β1 signalling, enhancing SMAD-mediated transcription and improving downstream signalling outcomes. This relationship is crucial for promoting the epithelial-mesenchymal transition (EMT), a phase required for cancer cell invasion and metastasis. Reduced E-cadherin expression and increased levels of EMT markers, including vimentin and N-cadherin, have been associated with overexpression of ATAD2; this alteration in expression is at least partially dependent on TGF-β1 activity. Numerous cancer kinds have been studied, which supports this potential: ATAD2 silencing inhibits TGF-β1-driven cell migration and invasion in breast cancer; ATAD2 upregulation has been connected to TGF-β1-induced EMT and tumor aggressiveness in hepatocellular carcinoma; and ATAD2 has been connected to promoting TGF-β1 pathway activation through chromatin remodeling at SMAD-binding regions in lung cancer [66]. Interacting with key transcriptional regulators such as MYC, ERα, and β-catenin may enhance the impact of TGF-β1 signalling on fibrosis and cellular transformation.

3.2.8. NFκB pathway

ATAD2 stimulates NFκB signalling through chromatin remodeling, which raises the synthesis of NFκB target genes linked to inflammation, cell survival, and proliferation, such as IL-6, TNFα, COX-2, and MMP9. This activity contributes to developing a pro-inflammatory tumor microenvironment, stimulating tumor growth, invasion, and metastasis. Moreover, ATAD2-induced chronic NFκB activation is associated with improved chemoresistance and immune evasion in various cancers [67]. ATAD2 may interact directly or indirectly with NFκB subunits, particularly p65/RelA, to enhance their transcriptional activity. It also appears to regulate histone acetylation at NFκB-responsive gene promoters to facilitate gene transcription further. The decrease in NFκB nuclear localization and transcriptional activity following ATAD2 knockdown implies that ATAD2 is essential for NFκB signalling maintenance. In liver and breast cancers, elevated ATAD2 expression has been associated with

poor prognosis and NFκB activation. ATAD2 suppression disrupts NFκB-mediated inflammation and survival signalling and may also interfere with other carcinogenic pathways such as MYC or TGF-β1. Therefore, bromodomain inhibitors that target ATAD2 may be used as anti-inflammatory and anti-tumor drugs [9].

3.2.9. Epithelial-to-mesenchymal transition pathway

The EMT regulators Snail and Slug, which suppress the epithelial marker E-cadherin and increase mesenchymal marker proteins (N-cadherin, Vimentin, and MMPs) [48,68], are upregulated by ATAD2 and facilitate the migration and invasion of cancer cells, as shown in Fig. 5.

The development of cancer cells depends on ATAD2 through cell-cycle control and hormone signalling. To improve survival, it also suppresses apoptotic pathways and improves metabolic reprogramming. Since PI3K/AKT, Hedgehog, hypoxia, and EMT are among the carcinogenic signalling and cancer metastasis factors, ATAD2 is a desirable and potential therapeutic target. As a result, some inhibitors have been developed to reduce ATAD2's carcinogenic effects.

4. Strategies for targeting ATAD2 in cancer therapy

4.1. Small-molecule inhibitors

The selective inhibitor BAY-850 prevents ATAD2 from interacting with acetylated histones with IC_{50} of 166 nM. In ovarian cancer models, it successfully halts apoptosis and cell cycle progression. Among its actions is suppressing carcinogenic regulatory gene transcription, which presents a possible treatment avenue. GSK8814 is another stage in developing therapies that target ATAD2, even though its precise actions are less well understood. Similarly, AZ13824374 is recognized for its potential as an ATAD2 inhibitor. Further studies are exploring its application across cancer types [67]. Using TR-FRET assays, significant antiproliferative action was shown by AM879, with 90 % inhibition at 20 μM. In various breast cancer cell lines, AM879 demonstrated strong, dose- and time-dependent antiproliferative effects; at 72 h, MDA-MB-231 cells showed an IC_{50} of 1.05 μM. AM879's function as an ATAD2 inhibitor was confirmed by Western blot analysis, which revealed that it decreased ATAD2 expression and prevented downstream c-Myc phosphorylation (Fig. 6) [68].

4.2. Fragment-based and scaffold-guided inhibitors (theophylline inhibitor)

Using a scaffold growth and fragment-based screening approach, several ATAD2 inhibitors from theophylline derivatives were identified. With an IC50 value of 0.27 μM against ATAD2, compound N-cyclopentyl-3–(2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9 h-purin-9-yl) acetamido)-4-methoxybenzamine stood out among them as a potent inhibitor. Its distinct hybrid binding style blends traditional and unconventional interactions. In BT-549 cells, it markedly reduced ATAD2 activity, decreased c-Myc activation, caused apoptosis, and showed anti-migration properties [69].

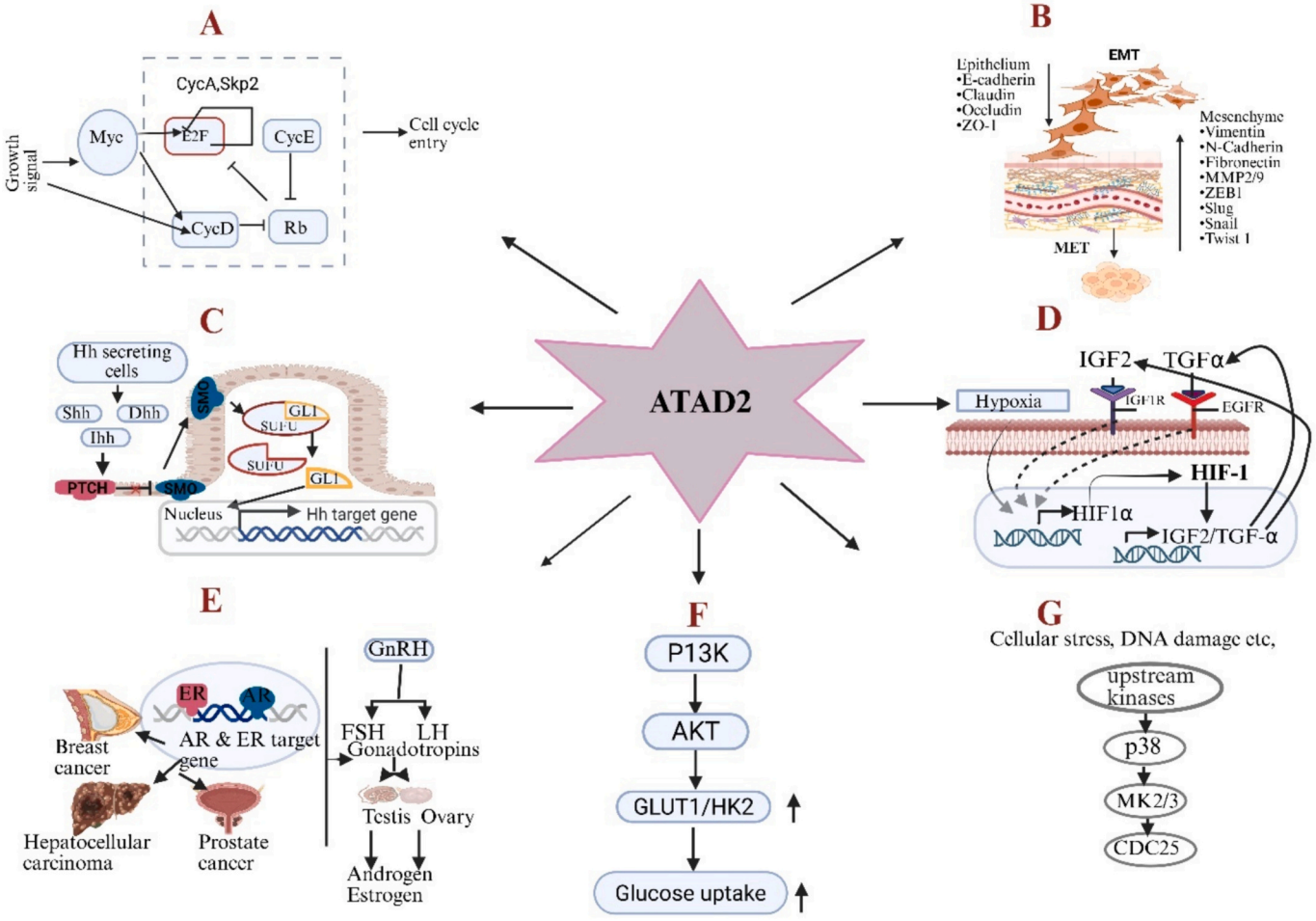

Fig. 5. ATAD2-Mediated Regulation of Key Cancer-Associated Signalling Pathways: A) Rb/E2F-cMyc Pathway, B) Epithelial-Mesenchymal Transition (EMT), C) Hedgehog Signalling, D) HIF1α-driven hypoxia signalling, E) Hormonal Signalling, F) PI3K/AKT Signalling & Glycometabolism, G) p53 and p38-MAPK apoptotic signalling.

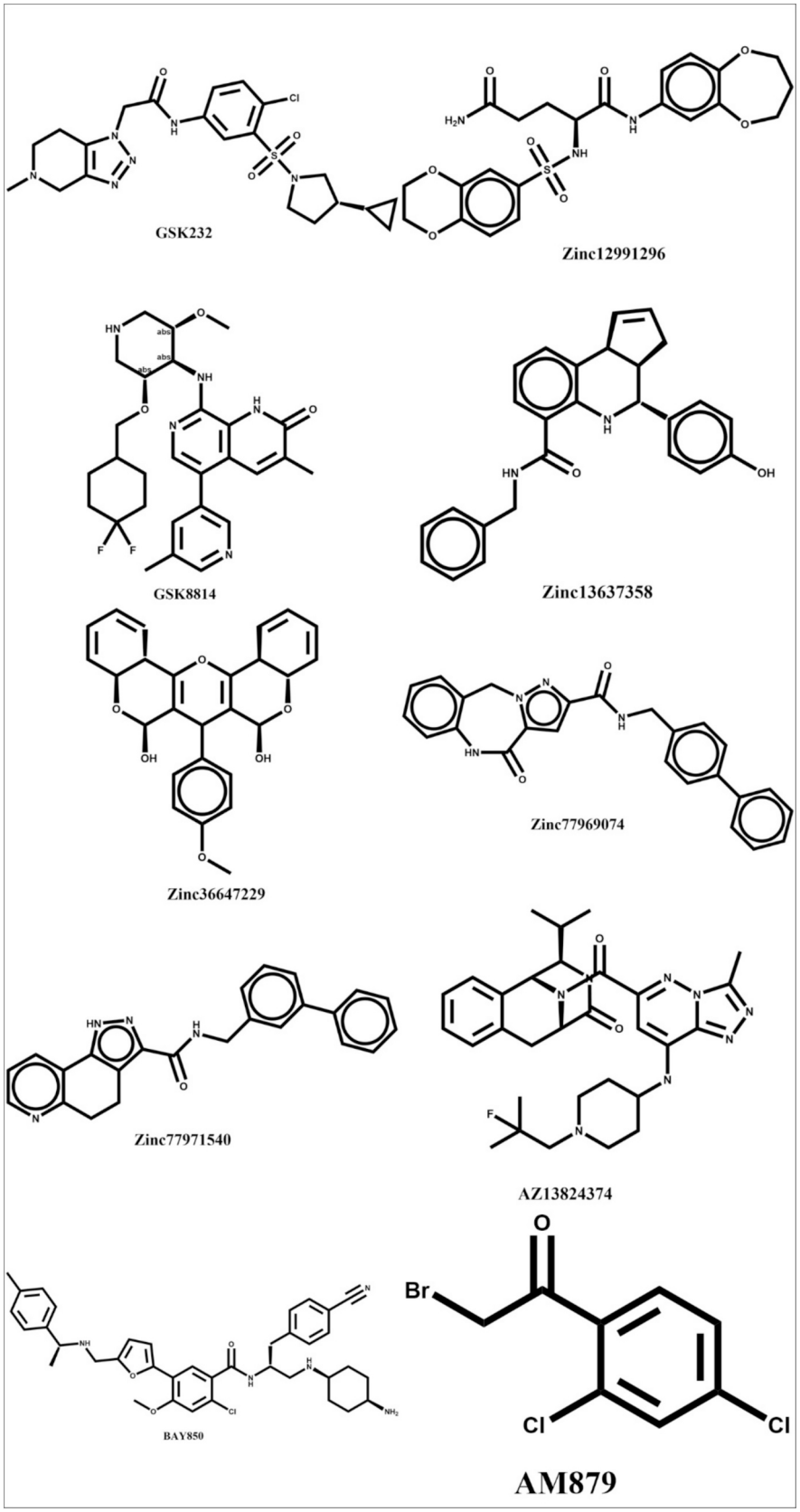

Fig. 6. Small molecule inhibitors of ATAD2 in cancer therapy.

4.3. Phenyl sulphonamides-based inhibitors

Most bromodomain inhibitors imitate the interactions of natural acetylated lysine (KAc) histone substrates by engaging with significantly conserved asparagine and tyrosine residues inside the binding pocket. This strategy targets non-BET bromodomains to optimize several phenyl sulphonamides. The researchers identified GSK232 (Fig. 6) toward the ATAD2 and the Bromodomains of Cat Eye Syndrome Chromosome Region (CECR2).It has remarkable physicochemical properties and strong cellular permeability [70].

4.4. In silico-derived hit compounds (zinc database derivatives)

To find new ATAD2 bromodomain inhibitors, ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS) were used. Six hit compounds with the lowest binding energies were identified after a more thorough molecular docking analysis are zinc36647229, zinc77969074, zinc13637358, zinc77971540, zinc12991296, and zinc19374204 (Fig. 6) [71].

4.5. Ligand analogue and binding site exploration (thymidine analogues)

The structure exhibited the typical binding technique for acetyl-lysine with significant interactions involving a conserved asparagine (Asn1064), a water-mediated hydrogen bond with tyrosine (Tyr1021), and a network of water molecules at the bottom of the binding pocket. Researchers investigated alternate ligand options by examining MPD and *N*-methyl-2-pyrrolidone (NMP) as acetyl-lysine substitutes. Furthermore, thymidine's sugar component arrived at the binding site comparably [74]. Similar, slightly weaker interactions were seen in subsequent tests employing thymidine analogues, such as 5-methyl uridine and 3′-deoxythymidine. Additionally, the adaptability of the ZA loop in ATAD2 offers important information for creating better inhibitors [75].

4.6. Monoclonal antibodies

No monoclonal antibodies (mAbs) have been developed in preclinical or clinical trials to target ATAD2. This specific approach most likely relates to the intracellular location of ATAD2, primarily in the nucleus, which prevents it from being accessible by traditional monoclonal antibodies, which typically target external proteins. Moreover, direct antibody-based targeting is not viable due to its lack in membrane-bound or extracellular regions. However, new opportunities for therapeutic interventions are presented by developments in intracellular delivery systems and antibody engineering [72].

4.6.1. RNA-based therapeutics

Targeting BRDs using RNA interference (RNAi), antisense oligonucleotides (ASOs), and messenger RNA (mRNA) therapies shows considerable promise for RNA-based therapeutics. RNA-based treatments offer a novel strategy to treating cancers and overcoming drug resistance, given the precision and adaptability of RNA molecules [39,77,78]. RNA-binding proteins (RBPs), non-coding RNAs, and microRNAs (miRNAs) are the main mechanisms post-transcriptional regulation governs ATAD2 expression. Several miRNAs have been shown to directly regulate ATAD2 by focusing on its 3′ untranslated region (3' UTR), which results in translational repression or mRNA destruction. For instance, miR-372 reduces ATAD2 in hepatocellular carcinoma, while miR-200b and miR-490-3p target ATAD2 in colorectal and gastric cancers, respectively. Additionally, in non-small cell lung cancer, miR-186 suppresses ATAD2, which reduces tumor growth. These miRNAs typically function as tumor suppressors, but when they are downregulated, they often increase the expression of ATAD2 in tumors. Although RBPs directly regulating ATAD2 have not been thoroughly characterized, RNA-binding proteins (RBPs) may also affect ATAD2 mRNA stability and translation in addition to miRNAs. Although there is currently little evidence, alternative splicing may also contribute to producing functionally different ATAD2 isoforms. Furthermore, by serving as molecular sponges for miRNAs, circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs) might indirectly control ATAD2. For instance, lncRNA HOTAIR can sequester miRNAs that would otherwise suppress the expression of ATAD2, thereby upregulating it, as shown in Table 1. Overall, post-transcriptional regulation is a complex mechanism significantly affecting ATAD2 expression and function in cancer. Particularly in tumors where ATAD2 is overexpressed, understanding these regulatory mechanisms may pave the way for targeted therapeutic intervention [65,79].

5. Status of ATAD2-targeted therapies

5.1. In vitro studies

The analysis of ESCC expression microarrays GSE100942 and GSE20347 revealed 198 and 423 differentially expressed genes (DEGs), respectively, with five DEGs (KIF4A, ATAD2, TRIP13, UBE2C, and HJURP) resulting in the identification of ATAD2 as a key oncogene in ESCC. ATAD2 was markedly elevated in ESCC cell lines and tissues, indicating a possible involvement in cancer development [80]. Similarly, Western blot analysis revealed that Eca-109 ESCC cells had higher levels of ATAD2 protein than normal human oesophageal epithelial cells (HEECs) ($p < 0.05$). ATAD2 expression was significantly correlated with tumor node metastasis (TNM) stage and histological grade ($p > 0.05$), while it was not associated with age or gender. Therefore, the advancement of ESCC is correlated with high expression of ATAD2. The silencing effectiveness of three siRNAs that target ATAD2 (si-ATAD2–1, si-ATAD2–2, and si-ATAD2–3) was evaluated. Since si-ATAD2–1 had the most excellent knockdown efficiency at the mRNA and protein levels, it was selected for further research. The expression of genes linked to the hedgehog pathway (Gli1, SMO, and PTCH1) was dramatically decreased by ATAD2 downregulation using si-ATAD2–1, but ATAD2 overexpression boosted this expression ($p < 0.05$). Compared to Cyc alone, the combined treatment of si-ATAD2 and hedgehog inhibitor (Cyc) demonstrated a more significant inhibitory effect on pathway activation.

After ATAD2 knockdown, flow cytometry showed a decrease in CD^{44+} and CD^{133+} ESCC stem cell populations. Additionally, the expression of the stem cell markers OCT4 and SOX2 was decreased ($p < 0.05$) when ATAD2 was silenced, suggesting a loss of stemness characteristics. According to flow cytometry and apoptosis marker analysis, higher Bax and reduced Bcl-2 and MMP2 expression indicated enhanced apoptosis rates following ATAD2 silencing. ATAD2 knockdown dramatically reduced the invasion and migratory potential of ESCC stem cells, according to scratch and trans well experiments ($p < 0.05$). Further lowering the capacity for migration and invasion, the combination effect of si-ATAD2 and Cyc was more substantial than Cyc-alone [33].

5.2. Targeting breast cancer

ATAD2 mRNA expression is substantially higher in breast tumor tissues than in normal tissues, as supported by TCGA data. Additionally, immunohistochemistry revealed that normal tissues expressed very little ATAD2, whereas cancer tissues, especially those with advanced tumors, showed strong staining. Likewise, ATAD2 protein was found in breast cancer cell lines but not in MCF-10 A, a normal breast cell line. Depleting ATAD2 in SKBR3 and T47D cells using shRNAs significantly reduced cell proliferation, migration, and invasion without affecting apoptosis, suggesting ATAD2s role in promoting malignant behavior [81]. In SKBR3 and T47D cells, transfection of miR-302a, b, and c mimics decreased ATAD2 expression and prevented invasion, migration, and cell division. The inhibitory effects of miR-302 on cancer cell behavior were reversed by overexpressing ATAD2, confirming that miR-302 inhibits the growth

Table 1
Role of miRNAs in cancer: Targets, Mechanisms, and Pathways.

MiRNA / Target	Cancer Type	Role/Findings	Mechanism	Therapeutic Potential	References
MiRNA-106b-5p	Multiple	Regulates cancer onset and progression by influencing cell division, apoptosis, migration, and angiogenesis	PI3K/Akt and Wnt/β-catenin pathways	Potential biomarker for diagnosis and prognosis; therapeutic target to overcome drug resistance	Lu et al., [73]
miR-520f-3p/ SOX9	Gastric	Inhibits cancer proliferation by targeting SOX9, reducing Wnt signalling activity	Wnt signalling pathway	Promising therapeutic option for slowing cancer progression	Chen et al., [74]
miR-302/ ATAD2	Breast	Downregulates ATAD2, reducing invasion, migration, and tumor growth. ATAD2 overexpression negates miR-302's tumor-suppressive effects	ATAD2 regulation	Targeting miR-302 and ATAD2 may inhibit malignancy	Hwang et al., [75]
miRNAs	CRC	They serve as tumor suppressors or oncogenes and control drug resistance, tumor growth, and metastasis	Multiple pathways depending on miRNA type	Biomarker for early detection, disease monitoring, and therapeutic interventions	Sado et al., [76]
miR-186/ ATAD2	RB	Suppresses RB progression by downregulating ATAD2 and deactivating the Hedgehog pathway, reducing invasion, migration, and angiogenesis while promoting apoptosis	Hedgehog signalling pathway	Therapeutic target to control RB progression	Wu et al., [77]
miR-372/ ATAD2	RCC	Inhibits EMT, invasion, and migration; low miR-372 levels correlate with poor prognosis	EMT regulation via ATAD2	Potential therapeutic target and biomarker	Ji et al., [78]
miR-372	Ovarian	Promotes apoptosis and reduces proliferation by downregulating ATAD2 and other cell cycle-related proteins	Cell cycle regulation	miR-372 overexpression as a therapeutic strategy	Guan et al., [79]
miR-520a/ ANCCA (PRO2000)	HCC	Regulates E2F2-mediated cell proliferation and migration; ANCCA is directly targeted by miR-520a	E2F2 and cell migration pathways	Targeting the ANCCA-miR-520a-E2F2 loop offers therapeutic potential	Huang et al., [36]
miR-372/ ATAD2	HCC	Suppresses ATAD2, reducing proliferation and metastasis; downregulates CTNNA1 and upregulates APC	ATAD2 and downstream gene regulation	miR-372 as a negative regulator of ATAD2 therapeutic interventions	Wu et al., [66]

of breast cancer via targeting ATAD2 [75].

5.3. Targeting ovarian cancer

The mRNA expression results revealed that ATAD2 is significantly overexpressed in the ovarian cancer samples. Researchers performed a CUT & RUN test on SK-OV3 cells that overexpressed Ad-p53 or Ad-LacZ. They demonstrated that p53 binds directly to the ATAD2 promoter, causing transcriptional suppression of the gene [52]. The cell viability of two ovarian cancer cell lines, PA-1 and SK-OV3, was evaluated using MTT assays after being treated with different concentrations of BAY-850. The results demonstrated dose-dependent suppression of cell viability. Furthermore, soft-agar assays showed a lower capacity to develop tumors after BAY-850 treatment, whereas clonogenic assays decreased long-term survival [82]. Researchers used a mouse model to test SK-OV3 ovarian cancer cells. Tumor growth was closely monitored in mice that received BAY-850. The treatment significantly reduced tumor growth in comparison to the control group [83]. Additionally, annexin V-positive cells increased after BAY-850 therapy, and PARP cleavage was seen, suggesting that ovarian cancer cells underwent apoptosis. To sum up, BAY-850 successfully prevents the growth and spread of ovarian cancer by causing cell cycle arrest and initiating programmed cell death [83]. The protein CENPE, necessary for chromosomal alignment during mitosis, was also the subject of the

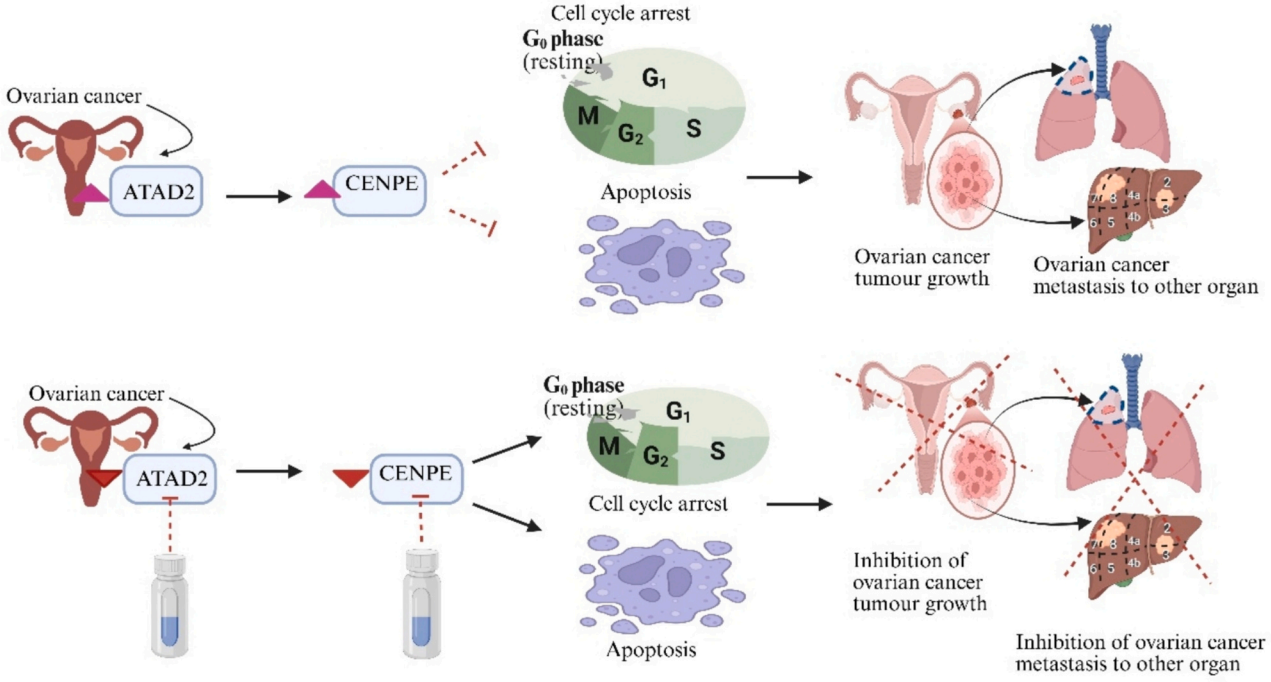

Fig. 7. ATAD2-mediated regulation of CENPE in ovarian cancer progression and therapeutic intervention.

investigation. As seen in Fig. 7, the highly specific inhibitor GSK923295 blocked CENPE, causing mitotic arrest and consequent cell death. Compared to independent treatments, the combination of GSK923295 and BAY-850 in ovarian cancer cells showed improved apoptotic induction, as shown in Table 2. Therefore, it can be concluded that ATAD2 and CENPE are simultaneously targeted, demonstrating their synergistic effect in preventing the progression of ovarian cancer and making them an improved therapeutic target [84].

5.4. Clinical studies

An open-label, dosage-escalation Phase I trial examining the pharmacokinetic characteristics, safety profile, and maximum tolerated dose of GSK923295, a novel CENP-E inhibitor intended to block a crucial protein required for chromosome alignment during mitosis, in adult patients with solid cancers. GSK923295 was administered as a one-hour intravenous infusion once a week for three weeks in a four-week cycle. Pharmacokinetic studies revealed a terminal elimination half-life of 9 to 11 h along with dose-proportional behavior and no appreciable drug buildup. GSK923295 showed encouraging pharmacokinetics, a tolerable safety profile, and a few serious adverse event rates, suggesting additional research as a possible antiproliferative drug for solid tumors. The most frequent adverse event linked to drugs was fatigue, along with elevated AST, hypokalemia, and hypoxia. Neutropenia, neuropathy, mucositis, and alopecia were uncommon, while gastrointestinal effects such as nausea, vomiting, and diarrhea were typically minor [86–88]. There is currently no clinical application for ATAD2 inhibitors. In preclinical research using cell lines and animal models, several drugs targeting ATAD2, including BAY-850, AZ13824374, and GSK8814, have shown encouraging anti-cancer effectiveness; however, none have advanced to human clinical trials.

5.4.1. Off-target effects

ATAD2 knockdown or inhibition may impair these essential processes, like DNA damage repair and transcription control, which could hurt healthy cells. Cellular integrity is compromised in prostate cancer models when ATAD2 is suppressed by small molecules or RNA silencing, which alters DNA repair processes. There is evidence that ATAD2 is essential for certain cell cycle components; in particular, its inhibition in cancerous cells results in changes to gene expression and hinders the cell cycle. However, changes in the structure of chromatin might inadvertently affect non-cancerous cells and have negative consequences [44]. Although ATAD2 is overexpressed in many cancers and is key in promoting tumorigenesis, it is also expressed in several healthy, rapidly dividing tissues such as the testis, ovary, bone marrow, and gastrointestinal epithelium. This raises significant concern that systemic inhibition of ATAD2 could lead to unintended adverse effects in normal physiological processes. In tissues like bone marrow and gut lining, which rely on constant cell renewal, ATAD2 supports essential functions including DNA replication, chromatin remodeling, and cell cycle progression. Its inhibition may impair cell proliferation, resulting in conditions such as myelosuppression (reduced blood cell production), gastrointestinal toxicity, and reproductive dysfunction. Additionally, ATAD2 serves as a transcriptional co-regulator by binding to acetylated histones and modulating the expression of genes critical for metabolism, DNA repair, and cell cycle control. Disrupting this regulation may lead to dysregulated gene expression, genomic instability, and apoptosis in non-cancerous cells. ATAD2 also plays a crucial role during embryogenesis and spermatogenesis, and its inhibition could result in infertility, hormonal imbalances, or developmental defects. Although less extensively studied, ATAD2 is thought to be involved in immune cell proliferation and function. Thus, its inhibition may contribute to immunosuppression, altered immune responses, or potentially even autoimmune disorders due to misregulation of immune cell development. These risks highlight the importance of carefully evaluating therapeutic strategies targeting ATAD2, especially in terms of selectivity, delivery, and patient stratification [89].

5.4.2. Toxicity in healthy tissues

ATAD2 inhibition negatively affected healthy tissues in preclinical animal tests, particularly at high dosages. The consequences, which include bone marrow and liver dysfunctions, decreased body mass, and hematological abnormalities, highlight the importance of ATAD2 in preserving the integrity of healthy tissues [90]. ATAD2 inhibitors are emerging as promising anticancer agents due to ATAD2's role in promoting tumor cell proliferation and survival. However, early development of these inhibitors has highlighted potential toxicity concerns, primarily related to off-target effects and disruption of normal epigenetic regulation. These toxicities can manifest as hematologic abnormalities, liver damage, or gastrointestinal issues, especially in tissues with high cellular turnover. To address these challenges, researchers are focusing on improving the selectivity of ATAD2 inhibitors to minimize interference with other bromodomain-containing proteins. Additionally, strategies such as targeted drug delivery systems, combination therapies, and predictive biomarkers are employed to enhance therapeutic precision and reduce systemic toxicity. These approaches aim to maximize the anticancer efficacy of ATAD2 inhibitors while minimizing adverse effects, paving the way for their potential use in clinical settings [9,70].

5.4.3. Effects on the immune system

ATAD2 suppression may interfere with immune cell functions like activation and proliferation. This disruption may result in altered tumor microenvironment, weakened immune responses, and decreased

Table 2
ATAD2 expression and regulation in breast and ovarian cancer.

Context	Expression pattern	Method used	Findings	References
Breast Cancer Tumors vs. Normal Tissue	Significantly upregulated in tumor tissues	RT-PCR, qPCR, TCGA data	ATAD2 mRNA expression is significantly elevated in breast cancer tissues compared to normal tissues	Hwang et al., [75]
Breast Cancer Cell Lines (SKBR3, T47D)	High protein expression	Western blot Immunohistochemistry	ATAD2 protein is strongly expressed in breast cancer cells	Hwang et al., [75]
Normal Breast Cell Line (MCF-10 A)	Undetectable or very low expression	Western blot	ATAD2 is not detected in normal breast epithelial cells	Zou et al., [85]
Ovarian Cancer Tumors vs Normal Tissue	Markedly upregulated in tumor tissues	mRNA expression datasets	ATAD2 is significantly overexpressed in ovarian cancer samples	Guruvaiah et al., [52]
Ovarian Cancer Cell Lines (PA-1, SK-OV3)	High transcript and protein levels	qPCR, Western blot	ATAD2 is strongly expressed in ovarian cancer cells	Wan et al., [51]
Regulation by miR-302 in Breast Cancer	Downregulated post-transcriptionally	miRNA transfection, Luciferase assay	miR-302a, b, and c target ATAD2 and reduce its expression in breast cancer cells	Hwang et al., [75]
Regulation by p53 in Ovarian Cancer	Transcriptionally repressed	CUT & RUN assay	p53 binds to the ATAD2 promoter and represses its transcription	Guruvaiah et al., [52]
Effect of ATAD2 Inhibitor (BAY-850) in Ovarian Cancer	Functional inhibition of ATAD2 activity	Pharmacological inhibition	BAY-850 disrupts ATAD2 binding to acetylated histones, reducing cancer cell viability and invasion	Guruvaiah et al., [52]

effectiveness of immunotherapeutic strategies [91]. In several cancer types, ATAD2 expression has been linked to different facets of immune cell infiltration and tumor immune regulation. The infiltration of $CD4^+$ T cells in malignancies including pheochromocytoma/paraganglioma (PCPG), uveal melanoma (UVM), and papillary thyroid carcinoma (PTC) is favorably correlated with ATAD2 expression, while $CD8^+$ T cells are positively correlated with thymoma (THYM), and PCPG. Specifically, ATAD2 expression is negatively correlated with cytotoxic T cells, natural killer (NK) cells, and plasmacytoid dendritic cells (pDCs), but significantly positively correlated with T helper cell infiltration, especially Th2 cells, in PTC. These trends point to ATAD2's possible involvement in forming an immunosuppressive tumor immune microenvironment (TIME). Single-cell sequencing findings support this by showing that proliferating T cells (Tprolif) and exhausted $CD8^+$ T cells (CD8Tex) had higher ATAD2 expression, indicating a state of functional T-cell depletion and decreased reactivity to tumor antigens. Additionally, multiple cancer types, including PTC and ATAD2 expression have a positive correlation with major histocompatibility complex (MHC) genes and several inhibitory immunological checkpoints, suggesting a function in immune evasion and tumor immunogenicity modulation. All these results suggest that increased ATAD2 expression could be a factor in compromised anti-tumor immune response and decreased effectiveness of immunotherapeutic strategies. Therefore, ATAD2 offers a viable therapeutic target to enhance the effectiveness of immunotherapy for a variety of cancer types [54]. Several strategies should be considered to mitigate the potential immunosuppressive effects of ATAD2 inhibition. Selective targeting is essential-designing inhibitors that specifically block ATAD2's oncogenic functions, such as bromodomain activity, while sparing its roles in immune regulation. Structure-guided drug design can help minimize off-target effects on immune-related pathways [92]. Dose optimization is also critical; using the minimal effective dose can inhibit tumor-promoting pathways while preserving immune cell integrity. This can be achieved by incorporating pharmacodynamic markers to guide dosing in preclinical and clinical settings [18]. Tumor-targeted drug delivery systems, including nanocarriers, liposomes, and antibody-drug conjugates (ADCs), offer a way to confine ATAD2 inhibitor action to tumor tissues and reduce systemic exposure that may impact immune cells. Combining ATAD2 inhibitors with immunomodulatory agents, such as immune checkpoint inhibitors (e.g., anti-PD-1 or anti-CTLA-4) or cytokine therapies (e.g., IL-2, IL-15), may help counterbalance immune suppression and restore immune activation. Biomarker-based patient selection is another important step-using ATAD2 expression levels in tumors versus immune cells to identify those most likely to benefit while avoiding treatment in patients whose immune cells rely heavily on ATAD2 function [93].Sequential or intermittent therapy, such as administering ATAD2 inhibitors before immunotherapy or allowing recovery periods between treatment cycles, could help maintain immune competence [9].Throughout treatment, it is advisable to monitor immune health by assessing T cell subsets, NK cells, and cytokine profiles, and adjusting treatment if signs of immune exhaustion or suppression emerge [94]. Looking ahead, cell-type specific gene editing using CRISPR and tumor-specific promoters may provide a future strategy to selectively suppress ATAD2 in cancer cells while sparing immune cells, thereby maximizing therapeutic benefits and minimizing immune-related risks [95].

6. Challenges and limitations

6.1. Drug resistance

Drug resistance accounts for around 90 % of cancer-related casualties, and multidrug resistance (MDR) significantly lowers treatment effectiveness while raising the risk of metastasis and recurrence. Both inherent and acquired resistance pathways affect individuals with drug-resistant cancers. ATAD2 is becoming more involved in cancer resistance, promoting MDR and treatment resistance by regulating transcription, chromatin remodeling, and oncogenic signalling pathways, including the PI3K/Akt/mTOR pathway [96]. ATAD2 protein levels fall in hypoxic conditions for a reason unrelated to the traditional HIF-1α–pVHL axis. The inactivation of enzymes from the Fe^{2+}/2-oxoglutarate-dependent dioxygenase (2-OGDD) superfamily, which depend on oxygen to function, causes this reduction. ATAD2 levels were reduced even in normal circumstances after treatment with drugs that block 2-OGDD activity, such as the iron chelator deferoxamine (DFO) or the 2-OG analogue dimethyloxalylglycine (DMOG), indicating that a 2-OGDD enzyme typically stabilizes ATAD2. Furthermore, this drop was abolished by the proteasome inhibitor MG-132, suggesting that the proteasome pathway mediates ATAD2 degradation under hypoxia. Interestingly, hypoxia-induced ATAD2 degradation was still shown in cell lines with mutant VHL, indicating that this mechanism functions independently of pVHL and HIFs. Based on these results, identifying and focusing on the 2-OGDD that stabilizes ATAD2 would be a viable method to inhibit chemotherapy resistance brought on by decreased ATAD2 levels under hypoxia. A feasible treatment option for overcoming drug resistance in solid tumors may be to restore appropriate cell cycle progression and sensitize hypoxic tumor cells to chemotherapy by maintaining ATAD2 protein levels through the prevention of its proteasomal degradation [97].

6.2. Drug efflux

Enhanced drug efflux, a primary mechanism of MDR, reduces intracellular drug concentrations and is mediated by ATP-binding cassette (ABC) transporters. ATAD2 regulates the transcription of *ABCB1* (MDR1/P-glycoprotein), a key efflux pump overexpressed in several cancers, including breast cancer (BC). In BC cell lines such as SKBR3 and MCF-7, increased ATAD2 expression correlates with elevated *MDR1* levels, leading to chemotherapy resistance. Through epigenetic processes such as promoter methylation and histone changes, ATAD2 may also alter the expression of ABCB1. Although ABCB1 hypermethylation has been associated with reduced expression and improved survival, ATAD2-driven transcriptional activation may be reversed by targeting ATAD2. Additionally, by upregulating ABCG2, a CSC marker linked to MDR, ATAD2 improves resistance in triple-negative breast cancer (TNBC) [98].

6.3. DNA senescence

ATAD2 contributes to resistance by improving DNA repair through interactions with elements of the DNA damage response (DDR). The expression of DDR-related genes is modulated by ATAD2, which could contribute to resistance to PARP inhibitors. Additionally, ATAD2 makes it easier for cells to evade therapy-induced senescence, enabling them to take on characteristics of CSCs, start growing again, and promote the growth of tumor [99].

6.4. Epigenetic modifications

ATAD2 is a chromatin regulator that affects epigenetic modifications that increase resistance. Drug tolerance is increased when ATAD2 activates oncogenes through interactions with histone acetylation indicators. Tamoxifen resistance frequently arises in estrogen receptor-positive (ER^+) breast cancer (BC) because of altered gene regulation that lowers ER levels. By increasing DNA accessibility and promoting gene activity independently of ER, ATAD2 exacerbates this resistance. By controlling microRNAs that impact cell proliferation and death, such as miR-27b-3p, miR-21, and miR-134, ATAD2 also affects therapeutic resistance. Targeting ATAD2 may provide a novel therapeutic strategy, even though FDA-approved medications that target gene regulation, such as DNMTs and HDACs, have had poor success in advanced breast cancer [100].

6.5. Tumor heterogeneity

Cancer stem cells (CSCs) contribute to tumor diversity, treatment resistance, and recurrence. ATAD2 helps maintain CSCs by regulating key pathways like Notch, Hedgehog, and Wnt/β-catenin. It is linked to higher levels of CD133, a marker of CSCs and treatment resistance in BC. ATAD2 also helps CSCs survive by altering the Rho C pathway, keeping them in a dormant state (G_0 phase), which makes them less affected by treatments targeting actively dividing cells [101].

6.6. Tumor microenvironment

The tumor microenvironment (TME)—which includes signalling molecules, fibroblasts, immune cells, and the extracellular matrix (ECM)—plays a significant role in cancer growth and resistance. ATAD2 affects genes involved in ECM remodeling and responses to low oxygen (hypoxia). In triple-negative and ER^+ BC, ATAD2 increases resistance and drives epithelial-to-mesenchymal transition (EMT) by boosting HIF-1 levels. Similarly, ATAD2 promotes tumor invasion, spread, and treatment resistance by encouraging ECM changes through vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) [102].

6.7. Epithelial-to-mesenchymal transition

EMT makes cancer cells more invasive, more likely to spread, and more resistant to therapy. By upregulating EMT transcription factors such as Twist, Snail, Slug, and ZEB, ATAD2 leads to resistance in BC. As shown in Fig. 8, ATAD2 amplifies EMT-related signalling pathways like Wnt and TGF-β, which increases treatment resistance and drives the EMT phenotype. Moreover, ATAD2 overexpression may enhance the production of EMT-like characteristics by chemotherapeutic medications etoposide, potentially leading to suboptimal treatment outcomes [103,104].

6.8. Toxicity concerns

The range of dosages at which ATAD2 inhibitors can effectively target tumor without endangering healthy tissues is limited. At the effective doses, side symptoms include myelosuppression, or reduced blood cell production, and gastrointestinal problems are common [105]. Combining ATAD2 inhibitors with chemotherapy medications may increase the likelihood of side effects while potentially making malignancies more responsive to treatment. For instance, pancreatic cancer treated with gemcitabine and ATAD2 inhibitors demonstrated better anti-tumor efficacy but exacerbated adverse effects [106]. The long-term safety of such treatments may be called into question by resistance to therapy, changes in the tumor microenvironment, or persistent side effects from continuous delivery [107].

6.9. Issues in drug delivery and bioavailability

Targeted drug delivery to the tumor is the main issue with ATAD2-targeted therapy. The body's ability to absorb these drugs and their effectiveness depend on various factors. Problems with their ability to penetrate cells because of the complex chemical structure make ATAD2 difficult to build highly selective inhibitors [108]. The absorption, distribution, and metabolism of ATAD2 inhibitors are critical to their therapeutic effectiveness. Pharmacokinetic damage, such as increased breakdown or decreased absorption, would reduce the inhibitor's therapeutic effectiveness. Furthermore, its uneven distribution across tumor tissues would also limit the inhibitor's effectiveness. The two functional domains of ATAD2—the bromodomain (BRD) and the AAA ATPase domain—as well as the availability of high-resolution 3-dimensional crystal structures, especially for the BRD, make it a potentially druggable target. These structural discoveries have made early drug development initiatives and computational evaluations easier. Nevertheless, ATAD2's BRD has proven infamously difficult to target, even though it shares characteristics with other druggable BRD family members like BRD4 and CREBBP. Its solvent-exposed, shallow, extremely polar binding pocket contains negatively charged residues that reduce ligand binding affinity. Creating high-affinity inhibitors is further hampered by significant structural variations, such as the flexible ZA loop and replacing the classical WPF motif with RVF. However, there have been notable developments in recent years. Fragment-based and structure-guided drug development initiatives are beginning to address these restrictions. Notably, research by Chaikuad et al. and Harner et al. established preliminary chemical footholds for more optimization by identifying weak-binding fragments using NMR-based screening. Building on this, GSK8814, a low-nanomolar, selective, and cell-permeable ATAD2 BRD inhibitor, was developed by GlaxoSmithKline using a structure-guided medicinal chemistry strategy. Sulfone and CF_2 groups were added to this optimization procedure to increase permeability and binding affinity. Notwithstanding these developments,

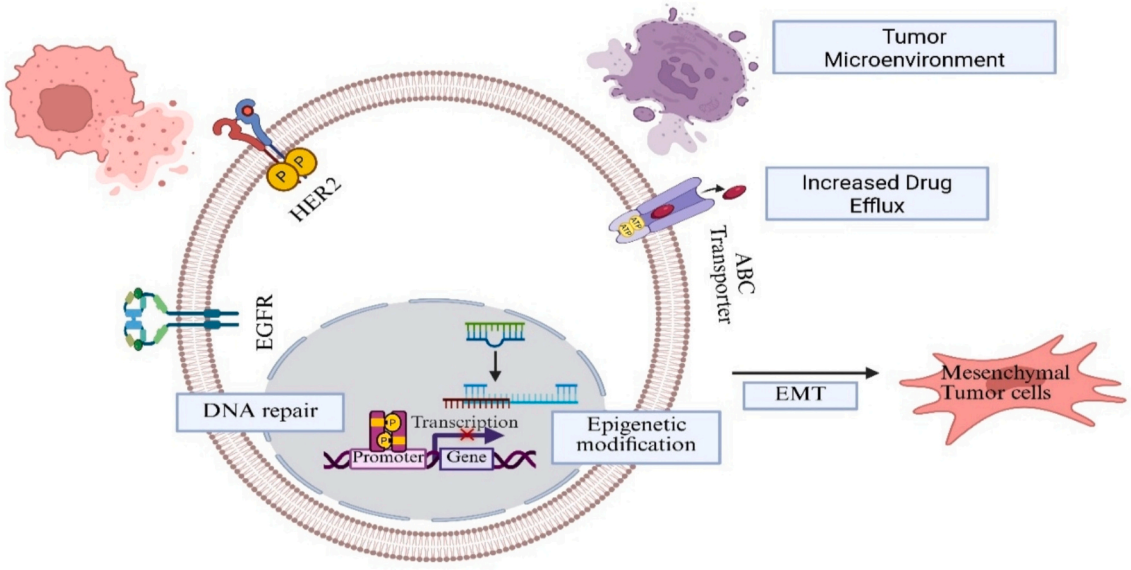

Fig. 8. Molecular mechanisms driving tumor progression and drug resistance

GSK8814 only demonstrated antiproliferative effects at comparatively high dosages, suggesting more pharmacological improvement was needed [18].

Nevertheless, these results show that ATAD2's BRD, which was previously believed to be undruggable, is a tractable target that can be treated with ongoing medicinal chemistry optimization. On the other hand, little is known about ATAD2's AAA ATPase domain. The absence of a 3-dimensional structure has hampered evaluating its drug ability. No strong or specific small compounds have yet been created for the ATPase domain of ATAD2, even though the development of effective inhibitors for related AAA^+ ATPases, including dynein, Pontin, and p97, supports theoretical interest. Furthermore, any future inhibitor development must have a high degree of selectivity due to homologous ATPases, such as ATAD3, ATAD4, and ATAD5, which are implicated in carcinogenesis, genomic stability, and mitochondrial biogenesis. Even if the ATPase domain shows promise as a new therapeutic target, it is still an unexplored possibility that needs careful structural and biochemical research.

6.10. Limited long-term safety data

ATAD2 is becoming a novel epigenetic and oncogenic target because of its dual-domain structure AAA+ ATPase domain involved in transcriptional regulation and chromatin remodeling, and a bromodomain (BRD). Because of its distinct structural characteristics and overexpression specific to cancer, ATAD2 stands out in comparison to well-characterized bromodomain targets such as BRD4 [18,47]. ATAD2 is a co-activator of important oncogenes like MYC and E2F and is connected to the control of important oncogenic pathways, such p53 suppression, epithelial-mesenchymal transition (EMT), and PI3K/AKT signalling [9,109]. Crucially, research indicates that ATAD2 depends on tumors and is not necessary for the survival of healthy adult cells. This selective expression pattern presents a prospective therapeutic window for focused intervention in cancer treatment [110].

Despite encouraging preclinical data, the long-term safety profile of ATAD2 inhibitors is still mostly unknown. Specificity is crucial because off-target effects on other proteins or ATPases that include bromodomains may have unforeseen physiological or epigenetic repercussions [18]. Although structure-based optimization techniques have placed a strong emphasis on increasing target specificity, more research is necessary because there is currently a dearth of evidence on *in vivo* efficacy or chronic toxicity [111]. The possibility of immune-related adverse effects has also been brought up because ATAD2 inhibition may change the tumor immunological milieu and interfere with the control of immune cells [9]. For the bromodomain of ATAD2, fragment-based screening has produced preliminary chemical leads; nevertheless, these drugs' pharmacokinetic and toxicological characteristics are unknown. Together, these results highlight the necessity of thorough *in vivo* research, such as long-term dosage studies and immunological monitoring, to properly evaluate the safety and therapeutic potential of long-term ATAD2 inhibition [112].

7. Future perspective

To overcome the abovementioned limitations, formulations that use nanocarriers, which are a highly flexible way to deliver ATAD2 antagonists. Improved biocompatibility, cellular absorption, and resistance against enzymatic degradation are characteristics of LNCs, including siRNA or small-molecule inhibitors. Nanocarriers made of biodegradable polymers, like PLGA or PEG, that are tailored for cytotoxicity, improve tumor targeting and the sustained release of medications and the EPR effect. Iron oxide and gold nanoparticles are examples of inorganic nanocarriers that are specifically designed to target cancer cells that express ATAD2 [113,114]. Liposomes are vesicular structures made of phospholipids that can hold lipophilic and hydrophilic medications. Targeting ATAD2 mRNA by RNA interference using siRNA or miRNA is a secondary technique. LNCs and other extracellular vesicles, such as exosomes, can help with practical tumor regression and nuclear-targeted delivery. Cell-penetrating peptides (CPPs) like as TAT and R9 are examples of peptide-mediated delivery methods that are very successful in facilitating the intracellular trafficking of inhibitors or siRNA with minimal cytotoxicity [115]. Using AAVs or nanocarriers, gene-editing methods like CRISPR-Cas9 may successfully wipe out or inhibit ATAD2, lowering its levels indefinitely and possibly easing resistance. Antibody-drug conjugates (ADCs) combine monoclonal antibodies directed against ATAD2 with cytotoxic drugs [116]. As illustrated in Fig. 9, these advantages include remarkable specificity, significant antitumor activity, and reduced extraneous interactions. Additionally, treatment strategies that target the tumor immune microenvironment may improve clinical outcomes by boosting the effectiveness of immune checkpoint inhibitors like anti-PD-1 or anti-CTLA-4 [117].

7.1. Advanced sequencing techniques

Next-generation sequencing (NGS) is essential for the detection of biological markers, especially for medications targeting ATAD2. This factor is a fascinating therapeutic target because its dysregulation has been linked to several diseases and cancers. Using a variety of approaches, NGS makes it easier to find biomarkers connected to medications that target ATAD2 [118,119]. Using whole-genome sequencing (WGS) or whole-exome sequencing (WES) to analyze tumor samples, researchers can find changes or mutations in the ATAD2 gene and related pathways. This will help determine which patients are most likely to respond to treatments intended to inhibit ATAD2 [120].

The relationship between tumor phenotype and ATAD2 activity is clarified using RNA sequencing, or RNA-Seq. This will help determine whether patients are eligible for targeted therapy if their cancers show ATAD2 overexpression. NGS may also reveal gene expression patterns associated with ATAD2 function, which might be used as biomarkers for the advancement of the disease and the effectiveness of treatment. ChIP-Seq epigenetic profiling could reveal changes in DNA methylation patterns or histone modifications associated with ATAD2, which would make it easier to find new therapeutic and diagnostic biomarkers [121].

7.2. Potential consideration for combination therapies

Therapeutic strategies that integrate ATAD2 inhibition provide promising results. ATAD2 inhibitors in existing treatments may augment therapeutic efficacy and circumvent resistance mechanisms. Targeting ATAD2 with PARP inhibitors may result in heightened apoptosis in cancer cells due to the concurrent dysfunction of both pathways [122]. In conjunction with medicines targeting other epigenetic modifiers, ATAD2 inhibitors may suppress ATAD2 and interfere with carcinogenic transcriptional pathways, enhancing anticancer efficacy [123]. Inhibiting ATAD2 with immune checkpoint inhibitors may augment the immune system's capacity to identify and eradicate tumor cells [124]. Combining ATAD2 inhibitors with conventional cytotoxic agents or targeted therapies may mitigate resistance mechanisms, potentially enhancing clinical outcomes [52]. In hormone-responsive malignancies, the combination of aromatase inhibitors plus ATAD2 inhibition may yield an enhanced therapeutic response [125].

The sensitivity of pancreatic cancer cells to gemcitabine was significantly enhanced by ATAD2 knockdown. The therapeutic effectiveness of gemcitabine, despite its widespread usage in the treatment of pancreatic cancer, is still restricted. There is mounting evidence that pharmacological inhibitors that target AAA+ ATPases can be useful cancer treatments [29–31]. Inhibition of the AAA+ ATPase p97, for example, causes apoptosis in various malignancies, initiates the unfolded protein response, and upsets protein homeostasis [32]. Due to the AAA+ domain present in ATAD2, small-molecule inhibitors that target this enzymatic function may improve gemcitabine's therapeutic impact. A conserved bromodomain essential for binding acetylated

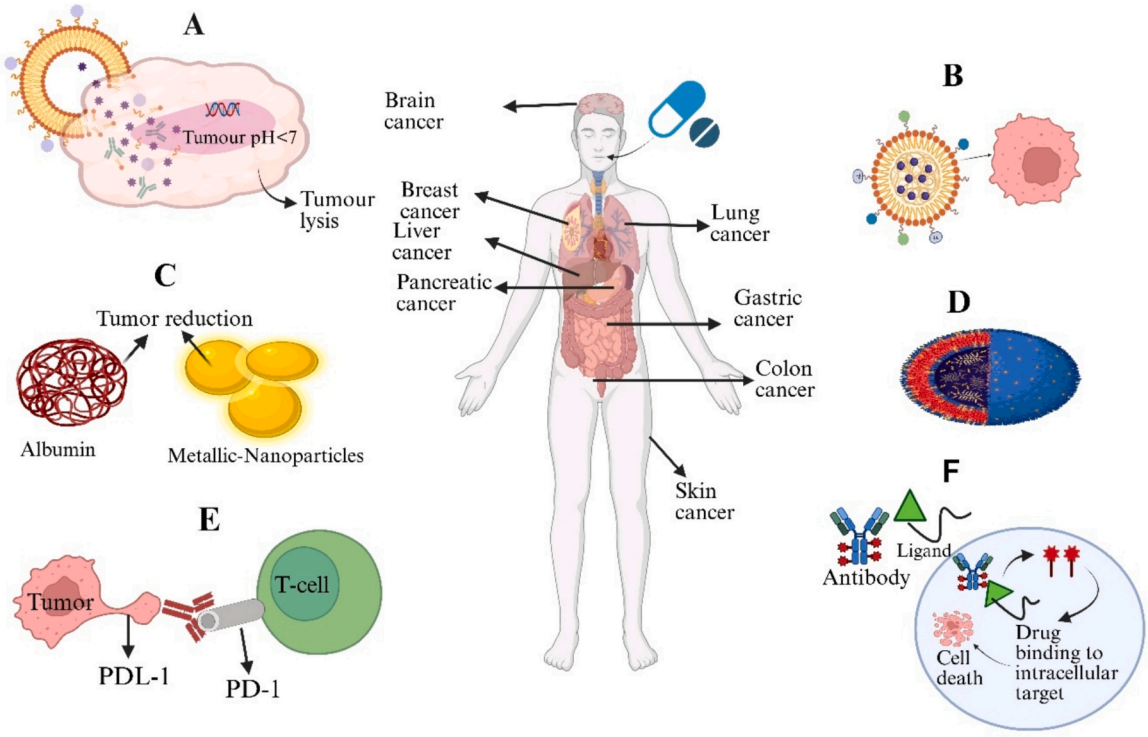

Fig. 9. Advanced drug delivery system:A) Liposomes, B) Polymer based delivery, C) Albumin based & Mettalic nanoparticles, D) Polymer micelles, E) Anti PDL-1 antibody, F) Antibody drug conjugate.

histones is another feature of ATAD2. The selective inhibition of this bromodomain by several drugs has been demonstrated [33,34], underscoring ATAD2 as a potentially effective therapeutic target [106,126]. The centromeric protein CENPE, which is required for tumor cell proliferation and mitosis, is expressed when ATAD2 is activated. RNA sequencing showed that several centromeric proteins, including CENPE, necessary for chromosome alignment and mitotic development, were downregulated in ovarian cancer cells treated with the ATAD2 inhibitor BAY-850. The study evaluated the impact of GSK923295 on ovarian cancer cells in the context of the importance of CENPE in cancer and the ongoing clinical trials of its inhibitor. The treatment dramatically decreased tumorigenic development, colony formation, and cell survival. Surprisingly, compared to either drug alone, combination therapy with suboptimal doses of GSK923295 and BAY-850 enhanced tumor growth inhibition and apoptosis. These results suggest that ATAD2 regulates CENPE to promote the growth of ovarian cancer, and that combined targeting of ATAD2 and CENPE may improve treatment outcomes [52].

By concentrating on the biological indicators linked to ATAD2, therapy selection based on biomarkers improves personalization. Patients with high ATAD2 levels may benefit from treatments designed specifically for this protein [127]. Epigenetic changes predict which people will likely react well to treatments, improving the approach and enhancing precision medicine. Customized combination therapy based on ATAD2 expression levels would be a novel approach to individualized therapy. ATAD2 inhibitors may be given to patients with increased ATAD2 expression in addition to DNA damage repair inhibitors such as PARP inhibitors, epigenetic modulators, or immunotherapeutic strategies. Targeting epigenetic changes and blocking ATAD2 simultaneously may improve treatment outcomes. Examining how ATAD2 affects the tumor microenvironment, particularly in relation to immune cell infiltration dynamics, may help precision immunotherapy become more integrated into customized medicine.

On the other hand, tumors with increased ATAD2 expression might be more responsive to response-based treatment, including immune checkpoint inhibitors and other immunotherapeutic strategies, by changing the immunological environment [128]. Finally, clinical trials might focus on patients with unique genetic fingerprints linked to ATAD2. Concentrating on these subgroups may increase the clinical development success rate and expedite the release of ATAD2-targeted therapies onto the market, guaranteeing that patients receive the best care possible based on their unique genetic and molecular profiles.

8. Conclusion

ATAD2 is an interesting target for cancer therapy since it is an important coactivator in the transcriptional regulation of oncogenes, such as the androgen receptor and MYC, which are necessary for the proliferation and survival of malignant cells. Since therapeutic targeting of ATAD2 is still in its early stages of development, its significance as a marker in pharmacological discovery cannot be overstated. However, the elusive nature of binding sites and the need for high selectivity would present significant obstacles for the formulation, including highly potent inhibitors. These targets will become clearer with more investigation into the molecular interaction mechanisms between ATAD2 and its ligands, requiring modification to promote the creation of medications with improved efficacy and selectivity. Creative strategies may provide innovative medicinal compounds with increased potential by finding new ligands and using advanced screening methods. Beyond this, inhibiting ATAD2 may revolutionize the treatment of cancer and other diseases associated with ATAD2 dysregulation; further research will continue to advance precision medicine.

CRediT authorship contribution statement

Conceptualization: TB, DNA, PP; Formal Analysis: CV, DBH, MS, NKM; Writing original draft preparation: TB, BGHD, BSK, SG; Writing review and editing: PP, DNA, MR, SK, PT, SM, KC; Visualization: PP; Project administration: PP, DNA. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank M.S. Ramaiah University of Applied Sciences, Bengaluru, India, for supporting this project by providing the necessary facilities. The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through a Large Group Research Project under grant number RGP.2/189/46.

Data availability

The manuscript files include all the data generated during the study.

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